Where Illness Comes From, Completed

A Reference Work on Every Chapter of Human Illness, Its Prevention, Its Cure, and What Can Be Done With Simple Means

J. Konstapel, Constable Research, Leiden

Second edition, 26 November 2026
Version 2.0

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The first edition, version 1.0, appeared in October 2026.

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How to use this book

This is a reference work. It covers every chapter of the International Classification of Diseases, eleventh revision, without exception. It is built from entries. One entry treats one condition.

What an entry contains. Every entry has the same eight sections, in the same order.

1. *What it is* — the condition in plain words.
2. *Measured* — prevalence or incidence, deaths, age pattern, geography.
3. *Where it starts* — the established risk factors, and what is genuinely not known.
4. *Cure status* — one of four values, defined below.
5. *Prevention* — what demonstrably prevents it, with a grade.
6. *Treatment* — what is standing, in order of evidence, with price and list status.
7. *Simple means* — what can be done with no industrial supply chain at all.
8. *Gaps* — where the evidence is thin and where good sources disagree.

The four cure statuses. This is the spine of the book, so the words are narrow.

SELF-LIMITING	The body completes the discharge itself. Intervention adds nothing.
CURABLE	A treatment exists that removes the condition.
CONTROLLABLE	The state can be held. The deviation remains.
RELIEF ONLY	Nothing removes it.

A treatment that must be continued for life does not cure. Phenylketonuria on a lifelong diet is CONTROLLABLE. Haemochromatosis managed by repeated phlebotomy is CONTROLLABLE. Gastric MALT lymphoma cleared by one course of antibiotics is CURABLE.

Where the honest answer differs by stage, cause or strain, the status is split and each label names its stratum. Most cancers are read this way, because one label for a cancer would be false at one end or the other.

The four prevention grades.

STRONG	Trials, or large studies that agree, or settled physiology.
MODERATE	One good trial, or consistent observation without trials.
WEAK	Little or indirect evidence.
CONTESTED	Good sources disagree. Both numbers are then printed.

A grade may carry a qualifier where the evidence needs one. “CONTESTED to negative” means good sources disagree and the weight of them leans against the intervention. Where a grade would otherwise be compound, the book takes the lower of the two, and CONTESTED takes precedence over any of the other three, because disagreement among sources is a statement about the state of the evidence rather than its strength.

How the figures are marked. Every numeric claim in this book was checked against a named source while it was compiled. Three things could happen. The figure was read off its source. The source was named but not opened again in this pass. Or the source could not be reached at all.

The first two are printed plainly. The third carries a dagger:

> Distant disease: CONTROLLABLE — 16.9 per cent†

A dagger does not mean the figure is wrong. It means the figure is one that is commonly carried in the literature, and that this compilation could not open the source to confirm it. It marks the difference between what was checked and what was taken on report. There are 2,361 daggers in this book, against 6,352 figures that rest on a named source — some of them opened during this compilation, the rest named by the research line that supplied them and not opened again.

Each figure was given one of these marks while the book was compiled, and the appendices call that mark its provenance tag. Only the dagger reaches the page.

No figure in this book is an estimate. Where no source could be found at all, the number was struck out and the sentence says in words what is known without it. A reference work that hides which of its numbers were checked is worse than one that shows it.

How prices are given. Prices were collected in October 2026 from the sources named. Where a price carries a year, that is the year its source states. Where a price carries none, its source states none, and the figure is as it stood when the source was read in October 2026. Prices in euro are European prices and prices in US dollars are United States prices, unless the text names another market.

Where a price could not be tied to a market at all — where the only figure available was an order-of-magnitude band drawn across several different reference classes — it is written in words rather than digits. "Tens of US dollars a course" is what the source supports. A false decimal would not be.

The corrections made during review. This book was written, then read against its sources by separate reviewers, then corrected. Every correction was recorded where it was made. Those records have been lifted out of the running text, so that the book reads as a book, and they are kept in full in a companion file, *The Review Record*, which travels with it.

What this book does not do. It is not a treatment guide. Nothing in it replaces care. It does not explain. Where it sets a measured fact beside the rules of Part 0, the sentence is marked as a reading, and a reading is called a reading.

Why the book was rewritten

An earlier book, *Where Illness Comes From* (ninth edition, September 2026), walked one frame from first chemistry to the human being and read illness at each layer. It took its cases where they illustrated a layer: cancer, autoimmunity, ageing, trauma.

It was never a catalogue, and it did not claim to be. Ask it about a particular condition and it may have nothing. Diverticulitis, to take the case that prompted this book, does not appear in it at all, although every rule needed to read it is there.

This book keeps that frame and adds what was missing: completeness. Every chapter of ICD-11 is covered. The conditions that carry the burden have their own entry. And three questions are asked of each, which the earlier book asked only of its chosen cases — whether it can be cured, what prevents it, and what can be done where there is no industry, no cold chain, and no money.

That third question turned out to be the one that reorganises the book.

About the second edition

This is the second edition. It is dated 26 November 2026. The first edition appeared in October 2026.

The first edition read every illness against the rules of Part 0. Since then one small system of the same theory has been worked out in full: the Trit Tile. It is the net written as a number system. This edition brings the book into line with it.

What is new. Four things.

1. Part 1b. It sets out the Trit Tile form of the net, a model of illness, and a model of cause, effect and recovery.
2. Two fixed sections in every entry, after *Gaps*: *Depth* and *Model reading*.
3. Appendix D, the record of the trials. Seven trials were run on the text of this book. For each, the protocol was fixed and hashed before the run. An eighth count was made afterwards and is marked as such.
4. Appendix E, the review points for a next edition, and Appendix F, an annotated list of sources.

What is repaired. The first edition had a fault in its setting. Fourteen entries, six section headings and two chapter headings were printed in a column one word wide. The fault ran over 268 pages. On 123 of those pages the column ran off the bottom of the page, and about 8,700 words could not be seen at all. The text itself was complete in the file. It is now set as normal text, and the headings are back in the Contents.

The fourteen entries are these. On the eye: myopia; age-related macular degeneration, dry form; retinitis pigmentosa and inherited retinal dystrophies; keratitis and corneal opacity. On the ear: acute otitis media; tinnitus; congenital and early-onset hearing loss. On the skin: contact dermatitis; alopecia areata; the cross-reference entry for scabies; pressure ulcers; diabetic foot ulcers. On injury: poisoning; traumatic brain injury.

In a further 234 paragraphs a list had run together into one block of text. Those lists are restored: 1,421 bullet items and 241 numbered items. No word was changed by this.

What is not changed. The text of the first edition. Every figure, every status, every grade and every dagger stands as it stood. The small repairs of setting are listed in Appendix E.

How to tell old from new. In the entries the two new sections are set with a rule in the left margin. Text without that rule is the text of the first edition.

How to read *Depth*. The section places the entry on the ladder of section 0.8. It names the structure in which this book puts the first deviation. It gives the size of that structure, the time to the first complaint, and the length of one untreated course. Each of the three is turned into a position: the number of factors of three that separate it from S_0 or from T_0.

The values carry marks.

Mark	Meaning
[B]	The value is stated in this book.
[W]	Wikipedia, table of incubation periods, opened on 25 November 2026.
[P]	A table of incubation periods in an article at PubMed Central (PMC7152212, table 56.2). Read only as a search excerpt.
[L]	A page of the Los Angeles County Department of Public Health. Read only as a search excerpt.
†	A value that is commonly carried. Its source was not opened. This is the dagger of the first edition.

Every size carries the dagger. Of the 348 times to a first complaint, 88 rest on the book or on a named source. Of the 138 lengths of a course, 60 do. The others carry the dagger.

A depth orders. It does not select. No trial in this book found that the depth of an illness, or the phase of the Trit Tile at that depth, tells whether the illness can be cured. Appendix D gives the numbers.

How to read *Model reading*. The section applies the model of Part 1b. It names the way in which the illness can end, the layer in which it starts, and the moment where the book records one. It states what the rule of the model gives. It sets that beside the status of the book. It is a reading in the sense of section 0.10. The status stands.

The coding in *Model reading* was made by reading each entry with its status in view. It is not the blind coding of the trials. So the agreement between reading and status is no evidence for the model. The evidence is in Appendix D, and it is modest.

What was checked. The first edition was read by separate reviewers, as Appendix C describes. The new material of this edition was not. By the standard of Appendix C it counts as unchecked. The numbers in Appendix D can be recomputed from the files that travel with this edition.

Part 0 — The Rules This Book Follows

Part 0 — The Rules

This part holds every rule the rest of the book uses. Nothing in the entries rests on anything stated elsewhere.

The rules come from the Vacuum.Net theory as published at constable.blog. The governing statement is the Foundational Paper, Eighth Edition, version 8.1, 17 October 2026. Where a second statement of the same rules differs in wording, the difference is noted.

The theory was not built for biology. It was built at the bottom, with one strand and one test, and no constants given in advance. This book applies it upward. It does not repeat the derivation.

0.1 The net

The image is a fishnet under tension.

The net is one strand. It runs everywhere. Where the strand crosses itself there is a crossing. Between the crossings lie openings.

Four words describe what the strand does.

Strand. The net itself, under tension. **Winding.** A stretch of strand that returns on itself in step. Physics calls this energy. **Knot.** Windings that hold each other in three directions. Physics calls this mass. **Mesh.** An opening between strands, with an extent in space or in time.

One rule decides what stays. A winding persists only if it returns on itself in step. What does not close does not stay as a form. Its tension moves to the meshes beside it.

0.2 The five starting rules

N1 — Strand. There is one strand. It is oriented and continuous. Its only local act is crossing itself. A self-crossing has three states: over, under, or none.

N2 — Closure. Only configurations that close — that return in phase onto themselves — persist. What does not close does not last. Closure is the selection rule. There is no external selector.

N3 — Memory. A closed configuration constrains the next rewrite. The net carries its history as its shape.

N4 — Context. The response of the medium is a state function, not a universal constant. Universality is the limiting case, where the state variable does not vary across the sample.

N5 — Scale. The net repeats its own construction across depth. One winding step deeper multiplies the count of distinguishable states by three. The same winding, read at another depth, is the same winding.

A second published statement of the same five rules words N2, N3 and N5 differently. It defines closure through the window and adds that what does not close passes on as tension; it states memory as an ordering of passages at a knot, where the first passage fixes the orientation; and it gives scale as an explicit coarse-graining into blocks, where what does not close at one scale is the material of the next. The two readings agree on what they select for. They differ in where they put the machinery.

0.3 The register

At a crossing the strand does one of three things. It passes over, it passes under, or it does not cross. These three states are written +1, −1 and 0. One such state is a trit.

Counting with +1, 0 and −1 is balanced ternary. Every whole number has exactly one writing in it. There is no separate minus sign: negation is mirroring, and zero sits in the middle rather than at the edge.

Three is also the cheapest base. Writing numbers in base r costs about r symbols per position, and the number of positions falls as one over the natural logarithm of r, so the total cost goes as r over ln r. That expression is smallest at r = e ≈ 2.718, and the nearest whole base is three: 3/ln 3 = 2.73, against 2/ln 2 = 2.89 for binary. Three wins.

The register is the whole of what this book needs from the theory's arithmetic. The test at a cell's rim, in Part 1, has the same three outcomes as a crossing.

0.4 Closure, windows and rings

Three crossings in a row form a window. A window is closed when its three trits add to a multiple of three. An open window carries tension. A closed window carries none.

Count them. Three crossings with three states each give 3 × 3 × 3 = 27 windows.

Kind	Example	Number	Closed?
Three equal	(+, +, +)	3	yes — the sums are 3, 0 and −3
Three different	(−, 0, +)	6	yes — −1 + 0 + 1 = 0
Two equal, one different	(+, +, 0)	18	no — the sum is never a multiple of 3

So 9 of the 27 windows close. They come in two kinds, and the difference matters for everything alive.

Uniform closure. Three equal trits. Nothing differs inside it. This is the form of a crystal. It holds and does not turn.

Mixed closure. Three different trits. This form can keep turning while it stays closed. Every crossing changes at every step, and every window stays closed. All content changes; the closure holds. This is the form of living matter.

Three consequences are used throughout the book.

Two fix the third. If two trits of a window are given, exactly one value of the third closes it.

The two kinds do not mix. A closed strand is uniform throughout or mixed throughout. Where a uniform stretch meets a mixed stretch, the window between them is open and carries tension. That seam is where this book finds most of its deviations.

A mixed strand keeps one direction, or it does not close. Join a strand running − → 0 → + to one running + → 0 → −, and the two windows on the seam stand open. Which direction is taken is not set by the rule. It is set by what lay there first, which is N3.

A ring is a strand closed on itself. Its depth is its number of crossings. Asking that every window of a ring be closed forces the trits to repeat with period three. Uniform rings exist at every depth, one per state. Mixed rings exist only where the depth is a multiple of three, and there are then exactly two: one running − → 0 → +, the other the mirror.

A mixed ring therefore cannot grow one crossing at a time. It grows by a whole group of three. And a mixed ring of depth six cuts into two rings of three, each of which closes, and each of which keeps the direction of the parent. The smallest full cycle is 3 → 6 → 3 + 3.

0.5 The two classes

Closure is all or nothing. A winding closes or it does not. So at every depth there are two classes of form.

The closed class holds its form. These are the things: atoms, molecules, machines, cells, bodies.

The unclosed class decays. While it lasts it carries tension from one closed form to the next. These are the events: light between atoms, signal molecules between cells, the nerve impulse and the hormone within a body, speech between people.

Only what ends can deliver. A closed form returns its tension to itself — that is what closure means — and can hand nothing over. That the carriers decay is what keeps a body readable: each message is erased after it is read.

An earlier book in this series names the same division as two layers. The **address layer** holds identity: frozen topology, counted in the ternary ladder. The **tension layer** is the only layer in which anything moves: charge and discharge. The words are that book's; the division is this one's closed and unclosed classes, read as what a thing is against what happens to it.

0.6 The test

When one form reads another, there are three outcomes, and only three. They are the three states of the register.

+1	It fits	The form stays
−1	It does not fit	Its tension is discharged and the form is taken apart
0	It is not read	Nothing happens

Hold on to the third outcome. Most of this book turns on it.

A form that is never read is neither kept nor removed. It simply remains. Health is not the absence of misfits; misfits arise every day, in everyone, in thousands. Health is a test that reads fast enough.

0.7 Widening and pruning

Whatever closes becomes a unit for the next weaving. That gives two strokes.

Widening. Units combine. The number of combinations grows with every step. **Pruning.** Only what closes persists.

A layer is what survives one round. The residue of one depth is the alphabet of the next.

The arithmetic is visible all the way up. About ninety stable rungs of matter give, on the order of 10^{60}, possible drug-sized molecules; life uses a few thousand. A protein chain of one hundred units drawn from twenty kinds has $20^{100} \approx 10^{130}$ possible orders; a human body runs on about twenty thousand. Widen by a hundred and thirty orders of magnitude; prune to twenty thousand. Same engine, one depth up.

And it never stops, because no closure is ever exact. Each depth leaves a remainder, and the remainder is carried upward. A ladder driven by a rest cannot end.

0.8 The ladder

The theory fixes two natural units from hydrogen.

Let R∞ be the Rydberg constant and m_e/m_p the electron-to-proton mass ratio. Then R_H = R∞/(1 + m_e/m_p) = 10,967,758.340 m^{-1}, and

$$S_0 = 1/(2\ R_H) = 4.55881671 \times 10^{-8}\ \text{m} = 45.59\ \text{nm}$$

$$T_0 = S_0/c = 1.52065757 \times 10^{-16}\ \text{s}$$

so that $S_0 = c \cdot T_0$, and a length and its period share one coordinate.

The position of a size is the number of factors of three between it and S_0:

$$\text{position} = \log_3(\text{size} / S_0)$$

and a time is placed the same way from T_0. One ladder step is a factor of three.

The ladder orders. It does not select. In the companion reference work on the body, the measured sizes of the body's parts were tested against the whole marks of the ladder and found spread between them — 192 of 388 within a quarter step, 49.5 per cent against 50 by chance. So positions are given, and no part of the body is assigned to a mark. The ladder is a coordinate system and is used as one.

This book uses the ladder only where a size or a duration is worth comparing across layers. Most entries do not need it.

0.9 Constants as states

The fourth rule is the theory's boldest and its most testable. If constants are states, they must move where the state moves and stand still where it does not.

The theory carries a measured anchor. The threshold at which gravitational anomalies begin, written a_0, comes out as $c \cdot H_0/2\pi$, where the 2π is the one full turn around a mesh.

With the Foundational Paper's own inputs, $c = 3.00 \times 10^8$ m/s and $H_0 = 70$ km s^{-1} Mpc^{-1} $= 2.27 \times 10^{-18}$ s^{-1}:

$$a_0 = (3.00 \times 10^8 \times 2.27 \times 10^{-18}) / 2\pi = 1.084 \times 10^{-10} \text{ m s}^{-2}$$

The measured threshold from galaxy rotation curves is about 1.2×10^{-10} m s^{-2}. The gap is 9.7 per cent.

Take instead $H_0 = 67$ km s^{-1} Mpc^{-1}, the value from the early universe, and the same arithmetic gives 1.050×10^{-10} and a gap of 12.5 per cent. Both are printed, because the gap is a function of which Hubble constant is taken, and the two measurements of it disagree. That disagreement is unresolved in cosmology and is not resolved here.

For this book the result matters in one way only. It shows the frame was not built for biology and bent to fit. It was built at the bottom, made testable there, and walked up.

0.10 What a reading is

This book sets measured facts beside the rules above. Where it does so, the sentence is marked as a reading.

A reading is not a cause. The theory does not say why a seam tears or why a cell is missed. It says which configurations persist. Describing at the right depth replaces explaining, and explaining is causal thinking: in a one-strand model there are not two separate things to put an arrow between.

So the book uses, in place of cause:

Selection by fit — only what returns in phase remains. **Identity over scale** — the same winding at another depth. **Constitutive relation** — a state function, simultaneous, no arrow. **Correspondence** — a measured pattern that has the form of a rule.

Every number in the chapters comes from the standing literature, and the references say which. The frame supplies the ordering, and nothing else.

0.11 The dictionary

Every word the chapters use maps onto one element of this part, and onto nothing else.

Word in the chapters	In Part 0
thread, strand	the strand, N1
loop, winding, closing	winding and closure, N2
the test	the closure test; the one selection
pattern, address	stored winding, N3
state, tension	the tension the net carries, N4
depth, layer	scale, N5
the register	balanced ternary {+1, 0, −1}
the legitimate zero	a lawful 0 in the register
discharge	tension release
phase, step	closure phase
the fishnet	the standing image of the net

No concept in the entries falls outside this list. That is what one frame, walked from first chemistry to the human being, means in practice.

Part 1 — How Illness Is Read

Part 1 — How Illness Is Read

Part 0 gave one strand and one test. This part walks the test upward, from the first chemistry to the human being, and asks at each layer the same two questions: what is a deviation here, and how is it prevented.

It is the shortest part of the book. Everything in it is a frame for the entries, not a substitute for them.

1.1 First chemistry

Why are there about ninety stable kinds of matter and not millions? Because closure is strict. A loop closes only at certain sizes. Too small and the wave does not come around; too large and it comes around out of step. Between those, nothing. The possible loops form a ladder with fixed rungs and gaps.

The rungs are the elements. Hydrogen is the simplest closure. Helium is the first complete one: everything comes back in step, nothing left over, which is why it joins with nothing. Carbon sits in the middle of a rung with four open ends, the maximum reach a small loop can have, which is why it builds everything alive.

Water is two small loops closing onto one middle loop at 104.5 degrees. That angle is not designed. It is where the tensions balance, and every property that makes life possible in water follows from it.

The deviation at this layer is a closure that does not sit still. Some heavy closures hold, but barely, and their tension leaks out in bursts. A leaking closure does not stay in its own layer: its bursts travel up and snap thread in the layers above. This is the oldest source of illness. It needed no biology to exist, and became illness only when there was a weave to disturb.

Prevention here is the oldest there is: distance and shielding. Everything else in this book assumes this floor is quiet. Where it is not — radon in houses, fallout, certain mining regions — the illness statistics of every higher layer rise, and no amount of higher-layer care fully compensates.

1.2 The cell

A cell is a pocket of ordered weaving with a boundary. The boundary is not a wall. It is a reading surface. Everything the cell is, it shows on its rim; everything that reaches the cell arrives at that rim first and is read before it enters.

Inside, the cell keeps its pattern, copies it, and reads its own copy. The pattern is stored as a wound thread — about three billion winding steps, coiled two metres long into a hundredth of a millimetre. On top of the steps sit removable marks that set which stretches are read and which stay silent: the same pattern, in different states.

Copying makes about one raw error per hundred million steps and proofreads most of them away. What remains is roughly one lasting change per few billion steps per division.

The deviation at this layer is a winding change the repair missed. Note the neutral word. A mutation is not damage by definition; it is a step that differs from the pattern. Most change nothing that matters. Some weaken the mesh. A very few change what the cell does and, crucially, what it shows on its rim. The rim signature shifts, and the cell now reads differently to its neighbours.

Prevention has one form: protect the copying and the repair. Everything that snaps thread raises the miss rate. Everything that starves the repair crews slows them. This is not moral advice. It is maintenance arithmetic.

1.3 The test layer

A body is tens of trillions of cells, each showing its signature on its rim. The body carries a dedicated reading layer whose only work is to run the one test at cell scale.

The readers press against a cell's rim, compare the signature to the pattern, and register one of the three outcomes of Part 0.6. Fits: move on. Does not fit: the cell is opened and dismantled, usually within the hour. Not read: nothing happens.

This runs continuously, everywhere, from before birth to death. On an average day it removes thousands of cells whose signature had drifted. Nobody notices. That is the point.

Now the subtlety that organises most of this book. There are places where the body must not discharge what it reads. The gut rim meets foreign material with every meal. The eye cannot afford inflammation without going blind. And a child in the womb is, by signature, half foreign; nine months long the reading must return zero there, or no mammal would be born.

So the body carries official tokens — signs a cell can show that turn the local reading to zero. Clinicians call them checkpoints.

The zero-token is not a flaw. It is load-bearing architecture. Without it: self-destruction. With it: a blind spot. Much of this book lives in that trade.

Deviation here comes in two mirror forms. A test that reads too weakly lets misfits through. A test that reads too sharply discharges healthy tissue — the autoimmune diseases, read as not-fitting while they fit. One layer, one dial, two directions of failure.

Prevention: the reading population is built in childhood by exposure, and the readers themselves carry marks from earlier encounters that reset how sharply they read next time. The test layer is not fixed equipment. Calibration needs material.

1.4 Where cancer sits

Three plain facts, and the third follows from the first two.

Copying makes lasting changes, always. The test discharges what reads as not-fitting, daily and silently. Therefore what accumulates over years is only what the test did not read as not-fitting.

That is why tumours persist, in one sentence. A tumour is the remainder of a selection. And since the body's own lawful zero-tokens are the most reliable way to go unread, long-standing tumours almost always end up wearing them — not by any decision, but because for years every variant without the token was discharged and every variant with it was not.

Oncology knows this sequence as immunoediting, and its three phases are correct. The reading here differs only in the verbs. The data say remainder; the standard words say actor. Verbs steer research questions.

The clearest support is in the autopsy rooms, and it is in this book's chapter 02 with its figures: a large fraction of people who die of something else carry small silent tumours that never became disease. The altered tissue was there. The test around it held it.

Read in the net: cancer is not a property of a cell. It is a relation between a mesh and the test around it. This is a reading, not a mechanism.

1.5 Where ageing sits

Ageing is not the pattern changing. An old hand has the same weave as a young one. What goes is the tension and the measure. Loops still close, but sloppily. Rhythms that once locked — sleep and light, heartbeat and breath, hormone tides — drift out of step.

The medical file of old age is a list of lost phase-locks. Heart-rate variability falls, deep sleep flattens, temperature and hormone cycles dampen, and the reading layer thins and slows. Which is exactly why cancer and infection climb after seventy: the misfit rate has not changed much. The discharge rate has fallen.

So lifespan, read this way, is coherence-span. And the question is not why someone does not wear out. It is what keeps a weave in step for ninety-six years.

The answer is four things, and they are known, and they are the four that every large study converges on. Loading keeps tension. Food supplies the thread and sets the clock. Not snapping thread is simply not snapping thread. And other people, which carries more weight than medicine expected, because human weaves phase-lock to each other.

What this frame adds is not a new recommendation. It is why those four and not others.

1.6 Where the mind sits

The net does not stop at the skull and does not change its rules there. The feelings are not commentary on the body's states; they are the body's tension, read at the surface where reading becomes noticing.

Stress is held tension without a discharge path. The alarm weave is healthy architecture: tension raised for an action. The modern condition is alarm without action, and the prevention that follows is not relaxation but discharge.

Trauma is a mesh locked out of phase. The event is over in the world and not over in the body. The treatments that demonstrably work are, without exception, closure procedures.

Depression in its exhausted form reads as coherence-loss arrived early, which is why the treatments with the strongest evidence are phase treatments as much as chemical ones.

Meaning is fit, felt. And its measured counterpart is among the least advertised figures in epidemiology.

Each of these has its entries, with the trials and the effect sizes, in chapter 06.

1.7 What this frame changes in practice

Medicine as built is organised around the tissue: find the abnormal part, image it, cut it, dissolve it, replace it. Its triumphs are tissue triumphs — surgery, antibiotics, transplantation — and this book does not diminish them. They are in chapter after chapter, with their figures.

Its hardest fronts are all at the test and phase layers. And its breakthroughs of the last decade are, without being named that way, test-layer and phase-layer breakthroughs.

So the frame orders diagnosis as well as treatment. Three questions decide the test-layer diseases, and all three are already measurable with instruments that exist, scattered across departments that do not speak to each other.

Is there a readable signal. Can the readers reach it. What does the register show.

Signal, access, register. Stated as a principle, it extends from oncology to autoimmunity, which is the same axis with the opposite deviation.

And the therapies order by layer rather than by molecule. Remove, rebuild, kill. Close one winding. Correct the register and let the body discharge. Restore step. Change what everyone hangs in.

That last layer carries the largest numbers in this book and the smallest budgets. It is the subject of Part 3.

Part 1b — The Model This Edition Adds

Part 1b — The Model

Part 0 gave the rules. Part 1 walked them up to the human being. This part adds three things. The first is the Trit Tile, the same net written as a number system. The second is a model of the illness itself: how it can end, and when. The third is a model of cause, effect and recovery, with a path that can be walked for any entry.

Every statement in this part carries one of four labels where it matters. *Proved* means a proof is given or cited. *Measured* means a count that can be repeated. *Known* means a published result of others. *Reading* means an interpretation. The labels are those of the Trit Tile.

1b.1 The Trit Tile: the net as a number system

The Trit Tile is a reference work of the same theory (J. Konstapel, *The Trit Tile*, Reference v1.1, 21 November 2026). It studies closure in one concrete system.

Take a point of the triangular lattice. Write it as a + bω, where ω is a cube root of one. Take the base β = 1 − ω. Subtract a digit −1, 0 or +1, chosen so that the result can be divided by β. Divide. Repeat.

> digit d ≡ a + b (mod 3), with d in {−1, 0, +1}
>
> step T(z) = (z − d) / β

Each step is one trit. The Trit Tile writes the three states as R, O and L: forward, standing still, backward. A state is a direction, not an amount.

Every path ends in one of three places: in 0, in +(1 + ω) or in −(1 + ω). *Proved* (elementary). A point that reaches 0 has a finite writing in trits. It closes. A point that ends in one of the other two never reaches 0.

About 31 per cent of all points never reach 0. That share does not settle. It swings between about 29.6 and 32.0 per cent, and it returns to the same value each time the norm grows by a factor of three. Its mean is 30.87 per cent. That the share has no limit is *proved*, with the help of a computer. The range, the period and the mean are *measured*.

The ground is the ground of Part 0.

- The same five rules. The Trit Tile cites the ninth edition of the theory. Part 0 cites the eighth. The wording of N2, N3 and N5 in the Trit Tile is the second wording that section 0.2 describes.
- The same register: balanced ternary, three states.
- The same ladder: one more trit is a factor of three.
- The same sentence about the rest. Section 0.7 says that no closure is ever exact and that a ladder driven by a rest cannot end. The Trit Tile proves one case of it.

1b.2 What the two forms share, and where they differ

The three ends are the three uniform rings. *Measured.* Follow a point that has arrived at one of the three ends, and write down the digit it pays at each step. At 0 the digits are 0, 0, 0 and so on. At +(1 + ω) they are −1, −1, −1. At −(1 + ω) they are +1, +1, +1. These are the three uniform rings of section 0.4. Their windows have the sums 0, −3 and +3, so all three are closed.

Two things follow.

The points that the Trit Tile calls turning are, in the words of Part 0, uniform and closed. The difference between a point that reaches 0 and a point that does not is not the difference between closed and open. It is the state in which the register comes to rest: 0, or one of the two directions.

Mixed rings do not occur as an end. Section 0.4 calls the mixed ring the form of living matter. In the Trit Tile every path ends in a uniform ring, the form of a crystal. If life has a place in the tile, that place is the passage and not the end. *Reading.*

Closure is defined twice. In section 0.4 a window of three trits closes when its sum is a multiple of three. That is a rule for one place. In the Trit Tile a point closes when its path reaches 0. That is a rule for a whole path. Both are rules modulo three. They are not the same rule. This edition keeps both and says each time which one is meant.

What does not close. Section 0.5 says that the unclosed class decays, and that only what ends can deliver. The Trit Tile says that what does not reach 0 goes on for ever. The two statements are not yet joined. This is an open point. It is listed in Appendix E.

Norm and length. *Proved* (elementary). The ladder of section 0.8 counts in length: one step is a factor of three in size. The period of the tile is a factor of three in the norm, and the norm is the square of the distance. In length the period of the tile is √3, half a step of the ladder. For an area it is 3. For a volume it is 3√3.

Section 0.8 reports a test: of 388 sizes in the body, 192 lay within a quarter step of a whole mark. That test looked for one phase of the whole step. It did not test the period of the tile. And the swing of the tile is small: about 1.2 percentage points on either side of its mean. A count of how many sizes lie near a whole mark would not have shown a swing of that size. The test can be repeated with the period √3. That has not been done.

Windows on the way. *Measured, weak.* In the disc of norm up to 22,500 there are 81,624 points. The share that never reaches 0 is 0.3082. The windows of three digits along each path were counted.

Path	Uniform windows	Mixed windows	Open windows
Reaches 0	0.100	0.246	0.654
Does not reach 0	0.115	0.208	0.677
By chance	0.111	0.222	0.667

Paths that reach 0 carry slightly more mixed windows on the way. The difference is small. The windows overlap, so they are not independent. No test was run.

1b.3 What the Trit Tile does not do in this book

A reader may expect that the tile tells which illness can be cured. It was tried. It does not.

The trial ran as follows. Each illness was given a depth: first from a table of sizes, then from a time found in the text, then from the *Depth* section built for this edition. The tile gives, for every depth, the share of points that close at that phase. That share was set against the cure status of the book. Five runs were made. None found a relation that held. In the last run the rank correlation was −0.02 for the size depth and +0.01 for the time depth. Appendix D has each run.

So this book makes no statement on cure from the phase of the tile.

What the tile describes is a rhythm that does not die out. If it bears on illness, the place to look is relapse and remission, not the four labels. The Trit Tile offers a procedure for finding a cycle in a series (its section 21). It could be run on the series of one person: heart rhythm, sleep, temperature, relapse. *Reading, and a proposal.* It has not been done.

What the theory does give to the model below is not the tile. It is the test with its three outcomes (section 0.6), the layers (section 1.7), and the ladder as a way to place things.

1b.4 Model A: the illness

An illness is read by two questions. How can it end? And when?

The way of ending. There are six.

Way of ending	What ends the illness	Examples in this book
Let close	The cause stops by itself.	Jet lag; gestational diabetes; acute diverticulitis
Remove	A foreign party is taken away.	Tuberculosis; a gallstone; contact dermatitis
Rebuild	The body's own structure is repaired, or the diseased part is taken out.	A fracture; cataract; a localised tumour
Supply from outside	A shortage is supplied from outside.	Iron deficiency; vitamin A deficiency
Supply from inside	The body does not make something. It is supplied for life, or the source is restored.	Type 1 diabetes; haemophilia
Restore proportion	A proportion or a rhythm is off. It is held.	Hypertension; lupus; depression

Four of the six come from one text of the author ("Research directions to cure all diseases", constable.blog, 29 October 2026). They are: let close, remove one party, supply what is missing, restore the proportion. Supply was split in two after the fifth trial. Rebuild was added after the sixth. Section 1.7 already orders the therapies of the mesh as remove, rebuild, kill.

The moment. There is a point after which nothing returns. Before it an illness can end. After it, what is lost stays lost. The author's text of 1 November 2026 ("Why some infections end and others do not") describes it as a race between two clocks: the process, and the capacity to recover. The book records the moment already. Many entries split their status into an early and a late stratum.

The layer. The layer is where the first deviation sits. There are six.

Layer	The deviation	The matching therapy
Mesh	In tissue: a foreign party, an injury, a worn structure.	Remove, rebuild, kill
Chain	In one winding: a gene or its product.	Close one winding
Word	In one signal: a hormone or a nutrient that is short.	Write the one signal
Reading	In the test: it reads too sharply or too weakly.	Correct the register
Phase	In step: a rhythm has drifted.	Restore step
Surround	In what everyone hangs in: air, water, a substance.	Change the surround

Five of these are the therapy layers of section 1.7. The word layer is named as its own layer in the short edition of this book (*Where Illness Comes From*, ninth edition, September 2026).

The depth. A body is a depth, and so is each part of it. The *Depth* section gives the position of the structure in which an illness starts. It serves to order. It does not enter the rule.

The rule. An illness can end when three things hold.

1. Its way of ending is one of four: let close, remove, rebuild, or supply from outside.
2. The moment is not late.
3. No bound applies.

In every other case the illness is held, or only eased.

> ends = (way is let close, remove, rebuild or supply from outside) and (moment is not late) and (no bound)

The bounds. Three were found by setting the rule against the book.

- Remove ends an illness only if the party can be reached in full. The provirus of HIV cannot. Dust in the lung cannot. A virus that lies latent in a nerve root cannot.
- Rebuild ends an illness only if the tissue regrows or can be replaced, and the cause has stopped. The spinal cord does not regrow. Air sacs do not. In an artery the process in the wall goes on.
- Supply from inside holds an illness. It ends it only if the source itself is restored, by a transplant or by gene therapy.

What the rule does not do. It tells an illness that ends from one that does not. It does not tell CONTROLLABLE from RELIEF ONLY. And within the illnesses that end, it does not tell SELF-LIMITING from CURABLE, except that let close points to the first.

1b.5 How well the model holds

All counts are on the text of this book. “Ends” means that the book gives SELF-LIMITING or CURABLE. Appendix D has the protocols and the numbers.

The way of ending. *Measured.* The way was coded blind, by keyword, from the first sentence of *What it is*. The counts are on the 145 entries with a single status. The book says “ends” for 23 of 27 coded remove and for 4 of 5 coded supply from outside. It says so for none of 8 coded supply from inside and for 24 of 105 coded restore proportion.

The moment. *Measured.* The strata of split entries were coded blind as early or late. Of 70 early strata, 61 end (87 per cent). Of 89 late strata, 17 end (19 per cent). Within one and the same entry the early stratum did better 25 times, the late stratum once, and 5 times they were equal.

The layer. *Measured.* Of 68 entries that start in the mesh, 40 end (59 per cent). Of 48 that start in the reading or the phase layer, 5 end (10 per cent).

The whole rule. With four ways and the moment, the rule gave the right class for 116 of 145 single-status entries (80 per cent). Choosing the largest class every time gives 65 per cent. On the 783 strata of split entries it gave 59 per cent against 53. With rebuild and let close added afterwards, on the same entries, it gave 83 per cent.

Four cautions belong with these numbers.

- The ways of ending were adjusted after the fifth trial, on the same 145 entries. The 80 and the 83 per cent are not an independent test.
- That early does better than late is what medicine expects. The count shows that the book uses the moment in a steady way. It does not show something new.
- Illnesses of the mesh end more often in part because means for the mesh exist: surgery, antibiotics. The count ties two parts of the same book together.
- Only one coder worked, and that coder knew many of the statuses.

What was not found. The phase of the Trit Tile (five runs). A difference between illnesses of the building years and illnesses of upkeep: 7 of 18 against 3 of 25, which did not pass the bound that was set beforehand. A link with the month of birth, in 15 entries.

1b.6 Model B: cause, effect and recovery

Model A says what an illness is. Model B says what follows. It has three steps.

Cause. The cause is the place where the deviation starts: the layer, the party or structure, and its depth. The *Depth* section holds these.

Effect. The effect is a race between two clocks. One clock is the process. The other is the capacity to recover. The moment is where that race stands. Before the point of no return the illness can still close. After it, a part does not come back.

Recovery. Recovery follows the way of ending.

Way of ending	Recovery route
Let close	Do no more than is needed. The cause stops by itself. Guard until it does.
Remove	Take the foreign party away, as early as possible.

Way of ending	Recovery route
Rebuild	Repair the body's own structure, or take the diseased part out.
Supply from outside	Supply what is short.
Supply from inside	Supply for life what the body does not make, or restore the source.
Restore proportion	Hold the proportion. Look for a reset. Work on the phase layer and the surround: light, rhythm, movement, other people.

Recovery can be measured as a return. The author's text of 3 November 2026 proposes two numbers: the fraction that came back, and the time the return took.

The path. For any entry the model can be walked in seven steps.

1. Is it an illness in the sense of the model? A property, a state or a form of care is not.
2. Where does it start? Read *Depth*: the structure, its size, its times. Name the layer.
3. How can it end? Name the way.
4. Does a bound apply?
5. What is the moment? Early or late.
6. Read off the route.
7. Measure the return.

Three entries walked.

Tuberculosis. It starts in a bacterium, in the mesh. The way is remove. No bound applies: the regimen reaches the organism. The rule says it ends. The book says CURABLE.

HIV. It starts in a virus, in the mesh. The way is remove. A bound applies: the provirus sits in resting cells and cannot be reached. The rule says it is held. The book says CONTROLLABLE.

Open-angle glaucoma. Depth places the start at the optic nerve head, in the mesh. The book calls the cause of the nerve's death not known. The way is restore proportion: pressure is lowered and held. The rule says it is held. The book says CONTROLLABLE. Appendix E gives a review point for this entry.

1b.7 The person: the blueprint

Model A and Model B describe the illness. They do not describe the person who has it. Closure belongs to the pair, not to one side.

The author's own instrument for the person is the blueprint. The page of the maze-doctor (constable.blog, 20 October 2026) puts it in three sentences: "The blueprint fixes where tension lands. The state fixes when. Illness needs both."

The blueprint b is fixed. It is taken from the data of birth. The state s(t) moves. The paper *The Biofield Monitor* (22 May 2026) joins the two in one number:

$$S(t) = \cos(s(t), b)$$

It names four bands: 0.85 and above, in step; 0.70 to 0.85, compensating; below 0.70, critical; below 0.50, deep loss of step.

In the terms of the model the fixed part answers *where*: which way of ending goes wrong more often for this person. The moving part answers *when*: how far this person stands from the point of no return.

The maze-doctor names four classes of failure. Their place in the model is given below. The third column is a reading of this edition.

Class	What goes wrong	Reading in Model A
Blue	Holds a script too long. The reference drifts.	A wrong closure that passes for normal. Restore proportion; phase layer.

Class	What goes wrong	Reading in Model A
Red	Registers a break late.	The moment is late; the body's own structure.
Green	Cannot call up experience. Step is lost.	Loss of phase. Restore proportion; phase layer.
Yellow	Does not revise the model, then collapses.	Reads too sharply. Restore proportion; reading layer.

Status. All of this section is *reading*. None of it is tested. The book holds illnesses and no persons, so the book cannot test it. One coarse trial was run: illnesses that a large study ties to the month of birth were set against the way of ending and the layer. In 15 entries nothing was found (Appendix D, trial 7).

The trial that would decide is this. Compute S(t) for a person with that person's own blueprint, with the blueprint of someone else, and without any blueprint. Fix beforehand what counts as an episode of illness. See which of the three foretells an episode two to six weeks ahead. If a person's own blueprint does no better than a stranger's, the blueprint adds nothing to the forecast.

Nothing in this section is a diagnosis, and nothing in it replaces care.

1b.8 The model in one page

Question	Where to look	Answer takes the form of
Where does it start?	*Where it starts*; *Depth*	A structure, a layer, a depth
How can it end?	*What it is*; *Model reading*	One of six ways
Does a bound apply?	*Cure status*; *Model reading*	Yes or no, with the reason
When?	The strata in *Cure status*	Early or late
What follows?	*Treatment*; *Simple means*	A route
Did it come back?	Measured on the person	A fraction and a time
For whom?	The blueprint; not in this book	A reading, untested

The measured status of each entry stands. Where the model and the status differ, the status is not corrected. The difference is listed in Appendix E.

Part 2 — The Illnesses

Chapter 01 — Certain Infectious or Parasitic Diseases

Forty-two entries. Forty-one conditions and one cross-cutting property, antimicrobial resistance, which is not a disease but reclassifies the diseases around it.

The chapter covers the conditions that carry the burden. Tuberculosis, HIV and malaria. The lower respiratory infections. The diarrhoeal diseases and their named pathogens. The viral hepatitides, the vaccine-preventable childhood infections and the neglected tropical diseases. The three principal bacterial sexually transmitted infections, and Ebola virus disease with the other viral haemorrhagic fevers, which share one entry. Where WHO publishes a fact sheet, that sheet is the spine of the entry. Where it does not, the entry says so and marks the missing figure.

Two things run through the chapter, and they sit at opposite ends of it.

The first is that the shortest supply chains in the chapter are here. A single oral dose of praziquantel kills the adult worms of schistosomiasis, and people in active transmission need re-treatment, because it does not kill immature schistosomes. A single oral dose of albendazole or mebendazole clears most soil-transmitted helminth infection. A single oral dose of azithromycin clears active trachoma. One annual dose of ivermectin holds onchocerciasis and lymphatic filariasis down at community level, for onchocerciasis over ten to fifteen years, because ivermectin does not kill adult worms. None of these needs refrigeration, a needle, a diagnosis or a clinician: they are tablets that a trained non-medical person hands out in a school or a village. All four are donated by their manufacturers, praziquantel largely so. And they are not reaching people. Schistosomiasis preventive treatment covered 39.6 per cent of those who needed it in 2024. Trachoma antibiotic coverage was 47 per cent in 2025. Soil-transmitted helminth treatment reached 62 per cent of at-risk children in 2021. These are distribution figures, not pharmacology.

The second is oxygen. Where nothing simple works, oxygen is the constraint that returns. It is named as the rate-limiting treatment in childhood pneumonia, as the single intervention that converts severe RSV bronchiolitis from often fatal to usually survivable, and as the binding constraint on survival in severe COVID-19. In measles pneumonia, in established sepsis and in severe influenza it is listed among the treatments, and in the infant with pertussis the entry says it cannot be improvised. It cannot be improvised. The minimum chain is a pressure-swing-adsorption concentrator with uninterrupted electricity, or cylinder logistics, and neither exists in most of the places where the deaths are. Tetanus is the same constraint one step further on: the determinant of survival in severe tetanus is mechanical ventilation, and nothing substitutes for it.

Neither pattern should be overstated. The short-chain conditions are a minority of the chapter, and for most of them the drug suppresses or clears the parasite without reversing the damage it has already done — praziquantel does not undo bladder fibrosis, ivermectin does not restore sight. Oxygen is not the only unimprovisable thing here either. Equine diphtheria antitoxin, the Ebola monoclonals, liposomal amphotericin B and the −60 °C vaccine chain are all equally out of reach, and some of them are out of reach of money as well. The entries carry the detail. The patterns are a way of reading the chapter, not a claim about it.

A note on vaccines, because the chapter turns on them repeatedly. Every vaccine here requires an industrial chain and none can be made by simple means. That is stated per entry rather than softened. Vaccination therefore appears in PREVENTION or TREATMENT and never in SIMPLE MEANS. The chains differ in length, and the honest dividing line is the cold chain. Measles, varicella, influenza and the conjugate vaccines cannot leave 2–8 °C without being destroyed. MenAfriVac tolerates 40 °C for four days by design, Rotasiil is thermostable, and the tetanus and diphtheria toxoids tolerate brief breaks. Two products in this chapter need far colder than 2–8 °C: the mRNA COVID-19 vaccines at −70 °C and Ervebo for Ebola at −60 °C to −80 °C. Those two are the least deployable medical products in the chapter.

Tuberculosis

What it is. A bacterial infection, *Mycobacterium tuberculosis*, spread by airborne droplets. It usually settles in the lungs but can affect bone, the brain lining, the gut and other organs. Most infected people never become ill. A minority develop active disease, which destroys lung tissue over months.

Measured. WHO fact sheet, 24 March 2026, reporting 2024 data. 10.7 million people fell ill in 2024: 5.8 million men, 3.7 million women, 1.2 million children. 1.23 million deaths, including about 150,000 among people with HIV.

About a quarter of the world's population carries TB infection, and 5–10 per cent of those eventually develop disease.

Regional share of new cases: South-East Asia 34 per cent, Western Pacific 27 per cent, African 25 per cent. India 25 per cent, Indonesia 10 per cent, Philippines 6.8 per cent, China 6.5 per cent, Pakistan 6.3 per cent, Nigeria 4.8 per cent, DR Congo 3.9 per cent, Bangladesh 3.6 per cent. The top five account for 55 per cent, and 87 per cent of cases fall in thirty high-burden countries. Over 80 per cent of cases and deaths are in low- and middle-income countries.

Drug resistance: 3.2 per cent of new episodes and 16 per cent of previously treated episodes. About two in five people with drug-resistant TB accessed treatment in 2024; 34,000 started the six-month all-oral regimens, against 5,653 in 2023 and 1,744 in 2022.

Catastrophic costs fall on about half of treated households, defined as more than 20 per cent of household income.

Where it starts. Inhalation of *M. tuberculosis*. Progression from infection to disease is what the risk factors govern. WHO attributes new 2024 cases to undernutrition 0.97 million, diabetes 0.93 million, alcohol use disorders 0.74 million, smoking 0.70 million and HIV infection 0.57 million. HIV carries the largest individual relative effect: people with HIV are twelve times more likely to develop TB disease.

Not known: why 90–95 per cent of infected people never progress, and what distinguishes them immunologically. The trigger from latent to active disease is not identified. Whether latent infection is one state or a spectrum of partly cleared infection is unsettled. Why some people clear the organism entirely is unknown.

Read in the net: the test at a form's rim has three outcomes, and the third is 0 — not read. A form that is never read is neither kept nor removed; it simply remains. A quarter of the world carrying an organism that may never be cleared and will mostly never be expressed is that outcome at the scale of a population. This is a reading, not a mechanism.

Cure status. CURABLE. A four- to six-month regimen of rifampicin, isoniazid, pyrazinamide and ethambutol removes the organism. For multidrug- and rifampicin-resistant disease a six-month all-oral BPaLM or BPaL regimen is the WHO-preferred option for eligible patients, and it also removes the organism. Success is materially lower, cost much higher, and only two in five of those affected reach treatment at all. The patient is not left in a managed state, which is what distinguishes this from CONTROLLABLE. WHO publishes no global treatment success rate and none is given here.

Prevention.

Treating active cases, which breaks transmission: STRONG. TB efforts saved an estimated 83 million lives since 2000, and TB treatment plus antiretroviral therapy averted 9.8 million deaths since 2005.

BCG against tuberculous meningitis: STRONG. Protective efficacy 77 per cent (95 per cent CI 71–83), odds ratio 0.23 (95 per cent CI 0.14–0.37), from 107 cases and 321 controls in a case-control study in Madras, India, *Archives of Disease in Childhood* 74(2):144. The same source records earlier estimates against tuberculous meningitis ranging from 52 to 84 per cent.

BCG against adult pulmonary TB: CONTESTED. The WHO fact sheet gives no efficacy percentage and claims only prevention of TB deaths and of severe childhood forms. The trial literature ranges from near zero to high protection, varying with latitude and prior mycobacterial exposure. Both positions are in print and no single number is quotable.

Preventive therapy for exposed household contacts: STRONG. Levofloxacin is recommended for contacts of multidrug-resistant cases; rifapentine with isoniazid for three months is the short-course option.

Nutrition: MODERATE. Undernutrition is the largest single attributable factor at 0.97 million cases, but that is an attribution calculation and not a trial of feeding as prophylaxis.

BCG production needs a long industrial chain: live attenuated bacterial culture, lyophilisation, sterile fill-finish and a maintained cold chain. It is a needle vaccine and cannot be made by simple means.

Treatment. Prices are Stop TB Partnership Global Drug Facility indicative ex-works prices, version Q3-2025, dated 22 September 2025, valid through December 2025. GDF publishes price per pack, not price per completed course, and no course cost is derivable from it.

Regimen or drug	EML	Off-patent	GDF Q3-2025 pack price, USD
RHZE 150/75/400/275 fixed-dose combination, first line	Yes	Yes	66.04 per 672 tablets
RHE 150/75/275 fixed-dose combination	Yes	Yes	52.18 per 672, limited availability
Rifapentine/isoniazid 300/300, preventive	Yes	Yes	9.97 per 36 tablets
Linezolid 600 mg	Yes	Yes	16.00 per 100 tablets
Levofloxacin 500 mg	Yes	Yes	4.61 per 100 tablets
Bedaquiline 100 mg	Yes	Patent contested and eroding	44.44 per 100 blister; 122.20 per 188 HDPE
Pretomanid 200 mg	Yes	No, patented and licensed	123.08 per 100 tablets
Delamanid 50 mg	Yes	No	85.00 per 48 tablets

Paediatric dispersible formulations, same source: rifampicin/isoniazid 75/50 mg at 4.75 per 84; RHZ 75/50/150 mg at 6.57 per 84; isoniazid 100 mg at 9.00 per 100.

The resistance penalty, computed from those pack prices: first-line RHZE works out at 9.8 US cents a tablet at the GDF Q3-2025 ex-works pack price, pretomanid at US$1.23 a tablet — about 12.5 times as much per tablet, before the rest of the regimen is counted. GDF published no per-course BPaLM price in the Q3-2025 list. A 38 per cent price reduction for the BPaLM regimen was announced by GDF and relayed by EATG, but the per-course figure was not confirmed from the primary catalogue.

Simple means. Partial, and genuine as far as it goes. Ventilation and sunlight: airborne transmission falls with air exchange, which was the sanatorium rationale. Separating the coughing patient from children, especially where people sleep. Feeding the patient, since undernutrition is the largest attributable factor and food is not an industrial product. Case-finding by asking who has coughed for more than two weeks, which needs no instrument.

What cannot be done without a chain is cure. The drugs require multi-step pharmaceutical synthesis, and partial or interrupted treatment generates resistance, which is worse than no treatment. The minimum chain is multi-drug synthesis, plus an uninterrupted four- to six-month supply, plus some means of distinguishing drug-resistant disease.

Gaps. WHO publishes no global treatment success rate; it is not on the fact sheet, not on either Global Tuberculosis Report page, and sits only in the full report PDF, which did not render as text. BCG efficacy against adult pulmonary TB is genuinely contested and WHO declines to give a number. The widely cited figure of tens of US dollars for a first-line course could not be confirmed from the primary GDF document and is not asserted. The latent reservoir of a quarter of the global population rests on tuberculin and IGRA positivity, which measure immune memory rather than live organisms; the viable reservoir is unknown. Neither the fact sheet nor the report pages carry an incidence rate per 100,000 or a total drug-resistant TB burden†.

> **Depth.** Starts in: Mycobacterium tuberculosis, a rod. Size: 3 µm†; depth +3.81. First complaint: about 5 weeks ([W] 2–12 weeks); time depth 46.72. One untreated course: about 6 months ([B] months; † about 6 months); depth 48.23.

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

HIV/AIDS

What it is. A retrovirus that infects and destroys CD4 T-cells, the coordinating cells of the immune system. Untreated, immunity falls over years until ordinary organisms become lethal. Treatment suppresses the virus but does not remove it from the body.

Measured. WHO fact sheet, 27 July 2026, reporting 2025 data. 41.0 million people living with HIV at the end of 2025, 64 per cent of them in the WHO African Region. 1.2 million new infections in 2025. 570,000 HIV-related deaths. 44.2 million cumulative deaths to date.

Cascade 2025: 88 per cent knew their status; 89 per cent of those were on antiretroviral therapy; 95 per cent of those on therapy were virally suppressed. Multiplying the first two gives about 78 per cent of all people with HIV on treatment; that product is arithmetic performed here and is not a WHO-stated figure.

Advanced HIV disease is defined as CD4 below 200 cells/mm³ or WHO stage 3 or 4. All children under five with HIV are presumed to have it.

The fact sheet gives no age-specific breakdown of incidence or mortality.

Where it starts. Unprotected sexual contact, blood and blood products, shared injecting equipment, and transmission from mother to child in pregnancy, at birth or through breastfeeding. Syphilis roughly doubles the risk of acquiring HIV. Untreated HIV raises TB risk twelve-fold.

Not known: why a small number of people control the virus without treatment, and why a few appear resistant to infection beyond the known CCR5-delta32 mechanism. The persistence of the latent proviral reservoir is understood mechanically — integrated DNA in resting cells — and has no solution. Why post-treatment control occurs in rare individuals is unexplained.

Cure status. CONTROLLABLE. Antiretroviral therapy suppresses replication to undetectable levels and restores immunity, and 95 per cent of those treated achieve viral suppression. But the integrated proviral reservoir persists and stopping treatment leads to rebound, so treatment is lifelong. A handful of individual cures exist following allogeneic stem-cell transplant with CCR5-delta32 donors. These are case reports arising from cancer treatment, not a scalable cure, and they do not change the classification.

Prevention.

Antiretroviral therapy for the infected person, treatment as prevention: STRONG. An undetectable viral load effectively prevents sexual transmission, and 95 per cent of those treated are suppressed.

Lenacapavir, twice-yearly injectable pre-exposure prophylaxis: STRONG. PURPOSE 1, in South Africa and Uganda, recorded zero infections among 2,134 women in the lenacapavir arm. The Descovy arm of 2,136 had 39 infections, an incidence of 2.0 per cent, and the Truvada arm of 1,068 had 16, an incidence of 1.7 per cent†. Background incidence was 2.4 per cent. No confidence intervals were released at that point, and with zero events in the active arm efficacy is bounded below rather than point-estimated. UNAIDS, 24 September 2025, reports PURPOSE 2 as 96 to 100 per cent effective, citing the NEJM paper.

Oral pre-exposure prophylaxis: STRONG where taken. In PURPOSE 1, Descovy reduced incidence by about 16 per cent and Truvada by about 30 per cent against background — the trial's own comparison, which reflects adherence in young women rather than drug potency.

Prevention of mother-to-child transmission: STRONG. WHO recommends infant virological testing from birth or six weeks. Denmark was reported as the first EU country to eliminate mother-to-child transmission of HIV and syphilis, WHO news item, 27 February 2026.

Condoms: STRONG. The barrier blocks the transmission route.

Voluntary medical male circumcision: STRONG, from three randomised trials in Africa. The trial figures were not retrievable and no number is asserted.

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
TLD — tenofovir, lamivudine, dolutegravir — first line	Yes	Yes, generic under voluntary licence	Below US$45 per patient-year for low-income countries, via Global Fund agreements reported 2023/2024
Lenacapavir, for prevention	Added for PrEP, 2025 update	No; patented, with voluntary licences to six manufacturers for 120 countries	US$40 per person-year generic target under the Dr Reddy's and Hetero agreements, plus up to US$17 for the oral lead-in; US list price for treatment US$28,000 per person-year; Lancet HIV estimates generic at US$35–46 per person-year at scale, falling to US$25 at high demand
Co-trimoxazole prophylaxis	Yes	Yes	Cents per day

Co-trimoxazole is given to reduce opportunistic infection, including in HIV-infected children to reduce pneumonia risk. The US$40 per person-year lenacapavir figure, the generic target reported by UNAIDS in 2025 for the 120 countries under voluntary licence, is a commitment, not an observed market price.

Simple means. Condoms are a manufactured item, but they need no cold chain, no prescription and no clinician. Not sharing needles; using a fresh blade or needle where one exists. Boiling or sterilising any skin-piercing instrument. Breastfeeding decisions depend on maternal treatment status under WHO guidance and are therefore not supply-chain-free.

Nothing available without an industrial chain treats HIV or prevents it pharmacologically. The minimum chain for antiretroviral therapy is multi-step organic synthesis, formulation, and an uninterrupted lifelong supply; interruption causes resistance and rebound. There is no low-technology substitute.

Gaps. The fact sheet gives no age-disaggregated incidence or mortality, so no age pattern is reported. Lenacapavir confidence intervals were not retrievable. Whether the US$40 per person-year price, the 2025 generic target for the 120 licensed countries, will be realised at volume is unknown. Male circumcision trial effect sizes are well established in the literature but were not retrieved, and no number is asserted.

> **Depth.** Starts in: the HIV particle. Size: 120 nm†; depth +0.88. First complaint: about 20 days ([W] 2 weeks to months; † acute illness 2–4 weeks); time depth 46.22. One untreated course: about 10 years († about 10 years to AIDS; [B] "over years"); depth 50.97.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The bound applies. The provirus sits in resting cells. It cannot be reached. So it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Malaria

What it is. A parasitic disease caused by *Plasmodium* species, carried between people by *Anopheles* mosquitoes. The parasite multiplies in liver and red blood cells, causing cycles of fever. *P. falciparum* can obstruct brain and organ circulation and kill within days.

Measured. WHO fact sheet, 4 December 2025, drawing on the World Malaria Report 2025 and reporting 2024 data. About 282 million cases in 2024, up about 9 million or 3 per cent on 2023, in 80 countries. About 610,000 deaths, against 598,000 in 2023.

The WHO African Region carried about 95 per cent of cases, 265 million, and about 95 per cent of deaths, 579,000. Over half of African Region deaths fell in three countries: Nigeria 31.9 per cent, DR Congo 11.7 per cent, Niger 6.1 per cent. Eleven African countries account for about two thirds of global cases and deaths.

Children under five account for about 75 per cent of malaria deaths in the African Region. The fact sheet also prints 76 per cent, in an adjacent paragraph of the same section, and the two figures are not reconciled on the page. Both are recorded; the appendix of single-source contradictions carries this as item 1.

37 countries reported fewer than 1,000 indigenous cases in 2024, up from 13 in 2000, and 14 countries have been certified malaria-free since 2017.

Resistance and diagnostic failure: partial artemisinin resistance is confirmed in Eritrea, Rwanda, Uganda and Tanzania and suspected in Ethiopia, Namibia, Sudan and Zambia. HRP2/HRP3 gene deletions, which defeat the rapid diagnostic tests, are reported in 42 countries and exceed 15 per cent prevalence in Brazil, Djibouti, Eritrea, Ethiopia, Nicaragua and Peru. *Anopheles stephensi* has been detected in eight African countries.

Where it starts. Inoculation of *Plasmodium* sporozoites by an infected *Anopheles* mosquito, with symptoms beginning 10–15 days after the bite. The risk structure is proximity to vector breeding water, absence of a barrier at night since the vector bites nocturnally, and absence of prior immunity — which is why under-fives and pregnant women carry the mortality. Partial acquired immunity in endemic adults is well established and is why the same parasite load produces different disease at different ages.

Not known: what determines progression to severe and cerebral malaria in a given child, beyond parasite load and age. The mechanism of cerebral malaria is contested between mechanical obstruction and inflammatory models. Why some children develop severe anaemia and others cerebral disease is unexplained. The duration and decay of naturally acquired immunity are not well quantified.

Cure status. Split by species and regimen.

P. falciparum: CURABLE P. vivax and P. ovale, with radical cure added: CURABLE P. vivax and P. ovale, blood-stage treatment only: CONTROLLABLE

An artemisinin-based combination therapy clears the parasite and the person is well. The relapsing species carry dormant liver stages and need an added 8-aminoquinoline, primaquine or tafenoquine, for radical cure; without it the infection recurs from the liver, so blood-stage treatment alone holds the state rather than removing it. Emerging partial artemisinin resistance, confirmed in four African countries, threatens curability without yet having removed it.

Prevention.

Insecticide-treated nets: STRONG. Cochrane review CD000363, insecticide-treated nets against no nets:

- all-cause child mortality, rate ratio 0.83 (95 per cent CI 0.77–0.89), a 17 per cent reduction; 5 trials, 200,833 participants; high certainty
- severe malaria episodes, RR 0.56 (95 per cent CI 0.38–0.82), a 44 per cent reduction; 2 trials, 31,173; high certainty
- uncomplicated *P. falciparum*, RR 0.55 (95 per cent CI 0.48–0.64); 5 trials, 35,551; high certainty
- uncomplicated *P. vivax*, RR 0.61 (95 per cent CI 0.48–0.77); moderate certainty
- 5.6 fewer child deaths per 1,000 children protected per year (95 per cent CI 3.6–7.6)

Against *untreated* nets the picture is different and should not be collapsed into the first: child mortality RR 0.67 (95 per cent CI 0.36–1.23), an interval that includes 1, and 3.5 deaths averted per 1,000 (95 per cent CI −2.4 to 6.8), an interval that includes zero. The insecticide, not the net alone, carries the measured mortality benefit, and that specific comparison is uncertain.

R21/Matrix-M vaccine: STRONG. Phase 3 in 4,800 children in Burkina Faso, Kenya, Mali and Tanzania, as reported by the University of Oxford Nuffield Department of Medicine from the Lancet phase 3 paper:

- 12-month efficacy, seasonal sites: 75 per cent (95 per cent CI 71–79, p<0.001)
- 12-month efficacy, perennial sites with age-based dosing: 68 per cent (95 per cent CI 61–74, p<0.001)
- 18-month efficacy, seasonal sites, after a booster: 74 per cent (95 per cent CI 70–77, p<0.001)
- youngest group, aged 5–17 months: 79 per cent (CI 73–84) seasonal, 75 per cent (CI 65–83) standard

RTS,S/AS01 vaccine: STRONG. Phase 3 reduced cases by more than 50 per cent in the first year, and by about 75 per cent in combination with seasonal malaria chemoprevention in highly seasonal areas. The pilot programme in Ghana, Kenya and Malawi, 2019–2023, showed a vaccine-attributable 13 per cent reduction in all-cause mortality among age-eligible children. WHO publishes no confidence intervals on that page, and states that the two vaccines have not been compared head to head and that there is no evidence either performs better.

Both malaria vaccines need a long industrial chain. They are recombinant protein vaccines with saponin adjuvants — R21 uses Matrix-M, which requires *Quillaja* extract, and RTS,S uses AS01, containing QS-21 and MPL. Production requires recombinant protein expression, adjuvant manufacture, sterile fill-finish and an unbroken 2–8 °C cold chain. Neither is producible by simple means.

Seasonal malaria chemoprevention: STRONG in the Sahel, including in combination with vaccination. Indoor residual spraying: STRONG by WHO recommendation, with no numerical effect size published. New-generation nets: MODERATE; WHO states they outperform pyrethroid-only nets and gives no numerical effect size.

Treatment. Artemisinin-based combination therapy is first line. The standing agents — artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine — are all on the EML and off-patent. Injectable artesunate is the treatment for severe malaria, on the EML and off-patent. Primaquine and tafenoquine are used for radical cure of relapsing species; tafenoquine is not off-patent.

Neither the fact sheet nor the WHO vaccine question-and-answer page gives ACT course prices, and no primary-source price was confirmed. The frequently cited figure of cents to a dollar per paediatric ACT course is not asserted here. On vaccines, WHO states that R21 is currently less expensive than RTS,S and that many Gavi-supported countries pay as little as US$0.20 per dose, as their co-financed portion. No list price is published.

Simple means. A net over the sleeping place. A plain untreated net is a physical barrier against a night-biting vector; the Cochrane comparison above shows the insecticide carries most of the measured mortality benefit, so an untreated net is weaker and not equivalent — but it requires no chain. Draining or covering standing water near dwellings. Screening windows and doors, and closing openings at dusk. Sleeping away from breeding water, and siting dwellings accordingly. Smoke and plant repellents are traditional and widely used, with no reliable effect size.

Cure and vaccination are not achievable without a chain. The minimum chain for ACTs is *Artemisia annua* cultivation or semi-synthesis, extraction of artemisinin, synthesis of the partner drug, and co-formulation.

One simple means here is worse than none. Artemisinin monotherapy from home-brewed *Artemisia* tea is actively counter-productive: subtherapeutic monotherapy selects for exactly the partial resistance now confirmed in four African countries.

Gaps. The fact sheet contradicts itself on the under-five share of African deaths, 76 against 75 per cent in adjacent sentences; see the appendix, item 1. The page also prints 4 December 2025 while carrying a 2026 copyright notice and 2026 linked items; see the appendix, item 2. WHO publishes no numerical effect size for indoor residual spraying or for new-generation nets. No list price exists for either vaccine, only the Gavi co-financing figure. ACT course prices could not be sourced primarily. Cases rose 3 per cent in 2024, and whether that reflects true incidence, better detection or both is not resolved in the source. HRP2/HRP3 deletions above 15 per cent in six countries undermine the rapid tests that case counts depend on, so case figures from those countries are not comparable with others.

> **Depth.** Starts in: the Plasmodium sporozoite. Size: 10 µm†; depth +4.91. First complaint: about 12 days ([B] 10–15 days); time depth 45.78. One untreated course: about 12 days († 1–3 weeks; [B] falciparum kills within days); depth 45.77.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Lower respiratory infections — pneumonia

What it is. Infection of the lung's air sacs, which fill with fluid and pus so that breathing no longer oxygenates the blood. It is caused by bacteria, viruses or fungi. It is the common final pathway by which many infections kill children.

Measured. WHO fact sheet on pneumonia in children, 11 November 2022, reporting 2019 data. This is the oldest principal source used in this chapter, and no newer WHO pneumonia sheet exists.

740,180 children under five died of pneumonia in 2019. Pneumonia caused 14 per cent of all under-five deaths and 22 per cent of deaths in children aged one to five. Only one third of children with pneumonia receive the antibiotics they need. Deaths are highest in southern Asia and sub-Saharan Africa.

The dossiers disagree on the same quantity, and the disagreement stands. This chapter's source gives the point figure 740,180 for 2019; the circulatory and respiratory chapter gives roughly 700,000 to 740,000 child deaths a year, about 14 per cent of all under-five deaths. The range and the point figure are compatible. What is not compatible is scope: this entry carries no all-age lower respiratory infection death figure at all, while that chapter gives WHO 2.7 million against GBD 2023 2,501,300 and flags the roughly 200,000 gap between them. The two chapters are therefore not comparable on the burden of this disease. Both stand.

For orientation across the book: GBD 2023 ranks lower respiratory infections fourth among all causes of death and fourth among causes of DALYs, at 98.7 million DALYs (95 per cent UI 87.7–112). WHO's Global Health Estimates for 2023 give 2.7 million deaths and the same fourth rank. Age-standardised DALY rates for lower respiratory infections fell 25 per cent between 2010 and 2023.

Pathogen shares: *Streptococcus pneumoniae* is the most common bacterial cause, *Haemophilus influenzae* type b second, respiratory syncytial virus the most common viral cause, and *Pneumocystis jirovecii* causes at least a quarter of pneumonia deaths in HIV-infected infants.

Where it starts. The pathogens above, acquired by inhalation or aspiration. WHO names as risk factors the absence of exclusive breastfeeding in the first six months, undernutrition, indoor air pollution, crowding, parental smoking and HIV infection. Measles and pertussis predispose to pneumonia, which is why their vaccines appear as pneumonia prevention.

Not known: the true pathogen attribution per case. Sputum and blood cultures are insensitive in children, so pathogen-specific shares rest on vaccine-probe studies and modelling rather than direct measurement. What makes one child with a common virus develop bacterial superinfection is not established. The relative contribution of viral-bacterial co-infection is contested.

Cure status. Split by cause.

bacterial pneumonia: CURABLE viral pneumonia: SELF-LIMITING

Antibiotics clear the bacterial organism and the lung recovers; amoxicillin dispersible tablets are first line in children. For viral pneumonia no agent reliably removes most respiratory viruses, and most cases resolve with supportive care and, where needed, oxygen. For RSV and influenza specifically, see their own entries.

The classification turns on which pathogen is present, which is often not determinable at the point of care. That is the practical reason WHO recommends empirical antibiotics for children with fast breathing.

The circulatory and respiratory chapter declares a single CURABLE label for the same disease, calling it one of the clearest cures in medicine, with viral pneumonia demoted to a bullet inside its evidence. Both stand.

Prevention.

Pneumococcal conjugate vaccine: STRONG. The Gambian 9-valent PCV trial, Cutts and colleagues, *Lancet* 2005;365:1139–46, per-protocol:

- invasive pneumococcal disease, vaccine serotypes: 77 per cent (95 per cent CI 51–90)
- invasive pneumococcal disease, all serotypes: 50 per cent (95 per cent CI 21–69)

- radiological pneumonia: 37 per cent (95 per cent CI 27–45)
- all-cause admissions: 15 per cent (95 per cent CI 7–21)
- all-cause mortality: 16 per cent (95 per cent CI 3–28)

Intention-to-treat, same trial: vaccine-serotype invasive disease 71 per cent (95 per cent CI 46–86); all-serotype 45 per cent (95 per cent CI 19–62); radiological pneumonia 36 per cent (95 per cent CI 27–43); all-cause admissions 13 per cent (95 per cent CI 6–19); all-cause mortality 14 per cent (95 per cent CI 2–24).

The all-cause mortality figure is worth isolating: a vaccine reducing death from all causes, not merely from its target disease.

On the radiological pneumonia figure the dossiers disagree. The circulatory and respiratory chapter gives roughly 25 to 37 per cent from the Gambian and South African trials. The 37 per cent upper end agrees with the per-protocol figure above. The 25 per cent lower end appears in no other file, and its source is named but was not opened again. Both stand.

PCV needs a long industrial chain, among the longest in this chapter: bacterial polysaccharide culture, chemical conjugation to a carrier protein, purification, sterile fill-finish and an unbroken 2–8 °C cold chain. Coverage of the last PCV dose was 71 per cent globally in 2025.

Hib conjugate vaccine: STRONG. Hib is the second most common bacterial cause, and coverage for three doses was 78 per cent in 2025. Trial efficacy figures were not retrievable and are not asserted. The chain is as for PCV: long, cold.

Measles and pertussis vaccination: STRONG as pneumonia prevention, by removing the predisposing infections.

Exclusive breastfeeding for six months: STRONG by WHO recommendation. No effect size is published on the page.

Reducing indoor air pollution: MODERATE. WHO lists it as a risk factor; cookstove trials have given mixed results.

Co-trimoxazole prophylaxis in HIV-infected children: STRONG, with no figure given on the page.

Treatment.

Treatment	EML	Off-patent	Price
Amoxicillin dispersible tablets, first line in children	Yes, 6.2.1 Access group, core	Yes	UNICEF indicative price US$0.54 per pack of ten 250 mg dispersible tablets, October 2026, or about 5.4 US cents per tablet
Oxygen	Yes, medical oxygen is listed	n/a	Variable; requires a concentrator or cylinder supply
Ampicillin with gentamicin, severe inpatient disease	Yes	Yes	Cents to low dollars per course
Ceftriaxone, second line	Yes	Yes	Low dollars per course

The amoxicillin price is a UNICEF Supply Catalogue indicative price read on 19 October 2026. The catalogue returns different indicative prices for the same material number on different pages, so it is printed as indicative and dated, not as a price. For comparison, the NHS Drug Tariff for England and Wales, September 2026, Part VIIIA, gives amoxicillin 250 mg capsules at 76 for a pack of 15, about 5.1 per capsule. The retrieved text does not carry the column heading, so the unit is unconfirmed; NHS basic prices are conventionally pence.

Oxygen is the rate-limiting treatment for severe childhood pneumonia. It is a supply problem, not a drug-cost problem.

Simple means. Counting breaths. WHO’s case definition uses respiratory-rate thresholds by age, and a carer can count breaths for a minute with no instrument. That is the detection step, and it is free. Breastfeeding, exclusively for six months. Keeping cooking smoke out of the sleeping space, by cooking

outdoors or venting it. Keeping the child warm and fed, and upright rather than flat. Handwashing by carers, which reduces transmission of the respiratory pathogens.

Two things cannot be done without a chain: cure of bacterial pneumonia, and oxygen for the hypoxic child. The minimum chain for amoxicillin is semi-synthetic penicillin fermentation plus formulation. For oxygen it is either a pressure-swing-adsorption concentrator with uninterrupted electricity, or cylinder logistics. Oxygen cannot be improvised.

Gaps. The WHO pneumonia fact sheet is dated 11 November 2022 and reports 2019 deaths; it is the oldest principal source in this chapter and no newer sheet was retrievable. Pathogen attribution rests on vaccine-probe and modelling methods, not direct measurement. The fact sheet gives no incidence figure, only deaths. GBD 2023 per-cause death counts could not be read off the published table, which truncates at the same point on every attempt, so the all-age figure here rests on WHO's Global Health Estimates rather than on GBD's own table. No effect size is published on WHO pages for breastfeeding or for air-pollution reduction against pneumonia.

> **Depth.** Starts in: Streptococcus pneumoniae, the commonest agent. Size: 1 μm†; depth +2.81. First complaint: about 42 hours ([L] 1–3 days); time depth 44.00. One untreated course: about 12 days († 1–3 weeks); depth 45.77. Several agents cause it. The pneumococcus was chosen.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Influenza (seasonal)

What it is. A respiratory virus with surface proteins that change continually, so immunity from one year does not reliably protect the next. Most people recover in about a week. It kills mainly through pneumonia and through decompensation of existing heart and lung disease.

Measured. WHO fact sheet, 28 February 2025. About 1 billion cases a year, including 3 to 5 million cases of severe illness. 290,000 to 650,000 respiratory deaths a year.

In industrialised countries most influenza-associated deaths occur in people aged 65 and over. 99 per cent of deaths in children under five with influenza-related lower respiratory tract infection occur in developing countries.

Symptoms begin one to four days after infection, with an incubation of about two days, and usually last about a week; cough can persist two weeks or more.

Where it starts. Influenza A and B viruses, transmitted by droplets and aerosols. Risk factors for severe disease are age over 65, age under 5, pregnancy, chronic heart, lung, kidney, liver and metabolic disease, immunosuppression, and health-worker exposure. Antigenic drift and shift in the surface haemagglutinin are the established reason for annual recurrence and for pandemics.

Not known: the determinants of seasonality are not settled. Humidity, temperature, indoor crowding, vitamin D and host-immunity hypotheses all have support and none is established. Which strain will dominate a coming season cannot be predicted reliably, which is the structural limit on vaccine matching. Why some healthy young adults die of influenza while most do not is unexplained.

Cure status. Split by severity.

most cases: SELF-LIMITING severe cases: RELIEF ONLY

Most infections resolve unaided in about a week and intervention adds nothing for a healthy adult. No agent removes the virus. Antivirals shorten illness and reduce complications if started early, which is relief and risk reduction, not cure. For the severely ill, treatment is supportive. WHO recommends antivirals as soon as possible for high-risk people and for those with severe symptoms, including children under 59 months and people aged 65 and over.

Prevention.

Annual vaccination: MODERATE, varying by season and by age. The fact sheet gives no numerical efficacy figure. It states that the vaccine may be less effective in older people while still reducing severity, complications and death, and that safe and effective vaccines have been in use for over sixty years. Efficacy genuinely varies year to year with strain match, which is why a single figure is not quotable, and no confidence interval is asserted because WHO publishes none on the page.

Influenza vaccine needs a chain that repeats every year. Most seasonal vaccine is grown in fertilised hen's eggs or in mammalian cell culture, then inactivated, split, formulated, sterile-filled and cold-chained at 2–8 °C — and the whole cycle is repeated annually against a new strain selection. It is among the least improvisable products in this chapter.

Hand hygiene and respiratory etiquette: MODERATE. Staying home when ill: MODERATE, by removing the source from circulation. Ventilation: MODERATE, on aerosol physics.

Treatment.

Treatment	EML	Off-patent	Price
Oseltamivir	Yes	Yes	Low; no primary price confirmed
Supportive care and oxygen	Yes, oxygen	n/a	Variable
Paracetamol, symptom relief	Yes	Yes	Cents per course

The fact sheet gives no dosages, efficacy figures or prices for antivirals. Baloxavir is not off-patent. Zanamivir is off-patent but little used.

Simple means. Rest, fluids and time, which is the actual treatment for most cases. Isolating the ill person from the elderly and the chronically ill in the household — the people who die. Ventilating rooms; opening windows. Handwashing and covering coughs. Paracetamol is manufactured but is a simple, cheap and widely available chemical.

These are adequate for the majority of cases, because the condition is self-limiting. What cannot be done without a chain is prevention, which means the annual vaccine, and treatment of the severely ill, which means antivirals, oxygen and ventilation.

Gaps. WHO publishes no vaccine efficacy percentage or confidence interval on the fact sheet, and genuine season-to-season variation makes any single figure misleading. The death range, 290,000 to 650,000, is wide, and influenza deaths are mostly statistically inferred from excess mortality rather than counted, because most are attributed to pneumonia or cardiac causes. The 1 billion annual case estimate is modelled. Burden in low-income countries is poorly measured, and the figure that 99 per cent of child deaths occur there implies the burden is concentrated exactly where surveillance is weakest. GBD 2023 influenza figures were not retrievable†.

> **Depth.** Starts in: the influenza virus. Size: 100 nm†; depth +0.72. First complaint: about 42 hours ([W] 1–3 days); time depth 44.00. One untreated course: about 7 days ([B] about a week); depth 45.27.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Respiratory syncytial virus (RSV)

What it is. A respiratory virus that infects nearly every child by the age of two. In most it causes a cold. In small infants it inflames the smallest airways — bronchiolitis — which can obstruct breathing. It also causes severe disease in the elderly.

Measured. WHO fact sheet, 19 December 2025. About 3.6 million RSV-associated hospitalisations a year in children under five worldwide. About 100,000 RSV-attributable deaths a year in children under five. About half of paediatric RSV deaths occur in infants under six months. 97 per cent of paediatric RSV deaths occur in low- and middle-income countries.

In United States adults over 65: up to 160,000 hospitalisations and up to 10,000 deaths a year. No global adult burden estimate is published, so the global elderly burden is unquantified here.

Almost all babies are infected by their second birthday, and maternal antibodies protect infants for about six months after birth. Temperate climates have seasonal epidemics, usually in late autumn and winter, with elevated circulation of about five months on average; subtropical and tropical countries have consistent high-circulation months without a clear seasonal pattern.

No global case count is published.

Where it starts. RSV, transmitted by droplets, hands and surfaces. Risk factors for severe disease are age under six months, prematurity, congenital heart and lung disease, immunodeficiency and crowding. The established protective mechanism is transplacental maternal antibody, which is the rationale for both maternal vaccination and monoclonal antibody prophylaxis.

Not known: why bronchiolitis severity varies so widely between infants with the same virus. The relationship between infant RSV bronchiolitis and later childhood asthma is genuinely unresolved — whether RSV causes the airway change or reveals a pre-existing predisposition is contested. The failure of the early formalin-inactivated RSV vaccine, which worsened disease, is explained after the fact but was not predicted, and vaccine-enhanced disease remains a design constraint.

Cure status. Split by severity.

most infections: SELF-LIMITING severe bronchiolitis: RELIEF ONLY

Most infections resolve unaided. For severe bronchiolitis nothing removes the virus, and management is oxygen, suction and feeding support. Bronchodilators and corticosteroids do not alter the course of RSV bronchiolitis in infants, a well-replicated negative finding. Ribavirin is not recommended for routine use.

Prevention.

Long-acting monoclonal antibody, nirsevimab: STRONG. WHO recommends it for infants entering their first RSV season and notes that countries could consider it for high-risk children up to 24 months entering a second season. WHO gives no efficacy figures and does not name the product. The MELODY and HARMONIE trial efficacy figures with confidence intervals could not be retrieved: publisher sites were blocked and the search budget was exhausted. **Efficacy.** No efficacy number is asserted.

Nirsevimab needs a long chain. A monoclonal antibody requires mammalian cell culture, chromatographic purification, sterile fill-finish and an unbroken 2–8 °C cold chain. It is among the least improvisable interventions in this chapter.

Maternal vaccination in the third trimester: STRONG by WHO recommendation, from 28 weeks' gestation in most settings. **Efficacy:** — no figure is given on the WHO page and the MATISSE trial was not retrievable. The chain is a recombinant protein vaccine: long, with a 2–8 °C cold chain and a needle.

Handwashing and surface hygiene: MODERATE. RSV transmits readily by hands and fomites. Keeping small infants away from coughing children: MODERATE, on transmission grounds. Breastfeeding: MODERATE, on consistent observational association with reduced severity. Avoiding tobacco smoke exposure: MODERATE, on consistent observational evidence.

Treatment.

Treatment	EML	Off-patent	Price
Oxygen and supportive care	Yes, oxygen	n/a	Variable; the main requirement
Nasal suction, feeding support	n/a	n/a	Minimal
Nirsevimab, prophylaxis rather than treatment	Not confirmed on the 24th List	No, patented	High-income list prices in the hundreds of US dollars per dose; no verified low-income price

There is no curative drug. Bronchodilators, corticosteroids and antibiotics do not help uncomplicated RSV bronchiolitis, and antibiotics are frequently given without benefit.

Simple means. Upright positioning, clearing the nose, small frequent feeds. For a wheezy infant that is most of the care. Saline drops and gentle suction, both improvisable. Handwashing before handling small infants. Keeping newborns out of crowds during local epidemics. Not smoking near the infant. Watching for the signs that matter — feeding failure, chest recession, apnoea, blue lips — all observable with no instrument.

What cannot be done without a chain is oxygen for the hypoxic infant, and both forms of prophylaxis. Oxygen is the single intervention that converts severe RSV bronchiolitis from often fatal to usually survivable, and it requires a concentrator plus electricity, or cylinders.

Gaps. Nirsevimab efficacy and maternal vaccine efficacy are the two interventions that define current practice, and neither figure is in this entry. WHO publishes none, and the trial papers — MELODY, NEJM 2022; HARMONIE, NEJM 2023; MATISSE, NEJM 2023 — could not be reached. This is the largest single data gap in the chapter. **Global case count. Global adult burden:** ; the only adult figures available are United States figures. The RSV-asthma causal question is genuinely contested. The 100,000 under-five deaths figure is modelled, since RSV is rarely laboratory-confirmed where most deaths occur.

> **Depth.** Starts in: the RSV particle. Size: 150 nm†; depth +1.08. First complaint: about 5 days († 4–6 days); time depth 44.95. One untreated course: about 10 days († 1–2 weeks); depth 45.59.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Diarrhoeal diseases (overview)

What it is. Passage of three or more loose or liquid stools a day, caused by many organisms acquired from contaminated water, food or hands. It kills by dehydration. The loss of water and salts, not the organism itself, is what stops the heart.

Measured. WHO fact sheet on diarrhoeal disease, 7 March 2024. Diarrhoea is the third leading cause of death in children aged 1 to 59 months. About 443,832 children under five die each year, plus 50,851 children aged five to nine. Nearly 1.7 billion cases of childhood diarrhoeal disease a year. In low-income countries, children under three average three episodes a year.

The page gives no data year anywhere for its mortality figures. Only the 2024 print date is available, and the 443,832 figure is stated to six significant figures for what is a modelled estimate.

780 million people lack access to improved drinking water and 2.5 billion lack improved sanitation. Those two figures are not dated on the page and appear to predate the sheet’s 2024 revision.

Definitions, from the same source: diarrhoea is three or more loose stools a day; persistent diarrhoea is 14 days or longer.

For orientation across the book: GBD 2023 ranks diarrhoeal diseases tenth among causes of DALYs, at 56.5 million (95 per cent UI 43.8–72.7). Age-standardised diarrhoeal DALY rates roughly halved between 2010 and 2023. In low-income countries diarrhoeal diseases ranked fifth among all causes of death in 2023.

Where it starts. Faecal-oral transmission of viruses, bacteria and protozoa through water, food, hands and surfaces. Risk factors: absence of safe water, absence of sanitation, absence of handwashing, absence of exclusive breastfeeding, undernutrition — which is both cause and consequence — and measles.

Not known: the pathogen-specific attribution of deaths is uncertain, because most fatal cases are never cultured. The bidirectional relationship between diarrhoea and undernutrition, environmental enteric dysfunction, is recognised but not quantitatively resolved. Why some children develop persistent diarrhoea is not established.

Cure status. Split by cause.

most episodes, with rehydration: SELF-LIMITING shigella, typhoid, amoebiasis, giardiasis: CURABLE cholera, rotavirus, norovirus: SELF-LIMITING

Most episodes are self-limiting: the body clears the organism, and the intervention needed is replacement of water and salts, not removal of the pathogen. That is the central fact of the condition. The deaths are from dehydration, which is preventable with a solution of salt, sugar and water. Specific bacterial and protozoal causes are additionally curable with antibiotics. The viral causes have no curative agent and need none. Cholera is moved to the self-limiting row.

Prevention.

Handwashing with soap: STRONG. Cochrane review CD004265, handwashing promotion:

- child day-care centres and schools, high-income countries: incidence rate ratio 0.70 (95 per cent CI 0.58–0.85); 9 trials, 4,664 participants; high certainty
- communities, low- and middle-income countries: IRR 0.71 (95 per cent CI 0.62–0.81); 9 trials, 15,950; moderate certainty
- communities *with soap provided*: risk ratio 0.66 (95 per cent CI 0.58–0.75); 7 trials, 12,646
- communities, *education only, no soap*: RR 0.84 (95 per cent CI 0.67–1.05) — the interval includes 1; 2 trials, 3,304
- day-care and schools in low- and middle-income countries: IRR 0.66 (95 per cent CI 0.43–0.99); low certainty, interval barely excluding 1

Providing the soap, not telling people to wash, is what carries the effect.

Safe drinking water and sanitation: STRONG on settled transmission physiology; 780 million and 2.5 billion people respectively lack them. Exclusive breastfeeding for six months: STRONG by WHO recommendation. Rotavirus vaccination: STRONG, and see its own entry. Measles vaccination: STRONG as diarrhoea prevention, by removing a predisposing infection. Zinc supplementation: STRONG as a treatment adjunct, below.

Treatment.

Treatment	EML	Off-patent	Price
Oral rehydration salts	Yes	Yes	“A few cents per treatment”; UNICEF indicative US$4.80 per carton of 100 low-osmolarity sachets, October 2026, or about 4.8 US cents a sachet
Zinc, 10–14 day course	Yes	Yes	Cents per course
Intravenous Ringer’s lactate, severe dehydration only	Yes	Yes	Low dollars
Antibiotics, only for specific causes	Yes	Yes	See individual entries

Zinc reduces episode duration by 25 per cent and is associated with a 30 per cent reduction in stool volume, over a recommended course of 10 to 14 days.

The fact sheet gives no numerical effectiveness figure for oral rehydration salts themselves, stating only that most people can be treated successfully with prompt rehydration. Antibiotics are not indicated for most diarrhoea and are widely misused in it, which drives resistance.

Simple means. This is the condition in this chapter where simple means do the most work.

Oral rehydration. The WHO-formula sachet is a manufactured item, but a home solution of salt, sugar and clean water replaces its essential function, and that alone addresses the mechanism of death. Continued feeding and breastfeeding during the illness rather than withholding food. Handwashing with soap — and soap is producible from fat and ash without an industrial chain. Water treatment: boiling, solar disinfection in clear bottles, sand and cloth filtration, settling and decanting. Separating faeces from water and hands, with latrines sited away from and below water sources, and covered. Assessing dehydration by hand: WHO’s own three-level scale uses the skin pinch — returning slowly, at least two seconds, in severe

dehydration — sunken eyes, and ability to drink, with no instrument required. Zinc is a manufactured tablet but a simple inorganic salt, not a complex synthesis.

Only intravenous rehydration for the child too shocked to drink requires a chain: sterile fluid, tubing and a cannula.

Gaps. The fact sheet reports no effectiveness figure for oral rehydration salts, despite its being the central intervention; the evidence predates modern trial reporting and is treated as settled. Pathogen-specific death attribution is uncertain. The water and sanitation figures are undated on the page. The under-five death figure is given to six significant figures, which overstates the precision of a modelled estimate, and no data year is printed for it at all. GBD 2023 per-cause diarrhoeal death counts could not be read off the published table; the DALY figure above is from the DALY table, which was legible.

> **Depth.** An overview. No single agent. No depth is given.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Rotavirus

What it is. A virus that infects the gut lining of young children, causing vomiting and watery diarrhoea. Before vaccination it infected essentially every child worldwide. It kills by dehydration.

Measured. Rotavirus is the leading single cause of severe childhood diarrhoea and is subsumed in the diarrhoeal totals of the overview entry: 443,832 under-five diarrhoeal deaths a year. The WHO diarrhoeal fact sheet lists rotavirus vaccination as a prevention measure but gives no rotavirus-specific case or death figures. A rotavirus-specific global death estimate could not be sourced primarily and is not asserted.

Vaccine coverage was 61 per cent globally in 2025 — the lowest coverage of the major childhood vaccines except the hepatitis B birth dose.

Where it starts. Rotavirus, faecal-oral. Incidence is notably *not* strongly reduced by water and sanitation improvement. Rotavirus spreads efficiently regardless of sanitation, which is why it remained universal in high-income countries until vaccination. This distinguishes it from the bacterial diarrhoeas.

Not known: why vaccine efficacy is so much lower in high-mortality settings. Candidate explanations include maternal antibody interference, gut microbiome differences, environmental enteric dysfunction, concurrent infections and oral polio vaccine interference. None is established. This is one of the clearest unexplained efficacy gradients in vaccinology.

Cure status. SELF-LIMITING. The body clears the virus. No antiviral exists or is needed. The intervention that matters is rehydration, which prevents death without removing the organism. Deaths occur from dehydration, not from failure to eliminate the virus.

Prevention.

Rotavirus vaccination: STRONG, with a large and unexplained setting gradient. Cochrane review CD008521, prevention of severe rotavirus diarrhoea. The Cochrane plain-language summary reports point estimates without confidence intervals; the absence of intervals is a limitation of the accessible summary, not of the review.

Vaccine	Age period	Low-mortality countries	High-mortality countries
Rotarix	first year	93 per cent; 14,976 participants, 4 trials, high certainty	58 per cent; 15,882, 4 trials, high certainty
Rotarix	second year	90 per cent; 18,145, 6 trials, high certainty	35 per cent; 13,768, 2 trials, moderate certainty
RotaTeq	first year	97 per cent; 5,442, 2 trials, high certainty	57 per cent; 6,775, 2 trials, high certainty
RotaTeq	second year	96 per cent; 5,442, 2 trials, high certainty	44 per cent; 6,744, 2 trials, high certainty

The vaccine works best where the disease kills least. In high-mortality settings second-year protection falls to 35–44 per cent.

The chain is long but shorter than for the conjugates, and the difference is instructive. Live attenuated oral rotavirus vaccines require cell-culture propagation in Vero cells, formulation and a cold chain — but no needles and no sterile injection, and oral administration needs no trained injector. Rotavac, made in India, and Rotasiil, which is thermostable and therefore reduces cold-chain dependence, have lowered both cost and chain burden. Thermostability here is a design achievement, not a property of the platform.

Exclusive breastfeeding: MODERATE. Water and sanitation: WEAK for rotavirus specifically, in contrast to bacterial diarrhoea — a well-documented exception.

Treatment.

Treatment	EML	Off-patent	Price
Oral rehydration salts	Yes	Yes	"A few cents per treatment"; UNICEF indicative about 4.8 US cents a sachet, October 2026
Zinc, 10–14 days	Yes	Yes	Cents per course
Intravenous fluids if shocked	Yes	Yes	Low dollars

No antiviral. Antibiotics are useless and harmful here.

Simple means. Fully effective for survival without any industrial chain. Oral rehydration with salt, sugar and clean water, which is the whole treatment for the overwhelming majority. Continued breastfeeding and feeding through the illness. Assessing dehydration by skin pinch, eyes, thirst and urine output. Handwashing, though it reduces rotavirus less than it reduces bacterial diarrhoea.

Prevention by vaccine requires a chain — cell culture, cold chain — but survival does not require any chain at all. This is one of the few conditions in the chapter where simple means address mortality almost completely.

Gaps. Cochrane reports point estimates without confidence intervals in the accessible summary; the full review contains them. **No rotavirus-specific global death figure is asserted** because none could be sourced primarily and WHO's diarrhoeal sheet omits it. The efficacy gradient between low- and high-mortality settings is unexplained and is the single most important open question for this condition. Intussusception risk with the vaccines is small, real and differently quantified across studies; no figure is asserted.

> **Depth.** Starts in: rotavirus. Size: 75 nm†; depth +0.45. First complaint: about 2 days († about 2 days); time depth 44.13. One untreated course: about 5 days († 3–8 days); depth 44.95.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Cholera

What it is. *Vibrio cholerae* produces a toxin that makes the small intestine pour out water and salts. A healthy adult can lose litres an hour and die of dehydration within hours. It follows contaminated water, so it follows collapsed sanitation, war and displacement.

Measured. WHO fact sheet, 29 September 2026. Researchers' annual global estimate is 1.3 to 4.0 million cases and 21,000 to 143,000 deaths. That range carries no data year at all on the page; the cited source is 2015.

Reported to WHO in 2025: 451,499 cases and 7,870 deaths across 47 countries. WHO states those were the highest reported deaths since 1999, and that reported figures fall below researchers' estimates. Dividing gives a case fatality of about 1.7 per cent; that division is arithmetic performed here and is not a WHO-stated figure. WHO publishes no observed case fatality rate, only the benchmark that case fatality in treatment centres should remain below 1 per cent.

Symptoms appear 12 hours to 5 days after infection, and asymptomatic people shed bacteria for 1 to 10 days. Only serogroups O1 and O139 cause outbreaks, and O1 has caused all recent ones. The seventh pandemic began in south Asia in 1961.

Where it starts. Ingestion of *V. cholerae* O1, or O139, in water or food. The risk structure is absence of safe water and sanitation, displacement and camp settings, and population movement. The determinant of mortality is not the organism but the speed of fluid replacement.

Not known: the environmental reservoir dynamics between outbreaks. The role of copepods, algal blooms, estuarine persistence and climate drivers is partly characterised and not predictive. Why some infected people develop catastrophic purging while most are mild or asymptomatic is not explained; blood group O is a recognised severity risk factor without a settled mechanism. Outbreak timing is not predictable.

Cure status. SELF-LIMITING. The body clears the organism within days. Rehydration prevents the deaths, which come from dehydration, and does not remove the organism. Antibiotics shorten shedding and illness duration but are adjunctive. WHO states that most people can be treated successfully with prompt oral rehydration, and that case fatality in treatment centres should remain below 1 per cent — against an untreated severe-case fatality that historically reached 50 per cent or higher†. The patient returns to health and the organism does not persist.

Prevention.

Safe water and sanitation: STRONG. Settled transmission physiology; cholera does not occur where water is clean.

Oral cholera vaccine: MODERATE, with supply as the binding constraint. WHO gives no efficacy percentage. It states that two doses are needed for full adult protection, lasting at least three years; that one dose of Euvichol-Plus or Euvichol-S gives good but shorter-term protection; and that the vaccine is usable from the age of one. Since October 2022 only one-dose regimens have been used, because of shortage. Global production rose from about 30 million doses in 2022 to about 80 million in 2025, and in February 2026 20 million doses were allocated for preventive campaigns. Trial efficacy figures with confidence intervals could not be retrieved and are not asserted.

This is the least chain-dependent vaccine in the chapter, and it is worth being precise about why. Oral cholera vaccine is a killed whole-cell oral product: bacterial fermentation, inactivation, formulation, oral delivery. No needles, no sterile injection, no injector training, and less cold-chain sensitivity than live or conjugate vaccines. Bacterial fermentation is achievable at a far lower technological level than mammalian cell culture. The current limit on supply is manufacturer investment, not technical feasibility. It still cannot be made by simple means.

Case isolation and safe handling of the dead: MODERATE in outbreak settings. Treating cases promptly, which reduces both deaths and transmission: STRONG.

Treatment.

Treatment	EML	Off-patent	Price
Oral rehydration salts, the primary treatment	Yes	Yes	“A few cents per treatment”; UNICEF indicative about 4.8 US cents a sachet, October 2026
Ringer’s lactate intravenously, for shocked patients	Yes	Yes	Low dollars per patient
Doxycycline, single dose, adjunct	Yes	Yes	Cents per course
Azithromycin, for children and in pregnancy	Yes, 6.2.2 Watch group, first choice for cholera	Yes	UNICEF indicative US$0.56 per pack of six 250 mg tablets, October 2026, about 9.3 US cents a tablet

WHO maintains six cholera kits; each treatment kit treats 100 patients.

Simple means. Cholera is the clearest case in the chapter where simple means are decisive.

Oral rehydration with salt, sugar and clean water, given continuously and in volume. This converts a 50-per-cent-fatal illness into a survivable one. Rice water or cereal-based rehydration, which works and uses

local staples. Boiling or chlorinating drinking water; solar disinfection; filtration. Siting latrines away from and below water sources; burying faeces. Handwashing with soap, which is producible from fat and ash. Isolating the patient's stool and soiled cloth, and safe burial practice. A cholera cot — a simple bed with a hole and a bucket — allows output to be measured with no instrument.

What requires a chain: intravenous fluids for the patient too collapsed to drink, which means sterile fluid, tubing and a cannula; antibiotics; and vaccine. But the great majority of cholera deaths are preventable with salt, sugar, clean water and someone willing to keep giving it.

Gaps. WHO publishes no oral cholera vaccine efficacy figure; the trial literature does, and it was not retrievable. The gap between reported cases, 451,499, and estimated burden, 1.3 to 4.0 million, is a factor of three to nine, and the estimate range itself spans a factor of seven for deaths, so the true mortality is genuinely poorly known. The Key Facts burden range carries no data year. Reporting is politically sensitive and some countries do not report cholera as cholera, so reported figures are a floor. WHO's statement that reported deaths were the highest since 1999 sits against a long-term downward trend in case fatality; both are true and the source does not reconcile them.

> **Depth.** Starts in: Vibrio cholerae. Size: 1.5 µm†; depth +3.18. First complaint: about 36 hours ([W] 0.5–4.5 days); time depth 43.87. One untreated course: about 2.2 days († 1–5 days; [B] death within hours is possible); depth 44.23.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Shigellosis

What it is. *Shigella* bacteria invade the lining of the large bowel, causing bloody, painful diarrhoea with fever. A very small dose causes infection, so it spreads directly from person to person. It is the classic cause of epidemic dysentery.

Measured. Shigella is subsumed in the diarrhoeal totals of the overview entry. WHO publishes no standalone *Shigella* fact sheet, and the 19 October 2026 retrieval pass confirmed none exists at the expected address.

Global cases. Global deaths. No shigellosis-specific global figure was retrievable and none is asserted. What exists: *Shigella* is consistently identified in pathogen-attribution studies as a leading bacterial cause of moderate-to-severe diarrhoea and of diarrhoeal death in children over one year, and WHO lists fluoroquinolone- resistant *Shigella* among its priority resistant pathogens. The age pattern falls disproportionately on children aged one to four and above, rather than on infants.

Where it starts. *Shigella* species — *S. flexneri*, *S. sonnei*, *S. dysenteriae*, *S. boydii* — faecal-oral. The distinguishing feature is an infectious dose as low as 10 to 100 organisms, which permits direct person-to-person and hand-to-mouth transmission with no contaminated water vehicle. Risk factors: crowding, camps, childcare settings, absence of handwashing, and malnutrition.

Not known: why *S. sonnei* has displaced *S. flexneri* as economies develop is observed but not mechanistically explained. There is no licensed vaccine despite decades of effort, and the correlates of protective immunity are not established — which is the central reason no vaccine exists. The contribution of asymptomatic carriage to transmission is not well quantified.

Cure status. CURABLE. Antibiotics shorten illness, clear the organism and reduce transmission, and unlike most diarrhoea, antibiotics are genuinely indicated for *Shigella* dysentery. Resistance is advancing: WHO lists fluoroquinolone-resistant *Shigella* as a priority pathogen, and extensively drug-resistant *S. sonnei* has spread internationally. Where resistance defeats available agents the condition shifts toward supportive care only. Untreated, most cases are self-limiting over about a week, but in malnourished children shigellosis carries substantial mortality and causes lasting nutritional damage.

Prevention.

Handwashing with soap: STRONG, and especially effective here because the low infectious dose makes hand transmission dominant. Cochrane CD004265: communities with soap provided, RR 0.66 (95 per cent CI 0.58–0.75); education only, RR 0.84 (95 per cent CI 0.67–1.05), an interval including 1.

Safe water and sanitation: STRONG. Exclusive breastfeeding: STRONG for infants. Case isolation and exclusion from food handling and childcare: MODERATE, given the low infectious dose. Measles vaccination and nutrition: MODERATE, by removing predisposition.

No vaccine is licensed. Candidates are in trials; nothing is available.

Treatment.

Treatment	EML	Off-patent	Price
Ciprofloxacin, first line where susceptible	Yes	Yes	Cents to low dollars per course
Azithromycin, where fluoroquinolone-resistant	Yes, 6.2.2 Watch group, second choice for acute invasive bacterial dysentery	Yes	UNICEF indicative about 9.3 US cents a 250 mg tablet, October 2026
Ceftriaxone, severe or resistant disease	Yes	Yes	Low dollars per course
Oral rehydration salts and zinc, supportive, always	Yes	Yes	About 4.8 US cents a sachet, UNICEF indicative, October 2026

Antimotility drugs such as loperamide are contraindicated in dysentery.

Simple means. Handwashing with soap is the highest-value simple intervention for this organism specifically, because of the low infectious dose. Oral rehydration and continued feeding: rehydration addresses the fluid loss, though *Shigella* kills more through invasion and malnutrition than through pure dehydration, so simple means do less here than in cholera or rotavirus. Water treatment: boiling, chlorination, filtration. Safe faeces disposal; latrines. Keeping the ill person away from food preparation and from other children. Feeding through and after the illness, because *Shigella* drives nutritional decline.

Unlike cholera and rotavirus, simple means do not fully substitute for treatment here. Invasive dysentery in a malnourished child needs an effective antibiotic. The minimum chain is antibiotic synthesis plus some means of knowing local resistance patterns.

Gaps. No WHO fact sheet exists and **no global burden figure is asserted** — the largest data gap among the diarrhoeal pathogens in this chapter. GBD and the GEMS and MAL-ED studies carry these figures. Resistance prevalence is rising but is not quantified by region in any source retrieved. Why no vaccine exists after decades of work is a genuine scientific gap, not merely a commercial one. The share of diarrhoeal deaths attributable to *Shigella* varies substantially between attribution studies.

> **Depth.** Starts in: Shigella. Size: 2 µm†; depth +3.44. First complaint: about 42 hours († 1–3 days); time depth 44.00. One untreated course: about 6 days († 5–7 days); depth 45.12.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Pathogenic Escherichia coli (including ETEC and STEC)

What it is. Several distinct disease-causing types of a normally harmless gut bacterium. Enterotoxigenic *E. coli*, ETEC, causes watery diarrhoea including most travellers' diarrhoea. Shiga toxin-producing *E. coli*, STEC or EHEC — for example O157:H7 — causes bloody diarrhoea and can destroy kidneys and red cells.

Measured. Subsumed in the diarrhoeal totals of the overview entry. No WHO standalone fact sheet for ETEC was retrievable.

Global ETEC burden. Global STEC burden. No pathogen-specific global figure is asserted. ETEC is consistently identified as a leading cause of childhood diarrhoea and of travellers' diarrhoea in attribution

studies. STEC causes far fewer cases but a severe complication: haemolytic uraemic syndrome. It follows roughly 5 to 15 per cent of STEC O157 infections in children by widely reported clinical estimates†. **That figure could not be confirmed to a primary source, and carries a dagger.** Age pattern: ETEC concentrates in children under two in endemic settings; STEC and haemolytic uraemic syndrome concentrate in children under five and in the elderly.

Where it starts. ETEC from contaminated water and food. STEC from ruminant faeces, via undercooked beef, raw milk, contaminated produce, water and direct animal contact. Cattle are the established STEC reservoir. ETEC enterotoxins drive secretory diarrhoea; Shiga toxin damages vascular endothelium, producing haemolytic uraemic syndrome.

Not known: why only a minority of STEC infections progress to haemolytic uraemic syndrome, and whether any intervention prevents that progression. Antibiotics in STEC are genuinely contested — some evidence indicates they increase the risk by promoting toxin release, other evidence does not, and practice guidance differs between countries. No ETEC vaccine is licensed despite being a long-standing target.

Cure status. Split by type.

ETEC: SELF-LIMITING STEC without HUS: SELF-LIMITING STEC with HUS: RELIEF ONLY

ETEC resolves with rehydration; antibiotics shorten travellers' diarrhoea but are not required. STEC without haemolytic uraemic syndrome also resolves, and antibiotics are of contested safety. For STEC with haemolytic uraemic syndrome nothing removes the toxin's effect: management is fluid management, transfusion and dialysis. No agent reverses it. Eculizumab has been used with contested benefit and is neither off-patent nor affordable.

Prevention.

Safe water, sanitation and handwashing: STRONG. The Cochrane handwashing figures from the overview entry apply.

Cooking meat thoroughly and avoiding raw milk: STRONG for STEC, on settled microbiology — the organism is killed by heat.

Separating raw meat from other food and washing produce: STRONG for STEC. Keeping children from direct contact with ruminant faeces, on farm visits and at petting zoos: MODERATE. Exclusive breastfeeding: STRONG for infant ETEC.

Avoiding antibiotics in suspected STEC: CONTESTED. Some studies show increased haemolytic uraemic syndrome risk with antibiotics, others show no effect. Both positions are held by good sources and no single number should be quoted.

No vaccine is licensed for either type.

Treatment.

Treatment	EML	Off-patent	Price
Oral rehydration salts and zinc	Yes	Yes	About 4.8 US cents a sachet, UNICEF indicative, October 2026
Azithromycin or ciprofloxacin, ETEC if treated	Yes	Yes	Azithromycin about 9.3 US cents a 250 mg tablet, UNICEF indicative, October 2026
Dialysis and transfusion, for HUS	n/a	n/a	High; requires hospital infrastructure
Antibiotics in STEC	—	—	Contested; may be harmful

Simple means. Oral rehydration with salt, sugar and clean water, which is the core of ETEC management. Cooking meat until no longer pink, and boiling milk: this is the single decisive STEC prevention and it needs only fire. Boiling or chlorinating water. Handwashing with soap, especially after animal contact. Not giving antibiotics for bloody diarrhoea in a child without advice, given the haemolytic uraemic syndrome controversy — a case where doing less may be safer. Watching urine output in a child with bloody diarrhoea: falling output is the sign of haemolytic uraemic syndrome, and it is observable without instruments.

For haemolytic uraemic syndrome there is nothing simple. The minimum chain is dialysis: a machine, sterile fluids, trained staff and reliable power. A child who develops it where dialysis is unavailable is likely to die regardless of what simple means are applied.

Gaps. No global burden figures for either type; pathogen-specific attribution is modelled. **The HUS progression rate, 5 to 15 per cent†, could not be confirmed to a primary source and is not relied upon.** Antibiotics in STEC is a genuine contested question with clinical consequences, and guidance differs by country. No licensed vaccine for ETEC despite long effort. The eculizumab evidence is weak and contested, and the drug is unaffordable in most settings.

> **Depth.** Starts in: Escherichia coli, a rod. Size: 2 µm†; depth +3.44. First complaint: about 2 days († 1–4 days); time depth 44.13. One untreated course: about 6 days († 5–7 days); depth 45.12.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Cryptosporidiosis

What it is. A protozoan parasite, *Cryptosporidium*, that infects the gut lining and causes prolonged watery diarrhoea. Its cysts resist chlorine, so it survives normal water treatment. In people with damaged immunity it can be unrelenting and fatal.

Measured. Subsumed in the diarrhoeal totals of the overview entry. No WHO standalone fact sheet was retrievable.

Global burden. No *Cryptosporidium*-specific global figure is asserted. The pathogen is consistently ranked among the leading causes of moderate-to-severe diarrhoea in young children in high-burden settings, and among the leading diarrhoeal causes of death in children under two in attribution studies, notably GEMS. The burden concentrates in infants and toddlers and in people with advanced HIV, and geographically in sub-Saharan Africa and south Asia.

Where it starts. Ingestion of oocysts from water, person-to-person contact, and animal contact, especially with calves. Three features are established. Chlorine resistance of the oocyst, which is why it causes outbreaks in treated municipal water and in swimming pools. A low infectious dose. And severity governed by immune status, with advanced HIV the dominant risk factor for fatal disease.

Not known: there is no reliably effective drug for cryptosporidiosis in the people who most need one. Nitazoxanide works in immunocompetent people but does not work in advanced immunodeficiency, and why is not fully explained. The link between repeated early-childhood cryptosporidiosis and lasting growth and cognitive impairment is observed consistently, but the mechanism and reversibility are unresolved. No vaccine candidate is near licensure.

Cure status. Split by immune status, and the split is stark.

immunocompetent: SELF-LIMITING advanced HIV or severe immunodeficiency: CONTROLLABLE malnourished infants: RELIEF ONLY

Immunocompetent infection resolves over one to two weeks, and nitazoxanide modestly shortens it. In advanced immunodeficiency no antiparasitic reliably clears the organism; the effective intervention is restoring immunity with antiretroviral therapy, which resolves the infection indirectly and is lifelong, so that the label is CONTROLLABLE. For a person with HIV, the treatment for cryptosporidiosis is HIV treatment, not an antiparasitic. In malnourished infants the illness is prolonged, has nutritional consequences, and has no reliable curative agent.

Prevention.

Filtration or boiling of drinking water: STRONG. Because the oocyst resists chlorine, boiling or physical filtration — not chlorination — is the effective treatment. This is settled physiology and a significant practical exception to standard water-treatment advice.

Handwashing with soap: STRONG. Cochrane figures as in the overview entry. Avoiding swallowing pool and surface water: MODERATE. Separating young children from calves and livestock faeces: MODERATE. Antiretroviral therapy for people with HIV: STRONG, by preventing the immunodeficiency that makes the infection lethal. Exclusive breastfeeding: MODERATE.

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
Oral rehydration salts and zinc, supportive and the mainstay	Yes	Yes	About 4.8 US cents a sachet, UNICEF indicative, October 2026
Nitazoxanide, immunocompetent only	Not confirmed on the 24th List	Yes	Low dollars per course; no verified price
Antiretroviral therapy, the effective intervention in HIV	Yes	Yes	Below US$45 per patient-year for TLD, Global Fund 2023/2024

Nitazoxanide does not work in advanced immunodeficiency. There is no second-line antiparasitic of established efficacy.

Simple means. Boiling drinking water is the decisive intervention, and chlorination will not substitute: a rolling boil kills oocysts, bleach does not. Cloth and sand filtration, which physically removes oocysts and is effective where chemical treatment is not. Oral rehydration and continued feeding, maintained over a longer period than for other diarrhoeas because the illness is prolonged. Handwashing with soap. Keeping toddlers away from livestock faeces and from drinking surface water. Sustained feeding after recovery, given the growth consequences.

Simple means do well on prevention — boiling and filtration genuinely work. But nothing simple, and nothing complex either, cures the immunocompromised patient other than restoring immunity, which requires antiretroviral therapy and therefore a long chain.

Gaps. No burden figure is asserted; no WHO fact sheet exists. The absence of an effective drug for the immunocompromised is a genuine therapeutic void, not a gap in the evidence about an existing drug. Nitazoxanide's EML status was not confirmed. The long-term growth and cognitive consequences of early repeated infection are consistently observed but not quantified to a reliable effect size. Chlorine resistance means that water judged treated by residual-chlorine testing may still transmit this organism, so the water-quality indicators used in household surveys do not track this pathogen.

> **Depth.** Starts in: the Cryptosporidium oocyst. Size: 5 µm†; depth +4.28. First complaint: about 7 days († about 7 days (2–10)); time depth 45.27. One untreated course: about 10 days († 1–2 weeks; [B] long-lasting); depth 45.59.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Measles

What it is. One of the most transmissible viruses known. It causes fever and a rash, and it temporarily erases part of existing immune memory, so children die in the following weeks of pneumonia and diarrhoea. One case can infect up to eighteen others.

Measured. WHO fact sheet, 15 July 2026. About 95,000 measles deaths in 2024, mostly in children under five, down from 780,000 in 2000. Measles vaccination averted nearly 59 million deaths between 2000 and 2024. Before the vaccine, which was introduced in 1963, epidemics every two to three years caused about 2.6 million deaths a year.

Coverage in 2025: first dose 84 per cent, against 86 per cent in 2019; both doses 77 per cent; about 29 million infants under-protected. The immunization coverage fact sheet of the same date gives the same figures and adds that nearly 21 million children missed the routine first dose, against 19 million in 2019.

The 84 per cent figure is described two ways on the measles page: as first-dose coverage in 2025 in Key Facts, and as the share who received one dose by their first birthday in the body. The immunization coverage sheet describes the same number as one dose by the second birthday. The value does not change; the definition drifts.

Transmission: the virus remains active in air or on surfaces for up to two hours; one case can generate up to 18 secondary infections; a case is infectious from four days before to four days after rash onset. Symptoms begin 7 to 14 days after exposure; early symptoms last 4 to 7 days; the rash appears 3 to 5 days after onset, spreads over about three days and lasts 4 to 8 days.

Complications are most common in under-fives and in adults over thirty. WHO publishes no global case count on the fact sheet. The cited source is the Weekly Epidemiological Record No. 48, 2025, pp. 591–604.

Where it starts. Measles virus, airborne, with a basic reproduction number among the highest of any human pathogen. That is why herd immunity requires about 95 per cent two-dose coverage†, and why coverage of 84 and 77 per cent produces recurrent epidemics. Risk factors for death: age under five, vitamin A deficiency, undernutrition, crowding and immunodeficiency.

Not known: the full extent and duration of measles-induced immune amnesia, the destruction of the pre-existing antibody repertoire, is a recent finding whose long-term consequences are not quantified. Why measles causes subacute sclerosing panencephalitis years later in a small number of children is not explained. The determinants of individual severity are not established.

Cure status. Split.

measles: SELF-LIMITING

Measles resolves unaided in the uncomplicated case, and no antiviral exists. Deaths come from complications — pneumonia, diarrhoea, encephalitis — which are treated on their own terms. Vitamin A is the one intervention that changes mortality: WHO recommends two doses for suspected cases under five, with a third at four to six weeks if eye signs of deficiency appear. That reduces death without removing the virus.

Prevention.

Measles vaccination: STRONG. CDC’s measles vaccine recommendations give one dose as 93 per cent effective, range 39 to 100 per cent, and two doses as 97 per cent effective, range 67 to 100 per cent. Those are the ranges CDC publishes across studies rather than confidence intervals. WHO publishes no efficacy figure of its own and states only that vaccine cost is less than a few US dollars per child.

Schedule: dose one at 9 months in high-burden countries, 12 to 15 months elsewhere; dose two usually at 15 to 18 months.

Measles vaccine needs an unbroken 2–8 °C cold chain and is one of the most cold-chain-dependent products in routine immunisation. It is a live attenuated vaccine requiring cell-culture propagation in chick embryo fibroblast, lyophilisation and sterile fill-finish; it is notably heat- and light-sensitive; and reconstituted vaccine must be discarded within hours. It cannot be produced or distributed without a long chain, and the cold chain is the specific reason coverage stalls where it does.

Post-exposure prophylaxis: STRONG. MMR within 72 hours of exposure; immunoglobulin within six days, at an intramuscular dose of 0.5 mL/kg regardless of immune status. MMR and immunoglobulin must not be given together — doing so invalidates the vaccine.

Vitamin A supplementation: STRONG for reducing measles mortality.

Isolation of cases: MODERATE, limited by infectiousness beginning four days before the rash, so transmission precedes recognition.

Treatment.

Treatment	EML	Off-patent	Price
Vitamin A, two doses	Yes	Yes	Cents per course

Treatment	EML	Off-patent	Price
Oral rehydration salts for diarrhoea	Yes	Yes	About 4.8 US cents a sachet, UNICEF indicative, October 2026
Antibiotics for bacterial complications	Yes	Yes	Amoxicillin about 5.4 US cents a 250 mg dispersible tablet, UNICEF indicative, October 2026
Oxygen for pneumonia	Yes, oxygen	n/a	Variable
Measles vaccine, also used post-exposure	Yes	Yes	Less than a few US dollars per child

No antiviral exists. Antibiotics are for complications, not for measles itself.

Simple means. Vitamin A, which is a cheap capsule and the single most effective simple measure for survival. Dark green leaves, orange vegetables, liver and palm oil supply it from food. Keeping the child fed and hydrated through the illness and through the weeks after, when immune suppression leaves them vulnerable. Oral rehydration for the diarrhoea that follows. Isolating the case from infants too young to be vaccinated — imperfect, since infectiousness precedes the rash. Keeping the child in a darkened, quiet room during photophobia, and watching the eyes for the corneal damage that causes blindness. Watching for fast breathing, which is the pneumonia that kills.

Prevention absolutely requires a chain. The vaccine cannot be improvised. But survival of a case is substantially improvable with vitamin A, food, water and attention, none of which needs an industrial supply chain.

Gaps. WHO publishes no global case count, only deaths, so incidence is not stated here. WHO publishes no vaccine efficacy figure; CDC's figures are used, and CDC gives ranges across studies rather than confidence intervals. First-dose coverage fell from 86 per cent in 2019 to 84 per cent in 2025 while deaths are reported as falling; the source does not reconcile the trajectory, and cases are reported as surging in a linked WHO news item. The duration and consequences of measles-induced immune amnesia are not quantified. The 95,000 deaths figure is modelled; measles deaths are rarely individually certified.

> **Depth.** Starts in: the measles virus. Size: 150 nm†; depth +1.08. First complaint: about 10 days ([W] 9–12 days); time depth 45.63. One untreated course: about 10 days († 1–2 weeks); depth 45.59.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status, given by stratum: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Hepatitis A

What it is. A virus spread by faecal contamination of food and water that inflames the liver. Children usually have no symptoms. Adults become jaundiced and unwell for weeks. It does not become chronic.

Measured. WHO fact sheet, 28 July 2026. 35,569 deaths worldwide in 2023, which is 2.6 per cent of viral hepatitis mortality; WHO attributes the figure to IHME's GBD 2023. No global case count is given.

In endemic settings 90 per cent of children are infected before the age of ten, usually without symptoms. Children under six usually have no noticeable symptoms and only 10 per cent of them develop jaundice. Adults show symptoms more often, and severity and fatality rise with age. Incubation is 14 to 28 days.

Geography: common in low- and middle-income countries, with low rates in high-income countries. The 1988 Shanghai epidemic affected about 300,000 people. Large United States outbreaks have occurred among people experiencing homelessness.

Where it starts. Hepatitis A virus, faecal-oral, through contaminated water, food — notably shellfish and raw produce — and person-to-person contact. The risk structure is absence of safe water and sanitation.

One paradoxical feature is well established and worth stating plainly: improving sanitation raises the average age of infection, and because severity rises with age, partial improvement can increase symptomatic disease and deaths even as infections fall.

Not known: why severity rises so sharply with age at infection is described but not mechanistically explained. The determinants of fulminant hepatic failure in the small minority who develop it are not established.

Cure status. SELF-LIMITING. The body clears the virus and immunity is lifelong. There is no antiviral and none is needed. Infection does not become chronic, which distinguishes it from hepatitis B and C. A small minority develop fulminant liver failure, for which the only intervention is transplantation.

Prevention.

Safe water and sanitation: STRONG, on settled transmission physiology.

Hepatitis A vaccination: STRONG. WHO states that several injectable inactivated vaccines are available with similar protection, and that a live attenuated vaccine is available in China. No vaccine is licensed for children under one year. **WHO publishes no efficacy percentage, and no figure with a confidence interval could be sourced primarily, so none is asserted.**

Inactivated hepatitis A vaccine needs a long chain: cell-culture propagation, inactivation, adjuvanting, sterile fill-finish and an unbroken 2–8 °C cold chain. It is a needle vaccine. Its chain sits in the middle of this chapter's range — more demanding than the toxoids, less than the conjugates.

Handwashing with soap: STRONG. Cochrane figures as in the diarrhoeal overview. Cooking food and boiling water: STRONG — the virus is inactivated by heat, though it is relatively heat-stable and steaming shellfish may be insufficient. Vaccinating at-risk adult groups: MODERATE where outbreaks occur in homeless or drug-using populations.

Treatment.

Treatment	EML	Off-patent	Price
Supportive care only	n/a	n/a	Minimal
Hepatitis A vaccine, prevention and post-exposure	Yes	Yes	No verified price
Liver transplant, fulminant failure only	n/a	n/a	Very high; requires transplant infrastructure

There is no antiviral treatment. Avoiding alcohol and hepatotoxic drugs during recovery is standard advice.

Simple means. Boiling drinking water and treating it. Handwashing with soap, particularly around food preparation and nappy changing. Safe faeces disposal, with latrines sited away from water. Cooking food thoroughly, especially shellfish. Rest and food during the illness, which is the whole of the treatment. Avoiding alcohol while the liver recovers.

Simple means cover this condition almost completely: prevention by water, sanitation and handwashing, and management by rest. Only the vaccine and the rare transplant require a chain.

Gaps. No global case count is published, only deaths. **No vaccine efficacy figure with a confidence interval is published by WHO and none was sourced.** The sanitation paradox means burden trends are hard to interpret: falling infection can coincide with rising disease. The 35,569 figure is given to five significant figures from GBD 2023 modelling, which overstates precision.

> **Depth.** Starts in: the hepatitis A virus. Size: 27 nm†; depth −0.48. First complaint: about 4 weeks ([P] 28–30 days (15–50)); time depth 46.51. One untreated course: about 4 weeks ([B] "weeks"; † 2–8 weeks); depth 46.53.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Hepatitis B

What it is. A virus that infects liver cells and, when acquired in infancy, usually persists for life. Decades of quiet inflammation cause cirrhosis and liver cancer. Infection in adulthood usually clears; infection at birth usually does not.

Measured. WHO fact sheet, 28 July 2026. About 240 million people with chronic HBV infection in 2024. About 0.9 million new infections a year. About 1.1 million deaths in 2024, mostly from cirrhosis and liver cancer.

Regional chronic infections: Western Pacific 102 million; African 64 million; South-East Asia 43 million; Eastern Mediterranean 16 million; European 9.7 million; Americas 5 million. Those sum to about 239.7 million against a stated global 240 million, which is consistent to rounding.

Under-five chronic prevalence in 2024: 0.6 per cent globally (95 per cent UI 0.5–0.8); African Region 1.4 per cent; Eastern Mediterranean 0.5 per cent. The European and Americas Regions have already passed the 2030 target of 0.1 per cent. Under-five prevalence was about 5 per cent in the pre-vaccine era and just under 1 per cent in 2019.

HBV prevalence among people with HIV is 7.4 per cent.

Diagnosis and treatment: 65 million people, 27 per cent of those infected, knew their status as of 2024. About 10 million were on antiviral treatment, stated as 4.3 per cent of those with chronic infection, while more than 50 per cent are estimated to need treatment under the 2024 WHO guidelines.

The 4.3 per cent does not follow from the page's own numbers: 10 million of 240 million is 4.2 per cent, and the page names no other denominator. The discrepancy stands; the appendix of single-source contradictions carries it as item 3.

A second, cross-page discrepancy stands as well: the WHO fact sheet on sexually transmitted infections, 10 September 2025, gives 254 million living with chronic hepatitis B in 2022, against this sheet's 240 million in 2024. Both are live WHO figures for the same quantity at different vintages. Both deaths figures are 1.1 million, but one dates it 2024 and the other 2022.

Where it starts. Hepatitis B virus, transmitted perinatally, by blood and by sexual contact. The decisive established fact is age at infection: adult-acquired infection becomes chronic in less than 5 per cent of cases, infant and early-childhood infection in about 95 per cent. That is why the birth dose exists and why prevention is concentrated at birth.

Not known: why the immune system of a neonate tolerates the virus while an adult's clears it is described but not fully explained. Which chronically infected individuals will progress to cirrhosis or cancer cannot be predicted for an individual. There is no cure because covalently closed circular viral DNA persists in the hepatocyte nucleus and no available agent removes it.

Cure status. Split by age at acquisition.

adult acute infection: SELF-LIMITING — resolves in over 95 per cent of cases chronic infection: CONTROLLABLE

Antivirals suppress replication and halt progression, but WHO states that most people who start treatment must continue it for life, and the fact sheet does not mention a cure. The persistent nuclear reservoir is the reason.

Prevention.

Hepatitis B vaccination: STRONG. WHO describes vaccine protection as "nearly 100 per cent", lasting at least 20 years and probably for life, with boosters not usually required after the series is completed. WHO gives no separate efficacy percentage with a confidence interval.

The birth dose within 24 hours of birth is the critical intervention, because 95 per cent of infant infections become chronic. The full series is two or three doses at least four weeks apart.

Coverage is the failure point. The hepatitis B birth dose reached only 43 per cent globally in 2025 — the lowest coverage of any vaccine in the routine schedule. Three-dose hepatitis B coverage was 84 per cent in the same year, which shows that the problem is timing rather than supply.

The chain is long but shorter than most here, and it matters that this is so. HBV vaccine is a recombinant surface-antigen protein expressed in yeast — *Saccharomyces* or *Hansenula* — then adjuvanted with aluminium salt, sterile-filled and cold-chained at 2–8 °C. Yeast fermentation is a far lower technological

threshold than mammalian cell culture, which is why HBV vaccine is among the cheapest vaccines in existence and is produced in many middle-income countries. It still requires sterile fill-finish, a needle and an unbroken cold chain, and it cannot be made by simple means.

Blood screening and sterile injection practice: STRONG. Antiviral prophylaxis in pregnancy for high-viral-load mothers: STRONG, alongside the birth dose. Condoms: STRONG for sexual transmission.

Treatment.

Treatment	EML	Off-patent	Price
Tenofovir (TDF)	Yes	Yes	The same molecule as in HIV TLD, where the full three-drug combination is below US$45 per patient-year, Global Fund 2023/2024; tenofovir alone is a fraction of that†
Entecavir	Yes	Yes	Low dollars per month generically
Hepatitis B vaccine	Yes	Yes	Among the cheapest vaccines; no verified unit price
Hepatitis B immunoglobulin, perinatal and high-risk	Yes	Yes	Higher; requires plasma fractionation

WHO names tenofovir as an oral treatment for chronic hepatitis B, also active against HBV in people with HIV, and gives no efficacy or dosing figures. The treatment gap is the salient fact: 4.3 per cent treated against more than 50 per cent needing it.

Simple means. Not reusing needles, blades or skin-piercing instruments; boiling or flaming them where no sterile supply exists. Not sharing razors or toothbrushes within a household. Condoms. Avoiding alcohol, which accelerates cirrhosis in chronic infection — a substantial intervention requiring nothing. Covering wounds.

Nothing available without an industrial chain prevents perinatal transmission or treats chronic infection. The minimum chain for prevention is yeast-fermented recombinant vaccine, plus sterile fill-finish, plus a cold chain capable of reaching a birth within 24 hours. That last requirement, not the manufacturing, is why birth-dose coverage is 43 per cent while three-dose coverage is 84 per cent. For treatment the chain is nucleotide analogue synthesis plus a lifelong uninterrupted supply.

Gaps. WHO describes protection as “nearly 100 per cent” without a figure or confidence interval, so no precise efficacy is stated. The treatment-need estimate, more than 50 per cent, is explicitly setting-dependent in the source and therefore soft. Why only 27 per cent know their status, while the vaccine has existed for decades, is a service-delivery gap rather than an evidence gap. No cure exists and no candidate is close; clearance of the nuclear reservoir is an unsolved problem. The stated treatment coverage of 4.3 per cent does not follow from the page’s own two numbers; see the appendix, item 3. The hepatitis B prevalence figure differs between two live WHO fact sheets, 240 million in 2024 against 254 million in 2022, and both stand.

> **Depth.** Starts in: the hepatitis B virus. Size: 42 nm†; depth −0.07. First complaint: about 11 weeks († mean 75 days (30–180)); time depth 47.43. One untreated course: no number ([B] lifelong when acquired in infancy).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The bound applies. In chronic infection the viral DNA stays in the liver cell. So it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Hepatitis C

What it is. A blood-borne virus that persists in the liver in most people it infects, causing slow scarring over decades. Since 2014 a short course of tablets removes it from the body in almost everyone. Most infected people do not know they have it.

Measured. WHO fact sheet, 28 July 2026. About 47 million people with chronic HCV infection. About 0.9 million new infections a year. About 239,000 deaths in 2024, mostly from cirrhosis and hepatocellular carcinoma.

The page's own regional figures do not reach its headline total. Eastern Mediterranean 12 million; South-East Asia 9 million; European 9 million; African 8 million; Western Pacific 7 million; Americas 5 million. Those sum to 50 million against the stated 47 million — a three-million gap between the headline and the page's own table, which the source does not explain. Both figures stand; the appendix of single-source contradictions carries this as item 4.

Natural course: acute infection clears spontaneously in about 30 per cent of people, range 15 to 45 per cent, within six months, and about 70 per cent, range 55 to 85, become chronic. Risk of cirrhosis in chronic infection is 15 to 30 per cent within twenty years.

Cumulative ever-infected, 2015–2024: 68 million (95 per cent UI 46–103 million).

Cascade to end-2024. 36 per cent know their diagnosis (95 per cent UI 17–57), about 24 million. About 20 per cent of those ever infected have been treated with direct-acting antivirals (95 per cent UI 10–31), about 13 million. 11 million are diagnosed but not yet treated (95 per cent UI 7.4–15 million).

WHO recommends general population testing where anti-HCV seroprevalence exceeds 2 per cent.

Where it starts. Unsafe injection and medical practice, unscreened blood transfusion, injecting drug use with shared equipment, and, less efficiently, sexual and perinatal transmission. The risk structure is iatrogenic and injection-related.

Not known: why about 30 per cent of people clear the virus spontaneously while 70 per cent do not. Host genetic factors such as IL28B explain part of it, not all. Reinfection after cure is possible because immunity is not protective, and why natural infection fails to generate protective immunity is the central reason no vaccine exists. The progression rate to cirrhosis varies widely between individuals and cannot be predicted.

Cure status. CURABLE. This is the clearest cure in the chapter. Direct-acting antivirals cure more than 95 per cent of people with hepatitis C, in 12 to 24 weeks depending on the presence of cirrhosis. The virus is eliminated from the body, confirmed by sustained virological response, and does not recur unless the person is reinfected. A chronic viral infection that was incurable in 2010 is now curable with oral tablets at low cost. It is the only transition of that kind in this chapter.

The body of the same fact sheet does not restate the 95 per cent figure, saying only "most persons" and "nearly all patients".

Prevention.

Safe injection practice and single-use equipment: STRONG. Blood screening: STRONG, having effectively eliminated transfusion transmission where implemented. Needle and syringe programmes for people who inject drugs: STRONG. Opioid agonist therapy: STRONG for reducing injecting risk. Treating the infected, as prevention: STRONG — curing a person removes them as a source, and because cure is achievable, elimination is arithmetically possible.

Condoms: WEAK for hepatitis C specifically. Sexual transmission is inefficient except in specific contexts, such as HIV co-infection and among men who have sex with men.

No vaccine exists and no candidate is near licensure.

Treatment.

Treatment	EML	Off-patent	Price
Direct-acting antiviral regimens, sofosbuvir-based: sofosbuvir/daclatasvir, sofosbuvir/velpatasvir	Yes	Generic under voluntary licence in most low- and middle-income countries	Under US$50 per standard curative course in many low- and middle-income countries, according to the WHO fact sheet printed 28 July 2026

For scale, the historical comparison, from the MSF Access Campaign, 3 November 2014. Sofosbuvir launched at US$84,000 per three-month course in the United States, and sofosbuvir/ledipasvir at nearly

US$95,000 per course. A University of Liverpool study estimated production cost at US$68–136 per treatment for sofosbuvir, and as little as US$10–30 for a twelve-week course of daclatasvir. The current WHO figure of under US$50 per curative course in many low- and middle-income countries, according to the WHO fact sheet printed 28 July 2026, is close to the estimated cost of production and roughly three orders of magnitude below the original launch price.

Simple means. Not reusing needles or syringes: one needle, one person, once. Not sharing razors, blades, or tattooing and piercing equipment. Sterilising any skin-piercing instrument by boiling or autoclaving where single-use supply does not exist. Covering wounds and avoiding blood contact. Avoiding alcohol, which markedly accelerates progression to cirrhosis — a genuine intervention requiring nothing.

Prevention by simple means is effective, because transmission is almost entirely through blood contact that can be avoided. But nothing simple cures it. The minimum chain is multi-step small-molecule synthesis, co-formulation, a twelve-week uninterrupted supply, and a test to confirm infection and cure. Unlike many conditions in this chapter that chain is short, cheap and already functioning. The barrier is diagnosis, not manufacture.

Gaps. The diagnosis gap is the binding constraint: 36 per cent know their status, with a 95 per cent uncertainty interval of 17 to 57 per cent, which is very wide. Regional figures sum to about 50 million against a 47 million global total, unexplained in the source; see the appendix, item 4. No vaccine and no clear path to one, because natural immunity is not protective. Reinfection after cure is possible, so individual cure confers no protection, which complicates elimination arithmetic. The price of under US$50 applies in many but not all low- and middle-income countries, according to the WHO fact sheet printed 28 July 2026; middle-income countries excluded from voluntary licences pay substantially more, and the source does not enumerate which.

> **Depth.** Starts in: the hepatitis C virus. Size: 50 nm†; depth +0.08. First complaint: about 7 weeks († 2–24 weeks); time depth 47.03. One untreated course: no number ([B] decades).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Hepatitis E

What it is. A virus spread by faecally contaminated water, causing liver inflammation that usually resolves. Its distinctive feature is lethality in pregnancy. It causes large outbreaks in camps and where water supply has failed.

Measured. WHO fact sheet, 28 July 2026. About 20 million infections globally each year, of which about 3.3 million are symptomatic. Approximately 4,431 deaths in 2023.

Up to 20 to 25 per cent of pregnant women can die if infected in the third trimester, in WHO's own wording.

Symptomatic infection is most common in people aged 15 to 40. Genotypes 1 and 2 spread person-to-person by the faecal-oral route; genotypes 3 and 4 are mainly zoonotic.

Geography: worldwide, most common in sub-Saharan Africa and in east and south Asia. Nearly 50 per cent of outbreaks occur in camp settings, among refugees or internally displaced people.

Incubation is 2 to 10 weeks, averaging 5 to 6; symptoms last 1 to 6 weeks; infection usually resolves in 2 to 6 weeks.

Where it starts. Contaminated drinking water for genotypes 1 and 2; undercooked pork, game and shellfish for genotypes 3 and 4. The risk structure is displacement and camp settings, where water and sanitation fail together — the reason half of outbreaks occur there. Pregnancy in the third trimester is the established determinant of mortality.

Not known: why hepatitis E kills pregnant women is not explained. This is the most consequential unexplained feature of the condition; hormonal and immunological hypotheses exist without resolution. Why genotype 1 behaves this way while genotype 3 largely does not is also unexplained. Chronic hepatitis

E in immunosuppressed patients was recognised only recently and its epidemiology is not well characterised.

Cure status. Split.

most immunocompetent people: SELF-LIMITING third-trimester pregnancy and fulminant disease: RELIEF ONLY chronic infection in the immunosuppressed: CURABLE

Most infection resolves in two to six weeks with no intervention. In third-trimester pregnancy and in fulminant hepatitis no agent alters the course, care is supportive, and mortality reaches 20 to 25 per cent. Chronic infection in immunosuppressed patients is cured by ribavirin, alongside reduction of immunosuppression where possible.

Prevention.

Safe drinking water and sanitation: STRONG, on settled transmission physiology. This is the primary measure, and its failure is why camps dominate the outbreak record.

Hepatitis E vaccine, Hecolin or HEV 239: MODERATE — effective but barely available. WHO states it has been licensed in China since 2011 for healthy adults aged 16 and over. It is given as three intramuscular doses at 0, 1 and 6 months, with a shelf life of at least 36 months. It was deployed in Bentiu, South Sudan, from March 2022 in three rounds, each reaching more than 24,000 people. It is the fifth vaccine approved under the International Coordinating Group mechanism. **WHO publishes no efficacy percentage; the Chinese phase 3 trial reported very high efficacy but could not be sourced primarily, so no figure with a confidence interval is asserted.**

The chain is long but comparatively modest. Hecolin is a recombinant protein — an HEV ORF2 capsid fragment — expressed in *E. coli*, then adjuvanted, sterile-filled and cold-chained at 2–8 °C. Bacterial expression is the lowest-threshold recombinant platform, lower than yeast and far lower than mammalian cell culture. The limit on availability is licensure and manufacturer commitment, not technical difficulty.

Cooking pork, game and shellfish thoroughly: STRONG for genotypes 3 and 4. Protecting pregnant women specifically during outbreaks, by prioritising their water supply and evacuation: MODERATE, on the established mortality gradient.

Treatment.

Treatment	EML	Off-patent	Price
Supportive care	n/a	n/a	Minimal
Ribavirin, chronic HEV in the immunosuppressed only	Yes	Yes	Low dollars per course generically; no verified price
Hepatitis E vaccine, Hecolin	Not confirmed on the 24th List	No; single manufacturer, China	No published international price

There is no treatment for acute hepatitis E, including in pregnancy. Ribavirin is contraindicated in pregnancy.

Simple means. Boiling drinking water — the decisive measure, and sufficient. Chlorination and filtration of water supplies. Safe faeces disposal, with latrines sited away from and below water sources, which in a camp is a layout decision rather than a technology. Handwashing with soap. Cooking meat thoroughly. Giving pregnant women the cleanest available water first in an outbreak, a triage decision requiring no resources and justified by a 20 to 25 per cent mortality. Rest and food for the ill, which is the treatment.

Simple means prevent this condition effectively. What they cannot do is save the pregnant woman who is already infected. For her, neither simple nor industrial medicine has an answer, which makes prevention the whole of the intervention.

Gaps. No vaccine efficacy figure with a confidence interval is asserted; WHO publishes none and the primary trial was not retrievable. The vaccine is licensed in one country only, fifteen years after licensure, despite a 20 to 25 per cent maternal mortality in outbreaks: a deployment gap, not an evidence gap. Why it kills pregnant women is genuinely unknown, and that is the central scientific gap. The death figure, 4,431 in 2023, is implausibly precise for a condition with 20 million annual infections and 3.3 million

symptomatic cases, and it sits oddly against a 20 to 25 per cent third-trimester mortality; the source does not reconcile these. Chronic hepatitis E in the immunosuppressed is recently recognised and its burden is unquantified.

> **Depth.** Starts in: the hepatitis E virus. Size: 30 nm†; depth −0.38. First complaint: about 4.7 weeks ([P] 26–42 days); time depth 46.68. One untreated course: about 3.5 weeks († 2–6 weeks; [B] “usually resolves”); depth 46.40.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Sepsis and neonatal sepsis

What it is. Not a single infection but the body’s own response to infection turning destructive: circulation fails, organs shut down, and the person dies of the response rather than of the organism. In newborns it can follow infection acquired at or shortly after birth.

Measured. WHO fact sheet on sepsis, 3 May 2024, citing data published in 2020. 48.9 million cases worldwide. 11 million sepsis-related deaths, about 20 per cent of all global deaths. Children under five account for almost half of all estimated cases, 20 million. An estimated 15 per 1,000 hospitalised patients develop sepsis as a complication of health care.

Incidence and mortality vary significantly by region and are highest in lower-middle-income countries; no regional counts are given. Average hospital-wide cost in high-income countries is more than US$32,000 per patient, according to the WHO sepsis fact sheet of 3 May 2024.

The fact sheet gives no separate figures for neonatal or maternal sepsis, stating only that sepsis is a significant cause of maternal, neonatal and child mortality.

Related, from the WHO fact sheet on newborn mortality, 14 March 2024, reporting 2022 data: 2.3 million neonatal deaths in 2022, about 6,500 a day, which is 47 per cent of all under-five deaths. About 75 per cent of neonatal deaths occur in the first week and about 1 million within the first 24 hours. Sub-Saharan Africa carries 57 per cent of under-five deaths, 2.8 million, with 30 per cent of global live births, and a neonatal mortality rate of 27 per 1,000 live births. Prematurity, intrapartum events, pneumonia and sepsis together account for almost eight in ten neonatal deaths.

The sepsis fact sheet reports 4.95 million deaths associated with antimicrobial resistance and 1.27 million directly attributable, for 2019. The AMR fact sheet of 16 July 2026 gives more than 4.7 million associated for 2021. The figures move between sources and years; see the antimicrobial resistance entry.

Where it starts. Any infection can precipitate it — pneumonia, abdominal infection, urinary infection, skin and soft tissue infection, meningitis, and in newborns infection acquired from the maternal genital tract, the birth environment or the umbilical stump. Risk factors: age under one and over 65, pregnancy and the postpartum period, immunosuppression, chronic disease, invasive devices and hospitalisation, and in neonates prematurity, low birth weight, prolonged rupture of membranes and unclean delivery. Antimicrobial resistance is a direct driver.

Not known: why two people with the same infection and similar health diverge, one recovering and one progressing to organ failure, is not explained. Decades of immunomodulatory trials in sepsis have failed, which indicates the underlying model is incomplete. Whether sepsis is one condition or a heterogeneous collection of host-response states is actively contested, and that question is the reason trials fail. The optimal fluid volume and type remain contested.

Read in the net: closure is all or nothing. A winding either returns in phase or it does not, and what fails to close passes its tension to the meshes beside it. Whether a host response that holds and one that cascades are two classes or two degrees of the same thing is not settled, as the entry above says. This is a reading, not a mechanism.

Cure status. Split by timing, more sharply than any other entry in the chapter.

early sepsis: CURABLE established septic shock with multi-organ failure: RELIEF ONLY

Treating the underlying infection with antibiotics plus fluids resolves early sepsis and the person recovers fully. For established septic shock no treatment removes the state; management supports organs — vasopressors, ventilation, dialysis — while the host response either resolves or does not. Mortality remains high despite full intensive care, and no immunomodulatory agent has succeeded in trials. The intervention that changes outcome is early recognition and early antibiotics, not any sepsis-specific drug, because no sepsis-specific drug exists.

Prevention.

Preventing the underlying infections: STRONG. Every vaccine in this chapter is sepsis prevention. The Gambian PCV trial measured exactly this pathway, reducing all-cause mortality by 16 per cent (95 per cent CI 3–28).

Clean birth practice: STRONG. Hand hygiene at delivery, clean cord cutting and clean cord care prevent neonatal sepsis. Settled physiology, and the historical basis of the entire field.

Hand hygiene in health facilities: STRONG. 15 per 1,000 hospitalised patients acquire sepsis as a complication of care, and hand hygiene is the principal countermeasure.

Chlorhexidine cord care: STRONG in high-mortality settings with unclean delivery practices.

Early recognition and early antibiotics: STRONG, as secondary prevention of death.

Intrapartum penicillin for mothers at risk of transmitting Group B streptococcus: STRONG.

Exclusive breastfeeding: STRONG for neonatal infection. Skin-to-skin contact and thermal care: STRONG for newborn survival generally.

Treatment.

Treatment	EML	Off-patent	Price
Ampicillin with gentamicin, first-line neonatal sepsis	Yes; amoxicillin is listed first choice for neonatal sepsis, 6.2.1 Access group	Yes	Cents to low dollars per course
Ceftriaxone	Yes	Yes	Low dollars per course
Intravenous fluids: Ringer’s lactate, saline	Yes	Yes	Low dollars
Oxygen	Yes	n/a	Variable
Vasopressors: noradrenaline	Yes	Yes	Low dollars per vial
Organ support: ventilation, dialysis	n/a	n/a	High; intensive care infrastructure

There is no sepsis-specific drug. Treatment is antibiotics for the source, fluids, oxygen and organ support. Corticosteroids have a contested, modest role in septic shock.

Simple means. Considerable, and concentrated at birth.

Washing hands before delivery and before touching a newborn: the single highest-value measure, requiring only water and soap. Clean cord cutting with a boiled or new blade, a clean tie, and the stump left dry and uncovered. Nothing applied to the stump except, where recommended, chlorhexidine: cow dung, ash and oils are a known cause of neonatal sepsis and tetanus. A clean delivery surface, clean hands and clean cloth. Immediate drying, skin-to-skin warmth and early breastfeeding. Recognising the sick newborn — poor feeding, lethargy, abnormal temperature, fast breathing, not waking — all observable without instruments. Wound care: cleaning with clean water, keeping wounds covered and dry. Oral fluids in the early, still-drinking patient.

Once sepsis is established nothing simple works. The minimum chain is injectable antibiotics, sterile intravenous fluids and a cannula, and for septic shock oxygen, vasopressors and organ support, which require hospital infrastructure and reliable power. Early prevention at birth is achievable with soap, a clean blade and attention. Established sepsis is not survivable by simple means.

Gaps. WHO publishes no separate neonatal or maternal sepsis figures despite naming sepsis a leading cause of neonatal and maternal death — the largest single data gap in this entry. The fact sheet is dated 3 May 2024 but cites data published in 2020, so the 48.9 million and 11 million figures come from an earlier modelling exercise. Sepsis is defined by clinical criteria that have changed across Sepsis-1, -2 and -3, so case counts are not comparable over time. Whether sepsis is one condition is genuinely contested, and the repeated failure of immunomodulatory trials suggests it is not. Attributing a death to sepsis rather than to the underlying infection is a coding decision, so the 20-per-cent-of- all-global-deaths figure overlaps heavily with other entries in this chapter and must not be added to them.

> **Depth.** A response to any infection. No single agent. No depth is given.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Bacterial meningitis

What it is. Bacterial infection of the membranes around the brain and spinal cord. It can kill within hours and leaves many survivors deaf, epileptic or brain-damaged. It occurs in epidemics across a belt of sub-Saharan Africa.

Measured. WHO fact sheet on meningitis, 29 September 2026. In the African meningitis belt in 2025: 21,526 suspected cases and 971 deaths reported to WHO, from 24 of the 26 countries in the enhanced surveillance network, giving a case fatality rate of 4.5 per cent.

Outcomes of bacterial meningitis generally: about one in six people die; about one in five develop severe complications; about one in five survivors may have long-lasting after-effects such as hearing loss, seizures or limb weakness.

The pathogens are meningococcus, pneumococcus, *Haemophilus influenzae* and Group B streptococcus, the last being the main concern for newborns. WHO gives no numerical breakdown.

The African meningitis belt, from Senegal to Ethiopia, has the highest burden globally. Outbreaks also occur in crowded settings: mining areas, mass gatherings, refugee and military camps. Serogroup A caused 80 to 85 per cent of epidemics before 2010.

Meningitis-belt vaccine coverage was 61 per cent in countries with the vaccine in their routine programme, and 30 per cent overall, in 2025.

Where it starts. The four bacteria above, carried asymptomatically in the nasopharynx and transmitted by respiratory droplets. Risk factors: crowding, the dry dusty season in the meningitis belt, concurrent respiratory infection, smoking, asplenia, complement deficiency, HIV, and for neonates maternal Group B streptococcal colonisation.

Not known: why the meningitis belt exists in that specific geography, and why epidemics begin and end when they do, is only partly explained by dust, humidity and the Harmattan. Why one carrier among many thousands develops invasive disease is not established: carriage is common and disease is rare. The determinants of which survivors are left deaf are not known.

Cure status. Split by timing and by outcome.

treated within hours: CURABLE established hearing loss and brain injury: RELIEF ONLY

Antibiotics clear the organism and many patients recover fully. WHO directs that antibiotics start as soon as bacterial meningitis is suspected, without waiting for lumbar puncture results — the clearest statement in the chapter that hours matter. Mortality remains about one in six even with treatment, and about one in five survivors retain permanent deficits for which nothing is curative.

Adjunctive corticosteroids: WHO recommends intravenous dexamethasone with the first antibiotic dose in non-epidemic settings, which reduces hearing loss and other complications.

Prevention.

Meningococcal A conjugate vaccine, MenAfriVac: STRONG, and among the most successful vaccine interventions on record. Serogroup A caused 80 to 85 per cent of epidemics before 2010. Mass campaigns from 2010 cut confirmed serogroup A disease by 99 per cent in vaccinated populations. No confirmed serogroup A case has been reported since 2017 in countries that introduced it.

Men5CV, pentavalent A, C, W, Y and X: STRONG, prequalified in 2023, with Niger running the first Gavi-supported campaign in 2025.

Pneumococcal conjugate vaccine: STRONG. The Gambian 9-valent trial gives invasive pneumococcal disease, vaccine serotypes, 77 per cent (95 per cent CI 51–90); all serotypes 50 per cent (95 per cent CI 21–69); all-cause mortality 16 per cent (95 per cent CI 3–28). WHO recommends universal use; coverage of the last dose was 71 per cent in 2025.

Hib conjugate vaccine: STRONG, in most national childhood programmes; coverage for three doses was 78 per cent in 2025. **Trial efficacy figures were not retrievable and none is asserted.**

Intrapartum intravenous penicillin for mothers at risk of Group B streptococcus transmission: STRONG.

Chemoprophylaxis for close contacts: MODERATE. Reducing crowding in sleeping quarters: WEAK.

All of these need long industrial chains. All are conjugate vaccines: bacterial culture, polysaccharide extraction, chemical activation and conjugation to a carrier protein, purification, sterile fill-finish, cold chain. MenAfriVac is the instructive exception on the cold chain, and only on the cold chain. It was developed specifically for African use at under US$0.50 per dose and formulated for controlled temperature chain, tolerating up to 40 °C for four days, which permitted vaccination beyond the 2–8 °C chain. That thermostability was a deliberate design achievement, not an inherent property of conjugates, and the vaccine still requires full industrial manufacture and a needle.

Treatment.

Treatment	EML	Off-patent	Price
Ceftriaxone, first line	Yes	Yes	Low dollars per course
Benzylpenicillin	Yes	Yes	Cents per course
Ampicillin with gentamicin, neonatal	Yes	Yes	Cents to low dollars
Chloramphenicol, oily suspension, epidemic settings, single dose	Yes	Yes	Low; one intramuscular dose
Dexamethasone, adjunct in non-epidemic settings	Yes	Yes	UNICEF indicative US$24.00 per 100 4 mg tablets, October 2026, about 24 US cents a tablet

Single-dose oily chloramphenicol is specifically valuable in epidemics because it needs one injection rather than a cannula and an infusion schedule.

Simple means. Limited, and that must be stated plainly.

Recognising it: the stiff neck; the inability to straighten the leg with the hip flexed; a bulging fontanelle in an infant; the rash that does not blanch under pressure, in meningococcal disease; fever with altered consciousness. These need no instrument, and recognition is what determines whether treatment happens in time. Moving the patient to where injections exist, immediately — the one decision that changes the outcome. Ventilating and decrowding sleeping quarters. Keeping an unconscious patient on their side, airway clear, and not giving oral fluids to someone who cannot swallow. Fever control by tepid sponging. After the illness, testing hearing by simple means and responding to deafness early, which matters for a child’s language development and requires no audiometry to notice.

There is nothing that cures bacterial meningitis without an industrial chain, and nothing simple that alters its course. The minimum chain is an injectable third-generation cephalosporin, or oily chloramphenicol, a syringe, and someone able to give it within hours of onset. This is among the conditions in this chapter where the absence of a supply chain is most directly fatal, because the time window is measured in hours rather than days.

Gaps. WHO gives **no numerical pathogen breakdown** and **no global case or death estimate** — only African belt surveillance figures and proportional outcomes. The belt figures are *suspected* cases, mostly without laboratory confirmation, so the 4.5 per cent case fatality mixes confirmed bacterial meningitis with other febrile illness. **Hib trial efficacy figures were not retrievable.** Why the meningitis belt exists in that geography is not fully explained. The one-in-six mortality and one-in-five sequelae figures are not setting-specific, and outcomes differ sharply between a hospital with dexamethasone and a village three days from an injection.

> **Depth.** Starts in: the meningococcus. Size: 1 µm†; depth +2.81. First complaint: about 4 days († 2–10 days (mostly 4)); time depth 44.76. One untreated course: about 24 hours ([B] can kill within hours; † about 1 day); depth 43.50.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Typhoid and paratyphoid fever

What it is. *Salmonella* Typhi and Paratyphi enter through contaminated water or food, pass through the gut wall and multiply in the bloodstream, causing weeks of fever. Untreated it can perforate the bowel. A small number of recovered people carry it in the gallbladder for years.

Measured. WHO fact sheet on typhoid, 30 March 2023, giving 2019 estimates. These are among the oldest figures in this chapter. About 9 million typhoid cases a year. About 110,000 deaths a year.

It is a public health problem in the WHO African, Eastern Mediterranean, South-East Asia and Western Pacific Regions. Children are at highest risk, and risk is higher where safe water and adequate sanitation are lacking.

On antibiotic resistance WHO says only “increasing” and “common”, with no figures.

Paratyphoid is included in the same disease framing. WHO gives no separate paratyphoid figures and none is asserted.

Where it starts. Ingestion of *S.* Typhi or Paratyphi in water or food contaminated with human faeces or urine. The organisms are human-restricted, so transmission is always ultimately from another person, including from asymptomatic chronic carriers. Risk factors: absence of safe water and sanitation, urban crowding, and food handling by carriers.

Not known: why about 1 to 5 per cent of recovered patients become chronic gallbladder carriers†, and how to identify them without invasive testing, is not settled. Why gallstones predispose to carriage is partly explained by biofilm formation. The relationship between *S.* Typhi carriage and gallbladder cancer is observed but contested. The true burden is poorly measured because blood culture, the only reliable test, is unavailable in most endemic settings.

Cure status. Split by strain and state.

acute susceptible infection: CURABLE XDR infection, azithromycin- or carbapenem-susceptible: CURABLE XDR infection, resistant to both: RELIEF ONLY chronic gallbladder carriage: CURABLE

Acute susceptible infection is cured by antibiotics. Extensively drug-resistant typhoid, as circulating in Pakistan since 2016, is resistant to chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones and third-generation cephalosporins, leaving azithromycin or carbapenems — and azithromycin resistance has now appeared. Where both fail, treatment options approach exhaustion, and the infection is then not curable. This is the clearest example in the chapter of a curable disease being made uncurable by resistance.

Chronic carriage is cured by prolonged antibiotics, sometimes requiring removal of the gallbladder. It is a cure, not a lifelong regimen, which is why the label holds.

Prevention.

Safe water and sanitation: STRONG, on settled transmission physiology and on the historical record. Typhoid disappeared from countries that built sewers and treated water, before antibiotics existed.

Typhoid conjugate vaccine: STRONG. WHO states it is a single dose, recommended from six months of age. Two vaccines were WHO-prequalified as of March 2023, the first since December 2017, with Gavi funding from 2019. It is recommended for adults up to 45 or 65 depending on the vaccine. **WHO publishes no efficacy percentage. The randomised trials in Malawi, Nepal and Bangladesh report high efficacy, broadly in the 80 per cent range at one to two years. The primary trial papers could not be retrieved: PMC was blocked by CAPTCHA and the search budget was exhausted. No efficacy figure with a confidence interval is asserted.**

The chain is long: a Vi polysaccharide conjugated to tetanus toxoid, requiring bacterial culture, polysaccharide purification, conjugation chemistry, sterile fill-finish and an unbroken 2–8 °C cold chain, delivered by needle. But it is produced by multiple manufacturers in India at low cost, and a locally manufactured product, Typhocon, has been through non-inferiority trials in Bangladesh under ClinicalTrials.gov NCT05475379. The manufacturing base is broader and cheaper than for most conjugates.

Older vaccines: injectable Vi polysaccharide from age two and oral live attenuated from age six, both less effective and shorter-lasting than the conjugate.

Handwashing with soap: STRONG. Cochrane figures as in the diarrhoeal overview. Food hygiene and excluding carriers from food handling: STRONG. Boiling or treating drinking water: STRONG.

Treatment.

Treatment	EML	Off-patent	Price
Azithromycin	Yes, 6.2.2 Watch group, first choice for enteric fever	Yes	UNICEF indicative about 9.3 US cents a 250 mg tablet, October 2026
Ceftriaxone	Yes	Yes	Low dollars per course
Ciprofloxacin, where susceptible	Yes	Yes	Cents to low dollars
Amoxicillin, co-trimoxazole, chloramphenicol — older, widely resisted	Yes	Yes	Amoxicillin about 5.4 US cents a 250 mg dispersible tablet, UNICEF indicative, October 2026
Meropenem, XDR strains	Yes	Yes	Substantially higher; hospital use
Oral rehydration salts and fluids, supportive	Yes	Yes	About 4.8 US cents a sachet, UNICEF indicative, October 2026

The fact sheet gives no dosing, duration or prices. Which antibiotic works depends entirely on local resistance, and in extensively drug-resistant settings most of the cheap off-patent options above no longer work.

Simple means. Boiling drinking water: decisive and sufficient against this organism. Chlorination, filtration, solar disinfection. Separating faeces and urine from water sources, with latrines sited below and away from wells. Handwashing with soap, particularly by anyone preparing food. Not allowing a recently ill person to prepare food for others — the carrier state is the engine of transmission, and this requires only a decision. Oral rehydration and continued feeding during the fever. Watching for sudden severe abdominal pain, which signals perforation and the need for surgery.

Prevention is almost entirely achievable with water, latrines and soap. But nothing simple cures an established bloodstream infection, and bowel perforation requires laparotomy. The minimum chain for cure is an effective antibiotic matched to local resistance, which in extensively drug-resistant settings means an injectable carbapenem and a hospital.

Gaps. Typhoid conjugate vaccine efficacy with confidence intervals is absent from this entry and should be filled from the Malawi TyVAC, Nepal and Bangladesh trials. The fact sheet is dated 30 March 2023 and reports 2019 estimates, among the oldest figures here. **WHO gives no numbers at all for antibiotic resistance in typhoid**, describing it only as increasing, while extensively drug-resistant typhoid is the most consequential current development in the condition. **No separate paratyphoid burden figures.**

Burden estimates rest on blood culture surveillance at a small number of sites, extrapolated, and the 9 million figure carries wide uncertainty that the fact sheet does not state. Chronic carriage prevalence is not quantified by WHO.

> **Depth.** Starts in: Salmonella Typhi. Size: 2.5 µm†; depth +3.64. First complaint: about 12 days ([W] 7–21 days); time depth 45.77. One untreated course: about 3.5 weeks ([B] weeks of fever; † 3–4 weeks); depth 46.40.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Dengue

What it is. A virus carried by *Aedes* mosquitoes that bite in daytime and breed in small containers of clean water around houses. Most infections are mild; a minority develop plasma leakage and shock. A second infection with a different serotype carries higher risk than the first.

Measured. WHO fact sheet on dengue, 21 August 2025. Reported cases rose from 505,430 in 2000 to 14.6 million in 2024, a record, with more than 12,000 deaths. The Americas Region reported over 13 million cases in 2024. January to July 2025: over 4 million cases and over 3,000 deaths from 97 countries.

Estimated infections per year: 100 to 400 million. A separate model on the same page gives 390 million infections of which 96 million are clinical, from Bhatt and colleagues, 2013. The page does not link the range to the single estimate.

On population at risk the page gives two figures. Key Facts says about half the world's population, roughly 4 billion. The body says 5.6 billion at risk of dengue and other arboviruses, from Lim and colleagues, 2025. The scopes differ — the body figure covers more than dengue — but the page sets the two against each other without reconciling them. Both stand; the appendix of single-source contradictions carries this as item 5.

Endemic in more than 100 countries. Europe in 2024: 308 cases in France, Italy and Spain; Mayotte and Réunion 1,291 cases and 4 deaths.

WHO states no case fatality rate. Dividing the 2024 reported figures gives about 0.08 per cent; that division is arithmetic performed here, is not a WHO figure, and is biased downward because mild cases dominate reporting in the Americas.

Timing: symptoms 4 to 10 days after infection, lasting 2 to 7 days; most people recover in 1 to 2 weeks; viraemia usually 4 to 5 days and up to 12.

Where it starts. Dengue virus serotypes 1 to 4, transmitted by *Aedes aegypti* and *Ae. albopictus*. The vector breeds in small artificial water containers near dwellings — tyres, pots, gutters, drums, plant saucers — and bites in daytime, which is why bed nets do little. The established risk mechanism for severe disease is secondary infection with a different serotype, via antibody-dependent enhancement, in which non-neutralising antibody from the first infection facilitates entry in the second. That is the central established fact of dengue immunology and the reason vaccination is complicated.

Not known: why most secondary infections are nonetheless mild. Which individuals will develop plasma leakage cannot be predicted. The relative contributions of viral factors, antibody-dependent enhancement and T-cell responses to severe dengue are contested. Whether the 2024 record reflects a true transmission increase, climate-driven vector expansion, better surveillance, or all three, is not resolved in the source.

Cure status. Split by severity.

most infections: SELF-LIMITING severe dengue: RELIEF ONLY

No antiviral exists. Most infections resolve over one to two weeks. For severe dengue nothing removes the virus, but careful fluid management is the difference between roughly 20 per cent mortality and under 1 per cent — supportive care that is not a cure and yet determines survival. WHO directs that pain be managed

with paracetamol and that NSAIDs such as ibuprofen, and aspirin, be avoided because of bleeding risk; severe dengue often requires hospitalisation.

Prevention.

Source reduction — emptying and covering water containers: STRONG on settled vector ecology, though community-level trial evidence of sustained effect is MODERATE, because programmes decay without maintenance.

Wolbachia-infected mosquito release: STRONG. The AWED cluster-randomised trial in Yogyakarta, Indonesia, reported a large protective effect against virologically confirmed dengue, widely cited as about 77 per cent efficacy†. **The primary paper was not retrievable, so the figure with its confidence interval is not asserted, and the widely cited figure carries a dagger.** This is the most promising dengue intervention and its effect size should be sourced.

QDenga, TAK-003: MODERATE, with important restrictions. WHO states it is available and licensed in some countries and recommended only for ages 6 to 16 in high-transmission settings. **WHO gives no efficacy figure and none is asserted.** The age and setting restriction exists because of the serostatus problem below.

Dengvaxia, CYD-TDV: CONTESTED, and now largely withdrawn. It increased severe dengue risk in seronegative recipients, confirmed after deployment in the Philippines — a vaccine that harmed those it was meant to protect. Both the protective effect in seropositive recipients and the harm in seronegative recipients are established, and both belong in any account of it. **Neither magnitude is asserted here, because neither could be confirmed to its source.** This is the reason subsequent dengue vaccines carry serostatus-dependent recommendations.

Both dengue vaccines need long chains. They are live attenuated chimeric viruses requiring cell culture, sterile fill-finish, needles and an unbroken 2–8 °C cold chain.

Personal protection — repellent, long sleeves, daytime avoidance: MODERATE. Bed nets are of limited value against a daytime biter, in contrast to malaria. Window screens: MODERATE.

Treatment.

Treatment	EML	Off-patent	Price
Oral fluids	n/a	n/a	Minimal
Paracetamol, the only recommended analgesic	Yes	Yes	Cents per course
Intravenous crystalloid, carefully titrated, for severe dengue	Yes	Yes	Low dollars
NSAIDs, aspirin	—	—	Contraindicated

There is no antiviral and no specific treatment. Platelet transfusion is not routinely indicated despite low platelet counts, and is frequently given without benefit.

Simple means. Substantial, and concentrated on the container.

Emptying, scrubbing and covering every water container around the dwelling, weekly. The vector breeds nowhere else in any quantity, so this is the single most effective measure, and it needs nothing but labour. Removing tyres, tins, bottles, blocked gutters and plant saucers; putting sand in plant trays. Covering stored water with tight lids, or adding a mesh. Keeping fish in ornamental ponds and water tanks, which eat larvae. Oral fluids, in quantity, for the ill person — the core of treatment. Paracetamol only, and specifically not aspirin or ibuprofen. Watching for the warning signs as fever falls, which is when deterioration occurs: severe abdominal pain, persistent vomiting, bleeding gums or nose, lethargy, cold clammy skin. Recognising these needs no instrument and is what prompts transfer in time.

What requires a chain: intravenous fluids for shocked patients, and vaccination. Severe dengue needs careful intravenous fluid titration — too little causes shock, too much causes fluid overload — and that requires sterile fluids, a cannula and repeated clinical assessment.

Gaps. The *Wolbachia* effect size with its confidence interval is missing and is the most important gap for dengue prevention. **No vaccine efficacy figures are published on the WHO fact sheet for QDenga and none were sourced.** Reported cases, 14.6 million, and estimated infections, 100 to 400 million, differ by a factor of about 7 to 27, so case fatality derived from reported figures is not interpretable. The two model-based estimates WHO cites are not reconciled on the page. The population-at-risk figures, about 4 billion and 5.6 billion, sit unreconciled on the same page; see the appendix, item 5. The page also prints 21 August 2025 while carrying a 2026 copyright and a June 2026 news item; see the appendix, item 6. Whether the 2024 record reflects transmission or surveillance is unresolved. Dengvaxia's serostatus-dependent harm is established but its magnitude differs between analyses, and good sources disagree on whether pre-vaccination screening makes the product usable.

> **Depth.** Starts in: the dengue virus. Size: 50 nm†; depth +0.08. First complaint: about 6.5 days ([W] 3–14 days); time depth 45.20. One untreated course: about 7 days († about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

COVID-19

What it is. A coronavirus, SARS-CoV-2, that entered the human population in late 2019 and spread worldwide. It causes respiratory illness ranging from nothing to fatal pneumonia, with risk rising steeply with age. It is now a recurring seasonal infection rather than a novel one.

Measured. WHO fact sheet, 27 November 2025. Nearly 780 million reported cases worldwide since December 2019. More than 7.1 million reported deaths, with WHO noting that actual numbers are thought to be higher. Over 13.64 billion vaccine doses administered by the end of 2024. About 6 per cent of people develop post-COVID-19 condition, long COVID.

Symptoms usually begin 3 to 6 days after exposure and last up to 10 days. Revaccination may be needed 6 to 12 months after the most recent dose for high-risk groups.

The central measurement fact of this condition is the gap between counted and estimated deaths. WHO's excess mortality analysis of 5 May 2022 gives 14.9 million excess deaths associated with the pandemic in 2020 and 2021, with a range of 13.3 to 16.6 million, against about 5.4 million reported COVID deaths for those two years. The excess figure is roughly three times the reported count for that period.

By 2023 the disease had receded in the rankings. WHO's Global Health Estimates place COVID-19 fourteenth among causes of death in 2023, at about 0.9 million. GBD 2023 places it twentieth, having been the leading age-standardised cause of death in 2021, and gives 797,600 deaths (95 per cent UI 722,900–857,000) and 12.5 million YLDs (95 per cent UI 5.33–25.7), ranking it twenty-first among YLD causes. The two agencies disagree on rank — fourteenth against twentieth — from different cause hierarchies.

Where it starts. SARS-CoV-2, transmitted by respiratory aerosols and droplets, with airborne transmission in indoor spaces established after initial dispute. Risk factors for severe disease: older age, being unvaccinated, and underlying conditions — diabetes, heart, lung, liver and kidney disease, obesity, cancer, dementia, immunosuppression including HIV. Pregnancy and health-care work are also listed. The age gradient in mortality is steep and is the dominant risk factor.

Not known: the origin of SARS-CoV-2 is genuinely unresolved. Zoonotic spillover and a laboratory-associated origin are both held by serious scientists, intelligence assessments differ, and no consensus exists. The mechanism of long COVID is not established, and candidate explanations — viral persistence, autoimmunity, microclotting, reactivated herpesviruses, dysautonomia — are all under investigation without resolution; the 6 per cent figure rests on varying case definitions. Why children were largely spared severe acute disease is not fully explained.

Cure status. Split.

most infections: SELF-LIMITING severe disease: RELIEF ONLY long COVID: RELIEF ONLY

Most infections resolve over about ten days. In severe disease antivirals given early reduce progression, and dexamethasone and oxygen reduce death in the hypoxic, but nothing removes the established lung injury. The RECOVERY trial established that dexamethasone reduces mortality in patients requiring oxygen or ventilation, while showing no benefit and possible harm in those not requiring oxygen. For long COVID no treatment removes it and no agent has established efficacy; management is symptomatic and rehabilitative.

Prevention.

Vaccination: STRONG against severe disease and death; weaker and waning against infection. The original mRNA trials reported about 95 per cent efficacy against symptomatic disease, but that figure applies to the ancestral strain in 2020 and does not describe current protection against current variants. Protection against severe disease has proved durable; protection against infection wanes within months. WHO gives no efficacy figure and recommends revaccination every 6 to 12 months for high-risk groups. **No single efficacy number is quotable for this condition now**, and presenting the 2020 trial figure as current protection would be wrong.

The chains are long and differ by platform, and this chapter's coldest requirement sits here. mRNA vaccines require nucleotide synthesis, enzymatic transcription, lipid nanoparticle formulation by controlled mixing, sterile fill-finish and, for some, an ultra-cold chain at −70 °C — the most demanding cold chain of any product in this chapter except Ervebo. Viral vector vaccines require mammalian cell culture. Inactivated vaccines require large-scale virus culture under high containment. Protein subunit vaccines have the lowest chain burden of the group. None is producible by simple means, and the mRNA cold chain was a decisive constraint on equitable distribution.

Ventilation of indoor spaces: STRONG, on aerosol physics.

Masks, meaning respirators: CONTESTED. Good sources disagree, and the disagreement is not resolvable by picking one. Mechanistic and observational evidence supports filtration efficacy for well-fitted respirators. The Cochrane review of randomised trials of mask *mandates and promotion* in community settings found no clear effect on respiratory illness. Both findings are real and they answer different questions: the filtration capacity of a device, against the population effect of asking people to wear one. **No single effect size is asserted for either.**

Isolation of cases: MODERATE, limited by presymptomatic transmission. Distancing and crowd avoidance: MODERATE.

Treatment.

Treatment	EML	Off-patent	Price
Dexamethasone, hypoxic patients only	Yes	Yes	UNICEF indicative about 24 US cents per 4 mg tablet, October 2026 — the most cost-effective treatment established in the pandemic
Oxygen	Yes	n/a	Variable; the principal requirement
Nirmatrelvir/ritonavir, early and high-risk	Yes	Ritonavir yes; nirmatrelvir no	High-income price around US$500–1,400 per course; generic licences exist for low-income countries; no verified price
Remdesivir	Yes	No	Several hundred US dollars per course
Tocilizumab, severe disease, with steroids	Yes	Biosimilars available	Hundreds of US dollars
Anticoagulation, selected inpatients	Yes	Yes	Low

Dexamethasone and oxygen are the two interventions that reduced mortality at scale, and both are cheap and off-patent. Nirmatrelvir/ritonavir must be started early to work, which in practice limits its use.

Simple means. Opening windows. Ventilation is the principal non-pharmaceutical measure and requires nothing. Moving gatherings outdoors. Rest, fluids and paracetamol, which is the actual management of most cases. Isolating the ill person from the elderly and the chronically ill in the household. Prone positioning of the breathless patient — awake proning — which improves oxygenation and requires only

turning the person, and is one of the few genuinely supply-chain-free interventions discovered during the pandemic. Counting breaths and watching lips and nails for colour change, to recognise deterioration.

What requires a chain: oxygen, dexamethasone, antivirals and vaccines. Oxygen was the binding constraint on survival in most of the world, and it cannot be improvised. The oxygen shortages of 2021 killed people for whom no simple substitute existed. The minimum chain is a pressure-swing-adsorption plant or concentrators plus uninterrupted electricity, or cylinder logistics.

Gaps. Reported deaths of 7.1 million against 14.9 million excess deaths for 2020 and 2021 alone differ by a factor WHO acknowledges but does not resolve; the true toll is not known. **No current vaccine efficacy figure is quotable**; the widely remembered 95 per cent describes a strain and a population that no longer exist. **Masks are genuinely contested** between mechanistic and observational evidence on one side and randomised-trial evidence on the other; both positions are printed above and neither effect size is asserted. **The origin of the virus is unresolved** and good sources disagree. On long COVID, the 6 per cent prevalence figure depends on case definition, which varies widely between studies, and no mechanism and no treatment are established. WHO and GBD place COVID-19 at different ranks for 2023, fourteenth against twentieth, from different cause hierarchies. The fact sheet is dated 27 November 2025 and reports doses to end-2024; case and death reporting has largely ceased in most countries, so the figures are no longer updated meaningfully.

> **Depth.** Starts in: SARS-CoV-2. Size: 100 nm†; depth +0.72. First complaint: about 5.3 days ([W] 2–14 days); time depth 45.02. One untreated course: about 10 days († 1–2 weeks); depth 45.59.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Pertussis (whooping cough)

What it is. A bacterial infection of the airway lining, *Bordetella pertussis*, causing weeks of violent coughing fits. In infants it causes apnoea rather than the classic whoop, and that is how it kills. Immunity from vaccination and from infection both wane.

Measured. The WHO pertussis fact sheet could not be retrieved. The URL returned only navigation, the corrected URL returned a client error, and the web search budget was exhausted before an alternative primary source could be reached. The 19 October 2026 retrieval pass did not close it.

Global cases. Global deaths. Case fatality. No pertussis-specific burden figure is asserted.

What exists, from retrieved sources. DTP3 coverage was 85 per cent of infants globally in 2025, about 110 million infants. About 15 per cent, nearly 20 million, had no or incomplete coverage. Of that nearly 20 million, about 6 million were partially vaccinated and 13.5 million were zero-dose children who received no vaccination at all; about 53 per cent of the un- and under-vaccinated live in ten countries. Pertussis vaccination is listed by WHO as pneumonia prevention.

Age pattern, established clinically rather than from a retrieved figure: deaths concentrate overwhelmingly in infants under six months, particularly under three months, who are too young to have completed the primary series.

Where it starts. *B. pertussis*, transmitted by respiratory droplets, highly infectious. The risk structure is infancy before completion of the primary series; waning immunity in older children and adults, who then transmit to infants; and absence of maternal immunisation. The established transmission pattern is that adults and adolescents with mild or unrecognised disease infect newborns.

Not known: why acellular vaccines protect against disease but less well against infection and transmission than whole-cell vaccines. The finding is genuine and consequential — baboon studies show vaccinated animals can carry and transmit — and its implications for herd immunity are not fully resolved. The resurgence of pertussis in countries using acellular vaccines is attributed variously to faster waning, reduced transmission-blocking, pathogen adaptation through pertactin-deficient strains, and better

diagnosis; good sources weight these differently. The duration of protection is not precisely established for either vaccine type.

Cure status. SELF-LIMITING, over weeks.

Macrolides eradicate *B. pertussis* from the nasopharynx and end infectiousness, which is their main value. They do not shorten the cough unless given in the first week or two, before the paroxysmal stage, and most patients present after that. So the organism is removable while the illness, once established, runs its course over weeks regardless, with the cough persisting up to three months. For infants, management is supportive: oxygen, feeding support, and monitoring for apnoea.

Prevention.

Primary infant immunisation, DTP or DTaP: STRONG. WHO recommends three primary doses from six weeks of age, and coverage was 85 per cent in 2025. **Precise efficacy figures with confidence intervals are not asserted**, because the WHO pertussis fact sheet could not be retrieved; acellular and whole-cell vaccines differ and should be reported separately when the source is consulted.

Maternal immunisation in pregnancy: STRONG. This is the single most effective measure for preventing infant deaths, because it protects the infant in the first months before their own doses take effect, via transplacental antibody. Observational studies report high effectiveness against infant hospitalisation and death. **No figure with a confidence interval is asserted.**

Booster doses in childhood and adolescence: STRONG, given waning immunity. Cocooning, meaning vaccinating household contacts of newborns: MODERATE. Post-exposure macrolide prophylaxis for close contacts of infants: MODERATE.

Whole-cell against acellular vaccine: CONTESTED. Whole-cell vaccines give longer-lasting protection and better transmission-blocking. Acellular vaccines have markedly fewer adverse effects, which is why high-income countries switched. Both positions are evidence-based and the trade-off is real: the switch reduced reactogenicity and is implicated in resurgence. Most low- and middle-income countries continue to use whole-cell vaccine, and WHO does not recommend switching. **Neither the protection differential nor the reactogenicity differential is asserted as a figure here.**

The chain is long for both, and markedly shorter for whole-cell. Whole-cell vaccine requires bacterial fermentation, inactivation and adjuvanting — a comparatively low technological threshold, achievable in many middle-income countries. Acellular vaccine requires purification of individual antigens — pertussis toxin, filamentous haemagglutinin, pertactin — chemical detoxification and precise formulation, which is substantially more complex and expensive. Both need sterile fill-finish, a needle and an unbroken 2–8 °C cold chain, and both are normally delivered combined with diphtheria and tetanus toxoids.

Treatment.

Treatment	EML	Off-patent	Price
Azithromycin, first line	Yes, 6.2.2 Watch group	Yes	UNICEF indicative about 9.3 US cents a 250 mg tablet, October 2026
Erythromycin	Yes	Yes	Cents to low dollars
Co-trimoxazole, alternative	Yes	Yes	Cents per course
Oxygen and feeding support, infants	Yes, oxygen	n/a	Variable
DTP-containing vaccine	Yes	Yes	Low; no verified unit price

Cough medicines, bronchodilators and corticosteroids do not help pertussis — a well-established negative.

Simple means. Keeping newborns away from anyone with a persistent cough, including adults who think they merely have a cold. Since adults are the usual source of infant infection, this single decision prevents infant deaths. Recognising the pattern: coughing fits ending in vomiting; a cough lasting more than two weeks; and in infants, pauses in breathing and going blue rather than whooping — apnoea is the lethal sign and it is observable without instruments. Small frequent feeds between coughing fits, and holding the infant upright. Keeping the air free of smoke and irritants. Isolating the case for the first days of antibiotic

treatment, or for about three weeks without treatment. Patience: the cough lasts weeks to months and nothing shortens it.

Prevention of infant death ultimately requires vaccination, of the mother in pregnancy and of the infant from six weeks, and that requires an industrial chain — bacterial fermentation at minimum for whole-cell vaccine, plus sterile fill-finish and cold chain. Simple means can reduce an infant's exposure but cannot substitute for maternal immunisation. The severely affected infant needs oxygen and sometimes ventilation, which cannot be improvised.

Gaps. This entry lacks burden figures entirely : the WHO pertussis fact sheet was not retrievable and the search budget was exhausted. Global case and death estimates, and vaccine efficacy with confidence intervals for both acellular and whole-cell products, are the additions this entry needs. The acellular-against-whole-cell question is genuinely contested and has direct policy consequences. Pertussis surveillance is poor: the disease is under-diagnosed in adults, and case counts largely reflect testing intensity. Whether resurgence reflects vaccine properties, pathogen adaptation or better detection is unresolved. Maternal immunisation effectiveness figures are observational, not trial-based.

> **Depth.** Starts in: Bordetella pertussis. Size: 1 µm†; depth +2.81. First complaint: about 10 days ([W] 7–14 days); time depth 45.59. One untreated course: about 7.7 weeks ([B] weeks of coughing; † 6–10 weeks); depth 47.13.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Tetanus (including neonatal tetanus)

What it is. *Clostridium tetani* spores live in soil and dust and enter through wounds. The bacterium does not spread through the body; its toxin does, locking muscles into spasm so the jaw clamps and the back arches. In newborns it follows infection of the cut umbilical stump.

Measured. WHO fact sheet on tetanus, 15 July 2026. Neonatal tetanus deaths: just over 7,700 newborns in 2021, down from an estimated 46,898 in 2000, an 84 per cent reduction. 85 per cent of infants worldwide received three doses of DTP-containing vaccine in 2025. Eight countries had yet to achieve maternal and neonatal tetanus elimination as of July 2026; the source does not name them.

The elimination threshold is fewer than one neonatal tetanus case per 1,000 live births in every district.

Timing: incubation 3 to 21 days, with most cases within 14 days. Neonatal tetanus occurs within the first 28 days of life, and the confirmed case definition is normal suckling and crying for the first two days, then loss of that ability between days 3 and 28. Maternal tetanus occurs during pregnancy or within six weeks of its end.

All-age cases. All-age deaths. Case fatality. WHO gives none of these on the fact sheet. This entry therefore has neonatal figures only.

Where it starts. *C. tetani* spores entering a wound, germinating in low-oxygen tissue, and releasing tetanospasmin. Risk factors: deep or dirty wounds, puncture wounds, burns, unclean delivery and unclean cord care, unsafe injection, and absence of maternal or individual immunisation.

Tetanus is not transmissible between people. It is an environmental infection, which is why it cannot be eliminated by herd immunity and why every individual must be vaccinated.

Not known: very little about causation is unresolved; this is among the best-understood conditions in the chapter. The open questions are therapeutic. The optimal dose and route of antitoxin, and the management of autonomic instability in severe tetanus, are not settled. Why some patients develop catastrophic autonomic dysfunction is not well explained.

Cure status. SELF-LIMITING in those who survive the spasm phase. Survival of the spasm phase depends on airway control and ventilation. The label does not mean that the patient needs no treatment. Once toxin is bound to nerve endings nothing removes it. Antitoxin neutralises only circulating, unbound toxin, so it prevents worsening but cannot reverse what has bound. Recovery occurs as nerve terminals regenerate over

weeks. Treatment is therefore to neutralise free toxin, remove the source, control spasms, and support breathing until the toxin's effect wears off.

The label rests on the course of the illness. The body completes it, and survivors recover completely without sequelae. What treatment changes is whether the patient survives the spasm phase. Case fatality without intensive care is very high, particularly in neonates, and falls substantially where ventilation is available. **WHO publishes no case fatality figure.**

Prevention.

Tetanus toxoid vaccination: STRONG — one of the most reliable vaccines in existence. WHO specifies six doses for lifelong protection, three primary and three boosters. The primary series can start at six weeks with at least four weeks between doses. Boosters fall at 12–23 months, 4–7 years and 9–15 years, with a recommended minimum four-year gap between them. **WHO publishes no efficacy percentage with a confidence interval on the fact sheet, and none is asserted.** The historical trial evidence is unusually strong and tetanus toxoid is generally regarded as near-fully protective when the series is complete.

Maternal immunisation: STRONG. Vaccinating the mother protects the newborn through transplacental antibody and is the basis of the 84 per cent reduction in neonatal deaths since 2000.

Clean delivery and clean cord care: STRONG. Together with maternal immunisation this is the whole of neonatal tetanus prevention.

Wound cleaning and debridement: STRONG on settled physiology. Removing devitalised, low-oxygen tissue removes the conditions the organism requires.

Post-exposure prophylaxis, toxoid with or without immunoglobulin according to wound type and vaccination history: STRONG.

The chain is long, and it is the lowest of any vaccine in this chapter. Tetanus toxoid is made by culturing *C. tetani*, harvesting the toxin, inactivating it with formaldehyde, and adsorbing it onto aluminium salt. That is bacterial fermentation plus chemical inactivation — a nineteenth-century-adjacent technology, produced cheaply in many low- and middle-income countries. It is heat-stable enough to tolerate brief cold-chain breaks better than measles or mRNA vaccines, so it sits on the forgiving side of the cold-chain dividing line. It still requires sterile fill-finish and a needle, and it cannot be made outside a pharmaceutical facility.

Treatment.

Treatment	EML	Off-patent	Price
Tetanus toxoid vaccine	Yes	Yes	Cents per dose; among the cheapest vaccines; no verified price
Tetanus immunoglobulin (human) or antitoxin	Yes	Yes	Higher; requires plasma fractionation
Metronidazole, to eradicate the organism	Yes	Yes	Cents per course
Diazepam or midazolam, spasm control	Yes	Yes	Cents to low dollars
Magnesium sulfate, spasm and autonomic control	Yes, 5.1.1 Antiseizure medicines, core — but listed for severe pre-eclampsia and eclampsia, with the restrictive note "not for other convulsant disorders"	Yes	UNICEF indicative US$33.11 per 100 ampoules of 5 g in 10 mL, October 2026, about 33 US cents an ampoule
Mechanical ventilation with neuromuscular blockade, severe disease	n/a	n/a	High; intensive care required
Wound debridement	n/a	n/a	Surgical, but basic

Note the EML qualification on magnesium sulfate: it is a listed medicine, but its listed indication is eclampsia and severe pre-eclampsia, and the 24th List carries an explicit note excluding other convulsant disorders. Its use in tetanus is outside that listing.

Ventilation is what determines survival in severe tetanus. No drug substitutes for it.

Simple means. Prevention is largely achievable. Treatment is not.

Clean cord cutting: a new or boiled blade, a clean tie, and the stump left dry, clean and uncovered. Applying nothing to the umbilical stump — no cow dung, ash, oil, mud or herbal paste. These practices are a direct and established cause of neonatal tetanus, and stopping them requires no resource at all. That is the highest-value simple intervention in this entry. Washing hands before delivery and before handling the newborn. A clean delivery surface. Wound care: washing wounds with clean water and soap, removing dirt and dead tissue, and leaving them open to the air rather than sealing deep puncture wounds. Not using contaminated instruments for piercing, circumcision or injection; boiling or flaming what must be reused. Keeping the patient in a dark, quiet room and minimising touch, since light, noise and handling trigger spasms — genuine symptomatic care requiring nothing.

Once tetanus is established, simple means cannot save a patient with respiratory spasm. The minimum chain is antitoxin, which means plasma fractionation; benzodiazepines or magnesium; and above all mechanical ventilation with reliable power and trained staff. A neonate with tetanus in a setting without a ventilator will usually die, and nothing available locally changes that. That is why the entire effort sits in maternal immunisation and the clean cord.

Gaps. WHO publishes no all-age case or death count, no case fatality rate, and no vaccine efficacy figure on the tetanus fact sheet. The eight countries yet to achieve elimination are not named in the source. Neonatal tetanus deaths are reported for 2021 while vaccine coverage is reported for 2025, so the figures are not contemporaneous. Neonatal tetanus is substantially under-reported, because deaths occur at home in exactly the settings without surveillance, so the 7,700 figure is a floor. Optimal antitoxin dose and route, and the management of autonomic instability, are not settled.

> **Depth.** Starts in: Clostridium tetani. Size: 4 µm†; depth +4.07. First complaint: about 12 days ([W] 7–21 days); time depth 45.77. One untreated course: about 3.5 weeks († 3–4 weeks); depth 46.40.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Diphtheria

What it is. *Corynebacterium diphtheriae* grows in the throat and produces a toxin that forms a grey membrane which can obstruct breathing. The toxin also damages heart muscle and nerves. It returns wherever immunisation programmes break down.

Measured. WHO fact sheet on diphtheria, 15 July 2026. Without proper treatment, diphtheria is fatal in around 30 per cent of unvaccinated cases, and children under five are at greater risk of dying.

Global cases. Global deaths. WHO gives neither on the fact sheet — a notable absence for a vaccine-preventable disease with 30 per cent untreated fatality.

Coverage in 2025: about 85 per cent of infants, 110 million, received the recommended three doses; about 15 per cent, nearly 20 million, had no or incomplete coverage. 83 countries have all three WHO-recommended booster doses in their national programmes, and 42 countries have no boosters.

No WHO region is completely free of diphtheria. Outbreaks were noted in Guinea and Nigeria in 2023, and prevention work in Rohingya refugee camps in Bangladesh in 2017.

Symptoms usually begin 2 to 5 days after exposure, and a grey coating may form in the respiratory tract within 2 to 3 days.

Where it starts. Toxigenic *C. diphtheriae*, and occasionally *C. ulcerans*, transmitted by respiratory droplets and by contact with skin lesions. The risk structure is absence or lapse of immunisation, crowding, displacement and camp settings, and waning adult immunity where boosters are absent — which is why 42 countries without booster programmes are a structural vulnerability. The toxin, not the organism's spread, causes the damage.

Not known: that toxin production requires a bacteriophage carrying the *tox* gene is understood mechanistically, but what governs the circulation of toxigenic against non-toxigenic strains in a population is not epidemiologically predictive. The duration of vaccine-induced protection in adults, and therefore the necessity and timing of boosters, is not precisely established — which is reflected in the fact that 42 countries use none. Antitoxin dosing rests on century-old empirical practice rather than on modern trials.

Cure status. Split by timing, on the same mechanism as tetanus.

treated early with antitoxin plus antibiotics: CURABLE toxin already bound: RELIEF ONLY

Antitoxin neutralises only unbound toxin. Once the toxin has entered heart and nerve cells nothing removes it, and myocarditis and neuropathy run their course. Treated early, full recovery is usual. Treated late, case fatality rises sharply with delay.

Antibiotics — penicillin or erythromycin — eradicate the organism, stop toxin production and end infectiousness, but do not neutralise toxin already released. Timing is the determinant, and the 30 per cent untreated fatality reflects what happens without antitoxin.

Prevention.

Diphtheria toxoid vaccination: STRONG. WHO states that combination diphtheria vaccines prevented more than 90 per cent of cases between 1980 and 2000. That is a programme-level effectiveness estimate, not a trial efficacy, and WHO states no confidence interval. The schedule is three primary doses in infancy plus three boosters in childhood and adolescence.

Booster doses: STRONG, and their absence in 42 countries is the identified weak point.

Maintaining coverage during conflict and displacement: STRONG, given that outbreaks follow programme collapse. Antibiotic prophylaxis and vaccination of close contacts: STRONG. Case isolation until no longer infectious: STRONG.

The chain is long but among the lowest in this chapter, comparable to tetanus. Diphtheria toxoid is made by culturing *C. diphtheriae*, harvesting toxin, inactivating it with formaldehyde and adsorbing it onto aluminium salt — bacterial fermentation plus chemical inactivation, normally formulated with tetanus toxoid and pertussis as DTP. It is cheap, widely manufactured and relatively heat-tolerant, so like tetanus toxoid it sits on the forgiving side of the cold-chain line. It requires sterile fill-finish, a needle and a cold chain, and it is not producible by simple means.

Antitoxin supply is a separate and serious problem, and it is a different kind of problem from the vaccine. Diphtheria antitoxin is equine serum, produced by immunising horses and fractionating their plasma. Global supply is small, few manufacturers remain, and shortages are recurrent. The specific treatment for the disease is the least secure item in this chapter's supply picture.

Treatment.

Treatment	EML	Off-patent	Price
Diphtheria antitoxin (equine)	Yes	Yes	Scarce; global supply constrained, few manufacturers; no reliable market price
Benzylpenicillin or procaine penicillin	Yes	Yes	Cents per course
Erythromycin	Yes	Yes	Cents to low dollars per course
DTP-containing vaccine	Yes	Yes	Low; no verified unit price
Airway management, intubation or tracheostomy	n/a	n/a	Requires surgical capability

WHO gives no antitoxin dosage figures on the fact sheet. Antitoxin scarcity, not cost, is the binding constraint.

Simple means. Recognising it: a sore throat with a grey-white membrane that bleeds when scraped, a swollen neck — "bull neck" — hoarseness and stridor in a child. Recognition needs only a light and a look, and it is what triggers the search for antitoxin. Isolating the case and keeping them from other children. Keeping the airway clear; sitting the child upright; not attempting to scrape the membrane, which causes bleeding. Watching for stridor and breathing difficulty, which signal imminent obstruction. Moving the

patient toward antitoxin immediately — the decision that determines survival. Handwashing and covering coughs.

Nothing simple treats diphtheria. The minimum chain is equine antitoxin — horses, immunisation, plasma collection, fractionation and an existing manufacturer — plus antibiotics, plus the surgical ability to secure an obstructed airway. Antitoxin cannot be improvised, and unlike many items in this chapter it cannot readily be substituted or scaled up quickly, because the manufacturing base has contracted. A child with obstructive diphtheria and no antitoxin and no airway capability will often die.

Gaps. WHO publishes no global case or death count. The "more than 90 per cent of cases prevented, 1980–2000" figure is a programme-level estimate without a confidence interval, and it is now a quarter-century old. The duration of adult immunity is not established, which is why 42 countries omit boosters and 83 include them — a genuine policy divergence from the same evidence base. **Antitoxin supply is fragile and unquantified in the source**; no figures on global production or stockpiles are published. Antitoxin dosing practice predates modern trial methods.

> **Depth.** Starts in: Corynebacterium diphtheriae. Size: 3 µm†; depth +3.81. First complaint: about 3.2 days ([L] 2–5 days); time depth 44.55. One untreated course: about 10 days († 1–2 weeks); depth 45.59.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names an early stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Rabies

What it is. A virus transmitted in the saliva of infected mammals, almost always dogs. It travels up nerves to the brain over weeks to months. Once symptoms appear it is essentially always fatal and there is no treatment. It is also entirely preventable after exposure.

Measured. WHO fact sheet on rabies, 17 September 2026. The page gives the death figure two ways. Key Facts says only "tens of thousands" annually. The body gives 44,203, from the 2021 Global Health Estimates model. WHO notes that the true number is likely substantially underreported. The appendix of single-source contradictions carries this page as item 7, because the same hedging pattern runs through three of its headline figures.

Fatality once clinical symptoms appear: 100 per cent in Key Facts, "virtually 100 per cent" in the body.

Dogs cause 99 per cent of human cases in Key Facts, "up to 99 per cent" in the body.

40 per cent of deaths are in children under 15, a figure in Key Facts that the body nowhere supports; the body says only that children aged 5 to 14 are frequent victims.

Geography: mainly Asia and Africa, and present on all continents except Antarctica. Dog-mediated rabies is largely controlled in the Americas, where haematophagous bats are now the primary source of human rabies. Dog-mediated human rabies elimination is validated in three countries — Bhutan, Chile and Mexico — and 17 countries have self-declared freedom from rabies virus infection to WOAH.

Over 29 million people receive human rabies vaccine annually, and three WHO-prequalified human rabies vaccines existed as of 2024.

Costs: about US$8.6 billion a year globally; average post-exposure prophylaxis cost US$108, as of 2018, excluding travel and lost income, while affected people often earn US$1–2 a day. Intradermal administration reduces costs by 60 to 80 per cent.

Incubation is typically 2 to 3 months, with a range of one week to one year. Paralytic rabies accounts for about 20 per cent of human cases.

Where it starts. Lyssavirus in saliva, entering through a bite, scratch or mucous-membrane contact, then travelling along peripheral nerves to the central nervous system. The long and variable incubation is established, and it is precisely what makes post-exposure prophylaxis possible: there is a window between

exposure and the virus reaching the brain. The risk structure is dog bites, up to 99 per cent; children, who are shorter, take more bites to head and hands, and are less likely to report; and absence of dog vaccination.

Not known: what determines the incubation period, which ranges from a week to a year, is not explained. Why a few people have survived symptomatic rabies — a handful of documented cases — is unexplained, and the Milwaukee protocol derived from one such case has not been reproducible. It is not an established treatment. Whether abortive, subclinical rabies infection occurs in humans is suggested by serosurveys and contested.

Cure status. The starkest split in this chapter.

after exposure, before symptoms: CURABLE once symptomatic: RELIEF ONLY — death near-certain

Prompt wound washing, vaccine and, for severe exposures, rabies immunoglobulin prevent the disease reliably. WHO states that post-exposure prophylaxis prevents the virus reaching the central nervous system, and gives no failure-rate figure; failures are almost always attributable to delayed or incorrect administration. Once clinical symptoms appear, care is palliative — sedation and analgesia — no treatment exists, and the Milwaukee protocol is not established therapy.

Prevention.

Mass dog vaccination: STRONG — the only measure that eliminates human rabies at source. **WHO does not state the coverage threshold on the fact sheet. The widely used figure of 70 per cent† of the dog population could not be confirmed from the retrieved page, and carries a dagger.** The evidence that it works is the elimination record: three countries validated, and the near-disappearance of dog-mediated rabies from the Americas.

Post-exposure prophylaxis: STRONG. Over 29 million people receive it annually.

Immediate wound washing: STRONG, on settled physiology. WHO recommends washing with water and soap for at least 15 minutes. **WHO gives no numerical effect estimate**; the mechanism — mechanical and detergent removal of virus from the inoculation site — is physiologically settled, and historical animal data show substantial risk reduction from washing alone.

Pre-exposure prophylaxis: STRONG for those at occupational or travel risk.

Keeping children away from unknown dogs, and teaching them to report every bite and scratch: MODERATE, given that 40 per cent of deaths are in children and that under-reporting by children is a known failure.

Both products need long chains. Human rabies vaccine is grown in cell culture — Vero cells or chick embryo fibroblasts — inactivated, purified, sterile-filled and cold-chained at 2–8 °C. Rabies immunoglobulin is either human plasma-derived, requiring plasma collection and fractionation, or equine. Monoclonal antibody replacements are now available and reduce dependence on plasma supply. Neither vaccine nor immunoglobulin can be produced by simple means.

One access measure is worth isolating. Intradermal administration — giving a fraction of the intramuscular dose into the skin — stretches the same vial across several patients and cuts cost by 60 to 80 per cent. That is a delivery innovation rather than a manufacturing one, and it is the single most important access measure in this entry.

Treatment.

Treatment	EML	Off-patent	Price
Rabies vaccine, post-exposure prophylaxis	Yes	Yes	Part of an average PEP cost of US$108, 2018; the intradermal route cuts cost by 60–80 per cent
Rabies immunoglobulin, severe exposures	Yes	Yes, plasma-derived	The expensive component of PEP; frequently unavailable
Monoclonal antibody, immunoglobulin substitute	Recently included	No	Variable; intended to be cheaper than the plasma product
Wound washing with soap and water	n/a	n/a	Essentially free

Treatment	EML	Off-patent	Price
Palliative sedation, symptomatic rabies	Yes	Yes	Cents

For symptomatic rabies there is no treatment. The entire therapeutic effort is prophylactic.

Simple means. This condition has one outstanding simple intervention and one hard limit. Washing the wound with soap and water for at least 15 minutes, immediately. This is free, requires nothing but water and soap, is explicitly WHO-recommended, and substantially reduces the risk of infection taking hold. It is the most important thing any person can do after a bite, anywhere, and it must happen within minutes to hours — not after travelling to a clinic. Flushing the wound under running water, and not suturing it closed. Reporting and seeking vaccine regardless, because washing reduces but does not eliminate risk. Teaching children to report every dog bite and scratch, which costs nothing and addresses the 40 per cent of deaths in under-fifteens. Confining and observing the biting animal for ten days where possible, which can spare unnecessary prophylaxis. Community dog population management: confining and caring for owned dogs, reducing free-roaming dog numbers, removing the food waste that sustains them.

The hard limit is absolute. No simple means prevents rabies once the virus has established, and nothing treats symptomatic disease. The minimum chain is cell-culture vaccine plus cold chain plus a clinician able to administer it, ideally intradermally, and for severe exposures immunoglobulin or a monoclonal antibody. A child bitten on the face in a village a week from a vaccine supply will probably die, and washing the wound — while genuinely worth doing — is not reliably sufficient for severe head and neck exposures.

Gaps. WHO does not state the dog vaccination coverage threshold; the commonly used 70 per cent figure is not asserted here. **WHO gives no numerical post-exposure prophylaxis effectiveness figure and no numerical effect estimate for wound washing**, despite both being central recommendations. Deaths are substantially under-reported, as WHO itself states; 44,203 is a modelled floor and the Key Facts section retreats to “tens of thousands”. The cost figure is from 2018. The handful of survival reports and the Milwaukee protocol are not reproducible and should not be presented as treatment. Whether human abortive infection occurs is contested. Three of the page’s headline figures are stated flatly in Key Facts and hedged in the body; see the appendix, item 7.

> **Depth.** Starts in: the rabies virus (its length). Size: 180 nm†; depth +1.25. First complaint: about 7.4 weeks ([W] 1–3 months; [B] a week to a year); time depth 47.10. One untreated course: about 4.5 days († 2–10 days after the first complaints); depth 44.86.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names an early stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Schistosomiasis

What it is. Blood flukes whose larvae emerge from freshwater snails and penetrate skin during contact with infested water. Adult worms live in blood vessels around the bladder or bowel for years, and their eggs cause chronic inflammation, scarring, bleeding and bladder cancer.

Measured. WHO fact sheet on schistosomiasis, 23 February 2026. At least 253.7 million people required preventive treatment in 2024, and more than 100.5 million were reported treated — a global coverage of 39.6 per cent. Among school-aged children requiring preventive chemotherapy, 61.7 per cent were treated.

39.6 per cent of 253.7 million is about 100.47 million, so the “more than 100.5 million” headline is a derived and rounded value that the body does not independently confirm. The figures are consistent.

At least 93.9 per cent of those requiring treatment live in Africa. Estimated deaths: 14,353 a year, which WHO itself says is likely an underestimate.

WHO gives no figure for the number currently infected — only the number requiring treatment, which is a programmatic denominator.

Transmission is reported from 79 countries, and preventive chemotherapy is needed in 50 endemic countries with moderate-to-high transmission. Sub-Saharan campaigns over the past ten years reduced school-aged prevalence by almost 60 per cent.

Species and geography: *S. mansoni* in Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname; *S. haematobium* in Africa, the Middle East and Corsica; *S. japonicum* in China, Indonesia and the Philippines; *S. mekongi* in Cambodia and Lao PDR; *S. guineensis* and *S. intercalatum* in the central African rainforest. Human–animal hybrids are reported in many sub-Saharan countries, and the 2013 Corsica outbreak was linked to them.

Where it starts. Cercariae released by freshwater snails penetrating intact skin during contact with infested water — wading, washing, fishing, swimming, irrigation work. The risk structure is occupational and domestic water contact; children playing in water carry the highest intensity; and absence of safe water supply and sanitation, since human urine and faeces complete the cycle.

Dams and irrigation schemes reliably increase transmission by creating snail habitat. This is an established and repeatedly documented effect of water development projects.

Not known: the contribution of animal reservoirs and hybrid schistosomes to human transmission is an active and unresolved question, with implications for whether elimination is achievable by treating people alone. Whether *S. haematobium*'s association with bladder cancer is causal in the strict sense is well supported, but the mechanism is not fully established. The determinants of individual morbidity at a given worm burden are not known. Praziquantel's mechanism of action is still not fully elucidated, and it does not kill immature worms — which is why single-dose treatment fails in some people and why re-treatment is needed.

Cure status. Split.

the infection: CURABLE established bladder, liver and portal fibrosis: RELIEF ONLY

A single oral dose of praziquantel kills adult worms and clears infection in the large majority. The cure is cheap, single-dose and off-patent. Two qualifications: praziquantel does not kill immature schistosomes, so people in active transmission need re-treatment; and established organ damage — bladder fibrosis, liver fibrosis, portal hypertension — is not reversed by killing the worms.

Prevention.

Mass preventive chemotherapy with praziquantel: STRONG. Sub-Saharan campaigns reduced school-aged prevalence by almost 60 per cent over ten years. This is the principal intervention, and coverage is 39.6 per cent overall and 61.7 per cent in school-aged children.

Safe water supply: STRONG, on settled transmission physiology. The parasite requires skin contact with infested freshwater, so an alternative water source removes exposure.

Sanitation: STRONG, as human excreta complete the life cycle.

Snail control, by molluscicides or habitat modification: MODERATE, but logistically demanding and now less emphasised than chemotherapy.

Health education to reduce water contact: WEAK where no alternative water source exists. People cannot avoid water they depend on.

Avoiding new transmission from dam and irrigation projects: STRONG in principle, by design and by accompanying control measures; routinely neglected in practice.

No vaccine is licensed. Candidates are in trials.

Treatment.

Treatment	EML	Off-patent	Price
Praziquantel, single oral dose	Yes, 6.1.1 Intestinal anthelminthics core, 6.1.3 Antischistosomals core, 6.1.4 Cysticidal complementary; tablets 150 and 500 mg, scored 600	Yes	WHO describes it only as "effective, safe and low-cost" and gives no numerical price. Merck KGaA has pledged

Treatment	EML	Off-patent	Price
	mg		supply sufficient to treat more than 100 million school-aged children a year through donation. **No per-tablet price was retrievable**
Paediatric formulation, arpraziquantel	Recently developed for under-sixes	No	Developed by the Pediatric Praziquantel Consortium; price not confirmed
Surgery for advanced complications	n/a	n/a	Variable

Praziquantel is one of the clearest cases in this chapter of a cheap, single-dose, off-patent cure that is nonetheless reaching under 40 per cent of those who need it. That is a distribution failure, not a pharmaceutical one.

Simple means. Substantial for prevention, nothing for cure.

Not entering infested freshwater, where any alternative exists, which is the whole of exposure avoidance. Drawing water and using it on land rather than washing and bathing in the water body. Boiling or storing water for 48 hours before use: cercariae survive only around 48 hours after leaving the snail and die in stored or heated water, which makes this a genuinely effective zero-chain measure. Towel-drying vigorously and immediately after unavoidable water contact, which removes cercariae still penetrating the skin — partial, but free. Using latrines, keeping urine and faeces out of water bodies, which breaks the cycle at the human end. Clearing vegetation at water-contact points, reducing snail habitat at the places people actually use. Siting water-collection points and washing slabs away from snail habitat.

Prevention is largely achievable without any industrial chain. Cure is not: praziquantel requires pharmaceutical synthesis, and there is no plant preparation or simple remedy that kills schistosomes. But the chain is among the shortest in this book: praziquantel manufacture plus periodic mass distribution, with no cold chain, no needles and no clinician. That is precisely why 39.6 per cent coverage is a logistical and funding failure rather than a technical limit.

Gaps. WHO publishes no figure for the number of people currently infected — only the number requiring treatment. **WHO publishes no numerical price for praziquantel, and none was confirmed primarily**, despite cost being central to mass treatment. The retrieval pass reached the UNICEF catalogue, but praziquantel was not on the pages read. The drug is largely donated rather than purchased, so a tender price may not be the right figure for it in any case. The death estimate, 14,353, is stated by WHO itself to be likely an underestimate; schistosomiasis deaths occur through bladder cancer, renal failure and liver disease and are rarely attributed to the parasite. The role of animal reservoirs and hybrid schistosomes in sustaining human transmission is unresolved and bears directly on whether elimination is feasible. Praziquantel's failure to kill immature worms means single-round coverage figures overstate effect. Emerging praziquantel resistance is a theoretical concern with limited current evidence, and sources differ on how seriously to weight it.

> **Depth.** Starts in: the cercaria. Size: 400 µm†; depth +8.26. First complaint: about 5.7 weeks ([P] 4–8 weeks (Katayama)); time depth 46.85. One untreated course: no number ([B] years).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Soil-transmitted helminths

What it is. Intestinal worms — roundworm, whipworm and hookworm — whose eggs or larvae are in soil contaminated by human faeces. They are swallowed or they penetrate the feet. They rarely kill, but they consume nutrients and blood, stunting growth and causing anaemia.

Measured. WHO fact sheet on soil-transmitted helminth infections, 18 January 2023. The Key Facts section of this page carries no numeric figures at all.

About 1.5 billion people infected, or 24 per cent of the world's population, with no year stated anywhere on the page. *Strongyloides stercoralis* separately: over 600 million people.

Populations requiring preventive treatment: preschool-age children over 260 million; school-age children 654 million; adolescent girls 108 million; pregnant and lactating women 138.8 million. The page's own metadata gives an estimated 836 million children in need. Adding the page's two child categories gives about 914 million. The metadata figure is about 78 million below the page's own body figures and appears nowhere in Key Facts or body. Both stand; the appendix of single-source contradictions carries this as item 9.

Coverage in 2021: over 500 million children treated, 62 per cent of all at-risk children; over 99 million women of reproductive age treated with albendazole through lymphatic filariasis programmes.

DALYs lost to soil-transmitted helminths fell by more than 50 per cent between 2010 and 2019.

WHO publishes no death figure. Mortality is low and the burden is morbidity.

Species: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and *Ancylostoma duodenale* (hookworms), plus *S. stercoralis*. Geography: tropical and subtropical areas with poor sanitation, with highest prevalence in sub-Saharan Africa, China, South America and Asia.

Recommended effective treatment coverage is 75 per cent or higher, with epidemiological assessment after five to six years of preventive chemotherapy. Eggs mature in soil in about three weeks.

Where it starts. The routes differ by species. *Ascaris* and *Trichuris* eggs are ingested from contaminated soil, food or hands. Hookworm larvae penetrate the skin of bare feet. *Strongyloides* likewise penetrates skin and can autoinfect, persisting for decades. The risk structure is open defecation and absence of latrines, absence of footwear, absence of handwashing, and soil contact. The transmission cycle requires human faeces to reach soil, which is the single point at which it is broken.

Not known: the morbidity attributable to light-intensity infections is genuinely contested. Whether mass deworming of lightly infected populations improves growth, haemoglobin, school attendance and later earnings is one of the sharpest active disputes in global health; see PREVENTION. The determinants of heavy worm burden in particular children, beyond exposure, are not established. The immunological consequences of chronic helminth infection, including possible effects on vaccine responses and allergic disease, are suggested and unresolved.

Cure status. CURABLE. A single oral dose of albendazole or mebendazole clears most infections, and the drugs are among the safest in medicine. Two qualifications: reinfection is rapid where sanitation is unchanged, so cure at the individual level is temporary without environmental change; and *Trichuris* responds poorly to single-dose therapy compared with *Ascaris* and hookworm, so the cure rate varies substantially by species. *Strongyloides* requires ivermectin rather than a benzimidazole.

Prevention.

Sanitation — latrines and safe faeces disposal: STRONG on settled transmission physiology, and the only measure that is permanent. The cycle cannot continue if human faeces do not reach soil.

Footwear: STRONG for hookworm and *Strongyloides* specifically, since the larvae penetrate skin. Shoes are not an industrial chain in any meaningful sense.

Handwashing with soap, and washing food: STRONG for the orally transmitted species. Cochrane handwashing figures as in the diarrhoeal overview.

Preventive chemotherapy, mass deworming: CONTESTED on broader outcomes, STRONG on worm burden. This requires both numbers.

On parasitological outcomes: STRONG. The drugs reliably reduce worm burden and intensity; WHO reports DALYs fell more than 50 per cent from 2010 to 2019, and that 62 per cent of at-risk children were treated in 2021.

On growth, haemoglobin, cognition, school attendance and later economic outcomes: CONTESTED. The Cochrane review of community deworming concluded that there is substantial evidence that mass deworming of children in endemic areas does *not* improve average weight, haemoglobin, cognition, school performance or survival. Against this, long-term follow-up of the Kenyan "Worms at Work" trial reports significant gains in school participation and adult earnings, and WHO maintains its recommendation. Good sources genuinely disagree, the dispute has run for over a decade, and both positions stand. Part of the disagreement is about which populations and intensities are studied: benefit is more plausible in heavily infected children than in lightly infected ones, and trials have mixed the two. **No single effect size is asserted for either position.**

Deworming in pregnancy: MODERATE, for maternal anaemia; 99 million women of reproductive age were treated via lymphatic filariasis programmes.

Treatment.

Treatment	EML	Off-patent	Price
Albendazole 400 mg, single dose	Yes, 6.1.1 Intestinal anthelminthics core, 6.1.2 Antifilarials core, 6.1.4 Cysticidal complementary; chewable scored 400 mg core, chewable 200 mg complementary	Yes	WHO describes the drugs as "effective, inexpensive and easy to administer by non-medical personnel" and gives no numerical price. Both are donated in large volumes for mass campaigns. **No per-tablet price was retrievable**
Mebendazole 500 mg, single dose	Yes	Yes	As above
Ivermectin, for *S. stercoralis*	Yes, 6.1.1 core, 6.1.2 core, 6.6 Medicines for ectoparasitic infections core; tablet 3 mg	Yes	WHO states generic ivermectin has been available at an affordable price since 2021, and gives no figure
Iron supplementation, hookworm anaemia	Yes	Yes	UNICEF indicative US$1.43 on one catalogue page and US$1.60 on another per bottle of 100 iron 60 mg tablets, October 2026, about 1.4 to 1.6 US cents a tablet

These are among the cheapest and safest medicines in existence, administrable by non-medical personnel without diagnosis, which is the basis of school-based mass treatment.

Simple means. This is the condition in the chapter where simple means come closest to being a complete answer for prevention.

Latrines, and using them. Keeping human faeces out of soil and water breaks every one of these life cycles permanently, and needs no technology beyond a pit and a slab. Wearing shoes: hookworm and *Strongyloides* enter through the soles of bare feet, and footwear is close to a complete barrier for those species. Handwashing with soap before eating and food preparation. Washing and peeling vegetables, and avoiding raw produce fertilised with untreated human waste. Not using untreated human faeces as fertiliser, or composting it long enough to kill eggs — *Ascaris* eggs are exceptionally durable, so composting must be prolonged. Keeping children's play areas away from defecation sites, and covering sandy soil near dwellings. Cutting and cleaning fingernails, which is trivial but relevant to egg transmission. Iron-rich food for hookworm anaemia: green leaves, legumes, offal.

Cure requires a chain, but a very short one: benzimidazole synthesis and tablet distribution, with no cold chain, no needle, no diagnosis and no clinician. The permanent solution, however, is sanitation, and that requires no industrial chain at all — which is why these infections disappeared from high-income countries before deworming drugs existed.

Gaps. WHO publishes no prices for albendazole or mebendazole, and none was confirmed primarily despite cost being central. **The deworming benefit dispute is genuinely unresolved** and is the most significant evidentiary conflict in this entry; the Cochrane conclusion and the WHO recommendation point in different directions, and both are printed above. The fact sheet is dated 18 January 2023 with coverage data from 2021, among the older sources in this chapter, and it gives no data year at all for the 1.5 billion

prevalence figure. **No mortality figure**, so the burden is expressed only as prevalence and DALYs. The 1.5 billion figure derives from prevalence mapping and modelling, not from individual diagnosis; intensity of infection, which determines morbidity, is not captured by prevalence at all. *Trichuris* responds poorly to single-dose benzimidazoles, so uniform coverage figures conceal differential cure. The page's metadata figure for children needing treatment, 836 million, does not match its own body figures, which sum to about 914 million; see the appendix, item 9. The long-term immunological consequences of chronic helminth infection are unresolved.

> **Depth.** Starts in: the egg or larva. Size: 60 µm†; depth +6.54. First complaint: about 6 weeks († 1–2 months); time depth 46.91. One untreated course: no number († years).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Lymphatic filariasis

What it is. Thread-like worms transmitted by mosquitoes that live in the lymphatic vessels for years. Most infected people have no symptoms, but damage to lymph drainage causes grossly swollen limbs — lymphoedema, elephantiasis — and scrotal swelling, hydrocele. The disfigurement is permanent.

Measured. WHO fact sheet on lymphatic filariasis, 21 November 2024. 51 million people infected as of 2018, a 74 per cent decline since 2000. The infection figure is from 2018 while the programme figures around it are from 2023, so the burden estimate is stale relative to its own page.

Baseline chronic disease estimates, with no year stated: 25 million men with hydrocele and over 15 million people with lymphoedema. At least 36 million people remain with chronic manifestations, not broken down.

Over 657 million people in 39 countries live in areas requiring preventive chemotherapy, dated 2023 in the body and undated in Key Facts. 871 million people no longer require it, a 58.6 per cent reduction in the population needing mass drug administration, and ten countries were found not to require it.

Cumulative treatments: 9.7 billion delivered between 2000 and 2023, to more than 943 million people in 71 countries.

81 countries were endemic at programme start in 2000. 21 countries and territories have been acknowledged as having eliminated lymphatic filariasis as a public health problem. 14 have stopped large-scale treatment and are under surveillance. 39 still require preventive chemotherapy, six of which had not reached all endemic areas by end-2023.

Those country counts do not reconcile on the page. 81 endemic at start minus ten not requiring chemotherapy gives 71 treated countries, which matches the cumulative-treatment figure. But 39 still requiring, plus 14 stopped, plus 21 eliminated, gives 74. The page does not explain the overlap between the stopped and eliminated groups, and 74 is not 71. The appendix of single-source contradictions carries this as item 10. The same page's metadata mentions six countries certified clear in 2016, a claim appearing nowhere in Key Facts or body.

Economic: about US$24 billion in benefit for 2000–2007, described as conservative, and at least US$100.5 billion in economic loss averted by treatments up to 2015.

W. bancrofti causes 90 per cent of cases, and adult worms live six to eight years.

WHO publishes no death figure. This is a morbidity and disability condition, not a fatal one.

Where it starts. *Wuchereria bancrofti* in the large majority, with *Brugia malayi* and *B. timori* elsewhere, transmitted by *Culex*, *Anopheles*, *Aedes* and *Mansonia* mosquitoes. The risk structure is repeated infective bites over years: single exposure rarely causes disease, so transmission is sustained in endemic communities with high vector density and poor housing.

The morbidity mechanism is lymphatic damage by adult worms, compounded by recurrent bacterial superinfection of the compromised limb, which is what drives progression to elephantiasis. That point is the basis of the entire morbidity-management approach, and it is the reason simple means matter so much here.

Not known: why most infected people never develop lymphoedema while a minority progress severely is not established. The role of the *Wolbachia* endosymbiont in worm viability is established enough to make doxycycline effective, but why its elimination sterilises and kills adult worms is incompletely understood. The relative contribution of adult-worm damage against bacterial superinfection to final disability is contested. There is no reliable test to confirm that adult worms have died.

Cure status. Split, and the split is the central fact of the condition.

infection, with doxycycline: CURABLE infection, with standard MDA regimens: CONTROLLABLE established lymphoedema: RELIEF ONLY hydrocele, corrected by surgery: CURABLE

Standard mass-treatment regimens — albendazole with ivermectin or diethylcarbamazine — kill microfilariae reliably and reduce transmission, but have limited action on adult worms, which live years. The person remains infected, which is control rather than cure. Doxycycline for four to six weeks, by killing the *Wolbachia* endosymbiont, does kill adult worms. Killing the *Wolbachia* bacteria kills the adult worm, and that cures the infection. The long course makes it unsuitable for mass campaigns.

Killing the worms does not reverse lymphatic damage. Lymphoedema is managed, not cured, for life. Hydrocele can be corrected by surgery.

Prevention.

Mass drug administration: STRONG, and among the most successful programmes in this chapter. The evidence is the outcome: infection down 74 per cent since 2000, 871 million people no longer requiring treatment, 21 countries having eliminated it as a public health problem, and 9.7 billion treatments delivered.

Triple-drug therapy — ivermectin plus diethylcarbamazine plus albendazole, “IDA”: STRONG where conditions permit. WHO lists the regimen for countries without onchocerciasis where programmatic conditions are met, and gives no numerical figures. It clears microfilariae far more completely and durably than two-drug therapy, shortening the number of annual rounds needed. It cannot be used where onchocerciasis or loiasis is co-endemic, because of severe reactions, which is why two-drug regimens persist in much of Africa.

Vector control, bed nets and indoor spraying: MODERATE, and notably synergistic. Malaria bed-net programmes have reduced lymphatic filariasis transmission as a side effect where *Anopheles* is the vector.

Limb hygiene to prevent progression: STRONG. See SIMPLE MEANS. This prevents disability rather than infection.

No vaccine exists and none is in prospect.

Treatment.

Treatment	EML	Off-patent	Price
Albendazole, 400 mg	Yes, 6.1.2 Antifilarials, core	Yes	Donated for mass drug administration; no price published by WHO and none confirmed
Ivermectin, 200 µg/kg	Yes, 6.1.2 Antifilarials, core	Yes	Donated through the Mectizan Donation Program; no price confirmed
Diethylcarbamazine, 6 mg/kg	Yes	Yes	Very low; no price confirmed
Doxycycline, 4–6 weeks, kills adult worms via *Wolbachia*	Yes	Yes	Cents to low dollars for a 4–6 week course† — the cheapest true cure in this entry
Hydrocele surgery	n/a	n/a	Low-cost surgical procedure; curative
Limb hygiene and skin care, for	n/a	n/a	Essentially free

Treatment	EML	Off-patent	Price
lymphoedema			

The three mass-administration drugs are donated by their manufacturers, which is why 9.7 billion treatments were deliverable.

Simple means. Unusually large, and decisive for disability.

Washing the affected limb daily with soap and clean water, drying carefully between toes and skin folds. This is the core of lymphoedema management and it demonstrably reduces the acute bacterial attacks that drive progression to elephantiasis. It requires soap, water and a cloth, nothing else, and it is the single highest-value simple intervention in this entry. Treating small wounds, cracks and fungal infections between the toes promptly, because these are the entry points for the bacterial attacks. Elevating the limb when resting, and moving and exercising it to assist lymph drainage. Wearing footwear to prevent the cuts and abrasions that start infections. Keeping nails trimmed and feet clean. Sleeping under a net, which reduces both lymphatic filariasis and malaria transmission. Draining standing water and covering latrines, since *Culex* breeds in polluted water and in pit latrines.

Prevention of infection requires the drug chain — a short one: oral tablets, no cold chain, no needles, administered by non-medical personnel once a year. But prevention of disability is almost entirely achievable by simple means. This is a condition where soap and water applied daily genuinely alter the outcome for the 36 million people already affected, for whom no drug will reverse the damage.

Gaps. The infection figure, 51 million, is from 2018 on a page dated 21 November 2024. The hydrocele and lymphoedema figures are described as baseline estimates, so they do not reflect current prevalence, and the current “at least 36 million with chronic manifestations” is not broken down. **WHO publishes no prices for any of the mass-administration drugs.** The page’s country counts do not reconcile with each other, and its metadata contradicts its body on countries certified clear; see the appendix, item 10. **WHO gives no numerical figures for triple-drug therapy performance** despite recommending it. No reliable test exists to confirm adult worm death, so cure at the individual level cannot be verified. Why only a minority progress to elephantiasis is unknown.

> **Depth.** Starts in: the L3 larva. Size: 1.5 mm†; depth +9.47. First complaint: about 10 months († 8–12 months (before it shows)); time depth 48.68. One untreated course: no number ([B] years; permanent).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Onchocerciasis (river blindness)

What it is. A worm transmitted by blackflies that breed in fast-flowing rivers. Adult worms live in nodules under the skin and release larvae that cause intense itching, skin damage and, over years, blindness. It depopulated fertile river valleys in West Africa.

Measured. WHO fact sheet on onchocerciasis, 4 December 2025. At least 252.3 million people required preventive treatment in 2024. More than 99 per cent of infected people live in Africa and Yemen; the remaining 1 per cent are on the Brazil–Venezuela border.

Burden estimates, from GBD 2017 — the oldest burden data cited in this chapter: 14.6 million infected people had skin disease and 1.15 million had vision loss. **WHO gives no separate figure for permanent blindness**, only vision loss.

Treatment in 2024: 26 countries treated, reaching 171.6 million people, against a minimum therapeutic coverage requirement of 80 per cent. By end-2024, 25.5 million people lived in areas no longer needing ivermectin, with Nigeria accounting for more than 16.6 million.

Treatment must continue 10 to 15 years, which is the lifespan of the adult worm.

Five countries are verified free: Colombia in 2013, Ecuador in 2014, Mexico in 2015, Guatemala in 2016, and Niger in 2025, the first African country. Senegal stopped treatment in 2022 and is under surveillance, and nine further countries have stopped mass administration in at least one focus. 25 African countries have National Onchocerciasis Elimination Committees, and ten countries are endemic for *Loa loa*.

WHO publishes no death figure.

Where it starts. *Onchocerca volvulus*, transmitted by *Simulium* blackflies that breed in rapidly flowing, well-oxygenated rivers and streams. The risk structure is living and working near such rivers — which is why the disease concentrates on the most agriculturally valuable land, and why it drove people away from it. Repeated bites over years are required; the disease is one of cumulative exposure. The morbidity mechanism is the inflammatory response to dying microfilariae in skin and eye, mediated substantially by the *Wolbachia* endosymbiont.

Not known: the relationship between onchocerciasis and epilepsy, including “river epilepsy” and nodding syndrome, is genuinely unresolved. A consistent epidemiological association exists, with a plausible but unproven causal link, and good sources differ on whether it is causal. Why ivermectin does not kill adult worms is understood — it is microfilaricidal — but it means no individual cure exists within mass programmes. Reports of sub-optimal ivermectin response in some Ghanaian and Cameroonian foci are contested as evidence of emerging resistance.

Cure status. Split, and the split has to be made explicitly because the standard of care is not a cure.

with ivermectin, the standard of care: CONTROLLABLE with doxycycline, 4–6 weeks: CURABLE established blindness and skin scarring: RELIEF ONLY

Ivermectin kills microfilariae, stopping transmission and preventing progression, but does not kill adult worms, which live 10 to 15 years. That is why WHO states treatment must continue for that period, and the person remains infected throughout. Doxycycline for four to six weeks kills *Wolbachia* and thereby sterilises and kills adult worms, which is a cure, but the course length and the contraindications in pregnancy and childhood make it unsuitable for mass administration. Moxidectin, approved in 2018, gives longer microfilarial suppression but also does not reliably kill adults. Nothing reverses established blindness or skin scarring.

Prevention.

Community-directed mass treatment with ivermectin: STRONG — one of the clearest successes in this chapter. The evidence is the outcome: five countries verified free, 25.5 million people in areas no longer needing treatment, and transmission interrupted in nine further foci. Required coverage is 80 per cent.

Vector control, larviciding of blackfly breeding sites: STRONG. The Onchocerciasis Control Programme in West Africa, 1974 to 2002, relied substantially on aerial larviciding and interrupted transmission across large areas before ivermectin was available. That is historical proof that the vector route works, independent of drugs.

Doxycycline for individuals: MODERATE, as a curative option outside mass campaigns.

Protective clothing and avoiding blackfly biting sites during peak hours: WEAK. Blackflies bite outdoors in daytime near rivers, so avoidance conflicts with farming and water collection.

Bed nets: NOT EFFECTIVE against this vector, which bites outdoors in daylight. That is a clear contrast with malaria and lymphatic filariasis and it should not be glossed.

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
Ivermectin, annual or biannual single dose	Yes, 6.1.2 Antifilarials, core; tablet 3 mg	Yes	Donated free by Merck through the Mectizan Donation Program since 1987, without time limit — the reason 171.6 million people were treated in 2024. No market price

Treatment	EML	Off-patent	Price
			applies in endemic programmes
Doxycycline, 4–6 weeks, kills adult worms	Yes	Yes	Cents to low dollars per course
Moxidectin	Not confirmed on the 24th List	No; approved 2018	Not established for endemic programmes
Nodulectomy	n/a	n/a	Minor surgery
Cataract and eye surgery for established damage	n/a	n/a	Variable

Ivermectin's donation is the single most important economic fact in this entry, and it is the reason a 10- to 15-year treatment requirement is affordable at all.

Simple means. Limited for prevention, real for comfort.

Settling and farming away from fast-flowing river stretches where blackflies breed — the historical adaptation, at the cost of abandoning the best land. Covering arms and legs during peak biting hours near rivers. Avoiding riverside work at dawn and dusk where possible. Clearing vegetation at river crossings and water-collection points used daily. Skin care: washing, keeping skin moisturised with available oils, treating scratch wounds, which reduces the secondary infection and the misery of onchocercal dermatitis, the most common manifestation. Not scratching open, and keeping nails short, to limit secondary bacterial infection. Guiding and supporting the blind within the household and community, with orientation and mobility practices that need no equipment.

Bed nets do not work here. There is no simple means of preventing or treating the infection itself. The minimum chain is ivermectin manufacture and annual community distribution — a short chain, with no cold chain, no needles and non-medical administrators — but it must run for 10 to 15 years without interruption to clear a community. Larviciding requires an organised programme. Blindness, once established, has no remedy simple or otherwise.

Gaps. The infection and disability figures are from GBD 2017, the oldest burden data in this chapter, while treatment figures are from 2024. **WHO gives no figure for permanent blindness**, only vision loss. **The onchocerciasis–epilepsy and nodding syndrome link is genuinely contested** and unresolved. Reports of sub-optimal ivermectin response are contested as resistance. **No death figure is published**, so the condition's mortality contribution is unstated. Whether the 2030 road-map targets are achievable depends on 10- to 15-year treatment continuity through conflict and funding interruption, which the source does not assess.

> **Depth.** Starts in: the L3 larva. Size: 700 µm†; depth +8.77. First complaint: about 15 months († 9–24 months (before it shows)); time depth 49.05. One untreated course: no number ([B] years).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Leishmaniasis

What it is. A protozoan parasite transmitted by sandflies. The visceral form attacks spleen, liver and bone marrow and kills almost everyone untreated. The cutaneous form causes disfiguring skin ulcers that heal slowly and scar.

Measured. WHO fact sheet on leishmaniasis, 12 January 2023. Overall, an estimated 700,000 to 1 million new cases annually.

Visceral leishmaniasis, kala-azar: an estimated 50,000 to 90,000 new cases annually, with only 25 to 45 per cent reported to WHO. Cutaneous leishmaniasis: an estimated 600,000 to 1 million new cases annually, with about 200,000 reported.

Visceral leishmaniasis is fatal if untreated in over 95 per cent of cases. **WHO gives no annual death count** — the most striking data gap in this entry, for a disease that is over 95 per cent fatal untreated.

Post-kala-azar dermal leishmaniasis develops in 5 to 10 per cent of kala-azar patients on the Indian subcontinent.

Geography, by form. Cutaneous: about 95 per cent of cases in the Americas, the Mediterranean basin, the Middle East and central Asia, with the Eastern Mediterranean Region accounting for 80 per cent of reported cases worldwide. Mucocutaneous: over 90 per cent in Bolivia, Brazil, Ethiopia and Peru. Visceral: mostly Brazil, east Africa and India, and highly endemic in Iraq, Somalia, Sudan and Yemen.

HIV co-infection was reported from 45 countries in 2021, with high rates in Brazil, Ethiopia and Bihar, India.

Diversity: over 20 *Leishmania* species, over 90 sandfly species, and about 70 animal species that can be a source.

Where it starts. *Leishmania* species inoculated by female phlebotomine sandflies. The risk structure is poverty, and poor housing, since cracked mud walls and organic debris are sandfly habitat. Malnutrition is an established risk factor for progression to visceral disease. So are population displacement, deforestation and urban encroachment. HIV co-infection markedly increases visceral risk and treatment failure. Reservoirs differ by species: human-to-human via sandfly on the Indian subcontinent, which is anthroponotic; dogs and rodents elsewhere, which is zoonotic. That difference determines whether control can target humans alone.

Not known: why most infections remain asymptomatic while a minority progress to visceral disease is not established beyond nutrition and immune status. The mechanism of post-kala-azar dermal leishmaniasis, and its role as a transmission reservoir between epidemics, is incompletely understood but programmatically important. Why cutaneous lesions self-heal over months in some species and not others is not fully explained. No human vaccine exists despite the fact that recovery confers immunity, which suggests one should be possible; its absence is unexplained by immunology alone.

Cure status. Split by form.

visceral leishmaniasis: CURABLE cutaneous, small single lesions: SELF-LIMITING cutaneous, large, multiple or facial: CURABLE mucocutaneous leishmaniasis: CURABLE visceral with HIV co-infection: CONTROLLABLE established scars and tissue loss: RELIEF ONLY

Visceral leishmaniasis is cured in the great majority by liposomal amphotericin B, miltefosine, paromomycin or antimonials, where these are accessible. Untreated, over 95 per cent die, so the gap between treated and untreated outcome is as wide as anything in this chapter.

Cutaneous disease largely heals over months to a year, leaving scars; treatment accelerates healing and limits scarring and is indicated for large, multiple, facial or mucosal lesions. Mucocutaneous disease is curable but destructive, requiring systemic treatment, and established tissue destruction of nose and palate is not reversed. With HIV co-infection, relapse is frequent and secondary prophylaxis is often needed, which is control rather than reliable cure.

Prevention.

Early diagnosis and treatment of cases: STRONG. In anthroponotic settings, on the Indian subcontinent, it is also transmission control, because humans are the reservoir.

Insecticide-treated nets and indoor residual spraying: MODERATE. Sandflies are small enough to pass through ordinary netting, so fine-mesh or insecticide-treated nets are required. A standard net is not sufficient, unlike for malaria.

House improvement — plastering cracked walls, removing organic debris and rubble: MODERATE on settled vector ecology. Sandflies breed and rest in exactly these micro-habitats.

Reservoir control: culling or treating infected dogs in zoonotic settings is CONTESTED on both effectiveness and ethics, and good sources disagree on whether dog culling achieves anything. Rodent control: MODERATE.

Vector control around dwellings, and avoiding sleeping outdoors at ground level: MODERATE. Nutrition: MODERATE, as malnutrition is an established progression risk.

No human vaccine exists. Canine vaccines exist in some countries.

Treatment.

Treatment	EML	Off-patent	Price
Liposomal amphotericin B, visceral first line in south Asia; single-dose regimens used	Yes	Yes for the originator formulation; generics exist	Preferential pricing for endemic public programmes has been reported at US$16–18 per vial historically†; cost per course depends on weight-based dosing
Miltefosine, oral, visceral and cutaneous	Yes	Yes	Low hundreds of US dollars per course historically
Paromomycin, injectable, visceral	Yes	Yes	Low
Pentavalent antimonials: sodium stibogluconate, meglumine antimoniate	Yes	Yes	Low, but toxic — cardiotoxicity, pancreatitis; resistance is high in Bihar, India
Combination therapies, e.g. liposomal amphotericin B with miltefosine	—	—	Used to shorten courses and limit resistance
Thermotherapy, cryotherapy, intralesional antimony, for cutaneous disease	n/a	Partly	Low-cost local treatment

WHO states that anti-leishmanial medicines are effective and safe, particularly for visceral disease, but can be difficult to use. **It does not name liposomal amphotericin B or miltefosine and gives no treatment costs.** The drug names and roles above are standard practice, and the absence of WHO-published prices is a gap.

Simple means. Meaningful for prevention and for cutaneous care.

Plastering and repairing cracked walls, and removing rubble, rubbish and organic debris from around the house. This removes the sandfly's breeding and resting habitat and requires only mud, lime and labour. Fine-mesh netting over sleeping places, since ordinary netting is too coarse — a material choice rather than an industrial product. Sleeping on raised beds rather than on the floor, since sandflies fly low. Keeping animal pens away from and downwind of sleeping quarters. Covering skin at dusk and at night, when sandflies bite. Wound care for cutaneous lesions: cleaning with clean water, keeping lesions covered and dry, preventing secondary bacterial infection — which is the main avoidable harm in a lesion that will largely heal on its own. Thermotherapy: localised heat applied to cutaneous lesions is an established treatment and can be delivered with simple heat sources, though controlled devices are better. Feeding the malnourished child, since malnutrition drives progression to visceral disease.

Nothing simple treats visceral leishmaniasis, and untreated it kills over 95 per cent. The minimum chain is substantial: liposomal amphotericin B requires lipid formulation manufacture and a cold chain, miltefosine requires synthesis and a 28-day supervised course, and the injectables require sterile delivery. This is one of the clearest cases in the chapter where a person beyond the reach of a supply chain dies of a curable disease.

Gaps. The fact sheet is dated 12 January 2023 and **gives no annual death count** for a disease that is over 95 per cent fatal untreated. **Only 25 to 45 per cent of visceral cases are reported to WHO**, so incidence is substantially unmeasured. **WHO names no first-line drugs and publishes no prices**; the drug names and prices here are from standard practice and are marked as not primary-sourced. **Dog culling is genuinely contested** on both effectiveness and ethics. Antimonial resistance in Bihar is established but not quantified in the source. No human vaccine exists despite recovery conferring immunity — an unexplained gap. Outcomes in HIV co-infected visceral disease are poor and the optimal regimen is not settled.

> **Depth.** Starts in: the promastigote. Size: 15 µm†; depth +5.28. First complaint: about 3.4 months († visceral form 2–6 months); time depth 47.73. One untreated course: no number ([B] usually fatal if untreated; † months).

> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Chagas disease (American trypanosomiasis)

What it is. A parasite transmitted by blood-sucking triatomine bugs that live in the walls and roofs of poor housing and defecate on the skin while feeding. After a mild acute phase it hides for decades, then damages the heart or gut in about a third of those infected.

Measured. WHO fact sheet on Chagas disease, 8 April 2026. About 8 million people infected worldwide, mostly in Latin America. More than 10,000 deaths each year. More than 100 million people at risk. Congenital transmission produces over 10,000 new cases annually.

In the chronic phase, one to three decades after infection, up to a third develop cardiac disorders and up to one in ten develop digestive, neurological or mixed alterations. The acute phase lasts about two months.

Geography: endemic in 21 continental Latin American countries, with infection detected in 44 countries, but national information systems existing in only six of those 44. Vector-transmission interruption is verified in eight countries: entirely in Chile, Paraguay and Uruguay, and partially in Argentina, Brazil, Colombia, Peru and Bolivia.

Economics: medical care costs for chronic cases are more than 80 per cent higher than the cost of residual insecticide spraying.

Treatment: courses last up to two months, with adverse reactions in up to 40 per cent of adults. WHO has donated nifurtimox for all ages since 2011 and benznidazole for children under 19 since 2020. The neglected tropical disease road map targets 75 per cent coverage of antiparasitic treatment among the eligible population.

Where it starts. *Trypanosoma cruzi*, by four established routes. Triatomine bug faeces entering through the bite site, mucous membranes or conjunctiva. Congenital transmission from mother to child. Blood transfusion and organ transplantation. And oral transmission through food or drink contaminated with bug faeces or infected bug material, which causes discrete outbreaks with higher acute mortality. The risk structure is housing with cracked walls, thatch and mud brick in which the bugs live; rural poverty; and, in non-endemic countries, migration from endemic areas plus unscreened blood.

Not known: why only about a third of infected people develop organ damage, and why some develop cardiac and others digestive disease, is genuinely unexplained. Parasite strain, host genetics, immune response and parasite persistence in tissue all have support without resolution. Whether antiparasitic treatment in the established chronic phase prevents progression of cardiomyopathy is contested. The BENEFIT trial found that benznidazole reduced parasite detection but did not reduce cardiac clinical deterioration in patients with established cardiomyopathy. Treatment remains recommended earlier in the chronic phase. There is no reliable test of cure.

Cure status. Split by stage, and the split is unusually consequential.

acute phase, congenital infection: CURABLE early chronic phase: CURABLE, parasitological cure established cardiomyopathy or megacolon: RELIEF ONLY

The cure in the early chronic phase is parasitological. The parasite is cleared. Established heart muscle damage is not reversed.

WHO states that benznidazole and nifurtimox are “fully effective in curing the disease when given early in the acute phase, including congenital cases”. Congenitally infected infants treated early are cured at high rates. In the early chronic phase — children and younger adults without organ damage — a substantial proportion are cured, and the figure could not be reached, with efficacy declining the longer the person has been infected.

For established cardiomyopathy or megacolon, antiparasitic treatment does not reverse the damage, and the BENEFIT trial found no reduction in cardiac deterioration. Management is then heart failure treatment, pacemakers, antiarrhythmics and surgery. **WHO gives no numerical cure rates by stage**, despite stage being the determinant of curability. The proportion cured in the early chronic phase is therefore not known, and falls with the years of infection.

Prevention.

Indoor residual insecticide spraying and house improvement: STRONG — the measure that achieved actual interruption of transmission. The evidence is the outcome: vector transmission interrupted entirely in three countries and partially in five more. WHO gives no numerical effectiveness data for vector control, but notes that chronic care costs exceed spraying costs by more than 80 per cent.

Housing improvement — plastering walls, replacing thatch roofs, laying cement floors: STRONG on settled vector ecology. The bug cannot colonise a house without crevices.

Blood and organ donor screening: STRONG. It effectively eliminates transfusion transmission where implemented, and it is the principal measure in the 44 non-endemic countries where infection is detected.

Antenatal screening and treating infected newborns: STRONG, given that early congenital infection is curable and that over 10,000 congenital cases occur annually.

Bed nets: MODERATE, where the vector is present and bites at night indoors. Food hygiene against oral transmission: MODERATE, for açaí, sugarcane juice and similar products.

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
Benznidazole, up to two months	Yes	Yes	Donated by WHO for children under 19 since 2020. No price published by WHO and none confirmed
Nifurtimox, up to two months	Yes	Yes	Donated by WHO for all ages since 2011. No price published
Heart failure therapy, antiarrhythmics, pacemakers, for chronic cardiac disease	Partly	Partly	Variable; cardiology infrastructure
Surgery for megacolon or megaoesophagus	n/a	n/a	Variable

Adverse reactions occur in up to 40 per cent of adults on a course lasting up to two months — a major reason treatment uptake is low even where the drugs are free.

Simple means. Substantial for prevention, concentrated on the house.

Plastering and sealing cracked walls, and replacing thatch roofs. The triatomine bug lives in crevices, and a smooth-walled, well-sealed house cannot sustain a colony. Mud plaster, lime wash and labour are sufficient, and this is the single most effective simple intervention here. Cement or smoothed floors, removing crevices. Keeping animals — chickens, dogs, guinea pigs — out of and away from sleeping quarters, since they sustain bug populations. Clearing woodpiles, rubble and debris from against house walls. Inspecting walls and beds for bugs and their droppings at night with a light, which is how infestation is detected without any equipment. Sleeping under a net where bugs are present. Not consuming unpasteurised sugarcane or açaí juice of uncertain preparation, which prevents oral transmission. Treating the newborn of an infected mother early, which requires the drug but is the point at which cure is most achievable.

Nothing simple cures the infection. The minimum chain is benznidazole or nifurtimox synthesis plus a supervised two-month course with monitoring for adverse effects in up to 40 per cent of adults. For established cardiomyopathy the chain extends to cardiology: pacemakers, antiarrhythmics and sometimes transplantation, none of which is improvisable. But house improvement genuinely prevents the disease, and three countries have interrupted transmission largely by that route plus spraying.

Gaps. WHO publishes no numerical cure rates by stage, despite stage being the determinant of curability — the central gap in this entry. **WHO publishes no prices for either drug. Whether treating established chronic infection prevents cardiac progression is genuinely contested**; the BENEFIT trial result and the continued treatment recommendations point in different directions, and both are stated above. **There is no reliable test of cure**, so individual treatment success cannot be confirmed. National information systems exist in only six of 44 countries where infection is detected, so burden outside endemic Latin America is essentially unmeasured. Why only a third progress to organ damage is unknown. The 8 million infected figure predates most current surveillance and is widely regarded as uncertain.

> **Depth.** Starts in: the trypomastigote. Size: 20 µm†; depth +5.54. First complaint: about 10 days († 1–2 weeks); time depth 45.59. One untreated course: no number ([B] decades).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Human African trypanosomiasis (sleeping sickness)

What it is. A parasite transmitted by tsetse flies that eventually crosses into the brain, destroying the sleep-wake cycle before causing coma and death. Untreated it is almost always fatal. Reported cases have fallen from tens of thousands to under a thousand a year.

Measured. WHO fact sheet on human African trypanosomiasis, 2 May 2023. Gambiense disease accounts for 92 per cent of reported cases and rhodesiense for 8 per cent.

On the decline the page contradicts itself. The body text gives a 97 per cent fall in new cases over the last 20 years; the page's metadata cites an 85 per cent reduction since 2000, using a different baseline. Both stand; the appendix of single-source contradictions carries this as item 8.

Counts: in 1998, almost 40,000 cases reported against an estimated 300,000 undetected and untreated; in 2017, under 2,000 cases; in 2018, under 1,000, and below that threshold as of 2022. In the mid-1960s the figure was below 5,000 annual cases continent-wide. Prevalence reached 50 per cent in several villages in Angola, the DRC and South Sudan at the peak.

Over the last five years the DRC reported 61 per cent of cases, a mean of 522 a year. Angola, Central African Republic, Chad, Congo, Gabon, Guinea, Malawi and South Sudan each declared 10 to 100 cases; Cameroon, Côte d'Ivoire, Equatorial Guinea, Uganda, Tanzania, Ethiopia and Zambia each declared 1 to 10.

WHO gives no annual death count. The page's metadata describes near-100 per cent fatality without prompt diagnosis and treatment.

Geography: *T. b. gambiense* in 24 countries of west and central Africa; *T. b. rhodesiense* in 13 countries of eastern and southern Africa. 55 million people were at risk for 2016–2020, with 3 million at moderate-to-high risk.

Melarsoprol's reactive encephalopathy is 3 to 10 per cent fatal — a treatment that itself killed a substantial fraction of those receiving it. Outcome assessment requires follow-up for up to 24 months.

Where it starts. *Trypanosoma brucei gambiense* or *T. b. rhodesiense*, transmitted by *Glossina*, the tsetse fly. The risk structure is rural occupational exposure — farming, fishing, hunting, animal husbandry — in tsetse habitat.

The two forms differ fundamentally, and the difference determines what control can achieve. Gambiense is chronic and anthroponotic: humans are the main reservoir, so treating people can interrupt transmission. Rhodesiense is acute and zoonotic: cattle and wild animals are the reservoir, so elimination in humans alone is not achievable.

Not known: the size and significance of the asymptomatic human carrier reservoir in gambiense disease is unresolved and bears directly on whether elimination of transmission by 2030 is achievable. Whether skin-

dwelling trypanosomes constitute a hidden reservoir is an active question. Why the disease remained at very low levels in the 1960s and then produced massive epidemics from the 1970s to the late 1990s is attributed to the collapse of surveillance and control, but the dynamics are not fully modelled. The determinants of progression speed from first to second stage vary widely and are not established.

Cure status. CURABLE, both stages. The change over the last decade has been substantial. Untreated, the disease is near-uniformly fatal.

Fexinidazole, an oral treatment effective for both first- and second-stage gambiense disease, removed the need in most cases for the lumbar puncture that previously determined staging, and for the arsenical melarsoprol, whose reactive encephalopathy was 3 to 10 per cent fatal. NECT, nifurtimox-eflornithine combination therapy, remains for severe second-stage cases and requires four times fewer eflornithine infusions than eflornithine alone. Acoziborole, a single-dose oral treatment, has completed trials and represents the near-term prospect of single-dose cure.

WHO gives no efficacy percentage for fexinidazole and none for NECT, beyond describing NECT as safer and more effective. Cure must be confirmed by follow-up for up to 24 months, which is the practical limit on declaring individual cure.

Prevention.

Active case-finding and treatment: STRONG, and for gambiense disease it is also transmission control, since humans are the reservoir. This is what produced the 97 per cent decline.

Tsetse vector control — insecticide-impregnated targets and traps, insecticide-treated cattle, sterile insect technique: MODERATE. Tiny insecticide-impregnated targets deployed along waterways have proved cheap and effective in gambiense foci.

Avoiding tsetse habitat during peak biting, and wearing neutral-coloured clothing: WEAK but genuinely free. Tsetse are attracted to dark blue and black and to movement.

Screening of at-risk populations with rapid diagnostic tests: STRONG, for finding the cases that sustain transmission.

Veterinary treatment of cattle: MODERATE for rhodesiense disease specifically, since cattle are the reservoir.

No vaccine exists, and the parasite's antigenic variation — continuous switching of its surface glycoprotein coat — makes one a remote prospect. That is the established immunological reason, not a funding gap.

Treatment.

Treatment	EML	Off-patent	Price
Fexinidazole, oral, both stages, gambiense	Yes	No; developed by DNDi with Sanofi	Donated by Sanofi to WHO for endemic countries; no market price applies
NECT: nifurtimox with eflornithine, severe second stage	Yes	Yes	Donated to WHO by Sanofi and Bayer; no market price applies
Pentamidine, first-stage gambiense	Yes	Yes	Donated; low
Suramin, first-stage rhodesiense	Yes	Yes	Donated; low
Melarsoprol, second-stage rhodesiense, now limited	Yes	Yes	Donated; 3–10 per cent fatal reactive encephalopathy
Acoziborole, single-dose oral, in development	Not yet	No	Not yet deployed

All drugs for this disease are donated to WHO by their manufacturers, which is the only reason treatment exists for a condition with a few hundred annual cases and no market. This is the clearest example in the chapter of a disease whose treatment is entirely outside market economics.

Simple means. Limited, and this must be stated plainly.

Wearing long sleeves and trousers in medium-weight, neutral-coloured fabric: tsetse bite through thin cloth and are attracted to dark blue and black. Avoiding known tsetse habitat — riverine thickets and dense

vegetation near water — particularly during the day, since tsetse are day-biters. Avoiding bushes during the hottest part of the day, where tsetse rest. Clearing vegetation around dwellings, water points and paths used daily, which removes tsetse resting habitat. Not travelling through tsetse areas in open vehicles, as tsetse are attracted to moving vehicles and dust. Reporting prolonged fever, swollen neck glands and sleep disturbance to whoever can test — recognition is what gets a person treated.

Bed nets are of little value against a daytime biter, as with onchocerciasis and dengue.

There is nothing simple that treats sleeping sickness, and untreated it is almost always fatal. The minimum chain is the most restrictive in this chapter: these drugs are made by a handful of manufacturers for a few hundred patients a year, donated rather than sold, and distributed through WHO. There is no generic market, no local production and no alternative. A person with second-stage disease and no access to the WHO supply chain will die, and no simple means alters that.

Gaps. WHO gives no annual death count and **no efficacy figures for fexinidazole or NECT.** The source contradicts itself on the decline: 97 per cent over 20 years in the body text, 85 per cent since 2000 in the metadata; see the appendix, item 8. The fact sheet is dated 2 May 2023 with "last five years" case figures. **The asymptomatic carrier reservoir is unquantified** and determines whether the 2030 transmission-interruption target is achievable. Cure requires 24-month follow-up, which is rarely completed, so cure rates in practice are not well measured. Case numbers are now so low that surveillance sensitivity, rather than true incidence, dominates the reported figures — and the 1998 comparison, 40,000 reported against 300,000 estimated, shows how far reporting can diverge from reality for this disease.

> **Depth.** Starts in: the trypanosome. Size: 25 µm†; depth +5.74. First complaint: about 12 days († 1–3 weeks (rhodesiense)); time depth 45.77. One untreated course: no number († gambiense years).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Leprosy (Hansen disease)

What it is. A slow-growing bacterium, *Mycobacterium leprae*, that damages skin and peripheral nerves. Loss of sensation means injuries go unnoticed, and the deformity that follows comes from unfelt wounds rather than from the organism. It has been curable since the early 1980s.

Measured. WHO fact sheet on leprosy, 23 January 2026. The Key Facts section carries no case counts at all; its only number is the six WHO regions.

Around 200,000 new cases are reported every year. The disease occurs in more than 120 countries.

Elimination as a public health problem means prevalence below one per 10,000 population, a threshold achieved globally in 2000 and in most countries by 2010.

2024 country data: Brazil, India and Indonesia each reported more than 10,000 new cases; 12 countries each reported 1,000 to 10,000; 117 countries reported fewer than 1,000; and 55 countries reported zero. Countries with 1,000 or more new cases in 2024 beyond the top three were Bangladesh, DR Congo, Ethiopia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, the Philippines, Somalia, Sri Lanka and Tanzania.

Most new case detection is in the South-East Asia Region, and cases are reported from all six WHO regions.

WHO gives no death figure, leprosy not being primarily fatal, and **no numerical disability figures**; the 2021–2030 strategy targets "zero disability". The share of children among new cases and the grade-2 disability count are not stated on the page.

Multidrug therapy is three drugs — dapsone, rifampicin and clofazimine — for six months in paucibacillary disease, defined as one to five skin lesions, or twelve months in multibacillary disease, more than five lesions. **WHO gives no cure rate percentage.**

Where it starts. *M. leprae*, and *M. lepromatosis*, transmitted probably by respiratory droplets during prolonged close contact, typically within households. The risk structure is prolonged household contact with an untreated case — and, notably, most exposed people never become infected; susceptibility appears largely host-determined. Incubation averages about five years and can exceed twenty. Armadillos are an established zoonotic reservoir in the southern United States, and red squirrels in Britain.

Not known: the transmission route is not definitively established. Respiratory transmission is most likely, but soil, armadillos and amoebae have all been proposed as reservoirs, and this is one of the oldest unresolved questions about any human pathogen. Why the overwhelming majority of exposed people never develop disease, and why some develop paucibacillary and others multibacillary forms, reflects host immune variation that is characterised genetically but not predictively. *M. leprae* cannot be cultured in vitro, which is the fundamental reason so much remains unknown. Why nerve damage continues or begins after bacteriological cure, through immune reactions, is incompletely understood.

Cure status. Split, and the split is essential and frequently misunderstood.

the infection: CURABLE established nerve damage, sensory loss and deformity: RELIEF ONLY

Multidrug therapy reliably cures leprosy — six months for paucibacillary disease, twelve for multibacillary. WHO states no cure-rate percentage, but relapse rates after completed therapy are low, and the drugs have been free since 1995.

Established nerve damage, sensory loss, paralysis and deformity are not reversed by curing the infection. WHO states that untreated disease may cause progressive, permanent disability, and that early treatment can prevent it — so the whole of disability prevention lies in early detection.

Immune reactions, type 1 and type 2, can occur during or after treatment and cause further nerve damage. These require corticosteroids and are the main cause of disability in people already cured of the infection.

Prevention.

Early detection and treatment of cases: STRONG, both to prevent that person’s disability and to remove the source of transmission.

Single-dose rifampicin post-exposure prophylaxis for contacts: MODERATE. WHO recommends contact screening plus a single dose of rifampicin and **gives no effectiveness figure**. The underlying COLEP trial reported roughly a 50 to 60 per cent reduction in incidence among contacts over two years, with the effect concentrated in the first two years and in more distant contacts. **That figure could not be confirmed to a primary source, and carries a dagger.**

BCG vaccination: MODERATE. It affords partial protection against leprosy as well as tuberculosis, an incidental and well-replicated cross-protection.

Contact tracing and screening of household members: STRONG, for early detection. Treating reactions early with corticosteroids: STRONG, for preventing disability.

No leprosy-specific vaccine is in routine use; candidates have been trialled.

Treatment.

Treatment	EML	Off-patent	Price
Multidrug therapy: dapsone with rifampicin and clofazimine	Yes	Yes	Free to all patients worldwide since 1995, donated through WHO — originally by the Nippon Foundation and since 2000 by Novartis. No market price applies
Single-dose rifampicin, prophylaxis for contacts	Yes	Yes	Cents per dose
Prednisolone, nerve reactions	Yes	Yes	Cents per course
Clofazimine or thalidomide, type 2 reactions	Yes; thalidomide partly	Partly	Low; thalidomide is restricted
Protective footwear, self-care materials	n/a	n/a	Low to free

Treatment	EML	Off-patent	Price
Reconstructive surgery, tendon transfers	n/a	n/a	Variable

Multidrug therapy has been free worldwide for thirty years. The barrier to leprosy control is not drug cost but detection, stigma, and the five-year incubation that hides new cases.

Simple means. Unusually large, because the disability — not the infection — is what disables, and the disability is prevented by daily self-care.

Daily self-examination of hands and feet for cuts, blisters, burns and pressure areas that were not felt. This is the single most important practice, and it requires only eyes and a few minutes. Soaking, filing and oiling dry, insensitive skin to prevent cracking, and moisturising with any available oil. Protective footwear — even simple sandals with a soft insole — to prevent plantar ulcers in feet that cannot feel pressure. That prevents more deformity than any drug. Checking the temperature of water and objects with a part of the body that still has sensation, before using insensitive hands. Wound care: cleaning, dressing, and above all resting an ulcerated foot until it heals. Rest is free and is the treatment. Protecting an eye that cannot close or blink: a cloth cover, keeping it moist, conscious blinking. Exercising weak hands and feet to prevent contractures. Recognising early signs: pale or reddish patches with loss of sensation, numbness, weakness — detectable by touching skin with a wisp of cotton, which costs nothing and is the standard field test.

Cure requires the drug chain — three-drug synthesis and a six- to twelve-month supply — but that chain is short, needs no cold chain and no needles, and the drugs are free. Prevention of disability, which is the actual harm of leprosy, is overwhelmingly achievable by simple means, and self-care training is the core of modern leprosy work.

Gaps. WHO publishes no cure rate, no disability figures and no post-exposure prophylaxis effectiveness figure, despite all three being central; the COLEP effect estimate, given above, carries a dagger. **The transmission route is still not definitively established** — remarkable for a disease known since antiquity. *M. leprae* cannot be cultured, which limits drug-susceptibility testing and resistance surveillance; emerging rifampicin resistance is detected by molecular methods and is not well quantified. New case detection fell during COVID-19 disruption, so the reported figures for 2020 to 2022 reflect detection rather than incidence, and the 2024 figures may include a backlog. The 55 countries reporting zero cases may reflect absence of disease or absence of detection; the source does not distinguish. Why most exposed people never develop disease is unknown.

> **Depth.** Starts in: Mycobacterium leprae. Size: 3 µm†; depth +3.81. First complaint: about 5 years ([B] mean about 5 years; [W] 1–20 years); time depth 50.34. One untreated course: no number († years).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Trachoma

What it is. Repeated chlamydial infection of the inner eyelid in early childhood, spread by flies, fingers and shared cloths. Decades of scarring turn the eyelid inward so the lashes scrape the cornea, which eventually blinds. It is the world’s leading infectious cause of blindness. That blindness is preventable at every stage before it.

Measured. WHO fact sheet on trachoma, 7 September 2026, with country elimination data as of 4 September 2026 and at-risk population from March 2026.

About 1.9 million people are blind or visually impaired from trachoma. Trachoma causes about 1.4 per cent of all blindness worldwide. 92 million people live in trachoma-endemic areas and are at risk of trachoma blindness, and require interventions.

Up to 90 per cent of preschool-aged children in endemic areas can have active, inflammatory trachoma. Visual impairment typically begins between the ages of 30 and 40. Blinding trichiasis appears in adults.

Women are blinded up to four times as often as men — the largest sex disparity of any condition in this chapter, attributed to close contact with infected children.

Economic: lost productivity is estimated at US$2.9–5.3 billion a year, rising to US$8 billion when trichiasis is included.

2025 activity: 47.4 million people treated with antibiotics, a global antibiotic coverage of 47 per cent, and 98,829 people receiving corrective surgery for trichiasis.

33 countries have been validated by WHO as having eliminated trachoma as a public health problem: Algeria, Australia, Benin, Burundi, Cambodia, China, Egypt, El Salvador, Fiji, Gambia, Ghana, India, Iran, Iraq, Lao PDR, Libya, Malawi, Mali, Mauritania, Mexico, Morocco, Myanmar, Nepal, Oman, Pakistan, Papua New Guinea, Saudi Arabia, Senegal, Timor-Leste, Togo, Tunisia, Vanuatu and Viet Nam.

It remains a public health problem in at least part of 29 countries according to Key Facts, while the page's own metadata says 32. The body gives no endemic count, so the conflict sits squarely between Key Facts and page metadata. Both stand; the appendix of single-source contradictions carries this as item 11.

The trend is falling sharply. The elimination target was 2020 under World Health Assembly resolution 51.11 and is now 2030.

Elimination thresholds: trichiasis unknown to the health system under 0.2 per cent in adults aged 15 and over, and trachomatous inflammation-follicular under 5 per cent in children aged 1 to 9, sustained at least two years without ongoing antibiotic mass administration.

Where it starts. Repeated conjunctival infection with *Chlamydia trachomatis* serovars A, B, Ba and C, transmitted by eye-seeking flies — *Musca sorbens*, which breeds in exposed human faeces — by fingers, and by shared face cloths and bedding. The risk structure is water scarcity, absence of latrines, crowded sleeping conditions, and proximity to livestock and flies.

Close contact with infected young children is the main route of transmission, and children are the reservoir. Lack of facial cleanliness matters, because ocular and nasal discharge on the face attracts the fly and carries the organism. Water scarcity limits face washing. Latrines interrupt transmission, because *M. sorbens* breeds in exposed human faeces. Female sex carries a higher risk of trichiasis.

Blindness is the cumulative result of *repeated* infection over years, not of a single episode. That is why it affects adults who were infected as children, and why interrupting childhood reinfection prevents adult blindness.

Not known: why some individuals progress to scarring and trichiasis while others with similar infection history do not is not established, though host immune and genetic factors are implicated. Whether mass azithromycin's observed reduction in all-cause child mortality, reported in the MORDOR trial, is a real and generalisable effect, and whether it justifies broader distribution given antimicrobial resistance concerns, is genuinely contested. The relative contribution of fly control, facial cleanliness and latrines to the F and E components of the SAFE strategy has never been cleanly separated. Why trichiasis sometimes recurs after apparently good surgery is not fully explained. The immunological determinants of progressive scarring are not settled. The part played by antibiotic coverage in the observed declines, beside fly control and face washing, has not been separated in practice.

Cure status. Split into three distinct states.

active chlamydial infection: CURABLE trichiasis, corrected by surgery: CURABLE established corneal opacity and blindness: RELIEF ONLY

A single oral dose of azithromycin clears active infection. Reinfection is the problem, not treatment failure, which is why treatment is given to whole communities repeatedly rather than to individuals. Trichiasis is corrected by a simple lid-rotation operation, performable by trained non-physician surgeons, which stops the lashes abrading the cornea and prevents blindness; 98,829 such operations were done in 2025. Established corneal opacity is not reversible, and corneal transplantation has poor outcomes in this setting.

Trichiasis surgery stops further scraping and prevents future loss. It does not clear an opaque cornea, which requires transplantation. The infection is curable. The blindness it has already caused is not.

Eliminating transmission in a district is achievable and has been achieved. 33 countries have been validated by WHO as having eliminated trachoma as a public health problem. That is cure at population scale, verified by an external body. It can be said of few diseases in this book.

Prevention. The WHO-adopted SAFE strategy, adopted in 1993: Surgery, Antibiotics, Facial cleanliness, Environmental improvement. **WHO gives no numerical targets or effect sizes for the individual components.**

Antibiotics, mass azithromycin: STRONG for clearing infection at community level. 47.4 million people treated in 2025, at 47 per cent coverage. **WHO gives no figure for azithromycin's clinical effect.**

Surgery for trichiasis: STRONG, for preventing blindness in those already scarred. It prevents the corneal damage that causes the blindness.

Facial cleanliness: MODERATE. Washing children's faces removes the ocular and nasal discharge that attracts flies and carries the organism. Trial evidence is consistent in direction but modest in size, and the mechanism is settled. Face washing reduces active trachoma. Whether the effect is modest is not settled: trial effect sizes could not be retrieved. Effect sizes vary between trials, and adherence is the limiting factor.

Environmental improvement — latrines and water access: MODERATE. *M. sorbens* breeds in exposed human faeces, so latrines remove the fly's breeding medium. This is the most durable component, and it is the reason trachoma vanished from Europe without any antibiotic.

The whole package, delivered together, has taken 33 countries to validated elimination. That is the strongest available evidence that the strategy works.

Mass azithromycin for child survival: CONTESTED. The MORDOR trial reported a reduction in all-cause under-five mortality with biannual mass azithromycin in high-mortality settings, while concerns about driving macrolide resistance are substantial and well founded. Good sources genuinely disagree on whether this justifies distribution beyond trachoma indications. Both the mortality benefit and the resistance concern are real and belong together. **The magnitude of the MORDOR mortality reduction is not asserted here.**

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
Azithromycin, single oral dose, by body weight with a maximum	Yes, 6.2.2 Watch group, first choice for trachoma	Yes	Donated through the International Trachoma Initiative by Pfizer, which is why 47.4 million treatments were delivered in 2025. No market price applies in endemic programmes. For comparison, UNICEF indicative price, October 2026: US$0.56 for a pack of six 250 mg tablets, about 9.3 US cents per tablet; an indicative tender price, not a market price. Generic cost otherwise well under a dollar per dose.
Tetracycline eye ointment, alternative where azithromycin is unavailable; usable in pregnancy and infancy	Yes	Yes	Cents per course, or cents per tube; requires twice-daily application for weeks, hence poorer adherence.
Trichiasis surgery, bilamellar tarsal rotation, the standard operation	n/a	n/a	Low-cost; performable by trained non-physician surgeons in field conditions, under local anaesthesia in a health post. Reported in the low tens of US dollars per eyelid in programme settings.
Corneal transplantation, for established opacity	n/a	n/a	Rarely available where trachoma is endemic; outcomes in trachomatous eyes are poor.
Epilation, plucking lashes	n/a	n/a	Free — a temporary measure where surgery is unavailable

Azithromycin cures the infection. It is used both for individual treatment and for mass administration. The dose is set by body weight, with a maximum. Tetracycline ointment is the alternative where azithromycin is unavailable, and it can be used in pregnancy and infancy.

Simple means. This is among the conditions in this chapter most amenable to simple means. Two of the four SAFE components require no supply chain at all. Trachoma is the clearest case in the book of a blinding disease held off by water, soap and latrines.

Washing children's faces, daily and whenever discharge appears. Water and a clean cloth. This is the F of SAFE and it requires nothing industrial. One cloth or towel per child, not shared, since shared cloths transfer the organism directly between eyes. Latrines, and using them, which removes the breeding medium of the eye-seeking fly: this is the E of SAFE and it is the measure that permanently ended trachoma in Europe and North America before antibiotics existed. Covering or burying faeces, especially children's, which are the preferred breeding substrate. Keeping livestock and their dung away from dwellings and from where children play. Reducing fly contact with children's faces: brushing flies away, screening, keeping food covered. Not sharing bedding and eye cosmetics. Epilation: plucking in-turned lashes with simple forceps gives temporary relief and protects the cornea where surgery is not available — imperfect, since lashes regrow, but free and genuinely sight-preserving in the interim. Recognising in-turned lashes by looking, and referring that person for surgery, which is the step that prevents blindness.

Face washing targets the transmission route directly, by removing the discharge that attracts the fly and carries the organism. Trials show an effect on active trachoma; the effect sizes were not retrievable. A pit latrine is a hole, a slab and a superstructure. That is environmental engineering at village cost. Donated azithromycin is free to programmes through the International Trachoma Initiative. It is one oral dose, with no cold chain and no needle, and a community health worker can deliver it to a whole village. Trichiasis surgery is done by trained non-physician surgeons, under local anaesthesia, in a health post, with a reusable instrument set.

Antibiotics and surgery require chains, but short ones: a donated single-dose oral tablet with no cold chain, and an operation performable by a trained non-physician with basic instruments. The durable solution — water, face-washing and latrines — needs no chain whatsoever, which is the central fact about trachoma.

The measured effect of the package is 33 countries validated as having eliminated trachoma as a public health problem. The remaining burden costs US$2.9 to 5.3 billion a year, rising to US$8 billion when trichiasis is included, and the drug component of the intervention is donated.

Gaps. The source contradicts itself on the number of countries where trachoma remains a public health problem: 29 in Key Facts, 32 in the metadata; see the appendix, item 11. **WHO gives no effect size for azithromycin or for any individual SAFE component**, despite SAFE being the entire strategy. The 1.9 million blind-or-visually-impaired figure is not dated on the page, while the at-risk population is dated March 2026. **The mass azithromycin child-mortality question is genuinely contested** and has major implications for antimicrobial resistance. Antibiotic coverage is 47 per cent, and the source does not state what coverage is required for interruption. The relative contributions of F and E have never been experimentally separated, so programme design rests on plausibility rather than on comparative trial evidence. Some analyses find that antibiotic mass administration does most of the work. Others find that durable decline requires the other two components. Trial effect sizes for the facial cleanliness and environmental components could not be retrieved. The number of people who currently need trichiasis surgery is not stated, only the number who received it. Recurrence rates after trichiasis surgery vary widely between programmes.

> **Depth.** Starts in: Chlamydia trachomatis (elementary body). Size: 300 nm†; depth +1.72. First complaint: about 7.8 days († 5–12 days); time depth 45.36. One untreated course: no number ([B] decades of scarring).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Scabies

What it is. A mite that burrows in the outer skin, provoking intense itching, especially at night. Scratching breaks the skin and lets bacteria in, which is how it causes serious disease. It spreads by prolonged skin-to-skin contact, so it runs through households. The mite lays eggs in the skin it burrows into. The rash appears in the finger webs, wrists, waist and genitals.

Measured. WHO fact sheet on scabies, 31 May 2023. At least 200 million people have scabies at any one time, in Key Facts, and more than 200 million in the body — a difference of qualifier, not of value. More than 400 million people are affected cumulatively each year. The fact sheet does not attribute either figure to a specific year.

An estimated 5 to 50 per cent of children in resource-poor areas are affected. That range is extremely wide and reflects heterogeneity rather than measurement.

Children and older people in resource-poor areas are affected. Infants and small children get a more widespread rash, including the palms, soles, ankles and scalp. Scabies is found in every country.

National survey prevalences: Fiji 23 per cent of all ages and 45 per cent of children aged 5 to 9, on a 2007 national survey. Solomon Islands 19 per cent of the total population and 34 to 45 per cent of children aged 5 to 9, on research surveys over the past decade.

Acute renal damage is found in up to 10 per cent of children with scabies in resource-poor settings, via secondary streptococcal infection, which is the principal serious consequence.

Impetigo can progress to abscess and invasive disease, including septicaemia. The renal damage is acute post-streptococcal glomerulonephritis, which can persist for years. There is growing evidence that *S. pyogenes* impetigo contributes to rheumatic fever and rheumatic heart disease. Crusted (Norwegian) scabies affects immunocompromised people, including those with HIV. It is life-threatening and highly infectious.

Most individuals are infested with only 10 to 15 mites. Mass drug administration is recommended where prevalence is 10 per cent or greater.

Geography: worldwide, most common in hot, tropical, low-income, densely populated areas. Large-scale mass administrations are ongoing in Papua New Guinea, Vanuatu, Fiji and the Solomon Islands. In high-income countries it is sporadic, with outbreaks in institutions.

WHO gives no death figure. DALYs are not reported on the page; the only burden source cited in its references is GBD 2015. Scabies was added to the neglected tropical disease list in 2017.

Timing: symptoms usually begin four to six weeks after infestation, earlier on reinfestation; eggs hatch in three to four days; mites mature in one to two weeks; mites usually die after two to three days away from human skin.

Where it starts. *Sarcoptes scabiei* var. *hominis*, transmitted by prolonged direct skin-to-skin contact and, less efficiently, via bedding and clothing. The risk structure is crowding, shared beds, institutional living and poverty.

The mite is the necessary cause. Crowding and high population density are named by the World Health Organization. Shared bedding and clothing are a secondary route, because mites survive off the host for two to three days. Poverty, limited water and inability to launder bedding add to the risk. Institutional settings, such as care homes, prisons and hospitals, carry outbreaks, and the World Health Organization notes outbreaks in health institutions and vulnerable communities in high-income countries. Immunosuppression and HIV matter for crusted scabies, where mite numbers reach thousands and transmissibility is extreme. Children and older people are the age groups affected.

The consequence chain, not the mite, is why scabies matters as a disease of populations: scabies, then scratching, then bacterial superinfection with *Streptococcus pyogenes* and *Staphylococcus aureus*, then impetigo and cellulitis, and then acute post-streptococcal glomerulonephritis and acute rheumatic fever.

Not known: the quantitative contribution of scabies to the global burden of rheumatic heart disease and chronic kidney disease is suspected to be substantial but is not established. Whether a single ivermectin dose is sufficient for mass administration is explicitly still under research in WHO's own words. WHO states that the evidence for mass administration is convincing where prevalence is 10 per cent or greater and less clear at lower prevalence, so the threshold is a judgement rather than a measured inflection. Emerging ivermectin and permethrin resistance is reported in some settings and is not well quantified. Why some people develop crusted scabies, and others with similar immunosuppression do not, is not known. Why the itch persists for weeks after successful treatment is not known. It is a hypersensitivity response and not ongoing infestation, and it is the commonest reason for unnecessary re-treatment.

Cure status. CURABLE. Topical or oral scabicides kill the mites and the infestation ends. The condition is straightforwardly curable and cheaply so. Three qualifications matter in practice.

The itch persists for weeks after successful cure. WHO notes that itchiness often worsens for one to two weeks after treatment starts. A second account gives the itch as persisting for two to four weeks after cure. Treatment failure must not be assumed from continued itching. Different numbers, both loosely attributed. Both stand. Either way the cause is the same: an immune reaction to dead mites and their products, not evidence of live infestation. That distinction is what prevents endless unnecessary re-treatment.

Reinfestation from untreated household members is the usual cause of apparent failure, which is why treating the whole household simultaneously is required whether or not others have symptoms. Treating the index case alone reliably fails.

Crusted, or Norwegian, scabies in immunosuppressed or neurologically impaired people involves thousands to millions of mites and requires repeated combined oral and topical treatment. It is curable but much harder.

Measured at population scale, in studies reported in PLOS Neglected Tropical Diseases, 2026:

- Fiji, ivermectin-based mass administration arm: prevalence fell from 32 per cent to under 2 per cent one year after mass administration, a 94 per cent relative reduction.
- Fiji, standard-care control arm: prevalence fell from 36.6 to 18.8 per cent, a 49 per cent reduction.
- Solomon Islands, single-arm mass administration integrated with trachoma control, about 26,000 people: prevalence fell from 18.7 to 2.3 per cent, an 88 per cent reduction.
- Impetigo fell by 60 to 88 per cent across all three studies.
- Fiji, mass administration integrated with lymphatic filariasis control, about 135,000 people: hospitalisations for skin and soft tissue infection fell 17 per cent in the following year.

The source read reports no confidence intervals for any of these figures.

The comparison that matters: individual standard care achieved a 49 per cent reduction, while community-wide mass administration achieved 88 to 94 per cent. Treating the individuals who present does not clear a community. Treating everyone at once does, because the reservoir is removed.

Prevention.

Treating the whole household simultaneously: STRONG, on established transmission dynamics. It is the single most important individual-level measure, because untreated asymptomatic contacts reinfest, and it costs only more of a cheap drug.

Mass drug administration in endemic communities: STRONG above 10 per cent prevalence, and lower below it, below. WHO states that mass administration can substantially reduce prevalence and impetigo, and that the evidence is convincing at prevalence of 10 per cent or more and less clear below. **WHO gives no quantified reduction.** The ivermectin mass-administration dose is two doses of 200 µg/kg. Where ivermectin is contraindicated or unavailable, a topical agent such as 5 per cent permethrin is used. Below 10 per cent prevalence the grade is CONTESTED: one research line graded the evidence weaker there and another graded it contested, and WHO states no threshold of its own The large island programmes in Fiji, the Solomon Islands, Vanuatu and Papua New Guinea are the evidence base, and reported reductions in both scabies and impetigo have been large.

Published studies give 88 to 94 per cent reductions in scabies prevalence from mass drug administration, citing PLOS Neglected Tropical Diseases 2026. That is not a contradiction of fact. The WHO fact sheet records the absence of a quantified figure, and the published studies supply one.

Washing clothing and bedding in hot water, or sealing it for a week: CONTESTED on settled mite biology. Mites die after two to three days off the skin, so WHO advises sealing unwashable items in a plastic bag for a week. A second account grades the washing of bedding and clothing MODERATE, because the main route is skin contact and bedding is secondary.

Avoiding crowded sleeping arrangements and shared beds, and improving access to washing water: MODERATE, structural. Treating secondary bacterial infection: STRONG, for preventing kidney and heart sequelae.

Treating institutional outbreaks by treating the whole institution at once: STRONG. Prompt treatment of crusted scabies cases: STRONG, because they are the source of institutional outbreaks, on account of their extreme mite burden.

Treating scabies to prevent impetigo, glomerulonephritis and possibly rheumatic heart disease: the measured impetigo reduction is 60 to 88 per cent, against renal damage in up to 10 per cent of affected children. STRONG for impetigo. MODERATE for the renal and rheumatic sequelae, which follow logically and are not directly measured as mass-administration endpoints.

No vaccine exists and none is in prospect.

Treatment.

Treatment	EML	Off-patent	Price
Ivermectin, oral, two doses of 200 µg/kg	Yes, 6.6 Medicines for ectoparasitic infections, core; tablet 3 mg	Yes	Low; donated for some mass programmes. Not for pregnant women or children under 15 kg. No price confirmed; a second account gives a few US cents per dose in generic and donation-supported programmes, among the cheapest drugs in this book.
Permethrin 5 per cent cream	**Yes.** Section 13.5, Scabicides and pediculicides, core list, cream 5 per cent and lotion 1 per cent, with scabies among three listed indications	Yes	Low dollars per tube; no price confirmed. A band a second account puts a tube at under a dollar to a few US dollars, naming no market; prices in high-income markets are far higher.
Benzyl benzoate 10–25 per cent	Yes. Section 13.5, listed first in that section, lotion 25 per cent, footnoted for over-twos	Yes	UNICEF indicative US$3.38 per 1,000 mL bottle of 25 per cent lotion, October 2026 — among the cheapest effective treatments in this chapter. Cents per application. It is irritant and it stings, especially in children.
Sulphur 5–10 per cent ointment, safe in pregnancy and infancy	Yes; precipitated sulfur topical ointment is listed as the therapeutic alternative to benzyl benzoate in section 13.5	Yes	Very low; compoundable locally. Malodorous and messy.
Malathion 0.5 per cent aqueous	Not established	Yes	Low.
Antibiotics for secondary infection	Yes	Yes	Cents to low dollars
Antihistamines, topical steroid and emollients for post-treatment itch	Yes	Yes	Low. Chlorphenamine and hydrocortisone are listed and off-patent, at cents.

On the EML question: section 13.5 of the 24th List carries both benzyl benzoate and permethrin, with benzyl benzoate listed first, and permethrin is a listed medicine in its own right, for scabies, pediculosis capitis and pediculosis corporis. A doubt recorded elsewhere in the book, to the effect that only benzyl benzoate appears in that section, was checked against both the list PDF and the electronic EML and is withdrawn: both are listed.

WHO gives no efficacy percentages for permethrin or ivermectin.

Permethrin cream is the topical standard. It is applied to the whole body and left on for hours, and it is safe in young children and pregnancy. Retreatment after 7 days is needed, because treatment does not kill eggs†. Oral ivermectin is given as two doses of 200 µg/kg, 7 to 14 days apart†. It is highly effective.

The WHO scabies fact sheet lists benzyl benzoate 10 to 25 per cent, sulphur 5 to 10 per cent and malathion 0.5 per cent aqueous as treatment options. Crusted scabies is treated with repeated ivermectin doses combined with topical treatment and a keratolytic, over weeks. Antibiotics treat secondary impetigo; see the entry on bacterial skin infections in the skin chapter. Mass-administration programmes co-administer azithromycin, and the World Health Organization notes the co-administration.

Sulphur ointment is notable and deserves its own sentence. It is effective, extremely cheap, safe in pregnancy and in infants under two months, and it can be compounded locally from elemental sulphur and any available ointment base — petrolatum, or fat. It is the nearest thing in this chapter to a scabicide producible without a pharmaceutical industry, and it has been used for over a century. It is the option where permethrin and ivermectin may be avoided.

Simple means. Substantial, and nearly sufficient. It is among the best cases in the book of a cheap intervention against a large burden.

Treating everyone in the household at the same time, which is a decision rather than a resource. Washing all clothing and bedding in hot water and drying in full sun; ironing seams. Sealing unwashable items in a bag for a week, since mites die in two to three days off skin. Sulphur ointment is a locally makeable treatment where no manufactured scabicide is available. Its preparation and strength are a pharmacy task and are not given here. Keeping fingernails short and clean, which limits skin-breaking and bacterial entry. Washing the skin and keeping it clean, and treating sores promptly with clean water and whatever antiseptic is available: this interrupts the chain to kidney and heart disease, which is where the real harm lies. Not sharing beds, towels and clothing during an outbreak. Understanding that itch persists for weeks after cure, so that families do not re-treat endlessly or conclude that treatment failed. Recognising it: itch that is worse at night, affecting several household members, with burrows in finger webs, wrists, waist and genitals, and in infants on palms, soles and scalp.

Ivermectin by mass administration is two oral doses at a few cents each. It reduced community scabies prevalence by 88 to 94 per cent and community impetigo by 60 to 88 per cent. It needs no cold chain, no needle and no clinician. The tablet is dosed by weight or by height stick, and community health workers can deliver it to a whole village.

Programme coverage achieved: register-based first-dose coverage was 49 per cent in the Solomon Islands (350,217 people) and 26 per cent in Fiji (231,351 people). Coverage-survey estimates were 78 and 45 per cent respectively. Of survey respondents, 86 to 87 per cent received ivermectin and 11 to 13 per cent received permethrin for a contraindication. Mild side effects occurred in 2 to 5 per cent.

Treating the whole household at once costs only more cheap drug, and it is the difference between cure and endless reinfestation. The 49 per cent reduction with individual standard care, against 88 to 94 per cent with community mass administration, is the measured demonstration.

Washing and sun-drying bedding and clothing costs nothing. Explaining that the itch continues for weeks after cure costs nothing, and it prevents repeated unnecessary re-treatment and the conclusion that the drug failed.

Integration with existing mass drug administration programmes shares the delivery cost with programmes already running. The Solomon Islands campaign was integrated with trachoma control and the Fijian one with lymphatic filariasis control. Compounded locally, sulphur ointment costs near nothing, and where nothing else is available it still works.

The minimum chain for ivermectin or permethrin is pharmaceutical synthesis and distribution — short, with no cold chain and no needles. But sulphur ointment means that even without any pharmaceutical supply an effective treatment exists, and the preventive measures are entirely free. Of all conditions in this chapter, scabies is among the least dependent on industrial medicine.

What the chain minimally requires: a tablet, or a tube, or sulphur and an ointment base. There is essentially no supply chain requirement beyond the drug itself.

Gaps. WHO publishes no efficacy figures for any scabicide, and no quantified mass-administration effect; published studies give a figure for the latter, set out under Cure status and Prevention. **Whether one ivermectin dose suffices is explicitly unresolved** by WHO's own statement. The prevalence range in children, 5 to 50 per cent, is extremely wide. The fact sheet is dated 31 May 2023, and DALYs are not reported on it. **The contribution of scabies to rheumatic heart disease and chronic kidney disease is unquantified** — the most important gap, because it is where scabies actually kills. Emerging ivermectin and permethrin resistance is reported but not quantified. Mass-administration evidence below 10 per cent prevalence is acknowledged by WHO to be unclear, so programme thresholds rest on limited data. The post-treatment itch duration is given as one to two weeks by WHO and as two to four weeks by a second account; both stand. The 200 million and 400 million figures are not attributed to a year on the fact sheet. Its cited sources span a 2015 Global Burden of Disease estimate, a 2019 consultation and a 2015 study, so the vintage of the global estimate is unspecified. The mass-administration source reports no confidence intervals for any prevalence or reduction figure, including the headline 94, 88 and 60 to 88 per cent values. Ivermectin cannot be given to pregnant women or children under 15 kg, and the optimal regimen for those groups in mass administration is not settled. Whether treating scabies reduces the incidence of rheumatic heart disease has not been measured, though the pathway is documented.

> **Depth.** Starts in: the scabies mite. Size: 350 µm†; depth +8.14. First complaint: about 3.5 weeks († 2–6 weeks (first infestation)); time depth 46.40. One untreated course: no number († permanent if untreated).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Syphilis (including congenital syphilis)

What it is. A bacterial infection, *Treponema pallidum*, acquired sexually or passed from mother to fetus. It progresses in stages over years and can eventually damage brain, nerves and heart. In pregnancy it causes stillbirth and infant death. It has been curable with penicillin since the 1940s.

Measured. Two WHO fact sheets, and they do not agree. The syphilis-specific sheet of 29 May 2025 and the sexually transmitted infections sheet of 10 September 2025 both carry syphilis figures.

8 million adults aged 15 to 49 acquired syphilis in 2022, in the Key Facts of the STI sheet. 7.1 million new infections in 2020 among the same age group, in the body of the same sheet. Two different magnitudes and two different years on one page, nowhere reconciled. Both stand; the appendix of single-source contradictions carries this as item 12.

About 1.1 million pregnant women were infected in 2022, resulting in over 390,000 adverse birth outcomes. Among pregnancies that are untreated, treated late, or treated with the wrong antibiotic, 50 to 80 per cent result in adverse birth outcomes.

Syphilis roughly doubles the risk of acquiring HIV.

Related, from WHO's stillbirth health-topic page: syphilis treatment could prevent an estimated 200,000 stillbirths.

Timing: the primary chancre usually lasts about 21 days and heals in 3 to 10 days; transmission typically occurs up to two years after infection.

No geography is published: no regional or country figures appear on either sheet, despite marked regional variation. Gay men and other men who have sex with men are described as disproportionately affected, without figures. Denmark was reported as the first EU country to eliminate mother-to-child transmission of HIV and syphilis, WHO news item, 27 February 2026.

WHO gives no death figures for syphilis or congenital syphilis on these pages, and no congenital syphilis case count — only "adverse birth outcomes".

Where it starts. Sexual contact with a person who has primary or secondary lesions, and transplacental transmission in pregnancy. The risk structure is unprotected sex with multiple or untreated partners, absence of antenatal screening, HIV co-infection, and — for congenital syphilis — failure of antenatal testing and treatment, which is a health-system failure rather than a biological one.

The established biological fact underlying prevention is that a single intramuscular injection of benzathine penicillin G before the third trimester prevents almost all congenital syphilis.

Not known: *T. pallidum* cannot be cultured in vitro by routine means, which limits resistance surveillance and has held back vaccine development. Why latent syphilis progresses to tertiary disease in only a minority is not established. The reasons for the global resurgence of syphilis since 2000, in high-income countries with good access to testing and penicillin, are debated — behavioural change, HIV treatment optimism, network effects and testing patterns are all proposed. Optimal treatment of neurosyphilis and of syphilis in HIV co-infection is not fully settled.

Cure status. Split.

the infection: CURABLE established tertiary organ and nerve damage: RELIEF ONLY

A single intramuscular dose of benzathine penicillin G cures early syphilis; later stages require weekly doses for three weeks. **WHO gives no cure-rate percentage.** There is no established penicillin resistance in *T. pallidum* after eighty years of use — a notable fact in a chapter dominated by resistance. Established tertiary organ and neurological damage is not reversed by cure, and cure confers no immunity, so reinfection is common.

Prevention.

Antenatal screening and treatment: STRONG — the highest-value intervention in this entry. Treating an infected pregnant woman with benzathine penicillin before the third trimester prevents the great majority of the 390,000-plus annual adverse birth outcomes. The arithmetic is stark: 1.1 million infected pregnancies, a single injection costing cents, and over 390,000 bad outcomes that largely need not occur.

Condoms: STRONG for sexual transmission, though lesions outside the covered area reduce protection relative to HIV.

Partner notification and treatment: STRONG. Screening and treating key populations: STRONG. Treating syphilis to reduce HIV acquisition: STRONG, given that syphilis roughly doubles HIV risk.

Dual HIV and syphilis rapid testing in antenatal care: STRONG — a single point-of-care test, requiring no laboratory, that enables same-visit treatment.

No vaccine exists, and the inability to culture the organism is part of the reason.

Treatment.

Treatment	EML	Off-patent	Price
Benzathine penicillin G, single intramuscular dose for early syphilis, weekly for three weeks for late	Yes, 6.2.1 Access group antibiotics, core, first choice for syphilis with no second-choice indication; injectable powder 1.2 and 2.4 million IU	Yes	UNICEF indicative US$29.49 per box of 50 2.4 MIU vials, October 2026, about 59 US cents a vial; the single-vial-with-solvent pack is US$3.01, five times as much per dose
Doxycycline, penicillin allergy, non-pregnant	Yes	Yes	Cents per course
Ceftriaxone, alternative	Yes	Yes	Low dollars
Aqueous crystalline penicillin G, neurosyphilis	Yes	Yes	Low; requires intravenous administration
Rapid point-of-care syphilis test	Yes, diagnostics list	Yes	A few US dollars or less per test

The UNICEF indicative price is dated and indicative, not a price: the same material number returned US$29.49 on one catalogue page and US$29.12 on another when read on 19 October 2026. Both values are

recorded. What the figures establish is the order of magnitude: the curative dose costs well under a dollar, and the packaging choice changes the per-dose cost fivefold.

WHO publishes no cure rate and no prices on these fact sheets. Penicillin desensitisation is preferred for pregnant women with penicillin allergy, since no alternative reliably protects the fetus.

Simple means. Limited for treatment, real for prevention.

Condoms, which are manufactured but need no prescription, cold chain or clinician. Fewer concurrent partners, and partner notification — behavioural measures requiring nothing. Recognising the primary sore: a painless ulcer on the genitals, anus or mouth, which heals by itself and is therefore frequently ignored — and recognising that its healing does *not* mean the infection has gone. Knowing that single fact changes whether a person seeks treatment. Recognising secondary syphilis: a rash including palms and soles, often with mouth lesions, weeks to months later. Attending antenatal care at all, and asking for a syphilis test, which is the step that prevents congenital syphilis. Abstaining from sex while a lesion is present and during treatment.

Nothing simple cures syphilis. The minimum chain is modest but irreducible: benzathine penicillin G requires penicillin fermentation and sterile injectable manufacture, plus a syringe and someone able to give an intramuscular injection. There is no oral single-dose equivalent for pregnancy, and no plant or household preparation works.

Given that the cure costs cents and has existed since the 1940s, congenital syphilis is almost entirely a failure of delivery. The recurrent global shortages of this cheap off-patent injectable are a manufacturing-economics failure, not a scientific one.

Gaps. WHO's two fact sheets give different figures for different years — 8 million in 2022 and 7.1 million in 2020 — without reconciliation; see the appendix, item 12. **WHO publishes no congenital syphilis case or death count on the syphilis fact sheet, and no death figures at all** — only adverse birth outcomes. **No geography is published** : no regional or country figures, despite marked regional variation. **No cure-rate figure and no prices. Recurrent benzathine penicillin shortages are documented in the wider literature but are not mentioned on the WHO fact sheets.** The reasons for the global resurgence since 2000 are genuinely debated. Optimal management of neurosyphilis and of syphilis with HIV co-infection is unsettled.

> **Depth.** Starts in: Treponema pallidum (its length). Size: 10 µm†; depth +4.91. First complaint: about 3 weeks († about 21 days (10–90)); time depth 46.27. One untreated course: no number ([B] years, in stages).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Gonorrhoea

What it is. A bacterial infection of the genital tract, throat, rectum or eyes, *Neisseria gonorrhoeae*. It often causes discharge and pain, but frequently nothing at all, especially in women. Untreated it damages fallopian tubes and causes infertility. It is becoming resistant to every antibiotic used against it.

Measured. WHO fact sheet on sexually transmitted infections, 10 September 2025, and the fact sheet on antimicrobial resistance, 16 July 2026.

82 million new infections in 2020 among people aged 15 to 49. That figure sits within a total of 374 million new infections of one of four curable sexually transmitted infections in 2020, and more than 1 million curable infections acquired per day.

Gonorrhoea resistance to ciprofloxacin: 75 per cent.

WHO's Gonococcal Antimicrobial Surveillance Programme shows high rates of resistance to quinolones, azithromycin and extended-spectrum cephalosporins; the STI fact sheet gives no percentages for these.

WHO reports no deaths from gonorrhoea. The burden is morbidity, infertility and neonatal eye infection. No geography or age breakdown is published on these pages. The STI sheet gives no treatment figures, stating only that gonorrhoea is generally curable with single-dose antibiotics.

Where it starts. *N. gonorrhoeae*, transmitted by unprotected vaginal, anal and oral sex, and from mother to baby during delivery, causing ophthalmia neonatorum — a cause of neonatal blindness. The risk structure is unprotected sex, multiple or concurrent partners, and asymptomatic infection, which in women especially sustains transmission and leads to untreated tubal damage.

The resistance mechanism is established: *N. gonorrhoeae* readily acquires and recombines resistance determinants, including from commensal *Neisseria* species in the pharynx. Pharyngeal infection, often asymptomatic, is the recognised crucible in which cephalosporin resistance develops, because antibiotic concentrations there are marginal.

Not known: whether a durable vaccine is achievable is unresolved. Natural infection confers no protective immunity and repeated reinfection is common, so the immunological basis for a vaccine is unclear. The observation that the meningococcal B vaccine, 4CMenB, affords partial cross-protection against gonorrhoea is established enough to have prompted programme recommendations in some countries, and it is the most promising current lead; its durability and magnitude are not settled. How quickly resistance to ceftriaxone will become widespread is not predictable, and extensively resistant strains have already been reported.

Cure status. CURABLE. This is the condition in the chapter with the clearest trajectory *away* from curability.

Ceftriaxone, given as a single injection, currently cures it. Ciprofloxacin is at 75 per cent resistance and effectively lost. Penicillins, tetracyclines, sulphonamides and macrolides are substantially lost, with azithromycin resistance rising. Ceftriaxone is the last reliable single-agent option, and extensively drug-resistant strains resistant to it have been reported in several countries.

WHO classifies drug-resistant *N. gonorrhoeae* as a high-priority pathogen. The honest classification is CURABLE today, with a credible prospect of becoming untreatable with existing agents. New agents, zoliflodacin and gepotidacin, have completed trials and represent the near-term alternative.

Prevention.

Condoms: STRONG. The barrier blocks the transmission route.

Screening of asymptomatic high-risk and pregnant people: STRONG, because asymptomatic infection drives both transmission and sequelae.

Partner notification and treatment: STRONG.

Neonatal eye prophylaxis at birth: STRONG on settled physiology. A topical antimicrobial applied to the newborn’s eyes prevents gonococcal ophthalmia and consequent blindness. Cheap, topical, long-established.

Treating promptly to limit transmission and resistance: STRONG.

4CMenB meningococcal vaccine cross-protection: MODERATE. Observational and some trial evidence supports partial protection; magnitude and duration are unsettled, and **no effect size is asserted here**. It is the only vaccine-based option currently available, and it is recommended for specific populations in some countries. The chain is long: a recombinant protein meningococcal vaccine requiring fermentation, protein purification, adjuvanting, sterile fill-finish, a needle and an unbroken 2–8 °C cold chain.

No gonorrhoea-specific vaccine exists.

Avoiding antibiotic use that selects for resistance, including azithromycin mass distribution: CONTESTED in its weighting against the benefits of such programmes; see the trachoma entry.

Treatment.

Treatment	EML	Off-patent	Price
Ceftriaxone, single intramuscular dose, current first line	Yes	Yes	Low dollars per dose
Azithromycin, formerly dual therapy; resistance rising	Yes, 6.2.2 Watch group, first and second choice for gonorrhoea	Yes	UNICEF indicative about 9.3 US cents a 250 mg tablet, October 2026
Cefixime, oral alternative, declining reliability	Yes	Yes	Low
Ciprofloxacin	Yes	Yes	Cents — but at 75 per cent resistance, largely useless
Spectinomycin, gentamicin, alternatives	Yes	Yes	Low
Topical neonatal eye prophylaxis: tetracycline or erythromycin ointment, povidone-iodine	Yes	Yes	Cents per newborn
Zoliflodacin, gepotidacin, new agents	Not yet	No	Not yet widely deployed; zoliflodacin developed partly through a non-profit partnership, GARDP

Simple means. Condoms, which prevent transmission entirely when used. Fewer concurrent partners; partner notification. Recognising symptoms — discharge, pain on urinating, testicular or pelvic pain — and recognising that absence of symptoms does not mean absence of infection, particularly in women and in pharyngeal and rectal infection. Abstaining from sex during treatment and until partners are treated, which prevents the reinfection that sustains transmission in couples. Cleaning the newborn's eyes at birth and applying whatever topical antimicrobial is available — and recognising purulent conjunctivitis in the first days of life as an emergency, because untreated gonococcal ophthalmia blinds within days. Noticing it requires only looking.

Nothing simple cures gonorrhoea. The minimum chain is injectable ceftriaxone — cephalosporin synthesis, sterile injectable manufacture, a syringe and an injector. There is no oral household remedy, and self-treatment with partial or inappropriate antibiotics is a direct contributor to the resistance that threatens the last working drug. For the newborn, topical ointment is a very short chain and prevents blindness for cents.

Gaps. WHO publishes resistance only as "high rates" for azithromycin and cephalosporins, with a figure for ciprofloxacin alone, so the state of resistance to the actual first-line drug is not quantified in the sources used. **No geography, no age pattern, no infertility burden figures.** The infection figure is for 2020. **Whether a vaccine is achievable is genuinely unresolved**, given that natural infection confers no immunity. 4CMenB cross-protection magnitude and durability are unsettled, and policy differs between countries from the same evidence. The timeline to untreatable gonorrhoea is unpredictable, and sources differ on urgency. **Neonatal ophthalmia burden is not quantified by WHO.**

> **Depth.** Starts in: Neisseria gonorrhoeae. Size: 800 nm†; depth +2.61. First complaint: about 3.7 days († 2–7 days); time depth 44.70. One untreated course: no number († months if untreated).
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Chlamydia

What it is. The most common bacterial sexually transmitted infection, *Chlamydia trachomatis*. In most people it causes no symptoms at all, which is why it spreads widely. Untreated, it scars fallopian tubes and causes infertility and ectopic pregnancy.

Measured. WHO fact sheet on sexually transmitted infections, 10 September 2025. 129 million new infections in 2020 among people aged 15 to 49 — the largest number of any bacterial sexually transmitted infection in this chapter, and the second largest of the four curable infections after trichomoniasis at 156 million.

WHO reports no deaths and no drug resistance for chlamydia. No geography, age breakdown or infertility burden figures are published on the page. WHO gives no treatment figures, stating only that it is generally curable with single-dose antibiotics.

The same organism, in different serovars and transmitted non-sexually, causes trachoma, the leading infectious cause of blindness. The two conditions share a pathogen and nothing else epidemiologically.

Where it starts. *C. trachomatis* serovars D to K, transmitted by unprotected vaginal, anal and oral sex, and from mother to baby at delivery, causing neonatal conjunctivitis and pneumonia. The risk structure is unprotected sex, young age — incidence is highest in adolescents and young adults — multiple or new partners, and above all asymptomatic carriage. The majority of infections in both sexes produce no symptoms, so infection persists unrecognised for months and is transmitted onward and causes tubal damage silently. Serovars L1 to L3 cause lymphogranuloma venereum.

Not known: whether population screening programmes actually reduce pelvic inflammatory disease and infertility at population level is genuinely contested. Screening is recommended in several high-income countries on the logic that treating asymptomatic infection prevents sequelae. But trial and programme evidence of population-level impact has been weaker than expected, and some analyses suggest screening may interfere with the development of partial protective immunity. Good sources disagree, and some countries have scaled screening back while others maintain it. Why only a minority of untreated infections progress to tubal damage is not established. No vaccine exists, although trachoma and genital chlamydia vaccine research is converging and early-phase candidates have shown immunogenicity.

Cure status. Split.

the infection: CURABLE established tubal scarring and infertility risk: RELIEF ONLY

Chlamydia is cured reliably by a short course of doxycycline or a single dose of azithromycin. There is no established clinically significant antimicrobial resistance in *C. trachomatis*, which WHO's own fact sheet reflects by reporting none — a genuine exception in this chapter.

Established tubal scarring, infertility and ectopic pregnancy risk are not reversed by curing the infection, and infertility treatment is a separate and expensive matter. Cure confers no durable immunity, so reinfection is common, particularly from untreated partners. Doxycycline has been shown superior to azithromycin for rectal infection.

Prevention.

Condoms: STRONG.

Partner notification and treatment: STRONG, and the principal determinant of whether cure holds.

Screening of asymptomatic young and pregnant people: CONTESTED at population level, STRONG at individual level. Both must be stated. Treating a detected infection in an individual prevents that person's sequelae. Whether organised screening programmes measurably reduce population rates of pelvic inflammatory disease and infertility is disputed, programme evaluations have given mixed results, and countries differ in policy from the same evidence base. **No single effect size is asserted for the population-level question.**

Retesting after treatment: MODERATE, given high reinfection rates.

Neonatal eye prophylaxis: MODERATE — topical prophylaxis is less effective against chlamydial than gonococcal ophthalmia.

No vaccine exists.

Treatment.

Treatment	EML	Off-patent	Price
Doxycycline, 7 days, first line	Yes	Yes	Cents per course — among the cheapest curative treatments in medicine
Azithromycin, single dose,	Yes, 6.2.2 Watch group,	Yes	UNICEF indicative about 9.3 US

Treatment	EML	Off-patent	Price
alternative and preferred in pregnancy	first choice for chlamydial STI		cents a 250 mg tablet, October 2026
Amoxicillin, pregnancy alternative	Yes	Yes	About 5.4 US cents a 250 mg dispersible tablet, UNICEF indicative, October 2026
Erythromycin, neonatal	Yes	Yes	Cents per course
Nucleic acid amplification test, for diagnosis	Yes, diagnostics	Partly	The expensive component; several US dollars per test, requiring laboratory capacity

The diagnostic, not the drug, is the costly part. Doxycycline costs cents, while confirming the infection requires molecular testing. In low-resource settings that inverts the usual economics, and it is why syndromic management — treating on symptoms — persists, despite most infections being asymptomatic and therefore invisible to it.

Simple means. Condoms. Partner notification and simultaneous treatment — a conversation, not a resource. Fewer concurrent partners. Abstaining from sex during treatment and until partners complete treatment. Recognising that most infection is silent, so that symptoms are not used as the criterion for seeking testing: this single piece of knowledge is the main non-material intervention available. Recognising neonatal conjunctivitis and infant pneumonia in the weeks after birth as possible chlamydial infection requiring treatment.

Nothing simple cures chlamydia, and nothing simple detects it. The second half of that sentence is the key limitation. Unlike syphilis, which produces a visible sore, and gonorrhoea, which often produces discharge, chlamydia is usually invisible without a molecular test. The minimum chain therefore has two parts: doxycycline manufacture, which is short, cheap, oral and needs no cold chain; and nucleic acid amplification testing capability, which needs a laboratory, reagents, a cold chain and trained staff. Without the second, most infections are never found. Syndromic management catches only the symptomatic minority.

Gaps. WHO publishes no deaths, no geography, no age pattern and no infertility burden for the most common bacterial sexually transmitted infection — the thinnest WHO data in this chapter relative to case numbers. The infection figure is for 2020. **Whether screening programmes reduce population-level sequelae is genuinely contested**, with countries diverging in policy. The proportion of untreated infections progressing to tubal damage is not well established. Whether screening interferes with partial natural immunity is an open and contested hypothesis. No vaccine, and no licensed candidate. The diagnostic cost barrier is not addressed in WHO's framing of the condition as curable with single-dose antibiotics.

> **Depth.** Starts in: Chlamydia trachomatis (elementary body). Size: 300 nm†; depth +1.72. First complaint: about 12 days († 7–21 days); time depth 45.77. One untreated course: no number ([B] months unnoticed).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Varicella (chickenpox) and herpes zoster (shingles)

What it is. One virus causing two diseases. Varicella-zoster virus causes chickenpox on first infection, then stays dormant in nerve roots for life. Decades later it can reactivate along a single nerve as shingles, which is painful and can leave lasting nerve pain.

Measured. No WHO fact sheet for varicella or herpes zoster was retrieved. The web search budget was exhausted before alternative primary sources could be reached, and the 19 October 2026 retrieval pass did not close it.

Varicella cases. Varicella deaths. Zoster incidence. Zoster lifetime risk. Post-herpetic neuralgia frequency. No case or death figures are asserted for either condition.

What can be stated without a numerical claim. Varicella is near-universal in unvaccinated populations, with infection typically in childhood in temperate climates and somewhat later in some tropical settings. It is substantially more severe in adults, in pregnancy and in the immunocompromised. Herpes zoster incidence rises steeply with age, and post-herpetic neuralgia risk rises with age as well. The commonly repeated figure, that roughly a third of people in unvaccinated populations experience zoster in a lifetime, was not sourced here and is **not asserted.**

Where it starts. Varicella-zoster virus, transmitted by respiratory aerosols and by contact with vesicle fluid. It is highly contagious.

Shingles is not caught from another person. It is reactivation of virus already latent in the person's own dorsal root or cranial nerve ganglia since their childhood chickenpox. A person with shingles can, however, transmit varicella to a susceptible person through vesicle contact. Risk factors for reactivation: increasing age, immunosuppression from HIV, chemotherapy, transplantation or corticosteroids, and physical and psychological stress.

Not known: what triggers reactivation in a given individual at a given time is not established. Declining cell-mediated immunity with age is the general explanation but not a predictive one. The mechanism of post-herpetic neuralgia, and why some patients develop persistent pain and others do not, is not established, and treatment is poor.

Whether childhood varicella vaccination increases zoster incidence in older adults — by removing the natural immune boosting that comes from exposure to infected children — is a genuinely contested hypothesis, with substantial modelling literature on both sides and no resolution. It has influenced some countries' decisions not to introduce universal varicella vaccination.

Cure status. Split three ways, and all three statements are needed.

varicella in a healthy child: SELF-LIMITING varicella in adults, pregnancy, immunosuppression: RELIEF ONLY latency: CONTROLLABLE herpes zoster and post-herpetic neuralgia: RELIEF ONLY

Varicella in a healthy child resolves unaided in about a week, and antivirals are not routinely indicated. In adults, pregnancy and immunosuppression antivirals materially reduce severity and are indicated, but nothing removes the virus; severe varicella pneumonia and disseminated infection can be fatal.

Nothing removes latent virus from nerve ganglia, so no one who has had chickenpox can be freed of the risk of shingles. That state is held at best, by vaccination to boost immunity.

For herpes zoster, antivirals started within about 72 hours reduce duration and severity and may reduce post-herpetic neuralgia, but nothing removes the virus. Post-herpetic neuralgia is often poorly relieved, managed with amitriptyline, gabapentin or pregabalin, topical lidocaine or capsaicin — all partial.

Prevention.

Varicella vaccination: STRONG, with a one-dose against two-dose distinction. This is a live attenuated vaccine. **Precise efficacy figures with confidence intervals are not asserted**, because no primary source was retrievable. The established pattern from the meta-analytic literature is that one dose gives good protection against severe varicella but incomplete protection against any varicella, with breakthrough cases, while two doses give substantially higher protection against any disease. The figures belong in the WHO position paper on varicella vaccines and in the one- against two-dose meta-analyses.

Varicella vaccine needs an unbroken cold chain and is among the more fragile vaccines in distribution terms. It requires human diploid cell culture, it is notably heat- and light-labile, and some formulations require frozen storage rather than 2–8 °C.

Herpes zoster vaccination: STRONG for the recombinant adjuvanted vaccine. The recombinant adjuvanted product, containing glycoprotein E with AS01B adjuvant, has substantially higher and more durable efficacy than the older live attenuated zoster vaccine, including in older age groups where the live vaccine performed poorly. **Figures with confidence intervals are not asserted** for want of a retrievable primary source; the ZOE-50 and ZOE-70 trials are the sources.

The recombinant zoster vaccine's chain is long. It needs recombinant protein expression plus AS01B adjuvant, which requires QS-21 saponin from *Quillaja saponaria* and MPL. Then sterile fill-finish, an unbroken 2–8 °C cold chain, a needle, and reconstitution of two components at the point of use.

Varicella-zoster immunoglobulin for susceptible high-risk contacts — pregnant women, neonates, the immunocompromised: STRONG. It requires plasma fractionation.

Post-exposure varicella vaccination within three to five days: MODERATE for susceptible healthy contacts.

Isolation of cases: MODERATE, limited by infectiousness beginning before the rash.

Universal childhood varicella vaccination: CONTESTED as policy — not on its direct efficacy but on the zoster-boosting question above. Some countries vaccinate universally and others deliberately do not, from the same evidence. **Neither side's modelled magnitude is asserted here.**

Treatment.

Treatment	EML	Off-patent	Price
Aciclovir, oral or intravenous; varicella in at-risk groups, and zoster	Yes	Yes	Cents to low dollars per course generically
Valaciclovir, famciclovir, better oral bioavailability	Partly	Yes	Low dollars per course
Paracetamol, symptom relief; **avoid aspirin in children**	Yes	Yes	Cents
Calamine, cool compresses, antihistamines, for itch	Partly	Yes	Cents
Amitriptyline, gabapentin, pregabalin, for post-herpetic neuralgia	Yes for amitriptyline and gabapentin	Yes	Cents to low dollars per month
Topical lidocaine, capsaicin	Partly	Yes	Low to moderate
Varicella-zoster immunoglobulin	Yes	Yes	High; plasma-derived
Varicella vaccine; recombinant zoster vaccine	Varicella yes; zoster status not confirmed on the 24th List	Varicella yes; recombinant zoster no	Varicella low; the recombinant zoster vaccine is expensive — roughly US$150–200 per dose in high-income markets, two doses required† — and is largely unavailable in low-income settings

Aspirin must not be given to children with varicella, because of Reye syndrome. This is a well-established and important contraindication.

Simple means. Considerable for varicella, modest for zoster.

Rest, fluids and time — the whole treatment for a healthy child with chickenpox. Keeping nails short and hands clean, and preventing scratching, which prevents the bacterial superinfection and scarring that are the main avoidable harms. Cool baths, oatmeal or baking-soda soaks, calamine, cool wet compresses for itch. Paracetamol, never aspirin in children. Keeping the case away from pregnant women, newborns and anyone immunosuppressed, for whom varicella is dangerous — a decision, not a resource, and the highest-value simple measure here. Keeping zoster lesions covered, which prevents transmitting varicella to susceptible people. For zoster pain: cool compresses, loose clothing avoiding pressure on the area, and keeping the rash clean and dry. Recognising zoster affecting the eye or the tip of the nose, the ophthalmic distribution, as needing urgent care, since it threatens sight — recognisable by looking. Watching for the danger signs in varicella: breathlessness, confusion, extensive or bleeding rash, high persistent fever, or any varicella in an adult or immunosuppressed person.

Nothing simple prevents shingles, and nothing simple relieves post-herpetic neuralgia well. Prevention of both diseases requires vaccines with long and fragile chains, and the recombinant zoster vaccine is additionally expensive and patent-protected — which makes it one of the least accessible interventions in

this chapter, despite addressing a condition of universal old age. Aciclovir, by contrast, is cheap, off-patent and oral.

Gaps. This entry lacks burden figures entirely. No WHO fact sheet was retrieved and the search budget was exhausted. Varicella and zoster incidence, mortality and post-herpetic neuralgia frequency are all missing and belong in the WHO position papers and in GBD. **Vaccine efficacy figures with confidence intervals are absent** for varicella, one and two dose, and for both zoster vaccines; these are the most important additions needed, and ZOE-50, ZOE-70 and the varicella dose meta-analyses are the sources. **The zoster-boosting hypothesis is genuinely contested** and has driven divergent national policy. The mechanism and treatment of post-herpetic neuralgia are poorly established, and treatment is frequently inadequate. The recombinant zoster vaccine's price places it outside most of the world, and no low-income pricing arrangement is documented. Zoster burden in HIV-endemic settings, where reactivation occurs in younger adults, is poorly quantified.

> **Depth.** Starts in: the varicella-zoster virus. Size: 180 nm†; depth +1.25. First complaint: about 14 days ([W] 9–21 days); time depth 45.89. One untreated course: about 7 days († 5–10 days; [B] then latent for life); depth 45.28.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The bound applies. The virus stays latent in the nerve root. So it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Ebola virus disease and other viral haemorrhagic fevers

What it is. A group of severe viral illnesses causing fever, organ failure and, in some, bleeding. Ebola spreads through direct contact with the body fluids of the sick and the dead, so it concentrates in families and in those who care for them. Case fatality has ranged from a quarter to nine-tenths.

Measured. WHO fact sheet on Ebola virus disease, 24 April 2025. Case fatality averages around 50 per cent, and past outbreaks have ranged from 25 to 90 per cent. Six *Orthoebolavirus* species have been identified, of which three cause large outbreaks.

Incubation is 2 to 21 days, and contacts are monitored for 21 days. Ebola virus has been found in semen up to fifteen months after recovery, and male survivors without access to a semen testing programme are advised to practise safer sex for 12 months.

The 1976 index outbreaks were Sudan virus disease in Nzara, now South Sudan, and Ebola virus disease in Yambuku, now DR Congo; the virus is named after the Ebola River near Yambuku.

WHO gives no case or death counts on this fact sheet — not for any outbreak, including the 2014–2016 West African epidemic, the largest on record. WHO's navigation listed a May 2026 public health emergency declaration for a Bundibugyo virus outbreak, but the fact sheet body carries no figures for it.

Other haemorrhagic fevers within this chapter's scope, for which no fact sheets were retrieved and **no figures are asserted** : Marburg virus disease, Lassa fever, Crimean-Congo haemorrhagic fever, Rift Valley fever, yellow fever and hantavirus infections. Lassa fever is endemic in West Africa with a large annual burden and a much lower case fatality than Ebola. Yellow fever is vaccine-preventable with a highly effective single-dose vaccine; WHO's immunization coverage sheet of 15 July 2026 gives yellow fever vaccine coverage at 53 per cent in the 40 at-risk countries and territories, against a recommended 80 per cent. Lassa fever and yellow fever carry substantial burden and warrant their own entries.

Where it starts. Ebolaviruses, with fruit bats the probable reservoir, introduced to humans through contact with infected wildlife — bats, non-human primates, forest antelope. From there it passes human to human by direct contact with blood, secretions, organs or other body fluids of infected people, with contaminated surfaces and materials, and with the bodies of the dead.

Two amplifying factors are established, and they are what the response addresses: funeral practices involving washing and touching the body, and care of the sick at home and in facilities without protective equipment. That is why health workers and family carers are disproportionately infected. Viral persistence

in semen, eye and central nervous system is established, with documented transmission from survivors months after recovery.

Not known: the reservoir has not been definitively confirmed. Bats are strongly implicated but the complete ecology of spillover is not established, and it is not known why outbreaks begin where and when they do. Why case fatality varies from 25 to 90 per cent across outbreaks is not explained: virus species, availability of supportive care, host factors and reporting completeness all contribute in unquantified proportions. The determinants and duration of viral persistence in survivors, and the frequency of survivor-derived transmission, are not well quantified. The mechanisms of post-Ebola syndrome — joint pain, eye disease, neurological symptoms — are unestablished.

Cure status. Split by species. The split is recent and it matters.

Zaire ebolavirus: CURABLE Sudan, Bundibugyo and other species: RELIEF ONLY

WHO names mAb114, ansuvimab, and REGN-EB3, Inmazeb, as WHO-recommended for Zaire ebolavirus, and **gives no efficacy figures**. These were established in the PALM randomised trial during the 2018–2020 DRC outbreak, which showed markedly lower mortality with these two agents than with the comparators; **the trial figures could not be retrieved**, so none is asserted. With early presentation and these agents plus intensive supportive care, survival is now the expected outcome rather than the exception. The label rests on a trial whose figures are not printed here.

The licensed monoclonals are specific to Zaire ebolavirus and do not work against Sudan ebolavirus, and neither does the licensed vaccine. The 2022 Uganda Sudan virus outbreak and the 2026 Bundibugyo outbreak had no licensed specific treatment or vaccine.

Supportive care alone substantially reduces mortality — aggressive fluid and electrolyte replacement, treatment of co-infections, and organ support. That is not a cure, but it is the difference between the high and low ends of the 25 to 90 per cent range.

Prevention.

Infection prevention and control in care settings: STRONG. Barrier precautions, isolation, safe injection and safe waste handling. This is what ends outbreaks.

Safe and dignified burial: STRONG. Funeral practices involving contact with the body are a major amplifier, and modifying them while respecting mourning is established outbreak practice.

Contact tracing and 21-day monitoring: STRONG.

Ervebo, rVSV-ZEBOV-GP vaccine: STRONG for Zaire ebolavirus. WHO notes that SAGE recommended it for outbreak response in July 2024, and **gives no efficacy percentage**. The Guinea "Ça Suffit" ring vaccination trial reported 100 per cent efficacy in the immediate-vaccination arm in its interim analysis, with no cases occurring ten or more days after randomisation. **The exact confidence interval could not be retrieved from a primary source and is not given.** It protects only against Zaire ebolavirus. A second vaccine regimen, Zabdeno with Mvabea — Ad26.ZEBOV and MVA-BN-Filo — is also available for preventive use.

Ervebo has the longest and most demanding chain of any product in this chapter. It is a live recombinant vesicular stomatitis virus requiring mammalian cell culture under containment, sterile fill-finish, and storage at −60 °C to −80 °C. That is an ultra-cold chain comparable to the mRNA COVID vaccines, deployed in some of the least electrified regions in the world. Ring vaccination in such settings required purpose-built passive cold boxes.

Ring vaccination strategy: STRONG, vaccinating contacts and contacts of contacts rather than whole populations.

Avoiding contact with bats, bushmeat and sick wildlife, and cooking meat thoroughly: MODERATE, for preventing spillover.

Survivor semen testing and safer sex for 12 months: STRONG, on the established persistence data.

Treatment.

Treatment	EML	Off-patent	Price
Ansuvimab (mAb114), Zaire ebolavirus only	Status on the 24th List not confirmed	No, patented	No published price for outbreak use; supplied through stockpiles
REGN-EB3 (Inmazeb), Zaire ebolavirus only	Status not confirmed	No, patented	No published price; US list prices for monoclonals of this class are in the tens of thousands of US dollars per course; outbreak supply is through donation and stockpile
Aggressive supportive care: oral and intravenous fluids, electrolyte correction, antimalarials and antibiotics for co-infection, oxygen	Yes, for fluids and oxygen	Yes	Low per patient, but requires staffed treatment units
Ervebo vaccine, prevention, Zaire only	Status not confirmed	No	Supplied via the ICG global stockpile; no market price applies
Nothing species-specific for Sudan or Bundibugyo	—	—	—

The monoclonals exist only for Zaire ebolavirus. That is the single most important qualification in this entry.

Simple means. Substantial for stopping transmission, almost nothing for curing.

Not touching the sick or the dead without protection. This is the central measure, and it is a matter of knowledge and practice rather than of supply. Safe and dignified burial: burial without washing and touching the body, conducted by trained teams or by families instructed in it, with mourning practices adapted rather than forbidden. Isolating the sick person in a separate space, with one designated carer rather than many. Improvised barrier protection: gloves, plastic sheeting, impermeable aprons, boots, eye covering — imperfect, far better than bare hands, and historically what available staff used. Handwashing with soap, and chlorine solution for surfaces and hands, which can be made from locally available bleach powder — a genuinely low-chain, highly effective measure. The dilutions are set by the outbreak response team and are not given here. Oral rehydration, given early and in volume: Ebola kills substantially through fluid and electrolyte loss, and oral rehydration alone measurably improves survival before any intravenous access exists, which makes it the single most valuable simple treatment here. Separating the carer's clothing and bedding; burning or chlorinating contaminated material. Contact tracing by local knowledge — listing who visited and who touched, which requires only pen, paper and trust. Keeping survivors' semen testing and safer-sex advice in circulation after the outbreak ends.

The monoclonals and the vaccine cannot be improvised, and the vaccine's −60 °C to −80 °C requirement makes it one of the least deployable products in existence outside an organised response. The minimum chain is mammalian cell culture under high containment, sterile fill-finish, an ultra-cold chain, an international stockpile, and an emergency response able to reach a village within days.

But the historical record is that Ebola outbreaks were stopped, repeatedly, before any vaccine or drug existed — by isolation, barrier precautions, safe burial and contact tracing. Those remain the measures that end outbreaks, and they are largely simple.

Gaps. WHO gives no case or death counts on the Ebola fact sheet — not even for the 2014–2016 West African epidemic. **No efficacy figures with confidence intervals are published by WHO for Ervebo, ansuvimab or REGN-EB3**, and the Ça Suffit and PALM trial figures could not be retrieved. **No figures at all are asserted for Marburg, Lassa, Crimean-Congo haemorrhagic fever, Rift Valley fever, yellow fever or hantaviruses**, all of which belong in this chapter; Lassa fever and yellow fever in particular carry substantial burden and need their own entries. The reservoir is not definitively confirmed. The 25 to 90 per cent case fatality range is unexplained, and the source does not disaggregate it by species or by care availability. No specific treatment or vaccine exists for Sudan or Bundibugyo virus, and the 2026 Bundibugyo outbreak had no published figures on the retrieved page. Post-Ebola syndrome and survivor viral persistence are poorly quantified.

> **Depth.** Starts in: the Ebola virus (its length). Size: 970 nm†; depth +2.78. First complaint: about 6.5 days ([W] 1–21 days); time depth 45.20. One untreated course: about 10 days († 1–2 weeks); depth 45.59.

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Antimicrobial resistance (cross-cutting)

What it is. Not a disease but a property that infections acquire: the organism stops responding to the drugs that used to kill it. It converts curable conditions into uncurable ones, which is why it appears in almost every entry in this chapter. It arises wherever antimicrobials are used.

This entry takes the eight sections of a condition because the book's form is uniform, and because the questions the form asks — what prevents it, what treats it, what can be done with simple means — all have answers here. It is not a condition, and the CURE STATUS section says so.

Measured. Two sources, and they are the same family of estimates at different vintages.

GBD 2021 bacterial AMR analysis, IHME, published in the *Lancet* in 2024:

- 2021 deaths *associated with* bacterial AMR: 4.71 million (95 per cent UI 4.23–5.19 million)
- 2021 deaths *attributable to* bacterial AMR: 1.14 million (95 per cent UI 1.00–1.28 million)
- 2050 forecast, attributable: 1.91 million (95 per cent UI 1.56–2.26 million)
- 2050 forecast, associated: 8.22 million (95 per cent UI 6.85–9.65 million)

Age pattern, 1990 to 2021: deaths in children under five fell by more than 50 per cent, while deaths in people aged 70 and over rose by more than 80 per cent. Under-five AMR mortality fell in every super-region, and mortality in those aged five and over rose in all super-regions. By 2050, people aged 70 and over are forecast to account for 65.9 per cent (95 per cent UI 61.2–69.8) of all-age attributable deaths.

WHO fact sheet on antimicrobial resistance, 16 July 2026:

- more than 4.7 million deaths associated with bacterial AMR in 2021, consistent with the GBD figure above
- about one in six, roughly 17 per cent, of laboratory-confirmed common bacterial infections were resistant in 2023; one in three reported infections were resistant in the WHO South-East Asia and Eastern Mediterranean Regions
- resistance rose in over 40 per cent of monitored pathogen-antibiotic combinations between 2018 and 2023, at an average annual increase of 5 to 15 per cent
- gonorrhoea: 75 per cent ciprofloxacin resistance
- tuberculosis: 3.2 per cent of new episodes drug-resistant, 16 per cent of previously treated episodes
- antibiotic use in 2022: Access group about 53 per cent of global human use; Watch group about 45 per cent, exceeding 70 per cent of total use in nearly one-third of countries; the target is at least 70 per cent Access by 2030
- economic projection: US$412 billion a year in treatment costs through 2035, plus US$443 billion a year in productivity losses
- target: a 10 per cent reduction in bacterial AMR-associated deaths by 2030, set at the 2024 UN General Assembly

Earlier figures, for comparison, from the WHO sepsis fact sheet of 3 May 2024 citing 2019 data: 4.95 million deaths associated with AMR, 1.27 million directly attributable. The figures move between sources and years and are not always labelled.

The two 2050 projections in circulation do not agree, and this book prints both.

Projection	Source	2050 figure
Deaths per year attributable to AMR	O'Neill review, 2016	**10 million**
Deaths per year attributable to bacterial AMR	GBD 2021 forecast, published 2024	**1.91 million** (95 per cent UI 1.56–2.26 million)

Projection	Source	2050 figure
Deaths per year associated with bacterial AMR	GBD 2021 forecast, published 2024	**8.22 million** (95 per cent UI 6.85–9.65 million)

The ten-million figure, from the 2016 review chaired by Jim O'Neill, is the number in public circulation. It rests on methodology that the GBD authors' own forecast does not reproduce. The GBD attributable forecast is about one fifth of it. The GBD *associated* forecast, 8.22 million, is within the same order of magnitude as the O'Neill figure. That is how the two can appear to agree in a summary that does not say which measure it is quoting. It is precisely the error to avoid. The discrepancy is methodological and unresolved. Both numbers are in circulation and they are not to be presented as agreeing.

Where it starts. Selection. Antimicrobial exposure kills susceptible organisms and leaves resistant ones to multiply; resistance genes then spread between bacteria on mobile genetic elements, including across species. This is settled evolutionary biology, not hypothesis.

The established drivers:

- antimicrobial use and misuse in human medicine, including treatment of viral illness, incomplete courses, and substandard and falsified medicines
- use in animal agriculture for growth promotion and prophylaxis, which accounts for a large share of global antimicrobial consumption by volume
- absence of diagnostics, which forces empirical broad-spectrum treatment. The chlamydia entry shows the mechanism exactly: the drug costs cents, the test costs more, so people are treated blind
- poor infection prevention and control, which spreads resistant organisms between patients; 15 per 1,000 hospitalised patients acquire sepsis as a complication of care
- inadequate water, sanitation and hygiene, which increases infection incidence and therefore antimicrobial use
- environmental contamination from pharmaceutical manufacturing effluent and from human and animal waste

Not known, and this is the central measurement problem: the attributable-against-associated distinction. The two figures differ by a factor of about four — 1.14 million against 4.71 million in 2021 — and they answer different questions. "Attributable" asks how many deaths would be averted if resistant infections became susceptible. "Associated" counts deaths in people who had a resistant infection. Which is the right number depends on the question, and both are legitimate. They are routinely quoted interchangeably, which is wrong.

The relative contribution of agricultural against human antimicrobial use to resistance in human pathogens is genuinely contested, with good sources differing substantially, and it is the most politically consequential open question in the field. Whether resistance is reversible at population level when antimicrobial pressure is withdrawn is partly established for some drug-organism pairs and unknown for others.

Read in the net: the one rule is that only what returns in phase persists. Antimicrobial exposure is a test applied to a population of forms, and the forms that fit remain. Resistance is not a response to the drug; it is what the drug selects from what was already there. This is a reading, not a mechanism — and in this case the standing account says the same thing, which is why no reading is needed to understand it. It is included because the rest of the chapter's readings are of the same shape.

Cure status. Not applicable as a condition. AMR is not itself curable, controllable or self-limiting. It is a property that reclassifies other conditions, and the classification that belongs here is a statement of how it moves them down the scale.

Condition	Without resistance	With resistance
Gonorrhoea	CURABLE	Credible prospect of untreatable. Ciprofloxacin at 75 per cent resistance is already lost; ceftriaxone is the last reliable single agent
Typhoid	CURABLE	XDR strains have exhausted chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones and third-generation cephalosporins, leaving azithromycin and carbapenems,

Condition	Without resistance	With resistance
		with azithromycin resistance now appearing
Tuberculosis	CURABLE with a cheap four-drug six-month regimen	MDR and RR-TB require six months of BPaLM at many times the cost, and only two in five of those affected access treatment
Shigellosis	CURABLE	Fluoroquinolone-resistant and XDR *S. sonnei* circulating internationally
Malaria	CURABLE	Partial artemisinin resistance confirmed in four African countries
HIV	CONTROLLABLE	Resistance follows treatment interruption, which is why supply continuity matters as much as supply
Neonatal sepsis, bacterial meningitis	CURABLE if treated early	First-line empirical regimens failing where resistance is high and alternatives unavailable
Cholera, leprosy, syphilis, chlamydia	CURABLE	So far substantially spared. No established penicillin resistance in *T. pallidum* after eighty years, and no clinically significant resistance in *C. trachomatis*

Those last exceptions are real and worth stating. The evidence for the reclassification is WHO's own: resistance rising in over 40 per cent of monitored pathogen-antibiotic combinations, one in six common infections resistant, one in three in two WHO regions.

Prevention.

Infection prevention and control, and hand hygiene in health facilities: STRONG. Preventing the infection removes the need for the antimicrobial.

Vaccination: STRONG, and under-recognised as an AMR measure. Every vaccine in this chapter prevents antimicrobial use. The Gambian PCV trial reduced all-cause mortality by 16 per cent (95 per cent CI 3–28). It reduced radiological pneumonia by 37 per cent per protocol (95 per cent CI 27–45), or 36 per cent by intention to treat (95 per cent CI 27–43). Each prevented pneumonia is an antibiotic course not given. Typhoid conjugate vaccine is the principal countermeasure to extensively drug-resistant typhoid.

Water, sanitation and hygiene: STRONG. Handwashing with soap where soap is provided gives a community risk ratio of 0.66 (95 per cent CI 0.58–0.75) for diarrhoea, Cochrane CD004265 — about a third fewer episodes — and most of that diarrhoea would otherwise attract antibiotics.

Diagnostics to direct treatment: STRONG in principle, limited in practice by cost, which is the binding constraint identified above.

Antimicrobial stewardship: STRONG. WHO's Access, Watch and Reserve framework carries a target of at least 70 per cent Access by 2030; Watch antibiotics exceed 70 per cent of use in nearly a third of countries, so the gap is large and measurable.

Completing prescribed courses, and not using antibiotics for viral illness: STRONG.

Reducing agricultural antimicrobial use, especially for growth promotion: STRONG on principle and on settled biology; CONTESTED in its quantitative contribution to human resistance. Both positions belong in print. The biological mechanism is not in doubt. The magnitude of the human health benefit from agricultural restriction is disputed, and **no effect size is asserted for it**.

Controlling pharmaceutical manufacturing effluent: MODERATE.

New antimicrobial development: STRONG in necessity, failing in practice. The commercial model does not reward drugs intended to be used sparingly, which is why zoliflodacin for gonorrhoea and the newer tuberculosis regimens have come through non-profit partnerships — GARDP, the TB Alliance, DNDi — rather than through ordinary commercial development.

Treatment. There is no treatment for antimicrobial resistance itself. What exists is treatment for resistant infections, which is uniformly more expensive, more toxic, longer and less effective than the first-line agents it replaces.

The pattern across this chapter, with the prices as sourced in the individual entries:

First-line: cheap, off-patent, on the EML	Resistant alternative	Cost and burden consequence
RHZE first-line TB, US$66.04 per 672-tablet pack, GDF Q3-2025	BPaLM: bedaquiline US$44.44 per 100, pretomanid US$123.08 per 100, linezolid US$16.00 per 100, levofloxacin US$4.61 per 100, GDF Q3-2025	Per tablet, RHZE is about 9.8 US cents and pretomanid about US$1.23 — roughly 12.5 times as much for one component of a multi-drug regimen; and only two in five of those needing the regimen are treated
Ciprofloxacin for gonorrhoea, cents	Ceftriaxone injection, low dollars	75 per cent ciprofloxacin resistance; the cheap oral option is gone, and the replacement needs a syringe and an injector
Chloramphenicol, ampicillin or co-trimoxazole for typhoid, cents	Azithromycin, then meropenem	XDR typhoid requires hospital-administered carbapenems
Ampicillin with gentamicin for neonatal sepsis, cents	Ceftriaxone, then carbapenems	Escalation in exactly the settings least able to supply it

Reserve-group antibiotics — carbapenems, colistin, ceftazidime-avibactam and others — are on the EML in the Reserve category. The older agents are mostly off-patent and the newer ones patented, and they cost from low dollars to hundreds of US dollars per course. **No primary prices were confirmed.**

Simple means. Unusually large, because AMR is driven by infection incidence and by drug use, and simple means reduce both.

Handwashing with soap: fewer infections, fewer antibiotic courses, less selection pressure. Soap is producible from fat and ash. Clean water by boiling, filtration, chlorination or solar disinfection, which cuts the diarrhoeal disease that drives much inappropriate antibiotic use. Latrines and safe faeces disposal. Not taking antibiotics for colds, influenza and most diarrhoea — a decision costing nothing that directly reduces selection pressure; most episodes in this chapter's diarrhoeal entries need salt, sugar and water, not antibiotics. Completing a course once started, and not sharing or saving leftover antibiotics. Oral rehydration, which substitutes for antibiotics in the majority of diarrhoeal illness. Breastfeeding, which reduces infant infection and therefore antibiotic exposure. Clean birth practice: handwashing, a clean blade, clean cord care, nothing applied to the stump — which prevents the neonatal sepsis for which resistant organisms are now a leading problem. Isolating the infectious, and ventilating rooms. Wound care: cleaning with clean water and soap, keeping wounds covered and dry, which prevents the skin infections that attract antibiotics. Keeping animals out of sleeping and cooking areas.

What cannot be done without an industrial chain is treating a resistant infection. The minimum chain for second-line therapy is substantial and rises with each step of resistance: injectable cephalosporins, then carbapenems requiring hospital administration, plus the laboratory capacity to identify the resistance in the first place.

The honest statement is that simple means can slow the generation of resistance considerably but can do nothing for the person already infected with a resistant organism. That person's survival depends on exactly the long chains that are least available where resistance is highest, and that is the structural shape of the problem.

Gaps. The attributable-against-associated distinction is the central measurement problem: 1.14 million against 4.71 million for 2021, a factor of about four, routinely conflated in public discussion. **The two most-cited 2050 projections disagree** — the O'Neill review's ten million a year against GBD's 1.91 million attributable and 8.22 million associated; the discrepancy is methodological and unresolved, and both figures are printed above. WHO's 2026 fact sheet cites 2021 GBD figures for deaths and 2023 figures for resistance proportions, while the sepsis fact sheet cites 2019 figures of 4.95 million and 1.27 million; the figures move between sources and years and are not always labelled. **The agricultural-against-human-use contribution is genuinely contested** and is the most consequential open question. Surveillance is weakest where resistance is highest: the one-in-six figure rests on laboratory-confirmed infections, and most infections in high-burden settings are never cultured, so the true proportion is unknown. **Fungal, viral and parasitic resistance is barely quantified**; WHO's 2026 fact sheet gives no figures for *Candidozyma auris*, *Aspergillus*, HIV, influenza, hepatitis or malaria resistance, despite naming them. Whether resistance reverses when drug pressure is withdrawn is established for some drug-organism pairs and unknown for

others. The economic projections of US$412 billion and US$443 billion a year are modelled and carry no published uncertainty interval in the source.

> **Depth.** A property, not an illness. No depth is given.
>
> **Model reading.** Not applied. A property, not an illness.

Chapter 02 — Neoplasms

This chapter covers the cancers and the benign tumours that carry clinical weight. The burden figures are GLOBOCAN 2022, with GLOBOCAN 2024 beside them, and the stage-specific survival figures are from the United States SEER programme. Where a WHO page or a retrieval of the Essential Medicines List closed a figure, that figure was read off its source and the figure it replaces is named.

A cure status without a stage is false at one end. For almost no other group of conditions in this book does one label mislead so completely. Colorectal cancer caught in the bowel wall has a five-year relative survival of 91.3 per cent; the same disease with liver and lung deposits has 16.9 per cent. One word cannot cover both. So nearly every entry in this chapter splits its cure status by stage, and each label names its stratum and carries the survival figure that supports it wherever the entry has one. The reader who wants the single answer should take the stage distribution with it: half of all lung cancer in the United States presents as distant disease, which is why the lung entry reads CURABLE at stage I to II, CONTROLLABLE at stage III and RELIEF ONLY at stage IV without a targetable driver.

The reservoir of cancer that never surfaces predicts how much screening will overdiagnose. The measurement comes from people who died of something else and whose organs were then examined. In men over 79, incidental prostate cancer is found at autopsy in 59 per cent, interval 48 to 71; screen-detected prostate cancer is judged overdiagnosed in 20 to 50 per cent of cases. On whole-gland examination, occult differentiated thyroid cancer is found in 11.2 per cent, interval 6.7 to 16.1; in South Korea, where ultrasound was added to routine health checks, incidence rose roughly fifteenfold with mortality flat, and the overdiagnosed fraction of screen-detected thyroid cancer in that setting approaches 90 per cent or more. Occult *invasive* breast cancer at autopsy is found in only 0.85 per cent, and breast overdiagnosis is correspondingly the most contested figure in cancer screening — 19 per cent against 30 per cent. The occult reservoir of ductal carcinoma in situ, at 8.9 per cent, is ten times the invasive reservoir, and that is where the breast dispute sits.

Nasopharyngeal carcinoma is the control case that proves the rule. No autopsy series shows occult nasopharyngeal carcinoma at any meaningful prevalence. Screening for it with plasma Epstein-Barr virus DNA in an endemic population shifts stage sharply. Roughly 70 per cent of screen-detected cancers were stage I or II against roughly 20 per cent in an unscreened comparison, and three-year progression-free survival was about 97 per cent against about 70. Those figures come from the Hong Kong prospective study published in the *New England Journal of Medicine* in 2017. No overdiagnosis percentage has been published for it, and the absence of an indolent reservoir is the reason the question does not arise. A cheap blood test, a defined high-risk population, a large stage shift and no overdiagnosis penalty: that combination appears once in this chapter. Read in the net: the test finds what is there to be found, and the size of what is there is a property of the organ, not of the test. This is a reading, not a mechanism.

A short list of cancers is curable at early stage with nothing on patent. Basal cell and squamous cell carcinoma of the skin, cured above 95 and above 90 per cent respectively by excision under local anaesthetic†. Localized melanoma, five-year relative survival 100.0 per cent, treated by wide excision with a scalpel and sutures. Localized endometrial cancer, 94.9 per cent, by hysterectomy with bilateral salpingo-oophorectomy. Localized thyroid cancer, 99.9 per cent, by lobectomy plus levothyroxine at a few dollars a year. Localized colorectal cancer, 91.3 per cent, by colectomy. Localized cervical cancer, 91.8 per cent, and its precursor cured by thermal ablation in one visit. Localized breast cancer, 100.0 per cent, by mastectomy plus tamoxifen at US$80 to 250 for five years at generic international prices, 2024, against US$785 to 1,241 for the same five years at one tablet a day, for orientation only, at the United States cash price of 43 to 68 cents a tablet, October 2026. Stage I testicular cancer, by inguinal orchidectomy. Localized kidney cancer, 93.6 per cent, by nephrectomy. Intraocular retinoblastoma, above 95 per cent, found with a torch and cured by enucleation†. Wilms tumour, above 95 per cent localized, by nephrectomy plus two drugs costing tens of dollars.

Four metastatic cancers are cured with Essential Medicines alone, and one cancer is cured by antibiotics. Widely metastatic testicular cancer is cured in roughly 90 to 95 per cent of good-risk and the

majority of poor-risk patients by bleomycin, etoposide and cisplatin, all off-patent, at a drug cost of a few hundred dollars. Stage IV Hodgkin lymphoma has a five-year relative survival of 82.8 per cent, and ABVD is four off-patent listed medicines. Acute promyelocytic leukaemia is cured in over 90 per cent by all-trans retinoic acid and arsenic trioxide, with no conventional chemotherapy at all in non-high-risk disease. Childhood acute lymphoblastic leukaemia is cured in roughly 90 to 94 per cent in high-income settings by a protocol built entirely from off-patent listed medicines. And early-stage gastric mucosa-associated lymphoid tissue lymphoma is cleared in roughly 60 to 80 per cent of cases by one to two weeks of generic antibiotics costing a few dollars. That is a very cheap cancer cure. Against it, the same Essential Medicines List now carries pembrolizumab and blinatumomab. The price range across the products in section F spans many orders of magnitude, and section F sets it out.

The entries

1. Lung cancer

What it is. A malignant tumour of the cells lining the airways or of the lung tissue itself. Two classes: non-small-cell, about 85 per cent of cases, including adenocarcinoma and squamous carcinoma; and small-cell, about 15 per cent, faster growing†. It is the most commonly diagnosed cancer in the world and the largest single cause of cancer death.

Measured. WHO gives 2.6 million new cases and 1.86 million deaths for 2024. GLOBOCAN 2022 gives 2,480,675 cases, 12.4 per cent of all cancers, and 1,817,469 deaths, 18.7 per cent of all cancer deaths; GLOBOCAN 2024 gives 2,637,005 cases and 1,861,839 deaths. Five-year relative survival in the United States is 29.5 per cent overall, and by stage: localized 65.5, regional 38.2, distant 10.5, unknown 17.5 per cent. Median age at diagnosis 71. Stage at diagnosis: localized 24, regional 21, distant 51, unknown 4 per cent. United States incidence is falling 1.9 per cent a year over 2014 to 2023 and the death rate 4.1 per cent a year over 2015 to 2024. The highest age-standardised incidence is Hungary, 61.8 per 100,000 in men. The decline tracks falling smoking prevalence at a lag of decades, so it has not begun where smoking peaked later.

Where it starts. Current smokers carry about twenty times the risk of never-smokers; smoking is estimated to cause about 85 per cent of lung cancer deaths, and tobacco about 90 per cent of lung cancers in men and 78 per cent in women. Ten years of abstinence lowers lung cancer mortality risk by 30 to 60 per cent relative to continuing, and never to never-smoker level. Second-hand smoke raises risk about 20 per cent. Radon is the attributable cause of a median 26 per cent of lung cancer deaths in lifelong non-smokers, range 13 to 50, and 10 per cent in ever-smokers. High occupational exposure to asbestos, arsenic, beryllium, cadmium, chromium or nickel raises risk more than fivefold, and occupational exposures together account for 9 to 15 per cent of lung cancer deaths. Outdoor fine-particle pollution raises risk about 40 per cent at the highest against the lowest exposure. Smoking-associated lung tumours sit well above the adult pan-cancer reference mutation rate of 1.8 mutations per megabase. Not known: why most heavy smokers never develop it; the cause of adenocarcinoma in never-smokers, a rising share of cases; the shape of the dose-response at low radon and low particulate levels.

Cure status. Localized, stage I to II: CURABLE — five-year relative survival 65.5 per cent. Regional, stage III: CONTROLLABLE — 38.2 per cent. Distant, stage IV, without a targetable driver: RELIEF ONLY — 10.5 per cent. Distant with a targetable driver mutation or high PD-L1 expression: CONTROLLABLE. Small-cell, extensive stage: RELIEF ONLY.

Prevention. Not starting, and cessation — STRONG. Twentyfold risk, 85 per cent attributable fraction, 30 to 60 per cent mortality reduction after ten years. Radon remediation — MODERATE: the attributable fraction is solid and no trial shows that remediation lowers incidence. Occupational exposure control — STRONG for asbestos. Beta-carotene supplementation — harmful, on strong evidence: lung cancer relative risk 1.18, interval 1.03 to 1.36, in the ATBC trial and 1.28, interval 1.04 to 1.57, in CARET, which was stopped early. Vitamin E — no effect, summary odds ratio 0.97, interval 0.87 to 1.08. Low-dose CT screening — STRONG for mortality reduction in heavy smokers. NLST reported a 20 per cent reduction in

lung cancer deaths against chest radiography. NELSON, at ten years or more, reported a lung cancer mortality rate ratio of 0.76 in men and 0.67 in women. The harms, with figures: NELSON gave a false-positive rate of 1.2 per cent across all rounds, a positive predictive value of 43.5 per cent, and an overdiagnosis upper threshold of 8.9 per cent. Secondary analyses of NLST put overdiagnosis substantially higher. The two trials used different intervals — NLST strictly annual, NELSON at one, two and two and a half years — and the literature has not reconciled them. Both are printed.

Treatment. Surgical lobectomy for stage I to II is the intervention with the clearest curative effect. Platinum doublet chemotherapy follows: cisplatin, carboplatin, etoposide, gemcitabine, paclitaxel, docetaxel and vinorelbine are all listed medicines and all off-patent, at generic prices in the tens to low hundreds of dollars a vial, so a full doublet course is achievable for a low-hundreds-of-dollars drug cost. Radiotherapy, definitive or palliative, requires a linear accelerator, which is the binding constraint in most of the world. Pembrolizumab is a selected medicine on the list, for metastatic non-small-cell lung cancer with oncogene-driver wildtype status and PD-L1 expression of 50 per cent or more, as monotherapy; it is not off-patent. Atezolizumab and cemiplimab are listed as therapeutic alternatives for that indication and nivolumab as a therapeutic equivalent to pembrolizumab, which is a weaker status than selection. Objective response as first-line monotherapy in PD-L1-high disease is in the region of 40 to 45 per cent in the registrational trials†, and the figure moves with the PD-L1 threshold, so it does not transfer across populations. Erlotinib, gefitinib and afatinib are listed; erlotinib and gefitinib are off-patent. Osimertinib is not listed and not off-patent, with a United States list price in the order of US$150,000 a year†. Objective response to EGFR inhibitors in mutation-positive disease is roughly 60 to 80 per cent†, in a minority subgroup that is far commoner in East Asian and never-smoker populations. ALK, ROS1 and KRAS G12C inhibitors are not listed and are all on patent.

Simple means. Very little works here without an industrial chain, and that should be said first. No dietary or low-technology intervention changes the course of established lung cancer, and lobectomy needs thoracic surgery, anaesthesia and chest drainage. What is available simply: tobacco cessation, which needs no technology and is the highest-yield action available; oral morphine for pain and breathlessness, listed, off-patent, cents per dose; thoracentesis for a malignant pleural effusion with a needle and a drainage set, which relieves breathlessness at once and needs no imaging if the effusion is large; nutritional support; oxygen where it exists. Nearly all of the simple-means benefit in lung cancer sits in palliative care.

Gaps. Overdiagnosis in low-dose CT screening is unsettled between NELSON's ceiling of 8.9 per cent and higher NLST-derived estimates. Checkpoint response rates are reported against varying PD-L1 thresholds and cross-trial comparison is unreliable. Never-smoker lung cancer has a rising incidence and no established dominant cause. Survival figures are United States figures; five-year survival in low-income settings is substantially lower and comparable site-specific data are sparse.

> **Depth.** Starts in: an airway epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 30 years († about 30 years after starting to smoke); time depth 51.97. One untreated course: about 12 months († about 1 year untreated); depth 48.87.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

2. Colorectal cancer

What it is. Cancer of the colon or rectum, in the great majority of cases developing over years from a benign adenomatous polyp. The slow precursor stage is what makes it screenable.

Measured. WHO gives 2.0 million new cases and 918,000 deaths for 2024. GLOBOCAN 2022 gives 1,926,425 cases, 9.6 per cent of all cancers, and 9.3 per cent of cancer deaths; GLOBOCAN 2024 gives 2,041,007 cases and 917,895 deaths. Five-year relative survival in the United States is 65.4 per cent overall: localized 91.3, regional 75.2, distant 16.9, unknown 49.7 per cent. Median age 66. Stage at diagnosis: localized 34, regional 37, distant 23, unknown 6 per cent. Incidence is falling about 0.5 per cent a year and

deaths 1.3 per cent a year in the United States, and the fall masks a rise in adults under 50 that is one of the clearest unexplained trends in oncology.

Where it starts. Physical activity is protective, relative risk 0.76, interval 0.72 to 0.81. Obesity raises colon cancer risk, relative risk 1.45, interval 1.02 to 2.07, in women above a body mass index of 29, with mortality relative risk 1.47 at 30 to 34.9. Smoking: incidence relative risk 1.18, mortality 1.25. Alcohol above 45 grams a day: 1.41, interval 1.16 to 1.72. Aspirin: colorectal cancer incidence hazard ratio 0.60, interval 0.47 to 0.76, at ten to nineteen years after starting, against 0.99 within the first ten years, with a twenty-year death hazard ratio of 0.67; the harm is major gastrointestinal bleeding, odds ratio 1.58, and about fourteen extra bleeds per thousand people over ten years at very low doses. Lynch syndrome carries a lifetime colorectal cancer risk of about 80 per cent, and aspirin in Lynch syndrome gave a hazard ratio of 0.65, interval 0.43 to 0.97, in CAPP2. On meat the authorities do not agree. NCI PDQ gives no relative risk and states there is no reliable evidence that a low-fat, low-meat, high-fibre diet reduces colorectal cancer risk by a clinically important degree. IARC classified processed meat as Group 1 and red meat as Group 2A in 2015, with a reported 18 per cent increase in risk per 50 grams a day of processed meat. Both positions are printed. Mutation burden splits the disease: microsatellite-stable tumours sit near the adult reference of 1.8 per megabase, and hypermutated microsatellite-unstable or POLE-mutant tumours one to two orders of magnitude above it. The hypermutated group is the group that responds to checkpoint blockade. Not known: the cause of the early-onset rise; whether the diet relation is causal and through which component.

Cure status. Precursor adenoma: CURABLE by polypectomy. Localized, stage I to II: CURABLE — five-year relative survival 91.3 per cent. Regional, stage III: CURABLE in 75.2 per cent (five-year relative survival). Distant with resectable liver-only or lung-only metastases: CURABLE in roughly 20 to 40 per cent (long-term survival after metastasectomy in selected series). Distant otherwise: CONTROLLABLE — 16.9 per cent.

Prevention. Screening — STRONG, and the randomised evidence is now complete at the colonoscopy end. Flexible sigmoidoscopy: four randomised trials pooled, 458,002 people, colorectal cancer mortality rate ratio 0.74, interval 0.68 to 0.80, over eleven to seventeen years. Guaiac faecal occult blood testing over two to nine biennial rounds: relative risk 0.78, interval 0.65 to 0.93, to 0.91, interval 0.84 to 0.98, at eleven to thirty years. Faecal immunochemical testing has no randomised trial; a Taiwanese cohort of 5,417,699 people gave an adjusted relative risk of 0.90, interval 0.84 to 0.95, at six years. Colonoscopy: the NordICC randomised trial reported ten-year colorectal cancer risk of 0.98 per cent in those invited against 1.20 per cent in usual care, an 18 per cent reduction, risk ratio 0.82, interval 0.70 to 0.93. Death from colorectal cancer was 0.28 against 0.31 per cent, risk ratio 0.90, interval 0.64 to 1.16, which is not significant. All-cause death was 11.03 against 11.04 per cent. The number needed to invite to prevent one colorectal cancer was 455, interval 270 to 1,429. Uptake was 11,843 of 28,220 invited, 42.0 per cent. An adjusted analysis estimating the effect had all invited been screened gives incidence 1.22 to 0.84 per cent and colorectal cancer death 0.30 to 0.15 per cent, without intervals; recomputed here, the adjusted incidence reduction is 31.1 per cent. Recommended ages: 50 to 75, Grade A; 45 to 49, Grade B; 76 to 85 selectively, Grade C; stop at 86. Harms, with figures: colonoscopy after a positive stool test gives about 17.5 serious bleeds and 5.4 perforations per 10,000 procedures; screening colonoscopy 14.6 bleeds and 3.1 perforations; flexible sigmoidoscopy 0.5 and 0.2; colonoscopy after abnormal sigmoidoscopy 20.7 and 12.0. Lifetime complications for screening from 45 to 75 are 10 to 16 per 1,000 adults screened. Overdiagnosis of colorectal *cancer* is not the principal harm; overdetection and removal of adenomas that would never have progressed is, and no percentage has ever been published for it. The underlying ratio is about twenty polypectomies for each cancer prevented, and entry 35 sets it out. Physical activity — MODERATE. Aspirin — MODERATE on the cancer effect and CONTESTED on net benefit: hazard ratio 0.60 against fourteen extra bleeds per thousand over ten years. Tobacco and heavy alcohol — MODERATE. Low-fat, high-fibre diet — CONTESTED, with both positions above.

Treatment. Surgical resection is curative for stages I to III and for resectable oligometastatic disease, and needs laparotomy capability rather than high technology. Polypectomy at colonoscopy is both preventive and curative for the precursor. Fluoropyrimidine-based adjuvant chemotherapy follows: fluorouracil, capecitabine, calcium folinate, oxaliplatin and irinotecan are all listed and all off-patent, and fluorouracil and calcium folinate are among the cheapest cytotoxics in use, so three to six months of FOLFOX or CAPOX is achievable at a drug cost in the low hundreds of dollars. Cetuximab and panitumumab for RAS-

wild-type disease are not listed, with originator costs in the tens of thousands of dollars a year; they are inactive and may be harmful in RAS-mutant disease. Bevacizumab is not listed for colorectal cancer; biosimilars have cut its price substantially. Pembrolizumab is a selected medicine for metastatic colorectal cancer, as monotherapy, restricted to mismatch-repair-deficient or microsatellite-instability-high tumours; it is not off-patent. Objective response in that subgroup in the first-line setting is in the region of 45 per cent with a substantial durable fraction†, and the subgroup is only about 4 to 5 per cent of metastatic colorectal cancer†, so the population effect is small.

Simple means. Colectomy and the formation of a stoma are achievable in a district hospital with a general surgeon, anaesthesia and basic instruments, and for localized disease that alone is curative in about 90 per cent of cases†. This is one of the highest-yield simple interventions in the chapter. A diverting colostomy relieves obstruction and is life-saving with no advanced equipment. Oral morphine is listed, off-patent and costs cents a dose. Iron treats the chronic blood-loss anaemia that often presents first, and the corollary matters: iron-deficiency anaemia in an adult requires investigation of the bowel, not iron alone. What has no simple substitute is the screening colonoscopy itself, which needs an endoscope, a reprocessing chain and a trained operator, and infusional chemotherapy, although oral capecitabine is far simpler to deliver than infusional fluorouracil.

Gaps. PDQ and IARC disagree on meat and on diet. The early-onset incidence rise is unexplained and its magnitude by country inconsistently reported. Faecal immunochemical testing has no randomised mortality evidence. NordICC's per-protocol and adjusted figures come from a secondary source and carry no intervals.

> **Depth.** Starts in: a bowel epithelial cell (adenoma). Size: 15 µm†; depth +5.28. First complaint: about 10 years ([B] over years from a polyp; † about 10 years); time depth 50.97. One untreated course: about 2 years († about 2 years); depth 49.50.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

3. Stomach cancer

What it is. Cancer of the stomach lining, mostly adenocarcinoma, divided into non-cardia disease, the great majority, which is tied to *Helicobacter pylori* infection, and cardia disease, which behaves more like oesophageal adenocarcinoma. It is the clearest case of a common cancer with a treatable infectious cause.

Measured. WHO gives 1.0 million new cases and 642,000 deaths for 2024. GLOBOCAN 2022 gives 968,784 cases, 4.9 per cent of all cancers, and 6.8 per cent of cancer deaths; GLOBOCAN 2024 gives 980,286 cases and 641,554 deaths. Five-year relative survival in the United States is 39.8 per cent overall: localized 78.1, regional 39.0, distant 8.1, unknown 33.6 per cent. Japan and South Korea report far better stage-specific and overall survival, because population endoscopic screening shifts the stage at diagnosis, so the United States figure understates what is achievable. Median age 68. Stage at diagnosis: localized 32, regional 23, distant 35, unknown 9 per cent. Incidence is concentrated in East Asia, parts of Latin America and Eastern Europe, following *H. pylori* prevalence and strain virulence. United States incidence is rising about 1.1 per cent a year against the global trend, while the death rate falls 2.0 per cent a year.

Where it starts. *H. pylori* is an IARC Group 1 carcinogen for non-cardia gastric carcinoma and for gastric MALT lymphoma, and about half the world's population is infected. de Martel and colleagues, in *The Lancet Global Health* in 2020, attributed about 810,000 cancer cases worldwide in 2018 to *H. pylori*, at an age-standardised incidence of 8.7 per 100,000, the largest single infectious cause of cancer. Against roughly a million annual gastric cases, the implied attributable fraction for non-cardia disease is in the region of 75 to 90 per cent†; that is an inference from two sources rather than a published figure, and is marked as one. Eradication lowers incidence: a pooled meta-analysis of 24 studies gave an incidence rate ratio of 0.53, interval 0.44 to 0.64. Ford and colleagues, in the *BMJ* in 2014, pooled six randomised trials in 6,497 asymptomatic infected adults: gastric cancer occurred in 51 of 3,294 treated, 1.6 per cent, against 76 of 3,203 controls, 2.4 per cent, relative risk 0.66, interval 0.46 to 0.95. The number needed to treat was 124,

interval 78 to 843, falling to about 15 for Chinese men and rising to about 245 for United States women if lifetime benefit is assumed. A Chinese trial in first-degree relatives gave a hazard ratio of 0.45, interval 0.21 to 0.94, at 9.2 years. Smoking: about 60 per cent higher risk in male smokers and 20 per cent in female. Excessive salt intake is associated with increased risk on correlational and case-control evidence, of a magnitude PDQ describes as small and difficult to determine. Epstein-Barr virus marks a recognised molecular subtype, roughly 9 per cent of gastric cancers in TCGA. Not known: why only a small minority of the infected develop cancer, and how much of that is strain, host or co-factor; whether population-wide eradication would do net good or harm.

Cure status. Infection with pre-malignant change: CURABLE — one week of oral antibiotics eradicates the organism and lowers subsequent cancer incidence by a third to a half, relative risk 0.53 to 0.66. Early cancer confined to the mucosa: CURABLE by endoscopic resection, with survival approaching that of the general population in Japanese and Korean series. Localized: CURABLE — five-year survival 78.1 per cent. Regional: CURABLE in 39.0 per cent (five-year relative survival). Distant: RELIEF ONLY — 8.1 per cent.

Prevention. *H. pylori* eradication — STRONG on the mechanism, MODERATE as population policy. Relative risk 0.53 to 0.66; number needed to treat 124 overall and about 15 in the highest-risk group. The limitation both PDQ and Ford state is that the trials are almost all Asian. Salt reduction — WEAK, on correlational evidence of uncertain magnitude. Tobacco cessation — MODERATE. Endoscopic screening — STRONG in high-incidence countries, not justified in low-incidence countries. Japan and South Korea run population endoscopic programmes and the measured effect is a large stage shift and substantially better survival; there is no randomised mortality trial of endoscopic gastric screening anywhere. The harms are the procedural risk of endoscopy and the overdiagnosis of indolent early lesions, and **overdiagnosis has never been quantified for gastric screening**, in a disease whose occult reservoir is not small. That is an evidence gap, not evidence of absence. Fruit and vegetable intake — CONTESTED: the association holds, causation is not established, and the benefit of change is unknown.

Treatment. Gastrectomy with D2 lymphadenectomy is curative for localized and regional disease. Endoscopic mucosal or submucosal resection cures intramucosal early cancer with the organ preserved. The eradication regimen is the cheapest cancer-preventive drug regimen in the chapter: amoxicillin, clarithromycin, metronidazole and a proton-pump inhibitor, with bismuth and tetracycline in quadruple regimens, all available as generics for a few dollars a course. Amoxicillin is a listed Access-group antibiotic and clarithromycin and metronidazole are listed, though the list's own first-choice indications for amoxicillin do not include *H. pylori* eradication. Perioperative chemotherapy uses fluorouracil, capecitabine, cisplatin, oxaliplatin and docetaxel, all listed and off-patent; epirubicin is not listed and doxorubicin is. Trastuzumab for HER2-positive disease, roughly 15 to 20 per cent of cases, is listed; the originator is off-patent in most markets with biosimilars available, and a precise current per-course figure could not be retrieved. Pembrolizumab is a selected medicine on the list, for other listed indications. Nivolumab's listing for this cancer needs checking against the 24th List (2025)†. Neither is off-patent. Benefit concentrates in PD-L1-high and microsatellite-unstable disease and is small in PD-L1-low disease†.

Simple means. Test and treat for *H. pylori* is the outstanding simple intervention in this chapter. A urea breath test or a stool antigen test, then one week of generic antibiotics costing a few dollars: no cold chain, no infusion, no imaging. Serology is simpler still, and less specific after treatment. Gastrectomy with a hand-sewn anastomosis is a general-surgical operation and does not require stapling devices. Gastrojejunostomy bypasses an obstructing unresectable tumour, stops vomiting and allows eating, for a large return in quality of life. Oral morphine is listed and costs cents a dose. Reducing salt-preserved food and increasing fresh food needs no industrial chain, though the evidence grade for the cancer effect is weak. Endoscopy, for diagnosis and for early-lesion resection, has no simple substitute.

Gaps. The eradication trials are overwhelmingly Asian and both PDQ and Ford decline to generalise from them. No randomised mortality trial of endoscopic screening exists despite decades of national programmes. Overdiagnosis from gastric screening is unquantified. The attributable fraction for gastric cancer specifically is given differently across sources, and the 75 to 90 per cent range above is an inference.

> **Depth.** Starts in: a stomach epithelial cell (with H. pylori). Size: 15 µm†; depth +5.28. First complaint: about 30 years († decades after H. pylori infection); time depth 51.97. One untreated course: about 12 months († about 1 year); depth 48.87.
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

4. Liver cancer

What it is. Cancer arising in the liver, most often hepatocellular carcinoma on a background of cirrhosis. The dominant causes are chronic hepatitis B and C infection, alcohol and, increasingly, fatty liver disease. It is one of the few cancers that a vaccine given in infancy prevents decades later.

Measured. WHO gives 732,000 deaths for 2024. GLOBOCAN 2022 gives 866,136 cases and 7.8 per cent of all cancer deaths; GLOBOCAN 2024 gives 843,045 cases and 732,489 deaths. Liver cancer is third among causes of cancer death and sixth or seventh in incidence, and that gap is the measure of the outcome. Five-year relative survival in the United States is 21.9 per cent overall: localized 37.4, regional 13.4, distant 3.6, unknown 11.6 per cent. Median age 68. Stage at diagnosis: localized 45, regional 23, distant 21, unknown 10 per cent. Rates are highest in East and Southeast Asia and sub-Saharan Africa, tracking hepatitis B prevalence and aflatoxin exposure. United States incidence is falling about 0.7 per cent a year as the hepatitis C birth-cohort bulge is treated, while the death rate is stable.

Where it starts. Chronic hepatitis B or C is the critical agent in at least 80 per cent of hepatocellular carcinoma worldwide. The relative risk for hepatitis B is at least fivefold on average, with some prospective studies above 50; for hepatitis C it is at least fifteenfold; with heavy alcohol the combinations reach about fiftyfold and about a hundredfold respectively. de Martel and colleagues, 2020, attribute about 360,000 cancer cases worldwide to hepatitis B and about 160,000 to hepatitis C, nearly all liver cancer. Cirrhosis of any cause is present in 80 to 90 per cent of those who die of hepatocellular carcinoma, and the five-year risk in established cirrhosis is 5 to 30 per cent. Aflatoxin B1 with chronic hepatitis B raises risk about sixtyfold and without it about fourfold, with population attributable risks of 20 per cent in the Western Pacific, 27 in Southeast Asia and 40 in Africa; replacing heavily contaminated food reduced liver cancer mortality by more than 50 per cent. Alcohol: relative risk 1.19 at 25 grams a day, 1.40 at 50 and 1.81 at 100. Obesity: summary relative risk 1.83, interval 1.59 to 2.11. Type 2 diabetes: 2.18, interval 1.58 to 3.01. Current smoking: 1.51, interval 1.37 to 1.67. Untreated hereditary haemochromatosis: at least twentyfold. Aflatoxin leaves a specific mutational signature, AFB1 with the R249S *TP53* change, which is among the clearest environmental fingerprints in tumour DNA. Not known: why most people with cirrhosis never develop it; the quantitative contribution of fatty liver disease without cirrhosis.

Cure status. Chronic hepatitis B: CONTROLLABLE — nucleos(t)ide analogues suppress the virus indefinitely and cut hepatocellular carcinoma incidence by about 50 per cent, and do not remove the integrated virus. Chronic hepatitis C: CURABLE — direct-acting antivirals achieve sustained virological response in over 95 per cent, which lowers subsequent risk by about 75 per cent, hazard ratio 0.31 with cirrhosis and 0.18 without. Localized small tumour in preserved liver function: CURABLE by resection, ablation or transplantation — selected transplant series report five-year survival above 70 per cent†, against a population-level localized figure of 37.4 per cent, because most localized disease arises in a liver that limits what can be done. Regional: RELIEF ONLY — 13.4 per cent. Distant: RELIEF ONLY — 3.6 per cent.

Prevention. Hepatitis B vaccination — STRONG, and with human papillomavirus vaccination the best-evidenced cancer vaccine effect in existence. Neonatal or early-childhood vaccination cut incidence in young adults by at least 50 per cent in immunised cohorts, and universal neonatal immunisation is predicted to prevent 70 to 85 per cent of global cases. Hepatitis B antiviral treatment — STRONG, about 50 per cent lower incidence. Hepatitis C direct-acting antivirals — STRONG on effect size, rated fair by PDQ on the cancer endpoint: about 75 per cent lower risk after sustained response. Aflatoxin-free food — STRONG: more than 50 per cent lower mortality, achieved by drying and storage practice rather than by industrial processing. Alcohol reduction — STRONG, on the dose-response above. Statins in viral hepatitis —

CONTESTED, rated fair but inadequate. Six-monthly ultrasound and alpha-fetoprotein surveillance of cirrhotic patients — MODERATE: widely recommended, with one Chinese randomised trial behind it, and a debated effect on mortality in Western cirrhotic populations. The harms are false positives leading to biopsy and to futile investigation in patients with little liver reserve, and **overdiagnosis has never been quantified for hepatocellular carcinoma surveillance**.

Treatment. Hepatitis B vaccination is listed, off-patent and costs well under a dollar a dose at UNICEF and Gavi prices: the highest-value intervention in this entry by a wide margin. Resection, radiofrequency or microwave ablation and transplantation are the curative options; transplantation is the most effective and the least available. Tenofovir and entecavir are listed and off-patent, and generic tenofovir costs in the region of US$30 to 60 a year in generic-supplied markets† — a global procurement figure, not comparable with the United States cash prices elsewhere in this chapter. Sofosbuvir, daclatasvir, velpatasvir and ledipasvir are listed. The originator launch price of sofosbuvir was US$84,000 for a twelve-week course in 2013 to 2014; a curative course now costs under US$50 in many low- and middle-income countries, according to the WHO fact sheet printed 28 July 2026. That is the largest originator-to-generic ratio in this chapter, of more than 1,680-fold. Transarterial chemoembolisation serves intermediate-stage disease and requires interventional radiology. Sorafenib and lenvatinib are not listed; sorafenib is off-patent with generics, and the measured benefit in the registrational trial was a median overall survival gain of under three months, with response rates in the single digits to low teens. Atezolizumab, listed for non-small-cell lung cancer, with bevacizumab gave the first clear survival improvement over sorafenib, with objective response in the region of 30 per cent†.

Simple means. Hepatitis B vaccination at birth is a single intramuscular injection under a dollar, with no cold-chain problem beyond routine immunisation, preventing 70 to 85 per cent of global cases if universal. This is the clearest case in the chapter of a simple means with a very large measured effect. Grain drying and storage to prevent aflatoxin needs no industrial chain at all and the measured mortality reduction exceeds 50 per cent. Alcohol reduction needs no technology. Oral morphine is listed and cheap. Large-volume paracentesis with a needle and a drainage set relieves ascitic distension at once and needs no imaging. For established disease, nothing simple is curative: resection requires hepatic surgery and blood, ablation requires imaging guidance, transplantation requires a national system. The simple means in liver cancer are almost entirely preventive.

Gaps. The randomised evidence for cirrhosis surveillance is thin and dominated by one trial. PDQ rates the obesity and diabetes associations as fair but inadequate to act on, while clinical guidance increasingly treats them as actionable. Overdiagnosis in surveillance is unquantified. The generic antiviral prices quoted come from global procurement and are not like-for-like with the United States cash prices used elsewhere here.

> **Depth.** Starts in: a liver cell. Size: 25 µm†; depth +5.74. First complaint: about 30 years († about 30 years after hepatitis B or C infection); time depth 51.97. One untreated course: about 6 months († about 6 months); depth 48.24.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

5. Breast cancer

What it is. Cancer of the breast tissue, in the great majority of cases arising in the milk ducts or lobules. Oestrogen-receptor-positive disease, HER2-positive disease and triple-negative disease behave differently enough to be treated as different diseases. It is the most commonly diagnosed cancer in women.

Measured. WHO gives 2.4 million new cases and 694,000 deaths for 2024. GLOBOCAN 2022 gives 2,296,840 female cases, 11.6 per cent of all cancers, and 6.9 per cent of cancer deaths; GLOBOCAN 2024 gives 2,434,087 cases and 693,660 deaths. Five-year relative survival in United States women is 91.9 per cent overall: localized 100.0, regional 87.5, distant 33.8, unknown 70.6 per cent. Median age 64. Stage at diagnosis: localized 64, regional 27, distant 6, unknown 2 per cent. Incidence is highest in high-income countries and the mortality-to-incidence ratio is highest in low-income countries: that gap is a treatment-

access gap, not a biology gap. United States incidence is rising about 0.7 per cent a year and the death rate falling 1.2 per cent a year.

Where it starts. Lifetime risk is 55 to 65 per cent in BRCA1 carriers and 45 to 47 per cent in BRCA2 carriers, against 13 per cent in the general population. Alcohol at about four drinks a day: relative risk 1.32, interval 1.19 to 1.45, rising about 7 per cent per additional drink a day. Obesity in postmenopausal women never using hormone therapy, heaviest against lightest: 2.85, interval 1.81 to 4.49. Menopausal oestrogen-progesterone therapy: 1.60 in years one to four and 2.08 in years five to fourteen; oestrogen alone 1.17 and 1.33; combination therapy raises invasive breast cancer about 26 per cent, number needed to harm 237. Physical activity is protective at about 20 per cent, summary relative risk 0.88 across 38 prospective studies. Ionising radiation, breast density, early menarche, late menopause, nulliparity, late first pregnancy and absence of breastfeeding are all rated solid. Mutation burden sits at or somewhat below the adult reference of 1.8 per megabase, with higher burdens and homologous-recombination-deficiency signatures in triple-negative and BRCA-deficient tumours. Not known: the cause of the large majority of cases — the established risk factors together account for only a minority, and most women diagnosed have no identifiable cause; why incidence is rising; the mechanism linking density to risk.

Cure status. Ductal carcinoma in situ: CURABLE — and this is where the overdiagnosis problem sits, because an unknown but substantial proportion would never have progressed to invasive cancer in the woman's lifetime, and almost all of it is treated. Localized, stage I: CURABLE — five-year relative survival 100.0 per cent, meaning survival indistinguishable from the general population at five years; twenty-year figures are lower, because relapse in receptor-positive disease continues for decades. Regional, stage II to III: CURABLE in 87.5 per cent (five-year relative survival). Distant, stage IV: CONTROLLABLE — 33.8 per cent. Within distant disease, receptor-positive cancer is often controlled for years with endocrine therapy, HER2-positive cancer now has median survival approaching five years, and triple-negative cancer has median survival of about 12 to 18 months†.

Prevention. Tamoxifen in high-risk women — STRONG. The Breast Cancer Prevention Trial gave 49 per cent lower incidence at four years, 85 against 154 invasive cases; pooled high-risk data give a 30 to 50 per cent reduction in receptor-positive cancer and ductal carcinoma in situ over five years of treatment, lasting at least sixteen years from starting. No overall mortality benefit has been demonstrated: relative risk 1.10, interval 0.85 to 1.43, at seven years. The harms are endometrial cancer, hazard ratio 2.18, interval 1.39 to 3.42, and venous thromboembolism, 1.73, interval 1.47 to 2.05. Raloxifene — STRONG for incidence reduction in postmenopausal women, with no endometrial excess, hazard ratio 1.09, interval 0.74 to 1.62, and an increase in thromboembolism. Aromatase inhibitors — STRONG. Exemestane in MAP.3 gave invasive cancer hazard ratio 0.35, interval 0.18 to 0.70, about 65 per cent, with 21 cancers avoided among 2,280 participants over 35 months and a number needed to treat of about 100; anastrozole in IBIS-II gave 53 per cent, persisting at eleven years. Risk-reducing bilateral mastectomy — STRONG for risk, reducing it by as much as 90 per cent, and unproven for survival, where reported benefits are generally attributed to selection bias. Risk-reducing salpingo-oophorectomy in BRCA carriers — STRONG. Physical activity — MODERATE. Alcohol reduction — STRONG on the dose-response. Mammographic screening — the mortality reduction is real and the overdiagnosis figure is genuinely contested, and both are printed. The UK Independent Breast Screening Review of 2012 gave a relative mortality reduction of 20 per cent, relative risk 0.80, interval 0.73 to 0.89; one death prevented per 235 women invited, equal to 43 deaths prevented per 10,000 women aged 50 invited over 20 years; and overdiagnosis of 19 per cent of breast cancers diagnosed in invited women, equal to 129 per 10,000. The implied ratio of about three overdiagnosed cancers per death prevented is an arithmetic inference from those two per-10,000 figures, which may not share an identical time frame, and the panel did not state it. The Cochrane review of 2013 gave breast cancer mortality at thirteen years as relative risk 0.90, interval 0.79 to 1.02, not significant, in the three adequately randomised trials, against 0.75, interval 0.67 to 0.83, in the four suboptimally randomised ones; it assumes a 15 per cent mortality reduction and 30 per cent overdiagnosis, and summarises that per 2,000 women invited over ten years about one woman avoids dying of breast cancer, about ten healthy women are treated unnecessarily, and more than 200 experience important psychological distress from false-positive findings. The disagreement is substantive. The two groups differ on which trials are adequately randomised and on the denominator for the overdiagnosis percentage. WHO recommends mammographic screening for women aged 50 to 69 where health systems are strong.

Treatment. Breast-conserving surgery with radiotherapy and mastectomy give equivalent survival, with curative intent for stages I to III. Endocrine therapy follows for receptor-positive disease. Tamoxifen is a listed medicine, for early-stage and for metastatic breast cancer, and off-patent: United States cash prices are US$0.43 to 0.68 per 20 mg tablet, US$20.48 for 30 and US$430.56 for 1,000, so five years of treatment at one tablet a day, for orientation only, costs US$785 to 1,241 at those United States cash prices, October 2026, against US$80 to 250 at generic international prices, 2024, and it reduces recurrence by about half and breast cancer mortality by about a third in receptor-positive disease. Anastrozole is listed and off-patent and also costs a few cents a tablet generically. Doxorubicin, cyclophosphamide, paclitaxel, docetaxel, fluorouracil, methotrexate and carboplatin are all listed and all off-patent, at tens to low hundreds of dollars a vial. Trastuzumab for HER2-positive disease is listed; the originator is off-patent in most markets and biosimilars have cut the price by a reported 50 to 75 per cent in several markets†. A precise current per-course figure could not be retrieved; the originator price for a year of adjuvant treatment was historically in the region of US$50,000 to 70,000 at United States list. Pertuzumab, trastuzumab emtansine and trastuzumab deruxtecan are not listed and all on patent, at annual costs in the region of US$100,000 to 200,000 and above at United States list†; trastuzumab deruxtecan has the highest measured response rates in the class, above 50 per cent in the registrational trials†. Palbociclib, ribociclib and abemaciclib are not listed and on patent at US$150,000 a year and above at United States list†; they roughly double progression-free survival added to endocrine therapy, and the overall survival benefit is not uniform across the class. Olaparib and talazoparib are not listed. Pembrolizumab is listed, for other indications, and used in triple-negative disease. Radiotherapy reduces local recurrence after conserving surgery and improves survival in node-positive disease, and requires a linear accelerator.

Simple means. Simple mastectomy with axillary clearance is achievable with basic instruments, anaesthesia and a general surgeon. For a woman with operable disease and no access to radiotherapy, mastectomy rather than conservation is the correct simple-means choice, because conservation depends on the radiotherapy. Tamoxifen is the most important simple means in this entry: oral, off-patent, pennies a day, no cold chain, no monitoring beyond clinical review, and for receptor-positive disease it delivers a large fraction of the total available survival benefit. Clinical breast examination and breast awareness need no equipment; the evidence that they reduce mortality is weak, and the measured effect is a stage shift. Oral morphine serves bone-metastasis pain, and single-fraction palliative radiotherapy is highly effective for it in one visit where a machine exists. HER2-positive and triple-negative disease have no simple-means answer: trastuzumab needs a cold chain and intravenous infusion, and without it HER2-positive disease is substantially worse. The gap between simple means and the full chain is wider in breast cancer than in cervical or gastric cancer.

Gaps. Mammography overdiagnosis is the most contested figure in cancer screening, and the dispute — 19 against 30 per cent, and a 20 per cent mortality reduction against a non-significant one — is unresolved. Tamoxifen prevention reduces incidence with no demonstrated mortality benefit. Risk-reducing mastectomy has no demonstrated survival benefit. Trastuzumab and biosimilar pricing could not be retrieved and the figures given are historical. The established risk factors explain only a minority of cases.

> **Depth.** Starts in: a milk-duct epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 62 years († median age 62); time depth 52.63. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

6. Cervical cancer

What it is. Cancer of the neck of the womb, caused in virtually every case by persistent infection with a high-risk human papillomavirus. It develops through a long pre-cancerous stage that can be detected and treated. It is the most preventable of the common cancers and the one where the gap between what is possible and what is delivered is widest.

Measured. GLOBOCAN 2022 gives 662,301 cases at an age-standardised rate of 14.1 per 100,000 and 348,874 deaths; GLOBOCAN 2024 gives 604,196 cases and 279,583 deaths. The WHO sexually

transmitted infections fact sheet gives over 311,000 cervical cancer deaths a year, and WHO records cervical cancer as the most common cancer among women in 26 countries. Five-year relative survival in the United States is 68.8 per cent overall: localized 91.8, regional 64.0, distant 20.5, unknown 62.3 per cent. Median age at diagnosis 50, which is why the burden in disability-adjusted life years exceeds what the case count suggests. Stage at diagnosis: localized 41, regional 37, distant 16, unknown 6 per cent. The geographical gradient is a screening and HIV gradient: the highest age-standardised incidences are Eswatini 95.9, Zambia 71.5, Malawi 70.9, Zimbabwe 68.2 and Tanzania 64.8, against 6.3 in the United States — a fifteenfold range. In countries with organised cytology screening, incidence fell by 60 to 80 per cent over the decades after the programme started†.

Where it starts. Persistent infection with certain high-risk human papillomavirus types causes about 95 per cent of cervical cancers, and types 16 and 18 cause around 76 per cent. It is the clearest single-cause cancer in this chapter. de Martel and colleagues, 2020, attribute about 690,000 cancer cases worldwide across all sites to human papillomavirus, at an age-standardised incidence of 8.0 per 100,000, the majority cervical, and the attributable rate rises as income falls, from 6.9 in high-income countries to 16.1 in low-income countries. Women living with HIV are six times more likely to develop cervical cancer, and about 5 per cent of all cases are attributable to HIV. Among infected women, current and former smokers have about two to three times the incidence of high-grade intraepithelial neoplasia or invasive cancer. Six or more lifetime sexual partners against one: relative risk 2.98 for squamous carcinoma. First intercourse at 17 or younger against 21 or older: 2.24. Oral contraceptives in infected women: odds ratio 0.73 under five years, not significant, 2.82 at five to nine years and 4.03 at ten years or more, returning to baseline about ten years after stopping. Diethylstilboestrol exposure in utero: about one in a thousand exposed daughters develop clear cell adenocarcinoma, and grade II or higher intraepithelial neoplasia occurred in 6.9 against 3.4 per cent, hazard ratio 2.28. The driving event is viral oncoprotein expression inactivating p53 and Rb rather than an accumulation of point mutations, so mutation burden is a poor description of this cancer. Not known: why only a small minority of infections persist and progress, most clearing within two years, and what determines persistence.

Cure status. Human papillomavirus infection: SELF-LIMITING — most infections clear spontaneously within one to two years with no treatment. This is the one place in the chapter where SELF-LIMITING is the right label for a precursor state. High-grade intraepithelial neoplasia, CIN2 or CIN3: CURABLE — cryotherapy, thermal ablation or large-loop excision cures the great majority in a single outpatient visit. Localized invasive, stage I: CURABLE — five-year relative survival 91.8 per cent. Regional, stage II to III: CURABLE in 64.0 per cent (five-year relative survival), with cisplatin chemoradiation. Distant, stage IV: CONTROLLABLE — 20.5 per cent.

Prevention. Human papillomavirus vaccination — STRONG, with efficacy figures among the highest in preventive medicine. Against incident and persistent infection: 91.6 per cent, interval 64.5 to 98.0, for type 16, and 100 per cent, interval 45 to 100, for type 18. The bivalent vaccine gave 100 per cent, interval 81.8 to 100, against persistent type 16 or 18 infection per protocol, and 100 per cent, interval 51.3 to 100, against CIN2 or worse in the total vaccinated cohort, neither analysis being intention-to-treat. The quadrivalent trials gave 100 per cent, interval 90.5 to 100, against CIN3 in the virus-naive, against 45.3 per cent, interval 29.8 to 57.6, by intention to treat: that gap is the measure of how much depends on vaccinating before exposure. Against invasive cancer, the endpoint that matters, the Swedish national cohort published in the *New England Journal of Medicine* in 2020 gave an incidence rate ratio of 0.51, interval 0.32 to 0.82, adjusted for age alone. After full adjustment, vaccination before age 17 gave an incidence rate ratio of 0.12, interval 0.00 to 0.34: an 88 per cent reduction. A Scottish cohort vaccinated at age 12 to 13 gave an 87 per cent relative reduction in cervical cancer, interval 72 to 94, and 97 per cent in CIN3. One dose is non-inferior to two for protection against the targeted types, which has large consequences for programme cost. WHO projects that widespread vaccination could cut incidence worldwide by as much as 90 per cent. Global first-dose coverage in girls reached 33 per cent in 2025, up from 17 per cent in 2019, against a 90 per cent target for 2030. Screening — STRONG. WHO recommends a high-performance human papillomavirus test every five to ten years from age 30, and every three to five years from age 25 for women with HIV, and states that self-collection is as reliable as provider collection. The elimination targets for 2030 are 90 per cent of girls fully vaccinated by age 15, 70 per cent of women screened with a high-performance test by 35 and again by 45, and 90 per cent of women with pre-cancer or invasive cancer

treated appropriately. Barrier contraception — MODERATE, relative risk 0.4, interval 0.2 to 0.9. Smoking cessation — MODERATE. The harms of screening are over-treatment of low-grade lesions that would have regressed, and excisional treatment carries a measurable increase in subsequent preterm birth, which is the most important harm in young women. **Overdiagnosis percentages comparable to the breast and prostate figures have never been published for cervical intraepithelial neoplasia**, partly because the treated entity is a precursor rather than a cancer. That is a gap in the literature, not evidence of no harm.

Treatment. Ablation or excision of high-grade pre-cancer — thermal ablation, cryotherapy or loop excision — is an outpatient, single-visit, curative procedure in the great majority. Radical hysterectomy with pelvic lymphadenectomy treats early invasive disease. Chemoradiation with cisplatin is the single most important curative treatment for stage II to III; cisplatin is a listed medicine, with cervical cancer among its listed indications, off-patent, at a drug cost of tens of dollars a course. The binding constraint is the machine, not the drug, and brachytherapy in particular is essential for cure in locally advanced disease and unavailable across much of sub-Saharan Africa. Carboplatin and paclitaxel are both listed and off-patent. Bevacizumab is not listed for this indication. Pembrolizumab is a selected medicine on the list for metastatic cervical cancer with PD-L1 expression of 1 per cent or more, in combination with platinum-based chemotherapy; it is not off-patent, at a United States cash price of US$1,530.35 per 4 mL (100 mg) unit and US$6,121.41 per four-unit pack at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price. A drug at that price being listed as essential for a cancer that is 95 per cent preventable by a vaccine costing under ten dollars a dose is the sharpest cost contrast in this chapter.

Simple means. This is the entry where simple means do the most work in the chapter. Visual inspection with acetic acid needs a speculum, a light source and a trained nurse or midwife: no laboratory, no pathologist, no electricity beyond a torch, and the result is immediate, so the woman can be treated at the same visit. WHO's current position has moved on: its cervical cancer guidance now recommends a high-performance human papillomavirus test as the primary screen and describes acetic acid application as the examination used after a positive screen to locate lesions. Where testing is genuinely unavailable, visual inspection with same-visit thermal ablation remains the only screen-and-treat approach that works with no industrial chain. Thermal ablation uses a hand-held battery or mains probe costing a few hundred dollars, with no gas cylinder and no cold chain, and cure rates for CIN2 and CIN3 comparable to cryotherapy†. Cryotherapy with a carbon dioxide or nitrous oxide cylinder needs no electricity, and the cylinder logistics are a real constraint. Self-collection removes the speculum, the clinic visit and much of the cultural barrier. Vaccination is one or two intramuscular doses in a girl aged 9 to 14, within the routine immunisation cold chain. Oral morphine matters disproportionately here, because so many women present with advanced disease, are young and have dependent children. What has no simple substitute is brachytherapy. Cure of locally advanced cervical cancer requires it and there is no low-technology equivalent: the prevention and the pre-cancer treatment are simple, and the treatment of established locally advanced disease is not.

Gaps. The Osmanabad cluster-randomised trials of visual inspection and human papillomavirus screening in India — the key randomised evidence that a no-laboratory screen reduces cervical cancer mortality — could not be retrieved, so no hazard ratio is quoted here. Over-treatment of intraepithelial neoplasia has no published percentage. WHO's downgrading of visual inspection from primary screen to triage is not always reflected in secondary sources, and programmes still run it as a primary screen. GLOBOCAN 2022 and 2024 give materially different figures — 662,301 against 604,196 cases and 348,874 against 279,583 deaths. A 20 per cent fall in deaths over two years is larger than any plausible real change and most likely reflects a methodological revision. It should not be read as a trend.

> **Depth.** Starts in: high-risk human papillomavirus. Size: 55 nm†; depth +0.17. First complaint: about 17 years († 15–20 years after infection); time depth 51.47. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

7. Prostate cancer

What it is. Cancer of the prostate gland. Most of it grows so slowly that it never causes symptoms or death, and a minority is aggressive and lethal. The central clinical problem is telling the two apart, and the central epidemiological fact is that very large numbers of men have prostate cancer without ever knowing it.

Measured. WHO gives 1.5 million new cases for 2024. GLOBOCAN 2022 gives 1,467,854 cases, 7.3 per cent of all cancers; GLOBOCAN 2024 gives 1,546,112 cases and 419,849 deaths. Five-year relative survival in the United States is 98.2 per cent overall: localized 100.0, regional 100.0, distant 40.1, unknown 94.1 per cent. The two 100 per cent figures mean five-year survival indistinguishable from the general male population, and they are the strongest single piece of evidence that much of what is diagnosed would never have caused harm. Median age 68. Stage at diagnosis: localized 69, regional 14, distant 9, unknown 8 per cent. Incidence is highest in high-income countries with prostate-specific antigen testing and in men of African ancestry everywhere, and the mortality-to-incidence ratio is far higher in sub-Saharan Africa and the Caribbean. United States incidence is rising 2.7 per cent a year, the steepest rise of any common cancer here, while the death rate falls 0.8 per cent a year.

Where it starts. Age dominates. Incidental prostate cancer is found at autopsy in 5 per cent of men under 30, interval 3 to 8, and 59 per cent of men over 79, interval 48 to 71, across 29 autopsy studies dated 1948 to 2013, rising about 1.7-fold per decade. About 15 per cent of men with prostate cancer have a first-degree relative with the disease against about 8 per cent of the United States population, and about 9 per cent of cases may result from heritable susceptibility genes. Risk of developing and of dying from it is highest in Black men, intermediate in White men and lowest in native Japanese men, and the incidence difference is not explained by access to care. PDQ's prevention summary does not mention BRCA2, although BRCA2 is established elsewhere as conferring elevated risk of aggressive disease; that is a gap in the source. Primary prostate adenocarcinoma has one of the lowest point-mutation burdens of any adult carcinoma, well below the adult reference of 1.8 per megabase, and is driven instead by structural rearrangement, most characteristically the TMPRSS2-ERG fusion present in roughly half of cases. The low burden is the leading explanation for its poor response to checkpoint blockade. Not known: what distinguishes the indolent majority from the lethal minority at diagnosis, reliably enough to act on; why incidence and mortality are so much higher in men of African ancestry. **No modifiable risk factor for prostate cancer has been established with the confidence that smoking is established for lung cancer**, and that is the largest void in the chapter for a cancer of this size.

Cure status. Indolent localized, Gleason 6 and low-volume: CONTROLLABLE by surveillance — the ProtecT randomised trial found no difference in prostate-cancer mortality between surgery, radiotherapy and active monitoring at ten and at fifteen years, with monitoring producing more metastases. Treatment is not indicated, and applying CURABLE to this stratum would mislead. Localized clinically significant, Gleason 7 and above: CURABLE — five-year relative survival 100.0 per cent. Regional: CURABLE — five-year relative survival 100.0 per cent, which understates the long-term relapse rate. Distant, metastatic: CONTROLLABLE — 40.1 per cent. Androgen deprivation with an androgen-receptor-pathway inhibitor or docetaxel now gives median survival in the region of five years in hormone-sensitive metastatic disease; castration-resistant disease remains uniformly fatal.

Prevention. There is no established means of primary prevention, and that is the honest summary. 5-alpha reductase inhibitors — CONTESTED, and the two findings point in opposite directions. The Prostate Cancer Prevention Trial gave finasteride incidence of 18.4 against 24.4 per cent, a relative reduction of 24.8 per cent, interval 18.6 to 30.6; REDUCE gave dutasteride an absolute reduction of 5.1 per cent at four years, relative 22.8 per cent, interval 15.2 to 29.8. Against that, finasteride produced high-grade cancers, Gleason 7 to 10, in 6.4 against 5.1 per cent, relative risk 1.27, interval 1.07 to 1.50, a statistically significant excess; dutasteride showed no significant difference in Gleason 8 to 10 over years one to four, 29 against 19 cases. Mortality: finasteride hazard ratio 0.75, interval 0.50 to 1.12, not significant, and PDQ states the evidence is inadequate to determine whether either drug reduces prostate cancer mortality. Screening with prostate-specific antigen — the mortality benefit is small, the overdiagnosis is large, and the trials disagree. Both sides are printed, from the USPSTF evidence review of 2018. ERSPC, in men aged 55 to 69, gave prostate cancer mortality at thirteen years of 4.3 against 5.4 deaths per 10,000 person-years, rate ratio 0.79, interval 0.69 to 0.91. The number needed to screen was 781, interval 490 to 1,929, to prevent one prostate

cancer death over thirteen years, an absolute reduction of about 1.28 deaths per 1,000 men screened. The metastatic-cancer rate ratio at twelve years was 0.70, an absolute reduction of 3.1 metastatic cases per 1,000 men. There was no reduction in all-cause mortality. PLCO gave prostate cancer mortality at a median of 14.8 years with a rate ratio of 1.04, interval 0.87 to 1.24, no significant difference, in a trial whose control group had about 78 per cent prostate-specific antigen testing, so it is better described as a trial of organised against opportunistic screening. CAP, a single invitation in the United Kingdom, gave a rate ratio of 0.99, interval 0.94 to 1.03, at a median of ten years, with only 34 per cent of invited men having a valid test. **Overdiagnosis: 20 to 50 per cent of screen-detected cancers.** About 21 per cent of screen-detected cancers in PLCO and about 50 per cent in ERSPC were judged overdiagnosed, and CISNET decision models estimated 22 to 42 per cent for United States screen-detected cancers from 1988 to 2000. That is a more-than-twofold disagreement between the two main trials, and both ends are printed. The USPSTF recommendation is grade C, an individual decision, for men 55 to 69, and grade D, against, for men 70 and older. Beyond overdiagnosis the harms are biopsy complications — infection, bleeding, sepsis — and the treatment harms that follow overdiagnosis: erectile dysfunction and urinary incontinence after prostatectomy, bowel and urinary toxicity after radiotherapy. Those harms fall on men whose cancer would never have hurt them.

Treatment. Active surveillance is the correct treatment for a large fraction of localized disease, and it is free. Radical prostatectomy and radical radiotherapy give equivalent survival for clinically significant localized disease. Androgen deprivation follows: goserelin, leuprorelin and triptorelin are all listed and off-patent with generics in many markets, and bicalutamide, flutamide and nilutamide are all listed, off-patent and cheap. Docetaxel added to androgen deprivation in metastatic hormone-sensitive disease is listed and off-patent at tens to low hundreds of dollars a vial. Abiraterone is listed and has been off-patent in most markets since about 2018 to 2019, with generics at a small fraction of the originator price†. That originator price was in the region of US$9,000 to 10,000 a month at United States list, and generics have fallen to the low hundreds of dollars a month in competitive markets. Enzalutamide is listed; its patent status is market-dependent and it remains expensive in most, in the region of US$10,000 a month and above at United States list†. Radium-223 and lutetium-177-PSMA are not listed and require a radiopharmacy. Olaparib is not listed. Checkpoint inhibitors are essentially inactive outside the rare microsatellite-unstable subset, with response rates in the single digits in unselected castration-resistant disease, consistent with the low mutation burden.

Simple means. Bilateral orchidectomy is the outstanding simple means in this entry. It is a short operation under local or spinal anaesthesia with basic instruments, it achieves castrate testosterone permanently in one sitting, it costs almost nothing, and it is therapeutically equivalent to lifelong agonist injections for metastatic disease. Where drug supply is unreliable it is the correct treatment rather than a compromise. Its disadvantages are irreversibility and psychological cost. Transurethral resection or a suprapubic catheter relieves retention from local disease at once. Oral morphine serves the bone pain that dominates advanced prostate cancer, and single-fraction palliative radiotherapy to a painful bone metastasis is one of the highest-value single interventions in oncology where a machine exists. Digital rectal examination needs no equipment; its sensitivity for early cancer is poor and it is not a screening test, and it detects locally advanced disease. Nothing simple prevents prostate cancer, and nothing simple distinguishes the indolent from the lethal: diagnosis requires biopsy and histopathology. The simple means here are all about controlling established disease, and orchidectomy is a genuinely large one.

Gaps. Overdiagnosis ranges from 20 to 50 per cent across sources, with PLCO at 21 and ERSPC at 50, and the disagreement is unresolved. ERSPC, PLCO and CAP give materially different mortality answers, attributed to control-group contamination and compliance, and the true effect size is not settled. The 5-alpha reductase question has not been resolved in two decades. No modifiable risk factor is established, so prevention has nothing to offer. PDQ's prevention summary does not address BRCA2. The excess burden in men of African ancestry is unexplained. SEER's 100 per cent five-year figures are uninformative about long-term outcome, and ten- and fifteen-year stage-specific figures are not published on the Stat Facts page. The intermediate age-group autopsy prevalences, between 5 and 59 per cent, are not in the retrievable abstract of Bell and colleagues.

> **Depth.** Starts in: a prostate gland cell. Size: 15 µm†; depth +5.28. First complaint: about 66 years († median age 66); time depth 52.68. One untreated course: no number ([B] usually very slow).

> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

8. Pancreatic cancer

What it is. Cancer of the pancreas, almost always ductal adenocarcinoma. It produces no symptoms until it is advanced, it spreads early, and it resists almost all drug treatment. Its incidence and its death rate are nearly the same number, which is the shortest description of the problem.

Measured. GLOBOCAN 2022 gives 510,992 cases; GLOBOCAN 2024 gives 531,318 cases and 490,786 deaths, so deaths are 92 per cent of incidence. No other major cancer comes this close. Five-year relative survival in the United States is 13.7 per cent overall: localized 43.6, regional 17.0, distant 3.4, unknown 12.5 per cent. Median age 71. Stage at diagnosis: localized 15, regional 28, distant 51, unknown 5 per cent. It is 3.2 per cent of United States cancer cases and 8.4 per cent of United States cancer deaths, and in several high-income countries it has overtaken breast cancer as the third leading cause of cancer death. United States incidence is rising about 0.9 per cent a year and the death rate is stable.

Where it starts. The NCI PDQ prevention summary for pancreatic cancer could not be retrieved, so the effect sizes here carry no evidence grade, which is an asymmetry against the rest of the chapter. Smoking is the best-established modifiable cause, with a relative risk for current smokers generally reported in the region of 1.7 to 2.2 and an attributable fraction of roughly 20 to 25 per cent of cases†. Obesity is reported at a relative risk in the region of 1.5 for a body mass index of 30 or more†. Type 2 diabetes is associated with roughly 1.5- to twofold risk†, with a large interpretive problem: new-onset diabetes is frequently an early manifestation of the cancer rather than a cause of it, so reverse causation confounds this association more than any other in the chapter. Hereditary pancreatitis confers a lifetime risk reported in the region of 40 per cent†. BRCA2, BRCA1, PALB2, ATM, CDKN2A, STK11, Lynch syndrome and hereditary pancreatitis together account for roughly 10 per cent of cases†. Mutation burden is low to moderate, around or below the adult reference of 1.8 per megabase, and the disease is dominated by four drivers — KRAS, mutated in roughly 90 to 95 per cent of cases, with TP53, CDKN2A and SMAD4. KRAS was undruggable for forty years, and the G12C inhibitors now entering use address a small minority of pancreatic KRAS mutations. Not known: why it is silent until advanced; whether the diabetes association is cause or consequence and in what proportion; why the dense stromal reaction makes it so resistant to drugs. **There is no validated early-detection test**, and that is the single largest unmet need here.

Cure status. Localized and resectable, about 15 to 20 per cent at presentation: CURABLE in roughly 30 to 50 per cent of patients who complete resection and adjuvant chemotherapy (five-year survival in trial populations); five-year relative survival for localized disease is 43.6 per cent. Borderline resectable and locally advanced: CONTROLLABLE — 17.0 per cent. Metastatic: RELIEF ONLY — 3.4 per cent. Median survival with FOLFIRINOX in fit patients is in the region of eleven months and with gemcitabine monotherapy in less fit patients about six. Pancreatic cancer belongs on the short list of cancers that are not reliably curable even when caught early, because early by current detection methods still usually means systemically disseminated.

Prevention. Smoking cessation — MODERATE on the measured pancreatic effect, with the figures above unverified. Weight control — WEAK. There is no screening programme in the general population and no basis for one: prevalence is too low and no test has adequate performance. Surveillance of high-risk individuals with defined germline mutations or a strong family history, using magnetic resonance imaging and endoscopic ultrasound, is offered in specialist centres and detects some resectable lesions; whether it reduces mortality has not been established in a randomised trial. The harms include a high rate of investigation of cystic lesions that would never have progressed, and pancreatic surgery carries a mortality of 1 to 3 per cent even in high-volume centres†, so an unnecessary resection is a serious harm. Population screening is not recommended, on no evidence of benefit. Pancreatic cancer is the major cancer with the least to offer in prevention: no vaccine, no eradicable infection, no dominant modifiable exposure of the kind smoking is for lung, and no effective screen.

Treatment. Surgical resection — pancreaticoduodenectomy or distal pancreatectomy — is the only curative modality, with 1 to 3 per cent mortality in high-volume centres and considerably higher elsewhere; the volume-outcome relationship is one of the strongest in surgery. Modified FOLFIRINOX is the standard adjuvant regimen for fit patients after resection and produced the largest survival gain of any adjuvant regimen in this disease, a median overall survival of roughly 54 against 35 months in PRODIGE-24†. **Fluorouracil, calcium folinate, irinotecan and oxaliplatin are all listed and all off-patent**, at a drug cost in the low hundreds of dollars for a full adjuvant course. That is the most important fact in this section: the best adjuvant regimen for pancreatic cancer is made entirely of off-patent listed medicines. Gemcitabine, alone or with capecitabine, serves patients unfit for FOLFIRINOX; both are listed, off-patent and cheap. Nab-paclitaxel is not listed and is not the same agent as the off-patent paclitaxel that is. Erlotinib added to gemcitabine is listed and off-patent, and the measured survival gain was about two weeks, which is worth stating as a calibration point on what statistical significance has meant in this disease. Olaparib maintenance in BRCA-mutant metastatic disease is not listed and benefits a few per cent of patients. Checkpoint inhibitors are inactive outside the roughly 1 per cent that is microsatellite-unstable, with response rates near zero in unselected disease: the clearest negative result for immunotherapy among the major cancers, consistent with the low mutation burden and the immunosuppressive stroma. Biliary stenting for obstructive jaundice is not a cancer treatment and is among the most valuable interventions available.

Simple means. Where endoscopic stenting is unavailable, a surgical double bypass — choledochojejunostomy or cholecystojejunostomy with gastrojejunostomy — relieves jaundice and duodenal obstruction with basic instruments and a general surgeon. It is a major but entirely conventional operation and it transforms the final months. Oral morphine in adequate dose matters more here than almost anywhere: coeliac plexus infiltration causes a boring epigastric and back pain that responds poorly to small doses. A coeliac plexus block with alcohol or phenol can be performed percutaneously using anatomical landmarks, and intraoperatively under direct vision during a bypass laparotomy at no extra cost, which is a genuinely simple and underused means. Oral pancreatin replaces the exocrine failure that causes steatorrhoea and weight loss; it is cheap, oral, off-patent and listed, for cystic fibrosis, and widely omitted. Nutritional support, antiemetics and dexamethasone, listed and off-patent at a United States-equivalent indicative price of 24 cents a 4 mg tablet in the UNICEF Supply Catalogue, October 2026, serve anorexia and duodenal oedema. For the cancer itself nothing simple exists: no simple prevention, no simple detection and no simple cure. The whole of the simple-means contribution in pancreatic cancer is palliative, and it is substantial on its own terms without extending life.

Gaps. The PDQ pancreatic prevention summary could not be retrieved, so the risk-factor effect sizes carry no evidence grade. The diabetes association is confounded by reverse causation to an extent that is acknowledged and not quantified. High-risk surveillance has no randomised mortality evidence. No early-detection test exists, and the biomarker claims in this field have not been validated.

> **Depth.** Starts in: a pancreatic duct cell. Size: 15 µm†; depth +5.28. First complaint: about 70 years († median age 70); time depth 52.74. One untreated course: about 6 months († about 6 months); depth 48.24.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

9. Oesophageal cancer

What it is. Cancer of the gullet, in two forms with different causes and geography. Squamous cell carcinoma is tied to tobacco, alcohol and hot drinks and dominates in Asia and Africa; adenocarcinoma is tied to reflux, obesity and Barrett’s oesophagus and dominates and is rising in Western countries. Both present late, because swallowing only becomes difficult when the lumen is already badly narrowed.

Measured. GLOBOCAN 2022 gives 511,054 cases; GLOBOCAN 2024 gives 494,320 cases and 441,994 deaths, so deaths are about 89 per cent of incidence. Five-year relative survival in the United States is 22.2 per cent overall: localized 48.6, regional 29.1, distant 5.3, unknown 15.9 per cent. Median age 69. Stage at diagnosis: localized 19, regional 32, distant 39, unknown 10 per cent. Squamous carcinoma was over 90 per

cent of oesophageal tumours in the 1960s, and adenocarcinoma is now more prevalent than squamous in the United States and Western Europe; globally squamous remains the majority. The highest squamous rates run in a belt from northern Iran through Central Asia to north-central China, with eastern and southern Africa also high. United States incidence is falling about 0.6 per cent a year and the death rate 1.1 per cent a year, a fall that combines falling squamous with rising adenocarcinoma incidence.

Where it starts. For squamous carcinoma: tobacco, relative risk 2.4, with a population attributable risk of 54.2 per cent, interval 3.0 to 76.2 — an interval so wide as to be nearly uninformative, and PDQ reports it without comment. Alcohol, in a multicentre case-control study of 221 cases and 695 controls, gave a population attributable risk of 72.4 per cent, interval 53.3 to 85.8, with ever-smoking at 56.9 per cent and the two combined at 89.4 per cent; cohort studies adjusted for tobacco give a two- to sevenfold increase for alcohol addiction. On hot beverages the sources disagree by omission: the PDQ oesophageal page does not address them, while IARC's 2016 evaluation classified drinking very hot beverages, above about 65 degrees Celsius, as probably carcinogenic to humans, Group 2A, largely on studies from South America, Iran and China. Both positions are noted. Achalasia, caustic stricture, Plummer-Vinson syndrome, tylosis, low fruit and vegetable intake and nutritional deficiency are established and not quantified on the PDQ page. For adenocarcinoma: PDQ gives no relative risks for smoking or alcohol, a notable asymmetry since both are established at smaller effect sizes. Recurrent reflux symptoms give an odds ratio of 7.7 in a Swedish study, long-standing severe symptoms 43.5, interval 18.3 to 103.5, and daily heartburn with regurgitation 8.0, interval 4.5 to 14.0. Barrett's oesophagus gives adenocarcinoma at about 1.2 cases per 1,000 person-years in a Swedish cohort, roughly 11.3 times the general-population rate, and PDQ adds that the absolute risk is still not high and that over half of adenocarcinoma cases are not linked to reflux symptoms. Obesity is named by PDQ with no risk estimate; elsewhere central obesity is established, with relative risks in the region of 2 to 3 for the highest body mass index categories†. PDQ's grade for reflux and adenocarcinoma is fair evidence of unknown magnitude, and it states that whether eliminating reflux reduces risk is unknown. Both forms carry high mutation burdens, and oesophageal adenocarcinoma is among the most heavily mutated of all tumours, with a very high rate of structural rearrangement and TP53 mutation in the large majority. Not known: why reflux progresses to Barrett's in a minority and Barrett's to cancer in a small minority of those; why over half of adenocarcinomas arise without reflux symptoms; the mechanism of the hot-beverage effect, where thermal injury is assumed rather than demonstrated.

Cure status. Barrett's oesophagus with high-grade dysplasia: CURABLE by radiofrequency ablation or endoscopic resection — one randomised trial with good internal validity, and PDQ states that the effect on cancer mortality is not known. Localized, stage I and mucosal: CURABLE — five-year survival 48.6 per cent for localized disease overall, by endoscopic resection for T1a and oesophagectomy for deeper lesions. Regional, stage II to III: CURABLE in 29.1 per cent (five-year relative survival), with neoadjuvant chemoradiation then oesophagectomy. Distant: RELIEF ONLY — 5.3 per cent. Oesophageal cancer is also one of the cancers where the curative treatment is itself dangerous: oesophagectomy carries an operative mortality of 2 to 5 per cent in high-volume centres and considerably more elsewhere, with major morbidity in a third of patients.

Prevention. Tobacco and alcohol avoidance — STRONG for squamous carcinoma. The combined population attributable risk is 89.4 per cent, one of the highest attributable fractions in the chapter, and it is addressable with no technology at all. Alcohol cessation specifically — CONTESTED: PDQ rates the cessation evidence inadequate, with odds ratios of 0.45 for oral cavity and 0.69 for larynx at twenty years or more after cessation and no support for an oesophageal reduction. Never starting is STRONG; stopping is contested. That asymmetry is real and is printed as PDQ states it. Avoiding very hot drinks — WEAK, on an IARC Group 2A classification with no intervention trial. Aspirin and other non-steroidal anti-inflammatory drugs — CONTESTED on net benefit: PDQ gives fair evidence of a small positive effect for squamous carcinoma against solid harms, an upper gastrointestinal excess of 4 to 5 events per 1,000 people a year and serious cardiovascular events up 50 to 60 per cent. Treating reflux to prevent adenocarcinoma — CONTESTED: PDQ states explicitly that it is unknown whether eliminating reflux reduces risk. Radiofrequency ablation of dysplastic Barrett's — MODERATE, one good randomised trial, effect on cancer mortality not known. Weight control — WEAK for adenocarcinoma, with no estimate given. There is no population screening programme outside high-incidence regions of China, where endoscopic screening with Lugol's iodine chromoendoscopy has been deployed and reported to reduce mortality in

cluster-randomised and cohort studies; **harms and overdiagnosis from that programme have not been published as percentages**. Barrett's surveillance in Western countries is widely practised with no randomised evidence that it reduces mortality.

Treatment. Endoscopic mucosal or submucosal resection cures T1a disease with the organ preserved. Neoadjuvant chemoradiotherapy then oesophagectomy treats resectable locally advanced disease; the CROSS regimen is carboplatin and paclitaxel with radiotherapy, and both drugs are listed and off-patent at a low drug cost. The radiotherapy and the surgery are the expensive and scarce components. Definitive chemoradiotherapy without surgery uses cisplatin and fluorouracil, both listed and off-patent at a trivial drug cost, and for squamous carcinoma it is a legitimate curative alternative to surgery. Palliative chemotherapy for metastatic disease is platinum with a fluoropyrimidine and taxanes second line, all listed and off-patent. Trastuzumab serves HER2-positive oesophagogastric adenocarcinoma and is listed, with the originator off-patent and biosimilars available. Pembrolizumab is a selected medicine on the list, for other listed indications. Nivolumab's listing for this cancer needs checking against the 24th List (2025)†. Neither is off-patent, and pembrolizumab costs US$1,530.35 per 4 mL (100 mg) unit at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price. Objective response as monotherapy in pre-treated oesophageal squamous carcinoma is in the region of 15 to 20 per cent†. A self-expanding metal stent is the single most effective palliative intervention, restoring swallowing in one endoscopic session.

Simple means. Avoiding tobacco and alcohol, with a combined population attributable risk of 89.4 per cent for squamous carcinoma, is the highest-yield no-technology intervention available for any cancer in this chapter other than lung. A feeding gastrostomy or jejunostomy placed surgically through the abdominal wall, with basic instruments and local or general anaesthesia, allows a patient with complete obstruction to eat. It does not treat the cancer and does not restore swallowing, and it prevents death by starvation and dehydration, which is otherwise how oesophageal cancer kills. Where endoscopic stenting is unavailable this is the intervention that matters most. Oral morphine has a specific limitation here: a patient who cannot swallow cannot take it, so sublingual, rectal or subcutaneous administration is required, and the rectal route needs no equipment at all. Dilatation of a malignant stricture with bougies or a balloon over a guidewire gives temporary relief and needs no fluoroscopy if done carefully, with a real perforation risk. The curative treatment has no simple-means version: oesophagectomy is one of the largest operations in general surgery and chemoradiation requires a linear accelerator. Simple means here are prevention, which is very large, and palliation of obstruction, which is very valuable, and nothing in between.

Gaps. PDQ gives smoking and alcohol relative risks for squamous carcinoma and none for adenocarcinoma, and gives no obesity estimate at all: an asymmetry in the source rather than in the evidence. PDQ does not address hot beverages while IARC classifies them Group 2A. Barrett's surveillance has no randomised mortality evidence. The Chinese endoscopic screening programme's mortality effect and harms are not reported in a form comparable with the Western screening literature. The tobacco attributable-risk interval, 3.0 to 76.2 per cent, is nearly uninformative.

> **Depth.** Starts in: an oesophageal epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 68 years († median age 68); time depth 52.71. One untreated course: about 9 months († about 9 months); depth 48.61.
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

10. Bladder cancer

What it is. Cancer of the bladder lining, almost always urothelial carcinoma. It divides sharply into non-muscle-invasive disease, which recurs repeatedly and rarely kills, and muscle-invasive disease, which does. Painless blood in the urine is the usual first sign. In parts of Africa and the Middle East a squamous form caused by schistosomiasis predominates instead.

Measured. GLOBOCAN 2022 gives 614,298 cases; GLOBOCAN 2024 gives 635,264 cases and 227,626 deaths. Five-year relative survival in the United States is 79.1 per cent overall: in situ 98.0, localized 73.0,

regional 41.8, distant 9.6, unknown 50.8 per cent. Median age at diagnosis 73, the oldest in this chapter. Stage at diagnosis: in situ 50, localized 34, regional 7, distant 6, unknown 3 per cent. Half of all United States bladder cancer is diagnosed in situ, which is why the overall survival figure is high and why it conceals a lethal minority. United States incidence is falling about 1.6 per cent a year, tracking the decline in smoking, and the death rate 1.3 per cent a year. Schistosomal squamous bladder cancer is concentrated in Egypt, Sudan and parts of sub-Saharan Africa, where schistosomiasis control has substantially reduced it.

Where it starts. The PDQ bladder prevention summary could not be retrieved, so the figures here carry no evidence grade. Smoking is the dominant cause, with a relative risk for current smokers generally reported in the region of 3 to 4 and an attributable fraction of roughly 50 per cent in men and 35 to 50 per cent in women in high-income countries†. Occupational aromatic amines — benzidine, 2-naphthylamine, 4-aminobiphenyl — in dye, rubber, leather, textile and painting work account for roughly 5 to 10 per cent of cases†; this was one of the first occupational cancers ever identified, in 1895. Arsenic in drinking water is an established dose-dependent cause, with the clearest evidence from Taiwan, Chile and Bangladesh. *Schistosoma haematobium* is an IARC Group 1 carcinogen causing squamous bladder carcinoma; de Martel and colleagues, 2020, include it among infectious causes of cancer, and the retrieved summary gave case counts for four agents only, which did not include it. In high-endemic areas schistosomal squamous carcinoma has historically been the majority of bladder cancer, and the attributable fraction there is high and not well quantified in any single source. Cyclophosphamide, itself a cancer drug, and pelvic radiotherapy are established iatrogenic causes, and chronic indwelling catheterisation with chronic infection causes squamous carcinoma in paraplegia. Urothelial carcinoma has one of the highest mutation burdens of any cancer, well above the adult reference of 1.8 per megabase, with prominent APOBEC and tobacco signatures, and that high burden is the explanation for its unusually good response to checkpoint blockade: it was one of the first solid tumours where these drugs were approved. Not known: why some non-muscle-invasive tumours progress to muscle invasion and most do not; why intravesical bacille Calmette-Guérin works, after forty years of use; the quantitative contribution of arsenic at the low concentrations found in many water supplies.

Cure status. Non-muscle-invasive disease — Ta, T1, carcinoma in situ: CONTROLLABLE — in situ five-year relative survival 98.0 per cent and localized 73.0 per cent. The qualification is recurrence: up to 50 to 70 per cent recur and 10 to 20 per cent progress to muscle invasion†, so lifelong cystoscopic surveillance is required and the disease is survived rather than eliminated in many patients. Muscle-invasive, non-metastatic: CURABLE in 41.8 per cent (regional five-year survival), by radical cystectomy with neoadjuvant cisplatin-based chemotherapy or by chemoradiation for bladder preservation. Metastatic with a durable checkpoint-inhibitor response, a minority: CONTROLLABLE. Metastatic otherwise: RELIEF ONLY — five-year survival 9.6 per cent.

Prevention. Smoking cessation — STRONG, against an attributable fraction around half. Occupational exposure control — STRONG: aromatic amines are among the best-established occupational carcinogens and their control is a demonstrated success, with bladder cancer rates in exposed trades falling after regulation. Arsenic removal from drinking water — STRONG on the causal evidence, and achievable by simple means. Schistosomiasis control — STRONG. Mass praziquantel administration and snail control have cut *S. haematobium* prevalence substantially, with a corresponding fall in squamous bladder cancer; WHO records at least 253.7 million people requiring preventive treatment for schistosomiasis in 2024, of whom more than 100.5 million were reported treated, a coverage of 39.6 per cent, and a fall of almost 60 per cent in prevalence among school-aged children in sub-Saharan Africa over the past ten years. Praziquantel is a listed medicine, off-patent, and costs under a dollar a treatment: one of the cheapest cancer-preventive interventions that exists. There is no population screening programme for bladder cancer and no recommendation for one. Haematuria dipstick screening detects cancers and has never been shown to reduce mortality, and its false-positive rate leads to large numbers of unnecessary cystoscopies. **Overdiagnosis has never been quantified, because no programme exists to quantify it in**, in a disease where half of all diagnoses are already in situ. Surveillance after treated non-muscle-invasive disease is surveillance of known disease rather than screening, and its intensity rests on recurrence risk rather than on randomised mortality evidence.

Treatment. Transurethral resection is both diagnostic and therapeutic for non-muscle-invasive disease and requires a resectoscope and cystoscopy capability. Intravesical bacille Calmette-Guérin is the most

effective agent for reducing recurrence and progression in high-risk non-muscle-invasive disease. The vaccine is on the Essential Medicines List as a vaccine, and the intravesical therapeutic preparation is off-patent and inexpensive; global supply has been chronically short for over a decade because few manufacturers make it. That is a supply failure rather than a price failure, and a genuine clinical problem. Intravesical mitomycin C or gemcitabine are alternatives; gemcitabine is listed and off-patent, mitomycin is off-patent, and a single post-operative instillation reduces recurrence cheaply. Radical cystectomy with urinary diversion is the curative surgery for muscle-invasive disease. Neoadjuvant cisplatin-based combination chemotherapy before cystectomy improves survival by about 5 to 8 percentage points absolute†; cisplatin, gemcitabine, methotrexate, vinblastine and doxorubicin are all listed and all off-patent at low generic cost. Chemoradiotherapy for bladder preservation gives comparable survival in selected patients. Pembrolizumab is a selected medicine on the list, for other listed indications. The listing of nivolumab and atezolizumab for this cancer needs checking against the 24th List (2025)†. None is off-patent, and pembrolizumab costs US$1,530.35 per 4 mL (100 mg) unit at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price. Objective response in platinum-refractory metastatic urothelial carcinoma is in the region of 15 to 25 per cent as monotherapy, with a long tail of durable responders† — the characteristic pattern of checkpoint blockade here. Enfortumab vedotin with pembrolizumab is not listed and is on patent; the combination produced objective response above 65 per cent and the largest overall survival gain yet seen in metastatic urothelial carcinoma, at an annual cost at United States list well above US$300,000†. Erdafitinib is not listed.

Simple means. Praziquantel for schistosomiasis is a single oral dose, listed, off-patent and under a dollar, and it prevents the squamous bladder cancer that follows chronic infection. That is the clearest simple-means cancer prevention available in the settings where schistosomal bladder cancer occurs. Arsenic removal from drinking water — switching to a deep tubewell, rainwater harvesting, or simple iron-based filtration — requires no industrial chain in its simplest versions. Smoking cessation needs no technology. Urinary catheterisation and suprapubic cystostomy relieve outflow obstruction or intractable bleeding immediately. Bladder irrigation through a three-way catheter for clot retention needs only saline and a catheter and stops a patient dying of retention and clot. Formalin or alum bladder instillation for intractable haemorrhagic cystitis from tumour is crude and painful and effective, requiring nothing beyond the chemical and a catheter where no radiotherapy or embolisation exists. Oral morphine serves pain and transfusion the chronic anaemia of recurrent haematuria. Against that, resection and cystectomy require urological equipment and training, and non-muscle-invasive disease cannot be managed without cystoscopy, for which there is no simple substitute. Bladder cancer is a disease where the prevention has excellent simple means and the treatment has almost none.

Gaps. The PDQ bladder prevention summary could not be retrieved, so the risk-factor effect sizes carry no evidence grade. The *S. haematobium*-attributable case count was not obtainable from the retrieved de Martel summary, which gave figures for four agents only. The mechanism of bacille Calmette-Guérin is unknown and the global supply shortage is unresolved. Haematuria screening has never been tested for mortality. Overdiagnosis is unquantified because no screening programme exists.

> **Depth.** Starts in: a urothelial cell. Size: 15 µm†; depth +5.28. First complaint: about 30 years († about 30 years after starting to smoke); time depth 51.97. One untreated course: no number ([B] keeps coming back).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

11. Kidney cancer

What it is. Cancer of the kidney, mostly renal cell carcinoma arising from the tubules, with clear cell the commonest subtype. A large and rising proportion is found by accident on scans done for other reasons, before it causes any symptom. It responds to immune treatment and is almost entirely resistant to conventional chemotherapy.

Measured. GLOBOCAN 2022 gives 434,840 cases; GLOBOCAN 2024 gives 442,570 cases and 144,871 deaths. Five-year relative survival in the United States is 79.2 per cent overall: localized 93.6, regional 77.6, distant 20.3, unknown 55.2 per cent. Median age 65. Stage at diagnosis: localized 66, regional 17, distant 15, unknown 3 per cent. United States incidence is rising about 0.7 per cent a year while the death rate falls 1.1 per cent a year. **That combination is the signature of incidental detection**: more small tumours are being found, and many of them would never have caused harm. Incidence is highest in Europe, particularly Czechia and Lithuania, and North America, and lowest in Africa and Asia.

Where it starts. The PDQ kidney prevention summary could not be retrieved, so the figures here carry no evidence grade. Smoking is an established dose-dependent cause with a relative risk generally reported in the region of 1.3 to 1.6 for current smokers, reversible with cessation†. Obesity is one of the strongest obesity-cancer associations, commonly reported at a relative risk in the region of 1.7 to 1.8 for a body mass index of 30 or more, with a clear dose-response†. Hypertension is an established independent risk factor at a reported relative risk in the region of 1.5 to 2†. Chronic kidney disease and end-stage renal failure on dialysis carry substantially elevated risk, partly through acquired cystic disease. Occupational trichloroethylene is IARC Group 1 for kidney cancer. Von Hippel-Lindau disease, hereditary papillary renal carcinoma, Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and renal cell cancer, succinate dehydrogenase deficiency and tuberous sclerosis together account for roughly 5 per cent of cases†. Von Hippel-Lindau is the key one, because the sporadic clear cell tumours use the same pathway: loss of VHL with constitutive hypoxia-inducible factor activation is near-universal in clear cell disease. Renal clear cell carcinoma has a low point-mutation burden, below the adult reference of 1.8 per megabase, which is a genuine anomaly: it responds well to checkpoint inhibitors despite that, which contradicts the general rule that burden predicts response, and no explanation is established. Not known: why a low-burden tumour is immunotherapy-responsive; why small renal masses behave so variably, some growing indolently for years and others metastasising early; the late and unpredictable relapse pattern, which can run a decade or more after nephrectomy; whether any of the rising incidence is real rather than detection-driven.

Cure status. Small renal mass under 4 cm, T1a: CURABLE by partial nephrectomy or ablation — localized five-year relative survival 93.6 per cent. Active surveillance is now an accepted option for small masses in older or comorbid patients, which is an implicit acknowledgement of overdetection. Localized larger, T1b to T2: CURABLE by radical or partial nephrectomy — 93.6 per cent. Regional, T3 to T4 or node-positive: CURABLE in 77.6 per cent at five years — with the proviso that late relapse is characteristic, so five-year figures overstate cure. Metastatic, in the small minority achieving a complete response that persists off treatment: CURABLE. Metastatic otherwise: CONTROLLABLE — five-year survival 20.3 per cent. Combination checkpoint-inhibitor therapy produces complete responses in roughly 10 per cent of patients, some of whom remain disease-free off treatment, which is one of the few settings where a genuinely metastatic solid tumour is sometimes cured by drug therapy; cytoreductive nephrectomy with metastasectomy can also render selected patients disease-free.

Prevention. Smoking cessation — MODERATE. Weight control — MODERATE on the association, with no trial showing that weight loss reduces incidence. Blood pressure control — MODERATE on the association, with no trial evidence on the cancer endpoint. Occupational trichloroethylene control — STRONG, on an IARC Group 1 classification. There is no screening programme and no recommendation for one: the disease is too uncommon and the great majority of what imaging the general population would find would be clinically unimportant. The overdetection is nonetheless already happening, through computed tomography and ultrasound performed for unrelated reasons. **That is unintended screening at scale, with no evidence base and no measurement of its net effect, and no published overdiagnosis percentage exists for kidney cancer comparable to the breast, prostate or thyroid figures.** The rising-incidence and falling-mortality pattern is the best available quantification of it. Kidney cancer has no established effective prevention beyond the general measures, and no screening.

Treatment. Partial or radical nephrectomy is the curative treatment, with partial nephrectomy preferred for smaller tumours because it preserves renal function. Thermal ablation serves small masses in unfit patients and is image-guided. Active surveillance is free. Checkpoint-inhibitor combinations are now first-line for metastatic disease: pembrolizumab is a selected medicine, for other listed indications; nivolumab's listing for this cancer needs checking against the 24th List (2025)†; neither off-patent, and ipilimumab is not listed and is on patent. Objective response in first-line metastatic clear cell disease is in the region of 40 to 60 per

cent for the combinations, with complete response in roughly 8 to 12 per cent†, at an annual cost at United States list above US$250,000†. Sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib are not listed; everolimus is listed and is now largely superseded in kidney cancer. Sunitinib and pazopanib are off-patent with generics available, which brings a VEGF-directed inhibitor within reach at a few hundred dollars a month in generic markets, against originator prices historically in the region of tens of thousands of US dollars a month and above; sunitinib's response rate as first-line monotherapy was about 30 to 47 per cent in the registrational trials†. For a setting without checkpoint inhibitors, a generic VEGF inhibitor is the realistic option and delivers a real though smaller benefit. Conventional cytotoxic chemotherapy is ineffective in renal cell carcinoma, which is worth stating plainly: the entire off-patent listed cytotoxic armamentarium that serves breast, colorectal and gastric cancer has nothing to offer here. Palliative radiotherapy is effective for bone and brain metastases.

Simple means. Radical nephrectomy is a conventional open operation that a general surgeon can perform with basic instruments, anaesthesia and blood availability, and for localized disease it is curative in over 90 per cent of cases†. That is a substantial simple-means cure for a cancer of this size, and it is the main one here. Oral morphine serves bone-metastasis pain and single-fraction palliative radiotherapy serves it better where a machine exists. Transfusion and iron treat the anaemia that is common at presentation. For metastatic kidney cancer nothing simple exists: chemotherapy does not work, so the off-patent cytotoxics are useless, and the effective drugs are either on patent or require a reliable oral supply chain and monitoring. A generic VEGF inhibitor is the lowest rung that still does something, and it is not simple in the sense of needing no industrial chain. There is no simple prevention either.

Gaps. The PDQ kidney prevention summary could not be retrieved, so the risk-factor effect sizes carry no evidence grade. Overdetection of small renal masses through incidental imaging is substantial and unquantified. The mechanism by which a low-burden tumour responds to checkpoint blockade is unexplained, and it undermines the general use of mutation burden as a predictor. Late relapse makes five-year survival an unreliable proxy for cure, and SEER does not publish longer-horizon stage-specific figures.

> **Depth.** Starts in: a kidney tubule cell. Size: 15 µm†; depth +5.28. First complaint: about 64 years († median age 64); time depth 52.66. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

12. Ovarian cancer

What it is. Cancer arising in the ovary, the fallopian tube or the peritoneum, now understood as largely one disease, with most high-grade serous carcinoma originating in the fallopian tube rather than the ovary. It produces vague abdominal symptoms and is usually widespread in the abdomen by the time it is diagnosed. It is the most lethal of the gynaecological cancers.

Measured. GLOBOCAN 2022 gives 324,603 cases; GLOBOCAN 2024 gives 330,731 cases and 203,850 deaths. Five-year relative survival in the United States is 52.0 per cent overall: localized 91.9, regional 70.1, distant 31.5, unknown 38.5 per cent. Median age 63. Stage at diagnosis: localized 22, regional 18, distant 54, unknown 6 per cent. More than half present with disease already spread through the abdomen, and that single fact determines the outcome. Lifetime risk of developing it is 1.12 per cent and of dying from it 0.71 per cent. United States incidence is falling about 1.4 per cent a year, one of the few clear falls in this chapter, attributed substantially to oral contraceptive use and to falling hormone therapy use, and the death rate is falling 2.9 per cent a year.

Where it starts. Oral contraceptives are protective and the effect is large and dose-dependent on duration. A collaborative reanalysis of 45 studies gave relative risks against non-users of 0.78 at one to four years, 0.64 at five to nine, 0.56 at ten to fourteen and 0.42 at fifteen years or more. A Danish cohort gave 0.58 for current users and 0.77 for former users, with no benefit from progesterone-only products. Parity is protective: parous against never-parous relative risk 0.69, one child 0.82, four or more 0.58, so parous

women carry about 30 per cent lower risk. Breastfeeding is protective. Tubal ligation gives a meta-analytic relative risk of 0.66 and a pooled odds ratio across thirteen studies of 0.71, about a 30 per cent reduction after adjusting for other contraception. Salpingectomy gives about a 50 per cent reduction: meta-analytic odds ratio 0.51, interval 0.35 to 0.71, a Swedish hazard ratio of 0.65 and a Danish bilateral odds ratio of 0.46 against 0.73 for unilateral, which is the clinical expression of the fallopian-tube origin. Menopausal hormone therapy is harmful: a meta-analysis of 52 studies gave a relative risk of 1.37, interval 1.29 to 1.46, for current or recent use in prospective studies. PDQ's ovarian prevention summary does not give a BRCA-specific lifetime risk, referring instead to its genetics summary, and rates family history and BRCA mutations as solid evidence of increased risk; elsewhere BRCA1 lifetime ovarian cancer risk is generally given as roughly 40 to 45 per cent and BRCA2 as roughly 15 to 20 per cent†. Endometriosis carries fair evidence of increased risk. On perineal talc the sources genuinely conflict and both are printed. Case-control meta-analysis gives a relative risk of 1.33, interval 1.16 to 1.45, with no dose-response, and the Ovarian Cancer Association Consortium pooled odds ratio is 1.24, interval 1.15 to 1.33, with no significant trend by number of applications. The two large prospective cohorts find nothing: the Nurses' Health Study relative risk 1.09, interval 0.86 to 1.37, and the Women's Health Initiative hazard ratio 1.06, interval 0.87 to 1.28. PDQ's conclusion is that the results are inconsistent and the data inadequate to show an association. The absence of dose-response in the positive studies is the strongest argument against causation. Dietary factors and aspirin carry inadequate evidence, and ovarian hyperstimulation for infertility treatment is rated uncertain on poor evidence. High-grade serous carcinoma has a moderate point-mutation burden with near-universal TP53 mutation, above 95 per cent, and extensive copy-number alteration; roughly half have homologous recombination deficiency, which is what PARP inhibitors exploit. Not known: why it is silent until advanced; the proportion arising in tube against ovary against peritoneum; whether talc matters at all.

Cure status. Localized, stage I: CURABLE — five-year relative survival 91.9 per cent. Regional, stage II: CURABLE in 70.1 per cent (five-year relative survival). Distant, stage III to IV, the majority: CONTROLLABLE — 31.5 per cent. Advanced ovarian cancer responds very well to initial platinum-based chemotherapy, with complete clinical remission in a large majority, and then relapses in most; the pattern is repeated response with progressively shorter intervals, over years. A minority, perhaps 10 to 15 per cent of stage III patients with complete surgical cytoreduction, remain disease-free long term and can be considered cured.

Prevention. Oral contraceptive use — STRONG, and among the largest preventive drug effects in this chapter: relative risk 0.42, interval 0.36 to 0.49, at fifteen years or more of use, a 58 per cent reduction, with a meta-analytic estimate of 185 women treated for five years to prevent one case. The harm is venous thromboembolism at about three per 10,000 woman-years, higher with smoking. Bilateral salpingectomy at the time of other pelvic surgery — MODERATE, and increasingly standard: about a 50 per cent reduction, odds ratio 0.46 to 0.51. Done opportunistically at hysterectomy or sterilisation it adds minutes to an operation already under way and removes the organ where the cancer starts. Tubal ligation — MODERATE, relative risk 0.66, with major morbidity at about 1.0 per 100 procedures and minor at about 6.0. Risk-reducing salpingo-oophorectomy in BRCA carriers — STRONG, about a 90 per cent reduction. The harm is large and must be set against it: menopausal symptoms, reduced sexual function, and with early menopause an increased cardiovascular disease risk at a relative risk of 4.55, interval 2.56 to 9.01, which is why the timing of the operation matters. Breastfeeding and parity — MODERATE, not policy-actionable. Avoiding menopausal hormone therapy — MODERATE. Screening does not work, and this is an unusually clear negative result. The PLCO trial of CA-125 and transvaginal ultrasound found no reduction in ovarian cancer mortality, with substantial harm from false positives leading to unnecessary oophorectomy and surgical complications; UKCTOCS, in over 200,000 women with long follow-up, likewise did not demonstrate a significant reduction in its final analysis despite achieving a stage shift. Neither trial could be retrieved in primary form, so no hazard ratios are quoted here. The qualitative conclusion is firm and is the basis of every guideline: ovarian cancer screening is not recommended in the general population, including in most guidelines for BRCA carriers, for whom risk-reducing surgery is recommended instead.

Treatment. Cytoreductive surgery aims at complete removal of all visible disease, and the completeness of cytoreduction is the strongest modifiable prognostic factor in advanced disease; it is extensive abdominal surgery, often including bowel resection and peritoneal stripping. Platinum-taxane chemotherapy follows:

carboplatin and paclitaxel are both listed and both off-patent, as is cisplatin, whose listed indications include ovarian germ cell tumours. That regimen produces complete clinical remission in the majority of advanced cases and costs a few hundred dollars at generic prices, and it is the single most important treatment in this entry. Other off-patent cytotoxics active in relapse are pegylated liposomal doxorubicin, gemcitabine and etoposide, all listed, and topotecan, which is not. Bevacizumab is not listed for this indication; biosimilars are available and off-patent in many markets. Olaparib, niraparib and rucaparib are not listed and all on patent. In BRCA-mutant advanced disease, olaparib maintenance after first-line chemotherapy produced the largest progression-free survival gain seen in this disease: in SOLO-1, median progression-free survival was not reached against 13.8 months, with a substantial fraction progression-free at seven years†. The annual cost at United States list is in the region of US$150,000 to 200,000†. Objective response as treatment rather than maintenance in BRCA-mutant platinum-sensitive relapse is in the region of 60 to 80 per cent†. Checkpoint inhibitors have been largely unsuccessful here, with response rates in the region of 10 per cent or below as monotherapy and no benefit in the randomised trials: ovarian cancer is one of the clear immunotherapy failures. Hyperthermic intraperitoneal chemotherapy has one positive randomised trial at interval debulking and is not widely adopted.

Simple means. Opportunistic salpingectomy at any pelvic operation, and risk-reducing salpingo-oophorectomy in a known mutation carrier, are straightforward operations needing basic instruments: prevention achievable in a district hospital with a measured 50 to 90 per cent risk reduction. Oral contraceptives are oral, off-patent, pennies a cycle and listed as contraceptives, for a 58 per cent risk reduction with long use, with no cold chain and no monitoring. Paracentesis is the single most valuable palliative procedure in ovarian cancer and requires almost nothing: a needle and a drainage set relieve massive abdominal distension, breathlessness and anorexia within an hour, and it can be repeated indefinitely. Removal of a large ovarian mass is a conventional operation; complete cytoreduction of miliary peritoneal disease is not, and the difference matters prognostically. Oral morphine, nasogastric drainage or a venting gastrostomy for malignant bowel obstruction, dexamethasone, listed and off-patent, and hyoscine butylbromide manage the obstruction that is how most patients with ovarian cancer die, and it can be managed medically without surgery. The chemotherapy that produces most of the benefit is off-patent and listed, and it still requires intravenous infusion, antiemetics, blood-count monitoring and safe handling: a modest but real industrial chain. PARP inhibitors, which deliver the largest recent gain, have no simple-means equivalent.

Gaps. The PLCO and UKCTOCS screening figures could not be retrieved, so the conclusion that screening does not reduce mortality is stated qualitatively without hazard ratios. PDQ's ovarian prevention summary gives no BRCA lifetime risks and does not cover screening. On perineal talc the case-control meta-analyses find an effect, the two large prospective cohorts find nothing, and there is no dose-response; PDQ calls the evidence inadequate and both sides are printed. Ovarian hyperstimulation is rated poor evidence and uncertain.

> **Depth.** Starts in: a fallopian-tube epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 63 years († median age 63); time depth 52.64. One untreated course: about 18 months († about 1.5 years); depth 49.24.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

13. Endometrial cancer

What it is. Cancer of the lining of the womb. Most of it is driven by unopposed oestrogen, from obesity, from oestrogen-only hormone therapy or from tamoxifen, and most of it announces itself early with abnormal bleeding, which is why it is usually caught at a curable stage. It is the one common cancer whose incidence is rising mainly because of obesity.

Measured. GLOBOCAN 2022 gives 420,368 cases; GLOBOCAN 2024 gives 434,620 cases and 100,680 deaths. Five-year relative survival in the United States is 80.9 per cent overall: localized 94.9, regional 70.1, distant 19.9, unknown 58.3 per cent. Median age 64. Stage at diagnosis: localized 67, regional 18, distant 11, unknown 4 per cent. United States incidence is rising about 0.7 per cent a year and the death rate

about 1.3 per cent a year. It is one of very few cancers in this chapter with a rising death rate, attributed to obesity and to a rising share of aggressive non-endometrioid histologies. Incidence is highest in North America and Europe, tracking obesity prevalence.

Where it starts. Obesity raises risk about 1.5-fold per 5 kg/m² of body mass index, and obesity-associated relative risks range from 2 to 10, rated solid with good internal validity, consistency and external validity: the strongest obesity-cancer relationship of any cancer in this chapter. Unopposed oestrogen gives at least twofold higher risk with five years or more of use, rising with duration, and older studies reported ten- to thirtyfold risk at five years or more; adding a progestogen abolishes most of that excess, which is why combined preparations replaced oestrogen-only therapy in women with a uterus. Tamoxifen used more than two years gives a relative risk of 2.3 to 7.5, the principal harm of tamoxifen in breast cancer prevention and treatment, corresponding to the hazard ratio of 2.18 in entry 5. Oral contraceptives are protective at a relative risk of 0.76 per five years of use, interval 0.73 to 0.78, a 24 per cent reduction per five years, with protection persisting more than thirty years after last use, from a meta-analysis of 36 studies covering 27,276 women; a separate United Kingdom cohort gave an incidence rate ratio of 0.66, interval 0.48 to 0.89, for ever-users. Lynch syndrome carries a lifetime endometrial cancer risk of up to 60 per cent, and in Lynch syndrome endometrial cancer is often the sentinel cancer, preceding colorectal cancer. Nulliparity, early menarche, late menopause, polycystic ovary syndrome, diabetes and oestrogen-secreting tumours all operate through the same unopposed-oestrogen route. Mutation burden splits the disease into four molecular groups and the split matters more here than almost anywhere. POLE-ultramutated tumours carry among the highest burdens ever measured in human cancer, often above 100 mutations per megabase, and have an excellent prognosis; microsatellite-hypermutated tumours are also high-burden; copy-number-low endometrioid tumours are moderate; and copy-number-high serous-like tumours are lower-burden with near-universal TP53 mutation and the worst prognosis. Against an adult reference of 1.8 per megabase, a single figure for endometrial cancer would be meaningless, and the extremes differ by more than two orders of magnitude. Not known: why POLE-ultramutated tumours, with the heaviest mutation load, have the best outcome; why the share of aggressive serous-like disease is rising; why obesity acts so much more strongly here than on any other organ.

Cure status. Atypical endometrial hyperplasia, the precursor: CURABLE by hysterectomy, and in women wanting fertility often reversible with progestogen therapy — a levonorgestrel intrauterine system or an oral progestogen produces regression in a majority. This is one of the few pre-cancers treatable with a cheap off-patent drug rather than an operation. Localized, stage I: CURABLE — five-year relative survival 94.9 per cent, with hysterectomy and bilateral salpingo-oophorectomy alone curative for most. Regional, stage II to III: CURABLE in 70.1 per cent (five-year relative survival). Distant, stage IV, mismatch-repair-proficient: RELIEF ONLY — 19.9 per cent. Distant, mismatch-repair-deficient or microsatellite-unstable: CONTROLLABLE. That subgroup is roughly 25 to 30 per cent of endometrial cancers, the highest proportion of any common cancer, and it responds to checkpoint blockade better than almost any other solid tumour.

Prevention. Weight control — STRONG on the association, 1.5-fold per 5 kg/m² and relative risks of 2 to 10, with no randomised trial showing that weight loss reduces incidence; bariatric surgery cohorts show reduced incidence and are observational. Combined oral contraceptives — STRONG: relative risk 0.76 per five years, interval 0.73 to 0.78, with protection lasting over thirty years after stopping, so a woman who used the combined pill for ten years has roughly half the lifetime risk, permanently. Adding a progestogen to oestrogen therapy — STRONG, abolishing most of the two- to thirtyfold excess, and settled practice. The levonorgestrel intrauterine system — MODERATE for preventing and reversing hyperplasia, including in obese and tamoxifen-exposed women. Raloxifene instead of tamoxifen where breast cancer prevention is the aim — a real and measurable trade-off: raloxifene's endometrial cancer hazard ratio is 1.09, interval 0.74 to 1.62, against tamoxifen's 2.18, interval 1.39 to 3.42. Hysterectomy is definitively preventive and is appropriate as risk-reducing surgery in Lynch syndrome, where lifetime risk reaches 60 per cent. There is no population screening programme and no recommendation for one. Transvaginal ultrasound and endometrial sampling have not been shown to reduce mortality in asymptomatic women, and the false-positive rate leads to unnecessary instrumentation. Prompt investigation of postmenopausal bleeding is not screening and functions as the de facto early-detection system, and it works — hence the 67 per cent localized rate. That is graded STRONG. Annual endometrial surveillance is recommended in

Lynch syndrome in most guidelines, on the strength of the risk rather than on randomised mortality evidence. **Overdiagnosis has never been quantified for endometrial cancer, because no screening programme exists.**

Treatment. Total hysterectomy with bilateral salpingo-oophorectomy is curative for the large majority, with sentinel node sampling or lymphadenectomy for staging. Progestogen therapy — medroxyprogesterone, megestrol, or a levonorgestrel intrauterine system — treats hyperplasia, allows fertility-sparing management of grade 1 stage IA cancer, and palliates advanced hormone-receptor-positive disease at response rates in the region of 15 to 25 per cent†. Medroxyprogesterone is off-patent and cheap and is not in the antineoplastic section of the Essential Medicines List, though progestogens appear elsewhere on it. Adjuvant radiotherapy, by vaginal brachytherapy or external beam, reduces local recurrence in intermediate- and high-risk localized disease. Carboplatin and paclitaxel are the standard regimen for advanced or high-risk disease, both listed, both off-patent, at low generic cost. Pembrolizumab is listed for other indications and is on patent at US$1,530.35 per 4 mL (100 mg) unit at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price; dostarlimab is not listed and is on patent. In mismatch-repair-deficient advanced disease the measured effect is among the largest for any checkpoint inhibitor in any solid tumour: objective response above 40 per cent as monotherapy in pre-treated disease, and randomised first-line trials adding a PD-1 inhibitor to carboplatin-paclitaxel showed hazard ratios for progression in the region of 0.3 in that subgroup†. In mismatch-repair-proficient disease the benefit is much smaller. Pembrolizumab with lenvatinib serves mismatch-repair-proficient advanced disease; lenvatinib is not listed, and the combination is expensive and toxic, with objective response around 30 per cent†. Trastuzumab serves HER2-positive uterine serous carcinoma and is listed, with the originator off-patent and biosimilars available.

Simple means. Abdominal total hysterectomy with bilateral salpingo-oophorectomy is a standard operation performable in a district hospital with basic instruments, anaesthesia and blood availability. For stage I disease, two-thirds of all cases, that single operation is curative in roughly 95 per cent of patients, with no drugs, no radiotherapy and no pathology beyond a confirmatory specimen. **Endometrial cancer is therefore the common cancer most completely curable by simple means in this chapter.** Endometrial biopsy with a suction curette or by dilatation and curettage is all that diagnosis of postmenopausal bleeding requires, plus a histopathologist; where no histopathology exists the diagnostic step fails, and that is the binding constraint. Oral progestogens or a levonorgestrel intrauterine system are oral or a single device insertion, off-patent, cheap and need no cold chain, and they treat hyperplasia, control bleeding and palliate advanced hormone-sensitive disease. Oral morphine, and vaginal packing or tranexamic acid, listed and off-patent, serve bleeding from advanced local disease. Weight reduction needs no technology and addresses the dominant cause. Advanced and serous-like disease has no simple-means answer, and the checkpoint inhibitors that transformed mismatch-repair-deficient disease are among the most expensive drugs in this chapter. But because two-thirds of the disease is localized and surgically curable, the simple-means fraction of the total achievable benefit is higher here than anywhere else in the chapter.

Gaps. No randomised evidence that weight loss reduces incidence, despite the strongest obesity association of any cancer. No randomised mortality evidence for Lynch syndrome endometrial surveillance, which is nonetheless recommended. Overdiagnosis is unquantified, as no screening programme exists. The rise in United States mortality is attributed to obesity and to a histology shift, and the relative contribution of each is not established.

> **Depth.** Starts in: an endometrial cell. Size: 15 µm†; depth +5.28. First complaint: about 62 years († median age 62); time depth 52.63. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

14. Thyroid cancer

What it is. Cancer of the thyroid gland, overwhelmingly the differentiated papillary and follicular types, which grow slowly and rarely kill. A small minority — medullary and anaplastic — behave entirely differently, and anaplastic thyroid cancer is among the most lethal of all human cancers. Thyroid cancer is the clearest case in medicine of an epidemic of diagnosis rather than an epidemic of disease.

Measured. GLOBOCAN 2022 gives 821,214 cases; GLOBOCAN 2024 gives 959,281 cases and 48,070 deaths, making it the seventh most commonly diagnosed cancer in the world, with deaths at 5 per cent of incidence — the lowest ratio of any cancer in this chapter by a wide margin. Five-year relative survival in the United States is 98.3 per cent overall: localized 99.9, regional 98.1, distant 48.3, unknown 91.9 per cent. Median age 51, and it is one of the commonest cancers of young adults and about three times commoner in women. Stage at diagnosis: localized 63, regional 31, distant 3, unknown 3 per cent. United States incidence and the death rate are both stable now, and that stability follows a roughly threefold rise in United States incidence between 1975 and about 2014 with a completely flat mortality rate throughout. **Incidence tripling with mortality unchanged is the definitive signature of overdiagnosis**, and it is the most-cited example of the phenomenon in oncology. The South Korean experience is the canonical case: after ultrasound screening was added opportunistically to national health checks, incidence rose roughly fifteenfold between 1993 and 2011 while mortality remained flat, and incidence fell sharply after public concern reduced screening uptake.

Where it starts. Ionising radiation to the neck, particularly in childhood, is the only well-established environmental cause. The evidence base is the atomic bomb survivor cohorts, childhood therapeutic irradiation cohorts, and the Chernobyl accident, after which childhood thyroid cancer incidence in the contaminated regions of Belarus, Ukraine and Russia rose by a large multiple, caused by radioiodine in milk. Risk is strongly inversely related to age at exposure, and exposure in adulthood carries much less. A pooled relative risk per unit dose could not be retrieved. Iodine deficiency is associated with follicular and anaplastic histology, and iodine sufficiency shifts the mix towards papillary; whether total incidence is affected is unclear. Medullary thyroid carcinoma occurs in multiple endocrine neoplasia type 2 with germline RET mutation, where penetrance approaches 100 per cent and prophylactic thyroidectomy in childhood is standard†; papillary carcinoma occurs in familial adenomatous polyposis, Cowden syndrome and Carney complex. Obesity shows a consistent positive association at relative risks generally in the region of 1.2 to 1.5 for a body mass index of 30 or more†, with confounding by increased medical contact, and hence more neck imaging, a serious and unresolved problem in interpreting it. Papillary thyroid carcinoma has one of the lowest point-mutation burdens of any adult cancer, far below the adult reference of 1.8 per megabase. It is driven by single dominant events: BRAF V600E in roughly 60 per cent of papillary carcinomas, RAS mutations in follicular variants, and RET or NTRK fusions, the latter characteristic of radiation-induced and paediatric cases. Anaplastic carcinoma carries a high burden with TP53 and TERT promoter mutations, consistent with its behaviour. Not known: what fraction of detected papillary microcarcinomas would ever progress — the autopsy reservoir bears directly on this; why the female preponderance; whether the obesity association is causal or a detection artefact; the cause of the great majority of sporadic papillary thyroid cancer, since most patients have had no radiation exposure. **For a cancer with nearly a million annual diagnoses the aetiology is strikingly unexplained.**

Cure status. Papillary microcarcinoma, 1 cm or less, incidentally found: CONTROLLABLE by active surveillance, and most of these need no treatment at all. Japanese active-surveillance cohorts followed over a thousand patients with low-risk papillary microcarcinoma for a decade or more: a small minority grew by 3 mm or more, a small minority developed node metastases, and none died of thyroid cancer. Labelling this stratum CURABLE would be technically true and practically misleading. Localized differentiated: CURABLE — five-year relative survival 99.9 per cent, by lobectomy or total thyroidectomy. Regional differentiated: CURABLE — 98.1 per cent; nodal spread barely affects survival in differentiated thyroid cancer, which is unlike almost every other cancer here. Distant differentiated, radioiodine-avid in a young patient: CURABLE. Distant differentiated otherwise: CONTROLLABLE — 48.3 per cent. Radioiodine-avid lung metastases from papillary carcinoma in a young patient can be eradicated by radioiodine; bone metastases and radioiodine-refractory disease cannot. Medullary carcinoma, confined: CURABLE by surgery, which is the only cure, since it does not take up radioiodine. Medullary carcinoma, metastatic:

CONTROLLABLE with RET-directed inhibitors. Anaplastic carcinoma: RELIEF ONLY — median survival 3 to 6 months†, one of the most lethal cancers known. The exception is genuine and recent: BRAF V600E-mutant anaplastic carcinoma, roughly 40 per cent of cases, responds to dabrafenib with trametinib at objective response above 50 per cent, and a minority achieve prolonged survival†. From a baseline of near-universal death within six months, that is a large proportional improvement.

Prevention. Avoiding unnecessary medical radiation to the neck, particularly in children — STRONG, and the only established primary prevention. Potassium iodide prophylaxis after a nuclear accident — STRONG: saturating the thyroid with stable iodine blocks radioiodine uptake, and it must be given within hours. Potassium iodide is listed, off-patent and costs a few cents a tablet. The failure to distribute it promptly after Chernobyl is the reason for the childhood thyroid cancer epidemic that followed, and it is the clearest avoidable cancer epidemic in the historical record. Universal salt iodisation — MODERATE, justified by the prevention of goitre and cretinism rather than of cancer, with an unclear effect on total incidence and a shift of histology towards the more favourable papillary type. Prophylactic thyroidectomy in RET mutation carriers — STRONG: near-complete penetrance makes this one of the few places where removing a healthy organ in a child is unambiguously correct. Screening — recommend against, and this is one of the few places in cancer screening where the recommendation rests on demonstrated harm rather than on absence of benefit. The USPSTF recommends against screening asymptomatic adults, grade D. The quantified harm: in South Korea, a roughly fifteenfold rise in incidence with flat mortality means essentially all of the additional diagnosed cancer was overdiagnosis, and the overdiagnosed fraction of screen-detected thyroid cancer in that setting approaches 90 per cent or more. IARC's 2016 analysis estimated that over twenty years more than half a million people in twelve high-income countries — about 470,000 women and 90,000 men — were overdiagnosed with thyroid cancer, the great majority then receiving thyroidectomy, lifelong hormone replacement and in many cases radioiodine. The harms are concrete and permanent: lifelong levothyroxine dependence, a 2 to 6 per cent rate of permanent hypoparathyroidism and a 1 to 2 per cent rate of permanent recurrent laryngeal nerve injury after total thyroidectomy, and the second-cancer risk from radioiodine. One respect is contested: those who defend case-finding argue that some of the mortality stability reflects effective treatment of detected disease rather than harmlessness of it, and that a small number of aggressive cancers are caught. The counter-argument is that mortality was flat before, during and after the incidence rise, which leaves little room for a treatment effect. The weight of evidence sits heavily on the overdiagnosis side, and this is the most settled of the overdiagnosis controversies in this chapter, unlike breast and prostate, where the dispute remains open. The autopsy reservoir explains why: occult differentiated thyroid cancer is found in 11.2 per cent of whole glands examined, interval 6.7 to 16.1, and 4.1 per cent on partial examination, interval 3.0 to 5.4, across 35 studies and 12,834 autopsies conducted between 1949 and 2007.

Treatment. The proportion of radioiodine-avid distant disease in a young patient that is eradicated is not given. Active surveillance for low-risk papillary microcarcinoma is free and increasingly the correct choice. Lobectomy or total thyroidectomy is the curative treatment, and lobectomy is now preferred for low-risk tumours up to 4 cm, because it avoids lifelong hormone replacement and halves the risk of parathyroid and nerve injury: one of the clearest recent reversals in surgical oncology. Levothyroxine is a listed medicine for hypothyroidism, off-patent, and costs a few dollars a year generically — one of the cheapest lifelong medications in existence. Radioiodine is uniquely effective in differentiated thyroid cancer, because the tumour keeps the iodine-uptake machinery of normal thyroid, and it requires a nuclear medicine facility and radiation protection; its use in low-risk disease has been substantially reduced over the past decade, as trials showed no benefit. Lenvatinib and sorafenib for radioiodine-refractory differentiated disease are not listed; sorafenib is off-patent and lenvatinib is not, and lenvatinib's objective response rate in radioiodine-refractory disease was about 65 per cent in the registrational trial, the highest of its class, at an annual cost in the region of US$150,000 to 200,000 at United States list†. Selpercatinib and pralsetinib for RET-altered disease are not listed and on patent, at objective response rates above 60 to 70 per cent, among the highest for any targeted agent in any cancer†. Larotrectinib and entrectinib for NTRK-fusion disease are not listed, at response rates around 70 per cent and above†. Dabrafenib with trametinib for BRAF V600E-mutant anaplastic carcinoma is not listed and both are on patent, at objective response above 50 per cent in a disease with median survival of 3 to 6 months†. External beam radiotherapy serves anaplastic carcinoma and unresectable local disease.

Simple means. Doing nothing comes first, deliberately. For low-risk papillary microcarcinoma, active surveillance is legitimate evidence-based management requiring no industrial chain at all, and for a large fraction of diagnosed thyroid cancer it is both the simplest and the best available option. Thyroid lobectomy and total thyroidectomy are classical operations requiring basic instruments, good lighting, meticulous technique and anaesthesia; energy devices and nerve monitors reduce complications and are not necessary. For localized differentiated disease — 94 per cent of cases are localized or regional — the operation is curative in over 98 per cent. That makes thyroid cancer the second most complete simple-means cure in this chapter after endometrial cancer. Levothyroxine is a single daily tablet, off-patent, listed, a few dollars a year, needing no cold chain and only a periodic measurement of thyroid-stimulating hormone, and in practice manageable on clinical grounds where no assay exists. Potassium iodide after a radiological accident costs cents, is listed, and is the only prophylaxis that works. Iodised salt needs no industrial chain beyond the salt supply. Tracheostomy prevents death by asphyxiation from anaplastic carcinoma or bulky local disease and is a basic operation. Oral morphine serves the pain of advanced local disease. Radioiodine has no simple-means equivalent, and for radioiodine-refractory and anaplastic disease the effective drugs are all on patent and expensive. Because almost all thyroid cancer is localized differentiated disease curable by an operation and a cheap tablet, thyroid cancer has one of the best simple-means profiles in the chapter, and its biggest problem is not undertreatment but overtreatment.

Gaps. A pooled relative risk for radiation-induced thyroid cancer per unit dose could not be retrieved. The obesity association may be a detection artefact, and that is unresolved. The aetiology of sporadic papillary thyroid cancer is largely unknown. The proportion of papillary microcarcinomas that would ever progress is unknown; the Japanese surveillance cohorts give an upper bound over a decade and not over a lifetime. The precise overdiagnosis percentage depends entirely on the screening intensity of the population described, so no single number can be given: the figures above are setting-specific. The confidence intervals for the thyroid autopsy meta-analysis are given as two subgroup estimates rather than one pooled figure, and the difference between them — 4.1 against 11.2 per cent — is itself the point, because how much cancer is found depends on how hard the pathologist looks.

> **Depth.** Starts in: a thyroid follicular cell. Size: 15 µm†; depth +5.28. First complaint: about 7 years († 5–10 years after radiation); time depth 50.65. One untreated course: no number ([B] grows slowly).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

15. Melanoma of the skin

What it is. Cancer of the pigment-producing cells of the skin. It is far less common than the other skin cancers and causes the great majority of skin cancer deaths, because it metastasises while still small. It is the cancer most clearly caused by a single avoidable exposure, and the cancer where immunotherapy first demonstrated that metastatic disease can be cured by a drug.

Measured. GLOBOCAN 2022 gives 331,722 cases; GLOBOCAN 2024 gives 337,969 cases and 58,398 deaths. GBD 2023 gives 66,600 deaths from malignant skin melanoma in 2023, interval 59,900 to 75,200. Five-year relative survival in the United States is 94.7 per cent overall: localized 100.0, regional 76.0, distant 34.0, unknown 95.4 per cent. Median age 67, and melanoma is also one of the commonest cancers in young adults, and in several countries the commonest cancer in people aged 20 to 39. Stage at diagnosis: localized 77, regional 10, distant 5, unknown 9 per cent. NCI PDQ gives about 104,960 United States diagnoses and 8,430 deaths for 2025, and states that melanoma is about 2 per cent of skin cancers and causes more than 80 per cent of skin cancer deaths. United States incidence is rising about 1.1 per cent a year and the death rate falling about 2.2 per cent a year. **That falling mortality is the clearest population-level signal of checkpoint-inhibitor efficacy anywhere in oncology**: the decline begins around 2013, the year the first PD-1 inhibitors and ipilimumab came into use, after decades of flat or rising mortality. Part of the rising incidence is detection-driven. Australia and New Zealand have by far the world’s highest rates, a consequence of fair-skinned populations at low latitudes; rates are low in Asia and Africa, where melanoma

when it occurs is more often acral or mucosal, unrelated to ultraviolet exposure, and carries a worse prognosis.

Where it starts. Total sun exposure in childhood gives an odds ratio of 1.81 to 4.4, and intermittent exposure with sunburn is the characteristic melanoma pattern, as distinct from the cumulative-exposure pattern that causes keratinocyte carcinomas; PDQ rates this fair evidence of unknown magnitude, with fair internal validity and consistency and poor external validity. Fair skin that burns easily carries about twofold risk against skin that never burns, and natural red or blond hair roughly twofold to fourfold. On indoor tanning PDQ cites studies and gives no relative risk; IARC classified ultraviolet-emitting tanning devices as Group 1 in 2009, and the commonly cited meta-analytic figure is a relative risk of roughly 1.2 for any use, rising to about 1.6 to 1.8 for first use before age 35†. PDQ's silence on this is itself notable. Naevus count, atypical naevi and family history are all established, with risk rising steeply with naevus count. CDKN2A germline mutation is the principal high-penetrance melanoma gene and MC1R variants the common low-penetrance ones. Immunosuppression raises risk. Cutaneous melanoma has the highest point-mutation burden of any common human cancer, an order of magnitude or more above the adult reference of 1.8 per megabase, dominated by the C-to-T transitions at dipyrimidine sites that are the direct chemical fingerprint of ultraviolet damage. BRAF V600E or V600K is present in roughly 40 to 50 per cent and NRAS in roughly 20 per cent. The high ultraviolet-induced burden is the accepted explanation for melanoma's exceptional responsiveness to checkpoint blockade: the mutations generate neoantigens the immune system can see. Acral and mucosal melanomas, which are not ultraviolet-driven, carry much lower burdens and respond far less well, which is strong internal evidence for that reading. Not known: why intermittent rather than cumulative exposure drives melanoma while the reverse holds for keratinocyte cancers; why some thin melanomas metastasise and most do not; the magnitude of the sunscreen effect; why acral melanoma occurs at similar rates across all skin colours with no ultraviolet involvement.

Cure status. Melanoma in situ: CURABLE by excision. Localized thin melanoma, 1 mm or less: CURABLE — five-year relative survival 100.0 per cent for localized disease. Wide local excision with a 1 to 2 cm margin is the entire treatment, and it is curative in the great majority: no drugs, no radiotherapy, no imaging. Localized thick melanoma, over 4 mm and ulcerated: CURABLE. Regional, node-positive stage III: CURABLE in 76.0 per cent (five-year relative survival). Distant, stage IV, in the substantial minority with a sustained complete response to combination checkpoint blockade: CURABLE. Distant, stage IV, otherwise: CONTROLLABLE — 34.0 per cent at five years in the 2016 to 2022 SEER cohort, a figure still catching up with practice. In the long-term follow-up of nivolumab with ipilimumab in advanced melanoma, roughly half of patients were alive at five years, and a substantial fraction were alive and off all treatment with no evidence of disease. Before 2011, median survival in metastatic melanoma was 6 to 9 months and five-year survival was under 10 per cent†.

Prevention. Sun avoidance, shade, clothing and hats — STRONG for the causal relationship, with the honest caveat that the intervention evidence is weaker than the aetiological evidence. PDQ rates sun exposure and keratinocyte carcinoma as solid evidence with good internal validity, consistency and external validity, and intermittent sun exposure with sunburn and melanoma as fair evidence of unknown magnitude. Sunscreen — CONTESTED, and the figures are genuinely weak. PDQ states there is inadequate evidence to assess magnitude, with poor internal and external validity and inconsistent results; randomised trials showed inconsistent benefit for squamous cell carcinoma and no benefit for melanoma, and an eight-year post-trial follow-up showed reductions in squamous cancers and melanomas with very wide confidence intervals. The trial in question is the Nambour, Queensland randomised trial, whose ten-year follow-up reported roughly a halving of invasive melanoma incidence in the daily-sunscreen group, on 11 against 22 melanomas† — a result based on very few events and wholly consistent with PDQ's assessment that the magnitude cannot be assessed. Both positions are printed: sunscreen is universally recommended, and its randomised evidence base for melanoma prevention rests on a single trial with 33 events in total. The possibility that sunscreen enables longer exposure, offsetting its protective effect, has never been excluded. Avoiding indoor tanning — STRONG on IARC's Group 1 classification, with no effect size from PDQ. Avoiding sunburn in childhood — MODERATE, odds ratio 1.81 to 4.4. Topical fluorouracil on sun-damaged skin — one good-quality randomised trial with moderate net benefit for preventing squamous cell carcinoma requiring surgery, which concerns keratinocyte carcinoma rather than melanoma. Screening — CONTESTED: the USPSTF position is that the evidence is insufficient, grade I,

for visual skin examination in asymptomatic adults, and there is no randomised trial showing that skin cancer screening reduces melanoma mortality. The German SCREEN project in Schleswig-Holstein reported a fall in melanoma mortality after a population programme, which was then not sustained when the programme was extended nationally — an inconsistent result cited on both sides. Overdiagnosis of melanoma is real and quantified in the same way as thyroid: a roughly sixfold rise in United States incidence since the 1970s with a far smaller change in mortality†. Estimates of the overdiagnosed fraction in high-screening populations range from around 15 per cent to as high as 60 per cent depending on method and country, with the higher end from Australian analyses. Both ends are printed; the figure is contested and the method — incidence-mortality divergence against modelling — drives the difference. The principal harm is excision of lesions that would never have progressed, plus the anxiety and insurance consequences of a cancer diagnosis. Melanoma excision is a small operation, so the harm per overdiagnosed case is lower than for thyroid or prostate overdiagnosis.

Treatment. The proportion of localized thick ulcerated melanoma that is cured is not given. Most are cured, the relapse risk is substantial, and adjuvant checkpoint-inhibitor or BRAF-directed therapy reduces it. Wide local excision is the curative treatment for localized disease, which is 77 per cent of cases, with margins of 1 to 2 cm depending on thickness. Sentinel lymph node biopsy is staging rather than therapeutic, and completion lymphadenectomy for a positive sentinel node was shown by randomised trials not to improve survival and has largely been abandoned. Checkpoint inhibitors are the transformative treatment, and melanoma is where they were first proven. Pembrolizumab is a selected medicine on the list for melanoma of the skin as monotherapy, and nivolumab is listed as a therapeutic equivalent to it for that same indication; neither is off-patent. Ipilimumab is not listed and is on patent. Objective response in advanced melanoma is in the region of 35 to 45 per cent for pembrolizumab or nivolumab monotherapy, and 55 to 60 per cent for nivolumab with ipilimumab, with complete response in roughly 20 per cent†; five-year survival with the combination is roughly 50 per cent in the registrational trial against under 10 per cent before 2011†. Pembrolizumab costs US$1,530.35 per 4 mL (100 mg) unit, US$6,121.41 per four-unit pack and US$12,234.94 for eight units at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price, and the combination costs substantially more. Adjuvant checkpoint therapy after resection of stage III and high-risk stage II melanoma roughly halves the recurrence rate. BRAF with MEK inhibitors for BRAF V600-mutant disease — dabrafenib-trametinib, vemurafenib-cobimetinib, encorafenib-binimetinib — are none of them listed and all on patent, at objective response rates of roughly 65 to 70 per cent, faster-acting than immunotherapy with a shorter median duration, and roughly a third of patients have durable long-term benefit. Dacarbazine is listed and off-patent and cheap, and almost inactive: objective response in advanced melanoma is in the region of 10 per cent with no demonstrated survival benefit†. That matters for the simple-means question, because the only melanoma drug on the list that is off-patent and affordable barely works, and it is the honest baseline against which the expensive drugs should be read. Interleukin-2, talimogene laherparepvec and tumour-infiltrating lymphocyte therapy are not listed and require cell-processing facilities. Radiotherapy serves brain metastases and palliation, and melanoma is relatively radioresistant.

Simple means. Sun avoidance — shade, long sleeves, a wide-brimmed hat, and staying indoors in the middle of the day — needs no industrial chain, costs nothing and addresses the dominant cause. It is the highest-yield simple means in this entry, and clothing and shade have better evidence than sunscreen and cost less. Excision of a suspicious pigmented lesion under local anaesthetic with a scalpel and sutures is the single most important point here: for 77 per cent of melanoma, a curative operation can be performed in an outpatient room with a blade, local anaesthetic, sutures and a histopathologist, at a five-year relative survival of 100 per cent. Melanoma is, alongside endometrial, thyroid and keratinocyte skin cancer, among the most completely curable-by-simple-means cancers in this chapter, provided the lesion is recognised and excised. Naked-eye examination of the skin, with or without a dermatoscope that costs a few hundred dollars and needs no power beyond a battery, is possible because melanoma is one of very few cancers visible from outside the body, which is an enormous practical advantage and the reason awareness matters so much; the asymmetry, border, colour, diameter and evolution rule requires no equipment. Oral morphine serves pain, and dexamethasone, listed and off-patent, relieves the symptoms of brain metastases, which are common in melanoma, within hours. For metastatic melanoma nothing simple exists, and the gap is stark: the off-patent listed drug has a response rate around 10 per cent† and no survival benefit, and the

drugs that cure a third to a half of metastatic melanoma cost over US$150,000 a year at United States list, and are all on patent. Melanoma therefore shows the widest divergence in this chapter between what simple means achieve for early disease, which is essentially complete cure, and for advanced disease, which is essentially nothing.

Gaps. Sunscreen's randomised evidence for melanoma prevention rests on one trial with very few events; PDQ calls the evidence inadequate while public health guidance recommends it universally, and that is a genuine disagreement between the evidence appraisal and the recommendation. PDQ gives no relative risk for indoor tanning despite IARC's Group 1 classification. Melanoma overdiagnosis estimates range from roughly 15 to 60 per cent depending on method and country, and the disagreement is unresolved. No randomised trial of skin cancer screening has mortality as an outcome, and the German SCREEN result was not reproduced. SEER's distant-stage five-year survival lags current practice, because the cohort partly predates routine combination immunotherapy, so the true current figure is higher.

> **Depth.** Starts in: a melanocyte. Size: 15 µm†; depth +5.28. First complaint: about 65 years († median age 65); time depth 52.67. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

16. Keratinocyte skin cancer — basal cell and squamous cell carcinoma

What it is. The two common cancers of the ordinary skin cells: basal cell carcinoma, which invades locally and almost never spreads, and cutaneous squamous cell carcinoma, which can spread to lymph nodes and occasionally kills. Together they are the most common cancers in human beings by a very wide margin, and they are so rarely fatal that most cancer registries do not count them.

Measured. This is the one entry in this chapter where the incidence figures are fundamentally unreliable, and the reason matters: keratinocyte carcinomas are not notifiable in most registries, people often have several, and registries that do count them count lesions rather than patients inconsistently. GLOBOCAN 2022 gives 19,976,499 cases including non-melanoma skin cancer and 18,741,966 excluding it, implying a non-melanoma skin cancer total of about 1,234,533; GLOBOCAN 2024 gives about 20.6 million including and 19.5 million excluding, implying roughly 1.1 million. The WHO cancer fact sheet gives non-melanoma skin cancer as 1.1 million cases in 2024, making it the fifth commonest cancer in the world on that count. These figures are certainly large underestimates. NCI PDQ estimated keratinocyte carcinomas combined at about 3 million diagnoses in the United States alone in 2012, from Medicare extrapolation, and states explicitly that exact figures are unavailable because these cases are not required to be registry-reported. The true global figure is plausibly several times the GLOBOCAN number. SEER publishes no Cancer Stat Facts page for basal or squamous cell carcinoma of the skin, for the same reason, so no stage-specific five-year relative survival table comparable to the other entries in this chapter exists. GBD 2023 gives 63,900 deaths from non-melanoma skin cancer in 2023, interval 54,400 to 71,600. Against that, PDQ's statement that melanoma is about 2 per cent of skin cancers and causes more than 80 per cent of skin cancer deaths implies keratinocyte carcinoma deaths in the order of 10,000 to 15,000 globally, almost all from squamous cell carcinoma and from neglected or immunosuppressed cases; that is an inference from PDQ's ratio rather than a published count, and the GBD figure of 63,900 is four to six times higher, so the two do not agree. Both are printed. Incidence is strongly age-dependent, rising steeply after 50 and reflecting cumulative lifetime ultraviolet dose, and basal cell carcinoma is roughly four times commoner than squamous. Australia has the highest rates in the world, with a majority of fair-skinned Australians developing at least one keratinocyte carcinoma in their lifetime. Rates are low in darkly pigmented populations.

Where it starts. PDQ rates sun and ultraviolet exposure in keratinocyte carcinoma as solid evidence with good internal validity, consistency and external validity — a stronger grade than it gives for melanoma — and gives no risk ratio. The pattern differs from melanoma: cumulative lifetime exposure drives keratinocyte carcinoma and intermittent exposure with sunburn drives melanoma, which is why keratinocyte carcinomas appear on the face, ears, scalp, forearms and hands and why they are an occupational disease of outdoor workers. People who tan poorly or burn easily are particularly susceptible.

Immunosuppression is the strongest single risk amplifier known for any cancer in this chapter: organ transplant recipients have cutaneous squamous cell carcinoma rates reported at roughly 65 to 250 times the general population, with basal cell carcinoma raised about tenfold, and in transplant recipients the normal four-to-one basal-to-squamous ratio inverts. Squamous cell carcinoma in transplant recipients is also far more aggressive and does metastasise. Ionising radiation, arsenic, chronic scarring and chronic ulceration, chronic inflammation, and beta-genus human papillomavirus — particularly in the immunosuppressed and in epidermodysplasia verruciformis — are all established. Basal cell naevus syndrome, from PTCH1 mutation in the hedgehog pathway, xeroderma pigmentosum, albinism and epidermodysplasia verruciformis are the genetic syndromes. Cutaneous squamous cell carcinoma and basal cell carcinoma carry the highest mutation burdens ever measured in human tumours, higher even than melanoma, frequently tens to over a hundred mutations per megabase against an adult reference of 1.8, and overwhelmingly the ultraviolet-signature C-to-T transition. Basal cell carcinoma is driven by hedgehog pathway activation, PTCH1 loss or SMO mutation in the great majority: a single-pathway disease sitting inside an extremely high mutation background. That is the molecular basis both for hedgehog inhibitors and for the striking checkpoint-inhibitor responses in both tumours. Not known: why basal cell carcinoma, with one of the highest mutation burdens in oncology, essentially never metastasises — a genuine and unexplained anomaly; the quantitative contribution of beta-genus human papillomavirus; why the basal-to-squamous ratio inverts under immunosuppression.

Cure status. Basal cell carcinoma, localized and locally advanced but operable: CURABLE — excision with clear margins cures over 95 per cent, and Mohs micrographic surgery exceeds 98 per cent for high-risk sites†. Metastatic basal cell carcinoma is so rare, well under 0.1 per cent, that it is reportable†. The harm basal cell carcinoma causes when neglected is local destruction of the eyelid, nose or ear, not death. Basal cell carcinoma, inoperable after long neglect: CONTROLLABLE with hedgehog inhibitors or a checkpoint inhibitor. Cutaneous squamous cell carcinoma, localized: CURABLE — excision cures over 90 to 95 per cent of ordinary lesions†. Cutaneous squamous cell carcinoma, high-risk or node-positive: CURABLE, with surgery plus radiotherapy. Metastatic cutaneous squamous cell carcinoma: CONTROLLABLE — cemiplimab produces objective responses in roughly 45 to 50 per cent†, among the highest checkpoint-inhibitor response rates in any cancer, consistent with the very high mutation burden.

Prevention. Sun avoidance — STRONG. PDQ's grade for sun and ultraviolet exposure in keratinocyte carcinoma is solid evidence with good internal validity, consistency and external validity, its strongest grading in the skin cancer summary. Shade, clothing, hats and avoiding midday exposure. Occupational sun protection for outdoor workers is the measure with the largest population effect and the least implementation. Sunscreen — CONTESTED, leaning positive for squamous cell carcinoma: the evidence is better here than for melanoma and PDQ still rates it inadequate to assess magnitude, with poor internal and external validity and inconsistent randomised results. The Nambour trial reported a reduction in squamous cell carcinoma incidence with daily sunscreen, and that is the most positive randomised sunscreen result that exists. Topical fluorouracil on sun-damaged skin — MODERATE: one good-quality randomised trial with moderate net benefit for preventing squamous cell carcinoma requiring surgery. Fluorouracil is listed and off-patent, and the topical 5 per cent cream is inexpensive. That makes it one of the few pharmacological cancer preventives in this chapter that is both proven in a randomised trial and cheap. Avoiding indoor tanning — STRONG on IARC Group 1, with no figure from PDQ. Reducing immunosuppression intensity, and switching transplant recipients from calcineurin inhibitors to sirolimus-based regimens — MODERATE, with randomised evidence of reduced squamous cell carcinoma incidence in transplant recipients. Nicotinamide — MODERATE: the ONTRAC randomised trial in patients with prior keratinocyte carcinoma reported roughly a 23 per cent reduction in new keratinocyte carcinomas over twelve months, and the effect ceases when the supplement stops. Screening — insufficient evidence, USPSTF grade I, as for melanoma. For a cancer that essentially never kills, mortality is the wrong endpoint, and no trial has used morbidity endpoints. Overdiagnosis in the usual sense is not the main issue here, and the conceptual point matters: a basal cell carcinoma left alone will grow and destroy tissue, so detecting and treating it is beneficial even though it would not have been fatal. The overdiagnosis framing that applies to thyroid, prostate and breast does not transfer, because the harm prevented is disfigurement rather than death. Overtreatment does occur, in the form of aggressive surgery for small lesions in very elderly patients with limited life expectancy, where observation or topical treatment would suffice.

Treatment. The proportion of high-risk or node-positive cutaneous squamous cell carcinoma cured by surgery plus radiotherapy is not given. Most are cured. Recurrence and nodal spread are real risks in large, deep, perineural, immunosuppressed or head-and-neck lesions. Simple surgical excision with clear margins under local anaesthetic is the standard curative treatment for both tumours, at a cure rate over 95 per cent for basal cell carcinoma and over 90 per cent for squamous†. Curettage and cautery, cryotherapy or shave excision serve small, low-risk, superficial basal cell carcinomas: faster, cheaper, no sutures, slightly higher recurrence. Mohs micrographic surgery serves high-risk sites — nose, eyelid, ear, lip — and recurrent lesions, at the highest cure rate, tissue-sparing, requiring on-site frozen-section pathology. Radiotherapy is a curative alternative where surgery would be disfiguring or the patient is unfit. For superficial basal cell carcinoma and in-situ squamous cell carcinoma, topical fluorouracil 5 per cent is listed, off-patent and inexpensive; imiquimod is not listed and is off-patent; photodynamic therapy requires a light source and a photosensitiser. Vismodegib and sonidegib for locally advanced or metastatic basal cell carcinoma are neither listed and both on patent, at objective response rates of roughly 45 to 60 per cent in locally advanced disease and an annual cost at United States list in the region of US$100,000 and above†. Their toxicity — muscle cramps, taste loss, alopecia — causes frequent discontinuation. Cemiplimab is on the list, as a therapeutic alternative for metastatic non-small-cell lung cancer rather than for its original approval in advanced cutaneous squamous cell carcinoma, and is on patent, at objective response in advanced cutaneous squamous cell carcinoma of roughly 45 to 50 per cent†; it is also active in hedgehog-inhibitor-refractory basal cell carcinoma at response rates around 30 per cent. Prices as for the class, US$150,000 to 200,000 a year at United States list†. Pembrolizumab is also active. Cisplatin and carboplatin are listed, off-patent and cheap for advanced squamous cell carcinoma; responses occur and are not durable, and checkpoint inhibitors have displaced chemotherapy where available.

Simple means. This entry has the strongest simple-means profile in the chapter. Excision under local anaesthetic with a scalpel and sutures cures over 95 per cent of basal cell carcinomas and over 90 per cent of squamous cell carcinomas†: no imaging, no staging, no drugs, no radiotherapy, no cold chain, no electricity beyond a light. A trained general practitioner, clinical officer or nurse can do it. Set beside the fact that these are the most common cancers in the world, that makes minor skin surgery arguably the highest-volume curative cancer intervention available by simple means anywhere. Curettage and cautery, or cryotherapy with liquid nitrogen in a hand-held flask, is simpler still for small superficial lesions: no sutures, minutes per lesion. Sun avoidance for outdoor workers is clothing rather than technology, and PDQ's grading for cumulative ultraviolet exposure here is its strongest in the skin summary. Topical fluorouracil 5 per cent cream is listed, off-patent, cheap and applied by the patient at home, with randomised evidence of reduced squamous cell carcinoma requiring surgery, and needs no clinic visit for the treatment itself. Nicotinamide is an inexpensive vitamin, associated with a roughly 23 per cent reduction in new keratinocyte carcinomas in the ONTRAC trial. Its dose and use are for a clinician and are not given here. Naked-eye diagnosis is possible: these cancers are visible and have characteristic appearances, so diagnosis is substantially clinical with histology confirming, and this is the only cancer group in the chapter where competent management is possible with essentially no diagnostic technology. Where nothing simple exists: neglected, deeply invasive facial basal cell carcinoma that has destroyed the orbit or the nasal skeleton requires major reconstructive surgery or a hedgehog inhibitor, and metastatic cutaneous squamous cell carcinoma requires cemiplimab, whose listing for this cancer was not checked and needs checking against the 24th List (2025)†, and which costs over US$150,000 a year. And for the xeroderma pigmentosum and albinism populations, who develop these cancers continuously from childhood, simple excision cannot keep pace: in several African countries albinism carries a high rate of fatal squamous cell carcinoma by early adulthood, and the simple answer — rigorous lifelong sun protection from infancy — is known and not delivered.

Gaps. The incidence data are the weakest in this chapter. These cancers are not notifiable in most registries, and GLOBOCAN's implied 1.1 to 1.2 million is inconsistent with PDQ's 3 million United States diagnoses in 2012 alone. No reliable global figure exists. No SEER stage-specific survival table exists, so this entry cannot give the stage-by-stage figures that every other entry gives. The mortality figure inferred from PDQ's ratio, 10,000 to 15,000 globally, is four to six times below GBD 2023's 63,900, and the discrepancy is unexplained. PDQ gives no risk ratio for sun exposure despite rating the evidence solid. The transplant-recipient risk multiples and the nicotinamide figure are not primary-source-verified. Why basal cell carcinoma does not metastasise despite an extreme mutation burden is unexplained. Sunscreen evidence is rated inadequate by PDQ while being universally recommended.

> **Depth.** Starts in: a keratinocyte. Size: 15 µm†; depth +5.28. First complaint: about 65 years († median age 65); time depth 52.67. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

17. Brain and central nervous system tumours

What it is. Tumours arising in the brain, spinal cord and their coverings. The dominant malignant type in adults is glioma, and the commonest and worst of these is glioblastoma. Unlike almost every other cancer, brain tumours kill by local growth inside a closed bony box rather than by spreading to other organs. Benign meningiomas are far more common than malignant gliomas and behave quite differently.

Measured. GLOBOCAN 2022 gives 321,731 cases of brain and central nervous system tumours; GLOBOCAN 2024 gives 324,095 cases and 248,964 deaths, so deaths are 77 per cent of incidence. Five-year relative survival in the United States is 32.9 per cent overall. SEER publishes no stage-specific table for these tumours, because the localized-regional-distant system does not apply: they are staged by histology and grade rather than by anatomical spread. The relevant breakdown is by histology, and the figures are from the general neuro-oncology literature: glioblastoma, WHO grade 4 astrocytoma, five-year survival in the region of 5 to 7 per cent with median survival of roughly 15 months; anaplastic astrocytoma, grade 3, median survival roughly 3 to 5 years; IDH-mutant low-grade glioma, grade 2, median survival often over 10 years; 1p/19q-codeleted oligodendroglioma, median survival often exceeding 15 to 20 years; grade 1 meningioma, five-year survival in excess of 90 per cent and often cured by excision; pilocytic astrocytoma, mostly paediatric, five-year survival above 95 per cent and frequently cured by surgery alone. Median age 61, although brain tumours have a bimodal age distribution and are the commonest solid tumour of childhood and the second commonest cause of cancer death in children. United States incidence is falling about 1.4 per cent a year and the death rate about 0.3 per cent a year. **That mortality decline is the smallest of any cancer in this chapter**, which is the plainest statement of therapeutic failure in glioblastoma.

Where it starts. Ionising radiation to the head is the only established environmental cause. Therapeutic cranial irradiation — historically for tinea capitis, currently for childhood leukaemia and other childhood cancers — raises the risk of meningioma and glioma years to decades later, dose-dependently. Hereditary syndromes account for a small percentage: neurofibromatosis type 1 for optic pathway glioma, neurofibromatosis type 2 for meningioma and vestibular schwannoma, tuberous sclerosis for subependymal giant cell astrocytoma, Li-Fraumeni syndrome, Turcot and Lynch syndromes, Gorlin syndrome, and rhabdoid tumour predisposition from SMARCB1 mutation. On mobile telephones the weight of evidence has moved against an effect and both positions are printed. IARC classified radiofrequency electromagnetic fields as Group 2B, possibly carcinogenic, in 2011, on the INTERPHONE and Hardell case-control studies, which reported elevated odds ratios in the heaviest users. The counter-evidence is strong and now dominant: glioma incidence has not risen in any national registry during the period of near-universal mobile phone adoption, which is difficult to reconcile with a causal effect of the magnitude the case-control studies suggested, and recall bias in those studies is the leading explanation; a WHO-commissioned systematic review in 2024 found no association. The registry data are the stronger evidence. Allergy and atopy are inversely associated with glioma, consistently across studies, for reasons not established. Head injury, dietary nitrosamines, occupational exposures and power lines have been studied extensively with no established effect. Gliomas have a low to moderate point-mutation burden, around or below the adult reference of 1.8 per megabase. Glioblastoma is characterised by EGFR amplification, PTEN loss, CDKN2A deletion and TERT promoter mutation; IDH1 or IDH2 mutation defines the better-prognosis gliomas and is the single most important prognostic marker in neuro-oncology; 1p/19q codeletion defines oligodendroglioma; MGMT promoter methylation predicts temozolomide benefit. The 2021 WHO classification of central nervous system tumours reorganised the field around these molecular features rather than histology, which is why older survival statistics are hard to compare with current ones. Hypermutation in glioma is mostly iatrogenic, induced by temozolomide itself at recurrence. Not known: **the cause of the overwhelming majority of brain tumours, which is the largest aetiological**

void in this chapter. Apart from radiation and rare syndromes, essentially nothing is established: there is no tobacco, no infection, no diet, no occupation, no obesity link of any consequence. Also unknown: why the blood-brain barrier and the brain's immune environment defeat drug and immune therapies that work elsewhere; why glioblastoma invariably recurs; the significance of the inverse allergy association.

Cure status. Grade 1 meningioma: CURABLE by complete excision — five-year survival in excess of 90 per cent†; many small asymptomatic meningiomas need only observation and never grow enough to matter, and they are extremely common as incidental findings. Grade 1 pilocytic astrocytoma, mostly in children: CURABLE by resection alone — five-year survival above 95 per cent†. IDH-mutant grade 2 to 3 glioma: CONTROLLABLE over many years — median survival often exceeding 10 years, and 15 to 20 years in 1p/19q-codeleted oligodendroglioma† — and patients nonetheless almost all eventually die of the disease. Glioblastoma: RELIEF ONLY, and this should be stated without euphemism — median survival roughly 15 months and five-year survival 5 to 7 per cent with maximal safe resection, radiotherapy and temozolomide†. The treatment gain over the last twenty years has been measured in months, and glioblastoma belongs with pancreatic cancer and anaplastic thyroid carcinoma on the short list of cancers where current medicine achieves very little. Diffuse midline glioma, H3 K27M-altered, a childhood tumour: RELIEF ONLY — median survival roughly 9 to 12 months†; it is inoperable by location and no treatment has ever improved survival in a randomised trial. Brain metastases from other cancers, far more common than primary brain tumours: CONTROLLABLE — stereotactic radiosurgery, surgery for single accessible lesions and drugs that cross into the brain have substantially improved outcomes. Early detection would not help in malignant glioma, because grade is determined at onset rather than acquired by delay: that is a fundamental difference from the epithelial cancers in this chapter and the reason there is no screening rationale.

Prevention. Avoiding unnecessary therapeutic and diagnostic cranial irradiation, particularly in children — STRONG, and the only established prevention. Everything else: no diet, no supplement, no behaviour and no exposure avoidance has demonstrated efficacy. This is the shortest prevention section in this chapter and the honest answer is that brain tumours cannot currently be prevented. Mobile phone avoidance — CONTESTED, and on the registry evidence unnecessary: IARC Group 2B from 2011 rests on case-control data, national incidence trends show no rise, and the 2024 WHO-commissioned systematic review found no association. Both printed. There is no screening programme anywhere and no rationale for one: prevalence is too low, there is no pre-malignant stage to intercept, and for the lethal tumours early detection does not change grade or outcome. Incidental detection of meningiomas and low-grade gliomas on magnetic resonance imaging done for other reasons is nonetheless common and growing, and it creates a real overdiagnosis problem, because a substantial proportion of incidental meningiomas never grow and intervening on them carries neurosurgical risk. **No overdiagnosis percentage has been published for incidental meningioma**, and it is a genuine and unquantified harm of expanding imaging use.

Treatment. Maximal safe surgical resection is one of the few modifiable prognostic factors in glioma and requires neurosurgical capability, imaging, and often intraoperative adjuncts. Radiotherapy is the single most effective modality in malignant glioma and requires a linear accelerator with planning capability. **Temozolomide is a listed medicine, for other specified gliomas of the brain and three further indications**. It is off-patent, and generic temozolomide is comparatively inexpensive, against an originator price in the thousands of dollars a cycle. Added to radiotherapy it increased median survival from roughly 12.1 to 14.6 months and two-year survival from 10 to 27 per cent in the pivotal Stupp trial†, and the benefit is concentrated almost entirely in MGMT-methylated tumours. PCV chemotherapy for oligodendroglioma and anaplastic glioma uses procarbazine and vincristine, both listed and off-patent, with lomustine, which is not listed. Lomustine has been subject to extreme price rises in the United States after acquisition by a single manufacturer, a documented increase of roughly 1,400 per cent between 2013 and 2018†. That is one of the clearest examples of off-patent price exploitation in oncology. PCV in 1p/19q-codeleted oligodendroglioma produced one of the largest survival gains in neuro-oncology, with median survival roughly doubled in long-term follow-up. Bevacizumab for recurrent glioblastoma is not listed for this indication; biosimilars are available, and it improves radiological appearance and reduces steroid need and has never improved overall survival in a randomised trial, which is worth stating plainly. Tumour-treating fields is a device rather than a drug, showed a survival benefit in a randomised trial, and is expensive and not widely adopted. Dexamethasone is listed and off-patent at an indicative 24 cents a 4 mg tablet in the

UNICEF Supply Catalogue, October 2026, and it is the most important drug in symptomatic brain tumour care: it reduces peritumoural oedema and can reverse hemiparesis, aphasia, headache and drowsiness within hours, and for a patient with a large brain tumour it does more for daily function, faster and more cheaply, than any antineoplastic agent here. Levetiracetam, phenytoin, carbamazepine and valproate are listed, off-patent and cheap, and phenobarbital is listed for epilepsy and status epilepticus at an indicative 1.7 cents a 30 mg tablet, US$6.24 a patient-year at one tablet a day in the UNICEF Supply Catalogue, October 2026; seizures affect a large proportion of glioma patients. In defined subsets, BRAF with MEK inhibitors serve BRAF V600E-mutant gliomas; everolimus is listed and shrinks subependymal giant cell astrocytoma in tuberous sclerosis, avoiding surgery; vorasidenib, approved in 2024 for residual or recurrent IDH-mutant grade 2 glioma, is not listed and is on patent, with a large progression-free survival gain in the INDIGO trial — the first genuinely new drug class in glioma in two decades. Checkpoint inhibitors have failed in glioblastoma: multiple large randomised trials of PD-1 blockade showed no survival benefit†, one of the most consistent negative results in immuno-oncology, attributed to the low mutation burden, the immunosuppressive microenvironment and the absence of normal lymphatic drainage.

Simple means. Dexamethasone is the single most valuable simple intervention in this entry: listed, off-patent, pennies a dose, oral or injectable, no cold chain. It relieves raised intracranial pressure and focal deficit quickly, restores the ability to walk, speak and eat in many patients, and transforms the final months, and its routine availability matters more for brain tumour patients in low-resource settings than any other intervention. Anticonvulsants — phenytoin, carbamazepine, valproate, phenobarbital — are all listed, off-patent, oral and cheap, and seizure control is a major determinant of quality of life and of the capacity to remain at home. Oral morphine serves headache, with antiemetics. A burr-hole, a simple decompressive craniotomy, or a ventriculoperitoneal shunt for obstructive hydrocephalus can be done with basic neurosurgical instruments where a trained surgeon exists, and a shunt for obstructive hydrocephalus from a posterior fossa tumour is life-saving and does not require an operating microscope. Nursing care is the substance of what is needed as patients become dependent for feeding, continence and mobility, and it requires no technology: pressure-area care, bowel management and carer support. For malignant brain tumours nothing simple extends life, and that should be plain. Resection requires a neurosurgeon and imaging; radiotherapy requires a linear accelerator; temozolomide requires a reliable oral supply and blood-count monitoring. **No diagnosis is even possible without computed tomography or magnetic resonance imaging**, which makes brain tumours the clearest case in this chapter where the diagnostic step alone is beyond simple means. The entire simple-means contribution in neuro-oncology is symptom control, and dexamethasone with anticonvulsants, morphine and nursing is a genuinely large contribution on those terms, without altering the disease.

Gaps. SEER publishes no stage-specific survival table for brain and central nervous system tumours, so the histology-specific figures are literature-derived. The aetiology of the great majority of brain tumours is unknown, which is a gap in the field. On mobile phones, IARC's Group 2B classification of 2011 stands against flat registry incidence and a null WHO-commissioned review of 2024; both are printed and the disagreement persists in public discussion despite the registry evidence. The 2021 classification reorganised the field molecularly, which makes survival statistics published before and after it non-comparable, and most quoted figures mix the two. Overdiagnosis of incidental meningioma and low-grade glioma from expanding imaging use is real and entirely unquantified. Lomustine pricing is literature-derived.

> **Depth.** Starts in: a glial cell. Size: 10 µm†; depth +4.91. First complaint: about 60 years († median age 60); time depth 52.60. One untreated course: about 3 months († about 3 months (glioblastoma)); depth 47.60.
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> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Leukaemias

Cancers of the blood-forming cells of the bone marrow. The four main types are treated separately below, because they share an organ and differ in almost everything else — age of onset, speed, treatment and curability. Chronic myeloid leukaemia is the single greatest therapeutic success in oncology and acute myeloid leukaemia in the elderly is among the greatest failures, so one label across the group would be false in both directions and none is assigned here.

GLOBOCAN 2022 gives 487,294 cases of leukaemia of all types; GLOBOCAN 2024 gives 495,113 cases and 292,234 deaths. GLOBOCAN reports leukaemia as a single category and does not disaggregate the four types, which is a significant limitation, so the type-specific figures below are from SEER. Leukaemia is the commonest cancer of childhood, with acute lymphoblastic leukaemia accounting for roughly three-quarters of childhood leukaemia.

18. Acute myeloid leukaemia

What it is. A rapidly progressive cancer in which immature myeloid cells fill the bone marrow and crowd out normal blood production. Untreated it kills within weeks to a few months, from infection or bleeding. It is predominantly a disease of older people, and age is the dominant determinant of whether it can be cured.

Measured. United States incidence is 4.4 per 100,000 a year, with 22,720 projected new cases and 11,500 projected deaths for 2026, about 1.1 per cent of United States cancer cases and 1.8 per cent of cancer deaths. Five-year relative survival is 33.4 per cent overall. SEER does not stage acute myeloid leukaemia, so no localized-regional-distant breakdown exists; the meaningful stratification is by age and by cytogenetic and molecular risk, and those figures are from the general haematology literature: children and young adults roughly 65 to 70 per cent; adults under 60 with favourable cytogenetics roughly 55 to 65 per cent; adults over 60 roughly 5 to 15 per cent; adverse-risk cytogenetics, including complex karyotype, monosomy 7 and TP53 mutation, under 10 per cent regardless of age; and acute promyelocytic leukaemia above 90 per cent. Median age at diagnosis 70, which is the central clinical fact: it is a disease of people too old to tolerate the treatment that cures it. Prevalence in the United States in 2023 was 83,311 people. Incidence is stable and the death rate falling about 0.9 per cent a year.

Where it starts. Prior cytotoxic chemotherapy and radiotherapy give a well-defined entity. Alkylating agents — cyclophosphamide, melphalan, chlorambucil — cause it at a latency of five to seven years with adverse cytogenetics; topoisomerase II inhibitors — etoposide, anthracyclines — at a latency of one to three years with KMT2A rearrangements†. This is an iatrogenic cancer, caused by the treatment of other cancers. Benzene is IARC Group 1 for acute myeloid leukaemia, the classic occupational cause, established in rubber, shoe-making, painting and petroleum work. Ionising radiation is established from the atomic bomb survivor cohorts, dose-dependently and with a latency of several years. Smoking is an established cause at a relative risk generally reported in the region of 1.4 for current smokers, with an attributable fraction of roughly 20 per cent of adult cases†. Myelodysplastic syndrome, myeloproliferative neoplasms and aplastic anaemia transform to it, and clonal haematopoiesis of indeterminate potential, present in over 10 per cent of people over 70, carries a small annual risk of progression of roughly 0.5 to 1 per cent a year†. Germline predisposition comes from Down syndrome, with a large increase in childhood megakaryoblastic disease, Fanconi anaemia, Li-Fraumeni syndrome, and germline RUNX1, CEBPA, GATA2 and DDX41 mutations. Acute myeloid leukaemia has one of the lowest point-mutation burdens of any adult cancer, typically fewer than ten coding mutations per genome, far below the adult reference of 1.8 per megabase, with the TCGA study finding a mean of thirteen coding mutations. It is driven by a small number of recurrent events — FLT3, NPM1, DNMT3A, IDH1 and IDH2, TET2, RUNX1, TP53 and the fusion genes — rather than by a mutational storm, and that low burden explains its near-total resistance to checkpoint blockade. Not known: the cause of the large majority of de novo disease; why the same genetic lesions give such different outcomes at different ages; whether the age effect is tumour biology, host tolerance of treatment, or both, and in what proportion; which carriers of clonal haematopoiesis will progress.

Cure status. Acute promyelocytic leukaemia, t(15;17) with PML-RARA: CURABLE, and it is the most important exception here — once the most rapidly fatal form of leukaemia, it is now cured in over 90 per

cent of patients†. The curative treatment is all-trans retinoic acid with arsenic trioxide, and in non-high-risk disease that combination cures without any conventional chemotherapy at all. Both are listed and both are off-patent. Children and fit adults under 60: CURABLE in roughly 55 to 70 per cent at five years, depending on cytogenetic risk†, with intensive induction, consolidation, and allogeneic stem cell transplantation for higher-risk disease. Adults over 60 who tolerate hypomethylating therapy: CONTROLLABLE — five-year survival roughly 5 to 15 per cent†. Adults over 60 who do not: RELIEF ONLY. Adding venetoclax to azacitidine changed this materially, with median survival in unfit older patients roughly doubled from about 10 to 15 months and complete remission rates above 60 per cent†, and it is not curative. Adverse-risk and TP53-mutated disease: RELIEF ONLY — five-year survival under 10 per cent even with transplantation†. Relapsed disease after transplantation: RELIEF ONLY. Early detection does not apply: there is no detectable preclinical phase that screening could find, no stages, and no benefit from earlier diagnosis beyond avoiding presentation in crisis. Curability is determined by the biology of the clone and the age of the patient, not by timing.

Prevention. Benzene exposure control — STRONG, on an IARC Group 1 classification. Occupational limits have reduced it substantially in regulated economies and less so elsewhere. Smoking cessation — MODERATE, at a relative risk of about 1.4 and an attributable fraction of about 20 per cent†. Minimising cumulative alkylating-agent and topoisomerase-inhibitor dose in the treatment of curable cancers — STRONG as a principle, and the reason de-escalation trials in Hodgkin lymphoma, testicular cancer and childhood leukaemia matter so much. This is prevention of a cancer caused by cancer treatment, and it is one of the main justifications for de-escalation research. Radiation protection — STRONG. There is no screening and no rationale for one: there is no pre-malignant lesion to intercept at population level. Clonal haematopoiesis is detectable incidentally on sequencing, carries roughly a 0.5 to 1 per cent annual progression risk, and has no intervention proven to reduce that risk, so detecting it creates anxiety without an action. Monitoring of known myelodysplastic syndrome and of germline predisposition carriers is surveillance of established risk rather than screening, and has no randomised mortality evidence. Overdiagnosis is not a meaningful concept here.

Treatment. Relapse after transplantation is not curable in most patients, and the proportion rescued is not given. All-trans retinoic acid with arsenic trioxide for acute promyelocytic leukaemia comes first. Tretinoin and arsenic trioxide are both listed and both off-patent, at a cure rate over 90 per cent†. Generic all-trans retinoic acid costs in the order of tens to low hundreds of dollars a course and generic arsenic trioxide is similarly inexpensive, against a far higher originator price. **That is a striking cost-effectiveness fact: a formerly near-universally fatal leukaemia is cured in over 90 per cent of patients by two off-patent Essential Medicines, one a vitamin A derivative and the other a traditional arsenic preparation.** Intensive induction chemotherapy, cytarabine with daunorubicin, follows for fit patients; both are listed and off-patent, at tens of dollars a vial, and this regimen, essentially unchanged since the 1970s, remains the backbone of curative therapy. The drugs are cheap and the supportive care is not. Consolidation uses high-dose cytarabine, listed and off-patent. Allogeneic haematopoietic stem cell transplantation is the most effective anti-leukaemic treatment available and the only cure for many higher-risk patients, at a treatment-related mortality of 10 to 20 per cent†, and it requires a transplant unit, tissue typing, a donor and intensive supportive care: the least transferable intervention in this chapter. Venetoclax with azacitidine serves unfit or older patients. **Venetoclax is not on the Essential Medicines List in any form: a query of the electronic list returns zero recommendations, zero medicines and zero therapeutic equivalents**. It is on patent, at a United States list price in the region of US$10,000 to 15,000 a month†; azacitidine is off-patent with generics available cheaply and is likewise not listed. Complete remission rates above 60 per cent and roughly doubled median survival in unfit older patients in the VIALE-A trial make this the most important advance in acute myeloid leukaemia in decades, and the key drug is not on the list. Midostaurin, gilteritinib and quizartinib for FLT3-mutant disease are not listed and all on patent, and add a survival benefit to chemotherapy. Ivosidenib, enasidenib and olutasidenib are not listed, and nor is gemtuzumab ozogamicin. Hydroxyurea is listed, for chronic myeloid leukaemia and for haemoglobinopathies, off-patent, at cents a day, and reduces a dangerously high white cell count quickly; in a setting with no capacity for intensive chemotherapy, hydroxyurea with transfusion support is palliative management achievable almost anywhere. Checkpoint inhibitors are inactive, consistent with the very low mutation burden. Supportive care — red cell and platelet transfusion, broad-spectrum antibiotics, antifungals, and

granulocyte colony-stimulating factor, with filgrastim and pegfilgrastim both listed and filgrastim off-patent with biosimilars — is not adjunctive. It is the reason intensive therapy is survivable at all.

Simple means. All-trans retinoic acid for acute promyelocytic leukaemia, started on clinical suspicion before confirmation, is the highest-value simple intervention in leukaemia care. Acute promyelocytic leukaemia kills by catastrophic haemorrhage in the first days, and the drug is an oral capsule, off-patent, listed, and reverses the coagulopathy within days. A clinician who suspects it from the blood film and the bleeding and starts the drug immediately, before cytogenetics are available, prevents deaths. It needs no cold chain, no infusion and no monitoring beyond clinical observation, and where confirmatory genetics are unavailable, starting on morphological suspicion is defensible and is practised. Arsenic trioxide requires intravenous administration and electrocardiographic monitoring for QT prolongation, which is a modest requirement. Hydroxyurea is oral, listed, off-patent and cents a day, and reduces hyperleucocytosis and relieves symptoms; in a setting with no chemotherapy capability it is the realistic option. Transfusion of red cells and platelets requires a blood bank, which is a real but attainable requirement. **The absence of a platelet supply is the binding constraint on treatment in most of the world: without platelets, intensive chemotherapy kills by haemorrhage, so the low drug cost is irrelevant.** Oral antibiotics and antifungals, handwashing, isolation where possible and prompt empirical antibiotics for fever carry much of what makes neutropenia survivable, and most of that is organisational rather than technological. Oral morphine, antiemetics, mouth care for mucositis and nutritional support follow. This entry requires an unusually sharp honest statement: the cytotoxic drugs that cure acute myeloid leukaemia are cheap, off-patent and listed, and they are useless without the supportive care chain. Cytarabine and daunorubicin cost tens of dollars; the four weeks of profound neutropenia and thrombocytopenia they cause require platelet transfusions, blood cultures, intravenous antifungals and an inpatient bed, and without those the treatment has a very high mortality. **Acute myeloid leukaemia is therefore the clearest case in this chapter where cheap off-patent drugs do not translate into simple means.** The promyelocytic exception is genuine and important precisely because it bypasses the marrow-ablating chemotherapy and therefore bypasses the supportive care requirement.

Gaps. GLOBOCAN does not disaggregate leukaemia by type, so all type-specific burden figures here are United States SEER. SEER publishes no risk-stratified survival table, so the age- and cytogenetic-risk figures are literature-derived. The smoking relative risk is not primary-source-verified. Venetoclax, the key advance for older patients, is confirmed absent from the Essential Medicines List and no rationale for its absence is retrievable. There is no established cause for most de novo disease. Clonal haematopoiesis progression risk is known and no intervention exists, so its detection has no actionable consequence.

> **Depth.** Starts in: a myeloid precursor cell. Size: 10 µm†; depth +4.91. First complaint: about 6 years ([B] 5–7 years after alkylating drugs); time depth 50.49. One untreated course: about 6.2 weeks ([B] weeks to a few months); depth 46.93.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

19. Acute lymphoblastic leukaemia

What it is. A cancer of immature lymphoid cells, predominantly affecting children, in whom it is the commonest cancer of all. In children it is now curable in the large majority; in adults the same disease with the same name is far less curable. The difference between those two outcomes is one of the most instructive facts in oncology.

Measured. United States incidence is 1.9 per 100,000 a year, with 6,250 projected new cases and 1,600 projected deaths for 2026, about 0.3 per cent of United States cancer cases. Five-year relative survival is 73.2 per cent overall. SEER publishes no child-specific survival figure on its page and records that people under 20 account for 52.1 per cent of new cases. The age split is the whole story, and the figures are from the general haematology literature: children aged 1 to 14 approximately 90 to 94 per cent in contemporary cooperative-group protocols in high-income countries; adolescents and young adults roughly 70 to 75 per cent; adults 40 to 60 roughly 40 to 50 per cent; adults over 60 roughly 20 per cent or less; and infants under

one year, usually with KMT2A rearrangement, roughly 40 to 50 per cent. Median age at diagnosis 18, the youngest of any entity in this chapter. Incidence has not significantly changed and the death rate is falling about 1.8 per cent a year. The geographical gap is not biological: WHO states that more than 80 per cent of children with cancer are cured in high-income countries against less than 30 per cent in most low- and middle-income countries. For childhood acute lymphoblastic leukaemia specifically the divergence is at its starkest, because the disease is highly curable with off-patent drugs and the cure depends on eighteen months to three years of uninterrupted protocol-adherent treatment with supportive care, which is exactly what fails when health systems are weak. Abandonment of treatment, not drug cost and not drug availability, is a leading cause of death from it in low-income settings.

Where it starts. The cause of childhood acute lymphoblastic leukaemia is not established, and it is one of the most studied unanswered questions in cancer epidemiology. The dominant hypothesis is a two-hit model. The first hit is an in-utero initiating translocation, detectable on neonatal blood spots in a proportion of children who later develop the disease, and present in far more children than ever develop it. The second is a genetic hit precipitated by an abnormal immune response to common infection, in a child whose immune system has had insufficient early microbial exposure. The epidemiological support is indirect — the association with higher socioeconomic status and with reduced early-life infection exposure, the protective associations of breastfeeding, day-care attendance and vaginal delivery, and the delayed infection pattern — and no single infectious agent has been identified. The hypothesis is widely regarded as the best available and it is not proven. Ionising radiation is established, including in-utero exposure, and is the clearest established environmental cause. Down syndrome gives a roughly twentyfold increase in childhood risk; ataxia-telangiectasia, Nijmegen breakage syndrome, Li-Fraumeni syndrome, Bloom syndrome, germline PAX5, ETV6 and IKZF1 variants and constitutional mismatch repair deficiency follow, and germline predisposition accounts for roughly 5 to 10 per cent of childhood cases†. Prior chemotherapy causes therapy-related disease, far less commonly than therapy-related acute myeloid leukaemia. Benzene and other occupational exposures are established for adult disease at much weaker effect sizes than for acute myeloid leukaemia. Childhood acute lymphoblastic leukaemia has among the very lowest mutation burdens ever measured in human cancer. Gröbner and colleagues, in *Nature* in 2018, analysed 961 tumours across 24 molecular cancer types and found an overall paediatric somatic mutation frequency of 0.13 mutations per megabase against the adult reference of 1.8 — about fourteen times lower — and this disease sits at or below the paediatric average. It is driven by structural events — ETV6-RUNX1, high hyperdiploidy, TCF3-PBX1, BCR-ABL1, KMT2A rearrangements and the Philadelphia-like signature — rather than by point mutations. That has a practical consequence: there is essentially no mutational burden for checkpoint inhibitors to exploit, and checkpoint blockade has no role here. The successful immunotherapies — blinatumomab and CD19-directed cell therapy — work by redirecting T cells against a lineage antigen that is present whether or not the tumour is mutated. Not known: the cause of the large majority of childhood cases; why the identical translocation is present in many more newborns than ever develop leukaemia; **why the same disease is 90 per cent curable at age 5 and 20 per cent curable at age 70** — the contributions of clonal biology, treatment tolerance and marrow reserve are not separable with current data.

Cure status. Childhood disease, ages 1 to 14: CURABLE, and the outstanding success of paediatric oncology — five-year survival approximately 90 to 94 per cent in high-income settings†, from essentially zero in 1960. The cure is achieved by two to three years of multi-agent chemotherapy with central nervous system prophylaxis, risk-stratified by minimal residual disease response. Adolescents and young adults: CURABLE, and a majority are cured, better with paediatric-intensity protocols than with adult protocols, a finding that changed practice. Adults 40 to 60: CURABLE, and roughly half are cured†. Adults over 60: CONTROLLABLE — roughly 20 per cent or less survive five years†. Philadelphia-positive disease, with the BCR-ABL1 fusion: CURABLE, including in the elderly — transformed from the worst-prognosis subtype to one of the better ones. Adding a tyrosine kinase inhibitor to chemotherapy raised long-term survival substantially, and chemotherapy-free regimens of dasatinib or ponatinib with blinatumomab have produced complete molecular response rates above 80 per cent in older adults who could not tolerate chemotherapy†. Relapsed childhood disease: CURABLE in roughly 40 to 50 per cent with reinduction and transplantation, or with CD19-directed therapy†. Infant KMT2A-rearranged disease: CURABLE in roughly 40 to 50 per cent†, the worst paediatric subgroup. Early detection does not apply: there is no pre-

clinical detectable phase and no stages, and curability is determined by age, immunophenotype, cytogenetics and minimal residual disease response rather than by how soon it is found.

Prevention. Avoiding unnecessary diagnostic and therapeutic ionising radiation, especially in pregnancy and childhood — STRONG, and the only established prevention. Everything suggested by the delayed-infection hypothesis — breastfeeding, day-care attendance, early microbial exposure — is CONTESTED: the associations are consistent and biologically coherent and there is no interventional evidence. A defined microbial exposure in infancy has been proposed as preventive; that is a hypothesis with no trial behind it and should not be presented as established. There is no screening and no rationale for one. Neonatal blood spots can detect the ETV6-RUNX1 fusion, and it is present in roughly 1 per cent of newborns while only about one in a hundred of those ever develops leukaemia, so a positive test would be wrong 99 times out of 100: a clear illustration of why a detectable pre-clinical marker does not make a screening test. Overdiagnosis is not a meaningful concept here. Childhood acute lymphoblastic leukaemia cannot currently be prevented. Its cure rate, not its prevention, is where the achievement lies, and the achievable gain now is in delivering existing treatment to the children who do not receive it.

Treatment. The proportion of Philadelphia-positive disease cured is not given. Adding a tyrosine kinase inhibitor to chemotherapy raised long-term survival substantially, including in the elderly. Multi-agent risk-stratified chemotherapy over two to three years, in phases — induction, consolidation, interim maintenance, delayed intensification and maintenance. The drugs are, almost without exception, listed and off-patent. Vincristine is listed, with leukaemias among its listed indications. Prednisolone, prednisone and dexamethasone are all listed, and dexamethasone's listed indications in the antineoplastic section include acute lymphoblastic leukaemia. Asparaginase and pegaspargase are listed. Methotrexate is listed, with leukaemias among its indications. Mercaptopurine, cytarabine, cyclophosphamide, daunorubicin, doxorubicin, tioguanine and calcium folinate are all listed and all off-patent. **The regimen that cures over 90 per cent of children with acute lymphoblastic leukaemia is built entirely from off-patent Essential Medicines, and the total drug cost of a full two- to three-year protocol is in the region of a few hundred to a low thousands of dollars**. The barrier to curing it worldwide is not drug cost and not patents. Intrathecal methotrexate, with or without cytarabine, gives central nervous system prophylaxis; both are listed, off-patent and pennies a dose. Without that prophylaxis the disease relapses in the central nervous system in a large proportion of children and is then usually fatal, so this cheap intrathecal injection is one of the most important single components of the cure, and it requires only a lumbar puncture needle and a skilled operator. Cranial irradiation, formerly used for the same purpose, has largely been abandoned because of its late effects — second cancers and cognitive impairment — which is itself an example of successful de-escalation. Imatinib for Philadelphia-positive disease is listed and off-patent, at United States generic cash prices, October 2026, of US$1.49 to 5.37 per 400 mg tablet and US$44.75 to 161.09 for thirty, which is US$540 to 1,960 a year at 400 mg daily. The originator price was in the region of US$90,000 to 145,000 a year at United States list by the time of generic entry in 2016†. Dasatinib is listed and off-patent in many markets; ponatinib is not listed and is on patent. **Blinatumomab is a listed medicine, for B-cell acute lymphoblastic leukaemia**, and is not off-patent. In relapsed or refractory paediatric and adult disease it produces complete remission in the region of 35 to 45 per cent as monotherapy†. Added to consolidation in first remission it improved survival substantially in randomised trials and is now moving into frontline use. The course cost at United States list is in the region of US$180,000 or more†. Its inclusion on the list at that price is notable, and section F returns to it. CD19-directed CAR T-cell therapy — tisagenlecleucel for paediatric and young adult relapsed or refractory B-cell disease, obecabtagene autoleucel and brexucabtagene autoleucel for adult disease — is on patent, and **no CAR-T product is on the Essential Medicines List**. In the pivotal paediatric trial complete remission was achieved in the large majority; NCI states that the treatment eliminated leukaemia in most children without giving a percentage, and the commonly cited figure is around 80 per cent complete remission with roughly half remaining in remission at longer follow-up. A precise per-treatment price could not be retrieved from the price guide, which states only that pricing varies; the United States list price of tisagenlecleucel for this indication has been reported at US$475,000 for a single infusion, with total episode costs higher once lymphodepletion, hospitalisation and toxicity management are included. Allogeneic stem cell transplantation serves high-risk and relapsed disease. Nelarabine for T-cell disease is not listed and is off-patent. Checkpoint inhibitors have no role. Supportive care — transfusion, antibiotics, antifungals, filgrastim, and rasburicase and allopurinol for tumour lysis syndrome, all listed and the last two off-patent — closes the regimen. Tumour

lysis syndrome is a specific early killer: a high tumour burden dissolving rapidly releases potassium, phosphate and urate and causes renal failure and arrhythmia. Allopurinol is listed for tumour lysis syndrome and costs cents, hydration costs almost nothing, and together they prevent most of it.

Simple means. Oral prednisolone, oral mercaptopurine and oral methotrexate carry the maintenance phase, which occupies most of the two to three years and is almost entirely oral, off-patent, listed and cheap. It requires a blood count every few weeks and a clinician to adjust the dose, so it is genuinely deliverable with modest infrastructure, and it is where much of the cure is consolidated. Vincristine and intrathecal methotrexate are injections given in an outpatient clinic, and the intrathecal route needs a lumbar puncture, a needle and training, with no imaging. Allopurinol and hydration prevent tumour lysis for cents, and are universally available. Oral antibiotics, infection control, oral rehydration and nutritional support follow. The honest statement here matters because the gap is organisational rather than technological: the drugs that cure childhood acute lymphoblastic leukaemia are cheap and listed, and the cure still fails in most of the world. What is missing is not the pharmacy but the system. It needs a reliable blood and platelet supply for the intensive phases, inpatient beds for febrile neutropenia, an uninterrupted drug supply for three years, and a laboratory that can do a blood count and a blast percentage. It also needs families who can afford to stay in treatment, and a service that follows up a child who misses an appointment. Abandonment of treatment is a leading cause of death in low-income settings, and it is a failure of social and financial support rather than of medicine. Where nothing simple exists: relapsed and refractory disease. Blinatumomab requires continuous intravenous infusion by pump for weeks; CAR-T requires apheresis, a cell-processing facility and intensive care for cytokine release syndrome; transplantation requires a transplant unit. None is achievable by simple means, and the reported CAR-T price of US$475,000 an infusion at United States list places it outside the reach of the large majority of the world's children who need it.

Gaps. GLOBOCAN does not disaggregate leukaemia by type. SEER's page gives no child-specific survival figure, only that under-20s are 52.1 per cent of cases, so the paediatric figure of 90 to 94 per cent is literature-derived. CAR-T pricing could not be retrieved from a primary source and NCI's own page gives no prices at all. NCI gives the paediatric response as "most children" without a percentage. The cause of childhood acute lymphoblastic leukaemia is unknown and the delayed-infection hypothesis has no interventional evidence. The reason for the age-curability gradient is not resolved. Blinatumomab is listed at a reported course price of US$180,000 at United States list, and no listing rationale was retrievable.

> **Depth.** Starts in: a lymphoid precursor cell. Size: 10 µm†; depth +4.91. First complaint: about 4 years († starts in utero, peaks at age 2–5); time depth 50.13. One untreated course: about 8.6 weeks († about 2 months); depth 47.23.
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> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

20. Chronic myeloid leukaemia

What it is. A cancer of the myeloid cells caused by a single specific genetic accident: a fusion of the BCR and ABL1 genes produced by a translocation between chromosomes 9 and 22. It produces one abnormal protein, and a tablet that blocks that protein converts the disease from fatal to compatible with a normal lifespan. It is the proof of principle for all targeted cancer therapy.

Measured. United States projections for 2026 are 9,650 new cases and 1,170 deaths, about 0.5 per cent of cancer cases and 0.2 per cent of cancer deaths. Five-year relative survival is 71.1 per cent, and that figure substantially understates current outcomes: it covers a cohort including older patients diagnosed across the period and those with advanced-phase disease. In contemporary series of patients diagnosed in chronic phase and treated with a tyrosine kinase inhibitor, ten-year survival is roughly 85 to 90 per cent and life expectancy approaches that of the general population. The long-term follow-up of the IRIS trial reports an estimated ten-year overall survival of 83.3 per cent†. Median age at diagnosis 67. United States incidence is rising about 1.0 per cent a year and the death rate falling about 0.7 per cent a year. Prevalence is rising steeply, because patients now live for decades on treatment rather than dying within three to five years, and that is a new kind of health-system problem: a growing population needing an indefinite daily tablet. Before

imatinib, median survival in chronic-phase disease was roughly three to five years and allogeneic transplantation was the only cure.

Where it starts. Ionising radiation is the only established cause, demonstrated in the atomic bomb survivor cohorts and in patients given therapeutic radiation, dose-dependently. No other risk factor is established: smoking, benzene, occupation, diet, infection and family history have all been studied and none is established, and there is essentially no familial disease and no germline predisposition syndrome that produces it. Chronic myeloid leukaemia has the lowest mutation burden of any cancer in this chapter and is the closest thing in oncology to a single-mutation disease. Chronic-phase disease carries very few somatic mutations beyond the fusion itself, often almost none detectable by exome sequencing, against an adult reference of 1.8 per megabase. The fusion is present in essentially 100 per cent of cases†: it is both necessary and, in chronic phase, very nearly sufficient. Progression to accelerated phase and blast crisis is accompanied by the acquisition of further lesions — TP53, RUNX1, ASXL1, IKZF1 and additional cytogenetic abnormalities — and that acquisition is what makes advanced-phase disease behave like acute leukaemia. Not known: what causes the translocation in the great majority of patients, who have had no radiation exposure; **why a small proportion of patients in deep molecular remission relapse after stopping treatment and most do not** — the biology of the residual leukaemic stem cell is the central unanswered question, and it determines whether a patient can ever stop treatment.

Cure status. Chronic phase on continuous therapy: CONTROLLABLE with near-normal life expectancy — roughly 85 to 90 per cent ten-year survival, with most deaths from unrelated causes†. That is the best outcome of any malignancy in this chapter achieved by a drug alone. Chronic phase in sustained deep molecular response who stop treatment: CURABLE in roughly 50 per cent — patients in sustained MR4.5 response for at least two years who stop remain in remission in roughly 50 per cent of cases at two to three years, and the remainder relapse and almost all regain response on restarting. For the half who remain off treatment, they have no detectable disease and take no drug, though residual leukaemic cells are usually still present and the field uses the term operational cure. Accelerated phase: CONTROLLABLE, with a worse prognosis. Blast crisis: RELIEF ONLY — it behaves as acute leukaemia with poor response and median survival in months; allogeneic transplantation after returning to chronic phase is the only curative option. Allogeneic stem cell transplantation: CURABLE — long-term disease-free survival above 60 to 70 per cent in young patients with matched donors, at a treatment-related mortality of 10 to 20 per cent†. It has been displaced to third or fourth line by the oral inhibitors, which achieve better survival with no mortality risk, and that displacement is one of the clearest cases in medicine of a curative but dangerous treatment being correctly abandoned in favour of a non-curative but safe one. Early detection partly applies: diagnosis in chronic phase rather than in blast crisis matters enormously, and the disease is often found incidentally on a routine blood count showing a high white cell count. This is close to the only cancer in this chapter where a full blood count — the cheapest laboratory test in medicine — functions as an effective early-detection test, even though no screening programme exists.

Prevention. Avoiding unnecessary ionising radiation — STRONG as the only established measure, and of negligible population impact, because radiation accounts for a tiny fraction of cases. No other prevention exists: there is nothing to avoid, nothing to take and no behaviour to change. There is no screening programme and no recommendation for one, because the prevalence is far too low. However, the disease is routinely detected incidentally by a full blood count done for another reason, and because it is silent in early chronic phase and highly treatable, incidental detection is unambiguously beneficial. **There is no overdiagnosis problem in chronic myeloid leukaemia**: every case detected is a real disease that would have progressed to blast crisis and death if untreated. It is one of very few entries in this chapter where more detection is simply good.

Treatment. Imatinib is listed and off-patent, with United States generic cash prices, October 2026, of US$1.49 to 5.37 per 400 mg tablet, US$44.75 to 161.09 for thirty tablets, and US$0.40 to 1.73 per 100 mg tablet, so US$540 to 1,960 a year at the standard chronic-phase dose of 400 mg daily. The originator was priced at roughly US$30,000 a year at launch in 2001 and had risen to roughly US$90,000 to 145,000 a year in the United States by the time of generic entry in 2016†, and the price guide lists the brand with no price. **The originator-to-generic ratio is therefore about 46- to 269-fold, and this is a large price fall in cancer medicine**: it converted the definitive treatment for a fatal leukaemia from one of the most expensive drugs in the world into one costing a few dollars a day. In generic-supplying markets it has been available at

under US$400 a year, and reported as low as US$100 to 200 a year at the most competitive prices†. Complete cytogenetic response is achieved in roughly 80 to 85 per cent of chronic-phase patients, with an estimated ten-year overall survival of 83.3 per cent in long-term follow-up†. Dasatinib and nilotinib are both listed; dasatinib is off-patent in many markets, with generic prices a fraction of the originator price of US$150,000 to 200,000 a year at United States list†, and nilotinib's patent status is market-dependent. They achieve deeper and faster molecular responses and are preferred in higher-risk disease and in some resistance mutations, and they have not been shown to improve overall survival over imatinib, which is worth stating plainly, because it means the cheap off-patent drug is not inferior on the endpoint that matters most. Bosutinib, ponatinib and asciminib are not listed and are on patent in most markets; ponatinib is the only inhibitor active against the T315I resistance mutation and carries substantial arterial thrombotic toxicity. Hydroxyurea is listed, with chronic myeloid leukaemia among its listed indications, off-patent, at cents a day, and reduces a very high white cell count at presentation while the diagnosis is confirmed and an inhibitor is obtained; in a setting with no access to any inhibitor it controls the count and the symptoms for a period and does not prevent progression to blast crisis. Interferon alfa was the pre-imatinib standard, produced long-term survival in a small minority, and is now used mainly in pregnancy, where the inhibitors are contraindicated; it is off-patent. Allogeneic transplantation is curative and now reserved for resistant disease and blast crisis. Molecular monitoring by quantitative polymerase chain reaction for the fusion transcript is integral to modern management: response milestones at three, six and twelve months determine whether to change drug, and achieving a deep molecular response determines eligibility for discontinuation. That is the binding infrastructure requirement.

Simple means. One oral tablet a day, off-patent, listed, at US$1.50 to 5 a day at United States generic cash prices, October 2026, and under a dollar a day at the most competitive international generic prices. No infusion, no cold chain, no inpatient bed, no transfusion support, no radiotherapy, no surgery. A patient takes a tablet and lives a normal lifespan. **In terms of benefit delivered per unit of infrastructure, imatinib for chronic myeloid leukaemia is the single best intervention in this chapter.** Diagnosis is possible by full blood count and blood film: a raised white cell count with the characteristic spectrum of myeloid maturation, with basophilia and splenomegaly on examination, is highly suggestive and can be recognised with a microscope and a trained eye. Confirmation requires cytogenetics or polymerase chain reaction, which is the one genuine technological requirement, and where that is unavailable the clinical and morphological diagnosis of chronic-phase disease is reliable enough that treating on it has been considered defensible, and some access programmes have operated that way. Hydroxyurea is oral at cents a day and controls the white count where no inhibitor is available. Splenectomy for massive symptomatic splenomegaly is rarely needed now and is a conventional operation. Allopurinol and hydration prevent tumour lysis at presentation for cents. The real constraint is that the drug is cheap and simple and the monitoring is not. Quantitative polymerase chain reaction at an international-standard reference laboratory is required to know whether a patient is responding adequately, to decide whether to switch drug, and above all to know whether a patient can safely stop treatment. Without molecular monitoring, patients can be treated and most will do well on imatinib, and they cannot be optimised, and treatment-free remission cannot be attempted at all, because stopping without molecular surveillance is unsafe. **This is the clearest example in the chapter of a disease where the therapeutic problem has been solved by simple means and the remaining gap is diagnostic infrastructure.** The second constraint is continuity: treatment is indefinite, and an interruption of supply allows the disease to progress.

Gaps. GLOBOCAN does not disaggregate leukaemia by type. SEER's 71.1 per cent five-year relative survival materially understates contemporary chronic-phase outcomes, and SEER publishes no phase-stratified or inhibitor-era-restricted figure. The ten-year IRIS figure, originator pricing, international generic prices and the treatment-free remission rate are all literature-derived. Why some patients relapse after discontinuation and most do not is unknown, and it is the central open question. The cause of the translocation in non-irradiated patients is unknown.

> **Depth.** Starts in: a blood stem cell (BCR-ABL1). Size: 8 µm†; depth +4.70. First complaint: about 6 years († about 6 years after radiation); time depth 50.50. One untreated course: about 4 years († chronic phase 3–5 years); depth 50.13.
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> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY.

> Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

21. Chronic lymphocytic leukaemia

What it is. A slowly accumulating cancer of mature B lymphocytes, the commonest leukaemia of older adults in Western countries. Many patients never need treatment at all and die of something else; others progress and require years of therapy. It is the cancer in which watch and wait is a proven standard of care rather than a failure to act.

Measured. United States projections for 2026 are 22,760 new cases and 4,350 deaths, about 1.1 per cent of cancer cases and 0.7 per cent of cancer deaths. Five-year relative survival is 90.2 per cent. SEER does not stage it in the localized-regional-distant scheme; the clinical staging systems are Rai and Binet, and the key prognostic markers are immunoglobulin heavy-chain variable-region mutational status, deletion of 17p or TP53 mutation, and deletion of 11q. The prognostic strata, from the general haematology literature: mutated variable region with no TP53 abnormality, median survival often exceeding 20 to 25 years, with many such patients never requiring treatment; unmutated variable region, shorter time to treatment and shorter survival; deletion of 17p or TP53 mutation, historically the worst subgroup with survival of a few years, substantially improved by the BTK and BCL2 inhibitors. Median age at diagnosis 71. United States incidence is falling about 0.7 per cent a year and the death rate about 1.9 per cent a year, with the mortality decline accelerating after the introduction of the BTK and BCL2 inhibitors from 2014. The geography is unusual and informative: the disease is roughly five to ten times less common in East Asian populations than in European-ancestry populations, and the difference persists in migrants and their descendants, which indicates a genetic rather than an environmental basis. It also has the strongest familial clustering of any leukaemia, at a roughly seven- to eightfold increased risk in first-degree relatives. Monoclonal B-cell lymphocytosis, the pre-malignant precursor, is present in roughly 3 to 5 per cent of adults over 40 and over 10 per cent of those over 80 on sensitive flow cytometry†. It progresses to disease requiring treatment at roughly 1 to 2 per cent a year†, which bears directly on the screening question.

Where it starts. Family history is the strongest established risk factor of any leukaemia, at a roughly seven- to eightfold increased risk in first-degree relatives; no single high-penetrance gene accounts for it, and genome-wide association studies have identified dozens of common low-penetrance variants. Ancestry gives a substantially lower incidence in East Asian populations, persisting after migration. Agricultural work and pesticide exposure show a consistent association in cohort studies of farmers, with the specific agents not established. Hepatitis C virus is associated with some B-cell lymphoproliferative disorders, more clearly with marginal zone lymphoma than with this disease. Notably, this is the one leukaemia not clearly caused by ionising radiation: the atomic bomb survivor cohorts show increases in acute myeloid, acute lymphoblastic and chronic myeloid leukaemia and not in this one, a long-standing and unexplained exception, and benzene is likewise not clearly associated with it. Chronic lymphocytic leukaemia has a low point-mutation burden, below the adult reference of 1.8 per megabase. Recurrent drivers include TP53, NOTCH1, SF3B1, ATM, BIRC3 and MYD88, and the key cytogenetic lesions are deletion of 13q, favourable, trisomy 12, and deletions of 11q and 17p, adverse. Richter transformation — the development of aggressive diffuse large B-cell lymphoma from it in roughly 2 to 10 per cent of patients — is accompanied by acquisition of further lesions and carries a poor prognosis. Not known: what causes it in the great majority; why familial clustering is so strong without a high-penetrance gene; why ionising radiation and benzene, which cause every other leukaemia, do not appear to cause this one; why incidence differs so markedly by ancestry; which carriers of monoclonal B-cell lymphocytosis will progress.

Cure status. Early-stage asymptomatic disease, Rai 0 or Binet A: CONTROLLABLE by watchful waiting — intervention adds nothing and demonstrably harms. Randomised trials of early chemotherapy in asymptomatic early-stage disease showed no survival benefit, and the French Cooperative Group trials of early chlorambucil showed a possible survival disadvantage. Watch and wait is the evidence-based standard, and a substantial minority of patients never require any treatment and die of unrelated causes with their disease untreated. Progressive or symptomatic disease: CONTROLLABLE — five-year relative survival 90.2 per cent overall. Modern targeted therapy produces very long progression-free intervals, with the majority of patients remaining progression-free at five to seven years in the first-line BTK inhibitor

trials, and the disease is not eradicated and treatment is often continuous or repeated. Fixed-duration venetoclax with obinutuzumab produces undetectable minimal residual disease in a majority and allows treatment-free intervals of years, which is the closest this disease comes to functional cure, and most patients eventually relapse. Allogeneic stem cell transplantation: CURABLE — and it carries 10 to 20 per cent treatment-related mortality† and has been almost entirely displaced by the targeted agents in a disease of elderly patients. Richter transformation: RELIEF ONLY — median survival under a year in most series, with no established effective treatment. Early detection confers no benefit, and this is the clearest case in the chapter where earlier detection is demonstrably useless: the pre-malignant state is extremely common, early-stage disease should not be treated, and randomised trials of early intervention showed no gain. It is the counterexample to the general principle that earlier is better.

Prevention. There is no established means of preventing it. No modifiable exposure of consequence has been identified, and the dominant risk factors — family history and ancestry — are not modifiable. Reducing occupational pesticide exposure — CONTESTED: consistent associations in agricultural cohorts, no identified agent, no interventional evidence. Notably the measures that prevent other leukaemias, radiation protection and benzene control, do not appear to prevent this one, since neither exposure is clearly causal for it. There is no screening, and screening would be actively harmful. The reasoning is unusually clear and this is the textbook case. The precursor is present in 3 to 5 per cent of adults over 40 and over 10 per cent over 80, and progresses at only 1 to 2 per cent a year†. Sensitive flow cytometry applied to a population would therefore label a large fraction of older adults with a pre-malignant haematological condition, and the great majority of them would never develop clinically significant disease. Early-stage disease should not be treated, on clear randomised evidence. A screening programme would therefore generate enormous numbers of diagnoses, offer no treatment for them, and deliver only anxiety, insurance consequences and follow-up appointments, and **the overdiagnosis fraction would approach the full population prevalence of the precursor, which has never been quantified as an overdiagnosis percentage.** Incidental detection on a routine blood count nonetheless happens constantly and accounts for a large proportion of diagnoses, with an estimated majority of patients now diagnosed while asymptomatic: unintentional screening at scale, and the reason the measured survival figures have improved partly without any treatment change.

Treatment. Observation for asymptomatic early-stage disease is free, evidence-based and the correct first-line management for a large fraction of patients; it is listed first here because it is the treatment of choice rather than the absence of one. Ibrutinib and zanubrutinib are both listed, which is notable for modern targeted agents, and neither is off-patent; acalabrutinib is not listed. United States list prices for BTK inhibitors are in the region of US$150,000 to 180,000 a year, with ibrutinib reported at US$17,000 a month†. In first-line treatment they give objective response rates above 90 per cent with progression-free survival at five to seven years in the majority, the largest and most durable benefit ever achieved in this disease, and ibrutinib is given continuously and indefinitely, which is what drives the cumulative cost. **Venetoclax is not on the Essential Medicines List in any form** and is on patent, at a United States list price in the region of US$10,000 to 15,000 a month†; combined with obinutuzumab as a fixed twelve-month first-line course it gives undetectable minimal residual disease in roughly 75 per cent and progression-free survival at four to five years in the large majority, with treatment then stopped, which makes the total cost finite rather than indefinite. Rituximab is a listed medicine, with chronic lymphocytic leukaemia among its listed indications; the originator is off-patent and biosimilars are widely available, having reduced the price by roughly 50 to 70 per cent in many markets†. **Rituximab's availability as an off-patent biosimilar is the single most important affordability fact in B-cell malignancy treatment**, and it applies here, to non-Hodgkin lymphoma and to several non-malignant diseases. Obinutuzumab is not listed and is on patent. Chemoimmunotherapy is now largely superseded and it is the off-patent option: fludarabine, cyclophosphamide, bendamustine and chlorambucil are all listed and all off-patent and inexpensive. Fludarabine with cyclophosphamide and rituximab produced long remissions and possible functional cure in the mutated-variable-region subgroup without TP53 abnormality†, which is genuinely important, because it means that for a defined subset there exists an entirely off-patent regimen producing outcomes comparable to the targeted agents. Chlorambucil as a single oral agent, the standard from the 1950s, remains the simplest option of all, and bendamustine with biosimilar rituximab is an off-patent regimen with high response rates. Allogeneic transplantation serves younger patients with high-risk or doubly refractory disease. Lisocabtagene maraleucel is approved for this disease, is not listed and is on

patent, with a price not retrievable from the price guide and reported in the general literature in the region of US$400,000 to 500,000 an infusion at United States list†. Checkpoint inhibitors are inactive, consistent with the low mutation burden. Supportive care matters disproportionately: immunoglobulin replacement for recurrent infection, because the disease causes profound secondary antibody deficiency and infection is the commonest cause of death; vaccination against pneumococcus and influenza; and aciclovir and co-trimoxazole prophylaxis during fludarabine or BTK-inhibitor therapy, both listed, off-patent and costing cents. **Infection prevention delivers more survival benefit per dollar here than anything except the decision not to treat early disease.**

Simple means. Observation comes first, deliberately. For a substantial proportion of patients the correct management requires nothing at all beyond a periodic blood count and clinical review, and the evidence for it is randomised. That is the cheapest correct cancer management in this chapter. Oral chlorambucil is listed, off-patent, a tablet at cents a day, with no cold chain, no infusion and no monitoring beyond a blood count. It controls disease, shrinks nodes and relieves symptoms, and it is inferior to modern therapy on progression-free survival; in a setting with no access to rituximab or a BTK inhibitor it is real and effective palliation that can be given in any clinic, and it was the standard of care for half a century. Diagnosis is possible by full blood count and blood film: a sustained lymphocytosis of mature-looking small lymphocytes, with smudge cells, in an older adult is recognisable with a microscope. Confirmation requires flow cytometry for the immunophenotype, which is the genuine technological requirement, and as with chronic myeloid leukaemia the morphological diagnosis in a typical case is reliable enough that treatment decisions have been made on it where flow cytometry is unavailable. Co-trimoxazole, aciclovir and vaccination cost cents and are listed, and infection is the commonest cause of death here, so these prevent a large share of it. Blood transfusion treats the anaemia of marrow infiltration or autoimmune haemolysis, and prednisolone, listed, off-patent and cents, treats the autoimmune haemolytic anaemia and immune thrombocytopenia that complicate the disease and respond well. Splenectomy serves massive symptomatic splenomegaly or refractory cytopenias and is a conventional operation. The modern agents that transformed the disease have no simple-means equivalent, require indefinite or twelve-month supply chains and cost hundreds of thousands of US dollars a year at list, and the two on the list are still on patent. The gap this creates is narrower here than in most entries, for two reasons: a large fraction of patients need no treatment at all, and the off-patent chemoimmunotherapy option delivers a substantial share of the achievable benefit. Chronic lymphocytic leukaemia is a disease where the simple means — observation, a cheap oral alkylator, infection prophylaxis and transfusion — go a surprisingly long way.

Gaps. GLOBOCAN does not disaggregate leukaemia by type. SEER publishes no prognostic-marker-stratified survival, so the variable-region and TP53 strata are literature-derived. Precursor prevalence and progression rates are literature-derived. Why ionising radiation and benzene do not cause this leukaemia when they cause every other one is unexplained. The strong familial clustering has no identified high-penetrance gene, and the ancestry difference in incidence is unexplained. BTK inhibitor, venetoclax and CAR-T prices are literature-derived; the price guide did not yield figures. Richter transformation has no established effective treatment and it is the principal unmet need.

> **Depth.** Starts in: a B lymphocyte. Size: 7 μm†; depth +4.58. First complaint: about 70 years († median age 70); time depth 52.74. One untreated course: no number ([B] often never needs treatment).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

22. Hodgkin lymphoma

What it is. A cancer of B lymphocytes in which a small number of large abnormal cells sit in a mass of reactive immune cells in the lymph nodes. It mostly affects young adults. It was the first disseminated cancer ever cured by drugs, and it remains one of the most curable cancers that exists, which has shifted the central problem from achieving cure to avoiding the long-term damage done by curing it.

Measured. GLOBOCAN 2022 gives 82,469 cases; GLOBOCAN 2024 gives 84,495 cases and 19,515 deaths. Five-year relative survival in the United States is 89.3 per cent overall, and this is one of the few

entries where SEER publishes survival by Ann Arbor stage: stage I, 13 per cent of cases, 92.7 per cent; stage II, 38 per cent of cases, 95.4 per cent; stage III, 19 per cent, 87.7 per cent; stage IV, 25 per cent, 82.8 per cent; unknown, 5 per cent, 82.1 per cent. **The flatness of that gradient is the most important number in this entry.** Stage IV Hodgkin lymphoma has 82.8 per cent five-year survival, higher than stage I survival in most of the cancers in this chapter. It is essentially stage-independent in its curability, which is almost unique among malignancies and is the reason there is no screening rationale. Median age at diagnosis 38, on a bimodal age distribution with a peak in the twenties and a second after sixty. United States incidence is falling about 1.3 per cent a year and the death rate about 3.1 per cent a year, one of the steeper mortality declines in this chapter. Incidence is higher in high-income countries; the childhood-onset, Epstein-Barr-virus-positive, mixed-cellularity form predominates in low-income settings and in HIV-positive populations, while the young-adult nodular sclerosing form predominates in high-income countries.

Where it starts. Epstein-Barr virus genome is present in the Reed-Sternberg cells in roughly 20 to 50 per cent of classical cases in high-income countries†. The proportion is substantially higher, often above 80 to 90 per cent, in children in low-income countries, in older adults, in the mixed-cellularity subtype and in HIV-positive patients. de Martel and colleagues, 2020, gave case counts for *H. pylori*, human papillomavirus and hepatitis B and C only, so no published Epstein-Barr-attributable case number for Hodgkin lymphoma is quoted here. The commonly cited global estimate is that the virus accounts for roughly a third of cases, which on GLOBOCAN 2024 incidence would be in the region of 25,000 to 30,000 cases annually; that is an inference and is marked as one. Prior infectious mononucleosis carries a relative risk of roughly 2.5 to 4 for virus-positive disease specifically†. HIV infection raises incidence roughly five- to fifteenfold, and unlike most AIDS-associated malignancies its incidence did not fall with antiretroviral therapy and may have risen — a genuine anomaly attributed to the partially restored but abnormal CD4 compartment that Reed-Sternberg cells appear to require. Immunosuppression after organ transplantation raises risk. Family history gives a roughly three- to ninefold increased risk in siblings, with very high concordance in monozygotic twins, indicating a substantial inherited component without an identified high-penetrance gene. Higher socioeconomic status and small family size are associated with the young-adult form, paralleling the delayed-infection pattern described for childhood acute lymphoblastic leukaemia. The Reed-Sternberg cells are a small minority of the tumour mass, which has made sequencing technically difficult, and the measured coding mutation burden is low to moderate against the adult reference of 1.8 per megabase. The defining molecular features are amplification at 9p24.1 causing PD-L1 and PD-L2 overexpression, and loss of major histocompatibility class I and II expression. **That amplification is the key fact for treatment: Hodgkin lymphoma overexpresses the PD-1 ligand constitutively, which is why checkpoint inhibitors produce response rates in relapsed disease of roughly 65 to 85 per cent**† — the highest of any cancer for this drug class, achieved despite a low mutation burden. This directly contradicts the general rule that mutation burden predicts checkpoint response, and it is the cleanest counterexample available. Not known: why a virus carried by more than 90 per cent of adults† causes lymphoma in a vanishingly small fraction; why the age distribution is bimodal; why incidence did not fall with antiretroviral therapy when other AIDS-defining cancers did.

Cure status. Early-stage favourable, stages I to II: CURABLE — five-year relative survival 92.7 per cent for stage I and 95.4 per cent for stage II, with short combined chemotherapy with or without involved-site radiotherapy. Long-term cure rates in trial populations exceed 90 per cent† and most relapses occur within five years, so five-year figures approximate cure here better than in most cancers. Advanced-stage, III to IV: CURABLE in 87.7 per cent at stage III and 82.8 per cent at stage IV (five-year relative survival). **That is a striking curability figure: a widely disseminated malignancy cured in over 80 per cent of patients.** Relapsed after first-line therapy: CURABLE, and roughly half are cured with salvage chemotherapy and autologous stem cell transplantation. Relapsed after transplantation: CONTROLLABLE — brentuximab vedotin and checkpoint inhibitors produce high response rates, 65 to 85 per cent for PD-1 blockade†. Some patients achieve durable remission and allogeneic transplantation can cure; the proportion cured is not given. Essentially no stage of Hodgkin lymphoma is incurable, which is close to unique in this chapter. Early detection barely applies, because it is also reliably curable when caught late: the flat stage gradient, 92.7 to 82.8 per cent, is why there is no screening programme and no rationale for one. Earlier detection would move patients from an 83 per cent cure rate to a 93 per cent cure rate at best, while exposing a young population to the harms of screening. The dominant clinical problem is not cure but the cost of cure. Survivors treated with the regimens of the 1970s to 1990s carry a substantial excess of second cancers.

Breast cancer after chest irradiation in young women runs at relative risks reported in the region of 4 to 7, with a cumulative incidence at thirty years of 20 to 30 per cent in women irradiated before age 30†. Lung cancer, sarcoma, and therapy-related acute myeloid leukaemia and myelodysplasia from alkylators and etoposide follow. So do cardiac disease from mediastinal radiation and anthracyclines, thyroid dysfunction and infertility. The excess mortality from these late effects in long-term survivors has in several cohorts exceeded mortality from the lymphoma itself. That is why the whole field has moved towards de-escalation: smaller radiation fields, lower doses, fewer alkylators, response-adapted therapy, and substitution of brentuximab vedotin or nivolumab for bleomycin and procarbazine. Hodgkin lymphoma is the clearest case in oncology where the research agenda is driven by iatrogenic harm rather than by failure to cure.

Prevention. There is no established means of preventing Hodgkin lymphoma. There is no vaccine against Epstein-Barr virus, candidates being in early trials, no behaviour to change, and the dominant risk factors — virus seropositivity, genetic background, socioeconomic pattern — are not modifiable. Antiretroviral therapy in HIV — CONTESTED for this cancer specifically: it reduces most AIDS-associated malignancies dramatically, and Hodgkin lymphoma incidence did not fall and may have risen. That should be stated plainly rather than assimilated to the general HIV-cancer picture. An Epstein-Barr vaccine, if developed, would be the only plausible primary prevention, and it would also address nasopharyngeal carcinoma, Burkitt lymphoma and a share of gastric cancer; it is a hypothetical rather than an available intervention. There is no screening and no rationale for one. The prevention that does exist and is real is prevention of the late effects of treatment, achieved by giving less treatment. Omitting or reducing radiotherapy where response permits — STRONG: randomised response-adapted trials showed that radiotherapy can be omitted in response-negative early-stage patients with a small loss of progression-free survival and no loss of overall survival, while removing the breast and lung cancer risk entirely. Replacing bleomycin, for pulmonary toxicity, and procarbazine, for leukaemogenesis and infertility, with brentuximab vedotin or nivolumab — MODERATE on the toxicity endpoint. Reducing radiation field size and dose — STRONG. Breast cancer surveillance in women irradiated to the chest before age 30 is recommended from eight years after treatment or age 25, using magnetic resonance imaging with mammography. **This is the one place in this chapter where intensive breast screening of young women is clearly justified**, because the absolute risk is high enough to change the balance that makes population screening of young women inappropriate, and no randomised mortality evidence exists for it: it is recommended on risk grounds. Smoking cessation in survivors — STRONG, because the lung cancer risk from chest radiation and smoking is multiplicative rather than additive.

Treatment. The proportion cured after relapse following transplantation is not given. ABVD chemotherapy — doxorubicin, bleomycin, vinblastine and dacarbazine — has been the standard for decades and is still widely used. **All four drugs are listed and all four are off-patent**, inexpensive generics, and the drug cost of six cycles is in the region of a few hundred to a low thousands of dollars. ABVD cures over 80 per cent of advanced Hodgkin lymphoma using four off-patent Essential Medicines, and with acute promyelocytic leukaemia and childhood acute lymphoblastic leukaemia that is one of the three clearest demonstrations in this chapter that high cure rates do not require expensive drugs. Escalated BEACOPP — bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone — gives a higher cure rate than ABVD in advanced disease at the cost of more toxicity, infertility and secondary leukaemia, and every single drug in it is listed and off-patent. Involved-site radiotherapy makes a curative contribution in early-stage disease, requires a linear accelerator, and is being de-escalated. Brentuximab vedotin is not listed and is on patent, at a United States list price in the region of US$15,000 to 20,000 a cycle and a course cost well above US$100,000†; in relapsed or refractory disease it gives objective response of roughly 75 per cent with complete response of roughly 34 per cent as monotherapy, and added to AVD in frontline advanced disease it improved overall survival in the ECHELON-1 trial. Pembrolizumab is a selected medicine on the list and nivolumab is listed as a therapeutic equivalent to it, for melanoma and for malignant neoplasms of the bronchus and lung; neither is off-patent, and pembrolizumab costs US$1,530.35 per 4 mL (100 mg) unit and US$6,121.41 per four-unit pack at the United States cash price, October 2026, which is about US$53,000 a year at 200 mg every three weeks, against US$150,000 to 200,000 a year at United States list price. Objective response in relapsed or refractory Hodgkin lymphoma is roughly 65 to 85 per cent, the highest for this drug class in any malignancy; pembrolizumab was superior to brentuximab vedotin in relapsed disease in KEYNOTE-204,

and nivolumab with AVD was superior to brentuximab vedotin with AVD in frontline advanced disease in SWOG S1826†. The mechanism is the 9p24.1 amplification, not a high mutation burden. Autologous stem cell transplantation after salvage chemotherapy for first relapse is curative in roughly half, and allogeneic transplantation serves multiply relapsed disease. The salvage regimens are built from ifosfamide, carboplatin, etoposide, cisplatin, cytarabine, dexamethasone and gemcitabine, all listed and all off-patent. Supportive care uses filgrastim, listed and off-patent with biosimilars, antiemetics, mesna with ifosfamide, listed and off-patent, and allopurinol, listed. Fertility preservation — sperm banking, or oocyte or ovarian tissue cryopreservation — should be offered before alkylating or BEACOPP therapy in a disease whose median age is 38 and whose cure rate is over 80 per cent, and the failure to offer it is a recognised and avoidable harm.

Simple means. ABVD is the outstanding fact in this section. Four off-patent Essential Medicines, given intravenously every two weeks for six months, cure over 80 per cent of advanced Hodgkin lymphoma, and the drugs cost a few hundred to a low thousands of dollars in total. No targeted agent, no antibody, no transplant and no radiotherapy is required for the majority of patients. The requirements are intravenous access, a reliable drug supply, an antiemetic, a blood count before each cycle, and a clinician who follows the protocol. In terms of lives saved per dollar of drug, ABVD for Hodgkin lymphoma is among the best interventions in this chapter. Diagnosis requires a lymph node biopsy and histopathology. A node can be excised under local anaesthetic with basic instruments, and the binding constraint is the histopathologist: the Reed-Sternberg cells are morphologically distinctive and a competent pathologist with a microscope and basic immunohistochemistry for CD30 and CD15 can make the diagnosis. **Where there is no pathology service the diagnosis cannot be made, and that is the single most common reason Hodgkin lymphoma goes untreated in low-income settings — not the cost of the drugs.** Prednisone or prednisolone alone, listed, off-patent and cents a day, produces rapid symptomatic improvement and nodal shrinkage, and is useful palliation and a bridge while a diagnosis is established or drugs obtained; it does not cure. Oral morphine serves pain and drainage of a pleural effusion with a needle and a set serves breathlessness. Sperm banking requires only a container and a freezer. Where nothing simple exists: relapsed disease requires autologous transplantation, or brentuximab vedotin, or a checkpoint inhibitor, all expensive and infrastructure-dependent. Because first-line ABVD cures over 80 per cent of all patients regardless of stage using only off-patent listed drugs, the proportion of total achievable benefit reachable by simple means is higher in Hodgkin lymphoma than in almost any other malignancy here. The gap is diagnostic and organisational, not pharmaceutical.

Gaps. A published Epstein-Barr-attributable case count for Hodgkin lymphoma was not retrievable; de Martel and colleagues gave figures for four agents only, and the one-third figure used above is an inference. Virus-positive proportions, the mononucleosis relative risk, the HIV relative risk and the familial relative risk are all literature-derived. Second-cancer and cardiac late-effect figures are literature-derived, and they are central to the management of this disease, so their absence from the retrievable primary sources is a real limitation. Brentuximab vedotin pricing is literature-derived. Why incidence did not fall with antiretroviral therapy is unexplained. Why a low-burden tumour responds to checkpoint blockade better than any high-burden tumour is mechanistically understood and it undermines mutation burden as a general predictive biomarker, and that tension is unresolved.

> **Depth.** Starts in: the Reed-Sternberg cell. Size: 30 µm†; depth +5.91. First complaint: about 39 years († median age 39); time depth 52.21. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

23. Non-Hodgkin lymphoma

What it is. Not one disease but a large family of cancers of lymphocytes, ranging from indolent types that may need no treatment for years to aggressive types that kill within months if untreated. The two commonest are diffuse large B-cell lymphoma, aggressive and curable, and follicular lymphoma, indolent

and not curable. Grouping them under one heading, as the cancer registries do, conceals more than it reveals.

Measured. GLOBOCAN 2022 gives 553,389 cases; GLOBOCAN 2024 gives 562,793 cases and 234,903 deaths. Five-year relative survival in the United States is 74.3 per cent overall, and SEER publishes Ann Arbor stage-specific survival: stage I, 21 per cent of cases, 87.6 per cent; stage II, 15 per cent, 79.7 per cent; stage III, 17 per cent, 74.0 per cent; stage IV, 37 per cent, 63.6 per cent; unknown, 10 per cent, 71.9 per cent. As with Hodgkin lymphoma the stage gradient is shallow compared with the epithelial cancers in this chapter, and the aggregate averages across subtypes with completely different natural histories, so it is of limited use. The subtype figures are the ones that matter, and they come from the general haematology literature: diffuse large B-cell lymphoma, roughly 30 to 35 per cent of cases, cured in roughly 60 to 65 per cent with R-CHOP and fatal within months if untreated; follicular lymphoma, roughly 20 per cent, median overall survival now exceeding 15 to 20 years and not cured, with many patients never needing treatment initially; marginal zone lymphoma, indolent with long survival, and gastric mucosa-associated lymphoid tissue lymphoma curable by *H. pylori* eradication alone; mantle cell lymphoma, historically poor, median survival now 8 to 10 years and not curable by chemotherapy; Burkitt lymphoma, extremely aggressive with a doubling time of about 24 hours, cured in over 85 to 90 per cent of children and roughly 70 to 80 per cent of adults with intensive short-course chemotherapy; peripheral T-cell lymphomas, roughly 10 per cent, markedly worse than the B-cell lymphomas at five-year survival of roughly 30 to 40 per cent; adult T-cell leukaemia-lymphoma, acute type, median survival under a year; and primary central nervous system lymphoma, five-year survival roughly 30 per cent. Median age at diagnosis 68, with Burkitt and lymphoblastic lymphomas childhood diseases and most other subtypes rising with age. United States incidence is 18.7 per 100,000 and the death rate 4.8 per 100,000, with a lifetime risk of about 2.0 per cent and 872,940 people living with the disease in 2023. Incidence is falling about 0.6 per cent a year and the death rate about 2.4 per cent a year, the decline following the introduction of rituximab from 1997. Burkitt lymphoma is endemic in the malaria belt of equatorial Africa, where it is the commonest childhood cancer in several countries; adult T-cell leukaemia-lymphoma clusters where HTLV-1 is endemic, in southern Japan, the Caribbean, parts of West Africa, Iran and Romania; and gastric mucosa-associated lymphoid tissue lymphoma follows *H. pylori* prevalence.

Where it starts. Non-Hodgkin lymphoma has more established infectious causes than any other cancer group in this chapter. *Helicobacter pylori* is classified as a Group 1 carcinogen for gastric mucosa-associated lymphoid tissue lymphoma as well as for gastric carcinoma. The attributable fraction for that lymphoma approaches 90 per cent, and — uniquely in oncology — eradicating the bacterium cures the lymphoma in roughly 60 to 80 per cent of early-stage cases†. Epstein-Barr virus causes Burkitt lymphoma, with the genome present in essentially 100 per cent of endemic African cases and roughly 20 to 30 per cent of sporadic cases†. It also causes post-transplant lymphoproliferative disorder, extranodal natural-killer T-cell lymphoma, a subset of diffuse large B-cell lymphoma in the elderly, and primary central nervous system lymphoma in immunosuppression. *Plasmodium falciparum* malaria is a cofactor for endemic Burkitt lymphoma, acting through chronic B-cell stimulation and immune dysregulation, and IARC classifies holoendemic malaria as a cause of Burkitt lymphoma in conjunction with the virus: the only parasitic co-carcinogen in this chapter apart from schistosomiasis in bladder cancer. WHO records 282 million malaria cases and 610,000 deaths in 2024, with 95 per cent of both in the African Region. HIV raises risk roughly sixty- to a hundredfold for aggressive B-cell lymphomas, and incidence fell substantially with antiretroviral therapy, unlike Hodgkin lymphoma. Hepatitis C virus causes splenic marginal zone lymphoma and a share of diffuse large B-cell lymphoma, and antiviral cure can induce lymphoma regression, which is a second instance of curing a lymphoma by treating its infectious cause; WHO records about 47 million people with chronic hepatitis C infection in its key facts, against regional figures in the body of the same page that sum to 50 million, and both are printed. HTLV-1 causes adult T-cell leukaemia-lymphoma, with a lifetime risk of roughly 2 to 5 per cent in those infected, usually acquired in infancy through breast milk; transmission is interruptible by avoiding prolonged breastfeeding in seropositive mothers, which has reduced incidence in Japan. Human herpesvirus 8 causes primary effusion lymphoma and multicentric Castleman disease. de Martel and colleagues, 2020, gave case counts for four agents, of which *H. pylori* at about 810,000 cases and hepatitis C at about 160,000 both contribute to the non-Hodgkin lymphoma total, and no published infection-attributable case count for non-Hodgkin lymphoma specifically was retrievable. Among the non-infectious causes, immunosuppression — organ

transplantation, congenital immunodeficiency, iatrogenic immunosuppression — is one of the strongest risk amplifiers in oncology. Autoimmune disease follows a consistent and mechanistically coherent pattern: chronic antigenic stimulation at a site, then lymphoma at that site. Sjögren syndrome gives a very large increase in parotid mucosa-associated lymphoid tissue lymphoma, at relative risks reported in the region of 15 to 20†; coeliac disease gives enteropathy-associated T-cell lymphoma; Hashimoto thyroiditis gives thyroid mucosa-associated lymphoid tissue lymphoma; and rheumatoid arthritis and systemic lupus follow. On pesticides the regulators disagree directly and both positions are printed: IARC classified glyphosate as Group 2A, probably carcinogenic to humans, in 2015 with non-Hodgkin lymphoma as the principal endpoint, and the European Food Safety Authority and the United States Environmental Protection Agency concluded it is unlikely to pose a carcinogenic hazard. The broader association of agricultural work with non-Hodgkin lymphoma is consistent and the agents are not identified. Prior chemotherapy and radiotherapy are established. Mutation burden varies enormously across subtypes. Diffuse large B-cell lymphoma carries a moderate burden with recurrent lesions in MYD88, CD79B, EZH2, BCL2, BCL6 and MYC, and the cell-of-origin classification and the double-hit MYC-BCL2 rearrangement are the key prognostic molecular features. Burkitt lymphoma is driven by a single defining event — MYC translocation to an immunoglobulin locus, present in essentially 100 per cent of cases — on a low mutational background. Follicular lymphoma is defined by the BCL2 translocation t(14;18), present in roughly 85 to 90 per cent, and notably that translocation is detectable in the blood of a substantial proportion of healthy adults who never develop lymphoma: a direct parallel to the ETV6-RUNX1 situation in childhood acute lymphoblastic leukaemia, and the same lesson about why a detectable marker is not a screening test. Not known: why chronic antigenic stimulation progresses to lymphoma in a small minority; why most carriers of t(14;18) never develop follicular lymphoma; the cause of the majority of diffuse large B-cell lymphoma; why T-cell lymphomas are so much less treatable than B-cell lymphomas.

Cure status. The answer differs more between subtypes here than anywhere else in this chapter, and a single label would be false. Gastric mucosa-associated lymphoid tissue lymphoma, early stage: **CURABLE by antibiotics alone** — eradication of *H. pylori* with a one- to two-week course of generic amoxicillin, clarithromycin or metronidazole and a proton-pump inhibitor produces complete histological remission in roughly 60 to 80 per cent of early-stage cases, with durable long-term remission†. That is the only malignancy in this entire chapter cured by a few dollars' worth of oral antibiotics, and it is stated first for that reason. Cases with the t(11;18) translocation or deeper invasion respond less well and need radiotherapy or rituximab. Diffuse large B-cell lymphoma: CURABLE — six cycles of R-CHOP cure roughly 60 to 65 per cent of all patients, including advanced-stage disease†, and localized disease is cured in over 90 per cent with abbreviated therapy†; the SEER stage-specific figures run from 87.6 per cent at stage I to 63.6 per cent at stage IV. Untreated it is fatal within months, so the gap between treating and not treating is as wide as in any cancer here. Burkitt lymphoma: CURABLE in over 85 to 90 per cent of children and 70 to 80 per cent of adults with intensive short-course multi-agent chemotherapy; untreated it kills within weeks. In endemic African settings cure rates with lower-intensity regimens have been reported at roughly 50 to 60 per cent†, far below the achievable figure and far above zero, and achieved with off-patent drugs. Follicular lymphoma: CONTROLLABLE — median overall survival now exceeds 15 to 20 years†. Early-stage asymptomatic follicular lymphoma should often not be treated at all; watch and wait is standard, and randomised evidence shows no survival benefit from early treatment. Localized stage I disease is curable in a minority by radiotherapy alone. Marginal zone and other indolent lymphomas: CONTROLLABLE, with the mucosa-associated exception above. Mantle cell lymphoma: CONTROLLABLE — median survival 8 to 10 years†, extended further by BTK inhibitors and cell therapy, and not curable by chemotherapy. Peripheral T-cell lymphomas: CURABLE in roughly 30 to 40 per cent (five-year survival), with most relapsing†; ALK-positive anaplastic large cell lymphoma is the exception, at cure rates above 70 to 80 per cent†. Adult T-cell leukaemia-lymphoma, acute type: RELIEF ONLY — median survival under a year. Primary central nervous system lymphoma: CURABLE in roughly 30 per cent (five-year survival) with high-dose methotrexate-based therapy. Relapsed aggressive B-cell lymphoma: CURABLE in roughly 30 to 40 per cent with salvage chemotherapy and autologous transplantation†. CD19-directed cell therapy cures a further substantial fraction of those who fail transplantation: NCI states that in large B-cell lymphoma trials more than 30 per cent of participants were alive without evidence of cancer five years after treatment, which in a population with otherwise near-universal mortality is a genuine cure fraction. Early detection cuts both ways here: for the aggressive B-cell

lymphomas it matters, and for the indolent ones it confers no benefit and early treatment has no survival advantage. Non-Hodgkin lymphoma therefore contains both patterns simultaneously, which is why there is no screening programme and no coherent rationale for one.

Prevention. *H. pylori* eradication — STRONG, and it prevents gastric mucosa-associated lymphoid tissue lymphoma as well as gastric carcinoma. Effect sizes are as in entry 3: incidence rate ratio 0.53, interval 0.44 to 0.64, for gastric cancer, with a number needed to treat of 124. HIV prevention and antiretroviral therapy — STRONG: incidence in people with HIV fell substantially with effective therapy, unlike Hodgkin lymphoma. WHO records 41.0 million people living with HIV at the end of 2025, with 570,000 HIV-related deaths and 1.2 million new infections in 2025. In the care cascade, 88 per cent knew their status, 89 per cent of those diagnosed were on treatment, and 95 per cent of those on treatment were virally suppressed. Hepatitis C treatment — STRONG: direct-acting antivirals cure more than 95 per cent, and associated marginal zone lymphoma regresses with viral clearance. HTLV-1 transmission interruption — STRONG and simple: avoiding prolonged breastfeeding by seropositive mothers reduces mother-to-child transmission substantially, and Japan's programme of antenatal screening and feeding advice has reduced carrier prevalence in younger cohorts. The trade-off against the benefits of breastfeeding must be weighed, and in settings where formula feeding is unsafe the calculation differs. Malaria control — MODERATE for endemic Burkitt lymphoma: reducing holoendemic transmission should reduce it, and the evidence is ecological rather than interventional, and insecticide-treated nets and antimalarials are simple, cheap and justified on other grounds anyway. Hepatitis B vaccination — MODERATE for the share associated with that virus. Reducing occupational pesticide exposure — CONTESTED, with the IARC and regulatory positions above, unresolved and politically charged. Minimising iatrogenic immunosuppression where possible — MODERATE. There is no screening and no rationale. The t(14;18) translocation is detectable in the blood of a substantial proportion of healthy adults who never develop lymphoma, the same problem as ETV6-RUNX1 in childhood acute lymphoblastic leukaemia: a detectable marker with a very low progression rate makes a useless screening test. **Overdiagnosis is not a quantified concept for non-Hodgkin lymphoma**, and the indolent lymphomas raise a closely related problem: incidental detection of asymptomatic follicular lymphoma on imaging leads to diagnoses in patients who should not be treated, and the benefit of knowing is unclear.

Treatment. *H. pylori* eradication for gastric mucosa-associated lymphoid tissue lymphoma comes first. Amoxicillin, clarithromycin, metronidazole, omeprazole, bismuth and tetracycline are all listed, all off-patent, and a complete course costs a few dollars, at a cure rate of 60 to 80 per cent in early-stage disease†: the cheapest cure for any cancer in this chapter. R-CHOP for diffuse large B-cell lymphoma — rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone — follows. Every component is listed, and rituximab's listed indications include diffuse large B-cell lymphoma, Burkitt lymphoma, chronic lymphocytic leukaemia and follicular lymphoma. Cyclophosphamide, doxorubicin, vincristine and prednisone are all off-patent and inexpensive, and rituximab's originator is off-patent with widely available biosimilars that have reduced its price by roughly 50 to 70 per cent in many markets†. Adding rituximab to CHOP increased cure rates by roughly 10 to 15 percentage points absolute†, one of the largest single advances in lymphoma treatment. A full six-cycle course is achievable at a drug cost in the region of a low thousands of dollars with biosimilar rituximab, and a few hundred dollars for the CHOP component alone. Polatuzumab vedotin with R-CHP superseded R-CHOP on progression-free survival in the POLARIX trial for higher-risk disease; it is not listed and is on patent. The Burkitt lymphoma regimens are built from cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine and rituximab, all listed, and all except rituximab fully off-patent. Tumour lysis prophylaxis with hydration, allopurinol, listed and off-patent, and rasburicase, listed, is essential, because Burkitt lymphoma has the highest tumour lysis risk of any cancer. Bendamustine with rituximab, or chlorambucil, serves indolent lymphoma; bendamustine, chlorambucil and rituximab are all listed, the first two off-patent and the third available as a biosimilar. Watch and wait for asymptomatic indolent lymphoma is free and evidence-based. Radiotherapy is curative for localized indolent lymphoma and for localized gastric disease unresponsive to antibiotics. Ibrutinib and zanubrutinib are both listed for mantle cell lymphoma and other B-cell lymphomas and neither is off-patent, at United States list prices in the region of US$150,000 to 180,000 a year†. Lenalidomide is listed and off-patent in many markets since about 2022, with generic prices a fraction of the originator price, which was in the region of US$200,000 a year and above at United States list†. CD19 CAR T-cell therapy — axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel and

brexucabtagene autoleucel across large B-cell, follicular, mantle cell and chronic lymphocytic disease — is not listed in any product and all are on patent. NCI reports that in follicular lymphoma, axicabtagene ciloleucel eliminated the cancer in nearly 80 per cent of participants in one trial of advanced disease, with many of those patients having no return of disease three years later. In large cell lymphoma, NCI reports that more than 30 per cent of participants were alive without evidence of cancer five years after treatment. A per-treatment price could not be retrieved from the price guide, which states only that pricing varies; United States list prices have been reported in the region of US$400,000 to 500,000 per single infusion, with total episode costs substantially higher once apheresis, lymphodepletion, hospitalisation and management of cytokine release syndrome and neurotoxicity are included. Glofitamab, epcoritamab and mosunetuzumab are not listed and are on patent; they are off-the-shelf rather than patient-specific, which makes them logistically simpler than cell therapy, at response rates in the region of 50 to 60 per cent in relapsed large B-cell lymphoma†. High-dose methotrexate-based therapy serves primary central nervous system lymphoma; methotrexate and calcium folinate are both listed and off-patent, and the requirement is the capacity to give high-dose methotrexate safely with rescue, hydration, alkalinisation and level monitoring. Autologous and allogeneic transplantation follow. Checkpoint inhibitors are largely inactive in most subtypes, in sharp contrast to Hodgkin lymphoma; the exceptions are primary mediastinal B-cell lymphoma and primary central nervous system lymphoma, which share the 9p24.1 amplification.

Simple means. *H. pylori* eradication for gastric mucosa-associated lymphoid tissue lymphoma is the single most remarkable simple-means fact in this chapter: a one-week course of generic oral antibiotics, costing a few dollars, cures 60 to 80 per cent of early-stage cases†. **It is a cancer cured by antibiotics.** It requires only the diagnosis, by endoscopic biopsy, and the drugs. CHOP chemotherapy without rituximab comes second: cyclophosphamide, doxorubicin, vincristine and prednisone are all off-patent listed drugs costing a few hundred dollars for a full six-cycle course, and CHOP alone cures roughly 45 to 50 per cent of diffuse large B-cell lymphoma, with biosimilar rituximab raising that to 60 to 65 per cent at a few thousand dollars†. In a setting where rituximab is unobtainable, CHOP alone is not a token gesture: it cures nearly half of patients with an otherwise rapidly fatal cancer, using four cheap generic drugs. Prednisone or prednisolone alone, listed, off-patent and cents a day, produces rapid nodal shrinkage and symptomatic relief and serves as a bridge or as palliation. Lymph node biopsy under local anaesthetic with basic instruments gives the diagnosis, and the binding constraint is histopathology with basic immunohistochemistry: a competent pathologist can distinguish aggressive from indolent lymphoma and B-cell from T-cell lineage with CD20, CD3 and Ki-67. Without that distinction treatment cannot be rationally chosen, and that is the commonest reason lymphoma is mistreated or untreated in low-resource settings. The drugs are not the problem. Allopurinol with intravenous or oral hydration prevents tumour lysis for cents and is essential in Burkitt lymphoma and bulky aggressive lymphoma, where tumour lysis is a major early cause of death: a very high-yield, very cheap intervention. Insecticide-treated nets and malaria treatment are simple, cheap, justified on other grounds and plausibly reduce endemic Burkitt lymphoma. Avoiding prolonged breastfeeding in HTLV-1-seropositive mothers requires a test and advice and prevents a lymphoma with a median survival under a year. Oral morphine, pleural and ascitic drainage with a needle and a set, and radiotherapy for localized disease where a machine exists complete the list. Where nothing simple exists: relapsed aggressive lymphoma, T-cell lymphomas, mantle cell lymphoma and primary central nervous system lymphoma. Cell therapy at a reported US$400,000 to 500,000 an infusion at United States list, bispecific antibodies requiring continuous monitoring for cytokine release, and autologous transplantation requiring apheresis and a transplant unit are none of them achievable by simple means, and they are where most of the recent progress has occurred. Gastric mucosa-associated lymphoid tissue lymphoma is cured by antibiotics, and CHOP cures nearly half and R-CHOP nearly two-thirds of diffuse large B-cell lymphoma using listed drugs that are off-patent or available as biosimilars. So non-Hodgkin lymphoma, like Hodgkin lymphoma and childhood acute lymphoblastic leukaemia, is a disease where a large fraction of the achievable cure is reachable cheaply. The constraint is diagnostic infrastructure and supportive care, not the price of the cytotoxics.

Gaps. GLOBOCAN and SEER report non-Hodgkin lymphoma as a single category, and the aggregate figures average across subtypes with completely different natural histories, curability and treatment. Every subtype-specific survival figure above is literature-derived, and that is the largest limitation of this entry, and a limitation of the source data rather than of this chapter alone. A published infection-attributable case count for non-Hodgkin lymphoma specifically was not retrievable. IARC and the European and United

States regulators disagree directly on glyphosate and non-Hodgkin lymphoma; both are printed and it is unresolved. The HIV, Sjögren and *H. pylori* attributable figures and the mucosa-associated eradication cure rate are literature-derived. Cell therapy pricing could not be retrieved from a primary source and NCI's page gives no prices. Why most carriers of t(14;18) never develop follicular lymphoma is unknown, the same unanswered question as for ETV6-RUNX1. T-cell lymphomas are under-researched relative to their lethality.

> **Depth.** Starts in: a lymphocyte. Size: 10 µm†; depth +4.91. First complaint: about 67 years († median age 67); time depth 52.70. One untreated course: no number ([B] months to years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

24. Multiple myeloma

What it is. A cancer of plasma cells, the antibody-producing cells of the bone marrow. It causes bone destruction, anaemia, kidney failure and high calcium. It is preceded in essentially every case by a symptomless precursor state that is common in older people. Survival has roughly tripled in twenty-five years and it is still not curable.

Measured. GLOBOCAN 2022 gives 187,952 cases; GLOBOCAN 2024 gives 196,157 cases and 119,029 deaths. Five-year relative survival in the United States is 63.7 per cent. SEER publishes no stage-specific table in the localized-regional-distant scheme; the staging systems are the Revised International Staging System and its successor, based on beta-2 microglobulin, albumin, lactate dehydrogenase and cytogenetics. The stage figures are from the myeloma literature: stage I, median overall survival not reached at five years in the defining analysis, so roughly 80 per cent or above five-year survival; stage III, with high lactate dehydrogenase and high-risk cytogenetics such as deletion of 17p or the t(4;14) or t(14;16) translocations, median overall survival roughly three to four years. Median age at diagnosis 69, and it is rare under 40. United States incidence is stable and the death rate falling about 3.0 per cent a year, one of the steepest mortality declines of any cancer in this chapter; modelled five-year relative survival was roughly 25 per cent in the mid-1970s and is 63.7 per cent now. Incidence is roughly two to three times higher in people of African ancestry than in people of European ancestry, one of the largest and most consistent ancestry differences in oncology, with the precursor state correspondingly commoner, and the difference is not explained by access or detection and appears to be constitutional. Monoclonal gammopathy of undetermined significance, the obligate precursor, is present in roughly 3 per cent of people over 50 and over 5 per cent of those over 70 in population screening studies, rising with age and roughly two to three times commoner in people of African ancestry. It progresses to myeloma or a related malignancy at roughly 1 per cent a year, and the risk does not diminish over time†. Smouldering myeloma, the intermediate state, progresses at roughly 10 per cent a year for the first five years†. Those figures bear directly on the screening question.

Where it starts. The precursor state precedes essentially every case. Stored-serum studies have shown a detectable monoclonal protein years to decades before diagnosis in virtually all patients. **Myeloma is therefore, uniquely among the cancers in this chapter, a malignancy with a known, universal, detectable and extremely common precursor state.** Age dominates, with incidence rising steeply after 60. African ancestry gives roughly two- to threefold increased incidence and precursor prevalence, persisting across settings. Male sex gives roughly 1.5-fold†. Family history gives roughly two- to fourfold increased risk in first-degree relatives, with no high-penetrance gene identified. Obesity shows a consistent association at relative risks in the region of 1.2 to 1.5 for a body mass index of 30 or more†, and it is one of the few modifiable risk factors identified. Ionising radiation is established at high doses from the atomic bomb survivor cohorts, with a weaker and debated relationship at occupational doses. Pesticides, benzene and firefighting have all been associated, and IARC classified occupational exposure as a firefighter as Group 1 in 2022, with mesothelioma and bladder cancer as the strongest endpoints and myeloma among those evaluated; the agents are not identified. Chronic inflammation and chronic infection have been proposed as drivers of the antigenic stimulation that precedes clonal plasma cell expansion, on associative

evidence. Myeloma has a moderate point-mutation burden, around or somewhat above the adult reference of 1.8 per megabase. It is characterised by primary immunoglobulin heavy chain translocations — t(11;14), t(4;14), t(14;16) — or hyperdiploidy, with secondary events in KRAS, NRAS, BRAF, TP53 and TRAF3, and MYC rearrangements. It is strikingly subclonal and genomically unstable: multiple competing clones coexist at diagnosis and the dominant clone changes under treatment, which is the accepted explanation for why the disease is so reliably controllable and so reliably incurable — there is always another clone. Deletion of 17p and the t(4;14) translocation define high-risk disease. Not known: **why the precursor progresses in roughly 1 per cent of carriers a year and not in the other 99 per cent** — the single most consequential unanswered question in this disease; why myeloma is so much commoner in people of African ancestry; whether the precursor is preventable from progressing; what causes the initiating translocation.

Cure status. Monoclonal gammopathy of undetermined significance: no treatment is indicated and treating it is harmful. Observation only. It is a risk state rather than a disease: roughly 1 per cent of carriers a year progress to myeloma or a related malignancy, so none of the four labels applies to it and none is assigned. Smouldering myeloma: observation is standard for most, and high-risk smouldering myeloma is now treated — randomised trials of lenalidomide, and of daratumumab, in high-risk smouldering disease showed delayed progression and, in one trial, a survival benefit. That is a genuine and recent change: for the first time a precursor state in myeloma is being treated, and whether this prevents myeloma or merely treats it early is not settled. Symptomatic multiple myeloma: CONTROLLABLE — five-year relative survival 63.7 per cent, with median overall survival in contemporary series exceeding seven to ten years for standard-risk patients and continuing to improve. A small fraction of patients achieving sustained absence of minimal residual disease for many years may be functionally cured, and no plateau has been convincingly demonstrated in the survival curves, and the consensus is that myeloma is not curable. High-risk myeloma, stage III or deletion of 17p: CONTROLLABLE — median survival roughly three to four years†. Plasma cell leukaemia and extramedullary relapse: RELIEF ONLY — median survival under a year. Penta-refractory myeloma, refractory to a proteasome inhibitor, an immunomodulator and an anti-CD38 antibody, in the substantial minority who respond to a cell or bispecific agent: CONTROLLABLE. Penta-refractory myeloma otherwise: RELIEF ONLY, which was the answer for the whole stratum until those agents arrived. Ciltacabtagene autoleucel produced objective responses above 95 per cent with complete response in roughly 80 per cent in heavily pre-treated myeloma†, among the highest response rates for any agent in any cancer in this chapter, and a proportion remain progression-free for years, and it is still not considered curative. Solitary plasmacytoma: CONTROLLABLE. Radiotherapy cures some, though a majority eventually progress to myeloma. Early detection does not deliver cure, and that is important and counterintuitive: myeloma has a universal, common, cheaply detectable precursor, and detecting it does not produce cure, because the disease is incurable at every stage, so moving diagnosis earlier moves treatment earlier without curing anyone. **Myeloma is the clearest demonstration in this chapter that a detectable precursor plus a sensitive test does not equal a useful screening programme.**

Prevention. There is no established means of preventing multiple myeloma. Age, sex, ancestry and family history are not modifiable. Weight control — WEAK, on a consistent association and no interventional evidence. Occupational exposure control — CONTESTED, the agents not being identified. Treating high-risk smouldering myeloma — MODERATE and genuinely new: lenalidomide, listed and off-patent in many markets, delayed progression to symptomatic disease and improved survival in one randomised trial. Whether that is prevention or early treatment is unresolved, and the distinction matters, because the drug carries toxicity, cost and second-cancer risk and the patients are asymptomatic. Screening is not recommended, and myeloma is one of the most instructive cases in this chapter for why. The precursor is detectable with a cheap serum protein electrophoresis and is present in roughly 3 per cent of people over 50 and over 5 per cent over 70, progressing at only about 1 per cent a year; there is no treatment for it and no evidence that treating it helps; and the Iceland iStopMM study screened over 75,000 people prospectively, whose principal finding so far is a very large prevalence of previously unknown precursor states with no established actionable consequence for the great majority. A population programme would therefore label millions of older adults with a pre-malignant haematological condition, offer them nothing, and generate lifelong surveillance. **The overdiagnosis fraction would approach the full precursor prevalence, and it has never been quantified as a percentage.** That is structurally identical to the monoclonal B-cell

lymphocytosis situation in entry 21, and both are the clearest counterexamples in this chapter to the assumption that finding cancer precursors earlier is beneficial.

Treatment. Radiotherapy cures some solitary plasmacytomas, and the proportion is not given. Bortezomib is listed and off-patent, with generics available at a small fraction of the originator price, which was in the region of US$5,000 to 8,000 a cycle at United States list†. Carfilzomib and ixazomib are not listed and are on patent. Thalidomide is listed, off-patent and extremely cheap, and its history is worth recording: withdrawn worldwide in 1961 after causing severe birth defects, found in 1999 to be active in refractory myeloma, and now an inexpensive off-patent Essential Medicine that transformed the disease. In settings without access to lenalidomide or bortezomib, thalidomide with dexamethasone and melphalan or cyclophosphamide is an effective, entirely off-patent regimen. Lenalidomide is listed and off-patent in many markets since about 2022, against an originator price in the region of US$200,000 a year and above at United States list†; pomalidomide is on patent and not listed. Melphalan, cyclophosphamide, dexamethasone and prednisolone are all listed and all off-patent and inexpensive, and dexamethasone's listed antineoplastic indications include multiple myeloma. Melphalan with prednisone was the standard of care from 1962 to the 2000s and produced median survival of roughly two to three years†, and it remains a legitimate option where nothing else is available. **Daratumumab is a listed medicine, for plasma cell myeloma**, and it too is frequently reported as absent. It is on patent, and isatuximab is not listed. Daratumumab added to standard regimens improved survival in every setting tested and is now part of first-line therapy in high-income countries, at a United States list cost in the region of US$120,000 to 150,000 a year†. Autologous stem cell transplantation after induction improves progression-free survival in fit patients and requires apheresis, high-dose melphalan — listed and off-patent — and an inpatient unit: the conditioning drug is a cheap off-patent listed medicine and the cost is entirely in the infrastructure. **Zoledronic acid is listed, in the supportive medicines section, for malignant neoplasm metastasis in bone or bone marrow and for osteogenesis imperfecta**; it is off-patent and costs a few dollars a generic infusion. It reduces skeletal events substantially and, in the MRC Myeloma IX trial, improved overall survival by a median of roughly five to six months compared with clodronate — a survival benefit from a cheap off-patent bone drug. Denosumab is not listed and is on patent. Idecabtagene vicleucel and ciltacabtagene autoleucel are both approved for myeloma, neither is listed and both are on patent; ciltacabtagene autoleucel produced objective response above 95 per cent with complete response around 80 per cent in heavily pre-treated myeloma and idecabtagene vicleucel roughly 70 to 75 per cent†, at reported United States list prices of US$465,000 to 525,000 per single infusion. Teclistamab, elranatamab and talquetamab are not listed and are on patent, off-the-shelf, at response rates roughly 60 to 75 per cent†. Selinexor, belantamab mafodotin and venetoclax — the last for t(11;14) disease — are none of them listed, and venetoclax is confirmed absent from the list in any form. Radiotherapy for painful bone lesions and for cord compression is highly effective and often needs only a single fraction. Supportive care covers erythropoiesis-stimulating agents for anaemia, which are listed with epoetin forms as therapeutic equivalents rather than as selected medicines, plasmapheresis for hyperviscosity, dialysis for renal failure, and prompt treatment of hypercalcaemia with hydration and of infection. Infection is the commonest cause of death, because of the profound secondary antibody deficiency, and prophylactic co-trimoxazole, aciclovir and vaccination are cheap and effective.

Simple means. Thalidomide with dexamethasone, with or without melphalan or cyclophosphamide, is all listed, all off-patent, all oral or simple, at a total drug cost in the region of tens of dollars a month. That is an effective myeloma regimen deliverable in a clinic with no infusion suite and no cold chain. It is not equivalent to daratumumab-based therapy, and it produces real responses, relieves bone pain and anaemia, and extends life by years in responders. Thalidomide requires strict pregnancy prevention, which is a real and non-negotiable requirement, and it is organisational rather than technological. Dexamethasone alone is listed, off-patent and cents a dose, at an indicative 24 cents a 4 mg tablet in the UNICEF Supply Catalogue, October 2026. High-dose dexamethasone produces rapid response in a substantial proportion of patients, relieves bone pain, reverses hypercalcaemia and can reverse spinal cord compression within hours while awaiting radiotherapy: in an emergency it is the most valuable single drug in this entry. Zoledronic acid is listed and off-patent at a few dollars an infusion every few weeks, reduces fractures and vertebral collapse, and improved overall survival by roughly five to six months in a randomised trial: a cheap generic bone drug with a measured survival benefit is an unusual and valuable thing. Hydration, oral or intravenous, treats hypercalcaemia and the cast nephropathy that causes myeloma kidney failure; early aggressive

hydration prevents renal failure, and renal failure at presentation is a major determinant of survival. It costs almost nothing and it is frequently done too late. Allopurinol for urate, and co-trimoxazole and aciclovir for infection prophylaxis, are all listed and cost cents, with vaccination. Oral morphine is essential, and myeloma bone pain is among the most severe in oncology; single-fraction palliative radiotherapy serves a painful lesion where a machine exists. A spinal brace and crutches prevent falls and vertebral collapse and require no technology, and surgical fixation of a long bone at risk of pathological fracture is a conventional orthopaedic operation. Diagnosis is possible by serum protein electrophoresis, a blood count, calcium, creatinine and a plain skeletal survey — cheap, widely available tests. Myeloma is one of the more diagnosable cancers by simple laboratory means, because the combination of anaemia, renal impairment, hypercalcaemia, bone pain and a monoclonal band is distinctive, and a bone marrow aspirate confirms it and requires a needle. The drugs that have produced most of the recent survival gain — daratumumab, carfilzomib, pomalidomide, the cell and bispecific products — are all on patent, mostly absent from the list, and cost from hundreds of thousands of US dollars a year to hundreds of thousands of US dollars an infusion, so there is a real and widening gap. Myeloma is nonetheless better served by simple means than that comparison suggests: thalidomide, melphalan, cyclophosphamide, dexamethasone, bortezomib, lenalidomide and zoledronic acid are all off-patent Essential Medicines, and a regimen built from them delivers a substantial fraction of the achievable benefit at a cost of tens of dollars a month. What cannot be replicated simply is the incremental gain of the last decade.

Gaps. SEER publishes no staging-system-stratified survival for myeloma, so the stage-specific figures are literature-derived. Precursor prevalence and progression rates are literature-derived and central to the screening argument. Why the precursor progresses in 1 per cent a year and not the rest is unknown, and it is the key question. The two- to threefold higher incidence in people of African ancestry is unexplained. The obesity relative risk is not primary-source-verified. Cell therapy pricing is literature-derived. Whether treating high-risk smouldering myeloma is prevention or early treatment is unresolved, and it determines whether the toxicity and cost are justified in asymptomatic people.

> **Depth.** Starts in: a plasma cell (MGUS). Size: 15 µm†; depth +5.28. First complaint: about 10 years ([B] years to decades after MGUS); time depth 50.97. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The clone is spread through the marrow. It cannot be cut out. So it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

25. Head and neck cancer

What it is. Cancers of the mouth, throat and voice box — lip, oral cavity, oropharynx, hypopharynx, larynx and salivary gland — almost all squamous cell carcinomas. They have two quite different causes: tobacco and alcohol, which cause the traditional disease in older people, and human papillomavirus, which causes a rising epidemic of oropharyngeal cancer in younger people with a far better prognosis. They are disfiguring and they damage speaking, swallowing and breathing.

Measured. GLOBOCAN 2022, with GLOBOCAN 2024 in brackets: lip and oral cavity 389,846 cases [452,205 cases and 194,108 deaths]; larynx 189,191 [193,937 and 96,619]; oropharynx 106,400 [107,887 and 51,823]; hypopharynx 86,257 [91,464 and 49,748]; salivary glands 55,083 [55,229 and 20,707]. Nasopharynx is reported separately and has its own entry. Combined excluding nasopharynx, that is roughly 826,800 cases in 2022 and roughly 900,700 in 2024, with roughly 413,000 deaths in 2024, which makes head and neck cancer collectively the sixth or seventh commonest cancer group in the world, larger than cervical cancer. WHO’s oral health fact sheet gives 389,846 new lip and oral cavity cases and 188,438 deaths for 2022, and records lip, oral cavity and oropharynx combined as the thirteenth most common cancer worldwide, with most cases in men. Five-year relative survival for oral cavity and pharynx combined in the United States is 69.9 per cent overall: localized 88.7, regional 69.7, distant 36.0, unknown 62.3 per cent. Stage at diagnosis: localized 26, regional 55, distant 12, unknown 6 per cent, and the very high regional proportion reflects early nodal spread, which is characteristic. Median age 65, with virus-associated oropharyngeal cancer presenting roughly a decade younger. United States incidence is rising

about 1.0 per cent a year and the death rate about 0.8 per cent a year: one of very few cancers in this chapter with both rising, and the explanation is the virus-associated oropharyngeal epidemic outpacing the decline in tobacco-related disease. The Indian subcontinent carries the world's largest burden of oral cavity cancer, where it is among the commonest cancers in men, driven by betel quid and smokeless tobacco; laryngeal and hypopharyngeal rates are highest in Eastern Europe and parts of South America, tracking tobacco and alcohol.

Where it starts. Current smokers against never-smokers carry about four to five times the risk for oral cavity, oropharyngeal and hypopharyngeal cancers and about ten times for laryngeal cancer, dose-relatedly. Two or more drinks a day against non-drinkers gives about two to six times the risk, dose-relatedly. The interaction is supra-multiplicative, about two to three times greater than the simple multiplicative effect, so heavy smoking with heavy drinking gives roughly five to fourteen times the risk of never-smoking, never-drinking; a pooled analysis of seventeen case-control studies comparing more than a pack a day with three or more drinks a day against neither reported fifteenfold for oral cavity, fourteenfold for oropharyngeal and **thirty-sixfold for laryngeal cancer**, among the largest relative risks for any exposure-cancer pair in this chapter. WHO records about 1.2 billion tobacco users worldwide, with around 80 per cent in low- and middle-income countries, more than 7 million deaths a year from tobacco and over 1.6 million from second-hand smoke, and tobacco as a cause of over twenty types or subtypes of cancer. On alcohol, WHO attributes 4.4 per cent of cancers diagnosed and 401,000 cancer deaths in 2019 to alcohol, within 2.6 million alcohol-attributable deaths overall. Oral infection with human papillomavirus type 16 is associated with about a fifteenfold increase in oropharyngeal cancer risk, with a meta-analysis giving odds ratios of 15.1 for tonsil cancer and 4.3 for other oropharyngeal sites. PDQ gives no population attributable fraction, and that fraction is the key number and is site- and country-specific: the virus accounts for roughly 70 per cent of oropharyngeal cancers in the United States and Northern Europe and a much lower proportion in India and Southern Europe, where tobacco dominates. For the global total, de Martel and colleagues, 2020, attributed about 690,000 cancer cases worldwide in 2018 to human papillomavirus, of which the great majority are cervical and the remainder oropharyngeal, anal, vulvar, vaginal and penile. Betel quid with tobacco gives about eightfold risk for oral cavity cancer on the Indian subcontinent and betel quid alone about twofold; for oropharynx, about fourfold with tobacco and about twofold alone; oral cavity risk in China or Taiwan is about tenfold. PDQ states that smokeless tobacco increases risk and gives no separate relative risk. Tobacco cessation gives about 50 per cent risk reduction for oral, oropharyngeal and hypopharyngeal cancers within five to nine years and about 40 per cent for laryngeal cancer, with risk returning to near never-smoker levels by twenty years. Alcohol cessation carries inadequate evidence: risk reduction for oral cavity and laryngeal cancer twenty years or more after cessation gives odds ratios of 0.45 and 0.69 respectively, with no support for an oropharyngeal or hypopharyngeal reduction. That asymmetry — strong evidence that alcohol causes the cancer, inadequate evidence that stopping reduces the risk — is stated as PDQ states it. Poor oral hygiene and chronic dental trauma, immunosuppression, Fanconi anaemia, occupational wood dust and formaldehyde, prior radiotherapy and Plummer-Vinson syndrome are the other established factors. Tobacco- and alcohol-associated disease carries a high mutation burden with a tobacco signature, near-universal TP53 mutation and frequent CDKN2A loss and FAT1, NOTCH1 and PIK3CA alterations. Virus-associated oropharyngeal carcinoma has a markedly lower burden, wild-type TP53 — because the viral E6 protein degrades the p53 protein instead of the gene being mutated — and a far better prognosis. The two diseases share a name and a site and almost nothing else, against an adult reference of 1.8 mutations per megabase. Not known: why only a small minority of people with oral infection develop cancer; why virus-positive disease responds so much better to treatment, where immune recognition, wild-type p53 and absence of field change are all proposed and none is established as the principal mechanism; the cause of the rising virus-positive incidence in cohorts born after about 1950.

Cure status. Pre-malignant lesions — leukoplakia, erythroplakia, oral submucous fibrosis: CURABLE by excision, though field change means new lesions frequently arise. Erythroplakia and non-homogeneous leukoplakia carry substantial malignant transformation risk and homogeneous leukoplakia much less. Localized, stage I to II: CURABLE — five-year relative survival 88.7 per cent, by surgery or radiotherapy alone, either curative, with the choice driven by functional outcome. Regional, stage III to IVB, the majority at 55 per cent of cases: CURABLE in 69.7 per cent (five-year relative survival), by surgery with adjuvant chemoradiotherapy or by definitive chemoradiotherapy with cisplatin. Virus-positive oropharyngeal carcinoma: CURABLE in roughly 80 to 90 per cent of non-smokers (five-year survival),

markedly better than virus-negative disease at the same stage, at roughly 45 to 55 per cent†. The staging system was rewritten in 2017 to give virus-positive oropharyngeal cancer its own staging, because the old system misclassified these patients as having advanced disease when their outcome was excellent. De-escalation trials are active, and several attempts to replace cisplatin with cetuximab failed and reduced survival, which is an important negative result. Distant, stage IVC: RELIEF ONLY — 36.0 per cent. Distant with a durable checkpoint-inhibitor response, a minority: CONTROLLABLE. Recurrent disease after chemoradiotherapy: CONTROLLABLE. Salvage surgery cures some, and is technically difficult in irradiated tissue. Early detection is most achievable by simple means here of anywhere in the chapter, because the mouth can be looked at, so the 26 per cent localized rate is a failure of examination and presentation rather than of technology. One honest note on the meaning of cure here is necessary: cure in head and neck cancer frequently costs the ability to speak, swallow or eat normally. Total laryngectomy cures laryngeal cancer and removes the voice. Chemoradiotherapy preserves the organ and frequently destroys its function — xerostomia, fibrosis, dysphagia and aspiration are common and permanent. The survival statistics do not capture this, and for this cancer group more than any other in the chapter the quality of the cure is as important as its probability.

Prevention. Tobacco cessation — STRONG: about 50 per cent risk reduction for oral, oropharyngeal and hypopharyngeal cancer within five to nine years, about 40 per cent for larynx, returning to near never-smoker levels by twenty years. This is the highest-yield intervention and it requires no technology. WHO records that over 60 per cent of smokers intend to quit and that counselling and medication can more than double quit success, with cessation services offering full or partial cost coverage in 31 countries. Never starting tobacco or betel quid — STRONG. Alcohol reduction — STRONG for never starting, CONTESTED for cessation, with both positions printed as PDQ states them. Betel quid and smokeless tobacco cessation — STRONG on the causal evidence; oral submucous fibrosis, caused by areca nut, is a pre-malignant condition affecting millions in South Asia and is itself a major source of morbidity. Human papillomavirus vaccination — MODERATE on mechanism and surrogate endpoint, and the cancer endpoint is unproven, and that must be stated honestly. PDQ records that vaccination against types 16 and 18 prevents about 90 per cent of oral type 16 and 18 infections within four years, and that no studies show reduced oropharyngeal cancer risk, rating the evidence for the cancer endpoint as no studies available. The reasoning for expecting benefit is strong: type 16 causes the cancer at an odds ratio of 15.1 for tonsil, the vaccine prevents oral infection by about 90 per cent, and the cervical cancer endpoint has now been demonstrated. But oropharyngeal cancer has a latency of decades and the vaccinated cohorts are not yet old enough. This is a genuine limitation and it is frequently overstated in public discussion. A further honest point: in most countries vaccination was introduced for girls only, and oropharyngeal cancer predominantly affects men, roughly three to four to one, so gender-neutral vaccination, now adopted in many countries, is the policy change that bears on this cancer, and it came late. Treating oral pre-malignant lesions — MODERATE: excision of erythroplakia and dysplastic leukoplakia, with no randomised evidence that it reduces cancer incidence and field change limiting it. Screening — CONTESTED, with one important positive trial. There is no routine population programme in high-income countries, and the USPSTF found insufficient evidence, grade I, for oral cancer screening by primary care clinicians. Against that, the Kerala cluster-randomised trial of oral visual inspection by trained health workers in tobacco and alcohol users reported a reduction in oral cancer mortality in that high-risk subgroup over long follow-up: the single positive randomised trial of oral cancer screening, conducted in a very high-incidence population using visual inspection alone. The specific hazard ratios could not be retrieved and are not quoted. The result supports targeted visual screening in high-risk, high-incidence populations and does not support general population screening. The harms are biopsy of benign lesions and **overdiagnosis of leukoplakia that would never have transformed, for which no percentage has been published.** Dental care and oral hygiene — WEAK.

Treatment. Salvage surgery cures some recurrences after chemoradiotherapy, and the proportion is not given. For localized oral cavity cancer, wide local excision with neck dissection is curative and is the primary treatment; free-flap reconstruction improves function enormously and requires microsurgical capability, and a simpler reconstruction or primary closure is adequate for smaller defects. Radiotherapy is curative alone for early laryngeal cancer: for T1 glottic cancer it cures over 90 per cent and preserves the voice, which is a better functional outcome than surgery, and it requires a linear accelerator. Concurrent chemoradiotherapy with cisplatin follows. **Cisplatin is a listed medicine, with head and neck cancer as a**

radiosensitiser among its listed indications, off-patent, at a trivial generic cost of tens of dollars a course: the standard radiosensitiser and the single most important drug in curative head and neck cancer treatment. Carboplatin, listed and off-patent, serves where renal function or hearing precludes cisplatin. Attempts to substitute cetuximab for cisplatin in virus-positive disease reduced survival in the De-ESCALaTE and RTOG 1016 randomised trials†, an important negative result, because cetuximab is better tolerated and the substitution was expected to work. Induction chemotherapy for larynx preservation uses docetaxel, cisplatin and fluorouracil, all three listed and off-patent. Cetuximab is not listed; biosimilars are emerging, and it adds a survival benefit to radiotherapy in patients unfit for cisplatin and is inferior to cisplatin where cisplatin can be given. Pembrolizumab is a selected medicine on the list, for other listed indications. Nivolumab's listing for this cancer needs checking against the 24th List (2025)†. Neither is off-patent, and pembrolizumab costs US$1,530.35 per 4 mL unit and US$6,121.41 per four-unit pack at the United States cash price, October 2026, and US$150,000 to 200,000 a year at United States list. In recurrent or metastatic head and neck squamous carcinoma pembrolizumab monotherapy produces objective responses in roughly 17 to 19 per cent overall, higher in PD-L1-high tumours, with a durable tail, and added to platinum-fluorouracil chemotherapy it improved overall survival in the first-line setting in KEYNOTE-048; nivolumab improved survival over chemotherapy in platinum-refractory disease in CheckMate 141 at an objective response of roughly 13 per cent. Those are modest response rates with a meaningful survival gain in a minority, the characteristic pattern. Palliative radiotherapy serves pain and bleeding. Supportive and functional care — percutaneous or surgical gastrostomy for nutrition during and after chemoradiotherapy, tracheostomy for airway obstruction, speech and swallowing rehabilitation, dental assessment and extraction before radiotherapy to prevent osteoradionecrosis, and saliva substitutes and fluoride for xerostomia — are not optional adjuncts: without them, curative treatment is not survivable or not tolerable.

Simple means. Head and neck cancer has one of the strongest simple-means profiles for early detection in this chapter and one of the weakest for treatment of advanced disease. Looking in the mouth comes first. The oral cavity is directly visible with a torch and a tongue depressor, and oral cancer and its pre-malignant lesions — leukoplakia, erythroplakia, submucous fibrosis, a non-healing ulcer — can be seen and felt by any trained health worker in under a minute, with no equipment. The Kerala cluster-randomised trial showed that visual inspection by trained non-specialist health workers reduced oral cancer mortality in tobacco and alcohol users. **In a population where oral cancer is common, this is the cheapest effective cancer screening that exists — cheaper even than visual inspection with acetic acid for the cervix, because it needs no speculum and no vinegar.** Against that, 26 per cent of United States cases are localized at diagnosis, which means that in a country with abundant medical resources the majority of a visible cancer is being found late. The barrier is not technology. Tobacco, betel quid and alcohol cessation need no technology, at a 40 to 50 per cent risk reduction within a decade for tobacco. Excision of a small oral lesion, or wide local excision of a small tongue or buccal cancer, under local or general anaesthesia with basic instruments, is curative at a five-year survival near 89 per cent. Primary closure or a simple local flap avoids the need for microsurgery. Tracheostomy is a basic operation that prevents death by asphyxiation from an obstructing laryngeal or hypopharyngeal tumour, and it is the single most immediately life-saving simple procedure in this entry. A feeding gastrostomy or a nasogastric tube allows nutrition when swallowing fails, and malnutrition is a major cause of death here and is preventable with a tube. Oral morphine matters, with the same caveat as in entry 9: head and neck cancer pain is severe and has a neuropathic component, and a patient who cannot swallow needs sublingual, rectal or subcutaneous morphine, and the rectal route requires no equipment. Mouth care, saline rinses and simple analgesia serve radiation mucositis, and dental extraction before radiotherapy prevents osteoradionecrosis and requires only a dentist and forceps. Where nothing simple exists: curative treatment of locally advanced disease requires chemoradiotherapy with a linear accelerator and cisplatin, or major resection with reconstruction. The cisplatin is cheap and listed; the linear accelerator is not, and radiotherapy is unavailable to a large fraction of the world's head and neck cancer patients, which matters disproportionately here, because radiotherapy alone cures over 90 per cent of early glottic cancer and preserves the voice. Free-flap reconstruction, speech rehabilitation and the full supportive-care package that makes cure tolerable have no simple-means version. And for metastatic disease the checkpoint inhibitors cost over US$150,000 a year at United States list, for a 13 to 19 per cent response rate.

Gaps. GLOBOCAN reports six separate head and neck sites and this entry aggregates them; the component sites differ in cause, treatment and prognosis, so the combined figures are of limited use, and SEER's oral

cavity and pharynx grouping is a different aggregation again, not directly comparable. PDQ gives no population attributable fraction for human papillomavirus in oropharyngeal cancer, so the 70 per cent figure is literature-derived. The Kerala trial hazard ratios could not be retrieved, so the single positive randomised trial of oral cancer screening is cited qualitatively only. PDQ rates the evidence that vaccination prevents oropharyngeal cancer as no studies available, so the benefit is inferred from surrogate endpoints and is genuinely unproven. PDQ finds the evidence that alcohol cessation reduces risk inadequate while the evidence that alcohol causes the cancer is solid, and that asymmetry is real. Virus-positive against virus-negative survival figures are literature-derived. Overdiagnosis of oral pre-malignant lesions is unquantified. Functional outcome after cure — voice, swallowing, eating — is not captured in any of the survival statistics quoted and no comparable quantitative source for it was retrieved, which for this cancer group is a substantial omission.

> **Depth.** Starts in: a squamous epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 30 years († about 30 years after starting to smoke); time depth 51.97. One untreated course: about 12 months († about 1 year); depth 48.87.
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

26. Nasopharyngeal carcinoma

What it is. Cancer arising at the very top of the throat, behind the nose. It is rare across most of the world and common in southern China, Southeast Asia and parts of North Africa and the Arctic — one of the most sharply geographically restricted cancers known. It is caused by Epstein-Barr virus in combination with inherited susceptibility and diet, and unlike the other head and neck cancers it is treated with radiotherapy rather than surgery.

Measured. GLOBOCAN 2022 gives 120,434 cases; GLOBOCAN 2024 gives 119,750 cases and 62,060 deaths. SEER publishes no separate page for nasopharyngeal carcinoma; it is folded into oral cavity and pharynx, at a five-year relative survival of 69.9 per cent overall, localized 88.7, regional 69.7 and distant 36.0 per cent. Nasopharynx-specific survival therefore comes from the clinical literature: stage I to II roughly 90 per cent; stage III roughly 75 to 80 per cent; stage IVA roughly 65 to 70 per cent; metastatic stage IVB median survival roughly two to three years with chemotherapy, markedly better than for other metastatic head and neck cancers; and overall five-year survival in endemic centres with modern intensity-modulated radiotherapy exceeding 80 per cent. The age distribution is unusual: incidence rises from adolescence, peaks around age 50 to 59 and then falls, unlike most epithelial cancers which rise monotonically with age, with a secondary juvenile peak in some endemic populations and a male-to-female ratio of roughly two to three to one. Geography is the defining feature and the gradient is extreme. Age-standardised incidence in southern China — particularly Guangdong province and among Cantonese-speaking populations — reaches roughly 20 to 30 per 100,000 in men, against under 1 per 100,000 in most of Europe and North America: a thirtyfold or greater gradient. Intermediate rates occur in Southeast Asia, among Inuit populations of Greenland and Alaska, and in North Africa, where there is a distinct juvenile peak. Incidence has been falling substantially in endemic southern China over recent decades, with reductions of roughly 30 to 40 per cent in age-standardised rates reported, attributed to reduced consumption of salt-preserved fish, improved living conditions and reduced smoking: one of the clearest examples in this chapter of a cancer declining because an exposure declined, with no medical intervention. Migrant studies are informative: incidence falls in Chinese populations who migrate to low-incidence countries and remains above the host population rate for generations, which indicates both a genetic and an environmental component and allows neither to be dismissed.

Where it starts. The attributable fraction for undifferentiated nasopharyngeal carcinoma, the form that predominates in endemic regions, is essentially 100 per cent. Epstein-Barr virus DNA and virus-encoded RNA are present in the tumour cells in virtually every case, and clonal viral episomes are present in the pre-invasive lesions, which establishes that infection precedes transformation. **That is the most complete viral attribution of any cancer in this chapter — more complete than human papillomavirus in cervical**

cancer, at about 95 per cent, and far more complete than *H. pylori* in gastric cancer. The keratinising squamous form, which predominates in low-incidence Western populations, is less consistently virus-associated and is more tobacco- and alcohol-related. de Martel and colleagues, 2020, gave figures for four agents not including this virus, so no published attributable case count is quoted here; on the near-100 per cent attribution for the endemic form and GLOBOCAN 2024 incidence of 119,750, the implied figure is in the region of 100,000 cases annually, and that is an inference. The crucial point is this: the virus infects more than 90 per cent of adults worldwide† and nasopharyngeal carcinoma is rare, so the virus is necessary and very far from sufficient. The attributable fraction being near 100 per cent does not mean the virus explains the disease. The geographic concentration does the explaining, and the virus is the common factor on which the other causes act. Read in the net: the configuration that persists is the one where all the conditions fit together, and naming the commonest condition does not name the fit. This is a reading, not a mechanism. Salt-preserved fish and other salt-preserved foods, particularly consumed during weaning and early childhood, contain volatile nitrosamines that are carcinogenic and that also reactivate the latent virus in vitro. The association is consistent across case-control studies in endemic regions, at odds ratios generally in the region of 2 to 7 for high childhood consumption, and the declining incidence in southern China has tracked declining consumption; IARC has evaluated Chinese-style salted fish as carcinogenic to humans, Group 1†. On genetic susceptibility, HLA class I alleles are the strongest determinants: HLA-A2, HLA-B46 and HLA-B17 are associated with increased risk and certain HLA-A11 alleles with reduced risk, and genome-wide association studies have confirmed the HLA region as the dominant locus. Family history confers roughly a four- to tenfold increased risk in first-degree relatives in endemic populations. The HLA association points directly at antigen presentation of viral peptides, which is a coherent and unusually specific mechanistic story. Tobacco smoking has a modest independent effect, more relevant to the keratinising form and to non-endemic populations, at relative risks generally in the region of 1.5 to 2†. IARC has evaluated occupational formaldehyde as causing nasopharyngeal carcinoma, Group 1, on evidence that remains debated, and wood dust exposure likewise. Nasopharyngeal carcinoma has a low to moderate point-mutation burden, below or around the adult reference of 1.8 per megabase. The driving events are the viral latent genes — LMP1, LMP2, EBNA1 — plus recurrent somatic alterations in CYLD, TRAF3 and NFKBIA, all converging on NF-κB activation, with CDKN2A loss and TP53 mutation. Notably it shows frequent genomic alterations in antigen-presentation and immune-evasion genes and high PD-L1 expression, which is the basis for its checkpoint-inhibitor responsiveness despite a low mutation burden: **a third clear counterexample, alongside Hodgkin lymphoma and renal cell carcinoma, to mutation burden as a general predictor of immunotherapy response.** Not known: why a virus carried by over 90 per cent of humanity causes cancer in a specific population in a specific place; the relative contributions of HLA genotype, viral strain variation — endemic-region-specific high-risk variants have been identified and this is an active line — and salt-preserved fish; why the age-incidence curve peaks and then falls; why the juvenile peak occurs in North Africa and not in China.

Cure status. Stage I to II: CURABLE — five-year overall survival roughly 90 per cent†, with radiotherapy alone or with concurrent chemoradiotherapy, and radiotherapy alone curative for stage I. Stage III to IVA, locally advanced, the majority at presentation: CURABLE in roughly 65 to 80 per cent (five-year overall survival)†, with induction chemotherapy followed by concurrent chemoradiotherapy. That is a markedly better outcome for locally advanced disease than any other head and neck cancer, and it is why nasopharyngeal carcinoma is treated separately. Metastatic, stage IVB: CONTROLLABLE — median survival roughly two to three years with platinum-gemcitabine chemotherapy, and longer with the addition of a checkpoint inhibitor, which is an unusually good prognosis for metastatic head and neck cancer. A small subset with oligometastatic disease treated with chemotherapy plus local radiotherapy achieves long-term survival and may be cured. Recurrent local disease: CONTROLLABLE. Re-irradiation or nasopharyngectomy cures some, and both carry substantial morbidity in previously irradiated tissue. Early detection works here, and uniquely among the cancers in this chapter there is an effective, cheap, blood-based early-detection test validated in a prospective screening study. Surgery has almost no role in primary treatment: the nasopharynx is anatomically inaccessible and the tumour is exquisitely radiosensitive. That is the key practical fact about this cancer — it is the one major head and neck cancer where surgery is not the answer and radiotherapy is, which inverts the simple-means calculation. One honest note is necessary: cure costs a great deal functionally. Radiotherapy to the nasopharynx irradiates the brainstem, temporal lobes, cranial nerves, pituitary, inner ear, salivary glands and carotid arteries, and the late effects —

xerostomia, hearing loss, hypopituitarism, cranial neuropathy, temporal lobe necrosis, carotid stenosis and stroke, trismus, dysphagia and second cancers — are common and permanent. Intensity-modulated radiotherapy reduced them substantially and is the reason outcomes improved; conventional two-dimensional radiotherapy, which is what is available in many endemic low-resource settings, causes far more late damage at a similar cure rate.

Prevention. Avoiding salt-preserved fish, especially in infancy and during weaning — MODERATE, and it appears to have worked. Incidence in endemic southern China has fallen by roughly 30 to 40 per cent over recent decades, tracking declining consumption alongside general improvements in living conditions. The evidence is ecological and observational and there is no trial, and it is nonetheless one of the few cancers in this chapter where a population-level decline is plausibly attributable to a specific dietary change. Tobacco cessation — MODERATE. An Epstein-Barr vaccine does not exist, and that is the central prevention gap. A vaccine would address nasopharyngeal carcinoma, Burkitt lymphoma, a third of Hodgkin lymphoma, virus-positive gastric cancer and post-transplant lymphoproliferative disorder — plausibly over 200,000 cancers a year — as well as infectious mononucleosis. Candidates targeting gp350 and gH/gL are in early-phase trials and nothing is available. **This is arguably the largest unrealised cancer-prevention opportunity in this chapter after tobacco control.** Screening with plasma Epstein-Barr virus DNA — STRONG in endemic high-incidence populations, and this is the single most important fact in this entry. A large prospective screening study in Hong Kong, published in the *New England Journal of Medicine* in 2017, screened over 20,000 asymptomatic middle-aged Chinese men with plasma viral DNA by polymerase chain reaction. Screen-detected cancers were shifted dramatically towards early stage — roughly 70 per cent were stage I or II against roughly 20 per cent in a historical unscreened cohort — and three-year progression-free survival in the screened group was markedly superior, roughly 97 per cent against 70 per cent. Serology for IgA antibodies to viral capsid antigen and EBNA1 has been used for screening in southern China for decades and also produces a stage shift. The harms: the false-positive rate on a single plasma DNA test is appreciable, which is why a repeat test at four weeks is used to improve specificity before nasendoscopy, and false positives lead to nasendoscopy and magnetic resonance imaging, which are uncomfortable and costly and not dangerous. **Overdiagnosis appears to be low, because there is no large reservoir of indolent subclinical disease comparable to thyroid or prostate — no autopsy series shows occult nasopharyngeal carcinoma at any meaningful prevalence**. No overdiagnosis percentage has been published, and the absence of an indolent reservoir is the reason this screening programme does not carry the overdiagnosis problem that dominates the breast, prostate and thyroid entries. The grade is STRONG in endemic high-incidence populations and not justified in low-incidence populations, where the positive predictive value would collapse. This is the clearest example in this chapter of a cancer screening programme that works well, with a cheap test, in a defined high-risk population, without a significant overdiagnosis penalty, and it is worth setting against the breast, prostate and thyroid entries, where the same cannot be said.

Treatment. Re-irradiation or nasopharyngectomy cures some local recurrences, and the proportion is not given. Radiotherapy is the primary curative modality, and intensity-modulated radiotherapy is the standard. It is curative alone for stage I, and it substantially reduced xerostomia and other late effects compared with conventional radiotherapy at equal or better tumour control, which is the main reason survival improved. It requires a linear accelerator with inverse planning capability, and that is the binding constraint worldwide. Concurrent chemoradiotherapy with cisplatin treats stage II to IVA; **cisplatin is listed, with nasopharyngeal cancer as a radiosensitiser among its listed indications**, off-patent, at a trivial generic cost of tens of dollars a course. Induction chemotherapy before chemoradiotherapy for locally advanced disease uses gemcitabine with cisplatin, or docetaxel-cisplatin-fluorouracil, and all four drugs are listed and all off-patent; induction chemotherapy improved survival in randomised trials in endemic populations. Adjuvant metronomic capecitabine after chemoradiotherapy is a notable and unusual result: capecitabine is listed and off-patent, oral and inexpensive, and a randomised trial in endemic disease showed that one year of low-dose oral capecitabine after chemoradiotherapy improved failure-free survival. A cheap off-patent oral drug adding benefit to an already curative regimen is well suited to low-resource settings. Platinum-gemcitabine chemotherapy treats metastatic disease, both listed, both off-patent and cheap, and superior to platinum-fluorouracil. Pembrolizumab is a selected medicine on the list, for other listed indications. Nivolumab's listing for this cancer needs checking against the 24th List (2025)†. Neither is off-patent. Camrelizumab, toripalimab and tislelizumab, PD-1 inhibitors developed and approved in China

specifically including for this disease, are not listed; toripalimab added to gemcitabine-cisplatin improved progression-free and overall survival in first-line metastatic disease in JUPITER-02†. PD-1 inhibitor monotherapy in recurrent or metastatic disease produces objective responses in roughly 20 to 30 per cent, and combined with chemotherapy in the first line the response rate exceeds 75 per cent†. An important access point: the Chinese-developed inhibitors are priced far below the Western originators in their home market, reported at a fraction of the United States price, which is directly relevant to the endemic populations that need them. Virus-specific cytotoxic T-lymphocyte therapy is experimental and requires cell-processing facilities. Salvage nasopharyngectomy or re-irradiation treats local recurrence. Supportive care — dental assessment and extraction before radiotherapy, management of xerostomia, hearing assessment, pituitary function monitoring and swallowing rehabilitation — matters, with lifelong surveillance for late effects required in a young patient population.

Simple means. Nasopharyngeal carcinoma inverts the usual pattern in this chapter: its early detection is achievable simply and cheaply, and its curative treatment is not achievable simply at all. Plasma viral DNA by polymerase chain reaction, or viral IgA serology, as a screening test in endemic populations, is a blood test: no imaging, no endoscopy, no specialist for the screening step itself, producing a large stage shift and markedly better survival with low overdiagnosis. Polymerase chain reaction requires a laboratory, which is a genuine but modest requirement, and serology requires even less. In an endemic region this is a highly cost-effective intervention. Avoiding salt-preserved fish during weaning and childhood is a dietary change with no cost, plausibly responsible for a 30 to 40 per cent incidence decline in southern China†. Nasendoscopy with a flexible or rigid scope and a biopsy forceps is needed for diagnosis, with a histopathologist; a rigid nasendoscope is inexpensive and durable, and it is the one piece of equipment that cannot be dispensed with for diagnosis. Cisplatin, gemcitabine, fluorouracil and capecitabine are all off-patent listed drugs costing tens to low hundreds of dollars a course, and oral capecitabine in particular, with randomised evidence of benefit as adjuvant metronomic therapy, needs only a tablet and a blood count. Oral morphine serves pain; nasogastric or gastrostomy feeding carries the patient through the mucositis of radiotherapy, when swallowing is impossible; tracheostomy serves airway compromise rarely. Myringotomy or grommet insertion is a minor procedure that restores hearing in the middle-ear effusion this cancer commonly causes by blocking the Eustachian tube, and that effusion is often the presenting complaint. **There is no simple means of curing nasopharyngeal carcinoma, because the cure is radiotherapy and surgery has essentially no role.** Unlike oral cavity cancer, endometrial cancer, skin cancer or thyroid cancer, all of which can be cured with a scalpel in a district hospital, nasopharyngeal carcinoma cannot be cured without a linear accelerator, and a general surgeon with basic instruments can do nothing curative for it. The disease is concentrated in populations where radiotherapy access is often limited. Conventional two-dimensional radiotherapy, where that is all that exists, still cures a large proportion at a much higher cost in permanent late damage than intensity-modulated radiotherapy, and the gap between what is achievable with and without modern planning is wide here and it is a quality-of-cure gap more than a cure-rate gap. So the honest summary is: the screening is simple and excellent, the chemotherapy is cheap and listed, and the irreplaceable component is a machine.

Gaps. SEER publishes no separate nasopharyngeal carcinoma page, so all stage-specific survival figures are literature-derived, which is the largest data gap in this entry. A published Epstein-Barr-attributable case count was not retrievable, and the 100,000 figure above is an inference from a near-100 per cent attribution. The screening study's figures — 70 against 20 per cent early stage, and 97 against 70 per cent three-year progression-free survival — are widely cited and could not be read off the paper itself, so the key screening evidence carries no primary verification. Endemic incidence rates, the incidence decline, the salt-fish odds ratios, the HLA associations and the familial relative risks are all literature-derived. No PDQ prevention summary specific to nasopharyngeal carcinoma was retrieved, so unlike most entries here the risk-factor effect sizes carry no evidence grade. Overdiagnosis has not been quantified, though the absence of an occult reservoir argues it is low. No Epstein-Barr vaccine exists, and that is the principal prevention gap. The relative contributions of HLA genotype, viral strain and diet are not resolved. Chinese inhibitor pricing is literature-derived.

> **Depth.** Starts in: the Epstein-Barr virus. Size: 180 nm†; depth +1.25. First complaint: about 40 years († about 40 years after infection in childhood); time depth 52.23. One untreated course: no number († years).

> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

27. Testicular cancer

What it is. Cancer of the testis, almost always a germ cell tumour arising from the sperm-producing cells. It is the commonest cancer of young men. It is also the most curable disseminated solid cancer that exists: widely metastatic testicular cancer is cured in the large majority of patients with off-patent chemotherapy, which no other metastatic solid tumour in this chapter can claim.

Measured. GLOBOCAN 2022 gives 72,040 cases; GLOBOCAN 2024 gives 70,714 cases and 9,240 deaths, so deaths are 13 per cent of incidence, the lowest ratio of any malignancy in this chapter apart from thyroid cancer at 5 per cent, and unlike thyroid cancer this is not an artefact of overdiagnosis. Five-year relative survival in the United States is 94.6 per cent. SEER's page publishes no stage-specific survival and no stage distribution, so those figures come from the clinical literature: stage I, confined to the testis, five-year survival roughly 99 per cent, with cure essentially universal; stage II, retroperitoneal nodes, roughly 95 per cent; stage III good-risk roughly 90 to 95 per cent; stage III intermediate-risk roughly 75 to 80 per cent; stage III poor-risk, with high markers, non-pulmonary visceral metastases or a mediastinal primary, roughly 50 to 70 per cent. Seminoma has a better prognosis than non-seminoma at equivalent stage. Median age at diagnosis 33, the second-youngest in this chapter after acute lymphoblastic leukaemia, and it is the commonest solid malignancy in men aged 15 to 40, which is why its late effects matter so much: survivors have fifty years of life ahead. United States incidence is rising about 0.7 per cent a year and the death rate about 2.3 per cent a year. That rising death rate is anomalous and worth flagging: for a cancer with 94.6 per cent five-year survival the absolute numbers are very small, at 630 projected United States deaths in 2026, so the percentage trend rests on few events and is unstable. It should not be read as a deterioration in treatment efficacy, and no established explanation exists. Incidence is highest in Northern and Western Europe — Norway, Denmark, Switzerland and Germany have the world's highest rates — and lowest in Africa and Asia; rates in men of African ancestry are roughly a quarter to a fifth of those in men of European ancestry, and the difference persists in the United States across the same healthcare system, indicating a constitutional rather than an access basis. Incidence has roughly doubled in many Western countries since the 1960s and the cause of that increase is not known†.

Where it starts. Cryptorchidism is the strongest and best-established risk factor, at a relative risk of roughly four- to eightfold. The risk applies to the contralateral normally descended testis as well, which indicates that cryptorchidism is a marker of an underlying developmental abnormality rather than purely a consequence of the testis being in the wrong place. Orchidopexy before puberty reduces but does not eliminate the risk and makes the testis examinable. A personal history of testicular cancer gives roughly a twelve- to twentyfold increased risk in the contralateral testis, with a cumulative incidence of a second primary of roughly 2 to 5 per cent†. Family history gives roughly a four- to sixfold increased risk in brothers and roughly fourfold in sons of affected men, with no single high-penetrance gene and many common variants identified, KITLG carrying an unusually large effect for such a locus. Germ cell neoplasia in situ is the precursor lesion and is present adjacent to essentially all germ cell tumours; it is detectable only by testicular biopsy and progresses to invasive cancer in roughly 50 per cent within five years†. Infertility and poor semen quality are associated with increased risk, consistent with the testicular dysgenesis syndrome hypothesis, which groups cryptorchidism, hypospadias, poor semen quality and testicular cancer as outcomes of disturbed fetal testicular development. Disorders of sex development and androgen insensitivity carry substantially increased risk, HIV a modest increase in seminoma risk, and height a consistent association at relative risks in the region of 1.1 to 1.2 per 5 cm, by an unknown mechanism†. What is not established matters here, because it is widely assumed: trauma, vasectomy, athletic activity, heat exposure and testicular torsion are not established causes, and tobacco and alcohol have no established role, which makes testicular cancer one of the very few cancers in this chapter where smoking is not a risk factor. Germ cell tumours have among the lowest point-mutation burdens of any cancer, far below the adult reference of 1.8 per megabase, characterised instead by near-universal gain of chromosome 12p, usually as an isochromosome, aneuploidy, and KIT mutations in a subset of seminomas;

TP53 mutation is rare, and that is the leading explanation for the extraordinary chemosensitivity, because an intact p53 pathway means cisplatin-induced DNA damage triggers apoptosis efficiently. **The combination of a low mutation burden and an intact apoptotic response is the molecular reason a metastatic solid tumour can be cured by chemotherapy, and it is the clearest demonstration in this chapter that curability is a property of tumour biology rather than of treatment intensity.** Not known: why incidence has roughly doubled in Western countries since the 1960s, where in-utero exposure to endocrine-disrupting chemicals is the leading hypothesis and is unproven; why rates differ so much by ancestry; why germ cell tumours are so uniquely chemosensitive in a way that cannot be reproduced in other cancers.

Cure status. Germ cell neoplasia in situ: CURABLE by orchidectomy or low-dose radiotherapy, with surveillance an alternative. Stage I: CURABLE, essentially universally — five-year survival roughly 99 per cent†. Orchidectomy alone cures roughly 70 to 80 per cent of stage I non-seminoma and 80 to 85 per cent of stage I seminoma, and of those who relapse almost all are cured by subsequent chemotherapy; active surveillance after orchidectomy is now the preferred management precisely because the salvage rate is so high, which avoids giving adjuvant treatment to the majority who do not need it. Stage II: CURABLE — roughly 95 per cent†. Stage III good-risk: CURABLE — roughly 90 to 95 per cent with three or four cycles of BEP chemotherapy†. Stage III poor-risk: CURABLE in roughly 50 to 70 per cent†. **Even with high-volume liver, brain and bone metastases and markedly raised tumour markers, cure is the goal and is achieved in the majority, and no other metastatic solid tumour in this chapter is treated with curative intent at that stage.** Relapsed after first-line chemotherapy: CURABLE in roughly 20 to 60 per cent depending on risk group, with salvage chemotherapy or high-dose chemotherapy with autologous stem cell support; late relapse, more than two years out, and platinum-refractory disease are the poor groups. A residual mass after chemotherapy is frequently cured by retroperitoneal lymph node dissection, because residual masses may contain viable tumour or teratoma that chemotherapy cannot eradicate. Platinum-refractory disease, and the rare primary mediastinal non-seminoma with poor response, a small minority: RELIEF ONLY. It is reliably curable when caught early and reliably curable when caught late, which is the more remarkable fact, and that is why there is no screening programme: the cure rate is so high at every stage that earlier detection would add little, and the test would generate large numbers of benign findings. The dominant clinical problem, as in Hodgkin lymphoma, is the cost of cure in a young population. Survivors carry excesses of second malignancies, at relative risks in the region of 1.5 to 2 overall and higher after radiotherapy, with leukaemia after etoposide and solid tumours after radiotherapy; cardiovascular disease; cisplatin-induced permanent sensorineural hearing loss and tinnitus; peripheral neuropathy; Raynaud phenomenon; nephrotoxicity; hypogonadism; metabolic syndrome; and infertility. Bleomycin causes pulmonary fibrosis, which can be fatal. The field's research agenda is accordingly dominated by de-escalation — fewer cycles, surveillance instead of adjuvant therapy, carboplatin instead of radiotherapy in seminoma, and avoiding radiotherapy altogether — the same pattern as Hodgkin lymphoma and for the same reason.

Prevention. Orchidopexy for cryptorchidism before puberty — MODERATE: it reduces risk, does not eliminate it, and places the testis where it can be examined and where a tumour will be noticed. The optimal timing is in infancy and earlier surgery appears to confer greater risk reduction, and the evidence is observational. There is no other established prevention: no modifiable exposure of consequence has been identified, and tobacco, alcohol, diet and obesity have no established role, which makes testicular cancer unusual in this chapter. If the endocrine-disruptor hypothesis is correct, reducing fetal exposure would be preventive; that is a hypothesis with no interventional evidence and should not be presented as established. There is no screening programme and no recommendation for one: the USPSTF recommends against screening asymptomatic adolescent and adult males, grade D. The reasoning is clear and is a useful counterpoint to other entries: the cure rate is extremely high at all stages, so screening cannot add much; the disease is uncommon, so the positive predictive value of any test would be low; and examination generates frequent benign findings — epididymal cysts, varicoceles, hydroceles — leading to ultrasound and anxiety. **Overdiagnosis in the classical sense is not the issue, because there is no large reservoir of indolent testicular cancer in autopsy series**; the issue is simply that screening has nothing to add. Self-examination and awareness are WEAK on evidence, and the practical point stands: a painless testicular lump in a young man needs immediate assessment, and delay in presentation, which is common from embarrassment or

from being misdiagnosed as epididymitis, is the one avoidable factor that worsens outcome. The intervention is awareness, not a programme.

Treatment. Radical inguinal orchidectomy is the first and sometimes only treatment. It provides the diagnosis and cures the majority of stage I disease, and it is a short operation through a groin incision, performable with basic instruments under spinal or general anaesthesia. Sperm banking should be offered before it. BEP chemotherapy — bleomycin, etoposide and cisplatin — is the curative regimen for metastatic disease, and **every one of its three drugs is listed and off-patent**; cisplatin's listed indications include testicular germ cell tumours. The drug cost of three to four cycles at generic prices is in the region of a few hundred dollars. **This is the single most important fact in this entry, and arguably one of the most important in the chapter: widely metastatic testicular cancer is cured in roughly 90 per cent of good-risk and the majority of poor-risk patients by three cheap off-patent Essential Medicines.** The regimen has been essentially unchanged since the late 1970s, and no targeted agent, no antibody, no immunotherapy and no cell therapy is involved. Complete response with durable cure runs at roughly 90 to 95 per cent in good-risk and 50 to 70 per cent in poor-risk metastatic disease†. Etoposide with cisplatin serves good-risk patients in whom bleomycin is to be avoided; both listed and off-patent. Single-dose carboplatin as adjuvant therapy for stage I seminoma is listed and off-patent: a single infusion reduces relapse, and it has replaced adjuvant radiotherapy because it avoids the second-cancer risk. Retroperitoneal lymph node dissection serves residual masses after chemotherapy and is an alternative to chemotherapy in some stage I to II non-seminoma; it is a major abdominal operation, and nerve-sparing technique preserves ejaculation. Salvage chemotherapy uses paclitaxel, ifosfamide, cisplatin, vinblastine and mesna, all listed and all off-patent. High-dose chemotherapy with autologous stem cell support for relapsed disease uses carboplatin and etoposide, both listed and off-patent, and the cost is in the stem cell infrastructure. Radiotherapy is curative for stage I to IIA seminoma and is now largely abandoned in favour of surveillance or single-dose carboplatin, because of the second-cancer and cardiovascular risk in young men with a fifty-year life expectancy: a clear and deliberate de-escalation. Checkpoint inhibitors have been disappointing in germ cell tumours, with low response rates in platinum-refractory disease, consistent with the very low mutation burden. There is no effective targeted or immunological therapy for refractory germ cell tumour, and this small group of young men who are not cured by chemotherapy represents a genuine and neglected unmet need. Testosterone replacement for post-treatment hypogonadism is off-patent and inexpensive. Tumour marker monitoring — alpha-fetoprotein, beta-human chorionic gonadotrophin and lactate dehydrogenase — uses cheap, widely available blood tests that are central to management: they establish risk group, monitor response and detect relapse earlier than imaging, and beta-human chorionic gonadotrophin can be measured with a urine pregnancy test strip in extremis, which is a genuinely useful piece of practical knowledge.

Simple means. Testicular cancer has the best simple-means profile of any metastatic solid cancer in this chapter. Radical inguinal orchidectomy is a short operation through a groin incision under spinal or general anaesthesia with basic surgical instruments; it makes the diagnosis and cures the majority of stage I disease, roughly 70 to 85 per cent, outright†, so for a young man with a localized testicular tumour a district hospital with a general surgeon can deliver a cure. BEP chemotherapy from three off-patent Essential Medicines, at a drug cost of a few hundred dollars, cures the majority of metastatic disease. The requirements are intravenous access, an antiemetic, hydration and magnesium for cisplatin nephrotoxicity, a blood count before each cycle and a creatinine. Cisplatin needs careful hydration, which is the main technical demand and requires fluids and attention rather than technology, and bleomycin needs awareness of pulmonary toxicity, which is assessed clinically. **No other metastatic solid tumour in this chapter can be cured with means this modest.** Diagnosis is possible by examination and scrotal ultrasound: a painless firm testicular mass in a young man is clinically distinctive, and ultrasound is cheap, portable, needs no contrast and no radiation and is highly accurate, so this is one of the few cancers in this chapter where a hand-held probe is close to diagnostic. Tumour markers are inexpensive standard laboratory tests that do most of the work of risk stratification and follow-up that would otherwise require repeated imaging, and beta-human chorionic gonadotrophin is detectable on a urine pregnancy test strip costing cents. Sperm banking requires a container and a freezer, and in a disease with 95 per cent survival and a median age of 33 that is not a luxury. Orchidopexy in infancy for cryptorchidism is a standard paediatric operation with basic instruments that reduces cancer risk and makes the testis examinable. Testosterone replacement is off-patent, cheap, intramuscular or transdermal. Awareness that a painless testicular lump in a young man requires immediate

assessment needs no technology at all, and delay from embarrassment or from misdiagnosis as epididymitis is a recognised and avoidable cause of advanced presentation. Oral morphine serves pain in advanced disease. Where nothing simple exists: retroperitoneal lymph node dissection for a post-chemotherapy residual mass is a major vascular operation requiring specialist expertise, and omitting it when indicated causes relapse from viable residual tumour; high-dose chemotherapy with stem cell support requires apheresis and a transplant unit; and for the small number of young men with platinum-refractory disease there is nothing effective at all, simple or otherwise. Those are the exceptions. The central fact stands: **testicular cancer is the clearest proof in this chapter that curing widely metastatic cancer does not require expensive drugs.** The barrier to curing it worldwide is access to orchidectomy, cisplatin and competent supportive care — not patents, and not price.

Gaps. SEER's page publishes no stage-specific survival and no stage distribution, so all stage-specific figures are literature-derived. No PDQ prevention summary for testicular cancer was retrieved, so the risk-factor effect sizes carry no evidence grade, unlike most entries here. The cryptorchidism, familial, contralateral and precursor-progression figures and the incidence gradients are all literature-derived. The roughly doubled incidence in Western countries since the 1960s is unexplained and the endocrine-disruptor hypothesis has no interventional evidence. The rising United States death rate rests on very few events and has no established explanation; it may be statistical noise and should not be over-interpreted. Second-cancer and late-effect figures are literature-derived despite being central to management. Platinum-refractory germ cell tumour has no effective treatment and is a genuinely neglected unmet need in a young population.

> **Depth.** Starts in: a germ cell (GCNIS, in utero). Size: 15 µm†; depth +5.28. First complaint: about 34 years († from conception to median age 33); time depth 52.07. One untreated course: no number († years).
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

28. Sarcomas of soft tissue and bone

What it is. Cancers of the connective tissues — muscle, fat, blood vessels, nerve sheath, cartilage and bone — rather than of the linings and glands that produce the common carcinomas. They comprise more than a hundred distinct diagnoses, several defined by a single characteristic chromosomal translocation. They are uncommon, they affect all ages including children, and they are the cancers for which specialist referral makes the largest difference to outcome.

Measured. GLOBOCAN does not report soft tissue sarcoma or bone sarcoma as categories in the site list that supplies the rest of this chapter, which is a significant limitation: the global burden of sarcoma as a group cannot be read off that table. Kaposi sarcoma is reported separately, at 35,813 cases in 2022 and 34,230 cases with 10,727 deaths in 2024, and mesothelioma separately, at 30,633 cases in 2022 and 27,350 cases with 22,715 deaths in 2024. Sarcomas are generally estimated at roughly 1 per cent of adult cancers and roughly 10 to 15 per cent of childhood cancers†, which against GLOBOCAN 2024's total implies in the region of 150,000 to 250,000 cases worldwide annually; that is an inference and is marked as one. For soft tissue sarcoma in the United States, projections for 2026 are 13,910 new cases and 5,400 deaths, 0.7 per cent of cancer cases and 0.9 per cent of cancer deaths. Five-year relative survival is 65.7 per cent overall: localized, 57 per cent of cases, 83.3 per cent; regional, 18 per cent, 58.2 per cent; distant, 17 per cent, 17.0 per cent; unknown, 8 per cent, 62.7 per cent. Median age 63. Incidence has not significantly changed and the death rate is falling about 0.6 per cent a year, with modelled five-year survival rising from about 63 per cent in 1975 to about 69 per cent in 2023: one of the smallest long-term survival improvements of any cancer in this chapter. SEER's bones and joints page was not retrieved, so the bone sarcoma figures come from the literature: osteosarcoma, the commonest bone sarcoma, peaking in adolescence, five-year survival roughly 65 to 70 per cent localized and roughly 20 to 30 per cent with metastases at presentation; Ewing sarcoma, a childhood and young-adult tumour, roughly 70 to 80 per cent localized and 20 to 30 per cent metastatic; chondrosarcoma, adult and usually low grade, roughly 75 to 80 per cent overall and far worse for dedifferentiated forms; and chordoma, rare, axial and slow-growing, median survival roughly seven

years. Among the soft tissue subtypes: localized gastrointestinal stromal tumour five-year survival above 90 per cent, with metastatic disease at a median survival of roughly five years on imatinib against roughly eighteen months before it; liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma are the commonest adult types, with outcome driven by grade and size; rhabdomyosarcoma, predominantly paediatric, roughly 70 per cent for localized embryonal disease and far worse for alveolar and metastatic disease; angiosarcoma, aggressive, roughly 30 to 40 per cent; and desmoid tumour, which is locally infiltrative, does not metastasise, and spontaneously regresses in a substantial proportion. Kaposi sarcoma is the dominant sarcoma globally by volume and is concentrated in sub-Saharan Africa, where it was among the commonest cancers in men in several countries at the height of the HIV epidemic and remains so in parts of Eastern and Southern Africa; endemic non-HIV Kaposi sarcoma has long been recognised in equatorial Africa. Mesothelioma incidence tracks historical asbestos use and is still rising in countries that used asbestos late.

Where it starts. Sarcomas have the highest proportion of cases with an identifiable germline or iatrogenic cause of any group in this chapter, and simultaneously the least known about the sporadic majority. Prior therapeutic radiotherapy is the best-established acquired cause: radiation-induced sarcoma arises in the irradiated field after a latency of typically ten to twenty years, with an absolute risk in the region of 0.1 to 0.2 per cent of irradiated patients†. It is most often osteosarcoma, undifferentiated pleomorphic sarcoma or angiosarcoma, and it carries a worse prognosis than the sporadic equivalent, with angiosarcoma of the breast after breast-conserving radiotherapy the classic example. This is an iatrogenic cancer, and it is one of the reasons for the radiotherapy de-escalation described in entries 22 and 27. Chronic lymphoedema gives angiosarcoma in a chronically lymphoedematous limb, classically after axillary dissection for breast cancer. The germline predisposition syndromes account for a substantial minority: Li-Fraumeni syndrome, with germline TP53 mutation, gives soft tissue sarcoma, osteosarcoma, breast cancer, brain tumours and adrenocortical carcinoma at a lifetime cancer risk approaching 90 per cent†; hereditary retinoblastoma, with germline RB1 mutation, gives a very large increase in osteosarcoma risk, markedly amplified by radiotherapy to the orbit; neurofibromatosis type 1 gives malignant peripheral nerve sheath tumour at a lifetime risk of roughly 8 to 13 per cent; familial adenomatous polyposis gives desmoid tumours, which are a major cause of morbidity and death after colectomy; and hereditary leiomyomatosis and renal cell cancer, Werner syndrome, Rothmund-Thomson syndrome and germline succinate dehydrogenase mutations follow. Human herpesvirus 8 causes Kaposi sarcoma, and the attributable fraction is essentially 100 per cent: the virus is present in the tumour cells in every case, in all four epidemiological forms — classic Mediterranean, endemic African, HIV-associated and iatrogenic post-transplant. de Martel and colleagues, 2020, gave case counts for four agents not including this one; on near-100 per cent attribution and GLOBOCAN 2024's 34,230 Kaposi sarcoma cases, the implied figure is roughly 34,000 cases annually, and that is an inference. HIV co-infection is the critical amplifier: incidence in untreated HIV infection is raised several thousandfold, and it falls dramatically with antiretroviral therapy. Asbestos causes mesothelioma, is IARC Group 1, and the attributable fraction is high — generally estimated at roughly 80 per cent or more in men in industrialised countries — with a latency of twenty to fifty years. Mesothelioma is the clearest single-exposure cancer in this chapter after tobacco and lung cancer, and it is wholly preventable by not using asbestos. Vinyl chloride monomer causes hepatic angiosarcoma, is IARC Group 1, and is a historical occupational cancer now largely controlled; Thorotrast, arsenic and anabolic steroids likewise cause hepatic angiosarcoma. Chronic immunosuppression gives post-transplant Kaposi sarcoma and other sarcomas. Sarcomas divide into two genetic classes and the division is the most useful thing to know about them. The translocation-driven sarcomas carry a single defining fusion gene on a quiet genomic background with a very low mutation burden: Ewing sarcoma with EWSR1-FLI1, synovial sarcoma with SS18-SSX, myxoid liposarcoma with FUS-DDIT3, alveolar rhabdomyosarcoma with PAX3 or PAX7 to FOXO1, dermatofibrosarcoma protuberans with COL1A1-PDGFB, inflammatory myofibroblastic tumour with ALK fusions, and infantile fibrosarcoma with ETV6-NTRK3. These are mostly tumours of children and young adults, and their mutation burden is among the lowest measured in human cancer: Gröbner and colleagues, in *Nature* in 2018, found an overall paediatric rate of 0.13 mutations per megabase against the adult reference of 1.8, and Ewing sarcoma sits at the bottom of even that range. The complex-karyotype sarcomas carry massive aneuploidy, chromothripsis, TP53 and RB1 loss and no defining fusion: leiomyosarcoma, undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, osteosarcoma and angiosarcoma, mostly adult tumours, with osteosarcoma in particular

showing extreme structural rearrangement and chromothripsis on a moderate point-mutation burden. Gastrointestinal stromal tumour is a third category, driven by activating KIT mutations in roughly 75 to 80 per cent or PDGFRA mutations in roughly 10 per cent, with succinate dehydrogenase deficiency in most of the remainder, and that single-driver biology is why imatinib works. The practical consequence is that the translocation-driven sarcomas have essentially no mutational burden for checkpoint inhibitors to exploit, and immunotherapy has largely failed in sarcoma as a class; the exceptions — undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma and alveolar soft part sarcoma — are the ones with either higher burden or distinctive immune features. Not known: **the cause of the great majority of sporadic sarcomas.** For a group this heterogeneous and this often arising in children, the aetiological void is almost complete: there is no tobacco, no diet, no obesity, no infection outside Kaposi sarcoma and no identified environmental exposure for the sporadic majority. Also unknown: why the characteristic translocations occur; why they are so cell-type and age specific; why a single fusion gene is sufficient to produce a malignant tumour in these cases when most cancers require multiple hits.

Cure status. Desmoid tumour, aggressive fibromatosis: SELF-LIMITING in roughly 20 to 30 per cent, which regress spontaneously without any treatment†; the remainder: CONTROLLABLE. It does not metastasise. Active surveillance is now the recommended first-line management, having replaced immediate surgery, and the shift to observation is a genuine and recent reversal of practice. HIV-associated Kaposi sarcoma: CONTROLLABLE by antiretroviral therapy alone, which is lifelong — restoring immune function causes regression in a large proportion of cases without any cytotoxic chemotherapy. **This is the only cancer in this chapter that routinely regresses on treatment of an underlying infection other than gastric mucosa-associated lymphoid tissue lymphoma on *H. pylori* eradication, and it is the single most important practical fact in this entry for global burden, because Kaposi sarcoma is the commonest sarcoma in the world.** Localized soft tissue sarcoma: CURABLE — five-year relative survival 83.3 per cent, by wide surgical excision with a clear margin, with radiotherapy to reduce local recurrence in high-grade or large deep tumours. The margin is everything: an inadequate first operation, performed by a non-specialist who did not suspect sarcoma, substantially worsens outcome and is the commonest avoidable error in sarcoma care. Regional soft tissue sarcoma: CURABLE in 58.2 per cent (five-year relative survival). Metastatic soft tissue sarcoma with resectable lung-only metastases: CURABLE in roughly 25 to 35 per cent (five-year survival after complete pulmonary metastasectomy); sarcoma is one of the cancers where metastasectomy is standard rather than exceptional. Metastatic soft tissue sarcoma otherwise: RELIEF ONLY — 17.0 per cent. Localized osteosarcoma and Ewing sarcoma: CURABLE in roughly 65 to 80 per cent with neoadjuvant chemotherapy, surgery and, for Ewing sarcoma, radiotherapy. Both were almost uniformly fatal before multi-agent chemotherapy was introduced in the 1970s, and survival rose from under 20 per cent to roughly 70, and both have seen essentially no further improvement in forty years, which is a notable plateau. Metastatic osteosarcoma and Ewing sarcoma with resectable lung-only deposits: CURABLE in roughly 20 to 30 per cent†. Metastatic osteosarcoma and Ewing sarcoma otherwise: RELIEF ONLY. Metastatic gastrointestinal stromal tumour: CONTROLLABLE, and the transformation is large — before imatinib, median survival was roughly eighteen months and chemotherapy was ineffective; on imatinib, median survival is roughly five years and a minority remain controlled for over a decade. Adjuvant imatinib for three years after resection of high-risk localized disease improves survival. Low-grade chondrosarcoma: CURABLE by excision. Dedifferentiated chondrosarcoma: RELIEF ONLY. Mesothelioma: RELIEF ONLY — median survival roughly twelve to eighteen months with chemotherapy, extended to roughly eighteen months with nivolumab and ipilimumab in non-epithelioid disease. Trimodality therapy in highly selected epithelioid pleural mesothelioma produces longer survival in some series and is not curative in the great majority. Mesothelioma is not curable at any stage and it is entirely preventable. Localized soft tissue and bone sarcoma is reliably curable when caught early, with the crucial proviso that caught early must mean caught and operated on correctly the first time. A sarcoma excised piecemeal or shelled out by a surgeon who thought it was a lipoma or a haematoma has a substantially worse outcome, and that is the dominant modifiable determinant of outcome in sarcoma. **The single most valuable intervention in sarcoma care is referral before the first operation.**

Prevention. Not using asbestos — STRONG, and mesothelioma is almost entirely preventable. Asbestos is IARC Group 1 and accounts for the large majority of mesothelioma; more than sixty countries have banned it and many large producers and users have not. Every mesothelioma occurring now reflects an exposure

twenty to fifty years ago, and every mesothelioma occurring in fifty years' time reflects an exposure happening now. That is the clearest avoidable cancer in this chapter after tobacco-related disease. Antiretroviral therapy for HIV — STRONG for Kaposi sarcoma: incidence in people with HIV fell dramatically with effective therapy and established disease frequently regresses on therapy alone. Since Kaposi sarcoma is the commonest sarcoma globally and is concentrated in sub-Saharan Africa, where WHO records 64 per cent of the 41.0 million people living with HIV, scale-up of antiretroviral therapy is quantitatively the most important sarcoma prevention that exists. Minimising therapeutic radiotherapy dose and field, especially in children and young adults — MODERATE, against an absolute radiation-induced sarcoma risk of roughly 0.1 to 0.2 per cent of irradiated patients at ten to twenty years†; this is a principal justification for de-escalation in Hodgkin lymphoma, testicular seminoma, retinoblastoma and childhood cancer generally, and avoiding orbital radiotherapy in hereditary retinoblastoma is the sharpest example, because the osteosarcoma risk in germline RB1 carriers is hugely amplified by radiation. Occupational control of vinyl chloride — STRONG, a historical success. Surveillance in germline predisposition syndromes — MODERATE: whole-body magnetic resonance imaging in Li-Fraumeni syndrome detects tumours early and has been associated with improved survival in cohort studies, with no randomised evidence, and annual clinical examination and imaging for malignant transformation in neurofibromatosis type 1 plexiform neurofibromas is recommended on risk grounds. There is no population screening for sarcoma and no rationale for one: the incidence is far too low, so any test would have a catastrophically low positive predictive value, and there is no pre-malignant lesion to intercept. Overdiagnosis is not a significant issue with one real exception: incidental detection of small lipomatous tumours, enchondromas and nerve sheath tumours on imaging done for other reasons is very common, and distinguishing an atypical lipomatous tumour from a benign lipoma, or an enchondroma from a low-grade chondrosarcoma, is genuinely difficult. That generates biopsies and operations on lesions that would never have caused harm. **No overdiagnosis percentage has been published for incidental lipomatous and cartilaginous lesions**, and it is an unquantified and growing harm of expanding imaging use.

Treatment. Wide surgical excision with a clear margin is the curative treatment for localized sarcoma, and the quality of the first operation is the dominant determinant of outcome. Limb-sparing surgery has replaced amputation for most extremity sarcomas with equivalent survival, and referral to a specialist centre before biopsy and before any excision is the single most important process measure in sarcoma care. Radiotherapy, preoperative or postoperative, reduces local recurrence in high-grade deep soft tissue sarcoma and is essential in Ewing sarcoma, and it requires a linear accelerator. Doxorubicin, with or without ifosfamide, is the standard chemotherapy for soft tissue sarcoma, and both are listed and off-patent, with mesna, listed and off-patent, required with ifosfamide to prevent haemorrhagic cystitis. Objective response to doxorubicin monotherapy in metastatic soft tissue sarcoma is roughly 15 to 20 per cent; adding ifosfamide raises response and has not clearly improved overall survival, at a generic cost of a few hundred dollars a course. For osteosarcoma, the MAP regimen of high-dose methotrexate, doxorubicin and cisplatin, with calcium folinate rescue, has all four components listed and all off-patent, and methotrexate's listed indications include osteosarcoma and cisplatin's include it too. That regimen raised localized osteosarcoma survival from under 20 per cent to roughly 65 to 70 per cent and has not been improved upon in forty years†; the entire curative regimen is off-patent and cheap, and high-dose methotrexate requires rescue, hydration, urinary alkalinisation and level monitoring, which is the technical demand. For Ewing sarcoma, vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide has every drug listed and every one off-patent, with vincristine's listed indications including Ewing sarcoma, and it cures roughly 70 to 80 per cent of localized disease†. For rhabdomyosarcoma, vincristine, dactinomycin and cyclophosphamide are all listed and all off-patent, and dactinomycin's listed indications include rhabdomyosarcoma. Imatinib for gastrointestinal stromal tumour is listed and off-patent, at United States generic cash prices, October 2026, of US$1.49 to 5.37 per 400 mg tablet and US$44.75 to 161.09 for thirty, which is US$540 to 1,960 a year at 400 mg daily. The originator price was in the region of US$90,000 to 145,000 a year at United States list by the time of generic entry in 2016†. Objective response or durable stable disease runs at roughly 80 per cent in metastatic disease, with median overall survival roughly five years against roughly eighteen months before it, and adjuvant imatinib for three years after resection of high-risk disease improves overall survival. That is the same drug and the same price story as in entry 20, and gastrointestinal stromal tumour is the second disease it transformed. Sunitinib, regorafenib, ripretinib and avapritinib are not listed. Pemetrexed with cisplatin treats mesothelioma: cisplatin is listed

and off-patent, and pemetrexed is not listed and is off-patent with generics available. Nivolumab with ipilimumab improved survival over chemotherapy in non-epithelioid mesothelioma in CheckMate 743; nivolumab's listing for this cancer needs checking against the 24th List (2025)†, ipilimumab is not listed, and neither is off-patent. Antiretroviral therapy for HIV-associated Kaposi sarcoma is the first-line treatment, is listed, off-patent, and available at generic prices in the region of US$30 to 75 a year in global procurement programmes†. For more advanced Kaposi sarcoma, pegylated liposomal doxorubicin, listed, and paclitaxel, listed and off-patent, are effective, and bleomycin with vincristine, both listed and off-patent, are the older and cheapest option and remain widely used in Africa. Trabectedin, eribulin, pazopanib, tazemetostat, larotrectinib and entrectinib, and atezolizumab for alveolar soft part sarcoma, are none of them listed except atezolizumab, which is listed for lung cancer, and all are on patent except where generics have emerged. Larotrectinib and entrectinib produce objective responses above 70 per cent in NTRK-fusion tumours including infantile fibrosarcoma, where they have allowed limb-sparing treatment in infants who would previously have been amputated: a small group with a very large benefit. Mifamurtide for osteosarcoma is approved in Europe, is not listed, and has marginal and contested benefit. Denosumab for giant cell tumour of bone is not listed and produces dramatic radiological response in a benign but locally destructive tumour. Pulmonary metastasectomy is standard in sarcoma and curative in a minority.

Simple means. Antiretroviral therapy for HIV-associated Kaposi sarcoma comes first: oral tablets, listed, off-patent, available at US$30 to 75 a year through global procurement, causing regression of the commonest sarcoma in the world with no cytotoxic drug. **In terms of cancer burden addressed per dollar, that is among the most important interventions in this chapter, and it is already a public health priority for other reasons.** Where cytotoxic therapy is needed, bleomycin and vincristine are off-patent listed drugs costing tens of dollars, and they are effective and widely used in African settings. Observation for desmoid tumour is the recommended first-line management and costs nothing, because a substantial proportion regress spontaneously. Wide excision of a localized extremity soft tissue sarcoma with a cuff of normal tissue is a conventional operation requiring basic instruments and anaesthesia, and it is curative in roughly 83 per cent of localized cases. Amputation, where limb-sparing excision is not feasible and no radiotherapy is available, is a definitive and curative operation achievable in any district hospital, and for a high-grade extremity sarcoma with no access to radiotherapy amputation may be the correct choice rather than an inadequate excision with a high local recurrence rate. That is an uncomfortable and honest point. **Recognising a sarcoma before operating on it is the single highest-value simple means in this entry and it costs nothing**: a deep soft tissue mass larger than about 5 cm, or any enlarging deep mass, should be imaged and biopsied with a needle along a planned track rather than shelled out, and bone pain with a lytic or sclerotic lesion and periosteal reaction in an adolescent is osteosarcoma until proven otherwise. Those are diagnostic rules rather than technologies, and getting them wrong is the commonest avoidable harm in sarcoma care worldwide. Core needle biopsy requires a needle and a histopathologist, and the binding constraint is pathology: sarcoma subtyping requires immunohistochemistry and increasingly molecular confirmation of the characteristic fusion, and misdiagnosis rates in non-specialist settings are high. Without reliable pathology the correct chemotherapy cannot be chosen, and the regimens differ completely between osteosarcoma, Ewing sarcoma and rhabdomyosarcoma. The paediatric bone and soft tissue sarcoma regimens are entirely off-patent: every drug in MAP, in the Ewing regimen and in the rhabdomyosarcoma regimen is listed and off-patent. A full curative course costs in the region of a few hundred to low thousands of dollars, and it cures 65 to 80 per cent of localized osteosarcoma, Ewing sarcoma and embryonal rhabdomyosarcoma. As with childhood acute lymphoblastic leukaemia, the drugs are not the barrier. What is the barrier: high-dose methotrexate needs rescue, hydration, alkalinisation and level monitoring; the regimens cause prolonged neutropenia requiring transfusion and antibiotic support; and treatment runs for many months, so abandonment is a major cause of failure. Imatinib for gastrointestinal stromal tumour is one oral tablet daily, off-patent, listed, at US$540 to 1,960 a year at United States generic prices, October 2026, and less in generic-supplying markets, with no infusion and no cold chain: a metastatic sarcoma controlled for years by a cheap daily tablet. Amputation with simple prosthetics, oral morphine, which matters especially in bone sarcoma where pain is severe, and orthopaedic fixation or bracing for an impending pathological fracture complete the list. Not using asbestos is prevention requiring no technology, only a decision. Where nothing simple exists: limb-sparing reconstruction with endoprostheses or allografts, radiotherapy, which is essential in Ewing sarcoma and in high-grade soft tissue sarcoma margins, pulmonary metastasectomy, and the

specialist pathology on which correct treatment selection depends. And for metastatic complex-karyotype sarcoma and for mesothelioma there is nothing effective at all: doxorubicin's response rate of 15 to 20 per cent and mesothelioma's twelve- to eighteen-month median survival are the honest figures. **The structural problem in sarcoma is different from the other entries in this chapter: the drugs are cheap and off-patent, and the diagnosis is difficult, the first operation determines the outcome, and both require expertise that is concentrated in a small number of centres. Sarcoma is the clearest case in this chapter where the scarce resource is skill rather than money or technology.**

Gaps. GLOBOCAN does not report soft tissue or bone sarcoma as categories, so there is no reliable global incidence or mortality figure for sarcoma as a group, and the inference above is labelled as one. That is the largest data gap of any entry in this chapter. SEER's bones and joints page was not retrieved, so all bone sarcoma survival figures are literature-derived. No PDQ prevention summary for sarcoma was retrieved, so the risk-factor effect sizes carry no evidence grade. All subtype-specific survival figures, the germline syndrome risks, the radiation-induced sarcoma absolute risk, the desmoid spontaneous regression rate, the gastrointestinal stromal tumour survival on imatinib and the metastasectomy outcomes are literature-derived. A published human herpesvirus 8-attributable case count for Kaposi sarcoma was not retrievable. The aetiology of the sporadic majority is unknown, and for a group that includes many childhood cancers that is a substantial void. Osteosarcoma and Ewing sarcoma survival have not improved in roughly forty years despite extensive trial activity, an unexplained plateau. Overdiagnosis of incidental lipomatous and cartilaginous lesions is real, growing and entirely unquantified. The dominant determinant of outcome — the quality of the first operation and the accuracy of the pathology — is not captured in any of the survival statistics quoted.

> **Depth.** Starts in: a mesenchymal cell. Size: 15 µm†; depth +5.28. First complaint: about 10 years († about 10 years after radiation); time depth 50.97. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Childhood cancer

Childhood cancer is a cross-cutting subject as well as a set of entries, and the material that runs through all four paediatric entries below is set out once here. The individual entries follow.

29. Childhood cancer as a class

What it is. Cancer in children is a different set of diseases from cancer in adults, not a younger version of the same thing. It arises in developing tissues rather than in surfaces worn down by decades of exposure, it carries far fewer mutations, it is not caused by tobacco or diet or obesity, and it is much more often curable. The commonest types are the leukaemias, brain tumours, lymphomas, and the embryonal solid tumours — neuroblastoma, Wilms tumour, medulloblastoma and retinoblastoma — which have their own entries below.

Measured. WHO estimates that about 400,000 children and adolescents aged 0 to 19 develop cancer each year worldwide. **Survival is the central fact: more than 80 per cent of children with cancer are cured in high-income countries, and in most low- and middle-income countries less than 30 per cent are cured**. That roughly threefold divergence, in a group of diseases largely curable with off-patent drugs, is the largest single inequity documented in this chapter. WHO's Global Initiative for Childhood Cancer targets at least 60 per cent survival for all children with cancer by 2030, roughly double the current global rate, which WHO estimates would save an additional one million lives over the decade. WHO names the commonest childhood cancers as the leukaemias, brain tumours and solid tumours such as neuroblastoma and Wilms tumour, with lymphomas, bone cancer and thyroid cancer more common in adolescence. SEER's childhood cancer page could not be retrieved, so United States aggregate childhood figures are

absent here; the type-specific SEER figures available in this chapter are acute lymphoblastic leukaemia at 73.2 per cent overall, with a median age of 18 and 52.1 per cent of cases under 20, and acute myeloid leukaemia at 33.4 per cent. The others are Hodgkin lymphoma at 89.3 per cent with a median age of 38, brain and central nervous system tumours at 32.9 per cent, and soft tissue sarcoma at 65.7 per cent. Childhood cancer mortality in high-income countries fell by roughly 70 per cent between 1970 and 2020, driven almost entirely by cooperative-group clinical trials using off-patent cytotoxic drugs. The age pattern peaks in the first five years of life, with the embryonal tumours and acute lymphoblastic leukaemia, troughs in middle childhood, and rises again in adolescence with bone sarcoma, Hodgkin lymphoma, germ cell tumours and thyroid cancer.

Where it starts. Paediatric tumours carry roughly fourteen times fewer somatic mutations than adult tumours. Gröbner and colleagues, in *Nature* in 2018, analysed 961 tumours from children, adolescents and young adults across 24 molecular cancer types and reported an overall somatic mutation frequency of **0.13 mutations per megabase, against the adult pan-cancer reference of 1.8 mutations per megabase**. The paper describes this as an overall rate rather than a median, and the figure is not in the abstract. Three consequences follow, and they run through every childhood cancer entry in this chapter. First, childhood cancers are driven by single structural or epigenetic events — fusion genes, translocations, aneuploidy, histone mutations, imprinting defects — rather than by accumulated point mutations from exposure, and that is why they occur in children at all: they do not require decades of mutational accumulation. Second, **there is almost no mutational burden for checkpoint inhibitors to exploit, and checkpoint blockade has broadly failed across paediatric oncology.** That is the clinical consequence and it is observed rather than predicted: the successful immunotherapies in children — dinutuximab in neuroblastoma, blinatumomab and CD19-directed cell therapy in acute lymphoblastic leukaemia — all target a lineage antigen rather than a neoantigen. Third, the absence of a tobacco, diet, alcohol or obesity signature is not a gap in research; it may reflect the fact that these exposures have not had time to act. Gröbner and colleagues also found that **7.6 per cent of children with cancer carry an unambiguous predisposing germline variant** (given as 7 to 8 per cent in the paper, 7.6 per cent in its main text), against WHO's figure of about 10 per cent, and the two are consistent. And they found that nearly 50 per cent of paediatric neoplasms harbour a potentially druggable event, 52 per cent of primary tumours after normalising for cancer incidence. On causation WHO's summary is the honest one and is quoted directly: most childhood cancers do not have a known cause, very few are linked to environmental or lifestyle factors, and childhood cancer generally cannot be prevented or found through screening. What is established: germline predisposition in 7 to 10 per cent of cases — Li-Fraumeni syndrome, retinoblastoma, neurofibromatosis types 1 and 2, Beckwith-Wiedemann syndrome and the Wilms tumour loci, DICER1, Fanconi anaemia, ataxia-telangiectasia, Down syndrome, familial neuroblastoma, rhabdoid tumour predisposition and constitutional mismatch repair deficiency; ionising radiation, the best-established environmental cause, including in-utero exposure and therapeutic irradiation; chronic infections, particularly in low- and middle-income countries, where WHO names HIV, Epstein-Barr virus and malaria as risk factors, the agents behind endemic Burkitt lymphoma, HIV-associated Kaposi sarcoma and lymphoma, and the juvenile North African nasopharyngeal peak; prior chemotherapy and radiotherapy for a first cancer; and Down syndrome, with a roughly twentyfold increase in childhood acute lymphoblastic leukaemia and a large increase in megakaryoblastic acute myeloid leukaemia. WHO recommends vaccination against hepatitis B and human papillomavirus to reduce later cancer risk; these prevent adult cancers in people vaccinated as children rather than childhood cancers, and the distinction should be kept clear. Not known: **the cause of the great majority of childhood cancer**, as WHO states explicitly. For childhood acute lymphoblastic leukaemia the delayed-infection hypothesis is the leading account and is unproven; for the embryonal tumours the initiating events occur in utero or in early development and nothing is known about what triggers them; for brain tumours, nothing. That is the largest aetiological void in this chapter and it is a void in the field.

Cure status. High-income settings: CURABLE — more than 80 per cent of children with cancer are cured. Most low- and middle-income settings: CURABLE — and less than 30 per cent are cured. The label is the same in both strata, and the stratum is named because the honest answer to whether this is curable differs by where the child lives, which is the point. **The difference is not biological.** The same diseases, with the same genetics, are cured at over 80 per cent in one place and under 30 per cent in another, using drugs that are almost all off-patent and listed. The determinants of the gap, drawn from the individual entries in this

chapter: diagnostic delay and advanced presentation, of which retinoblastoma presenting with proptosis rather than a white pupil is the sharpest example; absence of reliable histopathology, where the regimens for osteosarcoma, Ewing sarcoma and rhabdomyosarcoma are completely different; no blood or platelet supply for the intensive phases, without which acute myeloid leukaemia induction kills by haemorrhage regardless of drug cost; no inpatient capacity for febrile neutropenia; interrupted drug supply over the two to three years that acute lymphoblastic leukaemia maintenance requires; no radiotherapy, without which medulloblastoma cannot be cured; and treatment abandonment. **Treatment abandonment is specific to paediatric oncology in low-income settings and is a leading cause of death; it is a failure of social and financial support rather than of medicine, and it is measurable and addressable**. The second dominant problem, where cure is achieved, is the cost of cure. A cured child has sixty or seventy years ahead. Survivors carry substantial excesses of second cancers, cardiac disease from anthracyclines, hearing loss from cisplatin, infertility from alkylators, growth and endocrine failure from cranial and spinal irradiation, cognitive impairment from central-nervous-system-directed treatment, and renal impairment. In the large survivorship cohorts a majority of adult survivors of childhood cancer have at least one chronic health condition attributable to treatment. That is why de-escalation — risk-stratified therapy, omission of radiotherapy, reduced anthracycline dose, surveillance instead of adjuvant treatment — dominates the paediatric trial agenda, exactly as in Hodgkin lymphoma and testicular cancer.

Prevention. WHO states plainly that childhood cancer generally cannot be prevented or found through screening, and that is the honest headline and it differs from almost every other entry in this chapter. What does work: avoiding unnecessary diagnostic and therapeutic ionising radiation in pregnancy and childhood — STRONG, and the only established environmental cause across the class. HIV prevention and antiretroviral therapy — STRONG for Kaposi sarcoma and HIV-associated lymphoma in children; the therapy is listed, off-patent, US$30 to 75 a year at global procurement prices, and causes established Kaposi sarcoma to regress. Malaria control — MODERATE for endemic Burkitt lymphoma, on ecological evidence only, and nets and antimalarials are cheap and justified anyway; WHO records 282 million malaria cases and 610,000 deaths in 2024, with about 75 per cent of African Region deaths in children under five in its key facts, against 76 per cent then 75 per cent in two adjacent paragraphs of the body of the same page; both are printed. Minimising treatment intensity in curable childhood cancers — STRONG for preventing second cancers and late effects: this is prevention of iatrogenic disease and it is the main prevention activity in paediatric oncology. Genetic counselling and surveillance in predisposition syndromes — MODERATE, on cohort evidence with no randomised trials: whole-body imaging in Li-Fraumeni syndrome, renal ultrasound in Beckwith-Wiedemann syndrome and the Wilms tumour syndromes, and ophthalmological examination in familial retinoblastoma all detect tumours early, and avoiding radiotherapy in germline RB1 carriers is strongly indicated because of the amplified osteosarcoma risk. Hepatitis B and human papillomavirus vaccination in childhood — STRONG, and they prevent adult cancers of the liver, cervix and oropharynx rather than childhood cancers. There is no population screening for any childhood cancer, and one attempt is the most instructive failure in the whole screening literature: urinary catecholamine screening of infants for neuroblastoma, set out in entry 30. It detected large numbers of tumours, did not reduce neuroblastoma mortality, and was abandoned. The lesson is the same as for thyroid cancer, prostate cancer and the myeloma and chronic lymphocytic leukaemia precursors: a detectable lesion with a high rate of spontaneous regression or indolence makes screening harmful rather than helpful. The one exception is not a technology, and it is the red reflex test for retinoblastoma, set out in entry 33.

Treatment. The drugs that cure childhood cancer are, almost without exception, off-patent and listed. Drawing the regimens together from the individual entries, all of the following are in the antineoplastic section of the Essential Medicines List and all are off-patent: vincristine, dactinomycin, cyclophosphamide, ifosfamide, doxorubicin, daunorubicin, etoposide, cisplatin, carboplatin, methotrexate, mercaptopurine, tioguanine, cytarabine, asparaginase, pegaspargase, bleomycin, dacarbazine, melphalan, procarbazine, vinblastine, calcium folinate, prednisolone, prednisone, dexamethasone, hydroxyurea, all-trans retinoic acid, arsenic trioxide, mesna, allopurinol, rasburicase, filgrastim and zoledronic acid. The total drug cost for a full curative course of most childhood cancer protocols is in the region of a few hundred to a low thousands of dollars at generic prices. The modern expensive agents that matter in paediatrics: dinutuximab for neuroblastoma, not listed and on patent; blinatumomab, listed and on patent at US$180,000 a course at United States list; CD19-directed cell therapy, not listed, at a reported US$475,000

an infusion at United States list; larotrectinib and entrectinib for NTRK fusions, not listed; and selumetinib for neurofibromatosis type 1 plexiform neurofibroma, not listed. Radiotherapy is essential in medulloblastoma, Ewing sarcoma and several others and is being minimised wherever possible because of late effects. Surgery is curative or essential in Wilms tumour, neuroblastoma, retinoblastoma, hepatoblastoma and sarcoma. Supportive care — transfusion, antibiotics, antifungals, antiemetics, nutrition and central venous access — is not adjunctive. It is what makes the cheap curative drugs survivable, and its absence is the main reason cure rates differ threefold between settings.

Simple means. The drugs are cheap, off-patent and listed, and that is the single most important fact about childhood cancer worldwide: a curative course costs hundreds of dollars. What cannot be dispensed with: a histopathology service that can distinguish the tumour types, because the regimens differ completely; a laboratory that can do a blood count; a blood and platelet supply; inpatient beds for febrile neutropenia; and continuity of treatment for months to years. What is specific to children and is addressable with no technology at all is preventing treatment abandonment: accommodation for families, travel costs, food, income replacement, and someone who follows up a child who misses an appointment. In several documented programmes these measures alone raised cure rates substantially. **That is the highest-yield simple intervention in paediatric oncology and it is not medical.** Nutrition matters, because malnourished children tolerate chemotherapy worse and have higher treatment-related mortality, and feeding is cheap. Oral morphine for children is essential and frequently unavailable, and the palliative care figures in section G apply with particular force to children. The honest statement: the curative treatment of childhood cancer is not achievable by truly simple means, because it needs a hospital, a laboratory, a blood bank and months of continuity. It does not need expensive drugs, patented agents or advanced technology. The gap between an 80 per cent and a sub-30 per cent cure rate is made of organisation, supportive care and social support rather than of pharmacology.

Gaps. SEER's childhood cancer page could not be retrieved, so United States aggregate childhood cancer figures are absent. GBD 2023 childhood cancer figures were not retrieved; a GBD study of cancer in children and adolescents aged 0 to 19 exists and could not be retrieved in primary form. WHO's 400,000 annual cases and the over-80 against under-30 per cent survival figures are stated without a confidence interval or a data year on the retrieved fact sheet. The cause of most childhood cancer is unknown, which is WHO's own statement. Late-effect prevalence in survivors and the 70 per cent mortality decline from 1970 to 2020 are literature-derived. Treatment abandonment rates are reported in the paediatric oncology literature and no single global figure was retrieved.

> **Depth.** A class. Not one illness. No depth is given.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book's status, given by stratum: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

30. Neuroblastoma

What it is. A cancer of the developing sympathetic nervous system, arising in the adrenal gland or alongside the spine, almost entirely in young children. It is the commonest cancer of infancy. It is also the most biologically bizarre cancer in this chapter: some neuroblastomas disappear on their own without any treatment, and others are among the most lethal cancers in children, and the difference is largely determined by the tumour's genetics at the outset.

Measured. It is the commonest extracranial solid tumour of childhood and the commonest cancer of infancy, at roughly 6 to 10 per cent of all childhood cancer, with a median age at diagnosis of roughly 17 to 18 months and 90 per cent of cases under age 5†. Five-year survival is bimodal and the aggregate figure is uninformative: low-risk disease above 95 per cent, intermediate-risk roughly 90 to 95 per cent, high-risk roughly 50 per cent with maximal modern multimodality therapy, and MYCN-amplified metastatic disease in older children at the lower end of that. High-risk disease accounts for roughly half of all cases and the great majority of deaths, and neuroblastoma causes roughly 10 to 15 per cent of all childhood cancer deaths, disproportionate to its incidence. All figures in this entry are literature-derived: SEER publishes a neuroblastoma page which was not retrieved, and GLOBOCAN does not report neuroblastoma.

Where it starts. Essentially nothing environmental is established: no exposure, maternal factor, diet or infection has been established as a cause. Germline predisposition accounts for roughly 1 to 2 per cent: germline ALK and PHOX2B mutations cause familial neuroblastoma, and it also occurs in Hirschsprung disease, congenital central hypoventilation syndrome and Beckwith-Wiedemann syndrome. Germline ALK is the main one and it is actionable. The mutation burden is very low, consistent with the paediatric rate of 0.13 mutations per megabase against the adult 1.8: neuroblastoma is among the most quietly mutated cancers known. The dominant driver is MYCN amplification, present in roughly 20 to 25 per cent of cases and the single strongest adverse prognostic marker in paediatric oncology. Other recurrent events are ALK mutation or amplification in roughly 8 to 10 per cent, ATRX loss, TERT rearrangement and segmental chromosomal aberrations — loss of 1p and 11q, gain of 17q — while whole-chromosome gains without segmental changes mark the favourable, often spontaneously regressing tumours. Not known: **why some neuroblastomas regress spontaneously and completely, and others kill.** The spontaneous regression of stage 4S disease — widespread disease in infants involving liver, skin and marrow that disappears without treatment — is one of the most striking phenomena in oncology and it is not explained. Also unknown: what causes the initiating event, which occurs in utero; why MYCN amplification is so catastrophic; why high-risk disease relapses after apparently complete response.

Cure status. Stage 4S or MS disease in infants, and localized disease in infants without MYCN amplification: SELF-LIMITING — a substantial proportion regress completely without any treatment, and observation alone is the recommended management for selected infants. This is one of the very few genuine uses of SELF-LIMITING in this chapter. Low-risk disease: CURABLE above 95 per cent, frequently with surgery alone or observation†. Intermediate-risk disease: CURABLE at roughly 90 to 95 per cent, with moderate chemotherapy and surgery†. High-risk disease — metastatic in children over 18 months, or any MYCN-amplified disease: CURABLE in roughly 50 per cent (five-year survival), and only with the most intensive multimodality therapy in all of paediatric oncology: induction chemotherapy, surgery, high-dose chemotherapy with autologous stem cell rescue, radiotherapy, anti-GD2 immunotherapy and isotretinoin maintenance†. Relapsed high-risk neuroblastoma: RELIEF ONLY, among the worst outcomes in paediatric oncology. The early-detection question is inverted here: catching it earlier made outcomes worse rather than better. Risk is determined by biology at the outset, and screening found the tumours that were going to regress.

Prevention. No prevention exists. Screening was attempted, failed and was abandoned, and this is the single most instructive negative result in the cancer screening literature, so it belongs here in full. Urinary catecholamine metabolite screening of infants, measuring vanillylmandelic and homovanillic acid, was introduced as a national programme in Japan from 1984 and trialled in Germany, Quebec and elsewhere. **It worked as a test**: it detected large numbers of neuroblastomas, and incidence in the screened age group roughly doubled. **It did not reduce neuroblastoma mortality.** The Quebec and German studies both showed no mortality reduction, and the German study screened roughly 1.5 million children†. The explanation: screening detected the favourable, hyperdiploid, non-MYCN-amplified tumours that would have regressed spontaneously or never presented, while the high-risk MYCN-amplified tumours that cause the deaths developed and presented between screening rounds. The harm was concrete: infants with tumours that would have regressed were given surgery and chemotherapy, and treatment-related deaths occurred in children who had been destined to be well. Japan suspended its national programme in 2004†. **The overdiagnosis fraction approached the entirety of the additional detected disease, and it has never been published as a percentage.** These figures are literature-derived, and the conclusion is not in dispute and the programme was discontinued on this evidence. The general lesson applies directly to the thyroid, prostate, myeloma and chronic lymphocytic leukaemia entries in this chapter: a sensitive test applied to a population with a large reservoir of indolent or self-regressing disease produces diagnoses, treatment and harm without reducing mortality. The grade is recommend against, on demonstrated harm.

Treatment. Relapsed high-risk neuroblastoma is not curable in most patients, and the proportion rescued is not given. Observation for stage 4S and low-risk infant disease is the correct treatment and it costs nothing. Surgery is curative for localized low-risk disease. Multi-agent chemotherapy uses cyclophosphamide, doxorubicin, vincristine, cisplatin, carboplatin, etoposide and ifosfamide, all listed and all off-patent, at a total course cost in the low hundreds to low thousands of dollars. High-dose chemotherapy with autologous stem cell rescue uses melphalan, listed and off-patent, and the cost is in the stem cell infrastructure.

Radiotherapy treats the primary site in high-risk disease. **Dinutuximab, the anti-GD2 monoclonal antibody, is not on the Essential Medicines List and is on patent**. Adding it with granulocyte-macrophage colony-stimulating factor and interleukin-2 to isotretinoin maintenance improved two-year event-free survival from roughly 46 to 66 per cent in the pivotal trial†, one of the largest single advances in high-risk neuroblastoma, at a United States course cost in the region of US$100,000 to 300,000†. It is severely painful to administer, requiring an opioid infusion. Isotretinoin maintenance reduces relapse after high-dose therapy; it is not in the antineoplastic section of the list, where tretinoin is listed for acute promyelocytic leukaemia, and isotretinoin is off-patent and inexpensive. Crizotinib, lorlatinib and ceritinib for ALK-mutated disease are not listed and are on patent, and lorlatinib has produced responses in ALK-driven relapsed neuroblastoma and is the clearest targeted success in this disease. Iodine-131 MIBG therapy exploits the catecholamine uptake pathway and requires a nuclear medicine facility with radiation containment. GD2-directed cell therapy and bispecific approaches are experimental.

Simple means. Observation for stage 4S and low-risk infant disease is doing nothing, correctly, for a disease that regresses by itself. Surgical excision of a localized abdominal or paraspinal mass with basic instruments is curative for low-risk localized disease, which is a substantial fraction of all cases. Diagnosis is cheap: urinary catecholamine metabolite measurement is an inexpensive test, abdominal ultrasound detects the mass, and the diagnosis is usually straightforward in a child with an abdominal mass, bone pain and periorbital bruising. Histopathology with MYCN status determines treatment, and MYCN testing is the one genuinely necessary molecular test: without it risk cannot be assigned and treatment cannot be rationally chosen. Off-patent listed chemotherapy cures 90 to 95 per cent of intermediate-risk disease†. Oral morphine matters, because neuroblastoma bone pain is severe and dinutuximab-related pain is extreme. High-risk neuroblastoma has no simple-means answer and it accounts for half the cases and almost all the deaths: the curative package requires stem cell rescue, radiotherapy, MIBG therapy, and an antibody costing over US$100,000 a course in the United States, that is not listed. In a setting with off-patent chemotherapy and surgery alone, low- and intermediate-risk neuroblastoma — roughly half of cases — is curable, and high-risk neuroblastoma is not. That is the honest division.

Gaps. All figures in this entry are literature-derived: SEER's neuroblastoma page was not retrieved and GLOBOCAN does not report neuroblastoma. Why some neuroblastomas regress spontaneously is unexplained, and it is the central scientific question. Dinutuximab is not listed despite being the main recent advance in high-risk disease. The screening trial figures are literature-derived. No prevention exists and no aetiology is known. Relapsed high-risk neuroblastoma has no effective treatment.

> **Depth.** Starts in: a neural-crest cell. Size: 15 µm†; depth +5.28. First complaint: about 2.2 years († from conception to median age 17 months); time depth 49.59. One untreated course: no number ([B] can disappear by itself).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

31. Wilms tumour

What it is. A cancer of the developing kidney, occurring almost entirely in young children. It presents as a large painless abdominal mass. It is among the most curable cancers in this chapter, cured in roughly 90 per cent of children in high-income countries, and it was the first solid tumour of childhood for which multi-agent chemotherapy was shown to work, which makes it the founding success of cooperative-group paediatric oncology.

Measured. It is the commonest renal tumour of childhood and roughly 5 to 6 per cent of all childhood cancer, with a median age at diagnosis of roughly three to four years and roughly 10 per cent bilateral†. Five-year survival is roughly 90 per cent overall in high-income countries, above 95 per cent for favourable-histology localized disease, roughly 75 to 85 per cent for stage IV favourable histology, and roughly 50 to 60 per cent for anaplastic histology†. Survival in low-income settings is markedly lower, reported in the region of 25 to 50 per cent in several African series†, for the reasons set out in entry 29 — late presentation, abandonment, absent supportive care — rather than because of tumour biology. All figures are literature-derived: SEER publishes a Wilms tumour page which was not retrieved, and

GLOBOCAN does not report Wilms tumour. Survival rose from under 30 per cent in the 1950s to roughly 90 per cent now, achieved entirely with off-patent drugs and surgery through successive cooperative-group trials.

Where it starts. Nothing environmental is established. Germline predisposition accounts for roughly 10 to 15 per cent, higher than in most childhood cancers†. WAGR syndrome, from WT1 deletion, with Wilms tumour, aniridia, genitourinary anomalies and intellectual disability, carries a Wilms tumour risk of roughly 45 to 60 per cent†; Denys-Drash and Frasier syndromes, from WT1 point mutations, carry a very high risk; Beckwith-Wiedemann syndrome, from an imprinting defect at 11p15, carries roughly 5 to 10 per cent†; hemihypertrophy and isolated overgrowth raise risk; and germline TRIM28, REST, DIS3L2, DICER1 and Li-Fraumeni follow, with familial Wilms tumour rare. Nephrogenic rests — persistent embryonal kidney tissue — are the precursor lesion, present in roughly 40 per cent of unilateral and nearly all bilateral cases†. The mutation burden is very low, consistent with the paediatric rate of 0.13 mutations per megabase against the adult 1.8. The disease is driven by developmental and epigenetic lesions rather than by point mutations from exposure: WT1 mutation, loss of imprinting at 11p15 affecting IGF2, CTNNB1 and AMER1 mutation, and mutations in the microRNA-processing genes DROSHA, DGCR8 and DICER1†. It is a disease of failed differentiation rather than of accumulated damage. Not known: the cause of the sporadic majority; why nephrogenic rests persist and why only a minority transform; the trigger for the imprinting defect.

Cure status. Localized favourable histology, stages I to III: CURABLE above 90 to 95 per cent, with nephrectomy and chemotherapy, plus radiotherapy for stage III. Stage IV favourable histology, usually lung metastases: CURABLE in roughly 75 to 85 per cent†. Pulmonary metastases frequently resolve completely with chemotherapy and whole-lung irradiation, and cure with widespread metastases is routine. Bilateral disease, stage V: CURABLE with nephron-sparing surgery after chemotherapy, with cure and preserved renal function the goal. Anaplastic, unfavourable histology: CURABLE in roughly 50 to 60 per cent, worse with diffuse anaplasia and advanced stage†. Relapsed favourable-histology disease: CURABLE in roughly 50 per cent with salvage therapy†, unusually good for a relapsed childhood solid tumour. It is reliably curable when caught early and also when caught late: metastatic Wilms tumour is cured in the large majority, which makes it, after testicular cancer and Hodgkin lymphoma, the clearest example in this chapter of a metastatic solid tumour cured by off-patent chemotherapy. The dominant problem in high-income settings is the late cost of cure: renal insufficiency after nephrectomy, especially bilateral; cardiac toxicity from doxorubicin; second malignancy after radiotherapy; and in girls, uterine damage from abdominal irradiation affecting later pregnancy. Successive trials have accordingly reduced treatment for the lowest-risk groups, and some now receive no chemotherapy at all after nephrectomy.

Prevention. No prevention exists. Surveillance in predisposition syndromes — MODERATE: three- to four-monthly renal ultrasound until age five to seven is recommended in children with Beckwith-Wiedemann syndrome, WAGR syndrome, Denys-Drash syndrome, hemihypertrophy and other high-risk syndromes, and it detects tumours at a smaller size and lower stage. The evidence is cohort-based rather than randomised, and because the cure rate is already above 90 per cent with standard presentation the incremental benefit is in reducing treatment intensity rather than in preventing death. Ultrasound is cheap, portable and harmless, which makes the balance favourable. There is no population screening and no rationale: the incidence is far too low and the cure rate at presentation is already around 90 per cent, so screening has almost nothing to add. Overdiagnosis is not an issue, because Wilms tumour does not regress spontaneously and nephrogenic rests, while common, are not detectable by imaging at a useful scale.

Treatment. The proportion of bilateral disease cured with nephron-sparing surgery after chemotherapy is not given. Most are cured. Nephrectomy is the central curative treatment. A transabdominal radical nephrectomy in a child is a conventional operation requiring basic instruments, anaesthesia and blood availability, and avoiding tumour rupture during surgery matters a great deal, because rupture upstages the tumour and mandates whole-abdomen radiotherapy. Two standards coexist and both are correct. North American practice performs nephrectomy first and then chemotherapy based on stage and histology; European practice gives preoperative chemotherapy and then nephrectomy. Both achieve roughly 90 per cent survival, the European approach downstaging tumours and reducing rupture and the North American approach preserving accurate initial staging. In settings where surgical expertise is limited the preoperative-chemotherapy approach has practical advantages, because it shrinks the tumour first.

Vincristine and dactinomycin are both listed and both off-patent, and dactinomycin's listed indications include nephroblastoma. That two-drug regimen cures the large majority of localized favourable-histology disease, given over weeks to months, intravenously, at a total drug cost in the region of tens to low hundreds of dollars. Doxorubicin, listed, off-patent and cheap, is added for higher stages. Cyclophosphamide, etoposide, carboplatin and ifosfamide, all listed and all off-patent, serve anaplastic histology and relapse. Radiotherapy to the flank or whole abdomen for stage III, and to the whole lung for pulmonary metastases, requires a linear accelerator and is being minimised because of late effects. Nephron-sparing surgery serves bilateral disease after chemotherapy. Supportive care covers transfusion, antibiotics, antiemetics and nutrition. **There is no expensive targeted agent and no immunotherapy in standard Wilms tumour treatment. The entire curative armamentarium is off-patent and listed.** That is unusual and it should be said plainly.

Simple means. Wilms tumour has one of the strongest simple-means profiles of any cancer in this chapter. Radical nephrectomy in a child is a standard general or paediatric surgical operation requiring basic instruments, anaesthesia and blood, and combined with vincristine and dactinomycin it cures over 90 per cent of localized favourable-histology disease†. Vincristine with dactinomycin is two off-patent listed drugs at a total cost of tens to low hundreds of dollars, curing the majority, and they are intravenous and given as short injections rather than prolonged infusions, which makes delivery in an outpatient clinic feasible. Preoperative chemotherapy to shrink a very large tumour before operating is particularly well suited to settings where tumours present late and large and where surgical expertise is limited, because it reduces the risk of intraoperative rupture. Diagnosis is possible by abdominal examination and ultrasound: a large smooth painless abdominal mass in a well-looking toddler that does not cross the midline is clinically distinctive, and ultrasound is cheap, portable, needs no contrast and no radiation and distinguishes a renal from an adrenal or hepatic mass, which is the key distinction from neuroblastoma. A chest radiograph detects lung metastases. This is one of very few cancers in this chapter diagnosable to a treatable standard with a hand and an ultrasound probe. Renal ultrasound surveillance in syndrome-predisposed children is cheap, portable and harmless. Oral morphine, nutrition and transfusion follow. Where nothing simple exists: radiotherapy for stage III disease and for pulmonary metastases, and nephron-sparing surgery for bilateral disease, both requiring resources that are not simple; anaplastic histology requires intensified chemotherapy and worse outcomes follow without it; and the whole package requires reliable histopathology, because anaplastic histology changes the treatment entirely and because distinguishing Wilms tumour from neuroblastoma, clear cell sarcoma of the kidney and rhabdoid tumour determines which regimen is used. The central fact is strong: **Wilms tumour is cured in roughly 90 per cent of children by an operation a district surgeon can perform and two drugs that cost tens of dollars.** Where that does not happen, and survival in parts of Africa is reported at 25 to 50 per cent, the cause is late presentation, treatment abandonment and absent supportive care, not the price or availability of the medicines.

Gaps. All figures are literature-derived: SEER's Wilms tumour page was not retrieved and GLOBOCAN does not report it. The low-income-setting survival figures are literature-derived and the range is wide and poorly characterised. The syndrome-specific risks are literature-derived. There is no randomised evidence for syndrome surveillance. The cause of sporadic Wilms tumour is unknown. The North American and European approaches differ — nephrectomy first against chemotherapy first — and both are standard, which is a genuine and long-standing disagreement between two major cooperative groups with equivalent outcomes. Late effects on renal function and on later pregnancy after abdominal irradiation are literature-derived.

> **Depth.** Starts in: a nephrogenic cell. Size: 15 µm†; depth +5.28. First complaint: about 4.2 years († from conception to median age 3.5); time depth 50.19. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book's status, given by stratum: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

32. Medulloblastoma

What it is. A malignant tumour of the cerebellum, at the back of the brain, and the commonest malignant brain tumour of childhood. It blocks the flow of cerebrospinal fluid, so children present with headache, vomiting and unsteadiness. It seeds along the spinal cord, which is why treatment has to cover the whole brain and spine, and that is the source of almost all of the lasting damage it causes.

Measured. It is roughly 20 per cent of all childhood brain tumours and the commonest malignant paediatric central nervous system tumour, at roughly one to two cases per million children a year. The peak age is five to nine years, roughly 70 per cent occur under age 10, and the male predominance is roughly 1.5 to 2 to 1†. Five-year survival depends almost entirely on molecular subgroup, and the 2021 WHO classification reorganised the disease around four of them. WNT-activated disease, roughly 10 per cent of cases and in older children, has five-year survival above 90 to 95 per cent and is the subgroup in which de-escalation trials are active. SHH-activated TP53-wildtype disease, roughly 15 per cent, in infants and adults, runs at roughly 70 to 80 per cent. SHH-activated TP53-mutant disease, roughly 5 per cent, in children 4 to 17 and frequently with germline TP53 mutation, runs at roughly 40 per cent. Group 3, roughly 25 per cent, in infants and young children, frequently MYC-amplified and metastatic at diagnosis, runs at roughly 40 to 50 per cent and is the worst subgroup. Group 4, roughly 35 per cent and the commonest, runs at roughly 75 to 80 per cent†. Overall five-year survival in high-income countries is roughly 70 to 75 per cent for standard-risk and roughly 50 to 60 per cent for high-risk disease, with infants under three doing worst, partly because craniospinal irradiation is avoided in them. All figures are literature-derived: SEER folds medulloblastoma into brain and other nervous system, at 32.9 per cent overall five-year survival, which does not describe medulloblastoma, and GLOBOCAN does not report it separately.

Where it starts. Nothing environmental is established. Germline predisposition accounts for roughly 5 to 6 per cent, and identifying it changes management†. Li-Fraumeni syndrome, from germline TP53 mutation, gives SHH/TP53-mutant disease, and critically, radiotherapy in a germline TP53 carrier carries a very high risk of radiation-induced second malignancy, so the diagnosis should change the treatment plan. Gorlin syndrome, from PTCH1 or SUFU mutation, gives SHH disease usually in infants, and again radiotherapy causes a very high rate of basal cell carcinomas in the irradiated field in these children and should be avoided. Familial adenomatous polyposis gives WNT disease. Germline BRCA2, PALB2, ELP1 — recently identified and relatively common in SHH disease — and Fanconi anaemia follow. The mutation burden is low, consistent with the paediatric rate of 0.13 mutations per megabase against the adult 1.8, and the disease is driven by pathway activation and structural events: CTNNB1 mutation in WNT disease, PTCH1, SMO or SUFU mutation or GLI2 amplification in SHH disease, MYC amplification with GFI1 or GFI1B enhancer hijacking in Group 3, and KDM6A, SNCAIP and PRDM6 alterations with isochromosome 17q in Group 4†. Medulloblastoma is one of the clearest demonstrations that childhood cancers are diseases of developmental pathway dysregulation rather than of mutational accumulation. Not known: the cause of the sporadic majority; the cell of origin for Groups 3 and 4, where WNT disease arising from the lower rhombic lip and SHH disease from granule neuron precursors are both established and Groups 3 and 4 are not settled; why the subgroups differ so much in age distribution and metastatic propensity.

Cure status. WNT-activated, standard risk: CURABLE above 90 to 95 per cent†. De-escalation trials — reduced craniospinal radiotherapy dose, reduced chemotherapy — are active precisely because these children are cured and are being harmed by the cure. Group 4 and SHH/TP53-wildtype, standard risk: CURABLE in roughly 75 to 80 per cent†. Group 3, MYC-amplified, and metastatic disease: CURABLE in roughly 40 to 50 per cent†. SHH/TP53-mutant: CURABLE in roughly 40 per cent†. Infants under three: CURABLE in roughly 40 to 60 per cent, using intensive chemotherapy with or without high-dose therapy and stem cell rescue, specifically to avoid craniospinal irradiation in a developing brain. Relapsed medulloblastoma: RELIEF ONLY — relapse after craniospinal irradiation is almost always fatal, among the worst outcomes in paediatric oncology. Early detection partly applies, and the dominant determinant is subgroup rather than timing. There is no screening and no pre-symptomatic phase that could be found. What does matter is recognising raised intracranial pressure before the child is in extremis: early-morning headache and vomiting in a child, with ataxia or a head tilt, is medulloblastoma or another posterior fossa tumour until proven otherwise, and delay leads to presentation with coning, blindness from papilloedema,

or death from acute hydrocephalus. The cost of cure is the central problem, and in medulloblastoma it is more severe than in any other curable childhood cancer. Craniospinal irradiation in a developing child causes permanent loss of intelligence: reported losses run at roughly two to four points of measured intelligence quotient per year of follow-up, with greater loss at younger ages at treatment. It also causes growth hormone deficiency and short stature, hypothyroidism and other pituitary failure, hearing loss compounded by cisplatin, spinal growth arrest, stroke, and second malignancies in the irradiated field including meningioma, glioma and thyroid cancer. A child cured of medulloblastoma at age four frequently has lifelong cognitive and endocrine disability. **The whole modern research programme in medulloblastoma is about giving less radiation to the children who can be cured without it, and this is the clearest case in the chapter where the harm of successful treatment drives the research agenda.**

Prevention. No prevention exists. There is no screening and no rationale: the incidence is roughly one to two per million children, no test exists and no pre-symptomatic phase is detectable. Surveillance in predisposition syndromes — MODERATE: brain imaging surveillance is part of Li-Fraumeni and Gorlin syndrome protocols. The real prevention activity is prevention of treatment-induced harm, and it is substantial. Avoiding or reducing craniospinal irradiation — STRONG on the harm-reduction endpoint: infants are treated with chemotherapy-only or chemotherapy-plus-focal-radiotherapy strategies specifically to protect the developing brain, and risk-adapted reduction of craniospinal dose in WNT-subgroup and standard-risk disease is the subject of active trials. Avoiding radiotherapy entirely in germline TP53 and Gorlin syndrome carriers — STRONG, because radiation-induced second cancers in these children are frequent and often fatal. Proton beam therapy instead of photons — MODERATE: it reduces dose to the cochlea, pituitary, thyroid, heart and vertebral growth plates, which should reduce late effects, and the long-term comparative evidence is still accruing and it is available to a very small fraction of children worldwide.

Treatment. Relapse after craniospinal irradiation is not curable in most patients, and the proportion rescued is not given. Maximal safe surgical resection affects outcome, and relief of hydrocephalus is frequently the immediate life-saving act; it requires neurosurgical capability and imaging. Cerebrospinal fluid diversion — an external ventricular drain, a ventriculoperitoneal shunt or an endoscopic third ventriculostomy — is the emergency intervention: a child with acute obstructive hydrocephalus from a posterior fossa tumour will die or be blinded without it, and a shunt or a drain buys the time to do everything else. Craniospinal irradiation with a boost to the posterior fossa is essential for cure in children over three, because the disease seeds the whole neuraxis. **It is the single most effective and the single most damaging component of treatment.** It requires a linear accelerator with the capacity to plan a craniospinal field, which is technically demanding. Chemotherapy uses cisplatin, carboplatin, vincristine, cyclophosphamide, etoposide, lomustine and methotrexate; cisplatin, whose listed indications include low-grade glioma, carboplatin, vincristine, whose listed indications include low-grade glioma, cyclophosphamide, etoposide and methotrexate are all listed and all off-patent, and lomustine is not listed and has been subject to very large United States price increases, as entry 17 records. The standard regimens are built almost entirely from off-patent listed drugs at a total drug cost in the low hundreds to low thousands of dollars. High-dose chemotherapy with autologous stem cell rescue is used in infants to avoid irradiation and in some high-risk protocols. Vismodegib and sonidegib for SHH-subgroup disease are not listed and are on patent, and they are active in relapsed disease, with a specific and serious caution: hedgehog inhibitors cause irreversible premature growth plate fusion in growing children, so their use in paediatric medulloblastoma is restricted. That is an unusual and instructive toxicity — a drug that works and cannot be given to the patients who would benefit. No molecularly targeted approach is established for Group 3 or MYC-amplified disease, and that is the principal unmet need. Supportive care: dexamethasone, listed and off-patent at an indicative 24 cents a 4 mg tablet in the UNICEF Supply Catalogue, October 2026, for peritumoural oedema and raised intracranial pressure; anticonvulsants; antiemetics, cisplatin being among the most emetogenic drugs in use; audiological monitoring; growth hormone and thyroxine replacement, with levothyroxine listed for hypothyroidism, off-patent and a few dollars a year; and long-term neuropsychological and endocrine follow-up.

Simple means. Cerebrospinal fluid diversion is the highest-value simple intervention in this entry. A ventriculoperitoneal shunt or a burr-hole external ventricular drain can be placed with basic neurosurgical instruments and it is immediately life-saving in obstructive hydrocephalus, and where a shunt is all that can

be offered it still prevents death by coning and preserves vision. Dexamethasone is listed, off-patent, cents a dose, oral or injectable, and reduces peritumoural oedema and raised intracranial pressure within hours, relieving headache and vomiting and restoring consciousness; as in entry 17 it is the most valuable single drug available simply. Off-patent listed chemotherapy — cisplatin, vincristine, cyclophosphamide, etoposide and carboplatin — costs in the low hundreds of dollars. Levothyroxine is listed, off-patent and a few dollars a year, and treating the hypothyroidism that follows craniospinal irradiation is cheap and transformative; growth hormone is expensive and not listed. Recognising the clinical picture costs nothing: early-morning headache with vomiting, ataxia, a head tilt or a squint in a child, with or without papilloedema on fundoscopy, is a posterior fossa tumour until excluded, and fundoscopy needs an ophthalmoscope. The diagnosis is frequently missed for months, with the child treated for migraine or gastroenteritis. Oral morphine, antiemetics, nursing care and family support follow. The honest statement is stark: **medulloblastoma cannot be cured without a linear accelerator capable of craniospinal irradiation, and it cannot be diagnosed without computed tomography or magnetic resonance imaging.** Neither has a simple-means substitute. A district hospital can relieve the hydrocephalus and keep a child comfortable; it cannot cure medulloblastoma. And the irradiation that cures also permanently damages the child's brain, hearing, growth and endocrine function, so medulloblastoma is simultaneously the childhood cancer most dependent on advanced technology for cure and the one in which the cure does the most harm. There is no version of this that is simple.

Gaps. All figures are literature-derived: SEER folds medulloblastoma into brain and other nervous system and GLOBOCAN does not report it. Subgroup frequencies and subgroup-specific survival are literature-derived. The intelligence loss figures after craniospinal irradiation are literature-derived despite being central to treatment decisions. The 2021 classification reorganised the disease into molecular subgroups, which makes survival figures published before and after it non-comparable, and most quoted figures mix the two. Group 3 and MYC-amplified disease has no effective targeted therapy and is the principal unmet need. Relapsed medulloblastoma after craniospinal irradiation is almost uniformly fatal and there is no established salvage therapy. Hedgehog inhibitors work in SHH disease and cannot be given to growing children, an unresolved practical problem. The cause of sporadic medulloblastoma is unknown. Proton therapy's comparative late-effect benefit is not yet established with long-term data, and it is available to very few children.

> **Depth.** Starts in: a granule-neuron precursor. Size: 10 µm†; depth +4.91. First complaint: about 6.8 years († from conception to median age 6); time depth 50.61. One untreated course: about 4 months († months); depth 47.86.
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

33. Retinoblastoma

What it is. A cancer of the developing retina, occurring almost entirely in children under five. It is the commonest eye cancer of childhood. It is caused by loss of both copies of a single gene, RB1 — the first tumour suppressor gene ever identified, and the disease from which the two-hit model of cancer genetics was derived. In high-income countries almost every child survives; in low-income countries a large proportion die, and the difference is almost entirely one of how late the child presents.

Measured. Roughly 8,000 children worldwide develop retinoblastoma each year, at roughly one in 15,000 to 20,000 live births, which is roughly 2 to 4 per cent of all childhood cancer†. The median age at diagnosis is roughly 18 months for bilateral hereditary disease and roughly 24 to 30 months for unilateral disease†. Roughly 40 per cent is hereditary, from a germline RB1 mutation, and usually bilateral or multifocal; roughly 60 per cent is sporadic and unilateral†. **Survival shows the largest divergence of any cancer in this chapter.** In high-income countries five-year survival is above 95 to 98 per cent and death from retinoblastoma is now rare. In low-income countries, particularly in sub-Saharan Africa and parts of Asia, five-year survival is reported in the region of 30 to 50 per cent, and in some series below 30 per cent†. The reason is stage at presentation: in high-income countries children present with a white pupil or a squint while the tumour is intraocular and curable, and in low-income countries a large proportion present with

proptosis, the eye pushed forward by extraocular tumour, by which time the disease is frequently metastatic and usually fatal. A global multicentre study of presentation found the proportion presenting with extraocular disease ranging from near zero in high-income countries to a majority in low-income countries. All figures are literature-derived: GLOBOCAN does not report retinoblastoma and SEER publishes a page which was not retrieved.

Where it starts. RB1, and the attribution is essentially complete. Biallelic inactivation of RB1 is present in the great majority of retinoblastomas, germline in roughly 40 per cent and somatic in the remainder, and a small minority, roughly 2 per cent, are MYCN-amplified with intact RB1, which are unilateral, present very young and are histologically distinctive. Germline RB1 mutation carriers have a penetrance above 90 per cent for retinoblastoma; roughly 25 per cent of germline cases are inherited from an affected parent and roughly 75 per cent are new germline mutations†. Carriers are at risk of bilateral and multifocal disease and of a second primary tumour outside the eye, and they have a roughly 5 per cent risk of trilateral disease, an intracranial midline tumour, usually pineoblastoma, which is frequently fatal. **Second malignancies in germline carriers are the single most important long-term fact**: survivors of hereditary retinoblastoma carry a markedly increased lifetime risk of second cancers, principally osteosarcoma, soft tissue sarcoma and melanoma, at a cumulative incidence reported in the region of 25 to 40 per cent by age 50†. External beam radiotherapy to the orbit amplifies that risk substantially, with reported relative risks for radiation-associated sarcoma in the irradiated field several-fold above the already elevated baseline. That is why external beam radiotherapy has been largely abandoned in retinoblastoma. The mutation burden is very low, and retinoblastoma is, with chronic myeloid leukaemia, among the closest things in oncology to a single-gene cancer: loss of RB1 plus few additional events on a quiet genome, consistent with the paediatric rate of 0.13 mutations per megabase against the adult 1.8. Recurrent secondary events include MYCN and MDM4 gain, BCOR mutation and loss of 16q, and the disease requires remarkably little beyond RB1 loss†. Nothing environmental is established: no maternal, dietary or exposure risk factor is established, and advanced paternal age has been associated with new germline mutations. Not known: why RB1 loss produces a retinal tumour specifically and in a narrow developmental window, when the gene is expressed throughout the body; why the disease does not occur after about age five, even in germline carriers whose cells continue to lack one copy; the cell of origin, where cone precursors are the leading candidate and it is not settled.

Cure status. Intraocular retinoblastoma: CURABLE above 95 to 98 per cent survival in high-income countries†. Cure of the child is close to universal, and the clinical question is whether the eye and the vision can also be saved. Small tumours are cured by focal therapy — laser photocoagulation, cryotherapy or plaque brachytherapy — with vision preserved; larger tumours require systemic or intra-arterial chemotherapy to shrink them first; and advanced intraocular disease requires enucleation, removal of the eye, which cures the child and loses the eye. Extraocular retinoblastoma with orbital extension: CURABLE in roughly 30 to 50 per cent, with intensive chemotherapy, surgery, radiotherapy and sometimes high-dose therapy with stem cell rescue. Metastatic retinoblastoma without central nervous system involvement: CONTROLLABLE. High-dose chemotherapy with stem cell rescue cures some. Central nervous system metastatic disease and trilateral retinoblastoma: RELIEF ONLY — almost uniformly fatal. It is reliably curable when caught early, more completely than almost any cancer in this chapter, and the converse is equally stark. **Retinoblastoma is the clearest case in this chapter where the entire difference between a 98 per cent and a sub-30 per cent survival rate is the delay between the first visible sign and the first medical assessment.** The tumour biology does not differ between Boston and Bamako. The presentation does. The dominant long-term problem in germline carriers is the second cancer risk, at a cumulative incidence of roughly 25 to 40 per cent by age 50 and amplified by radiotherapy†: a child cured at 18 months has a substantial chance of developing osteosarcoma or melanoma as a young adult, and lifelong surveillance is required.

Prevention. Genetic counselling and prenatal or preimplantation genetic testing in families with a germline RB1 mutation — STRONG, and retinoblastoma is one of the few cancers where this is routine practice. In a family with a known mutation, affected pregnancies can be identified, and newborns at risk can be examined under anaesthesia from birth on a defined schedule, so that tumours are found at a size treatable by focal therapy with vision preserved. That changes the outcome from enucleation to vision-sparing cure. Avoiding external beam radiotherapy in germline carriers — STRONG: the radiation-amplified second

cancer risk is large enough that external beam radiotherapy has been largely abandoned, one of the clearest and most justified treatment de-escalations in oncology. No primary prevention of sporadic retinoblastoma exists. On screening this is the important case, because retinoblastoma is the one childhood cancer where a form of screening works. There is no population screening programme and no justification for one in a general population of this incidence. Targeted surveillance of at-risk newborns — children of germline carriers, siblings of affected children — by serial examination under anaesthesia is standard, effective and preserves vision, and that is surveillance of known high risk rather than population screening. And awareness-raising about leukocoria, a white pupil instead of a red reflex, is the single most effective intervention in this disease worldwide, and it is not a medical technology at all. A white reflex can be seen in a photograph taken with a flash. Public awareness campaigns, routine red reflex examination of every newborn and infant by any health worker with an ophthalmoscope or even a torch, and parental education have all been associated with earlier presentation. The red reflex test is part of routine newborn examination in many countries and costs nothing beyond an ophthalmoscope: where it is done, children present intraocular, and where it is not, they present with proptosis. The harms: a positive red reflex test is far more often a cataract, a retinal detachment, Coats disease or a benign finding than a retinoblastoma, so referrals are mostly false alarms. Given the consequence of a missed retinoblastoma, that is a strongly favourable trade. **No overdiagnosis problem exists: retinoblastoma does not regress and is not indolent.** The grades are STRONG for red reflex examination and leukocoria awareness, STRONG for genetic counselling and at-risk newborn surveillance, and population screening is not applicable.

Treatment. High-dose chemotherapy with stem cell rescue cures some metastatic retinoblastoma without central nervous system involvement, and the proportion is not given. Enucleation cures intraocular retinoblastoma. It is a short operation requiring basic instruments and anaesthesia, and the specimen provides the histology that determines whether adjuvant chemotherapy is needed. It is the correct treatment for advanced intraocular disease and it is definitively curative, and in settings without access to chemotherapy or focal therapy, prompt enucleation is the intervention that saves the child's life. Performing it early, before extraocular extension, is what distinguishes a 98 per cent from a sub-30 per cent survival rate. Focal therapy — laser photocoagulation, cryotherapy, episcleral plaque brachytherapy — serves small tumours and preserves the eye and vision, and requires an ophthalmologist with specific equipment. Systemic chemoreduction uses carboplatin, vincristine and etoposide, and all three are listed and all off-patent, with vincristine's listed indications including retinoblastoma, at a total drug cost in the region of tens to low hundreds of dollars a course. Chemoreduction shrinks tumours to a size treatable by focal therapy and has substantially reduced the need for enucleation and for radiotherapy, with one caution: etoposide carries a leukaemia risk, which matters particularly in germline carriers who are already cancer-prone. Intra-arterial chemotherapy — ophthalmic artery infusion of melphalan, topotecan or carboplatin — delivers high local drug concentration with minimal systemic exposure and has further improved eye salvage, and it requires interventional neuroradiology to pass a microcatheter into the ophthalmic artery of an infant and is available in a small number of centres. Intravitreal chemotherapy for vitreous seeding uses melphalan, listed and off-patent, or topotecan, in a technically simple injection with a specific safe-injection technique to avoid tumour spread along the needle track. Adjuvant chemotherapy after enucleation for high-risk histological features — optic nerve or choroidal invasion — uses off-patent listed drugs. External beam radiotherapy is effective and largely abandoned because of the second cancer risk in germline carriers, and is still used in some extraocular and salvage settings. High-dose chemotherapy with autologous stem cell rescue serves metastatic disease without central nervous system involvement. An ocular prosthesis after enucleation is a cosmetic shell, cheap and important: the social consequences of an empty socket in a child are substantial, and a prosthesis is a simple manufactured item. Lifelong second-cancer surveillance in germline carriers requires clinical examination, awareness of bone pain, skin surveillance for melanoma, and avoiding further radiation exposure throughout life.

Simple means. Retinoblastoma has, alongside keratinocyte skin cancer, the most favourable simple-means profile in this chapter, and the widest gap between what is possible and what is delivered. **The red reflex test comes first.** An ophthalmoscope, or in a dark room a torch, held at arm's length from an infant's eyes: a normal eye reflects red and a retinoblastoma reflects white. The test takes seconds, costs nothing beyond the instrument, requires no specialist, and detects retinoblastoma at a stage where the child's life and often the eye can be saved, and it can be taught to any health worker in minutes. **Per unit of cost, that is arguably the most effective cancer early-detection intervention described anywhere in this chapter.**

Leukocoria awareness among parents requires no equipment at all, only information: a white pupil in a flash photograph is a recognised presenting sign, and public awareness campaigns have brought children to attention earlier. Enucleation with basic instruments is a short operation under general anaesthesia performable in a district hospital, and it cures intraocular retinoblastoma. For a child with advanced intraocular disease and no access to chemotherapy or focal therapy, prompt enucleation is the life-saving treatment and it is wholly achievable by simple means. The barrier is frequently not surgical capability but parental refusal — understandably, since the operation removes a child's eye — and in several documented series refusal or delay of enucleation is a leading cause of death, so counselling and family support are part of the treatment and they are not technological. Carboplatin, vincristine and etoposide are three off-patent listed drugs at tens to low hundreds of dollars a course, which shrink tumours and save eyes. An ocular prosthesis is a simple manufactured shell, locally producible, with a substantial social benefit. Oral morphine serves pain in advanced disease. Where nothing simple exists: intra-arterial chemotherapy, plaque brachytherapy and laser therapy — the techniques that save the eye and the vision rather than merely the child — all require specialist ophthalmological or interventional radiology capability; metastatic and central nervous system disease requires high-dose therapy with stem cell rescue; and trilateral retinoblastoma is essentially untreatable. **But the central and uncomfortable fact about retinoblastoma is this: the difference between a 98 per cent survival rate and a sub-30 per cent survival rate is not made of intra-arterial chemotherapy or plaque brachytherapy. It is made of a torch, a trained health worker who looks at a child's eyes, a parent who knows that a white pupil is an emergency, and a surgeon willing and able to remove an eye promptly. Every one of those is simple. Retinoblastoma is the sharpest example in this chapter of a curable cancer killing children for want of means that are already simple and already cheap.**

Gaps. All figures are literature-derived: GLOBOCAN does not report retinoblastoma and SEER's page was not retrieved. The 8,000 annual global cases, the high-income against low-income survival figures and the extraocular presentation proportions are literature-derived, and these are the key figures of the entry, so their absence from primary verification is a real limitation. The second cancer cumulative incidence in germline carriers and the radiation amplification of that risk are literature-derived despite determining lifelong management. No PDQ prevention summary for retinoblastoma was retrieved, so no evidence grades are attached. No randomised evidence exists for red reflex screening, which is recommended universally on the strength of the stage-shift argument and the negligible cost; the evidence is observational and ecological. Why RB1 loss produces a retinal tumour in a narrow developmental window is unexplained. Trilateral retinoblastoma has no effective treatment. Rates of enucleation refusal and its contribution to mortality are reported in regional series and no global figure was retrieved.

> **Depth.** Starts in: a retinoblast. Size: 10 µm†; depth +4.91. First complaint: about 2.8 years († from conception to median age 2); time depth 49.79. One untreated course: no number.
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> **Model reading.** Way of ending: rebuild. Layer: reading. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Benign neoplasms of clinical importance

34. Uterine fibroids

What it is. Benign tumours of the smooth muscle of the womb. They are the commonest tumour of any kind in women, they are not cancer and they essentially never become cancer, and they are nonetheless one of the largest single causes of surgery and of iron-deficiency anaemia in women worldwide. They cause heavy bleeding, pain, pressure and infertility, and they shrink after the menopause.

Measured. The cumulative incidence of fibroids by age 50 is roughly 70 per cent in white women and above 80 per cent in black women, as measured by systematic ultrasound screening of asymptomatic women, and clinically significant symptomatic fibroids affect roughly 25 to 30 per cent of women of

reproductive age†. A second source line names the Baird ultrasound-screened cohort and gives about 70 per cent in white women and about 80 to 90 per cent in black women. The two source lines disagree. The first reads “above 80 per cent” and carries a dagger. The second reads “80 to 90 per cent” and names its source, which was not opened again. Both are printed. Incidence rises through the reproductive years and peaks in the forties. The ancestry difference is one of the largest in this chapter: black women develop fibroids earlier, in greater number and larger size, have more severe symptoms, and undergo hysterectomy at roughly two to three times the rate of white women, and the difference is not explained by access, body mass index or parity. In black women the fibroids often appear in the twenties. Vitamin D deficiency, genetic ancestry, hair relaxer use and allostatic load (the accumulated wear of chronic stress) have all been proposed as explanations, and none is established. Fibroids are the leading indication for hysterectomy: in the United States roughly 200,000 to 300,000 hysterectomies a year are performed for them, and they account for roughly a third to 40 per cent of all hysterectomies†. A second source line calls fibroids the leading indication for hysterectomy worldwide, at about 30 to 40 per cent of hysterectomies in many countries†. The two source lines differ in scope, the United States against many countries, and in the lower bound, a third against 30 per cent. Both are printed. GLOBOCAN and SEER do not report benign neoplasms, so there is no figure for fibroids in the sources that supply the rest of this chapter. GBD does report uterine fibroids as a cause of disability, and GBD 2023’s years-lived-with-disability table ranks gynaecological diseases tenth overall at 28.6 million, interval 19.5 to 40.0 million, with no fibroid-specific row retrieved. An earlier edition does give figures: GBD 2019 gave roughly 230 million women affected worldwide, about 0.6 to 0.8 million DALYs (disability-adjusted life years) and negligible deaths. Mortality is essentially zero directly: the mortality attributable to fibroids is surgical mortality and the consequences of severe anaemia, and in settings without safe blood transfusion or safe surgery, death from fibroid-related haemorrhage and anaemia does occur. Malignant transformation does not happen: uterine leiomyosarcoma is a distinct disease rather than a transformed fibroid. The risk that a clinically diagnosed fibroid is in fact a leiomyosarcoma is low and contested, with estimates clustering around one in 350 to one in 1,000 for women undergoing surgery for presumed fibroids and wide variation by age. That became practically important because of power morcellation.

Where it starts. Oestrogen and progesterone dependence is established: fibroids grow during reproductive life, enlarge in pregnancy, shrink after the menopause and do not occur before puberty. African ancestry gives roughly two- to threefold higher incidence with markedly earlier onset and greater severity. Early menarche and nulliparity raise risk, and parity is protective with risk falling with each birth, by about 20 to 30 per cent for each term pregnancy†. Obesity raises risk, at roughly 20 per cent per 10 kg of weight gain in some cohorts†. Family history gives roughly two- to threefold increased risk in first-degree relatives. Heritability is estimated at about 26 to 69 per cent depending on the study, and twin studies support a substantial genetic component. A second source line puts the risk for a first-degree relative at about 2.5 times†, which lies inside the range above. Hypertension and vitamin D deficiency are associated and causality is not established; vitamin D deficiency is more prevalent in women of African ancestry and has been proposed as a partial explanation for the ancestry difference, and that is a hypothesis rather than an established mechanism. Vitamin D is plausible because of its antifibrotic effects. Hair relaxer and phthalate exposure are CONTESTED. High red meat intake with low fruit and vegetable intake is weakly associated. Extended lactation is protective. Combined oral contraceptives and depot progestogens are associated with reduced risk on mixed evidence, and they are also used as treatment. Smoking is associated with reduced risk, presumably through anti-oestrogenic effects, and that is not a reason to smoke. Roughly 70 per cent of fibroids carry MED12 mutations; others carry HMGA2 rearrangements, frequently from a t(12;14) translocation, FH mutations, which in germline form cause hereditary leiomyomatosis and renal cell cancer where fibroids are a feature, or COL4A5 and COL4A6 deletions†. HMGA2 rearrangements are found in about 10 to 20 per cent of fibroids†. Fibroids are clonal neoplasms, each arising from a single cell, so a woman with multiple fibroids has multiple independent tumours, and the mutation burden is very low, as expected for a benign clonal lesion. Not known: the cause of the ancestry difference, which is large, consistent and unexplained; why fibroids are so common and leiomyosarcoma so rare, given a shared tissue of origin; what determines whether a fibroid stays small and silent or grows to the size of a term pregnancy. Also not known: what initiates the founding somatic mutation; why individual fibroids in the same uterus grow at different rates, and why some regress without treatment; and why some fibroids cause heavy bleeding and others do not, since submucosal location matters and does not explain everything. The link to

infertility and miscarriage is established for submucosal and large intramural fibroids and uncertain for small intramural ones.

Cure status. Perimenopausal symptomatic fibroids: SELF-LIMITING — fibroids regress after the menopause as oestrogen falls, and a woman approaching the menopause with symptomatic fibroids can often be managed expectantly until they shrink. That is a legitimate strategy and it is the only condition in this chapter for which SELF-LIMITING applies by virtue of a predictable physiological endpoint. Symptomatic fibroids treated by hysterectomy: CURABLE, definitively and permanently — the organ and the problem are removed and fibroids cannot recur. Symptomatic fibroids treated by myomectomy: CURABLE of the fibroids removed — about 15 per cent of women have recurrence at five years and 25 to 50 per cent at ten years, because myomectomy removes the existing tumours and not the propensity to form new ones, which arise as new clonal growths rather than as regrowth of the old. Symptomatic fibroids treated by uterine artery embolisation: CONTROLLABLE — the fibroids are shrunk rather than removed and bleeding is controlled effectively, with re-intervention in about 15 to 30 per cent at five years. Symptomatic fibroids managed medically: CONTROLLABLE — bleeding and symptoms can be controlled for years with a levonorgestrel intrauterine system, tranexamic acid, hormonal contraception or GnRH-pathway drugs, without removing anything. Asymptomatic fibroids require no treatment at all, and most fibroids are asymptomatic: the large majority of the women who have fibroids by age 50 never need anything done. A necessary distinction from the malignant entries: the goal is not survival, which is not threatened, but relief of bleeding, pain, pressure and infertility, and preservation of fertility where it is wanted. The treatment decision is accordingly driven almost entirely by what the woman wants rather than by a survival calculation, and that is unlike every other entry in this chapter.

Prevention. There is no established effective primary prevention. Parity, combined oral contraceptives and, unusably, smoking are associated with reduced risk, and none is a prevention strategy. Weight control — WEAK. Vitamin D supplementation — CONTESTED: biologically plausible, supported by observational association and small trials showing reduced fibroid growth, with no adequate randomised evidence of a clinically important effect. A second source line grades vitamin D sufficiency as CONTESTED and WEAK. The two source lines disagree on the grade, CONTESTED here and CONTESTED and WEAK there, and both are printed. Combined oral contraceptives and depot medroxyprogesterone — WEAK: the associations with reduced incidence are weak, and the drugs are used for symptom control and not for prevention. Extended lactation is likewise protective and not prescribable as prevention. Treating iron-deficiency anaemia does not prevent fibroids. It prevents their main consequence — STRONG, and the most neglected element of care. There is no screening and no rationale for one, and that is worth stating because ultrasound finds fibroids constantly. Systematic ultrasound screening of asymptomatic women finds fibroids in the majority, and finding them confers no benefit: they are not pre-cancerous, they do not require treatment when asymptomatic, and knowing about them generates anxiety, follow-up imaging and in some cases intervention on a lesion that would never have caused a symptom. **Incidental detection of asymptomatic fibroids on pelvic ultrasound and imaging done for other reasons is extremely common and is a genuine, substantial and unquantified overdiagnosis problem. No overdiagnosis percentage has been published, and the reason is simply that the condition is so common that the concept is rarely applied to it.** The power morcellation controversy is the one place where fibroids intersect with cancer, and both sides are genuinely held. Laparoscopic hysterectomy and myomectomy for large fibroids required the tissue to be cut up to remove it through small incisions, and if the lesion was in fact an unsuspected leiomyosarcoma, morcellation disseminated it through the abdomen and worsened the prognosis substantially. The United States Food and Drug Administration issued a safety communication in 2014 and a boxed warning, estimating the risk of unsuspected uterine sarcoma in women undergoing hysterectomy or myomectomy for presumed fibroids at roughly one in 350†. Critics argued that estimate was too high, derived from referral-centre populations and from studies with ascertainment bias, and that figures in the region of one in 1,000 to one in 2,000 were more appropriate for the general population of women having fibroid surgery, particularly younger women. The consequence of the warning was a shift from laparoscopic to open abdominal surgery, which carries higher rates of wound complications, infection, venous thromboembolism and longer recovery, and several analyses argued that the net harm from more open surgery exceeded the harm prevented from fewer morcellated sarcomas. Current practice uses contained morcellation in a bag, avoids morcellation in older women and in anyone with suspicious features, and counsels explicitly about the risk. Both figures are

printed because the disagreement is real: roughly one in 350 against roughly one in 1,000 to one in 2,000. The underlying problem is that there is no reliable preoperative test to distinguish a fibroid from a leiomyosarcoma, and that remains true.

Treatment. Expectant management for asymptomatic fibroids is correct for the majority and free. Size alone is not an indication for treatment, which corrects historical practice. Watchful waiting is also appropriate for mild symptoms approaching the menopause. **Tranexamic acid is listed, for haemorrhage not elsewhere classified and for postpartum haemorrhage**, off-patent, and costs cents a tablet. It reduces menstrual blood loss by roughly a third, is taken only during menstruation, and is one of the most cost-effective interventions in this entire chapter for a condition affecting hundreds of millions of women. A second source line gives the reduction as about 40 to 50 per cent†, against roughly a third here. The two source lines disagree on the reduction, and both are printed. That line places tranexamic acid in section 10.2 of the Essential Medicines List, core, under medicines affecting coagulation, and gives its cost as tens of US dollars a year, against cents a tablet here. The two source lines differ in how far their figures were checked, and state the price on different bases, a year against a tablet. That line calls tranexamic acid cheap, effective, under-used and safe in this use. In gastrointestinal bleeding, by contrast, the HALT-IT trial found no mortality benefit and more thromboembolism. Mefenamic acid and ibuprofen are off-patent and cheap and reduce bleeding modestly and relieve pain. A second source line puts the reduction in blood loss at about 20 to 40 per cent†, and notes relief of painful periods (dysmenorrhoea). A levonorgestrel-releasing intrauterine system is listed as a contraceptive, and a single device insertion lasts five to eight years, reducing menstrual blood loss by roughly 80 to 90 per cent and matching hysterectomy for quality of life in many women with heavy bleeding; it is less effective when the uterine cavity is distorted by submucosal fibroids, and it costs in the region of US$10 to 20 at public-sector procurement prices, and far more in private markets. That is the single most important non-surgical treatment and it is a one-visit procedure. A second source line gives the reduction in menstrual blood loss as about 70 to 95 per cent†, against roughly 80 to 90 per cent here. The two source lines disagree, and both are printed. That line records the device as on the Essential Medicines List and gives its cost as tens of US dollars, so a few dollars a year, against US$10 to 20† here. The two source lines differ in how far their figures were checked. That line calls the device outstanding value. Combined oral contraceptives and oral or injectable progestogens are listed, off-patent and cheap and control bleeding. **Ferrous salts are listed, off-patent and cost cents**, at a UNICEF indicative price of US$1.43 on one catalogue page and US$1.60 on another per bottle of 100 tablets of iron 60 mg, October 2026, which is about 1.4 to 1.6 US cents a tablet. Fibroid-related iron deficiency anaemia is extremely common and is the main systemic consequence of fibroids, and oral iron treats it: cheap, simple and frequently neglected. Iron may also be given intravenously. The anaemia is often the actual cause of the symptoms women present with, and iron is frequently the highest-value single intervention. A second source line gives about US$2 to 15 a year for oral iron, set beside the UNICEF indicative prices above, and records iron as on the Essential Medicines List. Goserelin, leuprorelin and triptorelin are all listed and shrink fibroids and induce amenorrhoea, used preoperatively to reduce size and correct anaemia; they cause menopausal symptoms and bone loss, so use is limited to a few months unless add-back hormone therapy is given. A second source line gives shrinkage of about 35 to 60 per cent over three to six months† and a limit of six months without add-back. It states that fibroids regrow within months of stopping, and gives the cost as thousands of US dollars a year. Elagolix, the relugolix combination and linzagolix are not listed and are on patent, oral and effective for bleeding and pain, allowing longer-term use than the agonists, at United States costs in the region of US$10,000 a year and above†. A second source line gives the cost of the antagonist combinations as about US$10,000 to 13,000 a year at United States list†, which lies inside the figure above, and reduction of blood loss in about 70 to 75 per cent†, with built-in add-back allowing longer use. Ulipristal acetate is effective and was restricted in Europe after cases of severe liver injury requiring transplantation, a genuine safety withdrawal worth recording. A second source line says it is restricted or withdrawn in several markets, and calls it a cautionary case. Myomectomy removes fibroids with the uterus preserved, by open, laparoscopic or hysteroscopic route depending on fibroid location; it preserves fertility, at a recurrence of roughly 15 to 30 per cent at five to ten years†. The cure status above gives recurrence of about 15 per cent at five years and 25 to 50 per cent at ten years, which is also the figure in the second source line. The two source lines disagree with the 15 to 30 per cent at five to ten years† given here, and both are printed. Hysteroscopic myomectomy for submucosal fibroids is highly effective for bleeding and for fertility, and is a day case. Myomectomy may also be robotic. Hysterectomy is a definitive cure, abdominal,

vaginal or laparoscopic. Vaginal or laparoscopic routes are preferred over open surgery where feasible. Uterine artery embolisation blocks the blood supply and shrinks fibroids, with comparable symptom relief to surgery and faster recovery, a higher reintervention rate, and effects on fertility not fully established, so it is used cautiously in women wanting pregnancy. It is generally avoided in women planning pregnancy. The FEMME trial of 2020 found that myomectomy gave better fibroid-related quality of life than embolisation at two years, though both improved substantially. Focused ultrasound and radiofrequency ablation are non-invasive or minimally invasive with limited availability. The focused ultrasound is MRI-guided. Both have less long-term data and variable re-intervention rates. Endometrial ablation is an option for bleeding with small fibroids and no wish for fertility. On morcellation: power morcellation of an unsuspected leiomyosarcoma can disseminate the malignancy. That led to regulatory warnings and to contained morcellation in extraction bags, as set out under Prevention. A second source line gives the risk as about one in 350 to one in 10,000, varying widely, and calls the magnitude CONTESTED†. The upper end, one in 10,000, lies outside the one in 1,000 to one in 2,000 given under Prevention, so the two source lines disagree. All the figures are printed.

Simple means. Fibroids are among the best-served conditions in this chapter by simple means, and the gap between what is cheap and what is done is correspondingly large. Tranexamic acid costs a few cents a tablet, is oral, is taken during menstruation only, is listed and off-patent, and reduces blood loss by roughly a third, with no device, no procedure, no cold chain and no monitoring. A second source line gives the reduction as about 40 to 50 per cent† at tens of US dollars a year. Those are the figures printed under Treatment, where the disagreement is set out. Oral iron costs cents, is listed and off-patent, and treats the anaemia that is the main systemic harm: the combination of tranexamic acid and ferrous sulphate costs pennies a month and addresses both the bleeding and its consequence. Iron, dietary and supplemental, treats the fatigue and breathlessness of the anaemia, at pennies. A levonorgestrel intrauterine system is a single insertion in an outpatient clinic lasting five to eight years, reducing blood loss by 80 to 90 per cent at a public-sector procurement cost in the region of US$10 to 20†. For a woman with heavy bleeding and a non-distorted cavity it is close to definitive management at trivial cost, and it also provides contraception. The second source line gives 70 to 95 per cent bleeding reduction† at a few dollars a year, the figures printed under Treatment. Abdominal hysterectomy and myomectomy are both conventional operations performable in a district hospital with basic instruments, anaesthesia and blood availability, and hysterectomy is definitively curative; for a woman with a very large fibroid uterus causing severe anaemia and pressure symptoms, abdominal hysterectomy is the correct and achievable treatment, and agonist pretreatment or iron repletion before surgery reduces operative risk. Combined oral contraceptives and injectable progestogens are listed, off-patent and cents, and control bleeding. NSAIDs are cheap and reduce both bleeding and pain. Continuous cheap combined oral contraceptives suppress bleeding. Diagnosis is possible by abdominal and pelvic examination and ultrasound: a firm irregular enlarged uterus is palpable, and ultrasound is cheap, portable, needs no contrast and no radiation and is diagnostic. Fibroids are among the easiest diagnoses in this chapter to make with simple means, and the difficulty is the opposite one, that they are found too easily and too often in women who have no symptoms. Expectant management until the menopause is free and correct for many women in their late forties. Watchful waiting is also the simple means of not intervening on asymptomatic fibroids. It avoids all surgical risk, and a significant number of hysterectomies have historically been done for size alone, without symptoms. Other simple means are heat for pain, exercise and weight management. Menstrual cups and washable pads are a practical way to manage heavy flow where disposable products are unaffordable. That is a real equity issue in low-income settings, where heavy bleeding causes absence from school and work. Measuring haemoglobin is a cheap test that identifies the treatable consequence. Where nothing simple exists: uterine artery embolisation, focused ultrasound and hysteroscopic resection of submucosal fibroids all require specific equipment, and hysteroscopic resection in particular is the best treatment for the submucosal fibroids that cause the heaviest bleeding and the most infertility, with no simple substitute. Large or submucosal fibroids causing severe symptoms need a procedure, and nothing simple shrinks them meaningfully. The GnRH antagonists that allow long-term medical control without surgery are on patent, expensive and not listed. And no simple means exists to distinguish a fibroid from a leiomyosarcoma preoperatively, which is the residue of the morcellation controversy. The central point stands: **for the commonest tumour in women, the two cheapest drugs in the pharmacy — tranexamic acid and iron — plus a US$10 to 20 intrauterine device at public-sector procurement prices, plus an operation a district surgeon can perform, cover**

the large majority of what needs to be done. The burden of fibroids worldwide is not a burden of expensive technology. It is a burden of untreated anaemia and unoperated symptomatic disease.

Gaps. GLOBOCAN and SEER do not report benign neoplasms, so this entry has no figures from the sources that supply the rest of this chapter, and no fibroid-specific GBD 2023 row was retrieved. The prevalence figures, the hysterectomy volumes and the ancestry disparity in hysterectomy rates are literature-derived. The ancestry difference is large, consistent and entirely unexplained, and vitamin D is a hypothesis. The occult leiomyosarcoma risk is genuinely contested, roughly one in 350 against roughly one in 1,000 to one in 2,000, both printed, unresolved, and there is no preoperative test. Overdiagnosis of asymptomatic fibroids by incidental imaging is extremely common and entirely unquantified. Ulipristal's liver toxicity led to regulatory restriction, a safety signal that emerged after approval. No effective primary prevention exists. Effects of uterine artery embolisation on subsequent fertility are not established. What initiates the founding somatic mutation is unknown. Fibroid growth is unpredictable, so prognosis for an individual woman cannot be given. The relationship between small intramural fibroids and fertility or miscarriage is unresolved, so advice on whether to remove them is uncertain. The racial disparity is a major research gap with clear equity implications. Morcellation sarcoma risk estimates vary by more than an order of magnitude in the second source line, which gives one in 350 to one in 10,000. Long-term comparative data between embolisation, ablation techniques and surgery are limited. Hysterectomy rates vary enormously between countries and systems for identical disease, which suggests substantial supply-driven treatment. Data from Africa, where symptomatic fibroids are a major surgical burden, are sparse relative to the problem.

> **Depth.** Starts in: a smooth-muscle cell of the womb. Size: 200 µm†; depth +7.63. First complaint: about 40 years († typical age 40); time depth 52.23. One untreated course: no number ([B] shrinks after the menopause).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

35. Colonic adenomas

What it is. Benign glandular tumours of the lining of the large bowel. They are extremely common in older people, they are the lesion from which almost all colorectal cancer develops, and removing them prevents that cancer. They are the single most important benign neoplasm in medicine, because the entire rationale for colorectal cancer screening rests on finding and removing them.

Measured. Adenomas are found in roughly 25 to 40 per cent of asymptomatic people over 50 undergoing screening colonoscopy, and in a higher proportion of men than women; advanced adenomas, 10 mm or larger or with high-grade dysplasia or villous histology, are found in roughly 5 to 10 per cent; and prevalence rises steeply with age, with autopsy and colonoscopy series in people over 70 finding adenomas in roughly 50 per cent or more. The adenoma detection rate is the principal quality metric for colonoscopy, with a recommended minimum in the region of 25 to 30 per cent in a mixed screening population†, and the fact that the quality metric is a detection rate rather than a miss rate is itself informative: operators differ substantially in how many they find. **The great majority of adenomas never become cancer.** The commonly cited figure is that roughly 5 per cent progress to cancer over about ten years, with the risk concentrated in advanced adenomas, and for a small tubular adenoma under 5 mm the lifetime risk of progression is very low†. The dwell time — the interval from adenoma to invasive cancer — is estimated at roughly ten years for the conventional sequence, and that long interval is what makes screening every ten years viable; serrated lesions and Lynch syndrome adenomas progress faster. GLOBOCAN and SEER do not report benign neoplasms, so the relevant outcome data are in the colorectal screening trials, in entry 2 and below.

Where it starts. The risk factors are essentially those of colorectal cancer, which is expected since the adenoma is the precursor: physical activity relative risk 0.76, interval 0.72 to 0.81; obesity colon cancer relative risk 1.45, interval 1.02 to 2.07, in women above a body mass index of 29; smoking incidence relative risk 1.18, interval 1.11 to 1.25; and alcohol above 45 grams a day 1.41, interval 1.16 to 1.72. Smoking is more strongly associated with adenomas, and particularly with serrated lesions, than with

cancer itself. Age dominates; male sex gives roughly 1.5-fold and family history of colorectal cancer or advanced adenoma roughly twofold. The hereditary syndromes define the extremes. Familial adenomatous polyposis, from germline APC mutation, produces hundreds to thousands of adenomas from adolescence and a near-100 per cent lifetime colorectal cancer risk without prophylactic colectomy, and it is the proof of the adenoma-carcinoma sequence. Lynch syndrome, from mismatch repair deficiency, carries a lifetime colorectal cancer risk of about 80 per cent, with fewer adenomas than polyposis and faster progression, which is why surveillance intervals are one to two years rather than ten. MUTYH-associated polyposis, serrated polyposis syndrome, Peutz-Jeghers syndrome and juvenile polyposis follow. The molecular pathways are two. The conventional adenoma-carcinoma sequence runs through APC loss, initiating, then KRAS mutation, then TP53 loss and chromosomal instability. The serrated pathway runs through BRAF mutation and CpG island methylation to microsatellite-unstable cancer, and sessile serrated lesions are flat, pale, right-sided and easy to miss at colonoscopy, which is now recognised as a major source of post-colonoscopy interval cancers. Mutation burden in an adenoma is low and accumulates through the sequence. Not known: **which individual adenoma will progress.** That is the central unanswered question and it is the reason all adenomas are removed. There is no test that distinguishes the roughly 5 per cent that would become cancer from the 95 per cent that would not†, so the only available strategy is to remove them all, and that means roughly twenty polypectomies are performed for every cancer prevented. Also unknown: why the right colon and the serrated pathway behave differently; why adenoma prevalence differs so much by sex.

Cure status. Sporadic adenoma: CURABLE, completely and permanently, by polypectomy. Snare polypectomy or endoscopic mucosal resection removes the lesion in a single outpatient procedure, and the removed adenoma cannot progress. **That makes it the most straightforwardly curable neoplasm in this entire chapter.** SELF-LIMITING is not correct, because adenomas do not regress spontaneously in any meaningful proportion; the great majority are biologically inert over a lifetime, which is a different thing and is the source of the overtreatment problem below. Familial adenomatous polyposis: CURABLE only by prophylactic colectomy or proctocolectomy, because the propensity to form adenomas is in every cell of the colonic epithelium. The operation is performed in adolescence or early adulthood and it prevents a near-certain cancer, and desmoid tumours and duodenal adenomas then become the leading causes of morbidity and death — see entry 28 on desmoids. Lynch syndrome: CONTROLLABLE by one- to two-yearly colonoscopic surveillance with polypectomy, which reduces colorectal cancer incidence and mortality substantially, and some patients elect prophylactic colectomy. A malignant polyp — an adenoma containing invasive carcinoma that has been removed endoscopically: CURABLE by polypectomy alone if the margin is clear, the invasion is superficial and the histology is favourable, and otherwise segmental colectomy is required.

Prevention. This section is the heart of the entry, because adenoma removal is itself the prevention of colorectal cancer. Screening with polypectomy — STRONG, and the randomised evidence is as in entry 2. Flexible sigmoidoscopy: four randomised trials pooled, 458,002 people, colorectal cancer mortality rate ratio 0.74, interval 0.68 to 0.80, over eleven to seventeen years. Guaiac faecal occult blood testing: relative risk 0.78, interval 0.65 to 0.93, to 0.91, interval 0.84 to 0.98, at eleven to thirty years. Faecal immunochemical testing: no randomised trial, with a Taiwanese cohort of 5,417,699 people giving an adjusted relative risk of 0.90, interval 0.84 to 0.95, at six years. Colonoscopy: the NordICC randomised trial gives ten-year colorectal cancer risk of 0.98 per cent in those invited against 1.20 per cent in usual care, an 18 per cent reduction, risk ratio 0.82, interval 0.70 to 0.93. Colorectal cancer death was 0.28 against 0.31 per cent, risk ratio 0.90, interval 0.64 to 1.16, which is not significant, and all-cause death was 11.03 against 11.04 per cent. The number needed to invite was 455, interval 270 to 1,429, on 42.0 per cent uptake. Recommended ages: 50 to 75 Grade A, 45 to 49 Grade B, 76 to 85 selectively Grade C, stop at 86. NCI PDQ on polyp removal specifically is more cautious than is generally assumed, and it should be stated plainly: **PDQ rates the benefit magnitude of polyp removal as unknown, probably greater for polyps larger than 1.0 cm, rates the benefit evidence as fair, and rates the harms as solid at 7 to 9 events per 1,000 procedures**. The authority that grades colorectal risk factors as solid grades the benefit of polypectomy itself as fair with unknown magnitude. Harms, with figures: colonoscopy after a positive stool test gives about 17.5 serious bleeds and 5.4 perforations per 10,000; screening colonoscopy 14.6 bleeds and 3.1 perforations; colonoscopy after abnormal sigmoidoscopy 20.7 and 12.0; flexible sigmoidoscopy 0.5 and 0.2; and lifetime complications for screening from 45 to 75 are 10 to 16 per 1,000 adults screened. The

overtreatment question is stated honestly here, because it differs from the breast, prostate and thyroid cases and is usually not discussed at all. Roughly 25 to 40 per cent of screened people over 50 have an adenoma, and roughly 5 per cent of adenomas progress to cancer over a decade, so the great majority of polypectomies remove lesions that would never have harmed the patient. In the classical overdiagnosis framing used for thyroid, prostate and breast cancer this would be described as massive overtreatment. It is not usually described that way, and there is a defensible reason: the intervention is a snare passed through an endoscope already in place, taking seconds, with a complication rate of a few per thousand, and it prevents a cancer in the one case in twenty. The harm per unnecessary intervention is very small and the benefit when it lands is very large, which is the opposite of the thyroid case, where the unnecessary intervention is a thyroidectomy with permanent consequences. The defence is not unlimited, and two real harms follow. First, the surveillance cascade: a person with a small adenoma is enrolled in repeat colonoscopy for years, with the complication risk repeated each time, on the basis of guidelines whose intervals rest on observational data. Second, in very elderly or comorbid people, screening and polypectomy continue past the point where any benefit could accrue, and the recommendation to stop at 86 and screen 76 to 85 selectively is an attempt to address that. **No overdiagnosis percentage has ever been published for colonic adenomas, and the reason is that the framework has not been applied. The underlying number — roughly twenty polypectomies per cancer prevented — is nonetheless available and is stated here.** Aspirin — MODERATE for adenomas and CONTESTED on net benefit: colorectal cancer incidence hazard ratio 0.60, interval 0.47 to 0.76, at ten to nineteen years after starting, against 0.99 within ten years, a twenty-year death hazard ratio of 0.67, and major gastrointestinal bleeding odds ratio 1.58 with about fourteen extra bleeds per thousand people over ten years at very low doses. In Lynch syndrome, CAPP2 gave a hazard ratio of 0.65, interval 0.43 to 0.97, the clearest case for aspirin, in a group with an 80 per cent lifetime risk. Non-steroidal anti-inflammatory drugs — CONTESTED: PDQ rates the evidence inadequate for the colorectal cancer endpoint, with adenoma reduction only and no relative risk given, against solid harms of 4 to 5 upper gastrointestinal events per 1,000 a year and serious cardiovascular events up 50 to 60 per cent. Celecoxib reduces adenoma recurrence and increases cardiovascular events, and that trade-off ended its use for chemoprevention in the general population. Physical activity — MODERATE. Avoiding tobacco — MODERATE, and the association with serrated lesions is stronger. Limiting alcohol — MODERATE. Diet — CONTESTED, with the authorities disagreeing: PDQ states there is no reliable evidence that a low-fat, low-meat, high-fibre diet reduces colorectal cancer risk by a clinically important degree, and IARC classified processed meat Group 1 and red meat Group 2A in 2015 with a reported 18 per cent increase per 50 grams a day of processed meat. Both are printed, and randomised trials of dietary fibre supplementation and of low-fat diets have not reduced adenoma recurrence. Calcium and vitamin D — CONTESTED: some trials showed reduced adenoma recurrence with calcium, and the large vitamin D and calcium polyp prevention study was negative for vitamin D.

Treatment. Snare polypectomy at colonoscopy is the definitive treatment and removes the lesion in seconds. Cold snare polypectomy is now preferred over hot snare for lesions under 10 mm, because it has a lower delayed bleeding and perforation rate: a technique change, costing nothing, that reduced harm. Endoscopic mucosal resection and endoscopic submucosal dissection serve larger and flat lesions and avoid surgery for lesions that would previously have required colectomy. Segmental colectomy serves lesions not amenable to endoscopic removal and malignant polyps with unfavourable features. Prophylactic colectomy or proctocolectomy with an ileal pouch serves familial adenomatous polyposis. Surveillance colonoscopy follows at intervals determined by the number, size and histology of adenomas removed, typically three years after advanced adenomas and seven to ten years after one or two small tubular adenomas under current guidelines, and those intervals rest on observational data rather than randomised trials. Aspirin is listed, off-patent and costs cents a tablet, recommended for chemoprevention in Lynch syndrome at a hazard ratio of 0.65 and not recommended for the general population, because the bleeding harm offsets the benefit. **There is no drug treatment for sporadic adenomas and no expensive agent anywhere in this entry. The entire management is endoscopic and surgical.**

Simple means. There is no simple-means substitute for colonoscopy, and that is the central honest point of this entry. Finding and removing adenomas requires a colonoscope, a light source, a processor, a snare, a reprocessing chain for the instrument, sedation, and a trained operator with a documented detection rate. None of that is simple, and the capital and maintenance cost of an endoscopy service is the binding

constraint on colorectal cancer prevention worldwide. What is simple is stool testing. A faecal immunochemical test kit costs a few dollars, is done by the patient at home, needs no bowel preparation, no sedation and no clinic visit, and has randomised evidence for guaiac testing and very large cohort evidence for immunochemical testing of colorectal cancer mortality reduction: relative risk 0.78 to 0.91 and adjusted relative risk 0.90, interval 0.84 to 0.95. It requires a laboratory to read it, which is a modest requirement, and it requires colonoscopy capacity for the positives, which is not. Stool testing is the single most transferable element of colorectal cancer prevention, and its limitation is that it is a cancer and advanced-adenoma detection test rather than an adenoma detection test, so it does not prevent cancer by finding precursors nearly as well as colonoscopy does. Flexible sigmoidoscopy uses a shorter, cheaper instrument, no sedation and no full bowel preparation, **and it has the strongest randomised evidence of any colorectal screening modality: a mortality rate ratio of 0.74, interval 0.68 to 0.80, from four randomised trials in 458,002 people**. It reaches only the left colon, which is a real limitation given the rise in right-sided and serrated lesions, and it is substantially simpler than colonoscopy and the evidence for it is better. That is worth stating clearly: the modality with the best randomised evidence is also the simpler one. Digital rectal examination and rigid sigmoidoscopy detect low rectal lesions with almost no equipment, at poor sensitivity for anything higher. Aspirin in Lynch syndrome costs cents a tablet, is listed and off-patent, at a hazard ratio of 0.65. Physical activity, not smoking and limiting alcohol need no technology. Oral iron, listed and costing cents, treats the iron-deficiency anaemia that a bleeding adenoma or cancer causes, with the corollary that matters: iron-deficiency anaemia in an adult, particularly a man or a postmenopausal woman, requires investigation of the bowel rather than iron alone, and treating the anaemia without looking for the cause is a recognised and avoidable error. The honest statement: colonic adenomas are the one entry in this chapter where the preventive intervention is highly effective, entirely off-patent in drug terms because there are no drugs, and nonetheless unavailable to most of the world, because it is an endoscopic service rather than a medicine. There is no cheap substitute for a colonoscope. Stool testing and flexible sigmoidoscopy are the realistic simple approaches and both have randomised evidence behind them. **The gap in colorectal cancer prevention worldwide is a gap in endoscopy capacity, and no amount of drug pricing reform touches it.**

Gaps. GLOBOCAN and SEER do not report benign neoplasms, so adenoma prevalence figures are literature-derived. Adenoma prevalence, advanced adenoma prevalence, the progression rate and the dwell time are all literature-derived, and those are the numbers on which the whole screening rationale rests. PDQ rates the benefit of polyp removal as fair evidence with unknown magnitude, while screening programmes worldwide rest on it, and that is a genuine and underappreciated tension. No overdiagnosis percentage has ever been published for colonic adenomas, though the underlying ratio of roughly twenty polypectomies per cancer prevented is calculable and is stated above; the framework applied to thyroid, prostate and breast has simply not been applied here. Surveillance intervals rest on observational data. Which individual adenoma will progress is unknown and no test exists, which is the fundamental gap. Sessile serrated lesions are easy to miss and are now recognised as a major cause of post-colonoscopy interval cancers, and the magnitude of the miss rate varies by operator and is incompletely characterised. PDQ and IARC disagree on diet and on meat, and both are printed.

> **Depth.** Starts in: a bowel epithelial cell. Size: 15 µm†; depth +5.28. First complaint: about 55 years († typical age 55); time depth 52.52. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Cross-cutting sections

A. The autopsy evidence, and why it predicts overdiagnosis

This is the evidence that bears most directly on the overdiagnosis figures printed throughout the chapter. It comes from people who died of something else and whose organs were then examined systematically. It measures the reservoir of cancer that a sensitive test can find.

Prostate. Bell and colleagues, in the *International Journal of Cancer* in 2015, pooled 29 autopsy studies dated 1948 to 2013. Incidental prostate cancer at autopsy was present in 5 per cent of men under 30, interval 3 to 8, and 59 per cent of men over 79, interval 48 to 71, rising non-linearly at approximately 1.7-fold per decade. The intermediate age-group figures are not reported in the abstract and could not be retrieved; they lie on the curve between 5 and 59 per cent.

Lifetime risk of a *diagnosis* of prostate cancer in a high-screening country is in the region of 12 to 15 per cent, and lifetime risk of *dying* of it roughly 2 to 3 per cent†. Against an autopsy prevalence of 59 per cent in men over 79, the great majority of prostate cancer that exists is never diagnosed and never causes harm. The overdiagnosis estimate of 20 to 50 per cent of screen-detected cancers — 21 per cent in PLCO, 50 per cent in ERSPC, 22 to 42 per cent in CISNET models — is entirely consistent with a reservoir of that size. The autopsy data do not resolve which cancers matter; they establish that the reservoir is very large and that any sensitive test applied to older men will draw from it.

Thyroid. Furuya-Kanamori and colleagues, in the *Journal of Clinical Oncology* in 2016, pooled 35 studies, 42 data sets and 12,834 autopsies conducted between 1949 and 2007. Incidental differentiated thyroid cancer was present in 4.1 per cent on partial thyroid examination, interval 3.0 to 5.4, and 11.2 per cent on whole thyroid examination, interval 6.7 to 16.1. The authors give those two subgroup estimates rather than a single pooled figure, and the difference between them is itself the point: how much cancer is found depends on how hard the pathologist looks. The Finnish series from which the phrase “a normal finding” comes reported occult papillary carcinoma in a very high proportion of thyroids examined in fine serial section; the specific figure could not be retrieved in primary form, and the study is the historical origin of the recognition that subclinical papillary thyroid carcinoma is near-ubiquitous when sought thoroughly.

Annual thyroid cancer incidence in high-screening populations is a small fraction of 11.2 per cent. Two findings are direct consequences of a reservoir of that size meeting a sensitive imaging test. The first is the South Korean experience: a roughly fifteenfold rise in incidence between 1993 and 2011 with flat mortality, after ultrasound screening was added to health checks. The second is IARC’s 2016 estimate that more than half a million people were overdiagnosed in twelve high-income countries over two decades, about 470,000 women and 90,000 men. The thyroid autopsy data are the clearest demonstration in medicine that the amount of cancer found is a function of the intensity of looking.

Breast. Thomas and colleagues, in *BMC Cancer* in 2017, pooled 13 studies from 1948 to 2010 covering 2,363 autopsies. At autopsy, invasive breast cancer was present in 0.85 per cent, in-situ cancer in 8.9 per cent, atypical hyperplasia in 9.8 per cent, and any cancer or precursor lesion in 19.5 per cent. The authors do not report confidence intervals in the abstract and they could not be retrieved.

The reservoir of occult invasive breast cancer is small, at 0.85 per cent, which is why breast overdiagnosis estimates are far lower than the thyroid figures and why the dispute is genuinely close. **The reservoir of in-situ cancer is ten times larger than the invasive reservoir, at 8.9 per cent, and almost all detected in-situ cancer is treated.** That is where the breast overdiagnosis problem principally sits, and the autopsy data support it. The 19.5 per cent figure for any cancer or precursor sits close to the Marmot panel’s 19 per cent overdiagnosis estimate, which is a coincidence of numbers rather than a derivation, and it indicates the order of magnitude.

The pattern across the three organs

Organ	Occult cancer at autopsy	Lifetime risk of diagnosis	Published overdiagnosis estimate from screening
Prostate	59 per cent, interval 48 to 71, in men over 79; 5 per cent, interval 3 to 8, under 30	roughly 12 to 15 per cent†	20 to 50 per cent of screen-detected cancers; PLCO 21, ERSPC 50, CISNET 22 to 42
Thyroid	11.2 per cent, interval 6.7 to 16.1, whole gland; 4.1 per cent, interval 3.0 to 5.4, partial	roughly 1 to 2 per cent†	approaching 90 per cent or more in high-screening settings; IARC about 560,000 overdiagnosed in 12 countries over 20 years
Breast	0.85 per cent invasive; 8.9 per cent in situ; 19.5 per cent any cancer or precursor	roughly 12 to 13 per cent†	19 per cent, Marmot 2012, against 30 per cent, Cochrane 2013

The relationship across these three organs is direct: the size of the occult reservoir tracks the magnitude of the overdiagnosis problem. Prostate and thyroid have large reservoirs and large overdiagnosis; breast has a small invasive reservoir and a contested, moderate overdiagnosis figure concentrated in in-situ disease. Read in the net: the test returns what is present at the depth it probes, and the reservoir is a property of the organ. This is a reading, not a mechanism.

The same reading is offered for the other screening results in this chapter, and it is a reading and not a finding, since most of the figures behind them carry a dagger. Neuroblastoma has a large reservoir of spontaneously regressing tumours in infants: screening doubled incidence, did not reduce mortality, and was abandoned. The myeloma precursor is present in roughly 3 per cent of people over 50 and over 5 per cent over 70, progressing at roughly 1 per cent a year†, so screening would label millions and offer nothing. The chronic lymphocytic leukaemia precursor is present in roughly 3 to 5 per cent of adults over 40 and over 10 per cent over 80, progressing at roughly 1 to 2 per cent a year†, and the same conclusion follows. Colonic adenomas are present in 25 to 40 per cent of people over 50, of which roughly 5 per cent progress over a decade†, so roughly twenty polypectomies are performed per cancer prevented — tolerated because the harm per unnecessary polypectomy is a few per thousand rather than a thyroidectomy. Lung cancer's NELSON overdiagnosis ceiling of 8.9 per cent is consistent with a modest reservoir, and the higher NLST-derived estimates remain disputed.

Nasopharyngeal carcinoma is a control case. No occult reservoir is found at autopsy, and plasma Epstein-Barr virus DNA screening in endemic populations produces a large stage shift and better survival without a significant overdiagnosis penalty; no overdiagnosis percentage has been published.

What the autopsy data do not show: they do not identify which lesion in a living person will progress. **No marker exists, in any of these organs, that reliably separates the indolent from the lethal at the time of detection.** That is the common root of every overdiagnosis controversy in this chapter, and it has not been solved for any of them.

B. Where overdiagnosis has never been quantified

Overdiagnosis has been quantified for breast, prostate, thyroid, lung, melanoma and neuroblastoma, and the figures are printed in those entries. It has never been quantified for gastric cancer, liver cancer, kidney cancer, bladder cancer, cervical intraepithelial neoplasia, colonic adenoma, uterine fibroids, incidental meningioma, monoclonal gammopathy of undetermined significance or monoclonal B-cell lymphocytosis — several of which have reservoirs as large or larger.

The absence of a figure is not evidence of the absence of harm. For gastric cancer, national endoscopic programmes have run for decades with no randomised mortality trial and no published overdiagnosis estimate. For liver cancer, six-monthly surveillance of cirrhotic patients is widely recommended on one randomised trial. For kidney cancer, overdetection of small renal masses through imaging done for other reasons is unintended screening at scale, with the rising-incidence-and-falling-mortality pattern as its only

quantification. For bladder cancer, there is no programme to quantify it in, and half of all United States diagnoses are already in situ. For cervical intraepithelial neoplasia, the treated entity is a precursor rather than a cancer, so the framing does not transfer, and over-treatment of lesions that would have regressed is the principal harm. For colonic adenoma, the framework has not been applied, and the underlying ratio is roughly twenty polypectomies per cancer prevented. For uterine fibroids, the condition is so common that the concept is rarely applied to it at all. For incidental meningioma, a substantial proportion never grow and intervening carries neurosurgical risk. And for the myeloma and chronic lymphocytic leukaemia precursors, the overdiagnosis fraction of a screening programme would approach the full population prevalence of the precursor.

In the kidney, fibroid and incidental-meningioma cases the harm from expanding imaging is real, growing and unmeasured.

C. The preventable fraction of all cancer

Three WHO figures are in current circulation, they are not the same quantity, and they are frequently conflated. All three are given here with their bases, and one of them has a published derivation.

The figure to use: 37.8 per cent of 2022 cases, about seven million. A WHO and IARC analysis published in *Nature Medicine* in 2026 found that **37.8 per cent of the roughly 18.7 million new cancer cases diagnosed globally in 2022 were attributable to modifiable risk factors — about seven million cases**. By sex: **4.3 million cases in men, 45.4 per cent, against 2.7 million in women, 29.7 per cent**. By risk factor, as a share of all new cancer cases: **smoking 15.1 per cent, infections 10.2 per cent, alcohol consumption 3.2 per cent**. High body mass index, low physical activity, smokeless tobacco, air pollution and ultraviolet radiation are also named, and the retrieved report gives no percentages or case counts for them. The denominator, 18.7 million, is the GLOBOCAN 2022 total excluding non-melanoma skin cancer, which is the convention used throughout this chapter. The method is a population attributable fraction calculation: exposure prevalence combined with relative risks from the epidemiological literature, applied to GLOBOCAN 2022 incidence. That is the standard approach, and it carries the standard limitations, set out below.

The two figures not used, and why. First, WHO's *Preventing cancer* activity page states that between 30 and 50 per cent of all cancer cases are preventable†. The page does not explain how the estimate was derived and cites no methodology or source; what it offers instead is a list of the risk factors on which prevention can act — tobacco, alcohol, physical inactivity, diet and overweight, infections including hepatitis and human papillomavirus, environmental pollution including outdoor and household air pollution, occupational carcinogens such as asbestos, and radiation. It is a range offered without a derivation. It is the most widely quoted cancer prevention figure in the world and it is, as published, unsourced, so it is treated here as an order-of-magnitude statement and is not used. Second, the WHO cancer fact sheet states that approximately 38 per cent of cancers are preventable. That is a point estimate without a stated derivation on the page, and it corresponds closely to the 37.8 per cent figure above, which does have one. Where the two could be used interchangeably, this chapter uses the figure with the published derivation and the figure-by-figure breakdown.

The infection-attributable component, independently measured. de Martel and colleagues, in *The Lancet Global Health* in 2020, estimated 2.2 million infection-attributable cancer cases in 2018, about 13 per cent of all new cancer cases worldwide, at an age-standardised incidence rate of 25.0 per 100,000 person-years. By agent: *Helicobacter pylori* about 810,000 cases at 8.7 per 100,000; human papillomavirus about 690,000 at 8.0; hepatitis B about 360,000 at 4.1; and hepatitis C about 160,000 at 1.7. By region, Eastern Asia at 37.9 and sub-Saharan Africa at 33.1 had the highest attributable rates and Northern Europe at 13.6 and Western Asia at 13.8 the lowest, with China accounting for about a third of all infection-attributable cases worldwide, driven by *H. pylori* and hepatitis B. The human papillomavirus attributable rate rises as income falls, from 6.9 in high-income countries to 16.1 in low-income countries. One important limitation: the retrieved summary reports four agents, so Epstein-Barr virus, human herpesvirus 8, HTLV-1 and *Schistosoma haematobium* are not among them, and no case counts for those agents could

be retrieved. That affects the Hodgkin lymphoma, nasopharyngeal carcinoma, Kaposi sarcoma, non-Hodgkin lymphoma and bladder cancer entries, each of which flags it.

The sources differ on the infection-attributable share and are not reconciled: de Martel gives 13 per cent for 2018 and the WHO and IARC analysis gives 10.2 per cent for 2022. The WHO cancer fact sheet gives approximately 10 per cent of cancers diagnosed globally in 2022 in its body, while stating in its key facts, with no year, that infections cause approximately 30 per cent of cancer cases in low- and lower-middle-income countries. The 13 against 10 per cent difference reflects different years, agent lists and methods. The 30 per cent figure is a different scope, and the WHO page sets the two against each other without reconciling them.

What the preventable fraction does and does not mean

Attributable to modifiable risk factors is not the same as preventable now. The 37.8 per cent figure assumes complete elimination of the exposures. Eliminating tobacco entirely would prevent 15.1 per cent of cancers, and no policy has ever eliminated tobacco anywhere: WHO records 1.2 billion tobacco users and smoke-free laws in 79 countries covering over a third of the world's population. The achievable fraction over any realistic horizon is substantially smaller than the attributable fraction.

The attributable fractions are not additive in a simple way. Tobacco and alcohol interact supra-multiplicatively in head and neck and oesophageal cancer: the combined population attributable risk is 89.4 per cent for oesophageal squamous carcinoma, and the relative risk for larynx with heavy use of both is thirty-sixfold. A case attributable to both is counted in a way that depends on the method.

Latency means today's prevention yields results in decades. Every mesothelioma now reflects asbestos exposure twenty to fifty years ago. Every human papillomavirus vaccination now prevents a cervical cancer in thirty years. The United States lung cancer mortality decline of 4.1 per cent a year now reflects smoking cessation that began in the 1960s.

The 62 per cent that is not attributable to modifiable factors, which is the complement of the 37.8 per cent above, is the part this chapter repeatedly reports as unknown. For breast cancer the established risk factors account for only a minority of cases. For prostate cancer no modifiable risk factor is established at all. For brain tumours, nothing beyond radiation. For childhood cancer, WHO states plainly that most has no known cause. For sarcoma, nothing for the sporadic majority. For pancreatic cancer the prevention summary could not be retrieved. These are the state of the field.

The infection-attributable fraction is the most actionable component, because the interventions are cheap and proven. Hepatitis B vaccination is listed at under a dollar a dose and would prevent 70 to 85 per cent of global hepatocellular carcinoma if universal; human papillomavirus vaccination is non-inferior at one dose; *H. pylori* eradication costs a few dollars of generic antibiotics at a relative risk of 0.66 and a number needed to treat of 124; hepatitis C direct-acting antivirals cost under US$50 a curative course in many low- and middle-income countries, according to the WHO fact sheet printed 28 July 2026; antiretroviral therapy costs US$30 to 75 a year in global procurement programmes; and praziquantel is listed at under a dollar. **The infection-attributable 10 per cent is where the gap between what is possible and what is delivered is widest, and the tools cost almost nothing.**

The single largest unrealised prevention opportunity after tobacco control is an Epstein-Barr virus vaccine, which does not exist. It would address nasopharyngeal carcinoma, Burkitt lymphoma, roughly a third of Hodgkin lymphoma, virus-positive gastric cancer and post-transplant lymphoproliferative disorder — plausibly over 200,000 cancers annually†.

D. Childhood cancer: mutation burden and its clinical consequence

The three quantities that run through every paediatric entry are collected here. The clinical detail is in entries 29 to 33.

Gröbner and colleagues, in *Nature* in 2018, analysed 961 tumours from children, adolescents and young adults across 24 molecular cancer types. The somatic mutation frequency was **0.13 mutations per megabase in paediatric tumours against 1.8 mutations per megabase in the adult pan-cancer reference — approximately fourteen times lower**. The paper describes this as an overall rate rather than a median, and the figure is not in the abstract. **Germline cancer predisposition was present in 7.6 per cent of children** (given as 7 to 8 per cent in the paper, 7.6 per cent in the main text), against WHO's figure of about 10 per cent, and the two are consistent. Nearly 50 per cent of paediatric neoplasms harboured a potentially druggable event, 52 per cent of primary tumours after normalising for cancer incidence.

Where the individual childhood cancers sit against that 0.13 per megabase paediatric rate and the 1.8 per megabase adult reference, as reported in the entries above:

Entity	Burden	Dominant driver type
Childhood acute lymphoblastic leukaemia	at or below the paediatric average	structural: ETV6-RUNX1, hyperdiploidy, KMT2A, BCR-ABL1
Ewing sarcoma	at the bottom of even the paediatric range	single fusion: EWSR1-FLI1
Retinoblastoma	very low	biallelic RB1 loss, and little else
Neuroblastoma	very low	MYCN amplification, ALK, segmental aberrations
Wilms tumour	very low	WT1, 11p15 imprinting, microRNA processing genes
Medulloblastoma	low	pathway activation: WNT, SHH, MYC amplification
Paediatric acute myeloid leukaemia	very low	fusion genes; adult disease averages about 13 coding mutations
Osteosarcoma	moderate point burden, extreme structural rearrangement	TP53 and RB1 loss, chromothripsis
Adult reference	1.8 per megabase	—
Adult melanoma, lung, bladder, keratinocyte skin	an order of magnitude or more above the adult reference	exposure signatures: ultraviolet, tobacco, APOBEC

Four consequences follow, and the second is the clinical one.

First, childhood cancers are diseases of developmental pathway dysregulation — fusion genes, aneuploidy, histone mutations, imprinting defects — rather than of accumulated exposure damage, and that is why they occur in children at all: they do not require decades of mutational accumulation.

Second, **there is almost no mutational burden for checkpoint inhibitors to exploit, and checkpoint blockade has broadly failed across paediatric oncology.** That is the observed clinical consequence, not a prediction. The successful immunotherapies in children — dinutuximab against GD2 in neuroblastoma, blinatumomab and CD19-directed cell therapy in acute lymphoblastic leukaemia — all target a lineage antigen rather than a neoantigen, which may be why they work where checkpoint blockade does not.

Third, the absence of tobacco, alcohol, diet and obesity signatures is not a research gap in the sense that those exposures are not the main drivers; whether they have had time to act is not established.

Fourth, fewer drivers has not meant easier treatment. A single fusion gene is frequently undruggable — EWSR1-FLI1, PAX3-FOXO1, MYCN — and osteosarcoma and Ewing sarcoma survival have not improved in roughly forty years.

A note on the general rule and its exceptions. This chapter reports three clear counterexamples to mutation burden as a predictor of checkpoint-inhibitor response: Hodgkin lymphoma, with a low burden and a 65 to 85 per cent response rate driven by 9p24.1 PD-L1 and PD-L2 amplification†; renal cell carcinoma, with a low burden and a 40 to 60 per cent response to combinations by an unexplained mechanism†; and nasopharyngeal carcinoma, with a low burden, a 20 to 30 per cent monotherapy response and high PD-L1 expression†. **Mutation burden is a useful heuristic and not a law.**

The survival divergence. WHO: about 400,000 children and adolescents aged 0 to 19 develop cancer each year; more than 80 per cent are cured in high-income countries; less than 30 per cent are cured in most low-

and middle-income countries; and the Global Initiative for Childhood Cancer target is at least 60 per cent survival for all children by 2030, roughly double the current global rate, which WHO estimates would save an additional one million lives over the decade. Childhood cancer mortality in high-income countries fell by roughly 70 per cent between 1970 and 2020, achieved almost entirely through cooperative-group clinical trials using off-patent cytotoxic drugs.

The threefold divergence is not biological, and entry 29 lists the determinants. Treatment abandonment is specific to paediatric oncology in low-income settings, is a leading cause of death, is driven by cost of travel, lost income, accommodation and loss of confidence, and is a failure of social and financial support rather than of medicine. The second problem, where cure is achieved, is the cost of cure, and it drives the whole paediatric trial agenda.

E. Oral morphine and palliative care

Every entry in this chapter refers to oral morphine. The figures that justify that emphasis are collected here once.

WHO's palliative care fact sheet: **about 56.8 million people need palliative care each year, including 25.7 million in the last year of life; roughly 14 per cent of those who need palliative care receive it; and in 2018, 79 per cent of the world's population, mainly in low- and middle-income countries, used only 13 per cent of the morphine consumed for pain management**†. WHO's cancer fact sheet adds that palliative care can relieve symptoms in more than 90 per cent of patients with advanced cancer, and that over 80 per cent of patients in the terminal phase suffer moderate to severe pain.

Oral morphine is a listed medicine, for pain, in oral liquid at 5 and 10 mg per 5 mL, immediate-release tablets at 10 mg, slow-release solid forms from 5 to 200 mg and slow-release granules. It is off-patent and costs cents a dose. Injectable morphine at 10 mg/mL is available at a UNICEF indicative price of US$5.71 for a box of ten ampoules, which is about 57 cents an ampoule, read off the catalogue in October 2026; the catalogue returns different indicative prices for the same material on different pages, so these are indicative and dated rather than a price.

The barrier is regulatory and organisational — restrictive controlled-drug legislation, prescriber licensing, supply-chain registration and fear of diversion — rather than price, patents or technology. Across this chapter, oral morphine is the single intervention that appears in the simple-means section of every entry without exception, and it is the one most consistently unavailable.

F. Price, and the two ends of one list

F.1 Cure at early stage with nothing on patent

Condition	Early-stage survival	Off-patent means that achieves it
Basal and squamous cell skin carcinoma	over 95 and over 90 per cent†	excision under local anaesthetic; curettage; cryotherapy; topical fluorouracil, listed
Melanoma, localized	100.0 per cent	wide local excision with a scalpel and sutures
Endometrial cancer, localized	94.9 per cent	total hysterectomy with bilateral salpingo-oophorectomy
Thyroid cancer, localized	99.9 per cent	lobectomy or thyroidectomy; levothyroxine, listed
Colorectal cancer, localized	91.3 per cent	colectomy; polypectomy for the precursor; fluorouracil, calcium folinate and oxaliplatin, all listed
Cervical cancer, localized	91.8 per cent	thermal ablation or loop excision for the precursor; hysterectomy; cisplatin, listed
Breast cancer, localized	100.0 per cent	mastectomy; tamoxifen, listed, US$80 to 250 for five years at generic international prices, 2024, against

Condition	Early-stage survival	Off-patent means that achieves it
		US$785 to 1,241 at United States cash prices, October 2026
Testicular cancer, stage I	roughly 99 per cent†	inguinal orchidectomy
Kidney cancer, localized	93.6 per cent	radical or partial nephrectomy
Wilms tumour, localized	above 95 per cent†	nephrectomy; vincristine with dactinomycin, both listed, tens of dollars
Retinoblastoma, intraocular	above 95 to 98 per cent†	enucleation; the red reflex test to find it; carboplatin, vincristine and etoposide, all listed
Bladder cancer, in situ and localized	98.0 and 73.0 per cent	transurethral resection, which needs a resectoscope; intravesical bacille Calmette-Guérin or gemcitabine
Stomach cancer, localized	78.1 per cent	gastrectomy; *H. pylori* eradication for the precursor, a few dollars
Gastric MALT lymphoma, early	60 to 80 per cent cured by antibiotics alone†	*H. pylori* eradication — a very cheap cancer cure
Colonic adenoma	cured by polypectomy	snare polypectomy, which needs a colonoscope
Uterine fibroids	cured by hysterectomy; controlled medically	tranexamic acid and ferrous sulphate, cents; intrauterine system US$10 to 20 at public-sector procurement prices†
Oral cavity cancer, localized	88.7 per cent	wide local excision; visual inspection of the mouth to find it
Sarcoma, localized soft tissue	83.3 per cent	wide excision with a clear margin — the margin is everything

F.2 Cure at metastatic stage with nothing on patent

Condition	Advanced-stage outcome	Off-patent regimen
Testicular cancer, metastatic	90 to 95 per cent good-risk; 50 to 70 per cent poor-risk†	bleomycin, etoposide and cisplatin, all listed, a few hundred dollars
Hodgkin lymphoma, stage IV	82.8 per cent	doxorubicin, bleomycin, vinblastine and dacarbazine, all listed
Acute promyelocytic leukaemia	over 90 per cent cured†	all-trans retinoic acid with arsenic trioxide, both listed; no chemotherapy needed in non-high-risk disease
Childhood acute lymphoblastic leukaemia	90 to 94 per cent in high-income settings†	vincristine, steroids, asparaginase, methotrexate, mercaptopurine and intrathecal methotrexate, all listed, a few hundred to low thousands of dollars over two to three years
Wilms tumour, stage IV	75 to 85 per cent†	vincristine, dactinomycin and doxorubicin, all listed
Diffuse large B-cell lymphoma	roughly 60 to 65 per cent cured; 45 to 50 per cent with CHOP alone†	R-CHOP, all components listed; CHOP fully off-patent; rituximab a biosimilar
Burkitt lymphoma	85 to 90 per cent in children†	cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide and cytarabine, all listed
Osteosarcoma, localized	65 to 70 per cent†	high-dose methotrexate, doxorubicin and cisplatin, all listed
Ewing sarcoma, localized	70 to 80 per cent†	vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide, all listed

F.3 Not curable at any stage

Pancreatic cancer beyond resectable disease, metastatic five-year survival 3.4 per cent; glioblastoma, 5 to 7 per cent at five years and median survival about 15 months†; diffuse midline glioma, median 9 to 12 months, with no treatment having improved survival in a randomised trial; anaplastic thyroid carcinoma, median 3 to 6 months, with the BRAF V600E exception†; mesothelioma, median 12 to 18 months and

entirely preventable†; multiple myeloma, CONTROLLABLE, median over 7 to 10 years and no plateau; follicular lymphoma, CONTROLLABLE, median over 15 to 20 years; chronic lymphocytic leukaemia, CONTROLLABLE at 90.2 per cent five- year survival; chronic myeloid leukaemia, CONTROLLABLE with near-normal life expectancy; the roughly 50 per cent who stay in remission after stopping treatment in deep molecular remission are the one exception in this list; metastatic prostate, breast, lung, liver, oesophageal, gastric, cervical, head and neck, bladder, ovarian and endometrial cancer, CONTROLLABLE to RELIEF ONLY with the subgroup exceptions each entry records; adult T-cell leukaemia-lymphoma, acute type, median under a year; Richter transformation, median under a year with no established treatment; relapsed high-risk neuroblastoma and relapsed medulloblastoma, both near-uniformly fatal; and platinum-refractory germ cell tumour, with no effective treatment, in young men.

F.4 The price range, in one place

Intervention	Price	Source and status
H. pylori eradication — amoxicillin, clarithromycin or metronidazole, proton-pump inhibitor	a few dollars a one- to two-week course	generic; cures 60 to 80 per cent of early gastric MALT lymphoma and cuts gastric cancer incidence by a third to a half
Praziquantel, listed	under a dollar a dose	prevents schistosomal bladder cancer
Hepatitis B vaccine, listed	under a dollar a dose	prevents 70 to 85 per cent of global hepatocellular carcinoma if universal
Oral morphine, listed	cents a dose; injectable 57 cents an ampoule, UNICEF Supply Catalogue, indicative, October 2026	reaches about 14 per cent of those who need palliative care†
Amoxicillin 250 mg dispersible, listed	about 5.4 cents a tablet, indicative, October 2026	UNICEF catalogue
Dexamethasone 4 mg, listed	about 24 cents a tablet, indicative, October 2026	UNICEF catalogue
Ferrous sulphate, iron 60 mg, listed	about 1.4 cents a tablet, indicative, October 2026	UNICEF catalogue
Allopurinol, levothyroxine, prednisolone, tranexamic acid, all listed	cents a dose	generic
Antiretroviral therapy, listed	US$30 to 75 a year†	global procurement; causes Kaposi sarcoma regression
Generic tenofovir for hepatitis B, listed	US$30 to 60 a year†	global procurement; cuts hepatocellular carcinoma incidence about 50 per cent
Generic hepatitis C direct-acting antivirals, listed	under US$50 a curative course in many low- and middle-income countries, fact sheet printed 28 July 2026	WHO hepatitis C fact sheet
Tamoxifen, listed	US$0.43 to 0.68 per 20 mg tablet; US$20.48 for 30; US$430.56 for 1,000 — five years at one tablet a day, for orientation only, US$785 to 1,241; the generic international price for five years, 2024, is US$80 to 250	United States cash price, October 2026 data stamps
Generic imatinib, listed	US$1.49 to 5.37 per 400 mg tablet; US$44.75 to 161.09 for 30 — roughly US$540 to 1,960 a year	United States cash price, October 2026 data stamps
Levonorgestrel intrauterine system, listed	US$10 to 20, public-sector procurement†	literature-derived
Full curative courses: BEP, ABVD, CHOP, MAP, Ewing and childhood leukaemia protocols	a few hundred to low thousands of dollars	all-generic listed regimens
Originator sofosbuvir at launch	US$84,000 a twelve-week course, 2013 to 2014	more than 1,680-fold above the generic price — the largest ratio in this chapter
Originator imatinib before generic entry	US$90,000 to 145,000 a year at United States list by the time of generic entry in 2016†	about 46- to 269-fold above the generic

Intervention	Price	Source and status
Pembrolizumab, listed, on patent	US$1,530.35 per 4 mL unit; US$6,121.41 per four-unit pack; US$12,234.94 for eight units; about US$53,000 a year at 200 mg every three weeks	United States cash price, October 2026 data stamps; the United States list price is US$150,000 to 200,000 a year
Blinatumomab, listed, on patent	US$180,000 a course at United States list†	literature-derived
BTK inhibitors, venetoclax, PARP inhibitors, CDK4/6 inhibitors, osimertinib, lenvatinib	US$100,000 to 200,000 a year†	United States list; mostly not listed
Dinutuximab, not listed	US$100,000 to 300,000 a course in the United States†	literature-derived
CD19 and BCMA CAR-T, not listed	US$400,000 to 525,000 per single infusion at United States list†	literature-derived; the price guide states only that pricing varies, and NCI's page gives no prices

F.5 Two statements the table makes unavoidable

The Essential Medicines List now contains both ends of this range, and it should be said once with the figures. Pembrolizumab, at US$150,000 to 200,000 a year, and blinatumomab, at US$180,000 a course, both at United States list are on the same list as morphine at cents a dose and amoxicillin at 5.4 cents a tablet at the UNICEF Supply Catalogue indicative price, October 2026. The committee's stated threshold for adding a cancer medicine is proven prolongation of life by at least four to six months. Pembrolizumab is a selected medicine for four indications: melanoma of the skin; metastatic colorectal cancer, restricted to mismatch-repair-deficient or microsatellite-instability-high tumours; metastatic cervical cancer with PD-L1 expression of 1 per cent or more, in combination with platinum-based chemotherapy; and metastatic non-small-cell lung cancer with oncogene-driver wildtype status and PD-L1 expression of 50 per cent or more, as monotherapy. Nivolumab is a therapeutic equivalent to it for melanoma and for malignant neoplasms of the bronchus and lung, which is a weaker status than selection. Blinatumomab is listed for B-cell acute lymphoblastic leukaemia.

Which drugs are absent from the list. Of the five absences this chapter was asked to record, two are not absences and three are. **Temozolomide is on the list**, for other specified gliomas of the brain, Ewing sarcoma of bone or articular cartilage, neuroblastoma not otherwise specified, and unspecified malignant neoplasms. **Daratumumab is on the list**, for plasma cell myeloma. **Venetoclax is not on the list in any form**: a query of the electronic list returns zero recommendations, zero medicines and zero therapeutic equivalents, and that absence is confirmed rather than inferred. **Dinutuximab is not listed**, despite being the main recent advance in high-risk neuroblastoma. **No CAR-T product is on the list**: not tisagenlecleucel, obecabtagene autoleucel, brexucabtagene autoleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, idecabtagene vicleucel or ciltacabtagene autoleucel. To those three absences this chapter adds carfilzomib, ixazomib, pomalidomide, isatuximab, obinutuzumab, acalabrutinib, brentuximab vedotin, polatuzumab vedotin, enfortumab vedotin, ipilimumab, osimertinib, lomustine, pemetrexed, the ALK, ROS1, KRAS, FGFR, RET, NTRK, hedgehog, IDH and FLT3 inhibitors, the CDK4/6 and PARP inhibitors, the BCMA bispecifics, and dostarlimab. No rationale for any of these absences was retrievable.

G. What is thin in this chapter

Stated plainly, because a reference work may carry gaps and may not carry unmarked ones.

The material this chapter was built from carries no per-figure provenance marking. Every figure taken from it therefore carries a dagger, unless it names a source and a year, in which case the source is named and was not opened again. Where a WHO fact sheet read off the page, or the retrieval of the 24th Essential Medicines List, or the GBD 2023 capstones, or the NordICC trial closed a figure, that figure was read off its source and the source is named in the entry.

GBD 2023 site-level cancer figures could not be retrieved, and that is the single largest gap. GBD 2023's Table 1 gives neoplasms as a group at 10,567.9 thousand deaths in 2023, interval 9,726.9 to 11,166.9 thousand, with malignant skin melanoma at 66.6 thousand and non-melanoma skin cancer at 63.9 thousand, and the remaining per-cause rows could not be read: three fetches at successive offsets into the published table each terminated at the same point, which is a property of the table's layout rather than of any one host. So every other quantitative burden figure in this chapter is GLOBOCAN, with 2024 beside 2022, or SEER, or a WHO fact sheet. The GBD contribution — disability-adjusted life years, years of life lost, risk-factor attribution by its own method — is absent for the individual cancers.

GLOBOCAN 2022 has been superseded by GLOBOCAN 2024, published in 2026 at 20,636,441 cases and 9,762,507 deaths, with a projection of 34.4 million cases by 2050. Both are given throughout. Where the two differ materially — cervical cancer at 662,301 against 604,196 cases and 348,874 against 279,583 deaths — the difference is almost certainly a methodological revision rather than an epidemiological change over two years, and should not be read as a trend. The GLOBOCAN 2022 site figures are quoted from a tabulation of the IARC release rather than from the source paper's own tables, which were not retrievable in full.

Several NCI PDQ prevention summaries could not be retrieved — pancreatic, bladder, kidney, sarcoma, testicular, nasopharyngeal, retinoblastoma, neuroblastoma, Wilms tumour and medulloblastoma. In those entries the risk-factor effect sizes carry no evidence grade, which is a real asymmetry against the entries where the summary was available.

Several SEER pages could not be retrieved — childhood cancers, bones and joints — and there is no page at all for basal or squamous cell skin carcinoma or for nasopharyngeal carcinoma separately. SEER also publishes no stage-specific table for brain and central nervous system tumours, acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, multiple myeloma or testicular cancer, so the risk-stratified figures in those entries are literature-derived.

Key randomised trials could not be retrieved in primary form and are cited qualitatively or not at all: the Osmanabad trials of visual inspection and human papillomavirus screening in India; PLCO and UKCTOCS for ovarian screening; the Kerala oral visual inspection trial; the Hong Kong plasma Epstein-Barr virus DNA screening study; the ERSPC sixteen-year follow-up, with the thirteen-year figures given instead; and the Swedish human papillomavirus cohort, with the summary of it given instead. NordICC, previously carried without any numbers, is now closed: 18 per cent incidence reduction, risk ratio 0.82, interval 0.70 to 0.93, 0.98 against 1.20 per cent at ten years, with its per-protocol and adjusted figures from a secondary source without intervals.

Drug prices are of two incompatible kinds and are not like-for-like. The figures for pembrolizumab, imatinib and tamoxifen are United States cash prices from a price guide whose data stamps are October 2026 and which does not date its prices; they are not international reference prices. The figures for antiretrovirals, tenofovir, generic antivirals and the intrauterine system are global procurement figures. The UNICEF catalogue figures are indicative prices read off the catalogue on 19 October 2026, and the catalogue returns different indicative prices for the same material number on different pages, so they are printed as indicative and dated and never as a price. The standing international reference — the MSH International Medical Products Price Guide — is retired: its last edition is 2017 and its site ceased to be accessible after 30 June 2024, so it cannot close this book's price debt. Prices for CAR-T, trastuzumab, blinatumomab, dinutuximab, brentuximab vedotin, the BTK inhibitors and venetoclax could not be retrieved, and the figures given for those are literature-derived and labelled.

Confidence intervals are missing in two places in the autopsy evidence: the breast meta-analysis does not report them in its abstract, and the intermediate age-group figures for the prostate meta-analysis are not in its abstract either.

de Martel and colleagues gave case counts for four infectious agents only, so Epstein-Barr virus, human herpesvirus 8, HTLV-1 and *Schistosoma haematobium* counts could not be retrieved, which affects the Hodgkin lymphoma, nasopharyngeal carcinoma, Kaposi sarcoma, non-Hodgkin lymphoma and bladder cancer entries.

Late-effect and survivorship figures are literature-derived throughout — second cancers, cardiac toxicity, cognitive loss after craniospinal irradiation, infertility. For Hodgkin lymphoma, testicular cancer, medulloblastoma, retinoblastoma and childhood cancer generally those figures are central to management, and their absence from primary verification is substantive.

Where sources disagree, both figures are printed. The genuine disagreements recorded in this chapter: mammography, at 19 per cent overdiagnosis with a relative risk of 0.80 against 30 per cent with a non-significant 0.90 in the adequately randomised trials; prostate-specific antigen screening, at rate ratios of 0.79, 1.04 and 0.99 across three trials, and overdiagnosis of 21 per cent against 50 per cent; low-dose CT lung screening overdiagnosis, at a NELSON ceiling of 8.9 per cent against higher NLST-derived estimates; melanoma overdiagnosis, at roughly 15 to 60 per cent; red and processed meat, where PDQ finds no reliable evidence and IARC classifies Group 1 and Group 2A with an 18 per cent increase per 50 grams a day; glyphosate and non-Hodgkin lymphoma, where IARC says Group 2A and the European and United States regulators disagree; perineal talc and ovarian cancer, where case-control meta-analyses give 1.24 to 1.33 with no dose-response and the prospective cohorts give null results; occult leiomyosarcoma in fibroid surgery, at one in 350 against one in 1,000 to one in 2,000; mobile phones and brain tumours, where IARC's Group 2B of 2011 stands against flat registry incidence and a null 2024 review; hot beverages and oesophageal cancer, where IARC says Group 2A and PDQ is silent; sunscreen, where PDQ finds the evidence inadequate with poor validity and public health guidance recommends it universally; the preventable fraction of all cancer, at 30 to 50 per cent unsourced, 38 per cent, and 37.8 per cent with a published derivation; the infection-attributable fraction, at 13 per cent for 2018 against 10 and 10.2 per cent for 2022, with 30 per cent for low- and lower-middle-income countries; and keratinocyte skin cancer mortality, where an inference from PDQ's ratio gives 10,000 to 15,000 globally against GBD 2023's 63,900. Two WHO pages also contradict themselves in figures this chapter uses: the cancer fact sheet on the infection-attributable share, and the malaria fact sheet on the under-five share of African Region deaths, at 75 per cent in its key facts and 76 then 75 per cent in two adjacent paragraphs of its body. Both are printed in the entries concerned.

End of chapter.

Chapter 12 — Blood, Immunity, and the Endocrine, Nutritional and Metabolic Diseases

ICD-11 chapters 03, 04 and 05

Forty-nine conditions. Twelve of the blood and blood-forming organs, fourteen of the immune system, twenty-three of the endocrine, nutritional and metabolic group.

Introduction

The third question this book asks of every condition — what can be done where there is no industry, no cold chain and no money — usually returns a partial answer. A cheap drug that helps. A free measure that prevents some of the harm. A test that costs little and changes the management. In this chapter it returns a different kind of answer ten times over. For ten of these forty-nine conditions the simple means is the whole of the treatment, not an adjunct to it. In seven of the ten it is also the cure. In three it is not: haemochromatosis, polycythaemia vera and phenylketonuria are CONTROLLABLE in their own entries, and in each the simple means holds the state without removing it.

Seven of the ten are nutritional deficiencies, and in each the deficiency ends when the nutrient arrives. Five are deficiencies of a single nutrient, one is of two (vitamin B12 and folate), and one is of food itself (protein-energy malnutrition). **Vitamin A deficiency**: the Cochrane review of supplementation in children aged 6 to 59 months pools 19 randomised trials and 1,202,382 children and finds all-cause mortality at a relative risk of 0.88 (95% CI 0.83–0.93), graded high certainty, with night blindness at 0.32 (0.21–0.50) (Imdad et al., 2022). The capsule costs cents and the delivered cost is of the order of one to two dollars per child per year. **Iodine deficiency**: potassium iodate added at the salt works costs a few cents a tonne, household coverage of iodised salt now stands near 89 per cent (Iodine Global Network Annual Report 2025), and endemic cretinism has been prevented across most of the world, while the brain damage already done is RELIEF ONLY. **Rickets**: a vitamin D drop given daily to a breastfed infant costs a few dollars a year, and Finland's fortification of fluid milks and fat spreads raised mean population 25-hydroxyvitamin D by roughly 20 nmol/L and cut the proportion below 50 nmol/L from roughly 55 to roughly 9 per cent between the 2000 and 2011 national health surveys. **Zinc deficiency**: a 10-to-14-day course of dispersible zinc costs well under two dollars†, and zinc shortens a diarrhoeal episode by 25 per cent and reduces stool volume by 30 per cent (WHO diarrhoeal disease fact sheet, 7 March 2024).

Iron deficiency is the largest of them by burden. Anaemia of all causes reached 1.92 billion cases in 2021, 24.3 per cent of the world population (GBD 2021 anaemia analysis, *The Lancet Haematology*, 2023), and dietary iron deficiency is the ninth-ranked cause of years lived with disability in the world at 39.3 million YLDs (95% UI 24.8–63.5) (GBD 2023). Oral ferrous sulphate costs one to three dollars a patient-year. **Vitamin B12 and folate deficiency** ends with replacement that is dietary or nearly so; mandatory folic acid fortification of flour roughly halves neural tube defect risk where it is introduced, and roughly 60 countries had mandatory fortification as of the 2023 Oxford systematic review of global fortification policies. **Protein-energy malnutrition** is the seventh: severe wasting is cured by food. Ready-to-use therapeutic food delivered through outpatient community programmes recovers roughly 80 to 90 per cent of children with case fatality under 5 per cent, against historical inpatient case fatality of 20 to 30 per cent†. The cost is roughly US$35 to US$50 for a full six-to-eight-week course at procurement prices, 2024†. The instrument that finds the cases is a paper tape measuring mid-upper arm circumference, and a mother can use it on her own child.

Two more are diseases of the blood whose treatment is the removal of blood. **Haemochromatosis** loads iron because hepcidin stays low for the body's iron burden; each 500 mL unit removed takes 200 to 250 mg of iron with it†, and a homozygote de-ironed before cirrhosis has normal life expectancy. The consumables

are a needle, a bag and a nurse, on the order of tens of US dollars a session in a public system; where the patient donates, the cost to the system is negative. In **polycythaemia vera** the lethal feature is thrombosis, and phlebotomy holds it: the CYTO-PV randomised trial compared a haematocrit target below 45 per cent with 45 to 50 per cent and found cardiovascular death or major thrombosis in 2.7 per cent against 9.8 per cent over a median 31 months (Marchioli et al., *NEJM*, 2013). Neither disease is cured — the genotype and the clone persist — but in both, the intervention that carries the benefit needs no patent and no supply chain.

The tenth is **phenylketonuria**, and it carries the qualification that the word simple needs. The heel-prick dried blood spot that detects it costs roughly one to five dollars within a multiplex panel, and it is the difference between normal development and severe permanent intellectual disability. The treatment is food. But the food is not food: the phenylalanine-free, tyrosine-enriched amino acid mixture that supplies the protein, vitamins and minerals the restricted diet cannot is a manufactured medical food from a small number of suppliers, and it costs roughly US$5,000 to US$25,000 a patient-year in high-income countries, 2024†. There is no generic pathway for medical foods. So the dietary treatment is cheap in principle and expensive in practice, and where the substitute is not reimbursed, families pay and adherence collapses. The same structure recurs through chapter 05: a condition detected for a few dollars and held by a product with no competitive market.

Set against those ten, the rest of the chapter runs the other way. Enzyme replacement for the lysosomal storage diseases costs roughly US$200,000 to US$600,000 a patient-year†. A single infusion of gene therapy for sickle cell disease was priced at about US$2.2 million on United States list (2023–2024)†. The published minimum sustainable production cost of biosimilar human insulin is US$72 a patient-year or less, and US$48 under high competition (Hill et al., *BMJ Global Health*, 2018), against United States analogue list prices that reached roughly US$275 to US$340 per 10 mL vial by 2019†. The chapter therefore holds both extremes of the book: the cheapest cures and the most expensive treatments in continuous long-term use in this chapter, on prices that are mostly, often for conditions that sit three entries apart.

A standing note on medicine list status. The governing edition of the WHO Model List of Essential Medicines is the 24th List, adopted by the 25th WHO Expert Committee in May 2025 and published September 2025 as WHO Technical Report Series 1064. The material this chapter was built from was checked against the previous edition throughout, so no listing claim in it could be carried across on its own authority. Where the status of a medicine was independently read off the electronic Model List in October 2026, it is given as read, including the distinction between a selected medicine and a therapeutic equivalent, which is load-bearing: a therapeutic equivalent is on the list as a permitted substitute, not as the selected medicine. Where it was not, the entry says the status needs checking against the 24th List, and the claim carries a dagger. The counts sometimes quoted for the 2025 lists — 523 medicines for adults and 374 for children — are not printed on the list’s title page and remain unconfirmed.

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Diseases of the blood or blood-forming organs

ICD-11 chapter 03

Twelve entries. The deficiency anaemias, the inherited haemoglobin and clotting disorders, marrow failure, iron overload, and two clonal diseases of the marrow.

Iron deficiency anaemia

What it is. Too little iron in the body to build enough haemoglobin. Red cells become small and pale and the blood carries less oxygen. Tiredness, breathlessness and poor concentration follow.

Measured. Anaemia of all causes reached 1.92 billion cases in 2021, 24.3 per cent of the world population (95% UI 23.9–24.7), against 28.2 per cent and 1.50 billion in 1990 (GBD 2021 anaemia analysis, *The Lancet Haematology*, 2023). Anaemia accounted for 52.0 million years lived with disability in 2021 (95% UI 35.1–75.1), with dietary iron deficiency the single largest contributor at a YLD rate of 422.4 per 100,000 (95% UI 286.1–612.9). In the GBD 2023 cycle, dietary iron deficiency ranks ninth among all causes of YLDs worldwide at 39.3 million (95% UI 24.8–63.5).

WHO estimates for the 2019 reference year give anaemia in 30 per cent of women of reproductive age, about 571 million women; 37 per cent of pregnant women; and 40 per cent of children aged 6 to 59 months, about 269 million children (WHO, 12 May 2023). The WHO and GBD figures are not interchangeable: WHO uses survey haemoglobin against fixed cut-offs, GBD models across causes.

Two age peaks: children under five, and women across the reproductive years. Sub-Saharan Africa and South Asia carry a disproportionate share, and the YLD rate falls as Sociodemographic Index rises. Anaemia is coded mainly as a cause of disability rather than death, and deaths are attributed to the underlying causes — haemorrhage, malaria, hookworm — so there is no reliable separate global death count. The World Health Assembly target of halving anaemia prevalence in women of reproductive age by 2025 is not on track (WHO, 2023).

Where it starts. Low dietary iron intake and low bioavailability. Absorption of non-haem plant iron runs at roughly 2 to 10 per cent against roughly 15 to 35 per cent for haem iron from meat†. Phytate in cereals and legumes and polyphenols in tea and coffee inhibit absorption; ascorbic acid in the same meal increases it several-fold.

Blood loss. Menstrual loss dominates in women of reproductive age. Gastrointestinal loss — ulcer, cancer, non-steroidal anti-inflammatory drugs — dominates in men and postmenopausal women, and in that group iron deficiency is itself an indication to investigate for gastrointestinal cancer.

Hookworm (*Ancylostoma*, *Necator*) and schistosomiasis: GBD 2021 counts other neglected tropical diseases among the top three contributors to anaemia YLDs. Malaria, by haemolysis and by marrow suppression. Pregnancy raises iron requirement roughly three-fold over its course. Low birthweight and early cord clamping reduce the infant's iron endowment, and delayed clamping beyond one minute raises infant iron stores measurably at four to six months.

Not a heritable disease. Haemoglobin concentration itself is heritable, with twin and family estimates in the range 0.2 to 0.4†, and variants in *TMPRSS6* and the *HFE* region shift iron indices without causing the deficiency.

Not known: the quantitative split between dietary inadequacy, chronic blood loss and infection at population level in most low- and middle-income countries. The three overlap and surveys rarely measure all three in the same people. Also unresolved: how much measured anaemia in inflammatory settings is iron deficiency rather than anaemia of inflammation, since ferritin rises with inflammation and the correction factors are contested.

Cure status. CURABLE. Replacing iron and stopping the loss returns haemoglobin to normal and ends the disease. Oral ferrous salts raise haemoglobin by roughly 1 g/dL per two to three weeks in uncomplicated deficiency, and full repletion of stores takes about three months of continued dosing after haemoglobin normalises. Intravenous iron corrects faster, in days to weeks. The cure is not durable while the cause of loss persists, so the cure is iron plus finding the bleeding source.

Prevention. Iron fortification of staple foods — wheat flour, maize flour, rice, condiments. The effect on anaemia at population level depends on the iron compound: ferrous sulphate and ferrous fumarate work, while the elemental iron powders used in older programmes are poorly absorbed. MODERATE overall; CONTESTED for programmes using elemental iron powders.

Double-fortified salt with iron and iodine, and iron-fortified fish and soy sauces: trials show reductions in iron deficiency, programme-scale data are thinner. MODERATE.

Antenatal iron and folic acid supplementation: standing WHO recommendation, reduces maternal anaemia at term. STRONG for maternal anaemia, weaker for birth outcomes.

Intermittent weekly rather than daily iron in menstruating women: effective, fewer side effects, better adherence. MODERATE.

Deworming in endemic areas with albendazole or mebendazole: the effect on haemoglobin is small per round and real where hookworm prevalence is high. MODERATE where hookworm is endemic, WEAK where it is not.

Malaria control with bed nets and seasonal chemoprevention reduces anaemia in children. STRONG in high-transmission settings.

Delayed cord clamping of at least one minute raises infant ferritin at four to six months. STRONG for the biochemical outcome.

Vitamin C with iron-containing meals increases non-haem absorption several-fold in metabolic studies. STRONG for absorption, WEAK for anaemia outcomes at population scale.

Treatment. Oral ferrous sulphate, fumarate or gluconate is first-line, at roughly one to three US dollars a patient-year of daily tablets at international generic prices (2024)†. Alternate-day dosing raises fractional absorption by limiting the hepcidin rise and is current practice in several guidelines. EML status needs checking against the 24th List†.

Intravenous iron — ferric carboxymaltose, iron sucrose, iron isomaltoside, low-molecular-weight iron dextran — where oral iron is not absorbed or not tolerated. An iron sucrose course runs roughly US$50 to US$150 (2024)†; ferric carboxymaltose in high-income markets runs roughly US$300 to US$1,500 a course on list prices, with wide variation (2024)†. Iron sucrose and iron dextran are off-patent; ferric carboxymaltose partly so, with generics entering. The listing status of iron dextran and of the newer high-dose single-infusion products needs checking against the 24th List†.

Treating the cause: endoscopy and treatment of the bleeding lesion; tranexamic acid or hormonal management for heavy menstrual bleeding. Tranexamic acid is a selected medicine on the 24th List, in section 10.2, medicines affecting coagulation, for haemorrhage not elsewhere classified and for postpartum haemorrhage; it is off-patent, at US$5 to US$20 per treated cycle-course at generic or lowest available acquisition cost, 2024†.

Transfusion is for haemodynamic compromise only, not for correcting iron deficiency.

Simple means. An iron cooking pot, or an iron ingot in the pot. Trials of cast-iron cookware and of the iron-fish ingot show measurable haemoglobin gains in deficient populations, with modest effect sizes that vary with food acidity and cooking time. No industrial chain.

A vitamin C source eaten with the meal — citrus, guava, tomato, raw leafy greens. Several-fold increase in non-haem absorption from the same meal.

Moving tea and coffee away from mealtimes. Tannins cut non-haem absorption sharply, and separating the drink from the meal removes the inhibition.

Soaking, germinating and fermenting cereals and legumes. Phytate falls and iron bioavailability rises. Traditional practice with a measurable effect.

Small amounts of meat, offal, fish or blood foods. Haem iron is absorbed several times better than non-haem and raises the absorption of non-haem iron eaten with it.

Latrines and footwear in hookworm areas, which break the transmission route. Delayed cord clamping at birth, which costs nothing.

Gaps. GBD 2023 disease-specific anaemia figures were not retrievable; the GBD 2021 analysis is used and labelled, except for the dietary iron deficiency YLD rank, which is GBD 2023. The haemoglobin threshold for anaemia is itself contested: the long-standing WHO cut-offs of 12 g/dL in non-pregnant women and 13 g/dL in men derive from a small mid-twentieth-century reference population, and WHO published revised thresholds in 2024 that are not yet reflected in most published prevalence estimates†. Whether population-wide iron fortification is net beneficial in malaria-endemic settings is contested, following trials in which iron supplementation in such settings was associated with increased malaria morbidity in children.

> **Depth.** Starts in: haemoglobin (iron shortage). Size: 6.5 nm†; depth −1.77. First complaint: about 6 months († months of low intake); time depth 48.23. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book's status: CURABLE. Reading and status agree. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Vitamin B12 and folate deficiency

What it is. Too little vitamin B12 or folate to build red cells. The marrow makes large immature cells and too few of them. B12 deficiency also damages nerves and the spinal cord, which folate deficiency does not.

Measured. B12 deficiency prevalence is reported at about 6 per cent under age 60 and about 20 per cent over 60 in the United States and United Kingdom, about 40 per cent in Latin America, and 70 to 80 per cent in parts of Africa and India, with marginal depletion in up to 40 per cent of Western populations†. These are compilations of heterogeneous surveys using different assays and cut-offs, and the same compilation gives two conflicting figures for Africa, 80 per cent in one place and 70 in another.

Pernicious anaemia, the autoimmune loss of intrinsic factor, affects about 2 to 3 per cent of people over 65 and is the main cause of B12 deficiency anaemia in high-income countries†.

For folate, the micronutrient survey synthesis of Stevens et al., *Lancet Global Health*, 2022 found that 1.2 billion non-pregnant women of reproductive age (1.0–1.4 billion), 69 per cent, had at least one of iron, zinc or folate deficiency, and that 372 million preschool children (319–425 million), 56 per cent, had at least one of iron, zinc or vitamin A deficiency.

B12 deficiency rises steeply with age through malabsorption and atrophic gastritis. Folate deficiency clusters in pregnancy, alcohol use disorder, malabsorption, and populations eating little fresh green food. Neither is separately counted in global mortality.

Where it starts. B12 malabsorption, not low intake, is the main mechanism in high-income countries: autoimmune destruction of gastric parietal cells, gastrectomy or bariatric surgery, terminal ileal disease or resection, achlorhydria, bacterial overgrowth, fish tapeworm. Low intake is the main mechanism where animal foods are scarce or avoided, because B12 occurs essentially only in animal-source foods and fortified products, and unsupplemented vegan diets reliably produce deficiency over years.

Long-term metformin and long-term proton pump inhibitors or H2 blockers reduce B12 absorption. The association is consistent; the causal size per year of exposure is not firmly quantified.

Folate: low intake of green vegetables, legumes and fortified cereals; alcohol; pregnancy, which roughly doubles requirement; haemolysis and other high-turnover states; methotrexate, trimethoprim, phenytoin, sulfasalazine.

MTHFR C677T homozygosity raises homocysteine and lowers red cell folate modestly. *FUT2* and *TCN1/TCN2* variants shift B12 concentrations. Transcobalamin II deficiency and Imerslund-Gräsbeck syndrome are rare monogenic causes. Heritability of serum B12 is estimated at 0.3 to 0.6 in twin studies†.

Not known: what serum B12 concentration marks functional deficiency. Serum B12 is a poor marker; methylmalonic acid and holotranscobalamin are better but not standardised, so the prevalence figures above are method-dependent and not comparable between studies. Also not known: whether treating biochemically low B12 without symptoms changes any outcome.

Cure status. Dietary B12 deficiency and folate deficiency: CURABLE. Replacement corrects the deficiency state completely, and the replacement is dietary or near-dietary. The macrocytic anaemia resolves within weeks. Neurological damage from B12 deficiency is only partly reversible and reversibility falls with the duration before treatment; long-standing subacute combined degeneration of the cord does not fully recover. Where the cause is permanent malabsorption, the replacement is lifelong: CONTROLLABLE. Folate deficiency is CURABLE, fully, by folate, with the caveat that giving folate to someone with untreated B12 deficiency corrects the anaemia and lets the neurological damage proceed.

Prevention. Mandatory folic acid fortification of flour is the single largest documented prevention effect in this entry. Pooled and country-level before-and-after data show roughly a halving of neural tube defect risk where mandatory fortification was introduced (Oxford CTSU/NDPH systematic review of global fortification policies, 2023). STRONG. Coverage remains partial: roughly 60 countries had mandatory folic acid fortification as of that review, and the majority of preventable neural tube defects worldwide were still not being prevented.

Periconceptional folic acid supplementation at 400 µg a day from before conception. The MRC Vitamin Study (1991) and the Chinese community trial showed large reductions in recurrence and occurrence. STRONG. The limitation is that it requires a planned pregnancy, which is why fortification outperforms it at population level.

B12 supplementation or fortification for populations eating little animal food, and for people on long-term metformin or proton pump inhibitors. MODERATE.

B12 supplementation in vegan and strict vegetarian diets, which prevents a deficiency that otherwise reliably occurs. STRONG.

Treatment. Hydroxocobalamin or cyanocobalamin intramuscularly is standard for pernicious anaemia and for neurological presentations, at US$5 to US$30 a patient-year on a maintenance schedule of injections every two to three months, at generic or lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

High-dose oral cyanocobalamin at 1,000 to 2,000 µg a day is absorbed passively, independent of intrinsic factor. Randomised comparisons show haematological equivalence to injections in most patients; the evidence is weaker for severe neurological disease and at least one review holds oral inferior there. US$5 to US$20 a patient-year at generic or lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

Folic acid, oral, 1 to 5 mg a day for folate deficiency, at under two dollars a patient-year (2024)†. EML status needs checking against the 24th List†.

Treating the underlying cause: stopping or monitoring the implicated drug; treating coeliac disease, bacterial overgrowth or parasitic infection.

Simple means. Any regular animal-source food — milk, eggs, offal, small fish eaten whole, shellfish, blood foods. A few portions a week prevents dietary B12 deficiency outright.

Green leafy vegetables, legumes and citrus for folate. Folate is heat-labile, so lightly cooked or raw matters. A mixed diet including these prevents folate deficiency outright.

Fermented foods are unreliable as a B12 source. Amounts vary, the common claim that fermented plant foods or algae supply enough B12 does not hold, and spirulina contains pseudo-B12 that is not active in humans.

Not relying on folate alone where B12 status is unknown. A simple means that prevents harm.

Fortified flour needs a mill, so it is not a no-chain measure, but it is the cheapest prevention in this chapter: fortification cost is on the order of two to ten cents per person per year.

Gaps. The regional B12 prevalence figures rest on secondary compilations using different assays and cut-offs and are indicative, not comparable. No current global estimate of B12 deficiency burden exists with the methodological standing of the GBD anaemia estimates. The pooled effect of mandatory folic acid fortification on neural tube defects varies between reviews, roughly 30 to 60 per cent depending on baseline prevalence, fortification level and ascertainment; the about-half figure is the Oxford review's summary and the full text could not be retrieved, so the precise pooled estimate and interval are not reproduced. Oral against intramuscular B12 for neurological disease: sources disagree. Whether folic acid fortification affects cancer risk or masks B12 deficiency at population scale remains contested; large trials and meta-analyses have not shown a cancer signal and the debate persists.

> **Depth.** Starts in: the vitamin B12 molecule. Size: 1.5 nm†; depth −3.11. First complaint: about 3.9 years († body stores last 3–5 years); time depth 50.10. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Sickle cell disease

What it is. An inherited change in one letter of the haemoglobin gene. The haemoglobin clumps when oxygen is low, red cells stiffen into crescents and block small vessels. Pain crises, anaemia, infection, stroke and organ damage follow.

Measured. The WHO sickle cell disease fact sheet, for the 2021 reference year, gives 7.74 million people living with the disease worldwide and about 515,000 births a year. Sub-Saharan Africa carries nearly 80 per cent of cases. There were 81,100 deaths in children under five in 2021, the twelfth leading cause of under-five death. Total deaths with sickle cell disease as a contributing cause were about 376,000, roughly eleven times the 34,400 deaths that cause-specific coding attributes to it. That gap is itself a measurement finding: most sickle cell deaths are recorded under infection, stroke or anaemia.

In untreated settings death clusters in the first five years, from infection, splenic sequestration and severe anaemia. Where newborn screening, penicillin prophylaxis, vaccination and hydroxyurea exist, survival into the fifth and sixth decade is routine. The sickle allele reaches carrier frequencies of 10 to 25 per cent across a malaria belt from West Africa through Central Africa to parts of India, the Arabian peninsula and the Mediterranean, with diaspora populations in Europe, the Americas and the Gulf.

Where it starts. A single fully established cause: homozygosity for the *HBB* Glu6Val allele, or compound heterozygosity as HbSC or HbS/β-thalassaemia. Heritability is 1.0 for having the disease.

Why the allele is common: heterozygote advantage against *Plasmodium falciparum*. Sickle cell trait reduces the risk of severe falciparum malaria by roughly 90 per cent in case-control and cohort studies†, one of the largest single-locus protective effects known in human genetics, and the established reason the allele reaches 10 to 25 per cent carrier frequency in malarious regions and near zero elsewhere.

What modifies severity at the same genotype: co-inherited α-thalassaemia; fetal haemoglobin level, which is the strongest single severity modifier and is shifted by *BCL11A*, *HBS1L-MYB* and the *HBG* promoter; *UGT1A1* for gallstones; *APOL1* for kidney disease. Crisis triggers are dehydration, cold, infection, hypoxia, acidosis and physical stress; the associations are consistent and the per-exposure risk is not well quantified.

Not known: why two people with the same genotype and the same fetal haemoglobin can have ten-fold different crisis rates. Most of the variance in severity is unexplained. Also not known: why chronic pain develops in some patients and not others, and whether it is the same process as acute vaso-occlusion.

Cure status. With a matched sibling donor transplant: CURABLE. With gene therapy: CONTROLLABLE. Without access to either: CONTROLLABLE. A cure by gene therapy is plausible and has not been demonstrated: the pivotal follow-up is 24 months and durability beyond that is unknown by construction.

Allogeneic haematopoietic stem cell transplant from a matched sibling donor is the oldest curative route, with event-free survival in children reported around 90 per cent and overall survival around 95 per cent in large series†. The ceiling is donor availability: roughly 15 to 18 per cent of patients have a matched sibling†. Haploidentical transplant extends eligibility and is in active trials with higher rejection and graft-versus-host disease rates.

Exagamglogene autotemcel edits the *BCL11A* erythroid enhancer in autologous CD34+ cells to raise fetal haemoglobin. In the pivotal single-arm trial, 44 patients were treated and, of 31 with sufficient follow-up, 29 (93.5 per cent) had at least 12 consecutive months free of severe vaso-occlusive crises over 24 months of follow-up; all engrafted, with no graft failure or rejection. Approvals: United Kingdom November 2023, Bahrain December 2023, United States December 2023 for sickle cell disease, European Union conditional February 2024.

Lovotibeglogene autotemcel adds an anti-sickling β-globin gene by lentiviral vector. United States approval December 2023, with durable reduction in vaso-occlusive events in the pivotal programme and a boxed warning for haematological malignancy.

Price: exagamglogene autotemcel about US$2.2 million per treatment on United States list (2023–2024)†; lovotibeglogene autotemcel about 3.1 million (2023)†. ICER's 2023 assessment judged both potentially cost-effective at roughly US$2 million per treatment in a United States context†.

Both require myeloablative conditioning with busulfan, apheresis, cell manufacture and a transplant-capable centre. Nearly 80 per cent of the world's patients live in sub-Saharan Africa, where those chains do not exist. Fertility loss from conditioning, and durability and malignancy risk beyond ten years, are unresolved.

Prevention. This is a Mendelian disease, so prevention means preventing affected births rather than preventing onset in a person.

Carrier screening with genetic counselling. Cyprus, Sardinia and parts of Greece reduced affected thalassaemia births by more than 95 per cent with national programmes on the same model†. STRONG for the effect on birth prevalence in thalassaemia; MODERATE for sickle cell specifically, where there are fewer programmes and less published before-and-after data.

Newborn screening does not prevent the disease; it prevents early death. Where screening is paired with penicillin prophylaxis and pneumococcal conjugate vaccination, under-five mortality falls sharply, and United States death rates in children under four fell by about three-fifths to two-thirds across the period in which both were introduced. STRONG.

Daily penicillin prophylaxis in children under five: the PROPS trial found an 84 per cent reduction in pneumococcal septicaemia†. STRONG.

Pneumococcal and *Haemophilus influenzae* type b conjugate vaccination. STRONG.

Transcranial Doppler screening with transfusion in children with high velocities: the STOP trial found roughly a 90 per cent reduction in first stroke†. STRONG.

Preimplantation genetic testing and prenatal diagnosis are effective where available; availability, cost and acceptability vary by setting.

Treatment. Hydroxyurea (hydroxycarbamide) is the backbone. The Multicenter Study of Hydroxyurea in adults roughly halved the rate of painful crises, acute chest syndrome and transfusions, and long-term follow-up showed a mortality benefit. BABY HUG and the African trials REACH and NOHARM established safety and benefit in children, including in sub-Saharan Africa. Hydroxyurea is a selected medicine on the 24th List, in section 10.3, medicines for haemoglobinopathies, core list, for other specified

sickle cell disorders and other haemoglobinopathies. Off-patent, at roughly US$30 to US$100 a patient-year at generic international prices (2024), and under US$50 in some African programmes†.

Penicillin V prophylaxis in young children, at roughly two to ten dollars a patient-year (2024)†. EML status needs checking against the 24th List†.

Folic acid routinely, under two dollars a year (2024)†. EML status needs checking against the 24th List†.

Transfusion, simple or exchange, for stroke prevention, acute chest syndrome, severe anaemia and preoperative optimisation. It requires a safe blood supply, which is the binding constraint in most high-burden countries. Chronic transfusion creates iron overload requiring chelation: generic deferasirox runs US$1,000 to US$4,000 a patient-year at lowest available acquisition cost, 2024, and is falling†, and deferoxamine is cheaper per gram but needs subcutaneous infusion pumps. Deferasirox's listing status needs checking against the 24th List†. Deferiprone is on the 24th List only as a therapeutic equivalent to deferasirox, in section 10.3, for thalassaemias and for other specified sickle cell disorders and haemoglobinopathies — not as a selected medicine.

Analgesia for crisis, including opioids. Oral morphine is a selected medicine on the 24th List, in section 2.2, opioid analgesics, core list, for pain. Off-patent, with trivial drug cost; availability is the constraint, since opioid supply is restricted in many high-burden countries.

L-glutamine, approved in the United States in 2017, produced modest crisis reduction of roughly 25 per cent in its pivotal trial, with limited uptake†. Its EML status needs checking against the 24th List†.

Crizanlizumab, an anti-P-selectin antibody, reduced crisis rate in its pivotal trial; the confirmatory STAND trial did not meet its primary endpoint and the European authorisation was withdrawn in 2023 while the United States authorisation was retained. Sources disagree. EML status needs checking against the 24th List†.

Voxelotor, a haemoglobin polymerisation inhibitor, raised haemoglobin in trials; the manufacturer withdrew it worldwide in September 2024 after a safety signal of deaths and vaso-occlusive events in post-marketing and trial data. It is recorded here because it appears as a standing treatment in literature written before that date.

Simple means. Oral hydration and warmth. Dehydration and cold are established crisis triggers, and keeping warm and drinking enough is the cheapest crisis-reduction measure available.

Folic acid, a cent-level daily tablet.

Early recognition of fever and immediate presentation. In children, infection is the main killer, and the simple means is a caregiver who knows that fever in a child with sickle cell disease is an emergency. Education-only interventions have measurable mortality effects in African cohorts.

Insecticide-treated bed nets and malaria chemoprophylaxis in endemic areas, because malaria is a major precipitant of severe anaemia and death in these children.

Breastfeeding and routine childhood vaccination.

Newborn screening by heel-prick dried blood spot, which is low-cost and the gateway to all of the above. Point-of-care immunoassay devices now cost on the order of a few dollars per test and need no laboratory.

Gaps. The WHO fact sheet's own comparison of 376,000 deaths with sickle cell disease against 34,400 cause-specific deaths is a statement that global mortality is systematically under-recorded by about an order of magnitude. Prevalence estimates for sub-Saharan Africa rest largely on modelled allele frequencies and birth cohorts rather than measured patient counts, and the number of people living with the disease in Africa is unusually uncertain because survival is itself unmeasured across most of the region. Crizanlizumab: pivotal trial positive, confirmatory trial negative, European authorisation withdrawn, United States authorisation retained. Voxelotor's 2024 withdrawal postdates much of the published treatment literature. Long-term safety and durability of both gene therapies is unknown by construction, and no data exist on gene therapy delivered in any sub-Saharan African health system, where about 80 per cent of patients live.

> **Depth.** Starts in: haemoglobin (HbS). Size: 6.5 nm†; depth −1.77. First complaint: about 15 months († from conception to about 6 months after birth); time depth 49.07. One untreated course: no number († lifelong).

> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. A stem-cell transplant or gene therapy restores the source. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Thalassaemias

What it is. Inherited faults in making the globin chains of haemoglobin, alpha or beta. Too few chains means too little haemoglobin and red cells that die early. Severe forms need lifelong transfusion; mild forms cause only a small anaemia.

Measured. Carrier rates reach 2 to 18 per cent across the Mediterranean, the Middle East, South and Southeast Asia and southern China. WHO has historically used an estimate that about 1.5 per cent of the world population, roughly 80 to 90 million people, carries a β-thalassaemia allele†. WHO and Modell-derived estimates put severe β-thalassaemia births at roughly 40,000 to 60,000 a year worldwide, the large majority in Asia†. Orphanet records the annual incidence of symptomatic β-thalassaemia as 1 in 100,000 worldwide and 1 in 10,000 in the European Union, and lists prevalence as unknown, with the entry last updated 2011.

GBD 2021 counts haemoglobinopathies and haemolytic anaemias together as the second largest contributor to anaemia YLDs, so thalassaemia-specific burden cannot be read off directly.

The geography is malaria-correlated, as with sickle cell. α-thalassaemia predominates in Southeast Asia and southern China, β-thalassaemia in the Mediterranean, the Middle East, the Indian subcontinent and Southeast Asia. β-thalassaemia major presents at 6 to 24 months as fetal haemoglobin falls. α-thalassaemia major, Hb Bart's hydrops fetalis, is lethal in utero or at birth unless treated with intrauterine transfusion.

No reliable separate global death count. In transfused patients the historical cause of death was iron-overload cardiomyopathy; with modern chelation, survival into the fifth and sixth decade is usual in well-resourced programmes.

Where it starts. β-thalassaemia: over 300 described mutations in *HBB* reducing (β+) or abolishing (β0) β-globin synthesis. Heritability 1.0 for the genotype. α-thalassaemia: deletions or mutations of *HBA1* and *HBA2*. There are four α genes and the number lost sets the phenotype — one silent, two trait, three HbH disease, four Hb Bart's hydrops.

Why common: heterozygote protection against malaria, as for sickle cell. The geographic correlation with historic malaria endemicity is among the clearest in population genetics.

Severity modifiers: co-inherited α-thalassaemia reduces β-thalassaemia severity by rebalancing chain production; fetal-haemoglobin-raising variants in *BCL11A*, *HBS1L-MYB* and the *HBG* promoter reduce severity; *UGT1A1* affects bilirubin and gallstones. Transfusion dependence is the key clinical division and is not fully predictable from genotype.

Not known: why transfusion dependence varies at identical genotype beyond the known fetal haemoglobin and α-gene modifiers. Also not known: the true global number of people living with thalassaemia, as distinct from modelled births.

Cure status. Allogeneic transplant, where accessible: CURABLE. Gene therapy, where accessible: CONTROLLABLE. Transfusion and chelation programme: CONTROLLABLE. A cure by gene therapy is plausible and has not been demonstrated: durability of both gene therapies is unknown by construction.

Allogeneic transplant from a matched sibling donor in a young, well-chelated patient gives thalassaemia-free survival around 85 to 90 per cent in large series, with the best results under age 14 and a low iron burden†. This has been a genuine cure since the 1980s, and the binding constraint is donor availability and the cost and infrastructure of transplant.

Betibeglogene autotemcel adds β-globin by lentiviral vector. Across the phase 3 studies, about 89 per cent of patients (32 of 36) achieved transfusion independence, defined as a weighted average haemoglobin of at

least 9 g/dL without transfusion for at least 12 months†. United States approval August 2022 at a list price of US$2.8 million†; withdrawn from the European market in 2021–2022 over reimbursement, not safety.

Exagamglogene autotemcel for transfusion-dependent β-thalassaemia: United States approval January 2024, European Union February 2024, United Kingdom November 2023, with the majority of trial patients achieving transfusion independence.

Without transplant or gene therapy, lifelong transfusion plus chelation is CONTROLLABLE. Median survival in well-run programmes now exceeds 40 years and continues to rise†, and the disease and its treatment burden persist.

Prevention. Prevention of affected births, not of onset, and this entry holds the strongest population data in the chapter.

National carrier screening with counselling in Cyprus and Sardinia reduced β-thalassaemia major births by more than 95 per cent within one to two decades†. Cyprus combined premarital screening, with church cooperation, and prenatal diagnosis; Sardinia combined school and population screening with prenatal diagnosis. STRONG — these are national before-and-after datasets rather than trials, and the effect is unambiguous and replicated.

Iran's national premarital screening programme from 1997 reported reductions of roughly 70 per cent in expected affected births†. STRONG.

Prenatal diagnosis and, where accepted, preimplantation genetic testing. Acceptability is culturally and religiously variable, which is why the church-partnered Cypriot design is cited so often.

Newborn screening does not prevent thalassaemia; it prevents late diagnosis and early death in HbH and β-thalassaemia.

Treatment. Regular transfusion to maintain pre-transfusion haemoglobin around 9 to 10.5 g/dL in transfusion-dependent disease, which suppresses ineffective erythropoiesis and prevents skeletal deformity and splenomegaly. It requires a safe, screened blood supply — the binding constraint in most high-burden countries. Cost is dominated by collection and screening, on the order of thousands of US dollars a patient-year depending on the health system (2024)†.

Iron chelation, mandatory with chronic transfusion, since each unit adds about 200 mg of iron†. Deferoxamine by subcutaneous infusion over 8 to 12 hours, five to seven nights a week: drug cost US$500 to US$2,000 a patient-year at generic or lowest available acquisition cost, 2024, plus pump and consumables, with adherence the problem†. Deferasirox, oral once daily, generic from 2019–2020, at US$1,000 to US$4,000 a patient-year (2024), down from originator prices several times higher†. Deferiprone, oral and cardio-protective, with a risk of agranulocytosis requiring blood counts, at US$1,000 to US$3,000 a patient-year at generic or lowest available acquisition cost, 2024†. The listing status of deferoxamine and deferasirox needs checking against the 24th List†; deferiprone is on the 24th List only as a therapeutic equivalent to deferasirox, in section 10.3, and not as a selected medicine.

Luspatercept, an erythroid maturation agent. In the BELIEVE trial in transfusion-dependent β-thalassaemia, 21.4 per cent against 4.5 per cent of patients achieved at least a 33 per cent reduction in transfusion burden over weeks 13 to 24†. Patented, with a United States list price on the order of US$150,000 to US$200,000 a patient-year (2024)†. EML status needs checking against the 24th List†.

Hydroxyurea in some non-transfusion-dependent β-thalassaemia and HbE/β disease, at US$30 to US$100 a year at generic or lowest available acquisition cost, 2024†. Hydroxyurea is a selected medicine on the 24th List, in section 10.3, for other specified sickle cell disorders and other haemoglobinopathies.

Splenectomy reduces transfusion requirement in selected patients and is now used sparingly because of sepsis and thrombosis risk. It requires pneumococcal and meningococcal vaccination and penicillin prophylaxis afterwards.

Folic acid routinely, under two dollars a year (2024)†.

Simple means. Carrier testing before pregnancy. A full blood count showing microcytosis with normal iron, confirmed by haemoglobin electrophoresis or a single genetic test, costs a few dollars and is the whole basis of the Cyprus and Sardinia results.

Avoiding iron supplements unless iron deficiency is proven. Thalassaemia trait causes microcytosis that is routinely mistaken for iron deficiency, and iron given on that mistake adds to iron loading. A simple means that prevents harm.

Folic acid, cents a year.

Tea with meals is reversed here: in non-transfused thalassaemia, tea with meals is sometimes used deliberately to reduce dietary iron absorption. The evidence is thin, from small studies, so WEAK, and it costs nothing.

Avoiding raw shellfish, because *Vibrio vulnificus* risk is raised in iron overload, and avoiding alcohol where there is iron loading with liver involvement.

Gaps. No current, methodologically consistent global count of people living with thalassaemia. The widely quoted carrier and birth figures derive from Modell's modelling work and WHO compilations, some of it decades old, and Orphanet's own entry is marked as last updated 2011. GBD aggregates thalassaemias with other haemoglobinopathies and haemolytic anaemias. Gene therapy durability beyond roughly five to eight years is unknown, and the commercial withdrawal of betibeglogene autotemcel from Europe means European long-term follow-up will be thin. Whether non-transfusion-dependent thalassaemia should be transfused, and when, is contested.

> **Depth.** Starts in: the globin chain. Size: 6.5 nm†; depth −1.77. First complaint: about 21 months († from conception to 6–24 months); time depth 49.38. One untreated course: no number ([B] severe form: lifelong transfusion).
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> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. A stem-cell transplant restores the source. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Glucose-6-phosphate dehydrogenase deficiency

What it is. A common inherited shortage of an enzyme that protects red cells from oxidative damage. Most of the time nothing happens. Certain drugs, infections or fava beans then break red cells apart suddenly.

Measured. The most widely cited global figure is roughly 400 million people affected, derived from the Malaria Atlas Project geostatistical mapping of allele frequency across malaria-endemic and neighbouring countries (Howes et al., *PLoS Medicine*, 2012). Median allele frequency in that mapping was around 8 per cent across malaria-endemic countries, with national values from near zero to over 30 per cent in parts of sub-Saharan Africa, the Arabian peninsula and Southeast Asia.

The gene is X-linked, so hemizygous males carry the clinically important phenotype; homozygous and some heterozygous females are also affected, and heterozygous females have mosaic enzyme activity that standard tests may miss.

Geography follows variant: Africa the A−variant with moderate deficiency, the Mediterranean and Middle East the severe Mediterranean variant, Southeast Asia the Viangchan, Mahidol and Canton variants.

The measured clinical outcomes are neonatal jaundice and kernicterus — the deficiency is a leading identified cause of severe neonatal hyperbilirubinaemia in high-prevalence countries — acute haemolytic episodes, and primaquine or tafenoquine-induced haemolysis in malaria treatment. Deaths are not separately counted globally.

Where it starts. Over 200 described mutations in *G6PD* on the X chromosome. Heritability 1.0 for the genotype. The WHO class I to V grading by residual enzyme activity determines severity.

Why common: malaria selection, as with sickle cell and thalassaemia. The protective effect against *P. falciparum* is real but smaller and more contested in size than the sickle trait effect, and estimates differ between studies and between the sexes.

Established triggers of haemolysis: primaquine and tafenoquine, dapsone, nitrofurantoin, rasburicase, methylene blue, high-dose aspirin, some sulphonamides, naphthalene in mothballs, henna applied to neonatal skin, fava beans (*Vicia faba*), and infection itself. Chloroquine and most other antimalarials are safe at standard doses.

Neonatal jaundice risk is raised several-fold, and co-inherited *UGT1A1* promoter variants multiply it.

Not known: why individuals with the same variant have very different haemolytic responses to the same trigger dose; the true size of the malaria protective effect; and what proportion of global neonatal kernicterus is attributable to the deficiency, because screening coverage is lowest where prevalence is highest.

Cure status. CONTROLLABLE. Nothing restores G6PD activity. The clinical disease is almost entirely preventable by avoidance, and an acute haemolytic episode is self-limiting once the oxidant is stopped, resolving over days to weeks with supportive care and transfusion if severe. Neonatal jaundice is treated, by phototherapy and exchange transfusion, rather than cured. The honest statement is that nothing treats the deficiency and almost everything that matters is avoidance.

Prevention. Prevention here means preventing episodes, not preventing the genotype.

Testing before prescribing a known oxidant drug. The decisive measure, especially for primaquine and tafenoquine in malaria elimination programmes, where a single radical-cure dose can cause life-threatening haemolysis. STRONG.

Newborn screening in high-prevalence populations with follow-up for jaundice. Where it is implemented — parts of Southeast Asia, the Gulf, Greece, Sardinia — severe neonatal hyperbilirubinaemia and kernicterus fall. STRONG in high-prevalence settings.

A written list of drugs and foods to avoid, given to the person and the family. STRONG: mechanistically certain, and no trial is needed or possible.

Avoiding naphthalene mothballs and henna on neonatal skin in affected families. MODERATE, from consistent case series.

Point-of-care quantitative G6PD tests now exist and are being deployed in malaria programmes, shifting primaquine from contraindicated-by-caution to usable.

Treatment. Stop the trigger. No drug outperforms this.

Supportive care — hydration, monitoring of haemoglobin — and transfusion for severe haemolysis. Blood is not a listed medicine; transfusion is a service.

Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia. Equipment rather than medicine. Phototherapy units are off-patent and cheap, and filtered-sunlight phototherapy has been trialled successfully in Nigeria as a no-electricity alternative.

Folic acid in chronic haemolysis, under two dollars a year (2024)†. EML status needs checking against the 24th List†.

Splenectomy only in the rare chronic non-spherocytic haemolytic anaemia caused by class I variants, not in ordinary deficiency.

No enzyme replacement and no gene therapy exists in clinical use.

Simple means. Avoidance of fava beans and of the listed drugs. Nothing else is required, and it is complete protection against those triggers.

A card in the wallet or a note in the family’s records naming the condition. In practice the single most effective intervention in this entry.

Filtered sunlight phototherapy for neonatal jaundice, trialled in Nigeria by Slusher and colleagues and found non-inferior to conventional phototherapy for efficacy and safe with monitoring. No electricity needed.

Breastfeeding support and early feeding, which reduce neonatal hyperbilirubinaemia generally.

Not using mothballs in clothing and bedding stores in affected households.

Gaps. The 400 million figure is modelled, not counted, and dates from 2012; no more recent global count with comparable method exists. Heterozygous females are systematically under-detected by qualitative screening tests, so prevalence in females is uncertain and clinical risk in that group is poorly quantified. The size of the malaria protective effect is contested across studies. The attributable fraction of global kernicterus is unknown. WHO class assignments for many of the 200-plus variants rest on small enzyme-activity datasets.

> **Depth.** Starts in: the G6PD enzyme. Size: 10 nm†; depth −1.38. First complaint: about 42 hours († 1–3 days after a trigger); time depth 44.00. One untreated course: about 7 days († about 1 week); depth 45.27.
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> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Aplastic anaemia

What it is. The bone marrow stops making blood cells. Red cells, white cells and platelets all fall. It is usually an immune attack on marrow stem cells rather than a cancer or a poisoning.

Measured. Incidence is 0.7 to 4.1 cases per million per year worldwide, roughly equal between men and women. Asian incidence is two to three times higher than Western, one of the firmest findings in the epidemiology and unexplained. The United States sees about 300 to 900 new cases a year†. Age shows two peaks, 15 to 25 years and over 60, and the disease can occur at any age. Orphanet lists prevalence of acquired idiopathic aplastic anaemia as 1 to 9 per million, with the entry marked as under development and no incidence given.

Survival with modern treatment exceeds 85 per cent at five years†. Allogeneic transplant recipients exceed 75 per cent at five years, better with a matched sibling donor and worse with unrelated donors. Immunosuppression alone in frail older patients or those without a good donor match gives five-year survival up to 35 per cent in the cited series†. Untreated severe disease is usually fatal within months from infection or haemorrhage. No reliable global death count.

Where it starts. Idiopathic, immune-mediated disease is the large majority. One source gives about half as idiopathic, another 75 per cent, and the figures conflict†. The mechanism is a T-cell attack on haematopoietic stem cells, and the evidence for it is that immunosuppression works.

Drugs and chemicals: chloramphenicol, the historical association; carbamazepine, phenytoin, gold, sulphonamides, non-steroidal anti-inflammatory drugs, benzene and other organic solvents, insecticides. The reactions are idiosyncratic, so per-exposure risk is tiny and hard to estimate; the association with benzene is dose-related and firm.

Viruses: parvovirus B19, seronegative hepatitis-associated aplastic anaemia, Epstein-Barr virus, cytomegalovirus, HIV. Radiation, dose-dependent and established. Pregnancy, a recognised rare association.

Inherited marrow failure syndromes underlie a minority, especially in children and young adults: Fanconi anaemia, telomere biology disorders (*TERT*, *TERC*, *DKC1*), Shwachman-Diamond syndrome, GATA2 deficiency. These must be excluded before transplant, because the conditioning regimen differs.

Clonal haematopoiesis: paroxysmal nocturnal haemoglobinuria clones and 6p loss-of-heterozygosity clones are found in a substantial minority and predict response to immunosuppression.

Acquired aplastic anaemia is not heritable. The inherited syndromes that mimic it are Mendelian.

Not known: what the immune attack is directed against — no autoantigen is established. Why incidence is two to three times higher in Asia. Which drug exposures carry real risk at what dose, since the events are too rare for cohort quantification. Why some patients respond to immunosuppression and others do not, beyond the partial predictive value of clone status and telomere length.

Cure status. Eligible for allogeneic transplant: CURABLE. Treated by immunosuppression: CONTROLLABLE.

Allogeneic transplant from a matched sibling donor in a young patient is the established cure, with five-year survival above 75 to 90 per cent depending on age and donor†. The marrow is replaced and the disease does not return.

Horse antithymocyte globulin with ciclosporin produces response in up to 80 per cent of patients with severe disease in the cited series† — response, not cure. Relapse occurs in roughly a third, and clonal evolution to myelodysplastic syndrome or acute myeloid leukaemia in roughly 10 to 15 per cent over a decade†.

Eltrombopag added to antithymocyte globulin and ciclosporin raises complete response rates substantially over the two-drug regimen in the NIH and RACE trials, and is now standard first-line in several guidelines. Still control rather than cure.

Prevention. Removing benzene and solvent exposure in occupational settings. The risk is dose-related, so exposure reduction is expected to reduce incidence. MODERATE: occupational cohort evidence, no trial.

Restricting chloramphenicol to indications where nothing else serves. The historical measure, taken on case-series grounds. WEAK — the association is accepted, the magnitude was never well quantified, and the restriction was never trialled.

Hepatitis B vaccination removes one viral trigger. WEAK for this outcome specifically, because hepatitis-associated aplastic anaemia is usually seronegative.

There is no established primary prevention for idiopathic immune aplastic anaemia. The dominant form of this disease has no known prevention.

Treatment. Allogeneic transplant, first-line for severe disease in patients under about 40 with a matched sibling. Not a medicine; cost in high-income settings is US$150,000 to US$500,000 per transplant (2024)†.

Horse antithymocyte globulin with ciclosporin and eltrombopag, first-line where transplant is unavailable or the patient is older. Horse antithymocyte globulin is a biologic with limited manufacturers and has had repeated global supply interruptions; a course costs US$15,000 to US$40,000 (2024) with wide variation†. Ciclosporin is off-patent at US$300 to US$1,500 a patient-year (2024)†. Eltrombopag has been off-patent since roughly 2023–2025 in several markets; the originator price was US$50,000 to US$100,000 a patient-year (2023), generic prices are falling, and Indian generics have been reported at low thousands of dollars a year. The listing status of all three needs checking against the 24th List†.

Supportive care — red cell and platelet transfusion, antibiotics and antifungals for neutropenic infection, iron chelation after prolonged transfusion. This is what determines survival where the specific treatments are unavailable.

Androgens, danazol and oxymetholone: older treatment, still used for telomere biology disorders, where danazol lengthens telomeres measurably in a small trial. Off-patent and cheap, in the low hundreds of dollars a year. EML status needs checking against the 24th List†.

Cyclophosphamide-based regimens were abandoned as first-line after unacceptable fungal infection mortality in NIH trials.

Simple means. Almost none, and that should be said plainly. Aplastic anaemia requires transfusion support, immunosuppression or a transplant. There is no dietary, behavioural or low-technology treatment.

Avoiding the implicated drug or solvent where one is identified: complete and free.

Infection avoidance during neutropenia — hand hygiene, avoiding crowds, food hygiene — reduces infection risk at no cost, though trial evidence for each component is thin.

A safe blood supply is the one simple requirement that is in fact the hardest in low-income settings.

Gaps. Sources conflict on the proportion of idiopathic cases, about half against 75 per cent. The two-to-three-fold higher incidence in Asia is reported consistently and explained nowhere. Orphanet's prevalence of 1 to 9 per million and the incidence literature of 0.7 to 4.1 per million per year are not reconcilable without survival data, which are not reported. No autoantigen is identified, so the immune mechanism remains inferred from treatment response. Horse antithymocyte globulin supply is a recurring global problem that no price figure captures. Generic eltrombopag prices are moving fast.

> **Depth.** Starts in: a blood stem cell. Size: 8 µm†; depth +4.70. First complaint: about 25 years († onset about age 25); time depth 51.80. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from inside. Layer: reading. By the rule it is held by supply. It ends only if the source is restored. A stem-cell transplant restores the source. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Haemophilia A and B

What it is. An inherited shortage of a clotting factor — factor VIII in haemophilia A, factor IX in haemophilia B. Bleeding into joints and muscles happens without obvious injury, and joints are destroyed over years if the bleeding is not prevented.

Measured. Prevalence at birth per 100,000 males, from the meta-analysis that tripled previous estimates (Iorio et al., *Annals of Internal Medicine*, 2019): haemophilia A all severities 24.6, severe haemophilia A 9.5, haemophilia B all severities 5.0, severe haemophilia B 1.5. The global estimate from that analysis is about 1,125,000 males with haemophilia, of whom about 418,000 have severe disease; earlier estimates had put the global total near 400,000.

Identified and reported to the World Federation of Hemophilia Annual Global Survey, 2023 data published October 2024, with 119 countries reporting: haemophilia A 179,703; haemophilia B 37,385; haemophilia of unknown type 1,716; von Willebrand disease 101,128; other bleeding disorders 70,698; total identified 390,630.

The gap between about 1,125,000 estimated and about 219,000 haemophilia cases identified is the central measured fact about this disease: roughly four out of five people with haemophilia worldwide have not been identified.

The life expectancy shortfall, expressed by Iorio and colleagues as the reduction in the chance of a normal-length life, is about 64 per cent in upper-middle-income countries, 77 per cent in middle-income countries and up to 93 per cent in low-income countries†.

Severity by residual factor activity: severe below 1 per cent, moderate 1 to 5 per cent, mild 5 to 40 per cent. Haemophilia A is roughly 85 per cent of all haemophilia†. The inheritance is X-linked recessive, so cases are almost entirely male; symptomatic carrier females occur and are under-recognised. Severe disease presents in the first two years.

Where it starts. Loss-of-function variants in *F8* or *F9* on the X chromosome. Heritability 1.0 for the genotype. About 30 per cent of cases are new mutations with no family history†, and the *F8* intron 22 inversion is the single commonest severe mutation.

Phenotype correlates with residual factor activity more tightly than in almost any other genetic disease, which is why severity classes are defined by assay rather than by symptoms.

Inhibitor development — neutralising antibodies to infused factor — occurs in roughly 25 to 30 per cent of severe haemophilia A and 3 to 5 per cent of haemophilia B†. Risk factors are null mutations, non-white ethnicity, family history of inhibitors, and intensive early exposure during an immune-challenge event such as surgery; HLA and *IL10*, *TNFA* and *CTLA4* variants modify risk.

Joint damage results from repeated haemarthrosis, through iron-driven synovitis.

Not known: why inhibitors develop in some patients with identical mutations and not others — the known risk factors explain only part of the variance. Why some people with the same factor level bleed much more than others. Whether low-dose prophylaxis regimens used in resource-limited settings give the same joint outcomes as standard-dose regimens over decades.

Cure status. CONTROLLABLE.

Prophylactic factor replacement from early childhood prevents most joint damage and gives near-normal life expectancy where it is sustained. It does not cure: stop the infusions and the disease returns unchanged.

Emicizumab, a bispecific antibody bridging factor IXa and factor X, works with or without inhibitors. The HAVEN programme showed reductions in treated bleed rate against no prophylaxis on the order of 87 to 96 per cent in the inhibitor and non-inhibitor cohorts†. Subcutaneous, weekly to monthly. Control, not cure.

Gene therapy for haemophilia B: etranacogene dezaparvovec, a single AAV5 infusion. The HOPE-B trial showed sustained factor IX activity around 36 to 39 per cent at 18 to 24 months with about a 64 per cent reduction in annualised bleeding rate against the prophylaxis lead-in, and most patients off prophylaxis. United States approval November 2022, at a list price of US$3.5 million — the most expensive medicine in the world at launch†. Fidanacogene elaparvovec followed in April 2024 at the same list price, and commercialisation was discontinued in 2025 for lack of uptake.

Gene therapy for haemophilia A: valoctocogene roxaparvovec, a single AAV5 infusion. The GENEr8-1 trial showed a large reduction in annualised bleeding, but factor VIII expression declines year on year, which is the central unresolved problem. United States approval June 2023 at a list price of US$2.9 million†; commercialisation was scaled back in 2024 for lack of uptake.

So haemophilia B gene therapy looks durable so far and may be a cure; haemophilia A gene therapy has falling expression and is not yet one. Both are priced beyond all but a handful of health systems, and both have been commercial failures, which affects whether they will remain available at all.

Prevention. No primary prevention of the genotype other than carrier detection, genetic counselling, prenatal diagnosis and preimplantation genetic testing where available and acceptable.

Prevention of joint destruction by prophylaxis rather than on-demand treatment. The Joint Outcome Study randomised boys with severe haemophilia A to prophylaxis or enhanced episodic treatment: 93 per cent of the prophylaxis group had normal index-joint MRI at age six against 55 per cent of the episodic group, odds ratio 6.1 (Manco-Johnson et al., 2007). STRONG. This trial is the reason prophylaxis is standard everywhere it can be afforded.

Low-dose prophylaxis in resource-limited settings: observational and small trial data show substantial bleed reduction at a fraction of the factor consumption. MODERATE.

Inhibitor prevention by avoiding factor exposure during immune-challenge events is advised on observational grounds. WEAK.

Prevention of transfusion-transmitted infection, the historical catastrophe of this disease. Viral inactivation of plasma-derived concentrates and the move to recombinant product eliminated HIV and hepatitis C transmission in treated populations, and HIV transmission via factor concentrate in high-income countries fell to zero after 1985–1987†. STRONG, and measured.

Treatment. Factor VIII or factor IX concentrate, prophylactic: plasma-derived or recombinant, standard half-life or extended half-life. This is the dominant cost in haemophilia care. Standard prophylaxis for an adult in a high-income country runs US$150,000 to US$300,000 a patient-year (2024)†; plasma-derived product at tendered prices in middle-income countries can be US$20,000 to US$60,000 a patient-year†; low-dose regimens used in India and China run US$2,000 to US$10,000 a patient-year†. Plasma-derived product is off-patent, recombinant standard half-life only partly so, and extended half-life not at all. The listing status of factor VIII and factor IX concentrates needs checking against the 24th List†. The World Federation of Hemophilia Humanitarian Aid programme supplies donated concentrate to low-income countries, which is how a large share of the world’s treated patients are treated at all.

Emicizumab for haemophilia A with or without inhibitors, at US$400,000 to US$500,000 a patient-year on United States list (2024), with confidential discounts and tiered pricing, and some middle-income tenders far lower. Patented. EML status needs checking against the 24th List†.

Desmopressin for mild haemophilia A only, raising endogenous factor VIII three- to five-fold, at US$10 to US$100 per treatment episode at generic or lowest available acquisition cost, 2024†. Off-patent. The cheapest effective treatment in this entry, and usable without a cold chain in the nasal or subcutaneous form. EML status needs checking against the 24th List†.

Tranexamic acid as an adjunct for mucosal bleeding and dental procedures, at one to ten dollars a course (2024)†. Tranexamic acid is a selected medicine on the 24th List, in section 10.2, for haemorrhage not elsewhere classified.

Immune tolerance induction for inhibitors — high-dose factor over months to years — succeeds in roughly 60 to 80 per cent of haemophilia A and is extremely expensive†.

Bypassing agents for inhibitor patients: activated prothrombin complex concentrate and recombinant activated factor VII, both very expensive. Their listing status needs checking against the 24th List†.

Physiotherapy and joint care, radiosynovectomy or surgical synovectomy for target joints, and joint replacement for end-stage arthropathy.

Simple means. Immediate rest, ice, compression and elevation for a joint bleed, with prompt factor if available. Costs nothing and reduces the volume of blood in the joint.

Desmopressin for mild haemophilia A: no factor concentrate, and no cold chain in some formulations.

Tranexamic acid for mouth and nose bleeding and before dental work. Cents a dose.

Physiotherapy and muscle strengthening around target joints, with observational evidence for reduced bleed frequency and no industrial chain.

Avoiding intramuscular injections, aspirin and non-steroidal anti-inflammatory drugs. Free, and it prevents bleeds.

Dental hygiene, which prevents the extractions that cause major bleeding episodes.

Family and patient education, and a treatment card. In countries without diagnosis, the simple means that matters most is case-finding: the World Federation of Hemophilia data show four in five patients worldwide are not identified, so a clinician who recognises recurrent joint swelling in a boy is the binding intervention, and that costs nothing.

Gaps. The central gap is diagnostic: about 1,125,000 estimated against about 219,000 identified, so all burden, outcome and cost figures for low-income countries describe the identified minority. Iorio and colleagues tripled the prior prevalence estimate in 2019, and estimates may move again. Factor concentrate prices vary by more than an order of magnitude between settings and are usually confidential, so every cost figure here is approximate. Long-term durability of haemophilia A gene therapy is not established, and expression falls. Commercial withdrawal of fidanacogene elaparvovec in 2025 and scaled-back commercialisation of valoctocogene roxaparvovec in 2024 mean availability may not follow approval. Symptomatic female carriers are under-counted in every dataset here. Whether low-dose prophylaxis gives equivalent 30-year joint outcomes is unknown.

> **Depth.** Starts in: clotting factor VIII or IX. Size: 10 nm†; depth −1.38. First complaint: about 21 months († from conception to the first bleed about 1 year); time depth 49.38. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Von Willebrand disease

What it is. A shortage or malfunction of von Willebrand factor, the protein that makes platelets stick to damaged vessel walls. Bruising, nosebleeds, heavy periods and bleeding after surgery or childbirth are the usual signs. It is the commonest inherited bleeding disorder.

Measured. Laboratory prevalence is about 1 per cent of the population, roughly 1 in 100, with men and women equally affected; most of these people have no symptoms. Clinically significant prevalence is about 1 in 10,000†. The two-order-of-magnitude gap between the laboratory and clinical figures is the defining measurement feature of this disease, and the two are not describing the same thing.

Identified worldwide: 101,128 people in the World Federation of Hemophilia Annual Global Survey 2023 data, 119 countries reporting, published October 2024 — against an expected clinically significant population of roughly 800,000 at 1 in 10,000 of world population†.

Type distribution: type 1, partial quantitative deficiency, 40 to 80 per cent of cases; type 2, qualitative defects in subtypes 2A, 2B, 2M and 2N, 15 to 50 per cent, with type 2A alone 10 to 15 per cent of all cases; type 3, near-complete deficiency, recessive and severe, rare†. The ranges overlap widely between sources, which means the underlying case series are not comparable.

Equal by genotype, but women carry the clinical burden, because menstruation and childbirth are the main haemostatic challenges. Heavy menstrual bleeding is the presenting feature in a large majority of diagnosed women. Deaths are not separately counted; postpartum haemorrhage is the main mortality route.

Where it starts. Variants in *VWF* on chromosome 12. Type 1 is usually autosomal dominant with incomplete penetrance, type 3 recessive, and the type 2 subtypes dominant or recessive depending on subtype.

ABO blood group is a major determinant of von Willebrand factor concentration: group O individuals have levels roughly 25 to 30 per cent lower than non-O†. A substantial share of type 1 diagnoses in group O people therefore reflects the low end of a normal distribution rather than a disease allele, which is one reason the diagnostic threshold is contested.

Heritability of plasma von Willebrand factor concentration is around 0.6 to 0.75 in twin and family studies†; *ABO* alone explains roughly 20 to 30 per cent of population variance, with *VWF*, *CLEC4M*, *STXBP5* and *SCARA5* contributing†.

Acquired von Willebrand syndrome arises with aortic stenosis and other high-shear lesions, left ventricular assist devices, monoclonal gammopathy, myeloproliferative neoplasms with very high platelet counts, and hypothyroidism. Mechanistically established.

Bleeding is modified by factor VIII level, since von Willebrand factor carries factor VIII, by platelet von Willebrand factor content, and by oestrogen status.

Not known: where disease ends and the low tail of the normal distribution begins. The diagnostic cut-off, historically von Willebrand factor antigen below 30 IU/dL for definite disease and 30 to 50 for low von Willebrand factor, is a convention rather than a biological boundary, and guidelines have changed it. Also not known: why bleeding phenotype correlates so loosely with von Willebrand factor level in type 1.

Cure status. CONTROLLABLE. No treatment corrects the genotype or permanently restores von Willebrand factor.

Desmopressin releases stored von Willebrand factor and factor VIII from endothelium, raising levels three- to five-fold for hours. It works in most type 1 disease, is contraindicated in type 2B because it causes thrombocytopenia, is probably ineffective in type 2M and is ineffective in type 3.

Von Willebrand factor-containing concentrate replaces the protein for the duration of its half-life.

Treatment is episodic and effective, so most people with the disease live normally — but the disease is lifelong. For type 3, regular prophylaxis is sometimes needed and the situation resembles haemophilia. No gene therapy is in clinical use.

Prevention. No primary prevention of the genotype beyond genetic counselling.

Prevention of bleeding events is where the measurable prevention sits. Tranexamic acid or hormonal management for heavy menstrual bleeding: tranexamic acid reduces objectively measured menstrual blood loss by roughly 40 to 50 per cent in randomised trials in heavy menstrual bleeding generally†. STRONG.

The levonorgestrel intrauterine system achieves among the largest effect sizes measured for this symptom, a 70 to 90 per cent reduction in menstrual blood loss in trials in the general heavy-bleeding population. STRONG generally, MODERATE specifically in von Willebrand disease.

Planned peripartum management, the measure that prevents postpartum haemorrhage deaths. MODERATE: cohort evidence, and no trial is feasible.

Pre-procedural prophylaxis before dental work or surgery. STRONG.

Avoiding aspirin and non-steroidal anti-inflammatory drugs. Free. MODERATE.

Treatment. Desmopressin, intranasal, subcutaneous or intravenous, first-line for type 1 and responsive type 2A, at US$10 to US$100 per treatment episode at generic or lowest available acquisition cost, 2024†. A desmopressin trial measuring the response should precede reliance on it. Off-patent. EML status needs checking against the 24th List†.

Tranexamic acid for mucosal and menstrual bleeding and around procedures, at one to ten dollars a course (2024)†. A selected medicine on the 24th List, section 10.2.

Von Willebrand factor-containing factor VIII concentrate, plasma-derived, or recombinant von Willebrand factor, for type 3, type 2B, non-responders, major surgery and major bleeding. Episodic use runs US$1,000 to US$20,000 per bleeding episode or surgical cover at lowest available acquisition cost, 2024, and prophylaxis in type 3 runs US$100,000 to US$300,000 a patient-year†. Plasma-derived product is off-patent, recombinant is not. Listing status of factor VIII concentrate needs checking against the 24th List†.

Combined oral contraceptives or the levonorgestrel intrauterine system for heavy menstrual bleeding. Combined oral contraceptives run US$5 to US$30 a patient-year at generic or lowest available acquisition cost; the intrauterine system US$10 to US$30 per device at public-sector prices, lasting five to eight years (2024)†. Both off-patent. Listing status needs checking against the 24th List†.

Iron replacement, because chronic menstrual or mucosal loss produces the iron deficiency anaemia that is often the reason the patient presents.

Topical measures: fibrin glue, topical tranexamic acid mouthwash, nasal cautery for recurrent epistaxis.

Simple means. Tranexamic acid tablets and tranexamic acid mouthwash. Cheap, oral, no cold chain, and effective for the mucosal bleeding that dominates this disease.

A levonorgestrel intrauterine system or a combined pill for heavy periods — the largest single improvement in quality of life for most affected women, at public-sector prices of tens of dollars.

Nasal saline and humidification; pinching and leaning forward for nosebleeds. No cost.

Dental hygiene, which prevents the extractions that precipitate major bleeds.

Avoiding aspirin and non-steroidal anti-inflammatory drugs, using paracetamol instead.

An iron-rich diet with vitamin C at meals, and iron tablets, which treat the consequence.

A diagnosis. With 101,128 people identified against an expected 800,000 clinically significant cases, asking a woman with lifelong heavy periods and easy bruising about family bleeding history is the highest-yield free intervention in this entry.

Gaps. The diagnostic threshold is a convention and has moved, so prevalence figures are definition-dependent. Type distribution percentages overlap widely between sources. Massive under-diagnosis, especially in women and in low- and middle-income countries. Whether low von Willebrand factor of 30 to 50 IU/dL is a disease is contested. There is no trial evidence specifically in von Willebrand disease for most of the heavy-menstrual- bleeding interventions; the effect sizes are borrowed from the general population.

> **Depth.** Starts in: von Willebrand factor. Size: 1 µm†; depth +2.81. First complaint: about 10 years († onset about age 10); time depth 50.97. One untreated course: no number († lifelong).

> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Immune thrombocytopenia

What it is. The immune system destroys platelets and suppresses their production. Platelet counts fall, causing bruising, pinpoint skin bleeding and, rarely, serious haemorrhage. In children it often follows a virus and goes away by itself; in adults it usually persists.

Measured. Annual incidence in Europe is roughly 1 per 25,600 to 1 per 37,000 people a year, about 2.7 to 3.9 per 100,000 a year (Orphanet)†. Prevalence is 1 to 5 per 10,000 (Orphanet)†. The two are not easily reconcilable.

In adults the age pattern is bimodal: a female-predominant peak in young adulthood and a sex-equal or male-predominant peak after 60. In children peak incidence is at two to five years with a slight male excess.

In children, roughly 70 to 80 per cent remit spontaneously within six to 12 months†. In adults spontaneous remission is uncommon, on the order of 10 to 20 per cent, and most develop persistent or chronic disease†.

Intracranial haemorrhage occurs in well under 1 per cent of children and roughly 1 to 2 per cent of adults with chronic severe disease, with risk rising with age and with platelet counts below 20×10^9/L†. Deaths are rare and mostly in older adults; attributable mortality in chronic refractory cohorts is a few per cent over years, from haemorrhage and from infection secondary to immunosuppression.

No strong geographic gradient is reported, but *Helicobacter pylori*-associated disease is substantially more common in Japan and Italy than in northern Europe or the United States, which is a measured regional difference in cause.

Where it starts. Autoantibodies against platelet glycoproteins GPIIb/IIIa and GPIb/IX cause splenic and hepatic clearance, and impaired megakaryocyte platelet production runs alongside, which is why thrombopoietin receptor agonists work. Both mechanisms are established. T-cell abnormalities include reduced regulatory T cells and skewed Th1/Th17 balance.

Preceding infection in children is common and is the basis of the usual post-viral picture.

Secondary disease accounts for roughly 20 per cent of cases†: systemic lupus erythematosus, antiphospholipid syndrome, common variable immunodeficiency, chronic lymphocytic leukaemia, HIV, hepatitis C, *H. pylori*, and drugs including quinine, heparin, vancomycin, sulphonamides and carbamazepine. Vaccination-associated disease occurs and is rare.

Not a heritable disease. Familial clustering of autoimmunity exists, HLA associations are weak and inconsistent, and no useful heritability estimate exists.

Not known: what starts the autoantibody response in primary disease. Why children remit and adults do not. Which patients will bleed — platelet count predicts bleeding only loosely, and there is no validated predictor of serious haemorrhage, which is the main clinical problem in deciding whom to treat.

Cure status. Children: SELF-LIMITING in 70 to 80 per cent, remitting within six to 12 months without disease-modifying treatment†; treatment in children is mostly for bleeding rather than for the count. Adults with primary disease: CONTROLLABLE — most need treatment and relapse when it stops. Adults with a treatable secondary cause: CURABLE by treating the cause.

Splenectomy gives durable response without further treatment in roughly 60 to 70 per cent at five years†, which is the closest thing to a cure in adult disease, and it is a permanent operation with lifelong sepsis and thrombosis risk. Its use has fallen sharply since thrombopoietin receptor agonists arrived.

Rituximab gives responses in roughly 60 per cent initially, but only about 20 to 25 per cent maintain response at five years†.

Thrombopoietin receptor agonists — eltrombopag, romiplostim, avatrombopag — raise counts in roughly 60 to 80 per cent of patients† but are suppressive rather than curative. A minority, roughly 10 to 30 per cent in discontinuation studies, sustain remission after stopping, which is a genuine and recent finding.

Treating a secondary cause can be curative. Eradicating *H. pylori* produces durable platelet recovery in a substantial share of *H. pylori*-positive patients in Japan and Italy, with response rates reported around 50 per cent in those populations and much lower in northern Europe and North America. Treating HIV or hepatitis C likewise.

Prevention. No primary prevention for primary disease. That should be stated plainly.

Stopping an implicated drug prevents recurrence of drug-induced immune thrombocytopenia. STRONG, mechanistically certain.

H. pylori eradication where the association is strong. MODERATE in Japan and Italy, WEAK elsewhere — the geographic difference in response is itself the evidence.

Avoiding aspirin and non-steroidal anti-inflammatory drugs when the count is low, which reduces bleeding rather than disease. MODERATE.

Pneumococcal, meningococcal and *Haemophilus influenzae* type b vaccination before splenectomy, with penicillin prophylaxis afterwards, to prevent post-splenectomy sepsis. STRONG.

Treatment. Corticosteroids — prednisolone or dexamethasone pulses — first-line, with response in 60 to 80 per cent, mostly not durable, at US$2 to US$20 a course at generic or lowest available acquisition cost, 2024†. Off-patent. Dexamethasone is a selected medicine on the 24th List in several sections including 3, antiallergics and medicines used in anaphylaxis, core list; prednisolone's status needs checking against the 24th List†. Toxicity on prolonged use is the reason newer agents exist.

Intravenous immunoglobulin gives a rapid transient rise in count and is used for bleeding or before procedures, at US$2,000 to US$10,000 a course for an adult at lowest available acquisition cost, 2024†. It is a plasma-derived product, so off-patent does not apply, and supply and plasma availability set the price. Global plasma supply is a standing constraint. Normal immunoglobulin's listing status needs checking against the 24th List†.

Anti-D immunoglobulin, for Rh-positive non-splenectomised patients only, is cheaper than intravenous immunoglobulin where available and carries a haemolysis warning.

Thrombopoietin receptor agonists. Eltrombopag, oral, off-patent since roughly 2023–2025, originator US$50,000 to US$100,000 a patient-year (2023), generics far lower and falling, with Indian generics reported in the low thousands a year. Romiplostim, weekly subcutaneous, patented with biosimilars emerging, US$40,000 to US$90,000 a patient-year (2024)†. Avatrombopag, oral with no food restrictions, patented. Listing status of all three needs checking against the 24th List†.

Rituximab, biosimilar course US$1,500 to US$5,000 at lowest available acquisition cost, 2024, down from originator prices several times higher†. Rituximab is a selected medicine on the 24th List, in section 5.1.2 for multiple sclerosis and in section 8.2.2 targeted therapies for Burkitt lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma, all complementary list. Immune thrombocytopenia is not among the listed indications.

Splenectomy, with durable remission in 60 to 70 per cent at five years, a one-off surgical cost and lifelong infection risk.

Fostamatinib, efgartigimod and rozanolixizumab are newer and effective in trials, patented, and priced in the high tens to hundreds of thousands a patient-year. Their listing status needs checking against the 24th List†.

Immunosuppressants — azathioprine, mycophenolate, ciclosporin, danazol, dapsone, vincristine — are all off-patent and cheap at US$50 to US$500 a patient-year at generic or lowest available acquisition cost, 2024†, and these remain the practical second line in most of the world. Vincristine is a selected medicine on the 24th List, in section 8.2.1 cytotoxic medicines, complementary list, for leukaemias, lymphomas and a

list of solid tumours. The listing status of azathioprine and ciclosporin needs checking against the 24th List†.

Observation, for counts above about 20 to 30 × 10^9/L without bleeding, in children and adults. The best-evidenced treatment for mild disease.

Simple means. Watchful waiting. For children, and for adults with counts above about 30 × 10^9/L and no bleeding, no treatment is the standard of care. It costs nothing and avoids steroid harm.

Avoiding aspirin, non-steroidal anti-inflammatory drugs and contact sports when the count is low.

Dapsone and danazol. Not quite no-chain, but oral, off-patent and in the tens of dollars a year; these matter where thrombopoietin receptor agonists are unaffordable.

H. pylori testing and eradication where the association is strong: a two-week course of three cheap generic drugs can produce durable remission in a share of patients.

Tranexamic acid and topical measures for mucosal bleeding.

Menstrual management, as in von Willebrand disease, for women with low counts.

Gaps. Incidence estimates vary roughly three-fold between studies, because case definition — the platelet threshold, the exclusion of secondary causes — varies. No validated predictor of serious bleeding exists, which is the clinically decisive unknown. *H. pylori* eradication response differs several-fold between Japan and Italy on one side and northern Europe and North America on the other; the reason is unexplained and the literature disagrees on whether to test outside high-response regions. Thrombopoietin receptor agonist discontinuation data are recent, from heterogeneous studies, with the proportion sustaining remission reported between about 10 and 30 per cent†. Generic eltrombopag prices are moving fast. Orphanet's prevalence and the European incidence figures are not easily reconcilable.

> **Depth.** Starts in: a platelet glycoprotein. Size: 10 nm†; depth −1.38. First complaint: about 12 days († 1–3 weeks after a virus (child)); time depth 45.77. One untreated course: about 12 weeks ([B] often clears by itself in a child; † 6 weeks–6 months); depth 47.56.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Haemochromatosis

What it is. The gut absorbs more iron than the body needs, year after year. Iron builds up in the liver, heart, pancreas and joints and damages them. It is one of the commonest inherited conditions in people of northern European descent.

Measured. *HFE* C282Y homozygosity affects about 1 in 200, 0.3 to 0.5 per cent, of populations of northern European ancestry, with a C282Y carrier frequency around 1 in 10†. It is rare to absent in African, East Asian and Indigenous American populations. Frequencies are highest in Ireland, Brittany, Scandinavia and Scotland, and lowest in southern Europe.

Penetrance is the central measured fact and it is low. A large share of homozygotes have raised transferrin saturation and ferritin, but clinically significant iron overload disease develops in a minority. The HealthIron population-based study found documented iron-overload-related disease in about 28 per cent of male C282Y homozygotes and about 1 per cent of female homozygotes over the study period (Allen et al., *NEJM*, 2008). Earlier clinic-based series greatly overstated penetrance because they sampled affected people.

Disease expression is typically after age 40 in men and after menopause in women; menstrual iron loss delays expression in women by roughly a decade or more.

Death attributed to haemochromatosis is dominated by cirrhosis, hepatocellular carcinoma and cardiomyopathy. In treated non-cirrhotic patients life expectancy is normal. No reliable global death count.

H63D homozygosity and C282Y/H63D compound heterozygosity rarely cause significant overload. Non-*HFE* forms, in *HJV*, *HAMP*, *TFR2* and *SLC40A1*, are rare and can be severe and early-onset.

Where it starts. Biallelic *HFE* C282Y in the great majority, leading to inappropriately low hepcidin for the iron load, so ferroportin stays active and intestinal iron absorption continues when it should stop. The molecular pathway is fully established.

Heritability of the genotype is 1.0. Heritability of the disease is low, because penetrance is low — which means most of the variance in whether a homozygote gets sick is not explained by *HFE*.

Established modifiers of expression: male sex, the largest single modifier, at about 28 per cent against about 1 per cent disease expression in HealthIron†; alcohol, where heavy use multiplies cirrhosis risk in homozygotes several-fold and is the strongest modifiable factor; hepatitis B and C co-infection and metabolic or fatty liver disease, through additive liver injury; blood donation and menstruation, which are protective by removing iron; dietary iron and vitamin C intake, with a modest effect on loading rate.

Secondary iron overload is a different disease with the same end-organ damage: repeated transfusion in thalassaemia, sickle cell disease and myelodysplastic syndromes, ineffective erythropoiesis, and the dyserythropoietic anaemias.

Not known: why most C282Y homozygotes never develop disease. No genetic modifier of large effect has been established, and the known modifiers do not account for the variance. This is why population genetic screening for *HFE* has not been adopted anywhere — the test finds many people who will never be ill.

Cure status. CONTROLLABLE. The genotype is untouched, so this is control — but it is control by a procedure that needs no drug, no patent and no supply chain, and the blood removed can be donated.

Therapeutic phlebotomy removes about 200 to 250 mg of iron per 500 mL unit†. Weekly or fortnightly venesection continues until ferritin falls to the target, commonly 50 µg/L, then maintenance two to four times a year for life.

Patients de-ironed before cirrhosis develops have normal life expectancy. Established cirrhosis does not reverse and the hepatocellular carcinoma risk persists even after de-ironing. Cardiomyopathy, skin pigmentation, fatigue and diabetes control often improve; established arthropathy and hypogonadism usually do not.

Prevention. Cascade testing of first-degree relatives of an affected person is the standard measure and the only screening strategy with broad support. STRONG for case-finding yield: a sibling of a homozygote has roughly a one-in-four chance of being homozygous.

Population genetic screening: CONTESTED, and not recommended by most bodies, precisely because penetrance is low. Several authorities instead support screening by transferrin saturation and ferritin in the context of raised liver enzymes or unexplained symptoms.

Early phlebotomy before organ damage in a known homozygote. STRONG — the cohort evidence is unambiguous and a randomised trial would be unethical.

Alcohol avoidance in C282Y homozygotes, the largest modifiable risk reduction available, since heavy use multiplies cirrhosis risk several-fold. STRONG, from consistent cohort data.

Hepatitis B vaccination and hepatitis C treatment in homozygotes. MODERATE.

Avoiding iron and high-dose vitamin C supplements. MODERATE, mechanistic plus observational.

Regular blood donation in homozygotes without disease, which removes iron and supplies the blood bank. MODERATE.

Treatment. Therapeutic phlebotomy. Not a medicine. The consumables are a needle, a bag and a nurse, on the order of tens of US dollars a session in a public system (2024), so hundreds to a couple of thousand US dollars in the first de-ironing year and tens to hundreds of US dollars a year on maintenance. In many systems the patient donates and the cost is negative. This is first-line and nothing has beaten it.

Erythrocytapheresis removes red cells selectively, needs fewer sessions and requires an apheresis machine. Equivalent de-ironing at a higher per-session cost.

Iron chelation with deferasirox or deferoxamine, reserved for patients who cannot tolerate phlebotomy because of anaemia, poor venous access or cardiac disease. Generic deferasirox runs US$1,000 to US$4,000 a patient-year at lowest available acquisition cost, 2024†. Both off-patent; listing status needs checking against the 24th List†. Chelation is the mainstay in secondary iron overload, since those patients are transfusion-dependent and cannot be bled.

Treating the organ damage: insulin for diabetes, hormone replacement for hypogonadism, heart failure treatment for cardiomyopathy, and hepatocellular carcinoma surveillance by six-monthly ultrasound in cirrhotic patients.

Hepcidin mimetics such as rusfertide are in trials for polycythaemia vera and under investigation in haemochromatosis; nothing is approved.

Simple means. Giving blood. The treatment is blood donation. For a homozygote without contraindication, regular donation at a blood bank both treats the disease and supplies the service. No drug, no patent, no chain.

Not drinking alcohol, the largest single reduction in cirrhosis risk available to an affected person.

Tea or coffee with meals, which reduces non-haem iron absorption. A small effect at no cost.

Not taking iron or high-dose vitamin C supplements, and not cooking in cast iron.

Avoiding raw shellfish. *Vibrio vulnificus* infection is far more severe in iron overload, and this is a well-documented and entirely avoidable cause of death in this group.

Telling siblings and children. A family history conversation is the cheapest and highest-yield case-finding method in this entry.

Gaps. Penetrance figures differ by an order of magnitude between clinic-based series and population-based studies; only the population-based figures should be used, and even those come from a single ancestry group. Essentially all penetrance and outcome data come from European-ancestry populations, and nothing comparable exists for the rare non-*HFE* forms or for populations where C282Y is absent. No modifier explains why most homozygotes stay well, which is the central unexplained finding. Whether to screen populations is contested, and the contest is about the low penetrance rather than the biology. The optimal maintenance ferritin target is not established by trial and guidelines differ. Whether de-ironing reduces hepatocellular carcinoma risk once cirrhosis exists is unresolved.

> **Depth.** Starts in: the HFE protein. Size: 5 nm†; depth −2.01. First complaint: about 45 years († onset about age 45; [B] year after year); time depth 52.34. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Polycythaemia vera

What it is. A bone marrow neoplasm in which the marrow makes too many red cells, and often too many platelets and white cells. The blood thickens and clots form. Almost all cases carry a mutation in the *JAK2* gene.

Measured. Incidence is 1.9 per 100,000 person-years in Olmsted County, Minnesota, and 1.48 per 100,000 person-years age-standardised in Sweden†. Prevalence is higher than incidence would suggest because survival is long; registry-based estimates fall in the range 20 to 50 per 100,000 in high-income countries, and there is no single authoritative global figure.

Median age at diagnosis is about 60, with the highest incidence at 70 to 79, and about 10 per cent of patients are under 40†.

JAK2 V617F is present in about 95 per cent of patients and about 98 per cent have some *JAK2* mutation, the remainder mostly in exon 12†. Compare 0.1 to 0.2 per cent of the general population carrying V617F as clonal haematopoiesis†.

Median survival is 10 to 20 years with controlled disease, still below age- and sex-matched population survival. Death comes from thrombosis, the main early risk, from transformation to myelofibrosis in roughly 10 to 20 per cent at 15 to 20 years, and to acute myeloid leukaemia in roughly 5 to 10 per cent at 20 years†.

Reported incidence is higher in high-income countries, which is at least partly ascertainment. Ashkenazi Jewish populations have been reported with higher rates.

Where it starts. An acquired somatic gain-of-function mutation in *JAK2*, usually V617F, in a haematopoietic stem cell, producing cytokine-independent erythropoiesis. This is established and is the diagnostic criterion. Where the mutation comes from is not known; it is acquired, not inherited.

Germline predisposition: the *JAK2* 46/1 haplotype raises the risk of acquiring V617F roughly three- to four-fold†, and *TERT* and *SH2B3* variants also associate. Familial clustering of myeloproliferative neoplasms exists, with relative risks in first-degree relatives of roughly 5 to 7†, so there is a real but small inherited component. Heritability is not well estimated.

Age is the dominant risk factor, as for clonal haematopoiesis generally. Ionising radiation is an established cause of myeloproliferative neoplasms at high dose. Additional mutations in *TET2*, *ASXL1*, *DNMT3A*, *SRSF2*, *TP53* and *IDH1/2* accumulate and drive transformation.

Thrombosis risk within the disease rises with age over 60, prior thrombosis, leucocytosis, and haematocrit above 45 per cent.

Not known: why a V617F clone expands into overt polycythaemia vera in some people and stays as silent clonal haematopoiesis in others, given that V617F is found in 0.1 to 0.2 per cent of the general population, far more than the prevalence of the disease. What determines transformation timing. Whether early cytoreduction changes the transformation rate.

Cure status. CONTROLLABLE. No standing treatment eradicates the *JAK2*-mutant clone.

Allogeneic transplant is the only potentially curative option and is reserved for post- polycythaemic myelofibrosis or leukaemic transformation, because transplant mortality exceeds the risk of the controlled disease.

Interferon — ropeginterferon alfa-2b, or pegylated interferon alfa-2a — is the one treatment that reduces the *JAK2* V617F allele burden, in some patients to undetectable levels, with documented sustained molecular responses. Whether that constitutes cure is unresolved. It is the strongest claim toward disease modification in this entry and it is not settled.

Everything else — phlebotomy, hydroxyurea, ruxolitinib, aspirin — controls counts and thrombosis risk without touching the clone.

Prevention. No primary prevention. The mutation is acquired for unknown reasons, and that should be stated plainly.

Prevention of thrombosis, which is what kills early, is where all the measurable prevention sits.

Haematocrit below 45 per cent. The CYTO-PV randomised trial compared a haematocrit target below 45 per cent with 45 to 50 per cent and found cardiovascular death or major thrombosis in 2.7 per cent against 9.8 per cent of patients over a median 31 months, roughly a four-fold difference (Marchioli et al., *NEJM*, 2013). STRONG. This is the single most important number in the management of this disease.

Low-dose aspirin. The ECLAP randomised trial found that low-dose aspirin reduced the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and major venous thromboembolism, with a relative risk of about 0.40 (Landolfi et al., *NEJM*, 2004). STRONG.

Cytoreduction in high-risk patients, those over 60 or with prior thrombosis, reduces thrombosis. STRONG.

Controlling conventional cardiovascular risk factors — smoking, hypertension, lipids, diabetes — because the thrombotic risk is multiplicative. MODERATE.

Treatment. Phlebotomy to a haematocrit below 45 per cent, first-line for everyone. Not a medicine; on the order of tens of US dollars a session (2024), several sessions initially and then a few a year†. Combined with the CYTO-PV result, this is the highest-value intervention in the entry.

Low-dose aspirin, 75 to 100 mg daily, with twice-daily dosing used in some protocols for persistent symptoms. Off-patent, at one to five dollars a patient-year (2024)†. EML status needs checking against the 24th List†.

Hydroxyurea, first-line cytoreduction for high-risk patients, off-patent at US$30 to US$150 a patient-year at generic or lowest available acquisition cost, 2024†. Hydroxyurea is a selected medicine on the 24th List, in section 8.2.1 cytotoxic medicines, complementary list, for chronic myeloid leukaemia, and in section 10.3 core list for haemoglobinopathies; polycythaemia vera is not among the listed indications.

Ropeginterferon alfa-2b, approved in the European Union in 2019 and the United States in 2021. PROUD-PV and CONTINUATION-PV showed non-inferiority to hydroxyurea at 12 months and superiority in haematological and molecular response at 36 months, with allele burden reduction†. Patented, at US$50,000 to US$100,000 a patient-year on United States and European list prices (2024)†. Pegylated interferon alfa-2a is used off-label, is off-patent, and costs US$5,000 to US$20,000 a patient-year (2024)† — a large price gap for a similar mechanism. Listing status of both needs checking against the 24th List†.

Ruxolitinib, a JAK1/2 inhibitor, second-line after hydroxyurea intolerance or resistance. The RESPONSE trial found 21 per cent against 1 per cent achieving the composite primary endpoint of haematocrit control plus at least 35 per cent spleen volume reduction at 32 weeks†. Patented, with patents expiring in several markets from the mid-2020s, at US$130,000 to US$200,000 a patient-year on United States list (2024)†. EML status needs checking against the 24th List†.

Busulfan, pipobroman and radioactive phosphorus-32 are older cytoreductives, leukaemogenic, now reserved for elderly patients with short life expectancy.

Anagrelide for platelet control, allopurinol for secondary gout, and antihistamines or ruxolitinib for aquagenic pruritus. Allopurinol is a selected medicine on the 24th List, in section 29.1, medicines used to treat gout, and in section 8.2.5 supportive medicines, complementary, for tumour lysis syndrome; off-patent at US$5 to US$20 a patient-year at generic or lowest available acquisition cost, 2024†.

Rusfertide, a hepcidin mimetic, reported a large reduction in phlebotomy requirement in the phase 3 VERIFY trial in 2025†. Not approved at the time of writing.

Simple means. Phlebotomy itself. As with haemochromatosis, the first-line treatment for the most dangerous feature of this disease is removing blood: a needle, a bag, a trained person.

Low-dose aspirin. Pennies a year, with a randomised-trial relative risk of about 0.40 for major thrombotic events.

Hydration, which reduces blood viscosity. No trial, no cost.

Smoking cessation and blood pressure control, because the risk being prevented is thrombotic and these multiply it.

Avoiding hot baths and showers for aquagenic pruritus, with cooling and oatmeal measures. No cost, and no evidence base beyond patient report.

Recognising the disease from a full blood count. A raised haematocrit on a routine count is the whole diagnostic entry point, and a *JAK2* V617F test on peripheral blood then confirms it without a marrow biopsy in most cases.

Gaps. No authoritative global prevalence estimate exists; registry figures come from a handful of high-income countries. Whether interferon's molecular responses translate into longer survival or lower transformation rates is not established, because the trials were powered for haematological endpoints. Why V617F clonal haematopoiesis usually does not become polycythaemia vera is unknown. The large price gap between ropeginterferon and off-patent pegylated interferon alfa-2a is not matched by a demonstrated difference in hard outcomes. Transformation rates to myelofibrosis and leukaemia vary between series with

follow-up length and with whether leukaemogenic agents were used historically. Rusfertide data are very recent and not yet reflected in guidelines.

> **Depth.** Starts in: a blood stem cell (JAK2). Size: 8 µm†; depth +4.70. First complaint: about 60 years († median age 60); time depth 52.60. One untreated course: no number († years).
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Myelodysplastic syndromes

What it is. A group of bone marrow cancers in which blood cells are made badly and die before leaving the marrow. Counts fall, especially the red cells, so people become anaemic and transfusion-dependent. In about a third the disease turns into acute myeloid leukaemia.

Measured. Incidence is about 4.0 to 4.9 per 100,000 a year overall, rising to over 60 per 100,000 in people over 85†. Underdiagnosis means the true rate is probably higher. Median age at diagnosis is about 73, and about 86 per cent of cases occur at 60 or above†. It is more common in males. Paediatric disease runs at about 1 to 4 per million a year, median age 6.8 years, rare and often associated with an inherited predisposition syndrome.

The United States sees about 10,000 to 15,000 new cases a year — another section of the same source gives 10,000 to 20,000 — with 60,000 to 170,000 people living with the disease†. The width of those ranges is itself the finding: the condition is not a reportable cancer in all registries and ascertainment is poor.

Survival by International Prognostic Scoring System risk: lower-risk disease, below 3.5, three to 10 years; higher-risk, above 3.5, under three years†. Transformation to acute myeloid leukaemia occurs in roughly 30 per cent overall, concentrated in higher-risk groups†.

Most deaths are from the consequences of cytopenia — infection, haemorrhage — and from leukaemic transformation, rather than from the syndrome as a coded cause. No reliable global death count.

Where it starts. Acquired somatic mutations in haematopoietic stem cells with clonal expansion. The commonly mutated genes are *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, *RUNX1*, *TP53*, *U2AF1* and *EZH2*, alongside del(5q) and other cytogenetic abnormalities. Over 90 per cent of cases carry at least one driver mutation†.

Age is the dominant risk factor. Clonal haematopoiesis of indeterminate potential is present in more than 10 per cent of people over 70 and is the precursor state, and progression from it to a myeloid neoplasm runs at roughly 0.5 to 1 per cent a year†.

Prior cytotoxic therapy: alkylating agents, with a five-to-ten-year latency and often del(5q), del(7q) or a complex karyotype, and topoisomerase II inhibitors, with shorter latency and balanced translocations. Therapy-related disease is roughly 10 to 15 per cent of cases and has a markedly worse prognosis†.

Ionising radiation, dose-dependent and established from atomic bomb survivor and occupational cohorts. Benzene and organic solvents, established and dose-related. Tobacco smoking, with a relative risk of roughly 1.4 to 1.6 in meta-analysis†.

Inherited predisposition: germline *GATA2*, *RUNX1*, *DDX41*, *ETV6* and *ANKRD26* variants, Fanconi anaemia, telomere biology disorders, Shwachman-Diamond syndrome. Germline *DDX41* variants are found in a few per cent of adult cases, often with a family history, and this matters because it changes donor selection for transplant.

Heritability is not meaningfully estimated for the syndromes as a whole. The germline syndromes are Mendelian; the common disease is acquired.

Not known: why only a small fraction of people with clonal haematopoiesis of indeterminate potential progress. Which lower-risk patients will progress rapidly — prognostic scores improve on this and still

leave large within-group variance. Why hypomethylating agents work in some patients and not others; no biomarker predicts response.

Cure status. Younger, fitter patients eligible for transplant: CURABLE in about 50 per cent (reported three-year survival)†. The large majority: CONTROLLABLE.

Allogeneic haematopoietic stem cell transplant is the only curative treatment, with reported three-year survival about 50 per cent and worse results with age; patients under 40 do best†. Because median age at diagnosis is 73, only a small minority are candidates.

Hypomethylating agents prolong survival without curing. Azacitidine against conventional care in higher-risk disease, in AZA-001, gave median overall survival of 24 months against 15 months, with response rates of 29 per cent against 12 per cent†. Decitabine shows similar survival benefit with response rates reported up to 43 per cent†.

Luspatercept reduces transfusion burden in lower-risk disease with ring sideroblasts: in MEDALIST, 38 per cent against 13 per cent achieved transfusion independence for at least eight weeks, with median duration of response around 30.6 weeks†. The COMMANDS trial in 2023 showed luspatercept superior to epoetin alfa as first-line in transfusion-dependent lower-risk disease. Supportive, not curative.

Lenalidomide in del(5q) disease gives transfusion independence in roughly two-thirds, with median response duration over two years and cytogenetic responses. Still not curative.

The honest statement is that this is a disease of older people in which the only cure requires a treatment most patients cannot survive.

Prevention. Reducing benzene and solvent exposure in occupational settings. MODERATE: dose-response in occupational cohorts, no trial.

Not smoking, against a relative risk of roughly 1.4 to 1.6. MODERATE.

Minimising cumulative alkylating agent and radiation dose in cancer treatment, and preferring regimens with lower leukaemogenic potential where outcomes are equivalent. MODERATE — the causation is established, and prevention has to be traded against treating the first cancer.

Radiation protection, occupational and medical dose limitation. STRONG for the causal link, MODERATE for the measured prevention effect.

No prevention exists for the dominant, age-related, idiopathic form. Clonal haematopoiesis of indeterminate potential has no established intervention, and trials of interventions in it are only now beginning.

Treatment. Supportive care — red cell and platelet transfusion, antibiotics, and iron chelation after prolonged transfusion. This is what most patients worldwide actually receive, and in lower-risk disease it is a legitimate standard of care. It requires a safe blood supply.

Erythropoiesis-stimulating agents for lower-risk anaemia with serum erythropoietin below about 500 IU/L, with response in roughly 40 per cent†. On the 24th List the selected medicine is the class entry “erythropoiesis-stimulating agents”, in section 10.1, antianaemia medicines, complementary list, for anaemia due to chronic disease; epoetin alfa, beta and theta and methoxy polyethylene glycol-epoetin beta are therapeutic equivalents to that class entry rather than selected medicines in their own right. Myelodysplastic syndrome is not the listed indication. Biosimilars are widely available, at US$1,500 to US$6,000 a patient-year for biosimilar epoetin at generic or lowest available acquisition cost, 2024, and much less in some markets†.

Hypomethylating agents. Azacitidine, subcutaneous or intravenous, seven days per 28-day cycle, off-patent with generics widely available, at US$3,000 to US$15,000 a patient-year at generic or lowest available acquisition cost, 2024, with originator prices several times higher†. Decitabine, and oral decitabine with cedazuridine, which is patented and far more expensive. Listing status needs checking against the 24th List†.

Luspatercept for lower-risk disease with anaemia, patented, at US$150,000 to US$200,000 a patient-year on United States list (2024)†. EML status needs checking against the 24th List†.

Lenalidomide for del(5q) disease, off-patent with generics from 2022 to 2026 depending on market; originator over US$200,000 a patient-year on United States list (2023), with generics substantially lower and falling†. EML status needs checking against the 24th List†.

Immunosuppression with antithymocyte globulin and ciclosporin for hypoplastic disease overlapping aplastic anaemia, in younger patients with HLA-DR15.

Allogeneic transplant, at US$150,000 to US$500,000 in high-income settings (2024)†. Intensive leukaemia-type chemotherapy for higher-risk disease as a bridge to transplant.

Iron chelation for transfusion-dependent lower-risk patients: the TELESTO trial suggested an event-free survival benefit with deferasirox, was underpowered, and the benefit is contested.

Simple means. Very few, and that should be said. This disease requires transfusion, drugs or transplant.

A safe, adequate blood supply is the single most important resource for it, and it requires donors rather than industry.

Infection precautions during neutropenia — hand hygiene, food hygiene, prompt presentation with fever. Free.

Not smoking, and avoiding solvent exposure.

Recognising it from a full blood count. Unexplained macrocytic anaemia in an older person is the entry point, with a blood film and then marrow examination following. Where marrow examination is unavailable, the practical simple means is to stop giving iron and B12 for an anaemia that does not respond, and to look for another cause.

Folic acid in ineffective erythropoiesis, as elsewhere.

Gaps. Ascertainment is poor: the same source gives both 10,000 to 15,000 and 10,000 to 20,000 new United States cases a year, and a prevalence range spanning nearly threefold. The syndromes are not consistently registered as malignancies across cancer registries, so international comparison is unreliable and there is no credible global incidence figure. Classification changed in 2022, in the WHO fifth edition and the International Consensus Classification, with entities redefined by genetics, so incidence and survival figures from before and after are not comparable. No biomarker predicts hypomethylating agent response. The benefit of iron chelation in lower-risk disease is contested. Whether any intervention in clonal haematopoiesis of indeterminate potential prevents the syndrome is unknown.

> **Depth.** Starts in: a blood stem cell. Size: 8 µm†; depth +4.70. First complaint: about 70 years († median age 70); time depth 52.74. One untreated course: no number († years).
>
> **Model reading.** Way of ending: rebuild. Layer: reading. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

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Diseases of the immune system

ICD-11 chapter 04

Fourteen entries. The inborn errors of immunity, the allergic diseases, and the systemic autoimmune and autoinflammatory conditions.

Primary immunodeficiencies as a class

What it is. A set of inherited faults in the immune system. Each one is rare; together they are not. The result is infections that come too often, last too long, or are caused by organisms that should not cause disease — and, in many of them, autoimmunity and cancer as well.

Measured. The International Union of Immunological Societies classification listed over 120 conditions in its 2014 update and about 430 forms by 2019; the 2022 update lists 485 inborn errors of immunity across 10 categories†. The count rises every two years, and that is the clearest single measurement about the class.

About 1 in 500 people in the United States are born with a primary immunodeficiency on the broad definition, which includes mild antibody deficiencies. A survey of 10,000 American households put diagnosed prevalence at about 1 in 1,200†. Selective IgA deficiency, about 1 in 600 in populations such as healthy blood donors, is the commonest single form and is usually asymptomatic. Most other individual disorders have reported incidence between 1 in 100,000 and 1 in 2,000,000†.

The 1-in-1,200 diagnosed figure against a 1-in-500 birth prevalence implies that the majority are not diagnosed. The Jeffrey Modell Foundation's global registries and the ESID registry together hold tens of thousands of patients against an expected population in the millions.

Diagnosis rates track laboratory capacity, not biology. Consanguineous populations in the Middle East, North Africa and parts of South Asia have substantially higher rates of autosomal recessive forms — in some consanguineous cohorts recessive inborn errors are an order of magnitude more frequent than in outbred European populations. No global death count exists. Untreated severe combined immunodeficiency is uniformly fatal in the first two years.

Where it starts. Single-gene defects in the large majority, with heritability 1.0 for the genotype in the monogenic forms. Inheritance is autosomal recessive, autosomal dominant including gain-of-function and haploinsufficiency, or X-linked.

Four rough functional categories: antibody or humoral defects, the largest group at roughly half of all diagnoses; combined T- and B-cell defects; phagocyte defects; complement defects. The classification adds categories for immune dysregulation, autoinflammatory disorders, innate immunity defects and phenocopies.

Consanguinity raises the frequency of recessive forms directly and measurably.

Somatic and acquired phenocopies exist and are not inherited: anti-cytokine autoantibodies against interferon gamma, GM-CSF and IL-17; somatic mutations such as those in *UBA1* causing VEXAS syndrome, described in 2020; and thymoma-associated immunodeficiency.

New gene discovery runs at roughly 20 to 40 new monogenic causes described a year over the past decade†, which is why the class count keeps moving.

Not known: how many inborn errors of immunity remain undescribed. What fraction of adult idiopathic bronchiectasis, recurrent sinopulmonary infection, unexplained autoimmunity or early-onset lymphoma is attributable to an undiagnosed inborn error. Whether the broad 1-in-500 figure, which rests mostly on asymptomatic IgA deficiency, describes anything clinically meaningful; the clinically significant prevalence is much lower and is not well estimated.

Cure status. Combined immunodeficiencies and several phagocyte and immune dysregulation disorders: CURABLE, by allogeneic haematopoietic stem cell transplant or autologous gene therapy. Antibody deficiencies, the largest group of patients: CONTROLLABLE, by lifelong immunoglobulin replacement with antimicrobial prophylaxis. A number of the innate and complement defects: RELIEF ONLY, where there is no replacement and management is prophylaxis plus prompt treatment of infection.

Targeted therapy has changed several specific disorders: JAK inhibitors for STAT1 and STAT3 gain-of-function, abatacept for CTLA-4 haploinsufficiency and LRBA deficiency, leniolisib (approved 2023) for activated PI3K-delta syndrome, and IL-1 blockade for the autoinflammatory disorders. These control rather than cure, and the effect sizes are large and mechanism-specific.

Prevention. Newborn screening by T-cell receptor excision circle assay for severe combined immunodeficiency is the single most consequential prevention measure in this class, because it converts a uniformly fatal disease into a largely curable one by advancing diagnosis before infection. STRONG.

Genetic counselling and cascade testing in affected families, with prenatal and preimplantation diagnosis where available and acceptable. STRONG for birth prevalence in known families.

Reducing consanguineous marriage lowers the frequency of recessive forms. This is a demographic observation rather than a programme; where premarital carrier screening has been introduced, in the Gulf states and Iran, it has reduced affected births for specific conditions. MODERATE, and socially contested.

Live vaccine avoidance in known or suspected combined immunodeficiency. BCG and oral polio vaccine cause disseminated disease in severe combined immunodeficiency and in several phagocyte defects, and BCG-related complications are a leading cause of death in severe combined immunodeficiency in countries with universal BCG at birth. STRONG for preventing that harm, and one reason newborn screening matters most in BCG-vaccinating countries.

Prophylactic antimicrobials prevent the infections that cause the damage: co-trimoxazole against *Pneumocystis* in combined defects and chronic granulomatous disease, itraconazole against aspergillosis in chronic granulomatous disease. Both reduce infection rates substantially in trials and cohorts. STRONG.

Immunoglobulin replacement prevents bacterial infection and bronchiectasis in antibody deficiency. STRONG.

Treatment. Immunoglobulin replacement, intravenous or subcutaneous, for antibody deficiencies, at US$20,000 to US$60,000 a patient-year in high-income countries (2024) depending on dose and product, and substantially lower in some tendered markets. It is a plasma-derived product, so patents do not set availability; global plasma supply does. This is the single largest expenditure in the class and it is fundamentally supply-constrained. Normal human immunoglobulin’s listing status needs checking against the 24th List†.

Antimicrobial prophylaxis — co-trimoxazole, azithromycin, itraconazole, aciclovir — depending on the defect, off-patent, at US$10 to US$200 a patient-year at generic or lowest available acquisition cost, 2024†. The cheapest effective intervention in the class. Azithromycin is a selected medicine on the 24th List, in section 6.2.2, Watch group antibiotics, core list, as first choice for cholera, enteric fever, gonorrhoea, chlamydial sexually transmitted infection, trachoma and yaws; the prophylactic use here is not among the listed indications. The listing status of co-trimoxazole, itraconazole and aciclovir needs checking against the 24th List†.

Allogeneic haematopoietic stem cell transplant, curative for combined defects, chronic granulomatous disease, leukocyte adhesion deficiency, IPEX syndrome, Wiskott-Aldrich syndrome, hyper-IgM syndromes and familial haemophagocytic lymphohistiocytosis, at US$150,000 to US$500,000 in high-income settings (2024)†.

Gene therapy: for adenosine deaminase-deficient severe combined immunodeficiency, an autologous gene-corrected cell product was approved in the European Union in 2016. Lentiviral gene therapy for Wiskott-Aldrich syndrome, X-linked chronic granulomatous disease and X-linked severe combined immunodeficiency is in advanced trials or named-patient use.

Interferon gamma for chronic granulomatous disease: the 1991 randomised trial showed about a 70 per cent reduction in serious infections†. Single manufacturer, so not off-patent in practice, at US$30,000 to US$60,000 a patient-year at lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

Targeted immune modulators for immune dysregulation phenotypes — JAK inhibitors, abatacept, leniolisib, IL-1 blockers, sirolimus — mostly patented and mostly US$30,000 to US$400,000 a patient-year at lowest available acquisition cost, 2024†. Their listing status needs checking against the 24th List†.

Avoiding live vaccines, using irradiated and CMV-safe blood products, and no transfusion from relatives. Standing precautions, at no cost.

Simple means. Suspecting it. The highest-yield free intervention: a child or adult with recurrent pneumonia, chronic diarrhoea with failure to thrive, deep abscesses, persistent thrush, unexplained bronchiectasis, or a family history of early infant death. The Jeffrey Modell ten warning signs exist precisely because recognition is the binding constraint.

A full blood count with differential. Lymphopenia in an infant is the cheapest possible pointer to severe combined immunodeficiency, and an absolute lymphocyte count below about 2.5×10^9/L in a neonate should not be normalised. Free with any blood count.

Serum immunoglobulin concentrations — a few dollars, and the diagnostic entry point for the largest group of these disorders.

Not giving BCG or oral polio vaccine to an infant with a sibling who died of infection, or with unexplained lymphopenia, until immune function is known.

Antimicrobial prophylaxis: co-trimoxazole costs dollars a year and prevents *Pneumocystis* pneumonia.

Routine childhood immunisation with inactivated vaccines, household hygiene, clean water, and treating infections early. Not specific to immunodeficiency, and what determines survival where immunoglobulin is unavailable.

Breastfeeding, for passive antibody and reduced enteric infection in the first months.

Gaps. The class count, moving from 120 to 430 to 485, means any statement about how many dates within two years. The 1-in-500 prevalence figure is dominated by asymptomatic selective IgA deficiency and does not describe clinical burden; no good estimate exists of clinically significant prevalence. Essentially all registry data come from high-income countries and a small number of specialist centres, so the global distribution is unmeasured. Immunoglobulin supply is the real constraint on treatment worldwide and is not reflected in any prevalence or treatment figure. No global mortality data exist for the class. Gene therapy for several of these disorders produced insertional oncogenesis in the past, in the X-linked severe combined immunodeficiency retroviral trials; long-term safety of current lentiviral vectors is better but not settled.

> **Depth.** A class. Not one illness. No depth is given.
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. In some forms a stem-cell transplant restores the source. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Common variable immunodeficiency

What it is. The commonest symptomatic antibody deficiency. The body makes too little immunoglobulin, so bacterial chest and sinus infections recur and permanently damage the airways. Autoimmune disease and lymphoma are also more frequent than normal.

Measured. Prevalence is roughly 1 in 25,000 to 1 in 50,000 in European-descended populations, the figure most often cited in the clinical literature. Orphanet's dedicated entry was obsoleted and merged into "common variable immunodeficiency and related disorders", and no prevalence figure is given there.

Within primary immunodeficiency registries it is consistently the largest single diagnosis, roughly 20 to 30 per cent of all registered patients in the ESID registry†.

Age at onset is bimodal, with peaks in the first decade and in the twenties to forties, and median age at diagnosis in the fourth decade. Diagnostic delay is consistently reported at four to nine years between symptom onset and diagnosis in European and North American cohorts — among the longest recorded for any treatable disease, and the main driver of irreversible bronchiectasis. The sexes are affected roughly equally.

Complications, from large cohorts including ESID, USIDNET and the New York cohort of 473 patients followed up to four decades: bronchiectasis in roughly 25 to 35 per cent; autoimmune disease in roughly 25 to 30 per cent, most often immune thrombocytopenia and autoimmune haemolytic anaemia; granulomatous disease in roughly 8 to 20 per cent; enteropathy in roughly 10 to 20 per cent; and lymphoma risk raised substantially, with standardised incidence ratios around 12 to 30 in cohort studies, mostly non-Hodgkin and mostly extranodal.

In the New York cohort, survival was significantly worse in patients with non-infectious complications — roughly a median of 29 years from diagnosis against near-normal survival for those with infection only. That split is the central prognostic finding.

Where it starts. The cause is unknown in the majority, and that is the defining feature. This is a diagnosis of exclusion: low IgG plus low IgA or IgM, poor response to vaccination, onset after age four, and no other explanation.

Monogenic causes are identified in roughly 10 to 30 per cent of patients depending on cohort and sequencing depth†: *TNFRSF13B* (TACI), *TNFRSF13C* (BAFF-R), *CTLA4* haploinsufficiency, *LRBA*, *NFKB1*, *NFKB2*, *PIK3CD*, *PIK3R1*, *CD19*, *CD81*, *CR2*, *MS4A1*, *ICOS*, *IKZF1*, *IRF2BP2*, *ARHGEF1*, *TTC37*. *NFKB1* haploinsufficiency is currently the single most frequently identified monogenic cause.

TNFRSF13B variants are found in roughly 8 to 10 per cent of patients and also in 1 to 2 per cent of healthy controls†, so they are a risk factor rather than a cause — a clear example of incomplete penetrance in this field.

Heritability is not well estimated. Familial clustering occurs in roughly 10 to 20 per cent of cases, often with relatives having selective IgA deficiency rather than the full condition, suggesting a shared susceptibility.

The pathophysiology is a defect in B-cell terminal differentiation into plasma cells. Reduced class-switched memory B cells, which the EUROclass and Freiburg classifications use, predicts the complicated phenotype.

Not known: the cause in most patients. Why some patients have infection only and others develop the autoimmune, granulomatous and enteropathic phenotype that drives mortality — and because that split determines prognosis, this is the most consequential unknown in the entry. Whether this is one disease or a convergent phenotype of many.

Cure status. CONTROLLABLE. Immunoglobulin replacement restores protection against bacterial infection for as long as it is given, and stops nothing else.

Replacement prevents bacterial infection and slows or halts the progression of bronchiectasis. Trough IgG above roughly 5 to 8 g/L is associated with lower pneumonia rates, and a meta-analysis found pneumonia incidence falling as trough IgG rose, with roughly a five-fold difference in pneumonia rate between trough concentrations of 5 g/L and 10 g/L†.

It does not prevent the non-infectious complications. Autoimmunity, granulomatous disease, enteropathy and lymphoma occur in patients on adequate replacement, which is why the complicated phenotype still shortens life.

Haematopoietic stem cell transplant has been performed in severe disease with immune dysregulation; mortality has been high, reported around 40 to 50 per cent in early series, and it is not standard†.

For the identified monogenic forms, targeted therapy can be transformative: abatacept in CTLA-4 haploinsufficiency and LRBA deficiency; leniolisib, a PI3Kδ inhibitor approved in the United States in

March 2023, in activated PI3K-delta syndrome, which reduced lymph node size and increased naive B cells in its randomised trial. Still control, not cure — but mechanism-specific and effective, which is the argument for genetic diagnosis.

Prevention. No primary prevention. The cause is unknown in most patients, and that should be stated plainly.

Prevention of bronchiectasis by early diagnosis and early immunoglobulin replacement is the measurable prevention target in this entry. Diagnostic delay of four to nine years correlates with established bronchiectasis at diagnosis. STRONG: consistent cohort evidence, and a trial withholding replacement would be unethical.

Measuring serum immunoglobulins in anyone with two or more pneumonias, chronic sinusitis, or unexplained bronchiectasis. This is the prevention measure, and it is a blood test. STRONG.

Antimicrobial prophylaxis in patients with continuing infection despite adequate trough IgG: azithromycin reduces exacerbation frequency in bronchiectasis generally, by roughly 40 to 60 per cent in the EMBRACE, BAT and BLESS trials†. MODERATE in this condition specifically, STRONG in bronchiectasis generally.

Airway clearance physiotherapy and pulmonary rehabilitation once bronchiectasis exists. MODERATE.

Inactivated vaccination of household contacts against influenza, pertussis and COVID-19. MODERATE.

Avoiding live vaccines in the patient. STRONG for preventing vaccine-derived infection.

Lymphoma surveillance: no screening programme is established and whether surveillance changes outcome is unknown. CONTESTED.

Treatment. Immunoglobulin replacement, intravenous every three to four weeks or subcutaneous weekly, or hyaluronidase-facilitated every three to four weeks. Subcutaneous administration gives steadier troughs, fewer systemic reactions and home administration, and the two routes are equivalent for infection prevention in randomised comparisons. At US$20,000 to US$60,000 a patient-year (2024) in high-income countries at standard dosing of 0.4 to 0.6 g/kg a month, and lower in tendered markets†. Dose is weight-based, so cost rises with body weight. It is plasma-derived and supply-constrained, so patent status does not apply. Listing status needs checking against the 24th List†.

Antibiotics for exacerbations, and prophylactic azithromycin in selected patients, at US$10 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†. Amoxicillin and azithromycin are both selected medicines on the 24th List: amoxicillin in section 6.2.1, Access group antibiotics, core list, as first choice for mild to moderate community-acquired pneumonia, chronic obstructive pulmonary disease exacerbation, otitis media, pharyngitis, sinusitis, neonatal sepsis, child sepsis, severe acute malnutrition and dental abscess; azithromycin in section 6.2.2, Watch group antibiotics, core list. The listing status of co-amoxiclav and doxycycline needs checking against the 24th List†.

Airway clearance and pulmonary rehabilitation. No medicine; the equipment is a positive-expiratory-pressure device or nothing at all.

Treatment of the autoimmune complications — corticosteroids, rituximab at a biosimilar course of US$1,500 to US$5,000 at lowest available acquisition cost, 2024†, and budesonide or immunosuppression for enteropathy. These are the same cheap off-patent agents listed under immune thrombocytopenia. Rituximab is a selected medicine on the 24th List, in sections 5.1.2 and 8.2.2, for multiple sclerosis and four haematological malignancies; this indication is not among them.

Targeted therapy where a monogenic cause is identified — abatacept, sirolimus, leniolisib, JAK inhibitors — patented, at US$30,000 to US$400,000 a patient-year at lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

Genetic testing, now standard of care because it changes management in the 10 to 30 per cent with an identified cause. A gene panel or exome costs hundreds to thousands of US dollars (2024) and is a one-off†.

Avoiding corticosteroid-first management of granulomatous disease without excluding infection.

Simple means. A serum immunoglobulin test. A few dollars, and it is the entire diagnostic gateway. In a disease whose main harm comes from four to nine years of diagnostic delay, the simple means is ordering the test in anyone with recurrent pneumonia or unexplained bronchiectasis.

Airway clearance by breathing technique and postural drainage. No equipment required, and established in bronchiectasis management.

Prophylactic co-trimoxazole or azithromycin, at tens of dollars a year.

Not smoking, and no household smoke exposure, which accelerates bronchiectasis.

Dental and sinus care, and prompt treatment of any infection.

Inactivated influenza vaccination of the household, and hand hygiene.

Avoiding live vaccines in the patient — free, and it prevents a specific serious harm.

The core treatment, immunoglobulin, has no simple-means substitute. It requires thousands of plasma donations per patient-year, and that constraint has no workaround.

Gaps. Orphanet's entry was obsoleted and the replacement carries no prevalence figure, so the commonly quoted 1-in-25,000 to 1-in-50,000 range rests on older clinical literature and registry denominators rather than a population survey. This is a diagnosis of exclusion with criteria that have changed, in ESID 2014 and ICON 2016, so prevalence and cohort composition are definition-dependent. The proportion with an identified monogenic cause rises with sequencing depth and differs three-fold between cohorts, meaning the category is shrinking as genetics advances. No trial establishes the optimal trough IgG target; the dose-response evidence is observational meta-analysis. Why the complicated phenotype develops is unknown, and it is what determines survival. No evidence shows that lymphoma surveillance improves outcome. Essentially all cohort data are from high-income countries.

> **Depth.** Starts in: a B lymphocyte. Size: 7 µm†; depth +4.58. First complaint: about 28 years († onset at age 20–40; [B] after 4 years); time depth 51.90. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: reading. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Severe combined immunodeficiency

What it is. A group of inherited defects that leave a baby with no working T cells, and often no working B or NK cells either. Infections that other infants shrug off are fatal. Without treatment it kills in the first one to two years of life.

Measured. Incidence from newborn screening, the only unbiased measurement: the United States multi-state T-cell receptor excision circle screening programme, covering 3,030,083 newborns across 11 programmes, found severe combined immunodeficiency in 1 in 58,000 births (95% CI 1 in 46,000 to 1 in 80,000) (Kwan et al., *JAMA*, 2014). That was roughly twice the pre-screening clinical estimate of about 1 in 100,000, because infants who died before diagnosis had never been counted. Later and larger United States datasets give incidence in the range 1 in 50,000 to 1 in 65,000†.

Incidence is higher in consanguineous populations, reported at 1 in 2,500 to 1 in 10,000 in some Middle Eastern and North African cohorts, and at roughly 1 in 2,000 in Navajo and Apache populations carrying a *DCLRE1C* founder mutation†.

Genotype distribution in Western cohorts: X-linked *IL2RG* about 40 to 50 per cent, adenosine deaminase deficiency about 10 to 20 per cent, *RAG1/RAG2* about 10 per cent, *IL7R* about 10 per cent, with *JAK3*, *DCLRE1C*, *CD3* subunits and others making up the remainder†. Male predominance, because *IL2RG* is X-linked.

Survival depends almost entirely on age at transplant. Transplanted under 3.5 months of age, overall survival is roughly 92 to 94 per cent; transplanted later with active infection, roughly 50 to 66 per cent

(Primary Immune Deficiency Treatment Consortium multicentre analyses; Pai et al., *NEJM*, 2014, and subsequent reports). Untreated, mortality is essentially 100 per cent by age two.

No global death count. In countries without newborn screening most affected infants die undiagnosed, which is why the pre-screening incidence estimate was half the true figure.

Where it starts. Monogenic defects in T-cell development or function, with over 20 established causal genes and heritability 1.0 for the genotype. X-linked recessive: *IL2RG*, the common gamma chain and the single commonest form. Autosomal recessive: *ADA*, *RAG1*, *RAG2*, *DCLRE1C* (Artemis), *IL7R*, *JAK3*, *CD3D/E/Z*, *PTPRC*, *LIG4*, *NHEJ1*, *AK2* (reticular dysgenesis), *PNP*, *CORO1A*, *ZAP70*, *DOCK2*, *RAC2*.

Consanguinity directly raises the frequency of the autosomal recessive forms, by an order of magnitude in highly consanguineous populations. Founder mutations occur in genetically isolated populations: *DCLRE1C* in Navajo and Apache communities, *RAG1* and *ZAP70* in Mennonite communities.

What makes it lethal: absence of T-cell immunity means no control of *Pneumocystis jirovecii*, cytomegalovirus, adenovirus, rotavirus, BCG, *Candida* and live vaccine organisms, and maternal T-cell engraftment can cause graft-versus-host disease.

The one modifiable determinant of outcome is age at treatment, which is a health-system variable rather than a biological one.

Not known: the proportion of cases worldwide accounted for by genes not yet described — new causes continue to be identified. Why some genotypes, such as hypomorphic *RAG1* variants, give leaky disease or Omenn syndrome rather than classical disease. The long-term immune reconstitution and malignancy outcomes of gene therapy beyond 20 years, which is too recent to measure.

Cure status. CURABLE. This is one of the clearest curable entries in the chapter, and it has been since the first successful transplant in 1968.

Allogeneic haematopoietic stem cell transplant: Primary Immune Deficiency Treatment Consortium data give overall survival roughly 92 to 94 per cent when transplanted before 3.5 months of age, falling to roughly 50 to 66 per cent when transplanted later with active infection†. Matched sibling donors give the best results, but with modern haploidentical and matched unrelated approaches donor availability is no longer the limiting factor. Age at transplant is.

Gene therapy for adenosine deaminase deficiency, using autologous CD34+ cells transduced with an *ADA* gene. The retroviral product approved in the European Union in 2016 achieved 100 per cent survival in its registrational cohort at a median follow-up of several years, with the large majority free of enzyme replacement, priced at €594,000 per treatment (2016) under an outcomes-based arrangement†; it is commercially near-dormant. Lentiviral adenosine deaminase gene therapy reported overall survival of 100 per cent and event-free survival around 95 per cent in pooled United States and United Kingdom cohorts at two to three years, with no insertional oncogenesis to date.

Gene therapy for X-linked disease. The first-generation retroviral trials of 1999 to 2006 cured the immunodeficiency but caused T-cell leukaemia in 5 of 20 patients through insertional activation of *LMO2*† — the defining safety event of the gene therapy field. Self-inactivating lentiviral vectors have since produced immune reconstitution in infants and in previously transplanted older children, in the St Jude and UCSF trials reported in *NEJM* in 2019 and later, with no leukaemia reported to date†. Not yet licensed.

Enzyme replacement for adenosine deaminase deficiency, with pegademase bovine and later elapegademase, bridges to definitive treatment and sustains some patients for years, but immune reconstitution is incomplete and declines. Control, not cure.

Thymus transplantation for complete DiGeorge syndrome or athymia — not severe combined immunodeficiency proper but the same clinical problem — using allogeneic processed thymus tissue approved in the United States in 2021, with survival roughly 70 to 75 per cent at one year and subsequent T-cell development†.

Prevention. Newborn screening by T-cell receptor excision circle assay on the dried blood spot. The decisive intervention. It does not prevent the disease; it prevents death from it by identifying affected

infants before infection. Measured effects: it doubled the measured incidence by finding infants who previously died undiagnosed; and it shifted transplant age below 3.5 months for the majority, which is the difference between roughly 92 and roughly 50 to 66 per cent survival†. Now implemented in all 50 United States states, completed 2018, and in a growing number of countries including Israel, Taiwan, Norway, Sweden, Iceland, Switzerland, Spain, parts of Germany, the Netherlands, Catalonia, New Zealand, parts of Canada, and England as a pilot. The assay adds on the order of five to seven dollars per newborn screened in United States estimates for 2014 to 2020†, and cost-effectiveness analyses in the United States and Europe find it cost-saving or highly cost-effective. STRONG. This is the best-evidenced prevention measure in chapter 04.

Avoiding BCG, rotavirus and other live vaccines before immune status is known in a screen-positive or at-risk infant. In countries with universal BCG at birth, disseminated BCG is a leading cause of death. STRONG.

Avoiding non-irradiated, non-CMV-safe blood products and transfusion from relatives. STRONG.

Carrier testing and genetic counselling in affected families, prenatal diagnosis, and preimplantation genetic testing. STRONG for birth prevalence in known families.

Premarital or preconception carrier screening in highly consanguineous populations, where it has reduced affected births for other recessive conditions. MODERATE, and socially contested.

Co-trimoxazole prophylaxis and immunoglobulin from diagnosis to transplant. STRONG.

Treatment. Allogeneic transplant, as early as possible, at US$150,000 to US$500,000 in high-income settings (2024)†. Not a medicine. The conditioning regimen varies by genotype and donor, and some *IL2RG* and *JAK3* patients engraft without conditioning from a matched sibling.

Gene therapy: licensed in the European Union for adenosine deaminase deficiency at €594,000 (2016)†; X-linked and *RAG1* products in trials.

Enzyme replacement with elapegademase, approved in the United States in 2018, patented, at US$300,000 to US$500,000 a patient-year (2024), used as a bridge†. EML status needs checking against the 24th List†.

Immunoglobulin replacement from diagnosis until B-cell function is established after transplant, which in some genotypes is never, at US$20,000 to US$60,000 a patient-year at lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

Co-trimoxazole for *Pneumocystis*, fluconazole or itraconazole for fungal prophylaxis, aciclovir, and pre-emptive cytomegalovirus and adenovirus monitoring with ganciclovir, valganciclovir or cidofovir. All off-patent, at US$50 to US$500 a patient-year at generic or lowest available acquisition cost, 2024†. Their listing status needs checking against the 24th List†.

Protective isolation until transplant. Irradiated, leucodepleted, CMV-negative blood products only. Nutritional support, because these infants present with failure to thrive and chronic diarrhoea.

Simple means. A full blood count with differential in a sick infant. Lymphopenia — an absolute lymphocyte count below roughly 2.5×10^9/L in a neonate, or below 2.0 in an older infant — is present in the great majority of cases and costs nothing extra on a blood count already being taken. Where there is no screening programme this is the only practical case-finding tool.

Not giving BCG, oral polio or rotavirus vaccine to an infant with unexplained lymphopenia, persistent thrush, chronic diarrhoea with failure to thrive, or a sibling who died in infancy. Free, and it prevents a specific fatal outcome.

Co-trimoxazole prophylaxis, at dollars a year, which prevents *Pneumocystis* pneumonia, the classic presenting killer.

Asking about previous infant deaths and about parental relatedness. In consanguineous populations this is the highest-yield question available and it costs nothing.

Breastfeeding, with the caveat that cytomegalovirus in breast milk is a recognised hazard here, so this is one of the few entries in the chapter where breastfeeding carries a specific risk and needs a clinical decision.

Protective isolation at home: hand hygiene, no visitors with infections, no crowds.

The cure requires a transplant centre. There is no simple-means cure. The simple means here are those that keep the infant alive until a transplant is possible, and those that prevent the iatrogenic deaths from live vaccines and unirradiated blood.

Gaps. The trade and international non-proprietary names of the adenosine deaminase gene therapy products have changed through development, and are distinct from the separate lentiviral products for metachromatic leukodystrophy and beta-thalassaemia; the product names should be checked against current regulatory listings before publication. Incidence outside countries with newborn screening is unknown, and because the pre-screening estimate was out by a factor of two, current figures for non-screening countries should be assumed to be underestimates by a similar margin. Long-term outcomes of lentiviral gene therapy beyond 20 years are unknown by construction. The insertional leukaemia experience in the X-linked retroviral trials means safety reassurance for current vectors rests on relatively short follow-up in small cohorts. Optimal conditioning intensity by genotype is not settled; the trade-off is between engraftment, B-cell reconstitution and late toxicity including infertility. Almost no data exist from sub-Saharan Africa or South Asia, where consanguinity rates in some populations predict high incidence.

> **Depth.** Starts in: a protein of T-cell development. Size: 5 nm†; depth −2.01. First complaint: about 13 months († from conception to 3–6 months); time depth 48.96. One untreated course: about 17 months ([B] death within 1–2 years); depth 49.19.
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. A stem-cell transplant or gene therapy restores the source. The book's status: CURABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Hereditary angioedema

What it is. An inherited shortage, or malfunction, of C1 inhibitor. Without it, bradykinin accumulates and causes sudden swelling of the skin, gut wall or throat. Antihistamines and adrenaline do not work on it, and laryngeal attacks can suffocate.

Measured. Prevalence is about 1 in 50,000, the long-standing and most widely used figure, with published estimates ranging from 1 in 10,000 to 1 in 150,000†. There is no population-based survey; all estimates derive from referral-centre case counts over defined populations.

Type I, with low C1-inhibitor antigen and function, is about 85 per cent; type II, with normal antigen and low function, about 15 per cent; and hereditary angioedema with normal C1 inhibitor, formerly type III, including *F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF* and *HS3ST6* variants and unknown causes, is a small and growing residual category.

The median age at first attack is in late childhood to adolescence, with roughly 50 per cent by age 10 and 90 per cent by age 20†. Untreated attack frequency is highly variable: a median of roughly one attack every one to two weeks in severely affected patients, with long attack-free intervals in others.

Historical series report mortality from laryngeal attacks of roughly 25 to 30 per cent in untreated patients†. That figure comes from pre-treatment-era cohorts and is the reason the condition is treated aggressively. With modern on-demand treatment and prophylaxis, death from it is rare.

Diagnostic delay is consistently reported at roughly 10 to 13 years from first attack to diagnosis in European and United States cohorts — among the longest in medicine, and the main avoidable harm. No major ethnic predilection is reported, and apparent differences track diagnostic capacity; Iceland, Denmark and Italy have the best-characterised national cohorts.

Where it starts. For types I and II, loss-of-function variants in *SERPING1*, autosomal dominant, with heritability 1.0 for the genotype. Roughly 20 to 25 per cent are de novo mutations with no family history†.

The mechanism is fully established: C1 inhibitor normally restrains plasma kallikrein and factor XIIa. Without it, kallikrein cleaves high-molecular-weight kininogen to release bradykinin, which binds the

bradykinin B2 receptor and causes vascular leak. Every effective modern drug targets a step in this pathway, which is unusually clean evidence for a mechanism.

For disease with normal C1 inhibitor, *F12* gain-of-function (p.Thr328Lys) is the best established, with *PLG*, *ANGPT1*, *KNG1*, *MYOF* and *HS3ST6* following. In many families no gene is found.

Attack triggers established by patient-report cohorts: mechanical trauma, especially dental work and intubation; emotional stress; infection; menstruation; and oestrogen — combined oral contraceptives and hormone replacement reliably worsen the disease.

ACE inhibitors are contraindicated. ACE degrades bradykinin, so inhibiting it worsens the disease markedly. This is a drug interaction with a clean mechanism and a large effect.

Penetrance is high, and attack severity within a family varies widely at identical genotype.

Not known: why attack frequency and severity vary so much within families carrying the same *SERPING1* variant. What determines which anatomical site an attack affects. The cause in the substantial share of normal-C1-inhibitor families where no gene is identified. Whether long-term prophylaxis started in childhood changes the natural history.

Cure status. CONTROLLABLE. No cure exists; nothing restores *SERPING1* function.

On-demand treatment aborts attacks reliably. Icatibant, C1-inhibitor concentrate and ecallantide all shorten attacks substantially against placebo in randomised trials, with time to onset of symptom relief typically reduced from many hours to under one to two hours.

Long-term prophylaxis now achieves near-complete attack prevention in a large share of patients, which is a recent and large change. Lanadelumab, an anti-plasma-kallikrein monoclonal antibody, reduced attack rate by 87 per cent against placebo at the 300 mg every-two-weeks dose in the HELP trial, with 44 per cent of patients attack-free throughout the 26-week treatment period†. Berotralstat, an oral plasma kallikrein inhibitor, reduced attack rate by roughly 30 to 44 per cent against placebo in APeX-2 — a smaller effect than lanadelumab, and oral and once-daily†. Subcutaneous C1 inhibitor reduced attack rate by roughly 95 per cent at the higher dose in the per-protocol analysis of COMPACT, with a large share attack-free. Donidalorsen, an antisense agent against prekallikrein approved in the United States in August 2024, and garadacimab, an anti-factor-XIIa monoclonal approved in the European Union and United States in 2025, both reported attack rate reductions of roughly 85 to 90 per cent in phase 3 with high attack-free proportions†. Sebetralstat, an oral on-demand plasma kallikrein inhibitor approved in 2025, is the first oral on-demand treatment and removes the injection requirement for acute attacks.

So the disease persists for life, and in treated patients with access, attacks can be reduced to near zero. The constraint is price and access, not efficacy.

Prevention. No prevention of the genotype beyond genetic counselling, cascade testing of relatives, and prenatal or preimplantation diagnosis.

Cascade testing of first-degree relatives. Autosomal dominant with high penetrance, so the yield is roughly 50 per cent per first-degree relative. This is the measure that shortens the 10-to-13-year diagnostic delay in the next generation. STRONG.

Avoiding oestrogen-containing contraceptives and hormone replacement. STRONG: a consistent, large, mechanistically explained effect.

Avoiding ACE inhibitors. STRONG, mechanistic plus case evidence; angiotensin receptor blockers are preferred where an antihypertensive is needed.

Short-term prophylaxis with C1-inhibitor concentrate before dental work, surgery and intubation, which prevents the perioperative laryngeal attacks that caused much of the historical mortality. STRONG.

Long-term prophylaxis in patients with frequent attacks, with the trial figures above. STRONG.

A medical alert card or bracelet, which prevents the fatal misdiagnosis of a laryngeal attack as anaphylaxis, where adrenaline, steroids and antihistamines do not work and time is lost. STRONG in practical terms, with no trial.

Treatment. On-demand, first-line: plasma-derived or recombinant C1 inhibitor concentrate, at US$3,000 to US$10,000 per attack treated on United States and European list prices (2024)†. Plasma-derived product is supply-limited rather than patent-limited. EML status needs checking against the 24th List†.

Icatibant, a bradykinin B2 receptor antagonist, subcutaneous and self-administered, off-patent with generics since roughly 2019 to 2021. Originator US$8,000 to US$11,000 a dose on United States list (2023); generic US$1,500 to US$4,000 a dose (2024)†. The price fall on generic entry is one of the clearest in the chapter. EML status needs checking against the 24th List†.

Sebetralstat, oral on-demand, approved 2025, patented, with price not established in most markets at the time of writing.

Ecallantide, United States only, with a risk of anaphylaxis requiring healthcare administration.

Fresh frozen plasma contains C1 inhibitor and is the fallback where nothing else exists, used successfully for decades, with the caveat that it also contains the substrates and can occasionally worsen an attack. It is universally available where there is a blood bank.

Long-term prophylaxis: subcutaneous C1 inhibitor at US$400,000 to US$600,000 a patient-year on United States list (2024); lanadelumab at 500,000 to 700,000; oral daily berotralstat at 500,000 to 600,000; donidalorsen and garadacimab of a similar order†. None is off-patent, and the listing status of each needs checking against the 24th List†.

Attenuated androgens — danazol, stanozolol, oxandrolone — reduce attack frequency substantially, with older trials and long cohorts reporting roughly 60 to 90 per cent reductions†. Off-patent, at US$200 to US$1,500 a patient-year at generic or lowest available acquisition cost, 2024†. Side effects — virilisation, dyslipidaemia, hepatic adenoma, growth suppression in children — are why high-income guidelines moved away from them. In most of the world they remain the only affordable prophylaxis, and they work. This price gap, roughly 300-fold, is the central economic fact of this condition. Listing status needs checking against the 24th List†.

Tranexamic acid, with weak evidence, used where androgens are contraindicated, particularly in children and in disease with normal C1 inhibitor, at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†. Tranexamic acid is a selected medicine on the 24th List, section 10.2, for haemorrhage not elsewhere classified; hereditary angioedema is not among the listed indications.

What does not work: antihistamines, corticosteroids and adrenaline. Stating this is itself a treatment point, because the attacks are bradykinin-mediated rather than histamine-mediated, and treating them as anaphylaxis wastes the time in which a laryngeal attack kills.

Airway management: early intubation or surgical airway in laryngeal attacks.

Simple means. A medical alert card naming the diagnosis and stating that adrenaline and antihistamines do not work. Costs nothing, and prevents the commonest fatal error in managing this disease.

Avoiding oestrogen contraceptives and ACE inhibitors. Free, and among the largest modifiable effects available.

Tranexamic acid tablets, at tens of dollars a year, oral and with no cold chain; weak evidence but real use.

Danazol or stanozolol, at hundreds of dollars a year, oral, off-patent and substantially effective. Not a no-chain intervention, and it is the difference between prophylaxis and none in most countries.

Fresh frozen plasma for an acute attack where no specific agent exists. It needs a blood bank, not a pharmaceutical supply chain.

Telling the family. Autosomal dominant, 50 per cent per first-degree relative, and a 10-to-13-year diagnostic delay. A family conversation is the highest-yield free intervention here.

Pre-procedure planning for dental work: telling the dentist, and arranging short-term prophylaxis or at least on-site airway capability.

Knowing the prodrome — erythema marginatum, tingling — so that treatment is taken early, when it works best.

Gaps. No population-based prevalence study exists; the 1-in-50,000 figure is conventional and the published range spans fifteen-fold. The 25-to-30-per-cent untreated laryngeal mortality figure comes from pre-treatment-era case series with ascertainment biased toward severe families; it is probably an overestimate of population risk and is nonetheless the number used to justify treatment. Prophylaxis prices in high-income markets are two to three orders of magnitude above the off-patent androgen alternative, with no head-to-head trial of modern prophylaxis against danazol, so the two cannot be compared on efficacy at equal cost. Disease with normal C1 inhibitor has no diagnostic test in most families, no agreed criteria, and contested response to the same treatments. Almost no published data exist from low-income countries; the condition is presumed undiagnosed rather than absent. Whether early long-term prophylaxis in childhood alters natural history is unknown.

> **Depth.** Starts in: C1 inhibitor. Size: 10 nm†; depth −1.38. First complaint: about 10 years († onset about age 10); time depth 50.97. One untreated course: about 3.2 days († an attack lasts 2–5 days); depth 44.55.
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Allergic rhinitis

Allergic rhinitis is an allergic reaction of the lining of the nose to inhaled pollen, dust mite, animal dander or mould. It brings sneezing, blockage, a running nose and itching, seasonally or year-round. ICD-11 codes it in chapter 12, among the diseases of the respiratory system, as CA08.0, and the full entry is there: "Allergic rhinitis", in the chapter on circulatory and respiratory diseases. It carries all eight sections.

A reader in the immune chapter is sent there because the condition is an IgE-mediated allergy, and a reader looking for allergy will look among the immune diseases first. ICD-11 classes it by the organ it affects. The respiratory entry also sets it beside asthma, which it often accompanies.

Food allergy

What it is. An immune reaction to a food protein, usually IgE-mediated, producing hives, vomiting, swelling, wheeze or collapse within minutes to two hours of eating. Milk, egg, peanut, tree nut, wheat, soy, fish, shellfish and sesame account for most of it.

Measured. Self-reported prevalence greatly exceeds confirmed prevalence, and this is the central measurement fact. Self-report runs at 10 to 20 per cent of the population; challenge-proven food allergy is roughly 1 to 5 per cent of adults and 5 to 8 per cent of children in high-income countries†.

HealthNuts, the largest population-based infant study using oral food challenge, found challenge-proven IgE-mediated food allergy in 10 per cent of 12-month-olds in Melbourne — raw egg 8.9 per cent, peanut 3.0 per cent, sesame 0.8 per cent†. This is among the highest measured anywhere, and Australia is a genuine high-prevalence outlier. United States surveys by Gupta and colleagues for 2018 to 2019 found about 7.6 per cent of children and 10.8 per cent of adults affected by stringent symptom criteria, though not challenge-confirmed. EuroPrevall, the standardised European multi-centre study with challenge, found challenge-confirmed prevalence of specific food allergies generally under 1 to 2 per cent per food, with large between-country differences.

Incidence peaks in the first two years. Milk and egg allergy resolve in the majority — roughly 50 to 80 per cent of milk allergy by school age, and similar for egg — while peanut, tree nut, fish and shellfish allergy mostly persist, with peanut allergy resolving in roughly 20 per cent of children†.

The trend is rising. Peanut allergy prevalence in United Kingdom and United States children roughly tripled between the mid-1990s and the mid-2000s, and hospital admissions for food-induced anaphylaxis rose several-fold in the United Kingdom, United States and Australia over two to three decades.

Measured prevalence is highest in Australia, the United Kingdom, the United States and northern Europe, and lower across much of Asia and Africa, though measurement there is sparse. Food patterns differ: buckwheat in Japan, chickpea in India, sesame in the Middle East.

Food-induced anaphylaxis fatality is rare, at population fatality rates of roughly one to three per million person-years among people with food allergy, and food allergy is a less common cause of anaphylaxis death than drugs or venom in most national series. The disparity between the fear and the measured mortality is itself a finding.

Where it starts. IgE sensitisation to a food protein, then mast cell and basophil activation on ingestion. Non-IgE mechanisms — food protein-induced enterocolitis syndrome, eosinophilic oesophagitis, coeliac disease — are separate entities.

The dual-allergen-exposure hypothesis holds that sensitisation occurs through an impaired skin barrier while oral exposure induces tolerance, and the trial that confirmed its practical consequence is LEAP. In LEAP (Learning Early About Peanut Allergy, Du Toit et al., *NEJM*, 2015), 640 infants aged four to 11 months at high risk, with severe eczema or egg allergy, were randomised to peanut consumption or avoidance to age five. Peanut allergy at age five was reduced by about 81 per cent in the consumption group in the intention-to-treat primary analysis — in the skin-prick-negative stratum 13.7 per cent against 1.9 per cent, and in the sensitised stratum 35.3 per cent against 10.6 per cent. In LEAP-On, after one year of avoidance, 18.6 per cent of the former avoidance group were allergic against 4.8 per cent of the former consumption group, so tolerance persisted after peanut was withdrawn. The EAT trial in general-population infants found no significant effect in intention-to-treat and a significant effect per-protocol, with adherence to early introduction of multiple allergens the limiting factor. PETIT, in Japan, found that early introduction of heated egg reduced egg allergy from 37.7 per cent to 8.3 per cent†.

Eczema is the strongest risk factor. Severe infantile eczema raises food allergy risk several-fold, and the earlier and more severe the eczema, the higher the risk.

Other established risk factors: male sex in childhood, family history of atopy, vitamin D insufficiency (contested), caesarean delivery (modest), Asian or Black ancestry in Western countries, where risk is higher than in white children in United States and Australian data and the reason is unexplained, and migration from low- to high-prevalence countries, where risk rises in the children of migrants.

Twin studies for peanut allergy give heritability estimates around 0.8†, and *FLG* loss-of-function variants, which cause skin barrier defects, are associated with peanut allergy, which supports the skin-sensitisation route.

Not known: why food allergy prevalence rose so sharply. Why milk and egg allergy resolve and peanut and shellfish allergy do not. Why Australia measures the highest prevalence in the world. What determines anaphylaxis severity — no clinical or laboratory marker reliably predicts who will have a severe reaction, which is why all food allergy is managed as if it could be severe, and this is the largest unsolved problem in the field.

Cure status. Milk and egg allergy in children: SELF-LIMITING, with the majority resolving by school age without any intervention; supervised reintroduction of baked milk and baked egg accelerates resolution in some children. Peanut, tree nut, fish and shellfish allergy: CONTROLLABLE by avoidance, with roughly 20 per cent of peanut allergy resolving spontaneously.

Oral immunotherapy achieves desensitisation, not cure. In PALISADE, the trial of peanut allergen powder approved in the United States and European Union in 2020, 67.2 per cent of treated participants tolerated 600 mg of peanut protein at exit challenge against 4.0 per cent on placebo†. That is desensitisation while on daily treatment; stop the daily dose and protection is lost in most patients. Sustained unresponsiveness, persisting after stopping, is achieved in a minority, roughly 20 to 35 per cent in trials that tested it after a period of avoidance†. Adverse events are common: gastrointestinal symptoms in most, eosinophilic oesophagitis in roughly 3 to 5 per cent, and systemic allergic reactions more frequent on oral immunotherapy than on avoidance — a meta-analysis found oral immunotherapy roughly tripled the risk of anaphylaxis compared with avoidance while achieving desensitisation. That trade-off is real and is why

uptake is contested. Epicutaneous and sublingual immunotherapy have smaller effects and are better tolerated.

Omalizumab, approved in the United States in February 2024 for reducing allergic reactions to accidental exposure in multi-food allergy: in the OUtMATCH trial, 67 per cent of treated participants could consume 600 mg of peanut protein against 7 per cent on placebo, with similar effects for other foods†. This is protection while on treatment, not cure.

Avoidance plus an adrenaline autoinjector is the standard of care worldwide, and nothing yet cures food allergy.

Prevention. This is the strongest prevention entry in chapter 04 after newborn screening for severe combined immunodeficiency, and the evidence reversed previous advice.

Early introduction of allergenic foods in infancy, from around four to six months, alongside continued breastfeeding. LEAP: about an 81 per cent reduction in peanut allergy in high-risk infants†. PETIT: egg allergy from 37.7 per cent to 8.3 per cent†. STRONG for peanut in high-risk infants, MODERATE for egg, MODERATE for the general population, where EAT was negative in intention-to-treat and positive per-protocol. This reversed the guidance of the 1990s and 2000s, which recommended delaying allergenic foods; Australian and United States guidelines changed in 2016 and 2017 following LEAP. After Australia's 2016 infant feeding guideline change, population studies reported a measurable fall in peanut allergy prevalence in subsequent infant cohorts, roughly a 16 per cent relative reduction in challenge-confirmed peanut allergy in Melbourne infants between the 2007–2011 and 2018–2019 cohorts† — one of the few documented before-and-after population effects of an allergy prevention policy.

Eczema treatment and skin barrier care in infancy: mechanistically compelling given the dual-allergen hypothesis, but the trials of emollient from birth to prevent eczema and food allergy, BEEP and PreventADALL, were negative for eczema prevention, and BEEP found more food allergy in the emollient group. CONTESTED. This is a clear case where mechanism and trial disagree and the trials should be believed.

Exclusive breastfeeding: CONTESTED for food allergy prevention; no consistent effect.

Maternal dietary avoidance during pregnancy or lactation: WEAK to no effect. Cochrane reviews find no benefit and it is no longer recommended.

Hydrolysed infant formula to prevent allergy: CONTESTED to negative. The evidence base was found to be weak and partly compromised, and a 2016 *BMJ* systematic review and subsequent guideline changes withdrew the recommendation.

Vitamin D supplementation: CONTESTED.

Prevention of death: adrenaline autoinjector availability, written anaphylaxis plans, school and restaurant policy, and allergen labelling law. MODERATE, from before-and-after policy data; no trials are possible.

Treatment. Adrenaline (epinephrine) intramuscularly, by autoinjector or ampoule and syringe, is first-line and the only treatment that alters the course of anaphylaxis. The molecule is off-patent — but autoinjector devices are not: device patents kept autoinjector prices at US$300 to US$700 per two-pack in the United States (2024), while an ampoule of adrenaline costs well under one dollar (2024) and a prefilled syringe only slightly more†. This gap between drug and device is the central economic fact of food allergy care. Intranasal adrenaline was approved in the United States in 2024. Epinephrine's listing status needs checking against the 24th List†.

Avoidance of the specific food, with label reading and cross-contamination awareness. The standard of care. No cost beyond the dietary constraint and the dietitian time.

Antihistamines, for skin symptoms only. They do not treat anaphylaxis, and giving them instead of adrenaline is a recognised cause of death. Off-patent, cents a dose. Listing status needs checking against the 24th List†.

Oral immunotherapy: the licensed peanut product for ages one to 17, and non-standardised food-protein oral immunotherapy in specialist centres. Patented, at about US$10,000 to US$15,000 a patient-year on United States list (2024)†. EML status needs checking against the 24th List†.

Omalizumab for multi-food allergy, at US$30,000 to US$60,000 a patient-year at lowest available acquisition cost, 2024†. **Omalizumab is not on the 24th List at all, for any indication: a live query of the electronic Model List returns zero recommendations, zero medicines and zero therapeutic equivalents**. Biosimilars are entering.

Supervised baked milk or baked egg introduction in children who tolerate it, which accelerates resolution, expands the diet and costs nothing but clinic time.

Dietitian input, to prevent the nutritional deficiency and growth faltering that multiple food exclusion causes in children. Under-provided everywhere.

A written anaphylaxis emergency plan, with training of the family, school and workplace.

Simple means. Early introduction of allergenic foods in infancy. Smooth peanut butter thinned with water or milk, or well-cooked egg, from around four to six months, continued regularly. This is food, not medicine; it costs nothing; and the measured effect in high-risk infants is about an 81 per cent reduction in peanut allergy. It is the clearest case in the chapter of a simple means being the prevention.

Continuing to eat the food regularly once introduced. LEAP-On showed tolerance was lost in a fifth of children after a year of avoidance, so regular ingestion is the maintenance.

Adrenaline in an ampoule with a syringe, where autoinjectors are unaffordable. The drug costs under a dollar. Training a parent to draw up and inject is feasible and is done in several countries. Not ideal — delay and dose error are real risks — and it is the difference between having adrenaline and not having it.

Label reading, and cooking from whole ingredients. The single most effective daily measure.

Lying flat with legs raised in anaphylaxis with hypotension, and not standing the person up, which is associated with fatal outcomes. Free, and it matters.

Telling people: a written plan, a bracelet, informing school and restaurant staff.

Breastfeeding alongside the introduction of solids. No evidence that it prevents food allergy, and good evidence for other outcomes.

Gaps. Self-reported prevalence exceeds challenge-proven prevalence by a factor of two to ten, so any figure must state which it is, and most published national figures are self-reported. Almost all population data with oral food challenge come from Australia, Europe and North America; prevalence in Africa, South Asia and most of Latin America is essentially unmeasured. Why prevalence rose, and why Australia is the outlier, are unexplained. BEEP and PreventADALL contradict the skin-barrier prevention hypothesis, and BEEP found more food allergy with emollient; mechanism and trial disagree. Hydrolysed formula recommendations were withdrawn after the underlying evidence base was found to be weak, and some national guidelines still carry the old advice. Oral immunotherapy increases anaphylaxis risk while achieving desensitisation, and whether that trade is worth it is contested, with patient and clinician views differing. No marker predicts reaction severity, which is the field's central unsolved problem. The EAT trial was negative in intention-to-treat and positive per-protocol, and sources cite whichever suits.

> **Depth.** Starts in: a food protein. Size: 5 nm†; depth −2.01. First complaint: about 24 minutes ([B] minutes to 2 hours); time depth 39.79. One untreated course: about 6 hours († hours); depth 42.24.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Anaphylaxis

What it is. A sudden, whole-body allergic reaction. Airways swell and narrow, blood pressure drops, and the person can die within minutes. Adrenaline into the muscle reverses it; nothing else reliably does.

Measured. Incidence is roughly 50 to 112 episodes per 100,000 person-years in systematic reviews of European and North American data, and lifetime prevalence of at least one episode roughly 0.3 to 5.1 per cent, with the commonly cited figure around 1.6 to 2 per cent†.

Hospital admissions rose several-fold over two to three decades in the United Kingdom, United States, Australia and Canada; in England, admissions rose roughly five- to sevenfold between the early 1990s and the late 2010s while case fatality fell†. The admissions rise is partly real and partly increased recognition and coding.

Case fatality is roughly 0.3 to 2 per cent of hospital-presenting episodes, and population mortality roughly 0.5 to 1 death per million population per year in high-income national series.

The cause distribution differs by age, and this is well measured. In children food is the dominant trigger, roughly 60 to 85 per cent of paediatric cases†. In adults drugs and insect venom dominate: in United Kingdom national fatality data, drugs — antibiotics, neuromuscular blockers, radiocontrast — and venom together account for the majority of anaphylaxis deaths, with food a minority.

Perioperative anaphylaxis occurs in roughly 1 in 10,000 to 1 in 20,000 anaesthetics, with neuromuscular blocking agents, antibiotics and chlorhexidine the leading causes; the United Kingdom Royal College of Anaesthetists national audit NAP6, in 2018, found mortality of about 4 per cent in perioperative anaphylaxis†.

Measured risk factors for a fatal outcome: delayed adrenaline administration; upright or sitting posture during the reaction; concomitant asthma, especially poorly controlled; adolescence and early adulthood; and peanut or tree nut as the trigger. Deaths run to a few hundred a year in large high-income countries, with no global count.

Where it starts. IgE-mediated mast cell and basophil degranulation in the majority, releasing histamine, tryptase, leukotrienes and platelet-activating factor, causing vasodilation, increased permeability, bronchospasm and myocardial depression. Non-IgE mechanisms: complement activation, direct mast cell activation via MRGPRX2 by vancomycin, fluoroquinolones and neuromuscular blockers, and NSAID-mediated reactions.

Established triggers: foods (peanut, tree nuts, milk, egg, shellfish, fish, sesame, wheat); drugs (beta-lactam antibiotics, NSAIDs, neuromuscular blockers, radiocontrast, chemotherapeutics, biologics); Hymenoptera venom from bee, wasp and ant; latex; chlorhexidine; and alpha-gal sensitisation after tick bite, which causes delayed anaphylaxis to mammalian meat and was described only in 2009 and is now recognised worldwide.

Measured cofactors that amplify a reaction: exercise, alcohol, NSAIDs, acute infection, menstruation and emotional stress. Food-dependent exercise-induced anaphylaxis, classically to omega-5-gliadin in wheat, requires both the food and the cofactor.

Mastocytosis and elevated baseline serum tryptase, including hereditary alpha-tryptasemia from extra copies of *TPSAB1* present in roughly 4 to 6 per cent of the general population, raise the risk of severe anaphylaxis, particularly to venom.

Heritability is not well estimated for anaphylaxis as an event. The underlying atopy is heritable, and hereditary alpha-tryptasemia is a Mendelian copy-number trait.

Not known: why a person reacts mildly on one exposure and fatally on the next to the same dose of the same allergen. No test predicts severity. Specific IgE concentration and skin test size correlate with the probability of reacting but not with the severity of the reaction. This is the central unknown, and it is the reason every allergic person is told to carry adrenaline. Also not known: whether the rise in admissions represents a true rise in incidence.

Cure status. The episode: SELF-LIMITING, and treatment is decisive. An anaphylactic episode either resolves, spontaneously or with adrenaline, within minutes to hours, or it kills. There is no cure of an event; there is treatment of one. The predisposition splits. Hymenoptera venom anaphylaxis: CURABLE. Drug allergy with an incorrect label: CURABLE by diagnosis. Food allergy: CONTROLLABLE by avoidance.

Venom immunotherapy is curative for Hymenoptera venom anaphylaxis, which is the strongest cure claim in allergy. After a three-to-five-year course, the risk of systemic reaction to a subsequent sting falls from roughly 40 to 60 per cent to 5 to 10 per cent, and protection persists for years to decades after treatment stops. The evidence is randomised trials plus sting challenge studies. This is a genuine cure for a potentially fatal condition, achieved with an off-patent biological extract.

Drug allergy is often curable by correct diagnosis. A large majority of people labelled penicillin-allergic are not; direct oral challenge, or skin testing followed by challenge, de-labels roughly 90 to 95 per cent of people carrying a penicillin allergy label†. The cure is removing an incorrect diagnosis.

Prevention. Prompt intramuscular adrenaline. Delay in administration is the most consistently identified factor in fatal cases. STRONG — no randomised trial exists and none is possible; the evidence is from fatality series and is accepted universally.

Lying the person flat, or flat with legs raised, and not standing or sitting them up. Fatality series document deaths occurring on sudden assumption of an upright posture, through the empty-ventricle mechanism. MODERATE, from case series.

Prescription and carriage of two adrenaline autoinjectors, with a written plan and training. MODERATE.

Venom immunotherapy for people with systemic sting reactions, reducing subsequent systemic reaction risk from roughly 40 to 60 per cent to 5 to 10 per cent. STRONG.

Penicillin allergy de-labelling, which removes both the risk from the alternative antibiotics and the false constraint. STRONG.

Asthma control in food-allergic patients, since poorly controlled asthma is a consistent risk factor for fatal food anaphylaxis. MODERATE.

Drug allergy prevention: accurate allergy records, test-before-prescribe for high-risk drugs, and perioperative protocols following the NAP6 recommendations on chlorhexidine and neuromuscular blockers. MODERATE.

Allergen labelling law and school and restaurant policy. MODERATE, from before-and-after national data.

Early allergen introduction in infancy, which prevents the food allergy that causes paediatric anaphylaxis. STRONG for peanut in high-risk infants.

Avoiding beta-blockers and ACE inhibitors in patients on venom immunotherapy or at high anaphylaxis risk is traditional advice; the evidence is weak and the guidance has softened. CONTESTED.

Treatment. Adrenaline (epinephrine), 0.3 to 0.5 mg intramuscularly into the anterolateral thigh in adults, 0.01 mg/kg in children, repeated after five to 15 minutes if needed. First-line, and there is no substitute. The molecule has been off-patent for a century. An ampoule of 1 mg/mL adrenaline costs well under one dollar (2024) at international generic prices†. An autoinjector two-pack runs US$300 to US$700 on United States list (2024), generic autoinjectors US$100 to US$300, and in Europe €50 to €150†. The device, not the drug, is the cost. Intranasal adrenaline was approved in the United States in August 2024 and is priced as a branded product. Epinephrine’s listing status needs checking against the 24th List†.

Positioning the patient flat, legs raised if hypotensive, on the side if vomiting, sitting up only if breathing is the dominant problem. Free, with evidence from fatality series.

Oxygen and intravenous fluids, with large-volume crystalloid for distributive shock. Sodium chloride and Ringer’s lactate are off-patent and cost cents to dollars; listing status needs checking against the 24th List†.

Inhaled salbutamol for bronchospasm, as an adjunct only, off-patent at two to ten dollars an inhaler (2024)†. Listing status needs checking against the 24th List†.

Antihistamines and corticosteroids are adjuncts, not treatments. They do not reverse airway obstruction or hypotension. Evidence that corticosteroids prevent biphasic reactions is weak and recent reviews question the practice. Giving them instead of adrenaline is a recognised contributor to death.

Glucagon for patients on beta-blockers who do not respond to adrenaline. Off-patent; listing status needs checking against the 24th List†.

Observation after the episode for a biphasic reaction, four to six hours or longer depending on severity. Biphasic reactions occur in roughly 1 to 5 per cent of episodes†.

After the episode: serum tryptase taken within one to two hours and again at baseline, referral for allergy investigation, autoinjector prescription, a written plan, and trigger identification. The follow-up is where the next episode is prevented, and it is the step most often omitted.

Venom immunotherapy for venom anaphylaxis, at US$1,000 to US$3,000 a patient-year for three to five years at lowest available acquisition cost, 2024† — against a cured, potentially fatal condition, which makes it one of the better-value interventions in this chapter. These are biological extracts and standardised products are manufacturer-specific. EML status needs checking against the 24th List†.

Simple means. Adrenaline in an ampoule with a 1 mL syringe. The drug costs under a dollar and has been off-patent for a century. Where autoinjectors cost hundreds, this is the difference between having adrenaline available and not. Several countries train patients and health workers to draw up and inject. The trade-off — delay and dosing error under stress — is real and should be stated, and so should the price.

Lying the person down. Free, and documented in fatality series as decisive.

Giving the injection into the outer thigh through clothing if necessary. No preparation needed.

Calling for help and not letting the person walk. Knowing not to wait for antihistamines to work.

Avoidance of the identified trigger, and a written card naming it.

Removing a bee sting by scraping rather than squeezing.

In alpha-gal syndrome, avoiding mammalian meat and preventing tick bites — long trousers, tick checks, prompt removal.

Early allergen introduction in infancy, which is prevention upstream of the whole entry.

Gaps. Incidence estimates span roughly two-fold and lifetime prevalence estimates roughly seventeen-fold, from 0.3 to 5.1 per cent, because case definition and ascertainment differ; there is no agreed clinical definition applied consistently across studies. Whether the several-fold rise in admissions is a real rise in incidence or improved recognition and coding is unresolved, and case fatality fell over the same period, which argues for ascertainment. No global incidence or mortality estimate exists. No test predicts reaction severity, which is the field's central unsolved problem and determines how the condition is managed worldwide. Corticosteroids for preventing biphasic reactions: long-standing practice, weak evidence, increasingly questioned, and sources disagree. Whether beta-blockers and ACE inhibitors meaningfully worsen outcomes is contested. The autoinjector price gap — under a dollar of drug against hundreds of dollars of device — is a market phenomenon rather than a manufacturing one, and no public figure for autoinjector production cost exists comparable to the published insulin analysis.

> **Depth.** Starts in: an allergen protein. Size: 5 nm†; depth −2.01. First complaint: about 12 minutes ([B] within minutes); time depth 39.16. One untreated course: about 4 hours († hours); depth 41.87.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Drug allergy

What it is. An immune reaction to a medicine. It ranges from a rash to anaphylaxis to severe skin and organ reactions that kill. Most people who believe they are allergic to a drug are not, and the wrong label does its own harm.

Measured. Penicillin allergy label prevalence is roughly 6 to 10 per cent of the general population in high-income countries, and higher in hospital inpatient populations. Roughly 90 to 95 per cent of those labels are wrong: direct oral challenge, or skin testing followed by challenge, de-labels about nine in ten people carrying a penicillin allergy label. This is one of the best-replicated findings in clinical allergy. True immediate, IgE-mediated penicillin allergy accounts for roughly 1 to 5 per cent of labelled patients†.

The measured harm of the incorrect label: patients labelled penicillin-allergic have longer hospital stays, roughly 10 per cent longer in a large United States cohort; roughly 14 per cent more meticillin-resistant *Staphylococcus aureus*; roughly 23 per cent more *Clostridioides difficile*; and more vancomycin, clindamycin and fluoroquinolone use (Macy and Contreras, *J Allergy Clin Immunol*, 2014; Blumenthal et al., *BMJ*, 2018). Surgical site infection rates are higher because of second-line surgical prophylaxis.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis occur at roughly one to six cases per million person-years, with mortality of roughly 5 to 10 per cent for Stevens-Johnson syndrome and 25 to 50 per cent for toxic epidermal necrolysis†. Drug reaction with eosinophilia and systemic symptoms occurs in roughly 1 in 1,000 to 1 in 10,000 exposures for high-risk drugs, with mortality roughly 5 to 10 per cent†. Acute generalised exanthematous pustulosis occurs at roughly one to five per million per year with low mortality.

Commonest culprits for severe reactions: allopurinol, carbamazepine, lamotrigine, phenytoin, nevirapine, abacavir, sulfonamides including co-trimoxazole, NSAIDs and beta-lactams.

Perioperative drug anaphylaxis occurs in roughly 1 in 10,000 to 1 in 20,000 anaesthetics; NAP6 found antibiotics, neuromuscular blockers and chlorhexidine as the leading agents and mortality of about 4 per cent†. Drug allergy labels accumulate with age and healthcare exposure, and women carry more labels than men.

Where it starts. Four established and distinct mechanisms. Type I, IgE-mediated: immediate urticaria, angioedema, bronchospasm and anaphylaxis, with beta-lactams, neuromuscular blockers and chlorhexidine. Types II and III: cytopenias, serum sickness, vasculitis. Type IV, T-cell-mediated: delayed maculopapular exanthem, Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. And non-immune pharmacological hypersensitivity: NSAID-exacerbated respiratory disease via COX-1 inhibition, MRGPRX2-mediated direct mast cell activation by vancomycin, fluoroquinolones and neuromuscular blockers, and ACE-inhibitor angioedema via bradykinin. The last group are not allergies and do not involve IgE, which matters for testing.

The HLA associations are among the strongest gene-drug associations in all of medicine, and they are actionable. *HLA-B*57:01* and abacavir hypersensitivity: the PREDICT-1 randomised trial showed that prospective screening eliminated immunologically confirmed hypersensitivity, 0 per cent against 2.7 per cent†. Screening before abacavir is now standard worldwide, and this is the clearest pharmacogenomic prevention success in medicine. *HLA-B*15:02* and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese, Thai and other Southeast Asian populations: odds ratios of roughly 25 to 100, and Taiwan's national screening programme before carbamazepine reduced carbamazepine-induced cases to near zero. *HLA-B*58:01* and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: odds ratio roughly 80 to 100 in Han Chinese†. *HLA-A*31:01* and carbamazepine-induced drug reaction with eosinophilia in Europeans. *HLA-B*13:01* and dapsone hypersensitivity.

The HLA associations mean severe cutaneous reactions have a strong, population-specific genetic component with very large effect sizes, which is unusual in this field. But penetrance is low: most carriers of *HLA-B*15:02* exposed to carbamazepine do not develop Stevens-Johnson syndrome, so the allele is necessary but not sufficient in most cases.

Established risk factors: concurrent viral infection, with Epstein-Barr virus and amoxicillin rash and HIV and sulfonamide reactions; high drug dose and parenteral route; repeated intermittent exposure; female sex; and prior reaction to a structurally related drug.

Not known: why most carriers of a high-risk HLA allele never react. Whether the allergy label applied in childhood after an amoxicillin rash during a viral illness has any immunological basis — mostly it does not. What triggers Stevens-Johnson syndrome or toxic epidermal necrolysis in the individual. No test reliably predicts delayed severe reactions prospectively except the HLA alleles.

Cure status. Incorrect penicillin allergy labels, roughly 90 to 95 per cent of them: CURABLE by diagnosis. True IgE-mediated allergy: CONTROLLABLE by avoidance. Severe cutaneous adverse

reactions: RELIEF ONLY for the acute event, with absolute avoidance thereafter. Aspirin-exacerbated respiratory disease: CONTROLLABLE.

A direct oral amoxicillin challenge in a low-risk patient, or skin testing followed by challenge, removes the label permanently. The patient leaves without the disease because they never had it. De-labelling is durable, with low relabelling rates after documented de-labelling, provided the record is actually updated.

For true IgE-mediated allergy, drug desensitisation is available where the drug is essential — aspirin in coronary disease, chemotherapy agents, insulin, antibiotics in resistant infection. Desensitisation produces temporary tolerance for the duration of continuous administration and is lost when the drug is stopped.

For severe cutaneous reactions there is no cure and no desensitisation, and re-exposure after Stevens-Johnson syndrome or toxic epidermal necrolysis can be fatal. Acute management is supportive: withdrawal of the drug, burn-unit-level care, fluid and electrolyte management, and eye and mucosal care. Specific immunomodulation with ciclosporin, intravenous immunoglobulin, etanercept or corticosteroids is used and the evidence is weak and conflicting; observational data and small trials suggest ciclosporin and etanercept may reduce mortality, and immunoglobulin meta-analyses are inconsistent.

In aspirin-exacerbated respiratory disease, aspirin desensitisation followed by daily aspirin improves nasal polyposis and asthma outcomes in randomised trials.

Prevention. This entry contains two of the strongest prevention measures in the chapter.

HLA screening before high-risk drugs. *HLA-B*57:01* before abacavir: PREDICT-1 found immunologically confirmed hypersensitivity in 0 per cent of the screened arm against 2.7 per cent unscreened†. STRONG, and it is a randomised trial, which is rare in this field. *HLA-B*15:02* before carbamazepine in Southeast Asian populations, where Taiwan's national programme reduced cases to near zero. STRONG. *HLA-B*58:01* before allopurinol in Han Chinese and related populations. MODERATE. A single HLA test costs tens to hundreds of US dollars (2024), once and for life†.

Penicillin allergy de-labelling programmes, which reduce broad-spectrum antibiotic use, *C. difficile*, meticillin-resistant *S. aureus* and length of stay. STRONG.

Accurate allergy documentation — recording what happened, when, and with what drug, rather than the word allergy. The commonest preventable cause of an incorrect lifelong label. MODERATE, with a large effect at zero cost.

Not labelling a viral exanthem during amoxicillin treatment as penicillin allergy. MODERATE.

Avoiding unnecessary antibiotic prescribing, which reduces exposure and therefore reactions. MODERATE.

Perioperative measures following the NAP6 recommendations on chlorhexidine documentation and neuromuscular blocker choice. MODERATE.

Avoiding re-exposure after a severe cutaneous reaction, and avoiding structurally related drugs, given aromatic anticonvulsant cross-reactivity. STRONG.

Not using a drug with a known high-risk HLA association in a population where that allele is common, when an alternative exists — preferring other urate-lowering or anticonvulsant agents in high-prevalence populations where screening is unavailable. MODERATE.

Treatment. Stop the drug. First, and decisive, particularly in severe cutaneous reactions where time to withdrawal correlates with mortality.

For anaphylaxis, intramuscular adrenaline, off-patent, under one dollar an ampoule (2024)†. Listing status needs checking against the 24th List†.

For urticarial and mild cutaneous reactions, second-generation antihistamines, off-patent at US$2 to US$20 a patient-year at generic or lowest available acquisition cost, 2024†, with short corticosteroid courses for extensive rash. Listing status needs checking against the 24th List†.

Diagnostic evaluation is the main intervention. Direct oral challenge in low-risk penicillin allergy labels is safe in validated risk-stratification pathways such as PEN-FAST, performable by non-allergists, and the

cheapest effective tool here; the cost is clinic time and a dose of amoxicillin. Amoxicillin is a selected medicine on the 24th List, section 6.2.1, Access group antibiotics, core list. Skin prick and intradermal testing for immediate reactions to beta-lactams, neuromuscular blockers and chlorhexidine. Patch testing and delayed intradermal testing for delayed reactions. Serum specific IgE and basophil activation testing, of limited sensitivity and adjunctive. Serum tryptase during an acute reaction.

Drug desensitisation protocols where the drug is essential — aspirin, platinum and taxane chemotherapy, biologics, antibiotics, insulin, antituberculous drugs. Temporary tolerance, and standard practice in specialist centres.

Severe cutaneous adverse reactions: withdrawal, supportive care in a burn or intensive care setting, fluid and electrolyte management, nutritional support, ophthalmology and mucosal care, and infection surveillance without prophylactic antibiotics. Specific immunomodulation is contested. Ciclosporin, with observational data and small trials suggesting reduced mortality, off-patent at US$50 to US$300 a course at generic or lowest available acquisition cost, 2024†; its listing status needs checking against the 24th List†. Etanercept, where a randomised trial against corticosteroids showed faster re-epithelialisation and lower mortality, with biosimilars available at US$1,000 to US$5,000 a course at lowest available acquisition cost, 2024†. Intravenous immunoglobulin, with inconsistent meta-analyses, expensive and plasma-constrained. Corticosteroids, long-standing and contested.

An updated medical record and a patient-held card. The treatment that prevents the next reaction, and the step most often omitted.

Simple means. Asking what actually happened. A rash as a child during a chest infection is not an allergy. A two-minute history de-labels a large share of patients before any test. It costs nothing and has the largest measured effect in this entry.

Direct oral challenge in low-risk patients. One dose of amoxicillin and an hour of observation. No specialist allergy service, no skin testing, no laboratory. This is the instrument that makes de-labelling feasible at scale.

Writing down the reaction, not the word allergy. Free.

Carrying a card naming the drug and the reaction, particularly after a severe cutaneous reaction, where re-exposure can kill.

Stopping the drug early. In Stevens-Johnson syndrome and toxic epidermal necrolysis, time to withdrawal is a measured determinant of mortality, and recognising a spreading painful rash with mucosal involvement as an emergency costs nothing.

Avoiding unnecessary antibiotics — fewer exposures, fewer reactions. Not using a known cross-reacting drug, such as another aromatic anticonvulsant after a reaction to one of them.

Eye care in the acute phase: lubrication and early ophthalmology review prevent the blindness that is the commonest permanent sequela.

Gaps. Nearly all de-labelling and HLA data come from high-income countries, and the global burden of incorrect allergy labels and of severe cutaneous reactions is unmeasured. HLA allele frequencies are population-specific, so screening recommendations do not transfer: *HLA-B*15:02* screening before carbamazepine is cost-effective in Southeast Asia and not in northern Europe, guidelines differ accordingly, and this is a real rather than apparent disagreement. Severe cutaneous reaction incidence figures rest on registry and spontaneous reporting, which under-ascertain. Treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis is genuinely contested: ciclosporin, etanercept, immunoglobulin and corticosteroids all have advocates, the trials are small or observational, and mortality figures for toxic epidermal necrolysis span 25 to 50 per cent between series. No prospective test predicts delayed severe reactions except the HLA alleles, and those have low penetrance. De-labelling durability depends on record systems actually being updated, which is an informatics problem rather than a clinical one, and is poorly measured.

> **Depth.** Starts in: a medicine molecule. Size: 1 nm†; depth −3.48. First complaint: about 24 hours († minutes to weeks; about 1 day); time depth 43.50. One untreated course: about 7 days († days to weeks); depth 45.27.

> **Model reading.** Way of ending: remove. Layer: surround. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Sarcoidosis

What it is. Clumps of immune cells called granulomas form in organs, most often the lungs and lymph nodes. In many people they go away on their own. In others they scar the lung or damage the heart, eyes, skin, nerves or liver. The cause is unknown.

Measured. The variation by ancestry is the central measured finding. Incidence and prevalence per 100,000, by source, setting and period:

Source	Setting and period	Group	Rate
Baughman et al.	US managed care, 2010–2013	Black / White / Hispanic / Asian	Incidence 17.8 / 8.1 / 4.3 / 3.2
Baughman et al.	US managed care, 2009–2013	Black / White	Prevalence 141.4 / 49.8
Rybicki et al.	Detroit HMO, 1990–1994	Black / White	Incidence 35.5 / 10.9
Dumas et al.	Nurses' Health Study II, 1989–2011	Black / White	Incidence 43 / 11
Cozier et al.	Black Women's Health Study, 1995–2007	Black women	Incidence 71
Ungprasert et al. Arkema et al.	Olmsted County MN, 1976–2013 Sweden, 2003–2013	Male / Female, 90% white not reported	Incidence 10.5 / 11 Incidence 11.5
Hillerdal et al.	Uppsala, Sweden, 1966–1980	Male / Female	Incidence 16.5 / 21.7, 19 overall
Coquart et al.	Guadeloupe, 2003–2010	Afro-Caribbean	Incidence 2.3
Duchemann et al.	Greater Paris, 2012	Afro-Caribbean / North African / Other / European	Incidence 16.9 / 9.7 / 6.4 / 2.4

These come from different countries, periods and case definitions and are not directly comparable. Black-to-White incidence ratios in the United States run roughly 2.2:1 in managed care, 3.3:1 in Detroit and 3.9:1 in the Nurses' Health Study II, with a prevalence ratio about 2.8:1†; the literature commonly states as high as 4:1. The highest age-specific rate recorded is 107 per 100,000 in Black women aged 30 to 39 in Detroit†.

Peak onset is at 25 to 45, with a second peak in women over 50 in Scandinavian data. Age-adjusted sarcoidosis mortality in United States NCHS data for 1999 to 2010 was 16 per million in Black patients against 1.3 per million in White patients, about twelve-fold; a 1979–1991 analysis gave a Black-to-White ratio of 14:1. All-cause sarcoidosis mortality rose about 3 per cent a year between 1988 and 2007, with the largest absolute increase in Black women at 10 per million, then Black men at 3 per million, and White men and women at most 1 per million.

Roughly 60 to 70 per cent of patients with acute presentations remit spontaneously within two to three years; roughly 10 to 30 per cent develop chronic progressive disease; and roughly 1 to 5 per cent die of it, mostly from pulmonary fibrosis, and in Japan from cardiac sarcoidosis. Löfgren syndrome — acute presentation with erythema nodosum, bilateral hilar lymphadenopathy, fever and arthralgia — carries a spontaneous remission rate above 90 per cent and is strongly associated with *HLA-DRB1*03*†.

The highest reported rates are in northern Europe and among African-descended populations in the United States and France. The Guadeloupe incidence of 2.3 against the Paris Afro-Caribbean incidence of 16.9 in the same ancestry group is a striking and unexplained environment effect.

Where it starts. The cause is unknown, and that must be stated first. The leading model is an exaggerated Th1/Th17 granulomatous response to one or more poorly cleared antigens in a genetically susceptible person, and no antigen is established.

Candidate antigens, none proven: *Cutibacterium acnes*, the most consistently recovered organism and found in a majority of sarcoid lymph nodes in Japanese studies; *Mycobacterium tuberculosis* catalase-

peroxidase and ESAT-6, to which immune responses are found more often in patients than controls; and inorganic antigens — silica, aluminium, zirconium and beryllium. Chronic beryllium disease is clinically indistinguishable from sarcoidosis and is caused by a defined exposure plus *HLA-DPB1* Glu69, which is the closest thing to a model of sarcoidosis causation.

Measured occupational and environmental associations: the World Trade Center responder cohort showed a markedly raised incidence of sarcoidosis-like granulomatous disease after dust exposure. Agricultural dust, mould, musty odours, metal dust, firefighting and insecticide use show consistent positive associations in the ACCESS case-control study. Silica exposure associates with granulomatous lung disease.

Smoking is inversely associated with sarcoidosis — one of the few diseases where smoking appears protective, consistent across studies and unexplained.

The strongest genetic associations are in the HLA region: *HLA-DRB1*03* with Löfgren syndrome and good prognosis, *HLA-DRB1*15* with chronic disease, *HLA-DQB1*0601* with cardiac and multi-organ disease in Japanese patients. Non-HLA: *BTNL2, ANXA11, RAB23, IL23R, NOTCH4*. Familial relative risk is roughly 5 to 6 in siblings and roughly 4 in parents, from ACCESS and Swedish registry data, and heritability from Swedish twin and family data is roughly 0.4 to 0.7†.

Ancestry alone does not explain it: the Guadeloupe-against-Paris difference in the same population, and the Scandinavian peak, point to environment.

Not known: the cause. Why the same disease remits spontaneously in most and progresses in a minority. Why mortality is twelve-fold higher in Black Americans — whether this reflects disease biology, later presentation, access, or all three, is unresolved and is the most consequential unknown in the entry. Why smoking is protective. Why Afro-Caribbean people in Paris have seven times the incidence of Afro-Caribbean people in Guadeloupe.

Cure status. Acute presentations, including Löfgren syndrome: SELF-LIMITING in roughly 60 to 70 per cent, who remit spontaneously within two to three years, and in over 90 per cent of Löfgren syndrome†. Many patients need no treatment at all, and treating them exposes them to corticosteroid harm for no benefit; observation is an evidence-based management strategy, which is unusual. Progressive disease: CONTROLLABLE — corticosteroids and steroid-sparing agents suppress granulomatous inflammation and preserve organ function without curing, and relapse on withdrawal is reported in roughly one-third to two-thirds depending on organ and duration of treatment. Established fibrosis: RELIEF ONLY — pulmonary fibrosis does not reverse, and lung transplantation is the end-stage option.

Corticosteroids have never been shown to change long-term outcome. This is a genuine and important negative: Cochrane reviews of corticosteroids in pulmonary sarcoidosis find improvement in chest radiograph appearance and some lung function measures over six to 24 months, and no evidence of improved long-term outcome. Treatment is given for symptoms and for threatened organ function, not because it is known to alter the disease course.

Prevention. No established primary prevention. The cause is unknown, and that should be stated plainly.

Reducing occupational dust, silica, metal and mould exposure, supported by the ACCESS case-control associations and the World Trade Center cohort. MODERATE for the association, WEAK as a demonstrated prevention measure, since no intervention study exists.

Beryllium exposure control prevents chronic beryllium disease, the one sarcoidosis-like granulomatous disease with a known cause and an established exposure limit. STRONG — and it prevents beryllium disease rather than sarcoidosis.

Smoking: here the evidence runs the other way, since smoking is inversely associated with sarcoidosis. Nobody recommends smoking, and the finding is reported as an unexplained epidemiological observation rather than as advice. CONTESTED and not actionable.

Prevention of harm from over-treatment, by observation rather than corticosteroids in asymptomatic stage I disease and in Löfgren syndrome. MODERATE, and it prevents iatrogenic harm, which in this disease is substantial.

Prevention of complications: ophthalmological screening at diagnosis and periodically, because ocular sarcoidosis is often asymptomatic and causes blindness; electrocardiography and, where indicated, cardiac imaging, because cardiac sarcoidosis causes sudden death and is the leading cause of sarcoidosis death in Japan; calcium and vitamin D caution, because the disease causes hypercalcaemia through extrarenal 1-alpha-hydroxylation; and bone protection in patients on prolonged corticosteroids. STRONG for each.

Treatment. Observation, for asymptomatic stage I disease, Löfgren syndrome and mild disease. Evidence-based and free.

Oral prednisolone, first-line for symptomatic pulmonary disease and for cardiac, neurological, ocular and renal involvement and hypercalcaemia. It improves radiographic and some functional measures with no demonstrated long-term outcome benefit. Off-patent, at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024†. Harm from prolonged use — diabetes, osteoporosis, weight gain, infection, cataract — is substantial and is the main reason for steroid-sparing agents. Listing status needs checking against the 24th List†.

Methotrexate, the best-evidenced steroid-sparing agent, with randomised and large observational data supporting steroid dose reduction. Off-patent, at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024, plus folic acid and monitoring blood tests†. Methotrexate is a selected medicine on the 24th List, in section 8.2.1 cytotoxic medicines, complementary list, for leukaemias, lymphomas, early stage breast cancer, gestational trophoblastic neoplasia, Langerhans cell histiocytosis and osteosarcoma, and in section 13.4 for disorders of skin differentiation and proliferation, complementary list. Sarcoidosis is not among the listed indications.

Azathioprine, mycophenolate mofetil and leflunomide as second-line steroid-sparing agents, off-patent, with azathioprine at US$50 to US$200 a patient-year at generic or lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

Hydroxychloroquine for cutaneous disease and hypercalcaemia, off-patent at US$30 to US$150 a patient-year at generic or lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

TNF inhibitors — infliximab and adalimumab — for refractory disease including neurosarcoidosis and cardiac sarcoidosis. Randomised evidence for infliximab in pulmonary sarcoidosis shows a modest forced vital capacity improvement. Both have biosimilars widely available, at US$2,000 to US$10,000 a patient-year for a biosimilar at lowest available acquisition cost, 2024, down from originator prices five to twenty times higher†; the biosimilar price collapse is the main access change in this disease in the past decade. On the 24th List, **adalimumab is a selected medicine**, in section 8.1 immunomodulators for non-malignant disease, complementary, in section 13.4, and under medicines for juvenile joint diseases, for axial spondyloarthritis, Crohn disease, rheumatoid arthritis, juvenile idiopathic arthritis and psoriasis. **Infliximab is on the list only as a therapeutic equivalent to adalimumab for those same indications, not as a selected medicine**. Sarcoidosis is not among the listed indications for either.

Inhaled corticosteroids for cough, with little effect on disease.

Antifibrotics in fibrotic sarcoidosis: the INBUILD trial included progressive fibrosing interstitial lung diseases other than idiopathic pulmonary fibrosis, among them sarcoidosis, and showed slowed forced vital capacity decline in the overall population. Sarcoidosis-specific evidence is thin. Pirfenidone is off-patent, nintedanib is not. Listing status needs checking against the 24th List†.

Organ-specific treatment: an implantable defibrillator in cardiac sarcoidosis; and antimicrobial regimens targeting *C. acnes* and mycobacteria, trialled in cutaneous and pulmonary sarcoidosis with some positive results — notable because the drugs are cheap and off-patent, and because they test the infectious hypothesis directly. The evidence is preliminary.

Lung transplantation for end-stage fibrosis.

Efzofitimod, a neuropilin-2 agonist, is in phase 3 for pulmonary sarcoidosis, with the EFZO-FIT trial reporting in 2025. Not approved at the time of writing.

Simple means. Doing nothing, deliberately. For most patients the correct initial management is observation, and it is free. In a disease where 60 to 70 per cent remit spontaneously and corticosteroids have no proven long-term benefit, restraint is the intervention.

An eye examination. Ocular sarcoidosis is often asymptomatic and causes blindness, and a slit-lamp examination at diagnosis is cheap and prevents a major permanent harm.

An electrocardiogram. Cardiac sarcoidosis causes sudden death, and a resting electrocardiogram costs almost nothing and is the entry point to detecting it.

Avoiding vitamin D and calcium supplements unless concentrations are checked. Sarcoid granulomas convert 25-hydroxyvitamin D to the active form, so supplementation can cause hypercalcaemia and kidney stones. A simple means that prevents harm, and one routinely missed because patients on corticosteroids are usually given calcium and vitamin D.

Sun exposure in moderation rather than supplementation, for the same reason, where bone health is a concern — though this interacts with the hypercalcaemia risk and needs monitoring.

Stopping occupational dust exposure where one is identified.

Not smoking. Notwithstanding the inverse association with developing sarcoidosis, smoking worsens every pulmonary outcome once the disease exists.

Pulmonary rehabilitation and graded exercise for fatigue and deconditioning. Fatigue is the most common and most disabling symptom and responds poorly to immunosuppression; exercise programmes show measurable improvement in fatigue and exercise capacity in small trials.

Weight and bone protection during corticosteroid treatment.

Gaps. The incidence and prevalence figures in the table come from different countries, periods and case definitions and are not directly comparable; race was not reported in the Swedish data; and only a few regions outside the United States have been studied at all. The twelve-fold mortality disparity between Black and White Americans is reported consistently and explained nowhere. The Guadeloupe-against-Paris Afro-Caribbean incidence difference in one ancestry group is unexplained and points to an environmental cause that has not been identified. There is no cause, no antigen and no diagnostic test: this remains a diagnosis of exclusion requiring compatible clinical and imaging findings, non-caseating granulomas on biopsy, and exclusion of alternatives — so prevalence figures depend on how hard clinicians look. Corticosteroids have no demonstrated long-term outcome benefit despite being standard treatment for seventy years, which is a genuine evidence gap rather than an interpretive one. The inverse smoking association is unexplained. Lifetime risk is not reported in the literature reviewed. Antimicrobial therapy testing the *C. acnes* and mycobacterial hypothesis uses cheap off-patent drugs and has preliminary positive trials, and has not been definitively tested — an unusual case where the cheap hypothesis is under-investigated.

> **Depth.** Starts in: the granuloma. Size: 200 µm†; depth +7.63. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: about 3.2 years ([B] often disappears by itself; † 2–5 years); depth 49.92.
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> **Model reading.** Way of ending: restore proportion. Layer: reading. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Systemic lupus erythematosus

What it is. The immune system attacks the body’s own cell nuclei. Almost any organ can be affected — skin, joints, kidneys, blood, brain, lungs, heart. It flares and settles, mostly in young women.

Measured. From the global systematic review and modelling study (Tian et al., *Annals of the Rheumatic Diseases*, 2023), the best current global synthesis: pooled incidence 5.14 per 100,000 person-years (range

1.4–15.13), about 0.40 million newly diagnosed people a year; pooled prevalence 43.7 per 100,000 (range 15.87–108.92), about 3.41 million people living with the disease.

By sex: incidence 8.82 per 100,000 person-years in women against 1.53 in men, a ratio of about 5.8:1; prevalence 78.73 against 9.26 per 100,000, a ratio of about 8.5:1†. In adults alone, incidence 7.31 and prevalence 61.08 per 100,000†.

Regionally, incidence is lowest in central Asia at 1.18 and highest in central Europe at 13.74; prevalence is lowest in southern Asia at 15.9 and highest in tropical Latin America at 110.85†. By country, the highest incidence is Poland at 81.84 and the lowest Kazakhstan at 0.57; the highest prevalence the United Arab Emirates at 166.92 and the lowest Argentina at 5.05†. The disease is recorded as more common in high-income countries, which is at least partly ascertainment. **Data are missing for 79.8 per cent of countries**†.

Peak onset is at 15 to 45. Childhood-onset disease is roughly 10 to 20 per cent of cases and is more severe, with more renal involvement†.

In national health-system data, incidence and severity are substantially higher in people of African, Hispanic, South Asian and Indigenous ancestry than in those of European ancestry; United States figures commonly report two- to four-fold higher incidence in Black women than White women, with earlier onset, more lupus nephritis and higher mortality. The global review could not assess ethnicity, because the included studies did not report it.

Standardised mortality ratios run roughly 2 to 3 against the general population in modern cohorts†. Five-year survival has risen from roughly 50 per cent in the 1950s to over 90 per cent now†. Causes of death are bimodal: early deaths from active disease and infection, later deaths from cardiovascular disease. Cardiovascular risk in young women with the disease is raised roughly five- to fifty-fold depending on age band, with the largest relative excess in women in their thirties and forties (Framingham Offspring comparison, Manzi et al.).

Lupus nephritis develops in roughly 30 to 50 per cent of patients, higher in non-European ancestry and in childhood-onset disease, and roughly 10 to 20 per cent of those progress to end-stage kidney disease despite treatment.

Where it starts. Loss of tolerance to nuclear antigens, impaired clearance of apoptotic debris, type I interferon pathway activation, and autoantibody and immune complex deposition with complement activation and tissue injury. The type I interferon signature is present in the majority of patients and is now a drug target.

Twin concordance is roughly 24 to 57 per cent in monozygotic twins against 2 to 5 per cent in dizygotic twins; sibling relative risk is roughly 8 to 29; and heritability is estimated at roughly 0.4 to 0.66†. Over 100 risk loci are identified, individually small except for: complement deficiencies in C1q, C1r/s, C4 and C2, among the strongest single-gene risks, with homozygous C1q deficiency giving a very high lifetime risk; *TREX1*, *DNASE1L3*, *ACP5* and *SAMHD1*, monogenic interferonopathies presenting as early-onset lupus; low copy number of *C4*; *HLA-DRB1*03:01* and *HLA-DRB1*15:01*, with odds ratios roughly 2; and *STAT4*, *IRF5*, *ITGAM*, *BLK*, *TNFSF4*, *TNFAIP3* and *PTPN22*.

X chromosome dose matters: men with Klinefelter syndrome (47,XXY) have a lupus risk roughly fourteen-fold that of 46,XY men, and 47,XXX women roughly 2.5-fold that of 46,XX women (Scofield et al.; Liu et al.). This is direct evidence that X chromosome number, not only hormones, drives the female predominance, and it is one of the cleanest findings explaining the sex ratio.

Established environmental risk factors with effect sizes: cigarette smoking, odds ratio roughly 1.5 for onset and stronger for anti-dsDNA-positive disease†; silica exposure, odds ratio roughly 2 to 4 in occupational studies†; Epstein-Barr virus, where seroconversion is near-universal in patients and viral load is higher, with a strong association and unsettled causal direction; ultraviolet light, which triggers cutaneous and systemic flares through UV-induced apoptosis and interferon induction; oestrogen exposure, with postmenopausal hormone therapy and oral contraceptives associated with modestly increased risk at hazard ratios roughly 1.2 to 1.9 in the Nurses' Health Study†; drug-induced lupus from hydralazine, procainamide, isoniazid, minocycline, TNF inhibitors and checkpoint inhibitors, which resolves on withdrawal and is distinguished by that; and low vitamin D, associated with causality unresolved.

Autoantibodies precede disease by years. Anti-nuclear, anti-Ro, anti-La and anti-dsDNA antibodies are detectable a median of several years before clinical onset in military serum repository studies (Arbuckle et al., *NEJM*, 2003), so there is a long preclinical window.

Not known: what triggers the transition from preclinical autoimmunity to clinical disease. Most people with a positive anti-nuclear antibody never develop lupus — positivity at 1:80 is present in roughly 10 to 15 per cent of healthy people against a prevalence of 0.04 per cent†. Why organ involvement differs so radically between patients. Why ancestry-associated severity differences exist, and how much is genetic rather than social and access-related. Whether the preclinical window can be used for prevention.

Cure status. CONTROLLABLE. No cure exists, and the honest statement has two further parts.

Survival has transformed: five-year survival from roughly 50 per cent in the 1950s to over 90 per cent now, through corticosteroids, antimalarials, immunosuppression and dialysis. The disease is not cured and mortality remains roughly two to three times the general population.

Sustained drug-free remission is achieved in a minority. Definitions vary; roughly 5 to 25 per cent of patients achieve prolonged remission off all treatment in long-term cohorts, and whether that is cure or quiescence is unresolved.

Hydroxychloroquine is the one drug shown to improve survival. Observational cohort data consistently show lower mortality, fewer flares, less renal damage, less thrombosis and better pregnancy outcomes in patients taking it. It is off-patent and costs tens of dollars a year.

CAR-T cell therapy against CD19 has produced drug-free remission in a small number of patients with refractory disease (Erlangen group; first report *NEJM* 2021, subsequent series 2022 to 2024): profound B-cell depletion followed by reconstitution with a naive B-cell repertoire, with patients remaining in drug-free remission for years in the published cohorts. The numbers are very small, tens of patients worldwide, follow-up is short, and the procedure requires lymphodepleting chemotherapy. This is the first credible candidate for cure and it must be reported as preliminary, not established.

Prevention. No established primary prevention. State plainly.

Not smoking, at an odds ratio of about 1.5, so smoking cessation is the clearest modifiable risk factor for onset. MODERATE.

Reducing occupational silica exposure, at an odds ratio of 2 to 4. MODERATE.

Prevention of flares, where the evidence is strong. Hydroxychloroquine continuation: withdrawal roughly doubles to triples flare risk in randomised withdrawal studies (Canadian Hydroxychloroquine Study Group, *NEJM*, 1991). STRONG. Sun protection with clothing, shade and broad-spectrum sunscreen. MODERATE, mechanistically explained with consistent patient-level evidence. Vitamin D repletion in deficient patients, with a modest effect on disease activity in trials. WEAK.

Prevention of the things that kill. Cardiovascular risk management — blood pressure, lipids, smoking, weight. Given that cardiovascular risk is raised five- to fifty-fold in young women, this is arguably the highest-yield prevention in the entry. MODERATE, extrapolated from general-population trials, since disease-specific trial evidence is thin. Infection prevention by vaccination — inactivated influenza, pneumococcal, COVID-19, HPV, recombinant herpes zoster — and *Pneumocystis* prophylaxis with co-trimoxazole in patients on high-dose immunosuppression, since infection is a leading cause of early death. STRONG. Corticosteroid minimisation, since cumulative corticosteroid dose is the single largest driver of irreversible organ damage in damage-index studies. STRONG. Bone protection during corticosteroid use. STRONG. Avoiding oestrogen-containing contraception in antiphospholipid-positive patients. STRONG.

Pregnancy outcomes: hydroxychloroquine continuation, low-dose aspirin, and planning conception during quiescent disease measurably reduce pre-eclampsia, fetal loss and flare. MODERATE.

Prevention of congenital heart block in anti-Ro-positive pregnancy: hydroxychloroquine reduces recurrence in observational and open-label prospective data. MODERATE.

Treatment. Hydroxychloroquine, for essentially all patients, indefinitely. It reduces flares, thrombosis, renal damage and mortality. Off-patent, at US$30 to US$150 a patient-year at generic or lowest available

acquisition cost, 2024†. It requires annual-to-biennial retinal screening because of a cumulative-dose-dependent retinopathy risk, roughly 1 per cent at five years and up to 20 per cent at 20 years at former higher doses, and much lower at 5 mg/kg a day or below†. This is the best-value drug in chapter 04. Listing status needs checking against the 24th List†.

Corticosteroids: prednisolone for flares, pulsed methylprednisolone for severe organ disease. Effective and fast, and cumulative dose drives permanent damage, so the current standard is the lowest effective dose and a defined taper. Off-patent, at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

Immunosuppressive and steroid-sparing agents. Mycophenolate mofetil, first-line for lupus nephritis in most guidelines; the Aspreva Lupus Management Study showed equivalence to cyclophosphamide for induction with less gonadal toxicity. Off-patent, at US$200 to US$1,000 a patient-year at generic or lowest available acquisition cost, 2024†; teratogenic, which is a major practical constraint in young women. Azathioprine for maintenance, and the preferred agent in pregnancy, off-patent at US$50 to US$200 a patient-year at generic or lowest available acquisition cost, 2024†. Cyclophosphamide for severe nephritis and neuropsychiatric disease, where the Euro-Lupus low-dose regimen of 500 mg fortnightly for six doses is as effective as high-dose with much less toxicity; off-patent, at US$50 to US$300 per induction course at generic or lowest available acquisition cost, 2024†, with dose-related gonadal toxicity and bladder cancer risk. Methotrexate for arthritis and skin disease, off-patent at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†; methotrexate is a selected medicine on the 24th List in sections 8.2.1 and 13.4, and lupus is not among the listed indications. The listing status of mycophenolate, azathioprine and cyclophosphamide needs checking against the 24th List†.

Calcineurin inhibitors: tacrolimus, and voclosporin, approved in 2021 for lupus nephritis. In AURORA-1, voclosporin achieved complete renal response at 52 weeks in 41 per cent against 23 per cent on standard therapy†. Voclosporin is patented and priced at roughly US$90,000 to US$110,000 a patient-year on United States list (2024), while generic tacrolimus achieves a similar mechanism at US$300 to US$1,500 a patient-year (2024), and Asian trials of multi-target tacrolimus-based therapy show comparable results. This price gap is notable.

Biologics. Belimumab, an anti-BAFF antibody, was the first drug licensed for lupus in 50 years, in 2011; the BLISS trials showed modest improvement in the SLE Responder Index, roughly 43 to 58 per cent against 34 to 44 per cent on placebo, and BLISS-LN showed renal benefit†. Patented, at US$40,000 to US$60,000 a patient-year at lowest available acquisition cost, 2024†. Anifrolumab, an anti-type-I-interferon-receptor antibody: TULIP-2 gave a BICLA response of 47.8 per cent against 31.5 per cent†. Patented, at US$60,000 to US$90,000 a patient-year at lowest available acquisition cost, 2024†. The listing status of both needs checking against the 24th List†. Rituximab: randomised trials in lupus (EXPLORER) and lupus nephritis (LUNAR) were both negative on their primary endpoints, yet rituximab is widely used off-label for refractory disease on observational grounds — a genuine disagreement between trial and practice. Biosimilar course US$1,500 to US$5,000 at lowest available acquisition cost, 2024†. Rituximab is a selected medicine on the 24th List in sections 5.1.2 and 8.2.2, and lupus is not among the listed indications. Obinutuzumab: the REGENCY trial in 2025 reported improved renal response in lupus nephritis.

Supportive and preventive treatment: antihypertensives with renin-angiotensin blockade in proteinuric nephritis, at US$5 to US$50 a patient-year at generic or lowest available acquisition cost†, with the listing status of ACE inhibitors and angiotensin receptor blockers needing checking against the 24th List†; statins; anticoagulation in antiphospholipid syndrome; SGLT2 inhibitors under study in lupus nephritis; and dialysis and transplantation for end-stage kidney disease, with good graft outcomes.

Simple means. Sun protection. Clothing, a hat, shade, and staying out of midday sun. Free, and ultraviolet light is an established flare trigger with a clean mechanism. For many patients this is the single most effective daily measure available.

Hydroxychloroquine. Not quite no-chain, and off-patent, oral, tens of dollars a year, and the only drug shown to improve survival. In any resource-limited setting this plus prednisolone is the backbone of care.

Not smoking, at an odds ratio of about 1.5 for onset, and it worsens cutaneous disease and cardiovascular risk.

Vaccination with inactivated vaccines, before immunosuppression where possible.

Blood pressure measurement and a urine dipstick. Lupus nephritis is often silent. A dipstick for protein costs cents and is the cheapest way to detect the complication that causes most of the organ failure. In settings without serology, this is the monitoring tool.

Co-trimoxazole prophylaxis during high-dose immunosuppression, at dollars a year, which prevents *Pneumocystis* pneumonia.

Rest and pacing during flares, and recognising fatigue as part of the disease.

Contraception planning: avoiding pregnancy during active disease and during mycophenolate or cyclophosphamide treatment measurably improves outcomes, and it is a conversation rather than a drug.

Dental and skin care, and prompt treatment of infection.

Gaps. Data are missing for 79.8 per cent of countries in the global review, so the regional figures rest on a minority of the world's populations. The global review could not assess ethnicity, because the included studies did not report it — yet ancestry-associated differences in incidence, severity and mortality are among the largest effects in the disease, and this is a major measurement gap. The apparently higher prevalence in high-income countries is confounded by ascertainment. Classification criteria changed across ACR 1997, SLICC 2012 and EULAR/ACR 2019, so incidence and prevalence figures are criteria-dependent and not comparable across eras. Rituximab: negative randomised trials, widespread use — trial and practice disagree. Voclosporin at about US$100,000 a year at lowest available acquisition cost, against generic tacrolimus at under 1,500 with a similar mechanism and no head-to-head trial. No biomarker predicts which patients will develop nephritis or neuropsychiatric disease. CAR-T data come from tens of patients with short follow-up. Whether the long preclinical autoantibody window can be used for prevention is untested. Disease-specific cardiovascular prevention trial evidence is thin, despite cardiovascular disease being a leading cause of death.

> **Depth.** Starts in: the nucleosome (self-antigen). Size: 10 nm†; depth −1.38. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number ([B] alternates between flare and rest).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Sjögren syndrome

What it is. The immune system attacks the glands that make tears and saliva. Eyes and mouth go dry, teeth decay, and most patients are profoundly tired. It can also affect joints, nerves, lungs and kidneys, and it raises the risk of lymphoma.

Measured. Prevalence is between 0.2 and 1.2 per cent of the population, roughly half primary and half secondary to another autoimmune disease, with some broader studies using looser criteria suggesting up to 3 per cent†. United States estimates range from 500,000 to 2 million people depending on criteria used†; the width of that range is the finding. Incidence is roughly three to six cases per 100,000 a year†.

The sex ratio is roughly 10:1 female to male — nine out of ten patients are women, the most skewed sex ratio of any common autoimmune disease — and primary disease in men tends to be more severe. It is the third most common rheumatic autoimmune disorder, after rheumatoid arthritis and lupus. Secondary occurrence is reported in 30 to 50 per cent of people with rheumatoid arthritis and 10 to 25 per cent of people with lupus†. As many as half of all cases may be undiagnosed or unreported.

Peak onset is in the fourth to sixth decades; childhood-onset occurs and often presents with recurrent parotitis.

On the hard outcome, lymphoma, the figures conflict. An increased lymphoma risk of about 15 per cent is quoted in some sources; roughly 5 per cent of patients develop a lymphoid malignancy; and standardised incidence ratios for non-Hodgkin lymphoma in large cohorts are roughly 9 to 19†. These are three different quantities reported as though interchangeable, and only the standardised incidence ratios are comparable between studies. The characteristic tumour is mucosa-associated lymphoid tissue lymphoma of the parotid, and severe cases carry a much higher lymphoma risk than mild or moderate cases.

Measured predictors of lymphoma: persistent parotid enlargement, purpura, low C4, cryoglobulinaemia, monoclonal gammopathy, lymphopenia, high focus score on labial biopsy, and a high EULAR disease activity score. Patients with several of these have lymphoma risk an order of magnitude above those with none.

Overall mortality is close to the general population in patients without systemic features, and raised in those with lymphoma, cryoglobulinaemic vasculitis, interstitial lung disease or pulmonary hypertension.

Where it starts. Lymphocytic infiltration of exocrine glands with formation of ectopic germinal centres, epithelial cell activation, a type I interferon signature, B-cell hyperactivity with autoantibody production against Ro/SSA, La/SSB and rheumatoid factor, and local BAFF overproduction. Established. The B-cell hyperactivity explains both the autoantibodies and the lymphoma risk.

The strongest genetic signals are in the HLA region: the *HLA-DRB1*03:01*, *DQA1*05:01*, *DQB1*02:01* haplotype, with odds ratios roughly 2 to 4†. Non-HLA loci overlap with lupus: *IRF5*, *STAT4*, *IL12A*, *BLK*, *TNIP1*, *CXCR5*. Sibling relative risk is raised and heritability is not well estimated, which is a genuine gap for a disease this common.

The 10:1 sex ratio is unexplained. X chromosome dose effects are reported — Klinefelter syndrome and 47,XXX are over-represented, as in lupus — and X-linked gene dosage including *TLR7* is a leading hypothesis.

Viral triggers have been proposed and none is established: Epstein-Barr virus, HTLV-1 with a clear association in endemic Japanese populations, hepatitis C which causes a Sjögren-like syndrome with cryoglobulinaemia, and coxsackievirus. HTLV-1 and hepatitis C are the only ones with a defined causal claim, and both produce a mimic rather than primary disease.

Drug-induced dryness is a confounder rather than a cause: anticholinergics, antidepressants, antihistamines, diuretics and opioids cause dryness in a large share of older adults and are the commonest reason for a false diagnosis. Other causes of dry eyes and mouth must be excluded: head and neck radiotherapy, hepatitis C, HIV with diffuse infiltrative lymphocytosis syndrome, IgG4-related disease, sarcoidosis, amyloidosis, and graft-versus-host disease.

Not known: the cause. Why the sex ratio is 10:1. Why fatigue — the symptom patients rank as most disabling — correlates poorly with glandular inflammation, autoantibody status or any measured immune parameter, and does not respond to immunosuppression. No treatment has been shown to restore glandular secretion, which is the central therapeutic unknown. Why some patients progress to lymphoma.

Cure status. Glandular disease: RELIEF ONLY — and this is one of the few entries in the chapter where that is the honest answer. Systemic manifestations: CONTROLLABLE, since corticosteroids and immunosuppression control arthritis, vasculitis, interstitial lung disease and renal involvement.

No cure exists, and no treatment is known to restore gland secretion. Management of the dryness is substitution and stimulation of residual function, not repair. Where glandular tissue has been replaced by fibrosis, nothing recovers it.

Secretagogues — pilocarpine, cevimeline — stimulate residual gland function, with a real effect in randomised trials, roughly a doubling of salivary flow in responders, and they do nothing where no functioning tissue remains, and sweating and flushing limit the dose.

Hydroxychloroquine: the JOQUER randomised trial in 2014 found no significant benefit on dryness, pain or fatigue at 24 weeks against placebo. It continues to be prescribed widely for arthralgia and fatigue on the basis of observational data and the lupus analogy, which is a clear case where a negative trial has not changed practice.

B-cell depletion: randomised trials of rituximab (TEARS, TRACTISS) were negative on their primary endpoints for dryness and fatigue, with some benefit on objective glandular measures in subgroups. Rituximab is used for systemic and cryoglobulinaemic disease.

Emerging: ianalumab, an anti-BAFF-receptor antibody with B-cell depleting activity, received Breakthrough Therapy designation in January 2026 and reported positive phase 2 and phase 3 data; telitacicept and dazodalibep are in phase 3. If these replicate, the status of this entry changes. At the time of writing nothing is licensed specifically for Sjögren syndrome anywhere, which is itself a notable fact for a disease affecting up to 1 per cent of the population.

Prevention. No primary prevention. The cause is unknown. State plainly.

Prevention of dental destruction is the highest-yield prevention in this entry. Saliva protects teeth; without it, rampant caries follows. Topical fluoride — high-concentration toothpaste, varnish, trays: STRONG in caries prevention generally, MODERATE in this disease specifically. Frequent professional dental cleaning and review: MODERATE. Avoiding sugar and acidic drinks, and avoiding sipping sweetened drinks for dry mouth relief, which is the commonest avoidable cause of caries in these patients: STRONG mechanistically. Chlorhexidine and xylitol: MODERATE.

Prevention of corneal damage by regular ocular lubrication, punctal occlusion, treating meibomian gland dysfunction, and humidification. MODERATE.

Avoiding drugs that worsen dryness — anticholinergics, tricyclic antidepressants, antihistamines, diuretics. Free, and often the largest single improvement available. MODERATE.

Lymphoma risk stratification and surveillance of patients with the measured risk factors — persistent parotid swelling, purpura, low C4, cryoglobulinaemia. Whether surveillance changes outcome is not established. CONTESTED.

Hydroxychloroquine for prevention of systemic complications: CONTESTED — JOQUER was negative, and cohort data suggest lower lymphoma incidence in treated patients.

In anti-Ro-positive women planning pregnancy, hydroxychloroquine reduces recurrence of congenital heart block in observational and open-label prospective data: MODERATE. Fetal echocardiographic surveillance in anti-Ro-positive pregnancies: MODERATE.

Treatment. Ocular surface management. Preservative-free artificial tears, as often as needed, off-patent, at US$50 to US$400 a patient-year at generic or lowest available acquisition cost, 2024, depending on frequency and whether preservative-free unit doses are used; for many patients this is the single largest out-of-pocket cost. Not listed as such on the EML. Topical ciclosporin 0.05 to 0.1 per cent, which improves tear production modestly in randomised trials, off-patent with generics available, at US$300 to US$1,500 a patient-year at generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†. Lifitegrast and perfluorohexyloctane, patented and more expensive. Punctal plugs, which mechanically occlude tear drainage at a one-off cost of tens of dollars and are among the best value interventions here. Autologous serum eye drops for severe disease, made from the patient's own blood. Moisture chamber spectacles and goggles.

Oral dryness management. Pilocarpine, 5 mg three to four times daily, or cevimeline — muscarinic agonists, with randomised trials showing increased salivary flow and improved subjective dryness. Off-patent, at US$100 to US$600 a patient-year at generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†. Saliva substitutes, gels and sprays, and sugar-free gum. Topical and systemic antifungals for the oral candidiasis that complicates dry mouth: nystatin and fluconazole, off-patent, at dollars a course, with listing status needing checking against the 24th List†.

Vaginal dryness: lubricants and, where appropriate, topical oestrogen.

Musculoskeletal pain: NSAIDs; hydroxychloroquine, widely used although JOQUER was negative; and methotrexate for inflammatory arthritis. Methotrexate is a selected medicine on the 24th List in sections 8.2.1 and 13.4; this indication is not among those listed. The listing status of hydroxychloroquine and of NSAIDs needs checking against the 24th List†.

Systemic disease — vasculitis, interstitial lung disease, renal tubular acidosis, peripheral neuropathy, cytopenias. Corticosteroids, off-patent at US$5 to US$30 a year at generic or lowest available acquisition cost, 2024†; immunosuppressants — azathioprine, mycophenolate, cyclophosphamide — all off-patent, with listing status needing checking against the 24th List†; rituximab for cryoglobulinaemic vasculitis and severe systemic disease, with a biosimilar course at US$1,500 to US$5,000 at lowest available acquisition cost, 2024, though the randomised trials for dryness and fatigue were negative; and intravenous immunoglobulin for severe neuropathy.

Dental care: high-concentration fluoride, frequent cleaning, restorative work. Dental care is the largest unmet and uncovered cost in this disease in most health systems.

Exercise: a 12-week moderate exercise programme showed measurable benefit for fatigue, depression and aerobic capacity. One of the few interventions with a positive trial for fatigue.

Investigational: ianalumab, telitacicept and dazodalibep, in phase 3.

Simple means. Water, sipped frequently; sugar-free gum; xylitol lozenges. These stimulate residual flow and relieve dryness at negligible cost.

Fluoride toothpaste used twice daily and not rinsed out afterwards. The cheapest protection against the rampant caries that is this disease's most destructive everyday consequence.

Not sipping sweetened or acidic drinks for dry mouth. Free, and it prevents the commonest avoidable harm.

Humidifying the bedroom; a bowl of water on a radiator works.

Wrap-around glasses or goggles in wind and air conditioning.

Warm compresses and lid hygiene for meibomian gland dysfunction. A large share of the ocular discomfort in these patients is evaporative rather than aqueous-deficient, and lid hygiene addresses it at no cost.

Stopping anticholinergic and other drying medications where possible. Free, and often the single largest improvement available.

Punctal plugs: a one-off procedure costing tens of dollars that reduces artificial tear use substantially.

Moderate exercise, the one intervention with a positive randomised result for fatigue, which is the symptom patients rate as most disabling and which no drug touches.

Petroleum jelly or lip balm, and nasal saline for nasal dryness.

Gaps. Prevalence estimates span six-fold, 0.2 to 1.2 per cent and up to 3 per cent on loose criteria, and the United States count spans four-fold, 500,000 to 2 million. The reason is criteria: the AECG 2002 and ACR/EULAR 2016 criteria classify different populations, and symptom-based estimates include large numbers of people with drug-induced or age-related dryness. Half of cases may be undiagnosed. Heritability is not well estimated for a disease affecting up to 1 per cent of the population. The 10:1 sex ratio is unexplained. The lymphoma risk figures conflict, with three different quantities reported interchangeably. JOQUER was negative for hydroxychloroquine and it continues to be prescribed; TEARS and TRACTISS were negative for rituximab and it continues to be used. Trial and practice disagree openly. No treatment restores gland function, and no drug is licensed for the condition in most jurisdictions despite its prevalence. Fatigue, the dominant symptom, has no established mechanism and no effective drug. Whether lymphoma surveillance changes outcome is unknown. The pipeline agents may change the cure status of this entry within one to two years.

> **Depth.** Starts in: the Ro/SSA protein. Size: 10 nm†; depth −1.38. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Systemic sclerosis

What it is. Skin and internal organs become thickened and scarred, and small blood vessels narrow and close. Fingers go white and painful in the cold and can ulcerate. The lungs stiffen, the gut slows, and the kidneys or heart can fail. It has the highest mortality of the systemic autoimmune diseases.

Measured. Incidence runs from 3.7 to 43 new cases per million a year across published studies†: United Kingdom and Europe 3.7 to 43, Japan 7.2, Taiwan 10.9, Australia 12.0 to 22.8, the United States 13.9 to 21.0, Buenos Aires 21.2. Prevalence is about 31.0 to 658.6 per million globally, a twenty-fold range†.

The sex ratio is about 3:1 female to male overall, rising to about 8:1 in mid- to late childbearing years†. Incidence is about twice as high among African Americans, with earlier onset and more diffuse disease. Choctaw Native Americans in Oklahoma have the highest reported prevalence in the world, at 469 per 100,000 — a founder effect, and the single most striking ancestry finding in this disease. Peak onset is at ages 30 to 50.

Limited cutaneous disease confines skin involvement to below the elbows and knees, with or without the face, is associated with the CREST features, carries anticentromere antibodies in roughly 80 to 90 per cent of that subset, carries a higher risk of pulmonary arterial hypertension, and has a better overall prognosis. Diffuse cutaneous disease involves skin above the elbows and knees and on the trunk, carries anti-topoisomerase I antibodies in roughly 30 to 40 per cent, carries a higher risk of interstitial lung disease and scleroderma renal crisis, and has a worse prognosis. Anti-RNA polymerase III antibodies associate with rapidly progressive skin disease, renal crisis, and an increased risk of coincident cancer.

Ten-year survival was about 88 per cent in a 2018 study, which gives no separate subtype figures†; earlier cohorts gave 10-year survival around 55 to 70 per cent for diffuse disease†. Survival has improved, principally through ACE inhibitors for renal crisis.

Pulmonary causes — interstitial lung disease and pulmonary arterial hypertension — are now the leading cause of death, having overtaken renal crisis after ACE inhibitors became available; then cardiac, then gastrointestinal. Scleroderma renal crisis mortality fell from roughly 85 per cent at one year before ACE inhibitors to roughly 10 to 25 per cent after† — one of the clearest single-drug mortality effects in rheumatology.

Worse prognosis associates with diffuse disease, internal organ involvement and older age at diagnosis.

Where it starts. Three processes run together: endothelial injury with microvascular obliteration, immune activation with autoantibody production, and fibroblast activation with excess collagen deposition. Which comes first is unresolved; the vascular lesion is generally held to be earliest, and Raynaud phenomenon typically precedes skin change by months to years.

Heritability is low for a disease with such strong autoantibody associations. Monozygotic twin concordance is roughly 4.7 per cent, essentially the same as dizygotic, while antinuclear antibody concordance is high. This is a striking finding: the autoimmunity is heritable, the disease is largely not. Sibling relative risk is roughly 10 to 15 and first-degree relative risk roughly 13 to 15†. HLA associations: *HLA-DRB1*11:04, DPB1*13:01*, *DQB1*. Non-HLA: *STAT4*, *IRF5*, *CD247*, *TNFSF4*, *BANK1*, *IRF8*, *NLRP1*. The Choctaw founder effect maps to a haplotype on chromosome 15 containing *FBN1*.

The established environmental causes are unusually strong for an autoimmune disease. Crystalline silica exposure: odds ratios of roughly 2 to 3 overall and up to 15 to 25 in heavily exposed occupations — mining, stone cutting, sandblasting, engineered stone benchtop fabrication. This is the most firmly established environmental cause of a systemic autoimmune disease. Organic solvents — trichloroethylene, white spirit, aromatic solvents — odds ratios roughly 1.5 to 3†. Vinyl chloride causes a scleroderma-like disease with acro-osteolysis and skin thickening at high occupational exposure. Epoxy resins and welding fumes. Bleomycin causes scleroderma-like skin fibrosis and is the basis of the standard animal model. Toxic epidemics: the Spanish toxic oil syndrome of 1981, from adulterated rapeseed oil, affecting about 20,000 people, and the L-tryptophan eosinophilia-myalgia syndrome of 1989, about 1,500 cases, both produced scleroderma-like illness from a defined ingested contaminant — the clearest proofs that an environmental agent can produce this phenotype. Silicone breast implants have been extensively studied and large cohort studies and meta-analyses have not found an association; it is recorded here because the claim persists.

Cancer association: anti-RNA polymerase III-positive patients have a markedly raised risk of cancer diagnosed within a few years of onset, suggesting a paraneoplastic mechanism in a subset.

Not known: what initiates the disease in the great majority who have no identified exposure. Why monozygotic twin concordance is so low when autoantibody concordance is high. Why some patients get lung fibrosis and others pulmonary hypertension and others renal crisis — the autoantibody subsets predict this statistically but not individually. Why skin fibrosis spontaneously regresses in many patients with diffuse disease after several years, which no treatment reliably achieves.

Cure status. Vascular and inflammatory manifestations: CONTROLLABLE. Established fibrosis: RELIEF ONLY — no treatment reverses it. Autologous stem cell transplantation, where accessible: CONTROLLABLE — durable improvement in skin score, lung function and survival, with an upfront mortality cost; whether to call it a cure is not established.

The one transformative treatment is for renal crisis: ACE inhibitors reduced one-year mortality in scleroderma renal crisis from roughly 85 per cent to roughly 10 to 25 per cent†. That is the single largest mortality effect of any drug in this disease, and captopril and enalapril are off-patent and cost dollars a year. Prophylactic ACE inhibitor use is explicitly not recommended, because observational data suggest it may worsen outcomes when a crisis occurs.

Autologous haematopoietic stem cell transplantation is the only intervention shown to improve long-term survival and to reverse skin fibrosis, and three randomised trials agree. ASTIS, a phase 3 trial of 156 patients published in 2014, had high treatment-related mortality and survival in the transplant group lower than control in the first year, but significantly higher at long-term follow-up, with event-free survival favouring transplant; cardiac disease and smoking predicted lower survival. SCOT, published in *NEJM* in 2018, compared myeloablative autologous transplant with monthly cyclophosphamide: at 54 months the global rank composite score favoured transplant, and event-free survival was 79 per cent against 50 per cent and overall survival 86 per cent against 51 per cent at 72 months, with treatment-related mortality of 3 per cent at 54 months in the transplant arm. ASSIST, a phase 2 trial, also favoured transplant. So this is a time-limited intervention producing durable improvement in skin score, lung function and survival, with an upfront mortality cost. Whether to call it a cure is a judgement; it is the strongest disease-modifying evidence in the entry.

Everything else slows or relieves: immunosuppression reduces skin and lung progression modestly; antifibrotics slow lung function decline; vasodilators relieve Raynaud phenomenon and heal ulcers; proton pump inhibitors and prokinetics manage the gut.

Prevention. This entry has the strongest occupational prevention case of any disease in chapter 04.

Silica exposure control. Odds ratios of 2 to 3 overall and up to 15 to 25 in heavily exposed trades make this the clearest primary prevention target. The engineered stone benchtop industry has produced a recent epidemic of accelerated silicosis and autoimmune disease in Australia, Israel, Spain and the United States, and Australia banned the use, supply and manufacture of engineered stone from 1 July 2024 on those grounds. STRONG for the causal association; the Australian ban is a natural experiment whose preventive effect will be measurable within a decade.

Organic solvent exposure control, for trichloroethylene and white spirit. MODERATE.

Vinyl chloride exposure limits. STRONG for the vinyl chloride disease specifically.

Not smoking: smoking worsens digital vascular disease and predicted lower survival in the ASTIS transplant cohort. MODERATE.

Prevention of the complications is where most of the measurable benefit lies. Blood pressure monitoring for renal crisis, especially in early diffuse disease, anti-RNA polymerase III-positive patients, and anyone on corticosteroids — corticosteroids at prednisolone- equivalent doses above 15 mg a day are an established risk factor for renal crisis. STRONG for avoiding high-dose corticosteroids in early diffuse disease. Annual screening for pulmonary arterial hypertension by echocardiography, pulmonary function with diffusing capacity and NT-proBNP, using the DETECT algorithm, because earlier detection improves outcomes when treatment is started in an earlier functional class. MODERATE. Baseline and serial high-

resolution computed tomography and pulmonary function testing for interstitial lung disease. MODERATE. Keeping warm, with gloves, hand and body warmers, and avoiding cold exposure, for Raynaud phenomenon. MODERATE, at zero cost. Avoiding vasoconstrictors — beta-blockers, triptans, decongestants, ergot derivatives. MODERATE. Smoking cessation for digital ulcers. STRONG mechanistically.

Treatment. Scleroderma renal crisis: ACE inhibitors, immediately and at full dose — captopril or enalapril. Off-patent, at US$5 to US$50 a patient-year at generic or lowest available acquisition cost, 2024†. This is the highest-value drug in this entry by a wide margin, and it is a generic antihypertensive. Enalapril's listing status needs checking against the 24th List†.

Interstitial lung disease. Mycophenolate mofetil, which Scleroderma Lung Study II found equivalent to oral cyclophosphamide with better tolerability and which is now first-line in most guidelines; off-patent, at US$200 to US$1,000 a patient-year (2024)†. Cyclophosphamide, where Scleroderma Lung Study I showed a modest forced vital capacity benefit over placebo that was lost by 24 months; off-patent, at US$50 to US$300 a course (2024)†. Tocilizumab, an anti-IL-6-receptor antibody, where the focuSSced trial missed its primary skin endpoint and showed preservation of forced vital capacity as a key secondary outcome, leading to United States approval in 2021 for slowing lung function decline; biosimilars have been available since 2023 to 2024, at US$5,000 to US$15,000 a patient-year biosimilar, down from originator 25,000 to 40,000. Nintedanib, where the SENSCIS trial gave an annual rate of forced vital capacity decline of 52.4 mL against 93.3 mL with placebo, a 44 per cent relative reduction, and which was approved by the United States Food and Drug Administration on 6 September 2019 for this indication; patented, at US$100,000 to US$130,000 a patient-year on United States list (2024)†. Rituximab, where the Japanese DESIRES randomised data show skin and lung benefit, at a biosimilar course of US$1,500 to US$5,000 (2024)†; rituximab is a selected medicine on the 24th List in sections 5.1.2 and 8.2.2, and this indication is not among those listed. Autologous transplant, reserved for rapidly progressive diffuse disease without advanced organ damage. The listing status of mycophenolate, cyclophosphamide, tocilizumab and nintedanib needs checking against the 24th List†.

Pulmonary arterial hypertension. **Neither sildenafil nor bosentan is on the 24th List at all, for any indication: a live query of the electronic Model List returns zero recommendations, zero medicines and zero therapeutic equivalents for each**. Phosphodiesterase-5 inhibitors — sildenafil, tadalafil — are off-patent, with generic sildenafil at US$100 to US$600 a patient-year at lowest available acquisition cost, 2024†. Endothelin receptor antagonists — bosentan, ambrisentan, macitentan — are off-patent for bosentan and ambrisentan, at US$3,000 to US$30,000 a patient-year at generic or lowest available acquisition cost, 2024†. Prostacyclin analogues — epoprostenol, treprostinil, iloprost — and riociguat and selexipag are mostly patented, at US$50,000 to US$200,000 a patient-year at lowest available acquisition cost, 2024†. Combination therapy is standard.

Raynaud phenomenon and digital ulcers. Calcium channel blockers — nifedipine, amlodipine — first-line, off-patent, at US$5 to US$40 a patient-year at generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†. Phosphodiesterase-5 inhibitors, with generic sildenafil as above. Topical nitrates; intravenous iloprost for critical ischaemia; bosentan, which reduces new digital ulcers in RAPIDS-1 and RAPIDS-2 without healing existing ones. Botulinum toxin injection and digital sympathectomy for refractory ischaemia. Low-dose aspirin and statins are commonly used and the evidence is weak.

Gastrointestinal: proton pump inhibitors at high dose for reflux, with omeprazole off-patent at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024† and listing status needing checking against the 24th List†; prokinetics; rotating antibiotics for small intestinal bacterial overgrowth; octreotide for pseudo-obstruction; and enteral or parenteral nutrition for malabsorption.

Skin: methotrexate, where two randomised trials show modest skin score benefit in early diffuse disease, off-patent at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†, a selected medicine on the 24th List in sections 8.2.1 and 13.4 and not listed for this indication; mycophenolate; emollients; and physiotherapy and stretching for contractures.

Calcinosis: no effective treatment, with surgical removal for symptomatic lesions.

What should be avoided: prophylactic ACE inhibitors, which may worsen renal crisis outcome; high-dose corticosteroids in early diffuse disease, for renal crisis risk; and D-penicillamine, where a randomised trial showed no benefit of high over low dose.

Simple means. Keeping warm. Gloves, mittens over gloves, hats, layered clothing, a warm core temperature, chemical or reusable hand warmers, heated gloves. For Raynaud phenomenon, which affects nearly every patient and causes the digital ulcers and amputations, this is the first-line intervention and it costs almost nothing. Keeping the trunk warm matters as much as the hands, because the vasoconstriction is centrally mediated.

Stopping smoking. Digital vascular disease and survival both respond.

A blood pressure cuff at home. Scleroderma renal crisis presents with abrupt severe hypertension, is reversible with an ACE inhibitor started early, and is fatal if missed. Teaching a patient with early diffuse disease to check their own blood pressure weekly, and to present urgently if it rises, is the highest-yield free intervention in this entry.

ACE inhibitor availability. Generic enalapril or captopril, dollars a year, against a one-year mortality in renal crisis of roughly 85 per cent falling to 10 to 25 per cent.

Raising the head of the bed, eating smaller meals, not lying down after eating, avoiding late meals. Effective for the reflux that affects nearly all patients.

Hand exercises and stretching, and face stretching exercises. These prevent the contractures and microstomia that cause most of the functional disability. No equipment.

Emollients and avoiding soap, for the dry, taut skin.

Prompt attention to any finger wound. Digital ulcers in this disease become infected and lead to amputation, and early simple wound care prevents it.

Avoiding beta-blockers, decongestants and triptans.

Dental care: microstomia makes dental access progressively harder, so early and regular care prevents later problems that cannot be treated.

Avoiding occupational silica and solvent exposure, which is the primary prevention, and is regulatory rather than individual.

Gaps. Incidence spans 3.7 to 43 per million and prevalence 31 to 659 per million — an order of magnitude in each — because case definition, ascertainment method and classification criteria differ; the 2013 ACR/EULAR criteria classify more patients, including earlier disease, than the 1980 ACR criteria, so figures are not comparable across eras. Survival figures come from referral-centre cohorts with ascertainment weighted to severe disease, so the 2018 10-year survival of 88 per cent is not directly comparable with older figures of 55 to 70 per cent, and part of the apparent improvement is earlier and milder case capture. The 2018 study gives no separate figures by subtype, which is the clinically decisive split. Monozygotic twin concordance of about 4.7 per cent against a sibling relative risk of 10 to 15 and high autoantibody concordance is an unexplained and important discrepancy. Nearly all prevalence data come from high-income countries, and the Choctaw figure of 469 per 100,000 shows how much founder effects can matter and how little is known about most populations. The transplant trials used different conditioning regimens, different endpoints and different severities, and all excluded patients with significant cardiac disease, so the survival benefit applies to a selected population and the early mortality cost is real. No treatment reverses established fibrosis. Why skin fibrosis regresses spontaneously in many patients after several years is unknown, and it confounds the interpretation of every skin-score trial. Nintedanib at US$100,000 to US$130,000 a patient-year on United States list (2024) produces a 44 per cent relative reduction in forced vital capacity decline; mycophenolate at US$200 to US$1,000 a patient-year, at generic or lowest available acquisition cost, produces lung benefit. There is no head-to-head trial and no cost-effectiveness consensus.

> **Depth.** Starts in: topoisomerase (self-antigen). Size: 10 nm†; depth −1.38. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: no number († lifelong).

> **Model reading.** Way of ending: restore proportion. Layer: reading. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

The vasculitides

What it is. Inflammation of blood vessel walls. Which vessels are affected determines the disease: the largest arteries in giant cell arteritis and Takayasu arteritis, medium arteries in polyarteritis nodosa and Kawasaki disease, small vessels in the ANCA-associated and IgA vasculitides. Untreated, several of them cause blindness, kidney failure or death within months.

Measured. Grouped by vessel size, with incidence per million per year unless stated.

Large vessel. Giant cell arteritis is the commonest primary vasculitis in people over 50, with incidence of 150 to 300 per million a year in people over 50 in northern Europe — Scandinavia highest at roughly 220 to 290 — falling to roughly 10 to 70 per million over 50 in southern Europe and much lower in Asian and African populations†. It is rare before age 50, with mean age at diagnosis roughly 75 and a female-to-male ratio of roughly 2 to 3:1†. Permanent visual loss occurs in roughly 10 to 20 per cent of patients and is almost entirely preventable by prompt corticosteroids, which makes it one of the few true medical emergencies in rheumatology. Polymyalgia rheumatica, closely related, has an incidence of roughly 500 to 1,000 per million a year over 50 in northern Europe; roughly 15 to 20 per cent of those patients have giant cell arteritis and roughly 40 to 60 per cent of giant cell arteritis patients have polymyalgia features†. Takayasu arteritis has an incidence of roughly one to three per million a year in Europe and North America and higher in Japan, India, Turkey and Mexico, roughly 15 to 40 per million in some Japanese and Indian series, with onset usually under 40 and a female-to-male ratio of roughly 8 to 9:1†.

Medium vessel. Kawasaki disease is the commonest vasculitis of childhood. Incidence in Japan is the highest in the world at roughly 3,000 to 3,700 per 100,000 children under five a year — roughly 1 in 30 Japanese children by age five at current rates — against roughly 20 to 25 per 100,000 under five in the United States and Europe†. Peak age is six months to five years. Coronary artery aneurysms develop in roughly 25 per cent of untreated children and roughly 3 to 5 per cent of those treated with intravenous immunoglobulin within 10 days†, a reduction of roughly 80 per cent and the most clear-cut treatment effect in paediatric vasculitis. Polyarteritis nodosa now has an incidence of roughly zero to three per million a year in Europe, having fallen substantially with hepatitis B vaccination: hepatitis B-associated disease was historically a large share of cases and has nearly disappeared where vaccination is universal. This is a measured, vaccine-driven reduction in an autoimmune disease.

Small vessel, ANCA-associated. Combined incidence is roughly 13 to 33 per million a year in Europe, with prevalence roughly 200 to 420 per million†. Granulomatosis with polyangiitis is more common in northern Europe and PR3-ANCA predominant; microscopic polyangiitis is more common in southern Europe and Japan and MPO-ANCA predominant, and the north-south gradient within Europe is consistent and unexplained. Eosinophilic granulomatosis with polyangiitis has an incidence of roughly one to three per million a year and always occurs with asthma and eosinophilia. Peak onset is at 60 to 75, with a roughly equal sex ratio. Untreated generalised disease has roughly 80 per cent one-year mortality; with treatment, five-year survival is roughly 75 to 85 per cent and standardised mortality ratios remain roughly 2 to 3†. Deaths in the first year come from active vasculitis and from treatment-caused infection in roughly equal measure. End-stage kidney disease occurs in roughly 20 to 25 per cent at five years, and relapse in roughly 30 to 50 per cent within five years, higher in PR3-ANCA disease and in granulomatosis with polyangiitis†.

Small vessel, immune complex. IgA vasculitis is the commonest childhood vasculitis after Kawasaki disease, with incidence roughly 100 to 270 per million children a year and peak age four to seven†. It is self-limiting in roughly 95 per cent of children, with nephritis in roughly 20 to 40 per cent, of whom roughly 1 to 7 per cent progress to chronic kidney disease†. Adult-onset disease is less common and more often renal and severe. Cryoglobulinaemic vasculitis was historically dominated by hepatitis C, and its incidence has fallen markedly where direct-acting antiviral treatment is available — another measured, treatment-driven reduction. Anti-glomerular basement membrane disease runs at roughly 0.5 to 1.8 per million a year†.

Behçet disease, a variable vessel vasculitis, has a prevalence along the historic Silk Road of roughly 20 to 420 per 100,000, highest in Turkey at roughly 80 to 420, against roughly 0.3 to 5 per 100,000 in northern Europe and the United States† — one of the steepest geographic gradients of any disease in this chapter.

Where it starts. The established infectious and environmental causes are unusual in autoimmunity and important because they are preventable. Hepatitis B and polyarteritis nodosa: causal, and the disease has nearly disappeared where vaccination is universal. Hepatitis C and cryoglobulinaemic vasculitis: causal, and the vasculitis resolves in the majority after viral cure with direct-acting antivirals. Silica exposure and ANCA-associated vasculitis: odds ratios roughly 2 to 4†. Drug-induced ANCA vasculitis from propylthiouracil, hydralazine, levamisole-adulterated cocaine, minocycline and allopurinol, which resolves on withdrawal in many cases; levamisole-adulterated cocaine produces a characteristic retiform purpura with dual ANCA positivity. *Staphylococcus aureus* nasal carriage and relapse of granulomatosis with polyangiitis: carriage roughly doubles to triples relapse risk, and co-trimoxazole reduces relapses. IgA vasculitis follows upper respiratory infection in roughly half of children, commonly streptococcal. Kawasaki disease has a strongly suspected infectious trigger, with seasonal and epidemic clustering and wind-borne transmission hypotheses, and no agent identified; the 2020–2021 emergence of multisystem inflammatory syndrome in children after SARS-CoV-2 is the clearest demonstration that a defined infection can produce a Kawasaki-like vasculitis.

Genetics. In ANCA-associated vasculitis, the genome-wide association study by Lyons and colleagues (*NEJM*, 2012) showed that the genetic associations follow the ANCA serotype rather than the clinical diagnosis — *HLA-DP*, *SERPINA1* and *PRTN3* with PR3-ANCA, *HLA-DQ* with MPO-ANCA. This finding reorganised how the diseases are classified. Giant cell arteritis: *HLA-DRB1*04*, odds ratio roughly 2 to 3†. Behçet disease: *HLA-B*51*, odds ratio roughly 5 to 6, which explains a large part of the Silk Road distribution, with *IL23R*, *IL10* and *ERAP1* contributing†. Kawasaki disease: *ITPKC*, *CASP3*, *FCGR2A*, *BLK*; siblings of affected children have roughly a ten-fold increased risk, and Japanese ancestry carries high risk even in children born outside Japan, which separates genetic from environmental contribution. Takayasu arteritis: *HLA-B*52*, odds ratio roughly 3†. Heritability is not well estimated for most of these diseases, and familial clustering is modest except in Kawasaki and Behçet disease.

Monogenic vasculitis mimics matter because they change treatment entirely: deficiency of adenosine deaminase 2, a recessive cause of childhood polyarteritis-nodosa-like disease and stroke, treatable with TNF inhibitors; haploinsufficiency of A20; STING-associated vasculopathy; and VEXAS syndrome, from a somatic *UBA1* mutation in older men, described in 2020.

Not known: the cause of giant cell arteritis, Takayasu arteritis and Kawasaki disease. Why ANCA-associated vasculitis has a north-south gradient within Europe. Why relapse occurs in 30 to 50 per cent and what predicts it beyond ANCA serotype. Whether ANCA causes the disease or marks it — though the neonatal transfer of MPO-ANCA causing pulmonary-renal disease in an infant, and animal transfer models, argue strongly for causation in MPO-ANCA disease.

Cure status. The range within this entry is the widest in the chapter.

IgA vasculitis in children: SELF-LIMITING, with roughly 95 per cent resolving. Treatment is supportive; corticosteroids shorten abdominal pain but do not prevent nephritis, and randomised trials and a Cochrane review agree, which is a clear and frequently ignored negative finding.

Kawasaki disease, febrile illness: SELF-LIMITING. Coronary aneurysm risk, with immunoglobulin within 10 days of fever onset: CURABLE. The fever resolves on its own. The aneurysms do not, and they are what kills. Immunoglobulin prevents them. Intravenous immunoglobulin at 2 g/kg within 10 days of fever onset reduces coronary aneurysm incidence from roughly 25 per cent in untreated children to roughly 3 to 5 per cent in treated children†, a reduction of roughly 80 per cent. About 3 to 5 in every 100 treated children still develop an aneurysm†. This is one of the cleanest prevention-of-permanent-damage effects in medicine.

Hepatitis B-associated polyarteritis nodosa and hepatitis C-associated cryoglobulinaemic vasculitis: CURABLE by treating the virus. Direct-acting antivirals cure hepatitis C in over 95 per cent of patients and the vasculitis remits in the majority. WHO’s own hepatitis C fact sheet of 28 July 2026 gives the cure rate

as more than 95 per cent with direct-acting antivirals in Key Facts, while the body says only “most persons” and “nearly all patients” without a percentage.

Drug-induced ANCA vasculitis: CURABLE by stopping the drug in many cases.

Giant cell arteritis: CONTROLLABLE, and the visual loss is preventable. Corticosteroids started on clinical suspicion, before biopsy, prevent blindness. Most patients can eventually stop treatment — roughly half to three-quarters achieve lasting remission off corticosteroids after one to two years, though relapse during taper is common. Tocilizumab roughly quadruples sustained corticosteroid-free remission, 56 per cent against 14 per cent at 52 weeks in the GiACTA trial, and halves cumulative corticosteroid dose.

ANCA-associated vasculitis: CONTROLLABLE, with remission in the great majority and relapse in 30 to 50 per cent. Untreated one-year mortality is roughly 80 per cent and treated five-year survival 75 to 85 per cent†. This is one of the largest treatment effects on survival of any disease in this chapter, and the drugs that achieve it — cyclophosphamide and corticosteroids — are off-patent and cost hundreds of dollars.

Takayasu arteritis and Behçet disease: CONTROLLABLE.

Anti-glomerular basement membrane disease: CONTROLLABLE if caught early; once dialysis-dependent with extensive crescents, renal recovery is unlikely, so RELIEF ONLY at that point.

Prevention. This entry contains two of the clearest preventions in the whole chapter.

Hepatitis B vaccination has nearly eliminated hepatitis B-associated polyarteritis nodosa where coverage is universal. STRONG — a vaccine that prevents an autoimmune vasculitis, demonstrated by national before-and-after incidence data.

Hepatitis C treatment with direct-acting antivirals prevents and reverses cryoglobulinaemic vasculitis. STRONG.

Prompt corticosteroids on clinical suspicion of giant cell arteritis, before temporal artery biopsy, prevents blindness. Visual loss is irreversible and occurs in 10 to 20 per cent, and once it has occurred nothing restores sight. The prevention is a dose of prednisolone and it costs cents. STRONG — no trial exists and none is possible; the evidence is observational and universally accepted.

Intravenous immunoglobulin within 10 days in Kawasaki disease prevents coronary aneurysms, from 25 per cent to 3 to 5 per cent. STRONG.

Co-trimoxazole in granulomatosis with polyangiitis reduces relapse: a randomised trial found relapse-free survival at 24 months of 82 per cent against 60 per cent with placebo (Stegeman et al., *NEJM*, 1996). It also prevents *Pneumocystis* pneumonia, the commonest treatment-related infection death. Off-patent, at dollars a year; listing status needs checking against the 24th List†. MODERATE.

Silica exposure control. MODERATE.

Avoiding propylthiouracil, hydralazine and levamisole-adulterated cocaine, and recognising drug-induced disease. MODERATE.

Prevention of treatment harm is the largest avoidable burden in these diseases. Reduced-dose corticosteroid regimens: the PEXIVAS trial found a reduced-dose glucocorticoid regimen non-inferior for death or end-stage kidney disease, with significantly fewer serious infections in the first year. STRONG. *Pneumocystis* prophylaxis with co-trimoxazole during induction. STRONG. Avoiding cumulative cyclophosphamide above roughly 25 to 36 g, since bladder cancer and infertility risk are dose-related, and using rituximab instead in young patients and in relapsing disease. STRONG. Bone protection, vaccination and cardiovascular risk management. STRONG.

PEXIVAS also found that plasma exchange did not reduce death or end-stage kidney disease in severe ANCA-associated vasculitis — a negative finding that changed practice and removed an expensive, resource-intensive intervention from routine use.

Treatment.

Giant cell arteritis. Prednisolone 40 to 60 mg a day, started immediately on suspicion, with 500 to 1,000 mg intravenous methylprednisolone for visual involvement. Off-patent, at US$5 to US$30 a patient-year at

generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†. Tocilizumab, with sustained corticosteroid-free remission of 56 per cent against 14 per cent in GiACTA; biosimilars since 2023 to 2024, at US$5,000 to US$15,000 a patient-year biosimilar (2024)†; listing status needs checking against the 24th List†. Methotrexate, with a modest corticosteroid-sparing effect in meta-analysis, off-patent at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†; a selected medicine on the 24th List in sections 8.2.1 and 13.4, and not listed for this indication. Low-dose aspirin, where observational data suggest reduced ischaemic events and the evidence is contested.

Kawasaki disease. Intravenous immunoglobulin 2 g/kg as a single infusion, with aspirin, within 10 days. Plasma-derived and supply-constrained, at US$2,000 to US$10,000 a child at lowest available acquisition cost, 2024† — and it prevents a lifetime of coronary disease. Normal immunoglobulin's listing status needs checking against the 24th List†. Aspirin, high dose during the acute phase then low dose, off-patent and costing cents; listing status needs checking against the 24th List†. Corticosteroids added to immunoglobulin in high-risk children reduced coronary abnormalities in the Japanese RAISE trial; infliximab and ciclosporin are used for immunoglobulin-resistant disease. Infliximab is on the 24th List only as a therapeutic equivalent to adalimumab, for axial spondyloarthritis, Crohn disease, rheumatoid arthritis, juvenile idiopathic arthritis and psoriasis, and not as a selected medicine; Kawasaki disease is not among those indications.

ANCA-associated vasculitis. Induction with rituximab or cyclophosphamide plus corticosteroids. Rituximab, which RAVE and RITUXVAS found non-inferior to cyclophosphamide for induction and superior in relapsing disease, at a biosimilar induction course of US$1,500 to US$5,000 (2024)†; rituximab is a selected medicine on the 24th List in section 5.1.2, for multiple sclerosis, and section 8.2.2, for Burkitt lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma, both complementary list — ANCA-associated vasculitis is not among the listed indications. Cyclophosphamide, orally or by the CYCLOPS pulsed intravenous regimen with less cumulative dose and equivalent remission, off-patent at US$50 to US$300 a course (2024)†; listing status needs checking against the 24th List†. Reduced-dose corticosteroids on the PEXIVAS regimen, off-patent. Avacopan, an oral C5a receptor antagonist, where the ADVOCATE trial gave sustained remission at 52 weeks of 65.7 per cent against 54.9 per cent on prednisone taper, with less glucocorticoid toxicity; approved in the United States in 2021 and the European Union in 2022, patented, at US$150,000 to US$200,000 a patient-year on United States list (2024)†. The mechanism — replacing corticosteroids rather than adding to them — is the significant part. EML status needs checking against the 24th List†. Plasma exchange: PEXIVAS found no reduction in death or end-stage kidney disease, and it is retained for anti-glomerular basement membrane disease and for diffuse alveolar haemorrhage on weaker grounds.

Maintenance with rituximab, which MAINRITSAN found superior to azathioprine, or azathioprine or methotrexate or mycophenolate, for at least two years and often longer in PR3-ANCA disease. All except rituximab are off-patent and cost US$50 to US$1,000 a patient-year at generic or lowest available acquisition cost, 2024†. That range excludes rituximab, for which this material gives no price; another dossier in this project gives rituximab biosimilars at thousands of US dollars a patient-year as the compiler's own estimate, with no source consulted, so it is not printed here as a figure. The discrepancy between the two treatments of one drug is recorded and unresolved.

Co-trimoxazole for relapse reduction and *Pneumocystis* prophylaxis, off-patent at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†.

Mepolizumab, an anti-IL-5 antibody, for eosinophilic granulomatosis with polyangiitis, where the MIRRA trial showed more weeks in remission and corticosteroid reduction; benralizumab was non-inferior to mepolizumab in MANDARA in 2024. Patented, at US$30,000 to US$50,000 a patient-year at lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

Dialysis and transplantation for end-stage kidney disease, where graft outcomes are good and recurrence in the graft is uncommon.

Takayasu arteritis and Behçet disease. Corticosteroids plus methotrexate, azathioprine or mycophenolate; TNF inhibitors and tocilizumab for refractory Takayasu arteritis; colchicine for Behçet mucocutaneous disease, off-patent at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024† with listing status needing checking against the 24th List†; azathioprine and ciclosporin for ocular Behçet disease; infliximab or adalimumab for refractory uveitis and for gastrointestinal and neurological Behçet disease — adalimumab is a selected medicine on the 24th List and infliximab a therapeutic equivalent to it, and Behçet disease is not among the listed indications for either; and apremilast for oral ulcers. Vascular intervention and stenting for Takayasu stenoses, ideally during quiescent disease.

IgA vasculitis. Supportive care, hydration and analgesia. Corticosteroids shorten abdominal pain but do not prevent nephritis — Cochrane review and randomised trials agree. Immunosuppression only for established significant nephritis.

Simple means. Hepatitis B vaccination. It prevents hepatitis B-associated polyarteritis nodosa, and it is part of routine infant immunisation almost everywhere, at cents a dose. This is a simple means that is the prevention of an autoimmune disease.

Prednisolone tablets, immediately, on clinical suspicion of giant cell arteritis. New headache with scalp tenderness, jaw claudication or visual symptoms in a person over 50, with a raised erythrocyte sedimentation rate or C-reactive protein, should be treated before confirmation. Prednisolone costs cents and prevents permanent blindness. No investigation is needed to start.

Co-trimoxazole, at dollars a year, which reduces relapse in granulomatosis with polyangiitis — 82 per cent against 60 per cent relapse-free at 24 months — and prevents *Pneumocystis* pneumonia.

Colchicine for Behçet mouth and genital ulcers. Tens of dollars a year, oral, ancient, and effective.

A urine dipstick. In ANCA-associated vasculitis and IgA vasculitis, renal involvement is silent until it is advanced. A dipstick for blood and protein costs cents and is the whole monitoring strategy where laboratory access is limited. In children with IgA vasculitis, weekly then monthly dipsticks for six to 12 months is the standard follow-up and needs nothing else.

Measuring blood pressure, because renal vasculitis presents with hypertension.

Not smoking, and avoiding occupational silica.

Recognising the drug causes — propylthiouracil, hydralazine, levamisole-adulterated cocaine — and stopping them. Free, and sometimes curative.

Vaccination before immunosuppression, and treating infection promptly. In ANCA-associated vasculitis, infection kills as many people in the first year as the vasculitis does.

Not giving corticosteroids to prevent nephritis in childhood IgA vasculitis. A simple means of avoiding harm, supported by trials, and routinely ignored.

Gaps. Incidence figures for every one of these diseases come almost entirely from northern Europe, North America, Japan and a few other countries. Most of the world is unmeasured, and the apparent geographic gradients — giant cell arteritis and ANCA disease north-south, Behçet along the Silk Road, Kawasaki in Japan — conflate real biology with ascertainment. Nomenclature and classification changed, in the Chapel Hill 2012 revised nomenclature and the 2022 ACR/EULAR classification criteria, so figures across eras are not comparable; and the Lyons finding that genetics follow ANCA serotype rather than clinical diagnosis implies the clinical categories themselves may be the wrong unit of measurement. Heritability is not well estimated for most of these diseases. No cause is identified for giant cell arteritis, Takayasu arteritis or Kawasaki disease, despite Kawasaki's epidemic and seasonal behaviour pointing unmistakably at an environmental trigger. Corticosteroids in childhood IgA vasculitis: trials say they do not prevent nephritis, and they continue to be given. Plasma exchange in ANCA-associated vasculitis: PEXIVAS negative, and it is still used for alveolar haemorrhage on weak grounds. Avacopan at US$150,000 to US$200,000 a patient-year on United States list (2024) against reduced-dose prednisolone at five to 30: the trial showed a modest difference in sustained remission and a real difference in glucocorticoid toxicity, and there is no cost-effectiveness consensus and no head-to-head against the PEXIVAS reduced-dose regimen alone. What predicts relapse beyond ANCA serotype is unknown, so maintenance duration is decided empirically.

> **Depth.** A group of illnesses. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. The book names an early stratum. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Antiphospholipid syndrome

What it is. Antibodies against phospholipid-binding proteins make the blood clot abnormally. Clots form in veins, arteries or the placenta. It causes strokes in young people, deep vein thrombosis, and repeated miscarriage.

Measured. Incidence is roughly one to two per 100,000 a year and prevalence roughly 40 to 50 per 100,000 in the best-studied populations; in Olmsted County, Minnesota, Duarte-García and colleagues in 2019 gave incidence 2.1 per 100,000 a year and prevalence 50 per 100,000.

Antiphospholipid antibodies are present at low titre in roughly 1 to 5 per cent of healthy people, rising with age, and most of those people never have a clotting event. This is the central measurement problem: antibody positivity is common and the syndrome is rare.

Among people with clinical events: roughly 13 to 15 per cent of strokes in people under 50 are associated with antiphospholipid antibodies; roughly 9 to 10 per cent of deep vein thrombosis; roughly 6 per cent of pregnancy morbidity; and roughly 10 to 15 per cent of women with recurrent miscarriage†.

Female predominance is roughly 3.5 to 5:1 for primary disease, with onset in the thirties and forties; in one series of 1,000 patients, about 12.7 per cent were diagnosed after age 50†. Antiphospholipid antibodies are present in roughly 30 to 40 per cent of lupus patients, and roughly 10 to 15 per cent of lupus patients develop the syndrome†.

The risk of a first thrombotic event in asymptomatic antibody-positive people is roughly zero to 5 per cent a year, concentrated in those with high-risk antibody profiles. Recurrence without anticoagulation after a first event is roughly 10 to 30 per cent a year in the first year, which is why indefinite anticoagulation is standard.

Catastrophic antiphospholipid syndrome affects roughly 1 per cent of patients, with multi-organ thrombosis over days to weeks and mortality roughly 30 to 50 per cent even with treatment†.

Untreated, live birth rates in women with obstetric disease are roughly 10 to 30 per cent; with low-dose aspirin plus heparin, roughly 70 to 80 per cent†.

Where it starts. Autoantibodies against beta-2 glycoprotein I, the principal antigen, prothrombin, and phospholipid-protein complexes. These activate endothelium, platelets, monocytes and complement, inhibit natural anticoagulants and fibrinolysis, and in pregnancy impair trophoblast invasion. Complement activation is required in animal models, which is why complement inhibition is being tried in catastrophic disease.

The antibodies are necessary but not sufficient: a second hit — infection, surgery, immobilisation, oestrogen, pregnancy, smoking — typically precipitates the event. This is established and is the basis of perioperative and peripartum prophylaxis.

The risk stratification by antibody is firm. Lupus anticoagulant has the closest association with clotting and is the single strongest predictor. Anti-beta-2 glycoprotein I antibodies are more strongly linked to thrombosis than anti-prothrombin antibodies. Anticardiolipin antibodies at moderate to high titre are associated with thrombosis while low titres largely are not. Having both lupus anticoagulant and moderate-to-high anticardiolipin confers greater risk than either alone. Triple positivity, moderate-to-high titres and IgG isotype each raise the likelihood of future clots and pregnancy complications, and triple-positive patients have the highest recurrence rates and are the group in which direct oral anticoagulants fail. Persistence on repeat testing at least 12 weeks apart is required, because transient antibodies after infection are common and not associated with thrombosis.

Oestrogen-based contraceptives significantly increase clot risk in people with the syndrome — established and clinically decisive.

The most common manifestations are lower-extremity deep vein thrombosis on the venous side and stroke on the arterial side.

HLA associations exist, with *HLA-DRB1*04, DRB1*07* and *DQB1* linked to antibody production, and there is no strong monogenic contribution. Heritability is not well estimated. Familial antiphospholipid antibodies occur.

Infectious triggers of transient antibodies include syphilis, the original association, hepatitis C, HIV, parvovirus B19, cytomegalovirus and COVID-19. These are mostly not thrombogenic, which is why persistence testing matters.

Not known: why most antibody-positive people never clot. What the second hit is in patients who clot without an obvious provocation. Why some patients have arterial and others venous events. Whether seronegative antiphospholipid syndrome exists as an entity. The mechanism of the non-thrombotic manifestations — thrombocytopenia, valve disease, livedo, cognitive dysfunction, nephropathy — which are not obviously explained by clotting and are not prevented by anticoagulation.

Cure status. Thrombotic and obstetric disease: CONTROLLABLE. Catastrophic antiphospholipid syndrome: RELIEF ONLY, with mortality roughly 30 to 50 per cent.

No treatment eliminates the antibodies or cures the syndrome; anticoagulation prevents the events for as long as it continues. Recurrence after stopping is high, roughly 10 to 30 per cent in the first year, so treatment is lifelong in nearly all patients.

In obstetric disease, treatment produces live births, which is as close to a cure of the clinical problem as exists here. Low-dose aspirin plus low-molecular-weight heparin raises live birth rates from roughly 10 to 30 per cent untreated to roughly 70 to 80 per cent in cohort and trial data†. Cochrane reviews of heparin plus aspirin against aspirin alone in recurrent miscarriage with antiphospholipid antibodies find a significant reduction in pregnancy loss, though trial quality is mixed and the effect size varies between reviews.

Antibody titres sometimes fall or disappear spontaneously or with treatment of an associated disease such as lupus or hepatitis C. Whether anticoagulation can then be stopped is unresolved and is an active clinical question without trial evidence.

In catastrophic disease, triple therapy — anticoagulation, corticosteroids, and plasma exchange or immunoglobulin — plus treatment of the trigger is standard, with eculizumab and rituximab used in refractory cases on case-series grounds. Mortality remains roughly 30 to 50 per cent.

Prevention. No primary prevention of the antibodies.

Prevention of a first thrombotic event in antibody-positive people. Low-dose aspirin in asymptomatic antibody carriers: CONTESTED. The APLASA randomised trial found no significant benefit of aspirin over placebo for first thrombosis in asymptomatic antiphospholipid-antibody-positive individuals, while observational data and guidelines nonetheless support aspirin in high-risk profiles — triple positivity, lupus anticoagulant, coexisting lupus. Trial negative, guidelines positive, sources disagree openly. Hydroxychloroquine in lupus patients with antiphospholipid antibodies, where observational data consistently show lower thrombosis rates: MODERATE. Avoiding oestrogen-containing contraception and hormone replacement: STRONG. Thromboprophylaxis around surgery, immobilisation, long travel and pregnancy, the second-hit periods: STRONG. Cardiovascular risk factor control — smoking, hypertension, lipids, diabetes — since antiphospholipid antibodies and conventional risk factors are multiplicative for arterial events: MODERATE.

Prevention of recurrence: indefinite warfarin with an international normalised ratio of 2.0 to 3.0 after a first venous event. STRONG.

Prevention of pregnancy loss: low-dose aspirin from before conception plus low-molecular-weight heparin from confirmation of pregnancy. MODERATE.

Prevention of catastrophic disease: not interrupting anticoagulation without cover, and treating infection promptly, since infection precedes a large share of catastrophic episodes. MODERATE.

Correct antibody testing — persistence at 12 weeks, standardised assays, and not testing during an acute event or on anticoagulation where lupus anticoagulant results are unreliable. This prevents both over- and under-diagnosis. MODERATE, at zero marginal cost.

Treatment. Warfarin, target international normalised ratio 2.0 to 3.0, indefinitely, after venous thrombosis. Higher targets of 3.0 to 4.0 were tested in two randomised trials and were not superior while causing more bleeding, so 2.0 to 3.0 is standard. For arterial events, practice varies between 2.0 to 3.0 plus aspirin and a higher target, and the evidence is weak. Off-patent, at US$10 to US$50 a patient-year for the drug at generic or lowest available acquisition cost, 2024, plus monitoring, which is the real cost and the real access barrier; point-of-care devices and self-monitoring reduce it. Listing status needs checking against the 24th List†.

Low-molecular-weight heparin — enoxaparin, dalteparin — in pregnancy, perioperatively, and where warfarin is unsuitable. Off-patent with generics and biosimilars, at US$500 to US$3,000 a patient-year at generic or lowest available acquisition cost, 2024, with prophylactic dosing much less than therapeutic†. Listing status needs checking against the 24th List†.

Low-dose aspirin in obstetric disease, and in arterial disease alongside anticoagulation. Off-patent, at one to five dollars a patient-year (2024)†. Listing status needs checking against the 24th List†.

Direct oral anticoagulants are a clear negative, and it is important. TRAPS, comparing rivaroxaban with warfarin in triple-positive disease, was terminated early for excess thromboembolic events and major bleeding in the rivaroxaban arm. RAPS and a Spanish randomised trial by Ordi-Ros and colleagues also failed to show non-inferiority for arterial events, and rivaroxaban was associated with more arterial thrombosis, particularly stroke. Consequently these drugs should not be used in triple-positive patients or in patients with prior arterial thrombosis, and regulatory warnings were issued in the European Union and elsewhere. They may be an option in selected low-risk venous patients who cannot take warfarin, and that remains contested. This is one of the clearest instances in modern medicine where a newer, more convenient, more expensive drug class is worse than the sixty-year-old generic alternative.

Hydroxychloroquine for disease with lupus, and increasingly in primary disease on observational grounds. Off-patent, at US$30 to US$150 a patient-year at generic or lowest available acquisition cost, 2024†. Listing status needs checking against the 24th List†.

Obstetric disease: low-dose aspirin pre-conception plus prophylactic low-molecular-weight heparin from a positive pregnancy test to six weeks postpartum, with live birth roughly 70 to 80 per cent. Hydroxychloroquine is added in refractory obstetric disease on observational grounds. Corticosteroids and immunoglobulin have been used in refractory cases with weak evidence.

Catastrophic disease: therapeutic anticoagulation, high-dose corticosteroids, and plasma exchange or immunoglobulin, plus treatment of the trigger. Rituximab at a biosimilar course of US$1,500 to US$5,000 at lowest available acquisition cost, 2024, and eculizumab at roughly US$400,000 to US$600,000 a patient-year (2024) in refractory disease, on case-series evidence only†. Rituximab is a selected medicine on the 24th List in sections 5.1.2 and 8.2.2, and this indication is not among those listed; eculizumab's status needs checking against the 24th List†.

Statins reduce endothelial activation markers with no outcome trial.

Non-thrombotic manifestations: thrombocytopenia treated as immune thrombocytopenia, valve disease by surveillance with surgery carrying high thrombotic risk, and nephropathy by anticoagulation plus renin-angiotensin blockade.

Simple means. Warfarin. The best treatment for this disease is a drug discovered in the 1940s that costs tens of dollars a year, and the newer oral anticoagulants are demonstrably worse in the high-risk group. The constraint is monitoring, not the drug.

Stopping oestrogen-containing contraception. Free, and among the largest single risk reductions available.

Not smoking, because arterial risk is multiplicative. Low-dose aspirin, at cents a year.

Compression stockings, walking, hydration and avoiding prolonged immobility, especially on long journeys and after surgery. Free.

Knowing the diagnosis and carrying a card, so that anticoagulation is not stopped casually before a procedure, and so that unexplained thrombosis is treated correctly.

Treating infection promptly, because infection precedes a large share of catastrophic episodes.

Pregnancy planning. A conversation plus aspirin plus prophylactic-dose heparin takes live birth rates from roughly 10 to 30 per cent to roughly 70 to 80 per cent. The aspirin costs cents; the heparin is the expensive part, and prophylactic-dose heparin in pregnancy is substantially cheaper than therapeutic dosing.

Repeat antibody testing at 12 weeks before accepting the diagnosis. This prevents lifelong anticoagulation given for a transient post-infectious antibody. It costs one blood test and prevents a large iatrogenic harm.

Self-monitoring of the international normalised ratio with a point-of-care device where available, which reduces the monitoring burden that is the real cost of warfarin.

Gaps. Population incidence and prevalence rest largely on a single well-characterised United States county population, and there is no global estimate. Antibody positivity, at 1 to 5 per cent of healthy people, and syndrome prevalence, at about 0.05 per cent, differ by two orders of magnitude, and no test distinguishes who will clot; this is the central unresolved problem. Assay standardisation for lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein I is poor between laboratories, so antibody-based prevalence figures are not comparable, and lupus anticoagulant cannot be reliably measured on anticoagulation. Classification criteria changed between the Sydney 2006 criteria and the 2023 ACR/EULAR criteria, which classify different populations, so figures are criteria-dependent and the newer criteria are more specific. Aspirin for primary prophylaxis: APLASA negative, guidelines recommend it, sources disagree. In arterial disease, the optimal anticoagulation target and whether to add aspirin are not established by trial. Whether anticoagulation can be stopped if antibodies become persistently negative is unknown. The non-thrombotic manifestations have no established mechanism and are not prevented by anticoagulation, which suggests the thrombosis-only model of the disease is incomplete. Obstetric trial quality is mixed, and effect sizes for heparin plus aspirin against aspirin alone differ between Cochrane reviews and later meta-analyses. Catastrophic disease treatment rests entirely on registry and case-series data; no trial exists and none is feasible.

> **Depth.** Starts in: β2-glycoprotein I. Size: 10 nm†; depth −1.38. First complaint: about 35 years († onset about age 35); time depth 52.11. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

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Endocrine, nutritional and metabolic diseases

ICD-11 chapter 05

Twenty-three entries. The diabetes group, obesity and undernutrition, the four great micronutrient deficiencies, the thyroid and adrenal and pituitary disorders, bone and urate disease, the lipid disorders, and the inherited metabolic conditions that newborn screening exists to find.

Type 1 diabetes

What it is. The immune system destroys the insulin-producing beta cells of the pancreas. Without insulin, glucose cannot enter cells, blood sugar rises, and the body burns fat into acid. Without injected insulin the person dies within weeks.

Measured. The IDF Diabetes Atlas, 11th edition (2025), gives 1.8 million children and young adults under 20 living with type 1 diabetes worldwide†. Broader estimates including adults, from the Type 1 Diabetes Index (Gregory et al., *Lancet Diabetes & Endocrinology*, 2022), give roughly 8.4 million people of all ages in 2021, projected to 13.5 to 17.4 million by 2040. The two measure different populations and are not interchangeable.

The same analysis estimated that in 2021 roughly 35,000 people died within a year of onset from undiagnosed type 1 diabetes, and that roughly 3.1 million additional people would be alive had they received the care available in high-income settings. This is the central measured injustice of the disease.

Incidence varies more than 100-fold between countries. Highest: Finland, at roughly 60 to 65 per 100,000 children a year, and Sardinia at roughly 45 to 50; Sweden, Norway, Kuwait and Saudi Arabia are also high. Lowest: China, Venezuela, parts of South America and sub-Saharan Africa, at under one to two per 100,000 a year†. That gradient is the strongest argument for an environmental component and it is unexplained.

Incidence is rising by roughly 3 to 4 per cent a year globally in children, consistently measured across the EURODIAB and DIAMOND/SEARCH registries over three decades, with the sharpest relative increase in the under-five age group. Rising incidence in a genetic disease, over a period too short for allele frequencies to change, is itself a finding.

Onset peaks at five to seven years and again around puberty, and roughly half of all new cases occur in adults, which is systematically under-recognised and leads to misclassification as type 2†. The sexes are roughly equal in childhood, with a slight male excess in adult-onset disease.

Median survival after diagnosis in some low-income settings has been estimated at under one year historically where insulin is unavailable, against near-normal life expectancy in well-resourced settings. Current high-income cohorts show life expectancy roughly eight to 13 years shorter than the general population in Scottish and Australian registry data, narrowing over time.

Type 2 accounts for over 90 per cent of all diabetes, and type 1 for roughly 5 to 10 per cent†. The IDF 2025 total for all diabetes is 589 million adults aged 20 to 79, about 11 per cent of adults†. Another dossier in this project dates the same 589 million figure and the same Atlas edition to 2024 — the same figure, the same edition, two different years. Both stand, unresolved.

Where it starts. T-cell-mediated autoimmune destruction of pancreatic beta cells, preceded by the appearance of islet autoantibodies against insulin, GAD65, IA-2 and ZnT8. The presence of two or more persistent islet autoantibodies confers a lifetime risk of clinical type 1 diabetes approaching 100 per cent: pooled birth cohorts showed progression to diabetes in 69.7 per cent within 10 years and 84 per cent within 15 years of seroconversion in children with multiple autoantibodies (Ziegler et al., *JAMA*, 2013). This makes the disease predictable years in advance, and it is now formally staged — stage 1, two or more autoantibodies with normal glucose; stage 2, autoantibodies plus dysglycaemia; stage 3, clinical disease.

HLA class II accounts for roughly 40 to 50 per cent of the genetic risk†. HLA-DR3-DQ2 and DR4-DQ8 heterozygosity confers the highest risk, with odds ratios of roughly 15 to 30†. HLA-DQB1*06:02 is strongly protective, at an odds ratio of roughly 0.03 to 0.1† — near- absolute protection, and one of the strongest protective alleles known in human genetics. Over 60 non-HLA loci contribute individually small effects: *INS*, *PTPN22*, *IL2RA*, *CTLA4*, *IFIH1*, *SH2B3*, *ERBB3*.

Monozygotic twin concordance runs roughly 30 to 70 per cent depending on follow-up length, dizygotic roughly 6 to 10 per cent, and sibling risk roughly 6 to 7 per cent against a background population risk of roughly 0.4 per cent, a sibling relative risk of roughly 15†. Heritability estimates are roughly 0.7 to 0.9, and yet 85 to 90 per cent of new cases have no family history, because the risk alleles are common.

The environmental factors are the central unresolved question. Enteroviruses, particularly Coxsackievirus B, are the best-supported candidate: enterovirus RNA and protein are found in islets of recently diagnosed patients more often than in controls, and the DIPP and TEDDY prospective cohorts show associations between enterovirus infection and autoantibody seroconversion. A Coxsackievirus B vaccine entered clinical trials in 2023, which will be the direct test. Early cow's milk introduction was tested directly: the TRIGR randomised trial of 2,159 infants at genetic risk, comparing hydrolysed with standard cow's-milk formula, was negative, with no reduction in islet autoimmunity or diabetes. A long-standing hypothesis, directly tested, and refuted. Gluten and cereal introduction timing showed associations in observational data, and the BABYDIET trial of delayed gluten introduction was negative. Vitamin D has observational associations and no adequately powered prevention trial. Caesarean delivery, early antibiotics and gut microbiome composition show consistent but modest associations in TEDDY and other cohorts with no causal demonstration. Higher birthweight, rapid early growth and childhood obesity — the accelerator hypothesis — show consistent associations, and insulin resistance may hasten clinical onset in autoimmune individuals. The hygiene and microbial exposure line has its sharpest natural experiment in the north-south European gradient and the Finland-against-Russian-Karelia comparison: adjacent populations with similar HLA risk and roughly a six-fold difference in incidence, which points firmly at environment. Multiple national datasets reported increased incidence and more diabetic ketoacidosis at presentation during and after the SARS-CoV-2 pandemic; whether this is viral causation, delayed presentation, or both, is unresolved.

Not known: the environmental trigger. Why incidence has risen 3 to 4 per cent a year for decades. Why Finland has sixty times the incidence of China. Why the under-five group is rising fastest. Why only a minority of genetically at-risk children seroconvert. What determines the rate of progression from autoantibody positivity to clinical disease, which ranges from months to decades.

Cure status. CONTROLLABLE. Insulin is replacement, not cure, and this has been true since 1922.

Nothing restores endogenous insulin production durably except islet or pancreas transplantation, which requires lifelong immunosuppression and is therefore reserved for specific indications. Pancreas transplantation, usually simultaneous with a kidney in diabetic nephropathy, gives insulin independence in roughly 70 to 80 per cent at one year and 50 to 60 per cent at five years, at the cost of surgery and lifelong immunosuppression. Islet transplantation gives insulin independence in roughly 50 to 60 per cent at one year, declining thereafter†; the first licensed allogeneic islet product was approved in the United States in June 2023. Most recipients regain some insulin requirement, and the durable benefit is abolition of severe hypoglycaemia.

Stem-cell-derived islet therapy is the live cure candidate. Zimislecel, allogeneic stem-cell-derived islets infused into the portal vein with immunosuppression, reported FORWARD trial results in 2025 showing 10 of 12 participants insulin-independent at one year, with all 12 free of severe hypoglycaemic events†. This is the first demonstration of insulin independence from a manufactured, scalable cell product. It still requires immunosuppression, which is the remaining barrier; encapsulated and hypoimmune-edited versions are in earlier trials.

Disease-modifying immunotherapy delays but does not prevent. Teplizumab, an anti-CD3 antibody approved in the United States in November 2022, was the first drug ever approved to delay type 1 diabetes: in the TN-10 trial, in relatives with stage 2 disease, a single 14-day course delayed clinical onset by a median of roughly two years, with median time to diagnosis 48.4 months against 24.4 months, and

extended follow-up showing the delay persisting†. In new-onset disease, the PROTECT trial in 2023 showed teplizumab preserved C-peptide†. The price is roughly US$193,900 per 14-day course on United States list (2023)†. Other agents preserving C-peptide in new-onset disease: low-dose anti-thymocyte globulin, abatacept, rituximab, baricitinib (2023, *NEJM*), and verapamil (2018 and 2023). Verapamil is notable: an off-patent generic calcium channel blocker costing tens of dollars a year that preserved C-peptide in randomised trials in new-onset disease in children and adults. None of these prevents the disease; they slow beta-cell loss.

Technology has transformed control without curing. Automated insulin delivery systems increase time in range by roughly 10 to 15 percentage points, roughly 2.5 to 3.5 extra hours a day in range, against sensor-augmented pump therapy in randomised trials, and reduce hypoglycaemia.

Prevention. No established primary prevention. This must be stated plainly: there is no intervention demonstrated to prevent type 1 diabetes. TRIGR and BABYDIET were negative. Nicotinamide in ENDIT, oral insulin in DPT-1 and the Fr1da/POInT programme, and parenteral insulin have not prevented it.

Delay is now possible: teplizumab delays onset by roughly two years in screen-detected stage 2 disease. MODERATE for delay, randomised and replicated in extended follow-up — and not prevention.

Screening for islet autoantibodies in the general paediatric population. The Fr1da study in Bavaria screened over 90,000 children and found that screen-detected children presented with far less diabetic ketoacidosis at clinical onset. Preventing ketoacidosis at presentation is the clearest measurable benefit of screening, and ketoacidosis at presentation is associated with worse long-term glycaemic control and, in low-resource settings, with death. MODERATE for preventing ketoacidosis.

Prevention of diabetic ketoacidosis at diagnosis by public and professional awareness campaigns: the Parma campaign in Italy reduced ketoacidosis at presentation from roughly 83 per cent to 13 per cent over eight years using posters and leaflets in schools and paediatric practices. Replication attempts have had mixed results, the original effect is large, and the intervention costs almost nothing. MODERATE.

Prevention of complications is where almost all the measurable prevention lies. Tight glycaemic control: the Diabetes Control and Complications Trial of 1993 and its EDIC follow-up found that intensive therapy reduced retinopathy by 76 per cent in primary prevention, progression of retinopathy by 54 per cent, microalbuminuria by 39 per cent and clinical neuropathy by 60 per cent, and in long-term EDIC follow-up reduced cardiovascular events by 42 per cent and all-cause mortality significantly, with the benefit persisting for decades after the trial ended. STRONG. This is one of the most consequential trials in medicine. Blood pressure control and renin-angiotensin blockade in nephropathy: STRONG. Statins for cardiovascular risk: STRONG. Annual retinal screening with treatment of detected disease, which prevents blindness: STRONG. Annual foot examination, which prevents ulceration and amputation: STRONG. Not smoking: STRONG. Coeliac disease and autoimmune thyroid screening, since both cluster with type 1 diabetes: MODERATE.

Treatment. Insulin is the treatment, and the price picture is the central fact.

Human insulin, soluble (regular) and isophane (NPH), produced by recombinant DNA since the 1980s. **Human insulin is a selected medicine on the 24th List, in section 18.5.1, as two entries: "Insulin (human, short-acting)" and "Insulin (human, intermediate-acting)", each for type 1 and type 2 diabetes**. Off-patent for decades.

Hill and colleagues (*BMJ Global Health*, 2018) estimated the minimum sustainable production cost from the cost of active pharmaceutical ingredient plus formulation, packaging, a 10 per cent margin and tax: **biosimilar human insulin, regular and NPH, at US$72 a patient-year or less, falling to US$48 with high competition**, for the 10 mL vial formulation. Actual prices: in low- and middle-income country tenders, human insulin is available at roughly two to ten dollars per 10 mL vial, roughly US$50 to US$200 a patient-year (2024)† — in the range of the Hill estimate. In the United States, list prices for human insulin have run roughly US$25 to US$100 a vial, and one retailer's human insulin has been sold at roughly US$25 a vial for years, roughly US$300 to US$600 a patient-year†.

Insulin analogues, rapid-acting (lispro, aspart, glulisine) and long-acting (glargine, detemir, degludec). **On the 24th List the selected medicines are the two class entries, "Insulin (analogue, long-acting)" and**

"Insulin (analogue, rapid-acting)", both in section 18.5.1 for type 1 and type 2 diabetes. The six named analogues — degludec, detemir and glargine long-acting, and aspart, glulisine and lispro rapid-acting — are listed as therapeutic equivalents to those class entries, not as selected medicines in their own right. A bare "on the EML" for the named analogues overstates the listing. The years in which long-acting and rapid-acting analogues were added have not been rechecked against the 24th List†.

Lispro, aspart and glargine are off-patent with biosimilars marketed; degludec is still patented in many markets.

Hill and colleagues estimated the minimum sustainable production cost for biosimilar analogues — lispro, aspart, glargine, glulisine, degludec — at **US$133 a patient-year or less, falling to US$78 to US$98 with high competition**, with estimated analogue cost 1.9 to 2.0 times the human insulin cost, except detemir at 5.1 to 5.9 times†.

Actual prices: United States list prices for analogue insulins reached roughly US$275 to US$340 per 10 mL vial by 2019, roughly US$3,000 to US$6,000 a patient-year at typical usage†. After public and legislative pressure, the three major manufacturers each announced list price cuts of roughly 70 to 78 per cent in 2023, and a 35-dollar monthly out-of-pocket cap applies to Medicare beneficiaries under the Inflation Reduction Act from 2023, with manufacturer programmes extending similar caps more broadly†. In Europe, analogue insulin costs roughly €300 to €700 a patient-year (2024)†. In India and other biosimilar-manufacturing markets, analogue biosimilars sell for roughly US$100 to US$400 a patient-year (2024)†.

The gap, stated plainly: the published minimum production cost of analogue insulin is US$133 a patient-year†; the United States list price before the 2023 cuts was roughly US$3,000 to US$6,000 a patient-year† — a factor of roughly 23 to 45. Even after the cuts the gap is roughly five- to ten-fold. Three manufacturers hold roughly 90 to 95 per cent of the global insulin market by value†.

On the clinical difference: Cochrane and other systematic reviews find small or no difference in HbA1c and a modest reduction in nocturnal hypoglycaemia with long-acting analogues against NPH. WHO's own analysis supported including analogues on the list on the basis of the hypoglycaemia benefit while noting the price. The honest statement is that analogues are somewhat better, by a margin far smaller than the price difference.

Delivery and monitoring. Syringes and needles cost cents each, and the recurring cost of needles and strips exceeds the cost of human insulin in many low-income settings. Blood glucose test strips run roughly US$0.10 to US$0.50 each (2024); at four tests a day that is US$150 to US$700 a patient-year, often more than the insulin†. Continuous glucose monitoring runs US$1,000 to US$4,000 a patient-year (2024) and reduces HbA1c and severe hypoglycaemia in randomised trials; it is a device and not on the Model List. Insulin pumps and automated insulin delivery run US$3,000 to US$8,000 upfront plus US$1,500 to US$4,000 a patient-year in consumables (2024)†. Insulin requires refrigeration before use, and clay-pot evaporative coolers and simple insulated containers have been validated for storage in hot climates — a genuine simple-means solution to a real access barrier.

Teplizumab for stage 2 disease, roughly US$193,900 a course on United States list (2023), patented†. EML status needs checking against the 24th List†.

Adjuncts: metformin does not improve HbA1c in type 1 diabetes but modestly reduces insulin dose and weight in the REMOVAL trial; SGLT2 inhibitors reduce HbA1c and weight but substantially raise the risk of euglycaemic diabetic ketoacidosis and are not generally recommended; and verapamil preserves C-peptide in new-onset disease, is off-patent at tens of dollars a year, and is not yet standard. Metformin is a selected medicine on the 24th List, in section 18.5.2, hypoglycaemic agents, for type 2 diabetes mellitus, for adolescents and adults, first added in 1997; type 1 diabetes is not the listed indication.

Treatment of diabetic ketoacidosis: intravenous fluids, insulin infusion and potassium replacement, all costing dollars. Insulin human is on the 24th List as above; the listing status of sodium chloride and potassium chloride needs checking against the 24th List†. Ketoacidosis mortality is roughly 0.2 to 2 per cent in well-resourced settings and far higher where these are unavailable.

Complication management: ACE inhibitors or angiotensin receptor blockers for nephropathy; statins; laser photocoagulation and anti-VEGF agents for retinopathy; SGLT2 inhibitors and finerenone for diabetic kidney disease; dialysis and transplantation.

Simple means. Human insulin rather than analogue, where cost is the binding constraint. The clinical difference is small and the price difference is large. This is the single most consequential substitution available in this disease.

Clay-pot and evaporative cooling for insulin storage. Validated in field studies in hot climates, it keeps insulin within an acceptable temperature range without electricity. It solves a real access barrier with a pot, sand and water.

Reuse of syringes by a single patient, practised widely out of necessity, with low infection rates in reported series when done with care. Not recommended, and it is what happens.

Urine ketone strips, at cents each, which detect impending ketoacidosis without a laboratory. In settings without blood ketone meters this is the tool that prevents death.

Public awareness of the four presenting symptoms — thirst, passing urine, weight loss, tiredness. The Parma campaign reduced ketoacidosis at presentation from 83 per cent to 13 per cent with posters and leaflets. This is the cheapest life-saving intervention in this entry.

A written sick-day plan — never stopping insulin during illness, which is the commonest cause of avoidable ketoacidosis. Free.

Carbohydrate counting and dose adjustment skills: education, not technology. Structured education programmes such as DAFNE and its equivalents improve HbA1c and reduce severe hypoglycaemia.

Daily foot inspection and well-fitting shoes, which prevent the ulceration that leads to amputation. Free. And not smoking.

There is no simple-means substitute for insulin. A person with type 1 diabetes without insulin dies. Everything in this section is about making insulin work with less infrastructure, not about replacing it.

Gaps. The IDF figure of 1.8 million under 20 and the Type 1 Diabetes Index figure of roughly 8.4 million all ages measure different populations and are not interchangeable, and there is no authoritative global count of adults with type 1 diabetes, because adult-onset type 1 is routinely misclassified as type 2. Incidence varies more than 100-fold between countries and nobody knows why. Incidence has risen 3 to 4 per cent a year for three decades and nobody knows why; genetic change cannot account for it. The environmental trigger is unidentified, and the enterovirus hypothesis will be tested directly by the Coxsackievirus B vaccine trials. TRIGR and BABYDIET were negative, which refuted two long-standing prevention hypotheses, and some guidance material still reflects the pre-trial advice. Whether SARS-CoV-2 increased incidence, or only brought presentations forward and made them more severe, is unresolved and national datasets disagree. Insulin prices are confidential in most tendered markets, so the figures here are approximate, and the Hill production-cost estimates are modelled rather than audited; the authors state their estimates in 2018 terms, cite 2019 market data as context, and do not themselves state a reference year for the cost estimates. The clinical superiority of analogues over human insulin is modest and the magnitude is contested between manufacturer-sponsored and independent analyses. Zimislecel and other stem-cell islet data come from fewer than 20 patients with one year of follow-up. No trial has tested whether screening the general population for islet autoantibodies improves long-term outcomes, as distinct from reducing ketoacidosis at presentation.

> **Depth.** Starts in: insulin (self-antigen). Size: 3 nm†; depth −2.48. First complaint: about 12 years († onset about age 12); time depth 51.13. One untreated course: about 3.5 weeks ([B] death within weeks without insulin); depth 46.40.
>
> **Model reading.** Way of ending: supply from inside. Layer: reading. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Type 2 diabetes

What it is. The body's cells stop responding properly to insulin, and the pancreas cannot make enough to compensate. Blood glucose rises over years, damaging eyes, kidneys, nerves and arteries. It is closely tied to body fat, especially fat in the liver and pancreas.

Measured. From the IDF Diabetes Atlas, 11th edition (2025), for all diabetes, of which type 2 is over 90 per cent†: 589 million adults aged 20 to 79 living with diabetes, nearly one in nine adults and about 11 per cent of the adult population; 252 million adults undiagnosed, more than four in ten of all people with diabetes; over 3.4 million deaths a year; health expenditure surpassing one trillion US dollars in 2024, up from 966 billion in 2021; a projection of 853 million adults by 2050; one in eight adults at high risk of developing type 2 diabetes; three in four adults with diabetes living in low- and middle-income countries; and an 84 per cent higher risk of heart failure in people with type 2 diabetes than in those without.

The WHO diabetes fact sheet, printed 14 November 2024, uses a different method and gives larger all-age figures: 14 per cent of adults aged 18 and over had diabetes in 2022, up from 7 per cent in 1990; the total across all ages rose from 200 million in 1990 to 830 million in 2022; 59 per cent of adults aged 30 and over with diabetes were not taking any medication for it in 2022, with treatment coverage lowest in low- and middle-income countries; and deaths in 2021 were 1.6 million directly caused by diabetes plus 530,000 from diabetes-caused kidney disease. The WHO Key Facts section states that more than half of all people with diabetes were untreated in 2022, while the body applies the 59 per cent figure only to adults aged 30 and over — a scope mismatch within the same page. The IDF and WHO global figures are not interchangeable and the difference is not reconciled in either publication.

Incidence rises steeply with age, and type 2 diabetes in children and adolescents is now established and rising, at roughly one to five per 100,000 a year in United States and United Kingdom youth, concentrated in specific ancestry groups and with a more aggressive course than adult-onset disease; the TODAY study showed rapid glycaemic failure and early complications.

At any given body size, risk is substantially higher in South Asian, East Asian, African, Hispanic, Middle Eastern, Pacific Islander and Indigenous populations than in European populations, and WHO recommends lower action points for Asian populations in consequence. The highest national prevalences are in Pacific Island nations, the Gulf states and parts of South and Southeast Asia, with adult prevalence above 20 per cent in several†.

Diabetes is a leading cause of blindness, end-stage kidney disease and non-traumatic lower-limb amputation worldwide, and roughly doubles cardiovascular mortality. In the GBD 2023 cycle, diabetes ranks fifth among causes of disability-adjusted life years at 90.2 million (95% UI 75.2–107) and seventh among causes of years lived with disability at 44.2 million (95% UI 31.0–59.7).

Where it starts. Insulin resistance in muscle, liver and adipose tissue, plus progressive beta-cell dysfunction. Hyperglycaemia appears when beta-cell compensation fails. Ectopic fat in the liver and pancreas is central: the twin cycle hypothesis holds that excess liver fat drives hepatic insulin resistance and excess pancreatic fat impairs insulin secretion, and that both are reversible with sufficient weight loss. This hypothesis generated the DiRECT and DIADEM-I trials and is the main reason remission is now a recognised outcome.

Adiposity is the dominant modifiable risk factor. GBD attributable-risk analyses attribute roughly 50 per cent of type 2 diabetes DALYs to high body mass index†. Relative risk rises roughly log-linearly with body mass index: in the Nurses' Health Study and the Health Professionals Follow-up Study, risk at the upper end of the measured range was roughly 20 to 40 times that at the lower end in women and roughly 20 times in men†. Weight gain in adulthood predicts risk independently of attained body size, and waist circumference and visceral fat predict risk beyond body mass index.

Physical inactivity is independently associated, with roughly 20 to 30 per cent higher risk in the least active against the most active, adjusted for body size.

Diet: higher risk with sugar-sweetened beverages, at roughly 13 to 26 per cent higher risk per serving a day in meta-analyses; with processed red meat; and with refined grains. Lower risk with whole grains, coffee,

nuts, and dietary patterns high in vegetables, legumes and unsaturated fat. Effect sizes are modest individually.

Smoking: roughly 30 to 40 per cent higher risk in smokers†. Short and long sleep duration and shift work are associated with higher risk. Gestational diabetes in the mother carries roughly a ten-fold higher subsequent maternal risk and higher risk in the offspring. Low birthweight and intrauterine undernutrition: the Dutch Hunger Winter and other famine cohorts show raised later glucose intolerance, and the developmental origins association is consistent. Lower income and education are associated with higher risk in high-income countries, and with higher risk in urban populations in low-income countries.

Over 600 loci have been identified by genome-wide association, individually small. *TCF7L2* is the strongest common variant at an odds ratio of roughly 1.4 per risk allele†. Monozygotic twin concordance is roughly 70 per cent, dizygotic roughly 20 to 30 per cent, and heritability estimates roughly 0.3 to 0.7; first-degree relative risk is roughly 2 to 3, and roughly 5 to 6 with both parents affected†. Common polygenic risk scores explain under 20 per cent of heritability and perform worse in non-European populations. Monogenic diabetes is roughly 1 to 4 per cent of diabetes and is routinely misdiagnosed as type 1 or type 2 — *HNF1A*, *HNF4A*, *GCK*, *HNF1B* — which matters because *HNF1A* disease responds dramatically to low-dose sulfonylurea and *GCK* disease needs no treatment at all.

Drug-induced: glucocorticoids, thiazides, atypical antipsychotics, statins (small effect), protease inhibitors, calcineurin inhibitors.

Not known: why some people with severe obesity never develop type 2 diabetes and others develop it at ordinary body size. What determines individual beta-cell reserve. Why ancestry groups differ so markedly at equal body size — the thin-fat South Asian phenotype is described and not explained. Whether the common polygenic architecture will ever be clinically useful.

Cure status. CONTROLLABLE. In a substantial minority of recent-onset cases remission is achievable and sometimes durable, and the word used in the literature is remission rather than cure, because the underlying susceptibility persists and relapse follows weight regain.

DiRECT (Diabetes Remission Clinical Trial; Lean, Taylor and colleagues, Scotland; cluster-randomised in primary care, 306 participants with type 2 diabetes of up to six years' duration, not on insulin). The intervention was total diet replacement followed by structured food reintroduction and weight-loss maintenance, delivered in primary care.

- **Remission at 12 months: 46 per cent of the intervention group against 4 per cent of the control group**†.
- **Remission at 24 months: 36 per cent against 3 per cent**†.
- **Remission at five years, in the extension study: 11 of the 48 participants who were in remission at the start of the extension, 23 per cent, remained in remission. The control group's five-year remission rate was 3.4 per cent**†.
- Remission was defined as HbA1c below 48 mmol/mol (6.5 per cent) while off all antidiabetes drugs.
- Weight change at five years: intervention group mean −6.1 kg; those still in remission at five years −8.9 kg; control group −4.6 kg†.
- Remission depended strongly on the weight loss achieved. At 12 months, remission occurred in roughly 86 per cent of those who lost 15 kg or more, roughly 57 per cent of those losing 10 to 15 kg, roughly 34 per cent of those losing 5 to 10 kg, and roughly 7 per cent of those losing under 5 kg†. This dose-response is the central finding.

DIADEM-I (Qatar; randomised controlled trial, 147 participants with type 2 diabetes of up to three years' duration, aged 18 to 50). The intervention was total diet replacement followed by structured food reintroduction and physical activity.

- **Diabetes remission at 12 months: 61 per cent of the intervention group against 12 per cent of the control group**†. It is widely reported as both 61 and 60 per cent.
- Normoglycaemia, defined as HbA1c below 5.7 per cent off medication, in 33 per cent of the intervention group against 4 per cent of control†.

- Mean weight loss at 12 months: 11.98 kg in the intervention group against 3.98 kg in control†.

The DIADEM-I participants were younger and had shorter disease duration than those in DiRECT, which is the likeliest reason for the higher remission rate.

Other remission evidence. Bariatric and metabolic surgery produces the highest and most durable remission rates. STAMPEDE, a five-year randomised trial of 150 patients, found HbA1c of 6.0 per cent or below off medication in roughly 29 per cent of gastric bypass and 23 per cent of sleeve gastrectomy patients against 5 per cent of intensive medical therapy patients at five years†. The Swedish Obese Subjects matched cohort found diabetes remission in 72 per cent at two years and 36 per cent at 10 years after surgery, against 21 and 13 per cent in matched controls†. Mingrone and colleagues, at 10-year randomised follow-up, found 37.5 per cent of biliopancreatic diversion and 25 per cent of gastric bypass patients maintained remission at 10 years against 5.5 per cent on medical therapy†. Surgery also reduces diabetes-related mortality and microvascular complications in cohort data.

Look AHEAD, an intensive lifestyle intervention in 5,145 participants with type 2 diabetes and overweight or obesity, achieved partial or complete remission in 11.5 per cent at one year and 7.3 per cent at four years, against 2.0 and 2.0 per cent in the control group† — lower rates than DiRECT because the weight loss achieved was smaller, roughly 8.6 per cent at year one and 4.7 per cent at year four†, and participants had longer disease duration. **Look AHEAD did not reduce cardiovascular events**, its primary endpoint, which is an important negative.

Determinants of remission are consistently measured: shorter diabetes duration, lower baseline HbA1c, not using insulin, greater weight loss, and better preserved beta-cell function. Remission is largely a window-of-opportunity phenomenon in the first few years. Relapse follows weight regain; in DiRECT, relapse tracked weight regain closely.

Stated precisely: CONTROLLABLE in all; remission achievable in roughly 30 to 60 per cent† of people with recent-onset disease given substantial weight loss, with roughly a quarter of those in remission still in remission at five years; and remission is not cure, because susceptibility and relapse risk persist.

Prevention. This entry has the strongest primary-prevention trial evidence of any condition in chapter 05.

Intensive lifestyle intervention in people with impaired glucose tolerance. The US Diabetes Prevention Program (*NEJM*, 2002; 3,234 participants with impaired glucose tolerance, mean follow-up 2.8 years):

Arm	Incidence per 100 person-years	Cumulative incidence at 3 years
Placebo	11.0	**28.9 per cent**
Metformin	7.8	**21.7 per cent**
Intensive lifestyle	4.8	**14.4 per cent**

- **Lifestyle intervention reduced incidence by 58 per cent (95% CI 48–66)**.
- **Metformin reduced incidence by 31 per cent (95% CI 17–43)**.
- **Number needed to treat over three years: 6.9 for lifestyle (95% CI 5.4–9.5) and 13.9 for metformin (95% CI 8.7–33.9)**.

Those two numbers needed to treat are correct as published and follow exactly from the cumulative-incidence row above: for lifestyle, 28.9 −14.4 = 14.5 percentage points, and 1 ÷ 0.145 = 6.90; for metformin, 28.9 −21.7 = 7.2 percentage points, and 1 ÷ 0.072 = 13.89. They do not follow from the per-100-person-year rates, which is why the cumulative-incidence row is printed here: a reader working from the rates alone would get 5.4 and 10.4 and conclude the published figures were wrong. The 58 and 31 per cent relative reductions are hazard-based, from the proportional-hazards model, as the paper states, and the crude cumulative-incidence ratios are 50.2 and 24.9 per cent. Lifestyle was significantly more effective than metformin.

The Diabetes Prevention Program Outcomes Study at 15 years found diabetes incidence remained 27 per cent lower in the lifestyle group and 18 per cent lower in the metformin group than placebo† — the benefit persisted long after the intensive intervention ended.

The Finnish Diabetes Prevention Study, in 522 participants, found a 58 per cent relative risk reduction, the same figure arrived at independently. The Da Qing study in China, 577 participants with 30-year follow-up, found that diet and exercise interventions reduced diabetes incidence, and at 30 years the intervention group had lower cardiovascular events, fewer microvascular complications, lower all-cause mortality, and roughly 1.44 years greater life expectancy† — the only diabetes prevention trial with mortality benefit demonstrated at three decades. The Indian Diabetes Prevention Programme and others replicate the effect at smaller magnitude. STRONG: replicated in multiple countries and ancestries, with long-term follow-up and, in Da Qing, mortality benefit.

Metformin for prevention: 31 per cent reduction, greater in those with higher body mass index and in women with prior gestational diabetes. Off-patent, cents a day. STRONG for the effect; it is not licensed for prevention in most countries.

Weight loss by any means. In the Diabetes Prevention Program, each kilogram of weight lost was associated with roughly a 16 per cent reduction in diabetes risk†. This is the clearest dose-response in the field. STRONG.

Bariatric surgery for prevention: in the Swedish Obese Subjects study, surgery reduced incident type 2 diabetes by roughly 78 to 87 per cent over 10 to 15 years against matched controls†. STRONG.

GLP-1 receptor agonists for prevention: in SCALE, liraglutide in prediabetes substantially delayed diabetes onset; in STEP 1 extension data and in the SELECT trial, semaglutide reduced progression to diabetes. MODERATE for the effect; cost and durability after stopping are the constraints, since glycaemic and weight benefits largely reverse on discontinuation.

Population-level measures. Sugar-sweetened beverage taxes produced measured reductions in purchases of roughly 10 to 20 per cent following taxes in Mexico, Chile, the United Kingdom and several United States cities; effects on diabetes incidence are modelled rather than directly measured. MODERATE for consumption, WEAK for diabetes incidence. The United Kingdom Soft Drinks Industry Levy produced substantial reformulation, reducing the sugar content of soft drinks by roughly 30 per cent across the market†. MODERATE for reformulation. Front-of-pack labelling, marketing restrictions and trans fat elimination are WHO-recommended, with effects demonstrated on intermediate measures and modelled on diabetes incidence. WEAK. Built environment and physical activity infrastructure: WEAK, observational.

Not smoking. MODERATE.

Screening for diabetes detects the 252 million undiagnosed. Whether screening itself reduces mortality is contested: the ADDITION-Cambridge trial found no mortality reduction from population screening over 10 years, while early treatment of detected cases clearly reduces complications. CONTESTED for screening as a mortality intervention, STRONG for treating what is found.

Treatment. Metformin, first-line everywhere. It reduces HbA1c by roughly 1.0 to 1.5 percentage points, and UKPDS showed reduced diabetes-related death and myocardial infarction in overweight patients. **Metformin is a selected medicine on the 24th List, in section 18.5.2, hypoglycaemic agents, for type 2 diabetes mellitus, as oral solid 500 mg hydrochloride, for adolescents and adults, first added in 1997** Off-patent, at US$2 to US$15 a patient-year at generic or lowest available acquisition cost, 2024†. The best-value drug in chapter 05.

Sulfonylureas — gliclazide, glibenclamide, glimepiride — reduce HbA1c by roughly 1.0 to 1.5 points, with hypoglycaemia and weight gain as the drawbacks and modified-release gliclazide carrying the lowest hypoglycaemia risk of the class. Off-patent, at US$3 to US$20 a patient-year at generic or lowest available acquisition cost, 2024†. These two drug classes treat the large majority of the world's type 2 diabetes. Gliclazide's listing status needs checking against the 24th List†.

SGLT2 inhibitors — empagliflozin, dapagliflozin, canagliflozin — reduce HbA1c by roughly 0.6 to 0.8 points, plus the outcome effects that changed practice: EMPA-REG OUTCOME gave a 38 per cent relative reduction in cardiovascular death, 32 per cent in all-cause death and 35 per cent in heart failure hospitalisation†; CREDENCE gave a 30 per cent reduction in the composite renal endpoint in diabetic kidney disease; and DAPA-CKD and EMPA-KIDNEY showed renal and mortality benefit extending beyond diabetes. Generics are available in India and several other markets; originator patents run to the late

2020s in the United States and Europe. United States list prices run US$6,000 to US$7,000 a patient-year (2024), European prices roughly €400 to €700 a patient-year, and Indian generics roughly US$30 to US$120 a patient-year (2024)† — a generic-to-originator ratio of roughly 50 to 200-fold. Their listing status needs checking against the 24th List†.

GLP-1 receptor agonists and the dual GIP/GLP-1 agonist are the class with the largest recent effect sizes. Semaglutide 1.0 mg subcutaneous weekly in type 2 diabetes reduces HbA1c by roughly 1.5 to 1.8 percentage points with weight loss of roughly 4 to 6 kg in the SUSTAIN programme†. SUSTAIN-6 gave a 26 per cent reduction in major adverse cardiovascular events†; LEADER, with liraglutide, a 13 per cent reduction in those events and 22 per cent in cardiovascular death†. STEP 1, with semaglutide 2.4 mg weekly in 1,961 adults without diabetes over 68 weeks, gave a mean weight change of −14.9 per cent against −2.4 per cent with placebo†. SURMOUNT-1, with tirzepatide in 2,539 adults without diabetes over 72 weeks, gave mean weight change of −15.0 per cent at 5 mg, −19.5 per cent at 10 mg and −20.9 per cent at 15 mg against −3.1 per cent on placebo, with at least 5 per cent weight loss in 85, 89 and 91 per cent against 35 per cent on placebo, and at least 20 per cent weight loss in 50 per cent at 10 mg and 57 per cent at 15 mg against 3 per cent†. The SURPASS programme in type 2 diabetes gave HbA1c reductions up to roughly 2.1 to 2.4 percentage points, the largest of any non-insulin agent†. SELECT, with semaglutide 2.4 mg in 17,604 participants with overweight or obesity and established cardiovascular disease but without diabetes, gave a 20 per cent reduction in major adverse cardiovascular events, hazard ratio 0.80, over a mean 39.8 months† — the first demonstration that treating obesity pharmacologically reduces cardiovascular events. FLOW gave a 24 per cent reduction in the composite kidney endpoint in type 2 diabetes with chronic kidney disease†, and SUMMIT, with tirzepatide in heart failure with preserved ejection fraction and obesity, reduced cardiovascular death or worsening heart failure.

On listing: GLP-1 receptor agonists were added to the WHO Model List of Essential Medicines in the 24th List (2025), specifically for adults with type 2 diabetes who also have established cardiovascular disease, chronic kidney disease or obesity, with semaglutide, dulaglutide, liraglutide and tirzepatide named. **That listing was not independently verified against the 24th List for this chapter, and carries a dagger pending a recheck.** The committee framed the listing as support for wider access as more affordable options become available. The counts sometimes quoted alongside it — 523 medicines for adults and 374 for children, with 20 added to the adult list, 15 to the children's list and new indications for seven already-listed products — are not printed on the list's title page and remain unconfirmed.

Liraglutide is off-patent with generics marketed; semaglutide, dulaglutide and tirzepatide are not, though semaglutide's primary patents expire in Canada, India, China and Brazil from 2026 and generic and biosimilar launches in those markets are expected from that year.

Prices, 2024 to 2025. Semaglutide on United States list: roughly US$1,000 to US$1,350 a month, roughly 12,000 to 16,000 a patient-year, with US$499 a month through direct-to-consumer cash channels from 2025, roughly 6,000 a patient-year†. Tirzepatide on United States list: roughly US$1,000 to US$1,080 a month, roughly 12,000 to 13,000 a patient-year, with US$349 to US$499 a month through direct cash channels†. Europe: semaglutide roughly €100 to €300 a month, roughly 1,200 to 3,600 a patient-year†. India: liraglutide generics have launched at roughly US$30 to US$100 a month†.

Published minimum production cost estimate (Barber, Hill and colleagues, *JAMA Network Open*, 2024): semaglutide could be manufactured and sold profitably at roughly US$0.89 to US$4.73 a month, roughly US$11 to US$57 a patient-year, at scale. Against a United States list price of roughly US$12,000 to US$16,000 a patient-year, that is a factor of roughly 250 to 1,500 — the largest price-to-production-cost gap in this chapter.

Gastrointestinal side effects are the main limitation. Discontinuation rates in real-world use are high, roughly 30 to 50 per cent within a year in United States claims data, and weight and glycaemic benefit largely reverse on stopping: the STEP 1 extension found roughly two-thirds of lost weight regained within a year of discontinuation, with STEP 4 withdrawal data concordant†.

DPP-4 inhibitors — sitagliptin, linagliptin — reduce HbA1c by roughly 0.5 to 0.8 points, are weight neutral, and have no demonstrated cardiovascular benefit. Sitagliptin is off-patent in several markets, at

US$30 to US$150 a patient-year at generic or lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

Pioglitazone reduces HbA1c by roughly 1.0 point; the IRIS trial showed reduced stroke and myocardial infarction in insulin-resistant patients with prior stroke, against weight gain, fluid retention and fracture risk. Off-patent, at US$20 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†. EML status needs checking against the 24th List†.

Insulin for beta-cell failure. Human insulin remains the appropriate choice in most of the world for type 2 diabetes and is a selected medicine on the 24th List, in section 18.5.1, for type 1 and type 2 diabetes, at US$50 to US$200 a patient-year for human insulin at lowest available acquisition cost, 2024†. See the previous entry for the full price picture.

Acarbose has a modest effect with gastrointestinal side effects and is widely used in parts of Asia. Off-patent and cheap.

Metabolic surgery is the most effective intervention for remission and for weight, at US$10,000 to US$30,000 one-off in high-income settings (2024)†, with cohort data showing reduced mortality and microvascular complications.

Complication prevention carries most of the mortality benefit. Blood pressure control: UKPDS and subsequent trials found tight blood pressure control reduced diabetes-related death, stroke and microvascular endpoints, with effect sizes larger than those for glycaemic control. ACE inhibitors, angiotensin receptor blockers, calcium channel blockers and thiazides are all off-patent at US$5 to US$50 a patient-year at generic or lowest available acquisition cost, 2024†, with listing status needing checking against the 24th List†. Statins: the Cholesterol Treatment Trialists' meta-analyses give roughly a 21 per cent proportional reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol, consistent in people with and without diabetes, at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024†; listing status needs checking against the 24th List†. Finerenone, in FIDELIO-DKD and FIGARO-DKD, reduced kidney and cardiovascular events in diabetic kidney disease; patented, at US$6,000 to US$8,000 a patient-year on United States list (2024)†. Annual retinal screening, annual foot examination and annual urine albumin-to-creatinine ratio are all cheap and all prevent irreversible outcomes. Aspirin for secondary prevention only.

Simple means. What the trials measured, with no protocol.

Weight loss, by any means. The DiRECT and DIADEM-I trials achieved remission with diet-based weight loss delivered in primary care, with no drug and no surgery. Remission occurred in roughly 86 per cent of DiRECT participants who lost 15 kg or more, and in roughly 7 per cent of those losing under 5 kg. In the Diabetes Prevention Program, each kilogram lost was associated with roughly 16 per cent lower diabetes risk. The intervention in both remission trials was a formula diet followed by structured food reintroduction, supported by a nurse or dietitian in ordinary primary care — a service, not an industrial chain.

Metformin. Off-patent, a selected medicine on the 24th List, at US$2 to US$15 a patient-year at generic or lowest available acquisition cost, reducing HbA1c by 1.0 to 1.5 points, with reduced diabetes-related death in UKPDS and a 31 per cent reduction in incident diabetes in prediabetes. The cheapest effective drug in this chapter.

Gliclazide. Off-patent, at US$3 to US$20 a patient-year at generic or lowest available acquisition cost.

Physical activity. Trial-measured: in the Diabetes Prevention Program and the Finnish study, physical activity was a component of interventions that reduced incidence by 58 per cent; in Da Qing, exercise alone was one of the effective arms, and the 30-year follow-up showed reduced mortality and increased life expectancy. Walking requires nothing.

Human insulin rather than analogue, where cost binds.

A urine dipstick for protein and a once-yearly look at the feet. Both cost almost nothing and both detect the complications that cause amputation and dialysis.

A blood pressure cuff. Blood pressure control delivers larger absolute risk reductions in type 2 diabetes than glycaemic control, and the drugs are generic.

Not smoking.

Case detection. 252 million people are undiagnosed, and 59 per cent of those aged 30 and over who have the disease are on no medication. A fasting glucose or an HbA1c costs a few dollars. The binding constraint is not technology.

Reduced sugar-sweetened beverage intake. Measured: each daily serving is associated with 13 to 26 per cent higher risk in meta-analyses; taxes reduced purchases by 10 to 20 per cent in Mexico, Chile, the United Kingdom and several United States cities; and the United Kingdom levy drove roughly a 30 per cent reduction in the sugar content of soft drinks through reformulation.

Gaps. The IDF and WHO give substantially different global figures — 589 million adults aged 20 to 79 (IDF, 2025) against 830 million all ages and 14 per cent of adults aged 18 and over (WHO, 2022 reference year). They use different age ranges, data sources and modelling, are not interchangeable, and the difference is not reconciled in either publication. Type 1 and type 2 are not reliably distinguished in most population datasets, so "over 90 per cent type 2" is an estimate. Monogenic diabetes, at 1 to 4 per cent, is routinely misclassified, and misclassification changes treatment radically. DiRECT and DIADEM-I enrolled people with short disease duration, not on insulin, within specified body-size ranges, so the remission rates do not generalise to long-standing or insulin-treated disease, and the trials say so. DiRECT's five-year figure of 23 per cent is reported on a subgroup of the original cohort rather than the original randomised population, so it is not directly comparable with the 46 and 36 per cent figures. Look AHEAD did not reduce cardiovascular events, which remains unexplained and sits awkwardly with the Da Qing mortality findings. ADDITION-Cambridge found no mortality benefit from population screening while treatment of detected disease clearly works, and sources disagree on what to conclude. GLP-1 discontinuation rates in real-world use are high and weight regain after stopping is substantial, and long-term effectiveness beyond five years outside trials is unmeasured. The semaglutide production-cost estimate is modelled from active pharmaceutical ingredient costs and is contested by manufacturers; no audited figure exists. SGLT2 inhibitor and GLP-1 prices differ by one to three orders of magnitude between United States list, European tendered and Indian generic markets, so any single price figure is misleading. Whether GLP-1 agonists' cardiovascular benefit is weight-mediated or independent is unresolved. Ancestry-specific anthropometric action points are empirically derived and the biological explanation for the difference is unknown.

> **Depth.** Starts in: an insulin-sensitive cell. Size: 100 µm†; depth +7.00. First complaint: about 55 years († onset about age 55; [B] over years); time depth 52.52. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gestational diabetes

What it is. Blood glucose that rises above normal during pregnancy and returns to normal after delivery. It raises the chance of a large baby, birth injury, caesarean delivery and pre-eclampsia, and it marks a high lifetime risk of type 2 diabetes in the mother.

Measured. The IDF Diabetes Atlas has given hyperglycaemia in pregnancy as affecting roughly one in six live births, about 16 to 17 per cent worldwide, of which roughly 75 to 80 per cent is gestational diabetes and the remainder pre-existing or first-detected diabetes in pregnancy; in the 9th and 10th editions this corresponded to roughly 20 to 21 million live births affected a year†. The 11th edition press materials do not restate a gestational diabetes figure.

Prevalence varies several-fold by diagnostic criteria, which is the dominant measurement problem. The IADPSG/WHO 2013 criteria — one abnormal value on a 75 g oral glucose tolerance test, fasting at or above 5.1, one hour at or above 10.0, or two hours at or above 8.5 mmol/L — classify roughly two to three

times more women as having gestational diabetes than older criteria. Under IADPSG criteria prevalence is roughly 15 to 20 per cent in many populations; under the older Carpenter-Coustan or NICE criteria, roughly 5 to 9 per cent†. The ScreenR2GDM randomised trial (2021, *NEJM*) compared one-step IADPSG with two-step screening in over 23,000 women: the one-step approach doubled the diagnosis rate, 16.5 per cent against 8.5 per cent, with no significant difference in perinatal or maternal outcomes. This is the central negative finding in the field and it is unresolved.

Prevalence is highest in South Asia, the Middle East and North Africa, roughly 20 to 25 per cent under IADPSG criteria in several Indian and Gulf studies, and lowest in sub-Saharan Africa and parts of Europe. Risk rises steeply with maternal age; prevalence in women over 40 is roughly two to four times that in women under 25†.

The hard outcome is maternal progression to type 2 diabetes. A meta-analysis (Vounzoulaki et al., *BMJ*, 2020) found that women with gestational diabetes had nearly a ten-fold higher risk of subsequently developing type 2 diabetes than women with normoglycaemic pregnancies, relative risk 9.51. Cumulative incidence of type 2 diabetes reaches roughly 20 to 50 per cent within 10 years of the index pregnancy in cohort studies, varying by ancestry and body size.

Perinatal outcomes, from the Hyperglycemia and Adverse Pregnancy Outcome study of 25,505 women with blinded oral glucose tolerance tests and no treatment: the risk of large-for-gestational-age birthweight, cord C-peptide elevation, primary caesarean delivery and neonatal hypoglycaemia rose continuously with maternal glucose, with no threshold. This finding is why the diagnostic cut-offs are conventional rather than biological, and why the criteria dispute exists.

Offspring show higher childhood obesity and glucose intolerance in observational follow-up; whether this is causal or confounded by maternal body size is contested and the Mendelian randomisation evidence is mixed. Recurrence in a subsequent pregnancy runs roughly 40 to 50 per cent†.

Where it starts. Pregnancy is physiologically insulin-resistant from the second trimester, driven by placental hormones — human placental lactogen, placental growth hormone, progesterone, cortisol. Insulin sensitivity falls by roughly 50 to 60 per cent by the third trimester in normal pregnancy†. Gestational diabetes occurs when beta-cell compensation fails against that background, so it is mechanistically a stress test of beta-cell reserve, which is why it predicts later type 2 diabetes so strongly.

Established risk factors with effect sizes: pre-pregnancy overweight and obesity, the strongest modifiable factor, with relative risk roughly 2 for overweight, 3 to 4 for obesity and 5 to 9 for severe obesity in meta-analysis†; maternal age over 35, roughly two- to threefold†; prior gestational diabetes, with recurrence 40 to 50 per cent; family history of type 2 diabetes in a first-degree relative, roughly two-fold; ancestry, with South Asian, East and Southeast Asian, Middle Eastern, Hispanic, Pacific Islander and Indigenous women at substantially higher risk at any given body size than European women, and South Asian women at roughly three- to four-fold higher risk than white European women in United Kingdom data at lower body size; polycystic ovary syndrome, roughly two- to three-fold; excessive gestational weight gain, dose-related; multiple pregnancy, prior macrosomic infant, prior stillbirth; and short stature and low birthweight of the mother herself, with consistent associations.

The risk loci overlap substantially with type 2 diabetes — *TCF7L2*, *MTNR1B*, *GCK*, *KCNJ11*, *CDKAL1* — with *MTNR1B* having a relatively larger effect in gestational than in type 2 diabetes. Heritability is not well estimated. First-degree family history roughly doubles risk.

GCK-linked monogenic diabetes is an important misdiagnosis: women with glucokinase mutations have mildly raised fasting glucose that does not respond to treatment and does not need it, and treating them to normal maternal glucose can cause fetal growth restriction. It accounts for roughly 1 to 2 per cent of gestational diabetes diagnoses†, and recognising it changes management entirely.

Not known: where the diagnostic threshold should be, given that the Hyperglycemia and Adverse Pregnancy Outcome study found a continuous relationship with no inflection. Whether treating the women identified by the lower IADPSG thresholds improves outcomes — ScreenR2GDM says no. Whether the offspring associations are causal. Whether gestational diabetes causes later maternal type 2 diabetes or

simply reveals pre-existing susceptibility; the evidence favours revelation, which matters for how the condition is framed.

Cure status. SELF-LIMITING. The hyperglycaemia resolves after delivery in the great majority: gestational diabetes is defined as hyperglycaemia first detected in pregnancy that does not meet the criteria for overt diabetes, and it remits with delivery of the placenta. The honest statement has a second part, and it is the important one: it marks roughly a ten-fold lifetime risk of type 2 diabetes, relative risk 9.51†, with cumulative incidence of 20 to 50 per cent within 10 years†. So the condition is self-limiting and the risk it reveals is not.

Treatment during pregnancy prevents the adverse pregnancy outcomes, and this is established by two randomised trials. ACHOIS (Crowther et al., *NEJM*, 2005; 1,000 women) found that treatment reduced the composite of serious perinatal outcomes — death, shoulder dystocia, bone fracture, nerve palsy — from 4 per cent to 1 per cent, and reduced macrosomia and pre-eclampsia. Landon and colleagues (*NEJM*, 2009; 958 women with mild gestational diabetes) found treatment did not change the primary composite outcome and significantly reduced birthweight, large-for-gestational-age births, shoulder dystocia, caesarean delivery and pre-eclampsia.

Postpartum type 2 diabetes is preventable: in the Diabetes Prevention Program, women with a history of gestational diabetes had diabetes incidence reduced by roughly 50 per cent by lifestyle intervention and roughly 50 per cent by metformin† — notably, metformin was as effective as lifestyle in this subgroup, unlike in the trial overall. This is the key actionable finding.

Prevention. Pre-pregnancy weight is the dominant modifiable factor, at a relative risk of 3 to 4 for obesity. STRONG for the association; MODERATE for weight reduction before pregnancy as a demonstrated intervention, since trials of pre-conception weight loss are few.

Exercise during pregnancy: meta-analyses of randomised trials show roughly a 25 to 40 per cent reduction in gestational diabetes incidence with structured exercise programmes. MODERATE.

Dietary intervention in pregnancy: smaller and less consistent effects than exercise, with meta-analyses showing roughly 10 to 25 per cent reduction†. MODERATE.

Metformin from early pregnancy in obese women: the EMPOWaR and GRoW trials did not reduce gestational diabetes incidence or birthweight. CONTESTED to negative.

Myo-inositol supplementation: several small Italian trials reported substantial reductions, and larger independent replication is lacking. WEAK.

Probiotics: the SPRING trial was negative. WEAK to negative.

Vitamin D: no consistent effect. CONTESTED.

Prevention of the adverse pregnancy outcomes by treating the hyperglycaemia: ACHOIS, serious perinatal composite from 4 per cent to 1 per cent. STRONG.

Prevention of later type 2 diabetes is the highest-value prevention in this entry. Postpartum glucose testing at six to 13 weeks and then at least every one to three years for life. Uptake is poor almost everywhere, with reported postpartum testing rates of roughly 30 to 60 per cent even in well-resourced systems†. The test costs a few dollars and identifies a group with 20 to 50 per cent ten-year risk. Lifestyle intervention or metformin postpartum, roughly 50 per cent risk reduction each in the Diabetes Prevention Program gestational diabetes subgroup. STRONG. Breastfeeding: observational data consistently associate longer lactation with lower maternal type 2 diabetes incidence, roughly 25 to 50 per cent lower risk with longer duration in cohort studies including SWIFT, with a dose-response by months of lactation. MODERATE — observational, with confounding by indication possible, and the dose-response is consistent. Avoiding interpregnancy weight gain. MODERATE.

Treatment. Diet and physical activity as first-line, with self-monitoring of blood glucose. Roughly 70 to 85 per cent of women achieve target glucose without medication†. The resource requirement is dietitian and midwife time plus glucose strips, and strips at US$0.10 to US$0.50 each, four times daily, are a real cost in low-income settings and often the binding constraint.

Insulin is the standard pharmacological treatment and the only one with unambiguous safety data in pregnancy. Human insulin, soluble and isophane, is appropriate and is what is used in most of the world; rapid-acting analogues lispro and aspart have pregnancy safety data and are also used. **Human insulin, short-acting and intermediate-acting, is a selected medicine on the 24th List, section 18.5.1, for type 1 and type 2 diabetes; the named rapid-acting analogues are therapeutic equivalents to the rapid-acting analogue class entry rather than selected medicines**. At US$50 to US$200 a patient-year for human insulin at lowest available acquisition cost, 2024, and a pregnancy is a fraction of a year†.

Metformin crosses the placenta. The MiG trial (Rowan et al., *NEJM*, 2008; 751 women) found metformin non-inferior to insulin for the composite perinatal outcome, with less maternal weight gain and better patient acceptability, though roughly 46 per cent of metformin-treated women required supplemental insulin. Offspring follow-up at seven to nine years in MiG TOFU showed larger measures of subcutaneous fat in metformin-exposed children, which is why some guidelines remain cautious. **Metformin is a selected medicine on the 24th List, section 18.5.2, for type 2 diabetes mellitus**; gestational diabetes is not the listed indication. Off-patent, at US$2 to US$15 a patient-year at generic or lowest available acquisition cost, 2024†.

Glibenclamide (glyburide) crosses the placenta, and meta-analyses show higher rates of macrosomia and neonatal hypoglycaemia than insulin or metformin, so it is now a third-line option where insulin is unavailable. Off-patent, at cents a day. Its listing status needs checking against the 24th List†.

Obstetric management: ultrasound growth surveillance; timing of delivery, where induction at 38 to 40 weeks is common practice in treated gestational diabetes and the evidence for optimal timing is weak; intrapartum glucose management; and neonatal blood glucose monitoring and early feeding, because neonatal hypoglycaemia is the commonest complication and is preventable with early feeding and, where needed, buccal 40 per cent dextrose gel. The Sugar Babies and hPOD trials showed dextrose gel reduces admission to neonatal intensive care for hypoglycaemia, and it costs pennies.

Postpartum: oral glucose tolerance test or HbA1c at six to 13 weeks, lifelong periodic testing, metformin or lifestyle intervention for those with persisting prediabetes, and contraception and interpregnancy planning advice.

Simple means. Walking. Structured exercise in pregnancy reduces gestational diabetes incidence by roughly 25 to 40 per cent in randomised trial meta-analyses. It requires nothing.

Breastfeeding. Associated with roughly 25 to 50 per cent lower maternal type 2 diabetes risk in cohort studies, with a dose-response by duration, and it is free. It also reduces neonatal hypoglycaemia through early feeding. WHO’s infant and young child feeding fact sheet of 4 August 2026 gives exclusive breastfeeding of infants aged nought to six months at about 47 per cent for 2018 to 2025.

Early feeding of the newborn, and buccal 40 per cent dextrose gel for neonatal hypoglycaemia. Dextrose gel costs pennies and reduced neonatal unit admissions in randomised trials.

Metformin. Off-patent, a selected medicine on the 24th List, at US$2 to US$15 a patient-year at generic or lowest available acquisition cost, non-inferior to insulin for perinatal outcomes in the MiG trial, and roughly 50 per cent effective in preventing later type 2 diabetes in the Diabetes Prevention Program gestational diabetes subgroup.

Human insulin rather than analogue where cost binds.

A postpartum glucose test. A few dollars, and it identifies a woman with 20 to 50 per cent ten-year risk of type 2 diabetes. Postpartum testing rates of 30 to 60 per cent mean this cheap test is the largest missed opportunity in the entry.

Diet change. DiRECT and DIADEM-I show what weight loss does for established type 2 diabetes; for a woman after gestational diabetes, the Diabetes Prevention Program shows roughly 50 per cent risk reduction from lifestyle intervention. The trials delivered this through nurses and dietitians in ordinary primary care.

Recognising *GCK*-linked monogenic diabetes — mildly raised fasting glucose with a family history, in a lean woman, that does not respond to treatment. Recognising it prevents harmful over-treatment.

Gaps. Prevalence depends on criteria and varies two- to three-fold between them. The IADPSG/WHO 2013 criteria and the older Carpenter-Coustan and NICE criteria classify different populations, and ScreenR2GDM found that doubling the diagnosis rate produced no outcome difference. This is an unresolved dispute at the centre of the field, and any prevalence figure is criteria-dependent. The Hyperglycemia and Adverse Pregnancy Outcome study found a continuous glucose-outcome relationship with no threshold, so the diagnostic cut-offs are conventions chosen at defined odds ratios rather than biological boundaries, and that should be stated whenever a prevalence figure is given. The IDF 11th edition press materials do not restate a gestational diabetes figure, so the one-in-six and roughly 20-to-21-million figures come from earlier editions and were not re-verified against the 2025 Atlas. Whether the offspring associations are causal or confounded by maternal body size and shared environment is contested, and Mendelian randomisation results are mixed. MiG TOFU showed more subcutaneous fat at seven to nine years in metformin- exposed children, and guidelines differ on how much weight to give this. Optimal timing of delivery is not established by adequate trial. Postpartum testing uptake is poor everywhere and the reasons are system-level rather than clinical. Almost no data exist on gestational diabetes outcomes from sub-Saharan Africa, where both the screening and the treatment infrastructure are thinnest.

> **Depth.** Starts in: a placental hormone. Size: 5 nm†; depth −2.01. First complaint: about 6 months ([B] from the second trimester; † week 24–28); time depth 48.23. One untreated course: about 12 weeks ([B] normal after delivery; † about 12 weeks); depth 47.53.
>
> **Model reading.** Way of ending: let close. Layer: word. By the rule it closes by itself. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Obesity

What it is. Body fat accumulated to a degree that raises the risk of disease. It is measured in populations by body mass index — weight divided by height squared — which is a crude proxy for fat mass and says nothing about where the fat sits. It raises the risk of type 2 diabetes, cardiovascular disease, several cancers, osteoarthritis, sleep apnoea and liver disease.

This entry reports epidemiology, physiology, trial outcomes and treatment evidence. Trial interventions are described as what the trials measured, not as instructions.

Measured. From the WHO obesity and overweight fact sheet, printed 7 October 2026, with data mainly for 2024:

- Adults aged 18 and over who were overweight: **2.6 billion, or 45 per cent of adults** — 44 per cent of men and 45 per cent of women — against 25 per cent in 1990. Regional prevalence runs from 32 per cent in the South-East Asia and African Regions to 68 per cent in the Americas.
- Adults with obesity: **940 million, about 16 per cent of adults**. Adult obesity more than doubled since 1990, and adolescent obesity quadrupled.
- Living with obesity in 2024, all ages: **one in seven, 1.1 billion people**.
- Children under five who were overweight: **35 million**, almost half of them in Asia, with the African figure up nearly 12 per cent since 2000.
- Children and adolescents aged five to 19 who were overweight: **400 million, 20 per cent** — 19 per cent of girls and 21 per cent of boys — against 8 per cent in 1990.
- Children and adolescents aged five to 19 with obesity: from **2 per cent, 31 million, in 1990 to 8 per cent, 170 million, in 2024**.
- **Deaths in 2023: 3.7 million attributed to higher-than-optimal body mass index.**
- Projected economic cost: **three trillion US dollars a year by 2030 and more than 18 trillion by 2060**.
- Return on investment: 14 times per unit invested in healthy-diet best buys; almost nine in ten countries have adopted obesity-reduction policy goals; and 34 frontrunner countries under the 2022 Acceleration Plan represent 1.3 billion people.

The “one in seven” all-ages figure and the 16 per cent adult figure use different denominators, and the deaths figure uses 2023 while the rest use 2024.

An earlier WHO malnutrition fact sheet, printed 1 March 2024 with 2022 data, gives 2.5 billion adults overweight including 890 million with obesity, 390 million underweight adults, 390 million overweight in ages five to 19 including 160 million with obesity, and 37 million under-fives overweight or with obesity. **The 2022 and 2024 figures are from the same organisation and are not interchangeable**: two WHO fact sheets live simultaneously with different counts, and a reference work must not mix them.

From the UNICEF/WHO/World Bank Joint Child Malnutrition Estimates, 2025 edition, 2024 reference year, children under five: overweight 5.5 per cent (95% CI 4.9–6.1), 35.5 million, against 5.3 per cent and 36.3 million in 2012. Under-five overweight prevalence is essentially unchanged since 2000, and the number affected is up about 2.4 million since then, with Asia holding 16.3 million affected children and Africa 9.7 million. Overweight is rising in several sub-regions including parts of Africa and Asia, and current progress is insufficient to meet the 2030 Sustainable Development Goal targets.

At any given body mass index, metabolic risk is higher in South Asian, East Asian and some other populations, and WHO recommends lower action points for Asian populations.

The limitations of body mass index are measured, not theoretical. It misclassifies muscular individuals and misses individuals of ordinary weight with high visceral fat and metabolic disease. In 2025 a *Lancet Diabetes & Endocrinology* Commission proposed distinguishing clinical obesity, with established organ dysfunction, from preclinical obesity, and recommended confirming excess adiposity by a second measure — waist circumference, waist-to-height ratio, or direct fat measurement — rather than body mass index alone.

The International Agency for Research on Cancer identifies 13 cancers with sufficient evidence of a causal link to body fatness: oesophageal adenocarcinoma, gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, corpus uteri, ovary, kidney, meningioma, thyroid and multiple myeloma.

Where it starts. Fat mass increases when energy intake exceeds expenditure over time. That is not in dispute. What is in dispute is what controls intake and expenditure, and why body weight is defended so strongly against change.

Weight is physiologically defended, and this is measured. After weight loss, resting energy expenditure falls below what would be predicted for the new body size: in the *Biggest Loser* cohort, resting metabolic rate was roughly 500 kcal a day lower than predicted six years after the intervention, and the suppression persisted despite substantial weight regain (Fothergill et al., 2016)†. Appetite hormones change in the direction favouring regain: after diet-induced weight loss, leptin falls, ghrelin rises, and peptide YY and cholecystokinin fall, and these changes persist for at least 12 months (Sumithran et al., *NEJM*, 2011). These are the measured reasons that weight loss by diet alone is usually not maintained, and they are physiological rather than behavioural findings.

Body mass index is among the most heritable common human traits. Twin studies give heritability of roughly 0.4 to 0.7, and in some twin studies up to 0.8 to 0.9 in childhood†. Adoption studies show adult body mass index tracks biological rather than adoptive parents. Genome-wide association studies have found over 1,000 loci, and the strongest common variant, *FTO*, carries an effect of roughly 1 to 1.5 kg per risk allele — small†. Common variants together explain only roughly 6 to 10 per cent of variance, which is the standing missing-heritability problem in this trait. Polygenic risk scores are meaningful at the extremes: individuals in the top centile of a polygenic score weigh roughly 13 kg more on average than those in the bottom centile (Khera et al., 2019)†.

Monogenic obesity: *MC4R* variants are the commonest, present in roughly 2 to 5 per cent of severe early-onset obesity, with leptin deficiency, leptin receptor, *POMC* and *PCSK1* deficiency rarer†. These matter because setmelanotide, an MC4R agonist approved between 2020 and 2022, produces substantial weight loss specifically in *POMC*, *PCSK1* and leptin receptor deficiency and in Bardet-Biedl syndrome, and recombinant leptin (metreleptin) is curative in congenital leptin deficiency — the clearest example in this field of a mechanism-matched treatment. Syndromic obesity: Prader-Willi, Bardet-Biedl, Alström and Cohen syndromes.

Food environment: the measured associations are with energy density, portion size, ultra-processed food availability and marketing. The best-controlled experiment is Hall and colleagues (*Cell Metabolism*, 2019), a randomised crossover metabolic-ward study in which participants given an ultra-processed diet consumed roughly 500 kcal a day more and gained roughly 0.9 kg over two weeks, against an unprocessed diet matched for presented macronutrients, sugar, sodium and fibre, with both diets eaten without restriction. This is the strongest causal evidence available that food processing itself, independent of nutrient composition, affects intake.

Other established contributors: short sleep duration, shift work, physical inactivity — though its causal contribution relative to intake is contested — certain drugs, particularly the antipsychotics olanzapine and clozapine with gains of 5 to 10 kg common, and corticosteroids, insulin, sulfonylureas, some antidepressants, valproate and beta-blockers; smoking cessation, with roughly a 4 to 5 kg average gain; hypothyroidism, a small effect; Cushing syndrome; and hypothalamic damage.

The socioeconomic gradient inverts with national income: in high-income countries obesity is inversely associated with income and education, while in low-income countries the association is positive and inverts as the country's income rises. This is one of the most consistent findings in nutrition epidemiology and is unexplained in mechanistic terms.

Developmental factors: maternal obesity and gestational diabetes associate with offspring obesity, and low birthweight followed by rapid catch-up growth associates with later central adiposity.

Gut microbiome differences are consistently observed, and faecal transplant studies in humans have produced modest and inconsistent metabolic effects, so the causal contribution in humans remains unestablished despite strong mouse data.

Not known: why body weight is defended at a higher level in some people than others. Why the socioeconomic gradient inverts with national income. What specifically about ultra-processed food raises intake — energy density, texture, eating rate and hyper-palatability are all candidates and the Hall experiment could not separate them. Why heritability is 0.4 to 0.7 while common variants explain under 10 per cent. Whether physical activity's contribution is to prevention of gain rather than to loss.

Cure status. CONTROLLABLE. The term used in the literature is weight loss and maintenance, and the physiology of defended weight is why cure is not the right word.

Lifestyle intervention produces measured weight loss that is largely regained. Intensive behavioural programmes produce roughly 5 to 10 per cent weight loss at six to 12 months and roughly 3 to 5 per cent maintained at two to four years in trial settings†. In Look AHEAD, with 5,145 adults with type 2 diabetes and overweight or obesity, the intensive lifestyle group lost roughly 8.6 per cent at year one and maintained roughly 4.7 per cent at year four, against roughly 1 per cent in the control group, and the trial did not reduce its primary cardiovascular endpoint. In the Diabetes Prevention Program, roughly 7 per cent weight loss at six months accompanied a 58 per cent reduction in diabetes incidence† — the weight loss was modest and the metabolic effect was large.

GLP-1-based pharmacotherapy produces weight loss of a different order, and it is treatment-dependent. STEP 1, with semaglutide 2.4 mg weekly in 1,961 adults without diabetes over 68 weeks, gave a mean weight change of −14.9 per cent against −2.4 per cent with placebo†. SURMOUNT-1, with tirzepatide in 2,539 adults without diabetes over 72 weeks, gave −15.0 per cent at 5 mg, −19.5 at 10 mg and −20.9 at 15 mg against −3.1 per cent on placebo, with at least 5 per cent loss in 85, 89 and 91 per cent against 35 per cent, and at least 20 per cent loss in 50 per cent at 10 mg and 57 per cent at 15 mg against 3 per cent†. SELECT, with semaglutide 2.4 mg in 17,604 adults with overweight or obesity and established cardiovascular disease and no diabetes, gave a 20 per cent reduction in major adverse cardiovascular events, hazard ratio 0.80, over a mean 39.8 months† — the first trial showing that pharmacological treatment of obesity reduces cardiovascular events.

Withdrawal reverses it. The STEP 1 extension found roughly two-thirds of lost weight regained within a year of stopping, and STEP 4 showed weight regain on withdrawal and continued loss on continuation. So this is treatment of a chronic condition, not a cure. Real-world discontinuation is high, roughly 30 to 50 per cent within 12 months in United States claims analyses, mainly for cost, side effects and supply.

Bariatric and metabolic surgery produces the largest and most durable effect. Mean weight loss is roughly 25 to 30 per cent of baseline weight at one to two years, with roughly 20 to 25 per cent maintained at 10 years for gastric bypass and roughly 15 to 20 per cent for sleeve gastrectomy†. The Swedish Obese Subjects matched prospective cohort, followed over 20 years and more, found surgery reduced overall mortality by roughly 24 to 30 per cent, reduced incident type 2 diabetes by roughly 78 to 87 per cent, reduced cancer incidence in women, and reduced cardiovascular events. Perioperative mortality is roughly 0.1 to 0.3 per cent in contemporary series†.

The honest status: obesity behaves as a chronic, relapsing, physiologically defended condition. The interventions with the largest and most durable effects are surgical; the pharmacological effects are large while treatment continues and reverse when it stops; and lifestyle intervention produces modest durable weight change with disproportionately large metabolic benefit.

Prevention. Population-level fiscal and regulatory measures are where the measured before-and-after data are. Sugar-sweetened beverage taxes produced purchase reductions of roughly 10 to 20 per cent after implementation in Mexico, with roughly a 7.6 per cent decline over two years, and in Chile, in Berkeley, Philadelphia and other United States cities, and in the United Kingdom. MODERATE for consumption change; WEAK for measured effect on obesity prevalence, because the follow-up is short and the effect size on body weight is small. The United Kingdom Soft Drinks Industry Levy of 2018 is the best-documented reformulation effect: manufacturers reduced sugar content rather than pay the levy, and the sugar content of soft drinks fell by roughly 30 per cent across the market, with subsequent analyses associating it with reduced obesity prevalence in older primary school girls. MODERATE. Chile's food labelling, marketing and school-sales law of 2016 produced measured reductions in purchases of high-in labelled products of roughly 24 to 27 per cent for sugary drinks†. MODERATE. Trans fat elimination, through WHO's REPLACE programme: by 2023, roughly 53 countries covering roughly 3.7 billion people had best-practice trans fat policies. A measured regulatory success, though its outcome is cardiovascular rather than obesity. Front-of-pack labelling, marketing restrictions to children and school food standards have demonstrated effects on purchasing and intake, with effects on obesity prevalence not demonstrated. WEAK.

Prevention in childhood: Cochrane reviews of school-based and community interventions find small effects on body mass index z-score, roughly 0.05 to 0.1 standard deviations, consistent in direction and small in magnitude†. MODERATE for the small effect, and no intervention has reversed a population trend.

Breastfeeding: associated with roughly 10 to 25 per cent lower odds of childhood obesity in meta-analyses, though residual confounding is likely and the PROBIT cluster-randomised trial of breastfeeding promotion found no effect on childhood body mass index. CONTESTED.

Sleep duration: short sleep in childhood is consistently associated with higher body mass index, and sleep extension trials in children show small reductions in intake. WEAK.

Pharmacological prevention of weight regain: GLP-1 agonists maintain loss while taken. STRONG for the effect during treatment.

The honest statement about prevention: no country has reversed its adult obesity trend. Adult obesity more than doubled globally between 1990 and 2024. The measures with demonstrated effects act on purchasing and product composition, and their demonstrated effect on body weight at population level is small. This is the central negative finding in the field.

Treatment. Structured behavioural and dietary intervention is the foundation of all guidelines and the comparator in all drug and surgery trials. Trial-measured effects: 5 to 10 per cent loss at six to 12 months, 3 to 5 per cent maintained at two to four years, with metabolic benefit disproportionate to the weight change, as the Diabetes Prevention Program's 58 per cent diabetes risk reduction shows. The resource requirement is trained personnel and contact time, which is the actual cost. Not a medicine.

GLP-1 receptor agonists and dual agonists, with effect sizes as above. GLP-1 receptor agonists were added to the Model List in the 24th List (2025) — semaglutide, dulaglutide, liraglutide and tirzepatide — for adults with type 2 diabetes who also have established cardiovascular disease, chronic kidney disease or

obesity, and not for obesity alone. **That listing was not independently verified against the 24th List for this chapter, and carries a dagger pending a recheck.** The distinction between the listed indication and obesity alone matters and is frequently misreported. Liraglutide is off-patent with generics marketed; semaglutide, dulaglutide and tirzepatide are not, and semaglutide's primary patents expire in Canada, India, China and Brazil from 2026.

Prices, 2024 to 2025: semaglutide 2.4 mg on United States list roughly US$1,000 to US$1,350 a month, about 12,000 to 16,000 a patient-year, with a direct-to-consumer cash price of US$499 a month from 2025, about 6,000 a patient-year; tirzepatide on United States list roughly US$1,000 to US$1,080 a month, with direct cash 349 to 499; Europe roughly €150 to €350 a month, about 1,800 to 4,200 a patient-year; and generic liraglutide roughly US$30 to US$100 a month in some markets. The published minimum production cost estimate for semaglutide (Barber, Hill et al., *JAMA Network Open*, 2024) is roughly US$0.89 to US$4.73 a month, roughly US$11 to US$57 a patient-year at a scale of millions of patients — against the United States list price, a factor of roughly 250 to 1,500. Side effects: nausea, vomiting, diarrhoea and constipation in a large minority; gallstones; pancreatitis, rare; and loss of lean mass alongside fat mass, which is measured and whose long-term significance is unresolved.

Bariatric and metabolic surgery — Roux-en-Y gastric bypass, sleeve gastrectomy, one-anastomosis gastric bypass — with effects as above including the Swedish Obese Subjects mortality reduction of roughly 24 to 30 per cent. At US$10,000 to US$30,000 one-off in high-income systems and far less in some middle-income settings (2024)†. Not a medicine. Long-term requirements are micronutrient supplementation for life — iron, B12, calcium, vitamin D, thiamine — and surveillance for internal hernia, dumping and hypoglycaemia.

Older pharmacotherapy. Orlistat, a lipase inhibitor, gives roughly 2.5 to 3.5 kg more weight loss than placebo at one year, and the XENDOS trial showed a 37 per cent reduction in incident type 2 diabetes over four years†. Off-patent and available over the counter in many countries, at US$100 to US$500 a patient-year at generic or lowest available acquisition cost, 2024†; gastrointestinal side effects limit use. EML status needs checking against the 24th List†. Phentermine, phentermine-topiramate and naltrexone-bupropion give roughly 5 to 10 per cent weight loss with limited or absent cardiovascular outcome data. Metformin gives roughly 2 to 3 kg, off-patent at US$2 to US$15 a patient-year at generic or lowest available acquisition cost†. Withdrawn for safety: sibutramine in 2010 for cardiovascular events, rimonabant in 2008 for psychiatric effects, and fenfluramine and dexfenfluramine in 1997 for valvular disease. That history is part of the evidence base for this class.

Mechanism-matched treatment for monogenic obesity: metreleptin for congenital leptin deficiency, effectively curative in that rare condition; and setmelanotide for *POMC*, *PCSK1* and leptin receptor deficiency and Bardet-Biedl syndrome, with substantial weight loss in the indicated genotypes, priced in the hundreds of thousands of dollars a patient-year.

Treatment of the complications regardless of weight change: metformin and the rest of the type 2 diabetes armamentarium; statins and antihypertensives; continuous positive airway pressure for obstructive sleep apnoea; joint replacement for osteoarthritis; and treatment of metabolic dysfunction-associated steatotic liver disease, where resmetirom, approved in the United States in 2024, is the first licensed drug for steatohepatitis.

Drug review — substituting a weight-neutral alternative for an obesogenic drug such as an antipsychotic, antidepressant or antiepileptic where clinically possible.

Simple means. What the trials measured, with no protocol.

Diet-based weight loss, delivered through primary care. DiRECT achieved diabetes remission in 46 per cent at 12 months and 36 per cent at 24 months using a formula diet followed by structured food reintroduction, delivered by practice nurses and dietitians in ordinary general practice, and DIADEM-I achieved 61 per cent remission at 12 months in a younger Qatari cohort†. The intervention required no drug, no device and no surgery; the resource was personnel time.

Physical activity. Trial-measured: exercise was a component of the Diabetes Prevention Program, Finnish and Da Qing interventions that reduced diabetes incidence by roughly 58 per cent, and in Da Qing the

exercise-only arm was effective, with reduced mortality and roughly 1.44 years greater life expectancy at 30 years. The measured effect on weight alone is small, the measured effect on cardiometabolic outcomes is substantial, and the effect on prevention of weight gain is better established than the effect on weight loss.

Reduced consumption of sugar-sweetened beverages. Measured: each daily serving associated with 13 to 26 per cent higher type 2 diabetes risk in meta-analyses; taxes reduced purchases by 10 to 20 per cent; and the United Kingdom levy reduced the market's soft drink sugar content by roughly 30 per cent†.

Unprocessed rather than ultra-processed food. The Hall metabolic-ward crossover trial measured roughly 500 kcal a day lower intake and 0.9 kg weight loss over two weeks on an unprocessed diet eaten without restriction, compared with a matched ultra-processed diet. Cooking from whole ingredients requires no industrial chain; it requires time, fuel and skill.

Sleep. Short sleep is consistently associated with higher body mass index, and sleep extension trials measured reduced energy intake.

Breastfeeding. Associated with roughly 10 to 25 per cent lower childhood obesity odds in meta-analyses; the PROBIT randomised trial found no effect on body mass index. Reported as contested.

Metformin and orlistat. Both off-patent, both measured to reduce incident diabetes, by 31 and 37 per cent respectively†, and both costing hundreds of dollars a year or less.

Waist circumference measured with a tape. A tape measure costs cents and adds information that body mass index does not, particularly in populations where body mass index misclassifies risk. The 2025 *Lancet* Commission recommends confirming adiposity with a second measure rather than body mass index alone.

Gaps. WHO's own figures for 2022 and 2024 differ substantially — 2.5 billion against 2.6 billion overweight, and 890 million against 940 million with obesity — and come from different fact sheets using different reference years and, in part, different modelling. They are not interchangeable and the difference is not reconciled in either publication. Body mass index is a poor individual measure of adiposity: it misclassifies in both directions, its risk relationship differs by ancestry, and the 2025 Commission recommended abandoning it alone for individual diagnosis — and all the prevalence figures in this entry are based on it. Heritability is 0.4 to 0.7 while common variants explain under 10 per cent of variance†, and the missing heritability is unexplained. The socioeconomic gradient inverts with national income and the mechanism is unknown. Look AHEAD did not reduce cardiovascular events despite achieving and maintaining weight loss, which remains unexplained. PROBIT found no effect of breastfeeding promotion on childhood body mass index while observational meta-analyses find a protective association; sources disagree. The causal element in ultra-processed food is not identified — energy density, eating rate, texture and palatability were not separable in the Hall design, and the trial had 20 participants over four weeks. GLP-1 long-term outcome, safety and effectiveness data beyond five years do not exist; the drugs are too new, real-world discontinuation is 30 to 50 per cent within a year, and weight regain after stopping is substantial. Loss of lean mass with GLP-1 treatment is measured and its long-term significance is unknown. No country has reversed its adult obesity trend, and the population measures with demonstrated effects act on purchasing and product reformulation rather than on measured obesity prevalence. The semaglutide production-cost estimate is modelled and contested by manufacturers; no audited figure exists. Under-five overweight prevalence has been essentially flat since 2000 while adult obesity doubled, and the discordance is not explained. Attributable-death figures depend on counterfactual assumptions and differ between WHO and GBD methods.

> **Depth.** Starts in: a fat cell. Size: 100 µm†; depth +7.00. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Protein-energy malnutrition

What it is. Not enough food energy and protein for the body's needs. In children it shows as wasting, too thin for height; stunting, too short for age; or the oedematous form, kwashiorkor. It kills both directly and by making every infection more dangerous.

Measured. From the UNICEF/WHO/World Bank Joint Child Malnutrition Estimates, 2025 edition, 2024 reference year, children under five:

Condition	2024 prevalence (95% CI)	2024 number	2012 prevalence	2012 number
Stunting	23.2 per cent (22.6–23.8)	150.2 million	26.4 per cent	180.4 million
Wasting, moderate and severe	6.6 per cent (5.3–8.1)	42.8 million	7.4 per cent	50.9 million
Severe wasting	1.9 per cent (1.4–2.5)	12.2 million	2.2 per cent	15.0 million
Overweight	5.5 per cent (4.9–6.1)	35.5 million	5.3 per cent	36.3 million

Stunting declined for more than two decades, and the 2025 report states that recent data show a halt and a possible rise, putting past progress at risk. Wasting is trending down, with about eight million fewer affected children than in 2012†.

Regionally in 2024, stunting affects 76.8 million children in Asia, down from 108.8 million in 2012, and 64.8 million in Africa, up from 61.7 million — Africa is the only region where the number significantly increased, and Africa's stunting prevalence is 30.3 per cent†. Wasting affects roughly 70 per cent of affected children in Asia, 30.0 million, and roughly 27 per cent in Africa, 11.7 million, with Southern Asia having the highest wasting prevalence of any sub-region. Current progress is insufficient to meet the 2030 Sustainable Development Goal targets†.

The source states a caveat that matters: wasting figures are prevalence-based snapshots, so they underestimate the number of children affected over a full year, because wasting episodes are short and recurrent. Annual incidence is roughly two to three times point prevalence.

The WHO malnutrition fact sheet, printed 1 March 2024 with 2022 data, gives 45 million children under five wasted, 149 million stunted and 390 million underweight adults, and states that nearly half of deaths among children under five are linked to undernutrition without giving an absolute number. The WHO infant and young child feeding fact sheet of 4 August 2026 gives, for 2024, about 150 million children under five stunted, 43 million wasted and 36 million overweight, and states that maternal and child malnutrition was associated with 2.4 million child deaths annually in 2021, more than 50 per cent of all child deaths. **Two WHO fact sheets therefore live simultaneously with different child undernutrition counts for different reference years, and the 2022 figures are superseded**.

The standing attributable-mortality estimate, from the *Lancet* Maternal and Child Nutrition Series of 2013, updated 2021, is that undernutrition underlies roughly 45 per cent of all deaths in children under five, roughly three million child deaths a year, mostly through increased severity of pneumonia, diarrhoea, measles and malaria. Case fatality in untreated severe acute malnutrition is roughly 10 to 30 per cent in community settings and was historically 20 to 30 per cent in inpatient facilities before modern protocols†.

Adult undernutrition is measured by body mass index under 18.5 and is concentrated in South Asia and sub-Saharan Africa, at 390 million underweight adults (WHO, 2022 data).

The Integrated Food Security Phase Classification framework measures acute food insecurity, and in 2024 to 2025 it recorded famine conditions or risk in Sudan, Gaza, Haiti, South Sudan and Mali. These figures move monthly and are not stable enough to quote as prevalence.

Where it starts. The immediate cause is inadequate dietary intake and disease, acting together. The UNICEF conceptual framework of immediate, underlying and basic causes remains the standard analytic structure and is empirically supported.

Underlying causes with measured contributions. Household food insecurity — availability, access, affordability: the cost of a healthy diet exceeded the income of roughly 2.8 billion people in 2022 (FAO/WHO/UNICEF/WFP/IFAD, *State of Food Security and Nutrition in the World*). Inadequate care and

feeding practices: exclusive breastfeeding for the first six months is practised for about 47 per cent of infants globally for 2018 to 2025 (WHO infant and young child feeding fact sheet, 4 August 2026), and inadequate complementary feeding from six months is near-universal in high-burden settings — roughly two-thirds of children aged six to 23 months do not receive a minimum acceptable diet, and only 30.8 per cent of children aged six to 23 months met minimum dietary diversity for 2018 to 2024, with only half having minimum meal frequency. Infection: diarrhoea, pneumonia, measles, malaria, HIV, tuberculosis, and environmental enteric dysfunction — chronic subclinical small-bowel inflammation from repeated faecal-oral exposure, which impairs absorption and is now considered a major contributor to stunting that food alone does not fix.

Water, sanitation and hygiene: the association with stunting is strong, yet the three large randomised trials — WASH Benefits Bangladesh, WASH Benefits Kenya and SHINE in Zimbabwe — found that water, sanitation and handwashing interventions did not reduce stunting, while nutrition interventions through complementary feeding did, modestly. This is a major and genuinely surprising negative result.

Maternal undernutrition and short maternal stature: maternal height and pre-pregnancy body size predict offspring birthweight and stunting, and low birthweight accounts for roughly 20 per cent of stunting in some analyses†. Adolescent pregnancy and short birth intervals. Women's education and status, consistently among the strongest predictors in multi-country analyses.

Basic causes: poverty, conflict, displacement, governance, climate shocks and food price shocks. Conflict is the dominant driver of acute malnutrition emergencies, and the large majority of people in the most severe Integrated Food Security Phase Classification conditions are in conflict-affected areas.

Kwashiorkor against marasmus: the oedematous form has resisted explanation for seventy years. It is not simply protein deficiency — the classic protein hypothesis has not held up. Current candidate mechanisms involve aflatoxin exposure, oxidative stress and glutathione depletion, sulphur amino acid deficiency, gut microbiome composition and leaky gut, and none is established. Why two children in the same household with similar diets develop marasmus and kwashiorkor respectively is unknown, and it is one of the oldest unanswered questions in nutrition.

Stunting's window is the first 1,000 days, from conception to age two, when most stunting accrues; after about 24 months catch-up in linear growth is limited. This timing finding underpins all current programming.

Not known: the cause of kwashiorkor. Why the water, sanitation and hygiene trials failed to reduce stunting when the observational association is so strong. How much stunting is reversible after 24 months — some catch-up occurs in adolescence and its functional significance is contested. What proportion of stunting is attributable to environmental enteric dysfunction as opposed to diet.

Cure status. Severe and moderate acute malnutrition, that is wasting: CURABLE, and the cure is food. Stunting established by about 24 months: RELIEF ONLY. Adult undernutrition: CURABLE with food, except where the cause is an untreated disease — tuberculosis, HIV, cancer, malabsorption — in which case the disease must be treated.

Severe acute malnutrition is curable with ready-to-use therapeutic food. Community-based management of acute malnutrition using that food achieves recovery rates of roughly 80 to 90 per cent in programme data, with case fatality under 5 per cent, against historical inpatient case fatality of 20 to 30 per cent†. This shift — from inpatient milk-based treatment to outpatient therapeutic food — is among the largest advances in child survival of the past thirty years. The food is a lipid-based paste of peanut, milk powder, oil, sugar and micronutrients requiring no water, no refrigeration and no cooking, which is why it works outside facilities.

Complicated severe acute malnutrition, with medical complications, oedema, or a failed appetite test, requires inpatient stabilisation with F-75 then F-100 therapeutic milk and careful management of electrolytes and infection; case fatality remains roughly 10 to 20 per cent even in good facilities, because these children are critically ill.

Simplified and reduced-dose protocols, in ComPAS and OptiMA, show non-inferior recovery with roughly 25 to 35 per cent less therapeutic food in randomised and programme evidence†, which matters because the cost of that food is the binding constraint on coverage.

Moderate acute malnutrition is treated with supplementary feeding, with recovery rates roughly 70 to 85 per cent, and relapse is common†.

Stunting is largely not reversible after about 24 months. This is the honest limit: linear growth faltering that has already occurred by age two is mostly permanent, and the associated cognitive and economic deficits persist into adulthood. Prevention is therefore the only effective approach to stunting.

Prevention. Exclusive breastfeeding for the first six months, then continued breastfeeding with adequate complementary food. The single largest preventive intervention. Pooled analyses estimate that non-exclusively breastfed infants under six months have roughly two to five times the risk of death from diarrhoea and pneumonia, with the highest relative risks in the first months. The *Lancet* Breastfeeding Series of 2016 estimated that scaling up breastfeeding could prevent roughly 823,000 child deaths and 20,000 breast cancer deaths annually; WHO's own fact sheet of 4 August 2026 gives nearly 400,000 under-five deaths a year as preventable by exclusive breastfeeding for six months and continued breastfeeding to two years or beyond, and the two figures are not the same quantity and are not reconciled. The current exclusive breastfeeding rate is about 47 per cent globally for 2018 to 2025, against a WHO target of at least 60 per cent by 2030. STRONG.

Complementary feeding interventions: in WASH Benefits Bangladesh and Kenya and in SHINE, the nutrition arms reduced stunting modestly, roughly 0.1 to 0.25 standard deviations in length-for-age, while the water and sanitation arms did not. MODERATE, a small but replicated effect.

Small-quantity lipid-based nutrient supplements for children aged six to 23 months: an individual-participant-data meta-analysis of 14 randomised trials in roughly 37,000 children found a 12 per cent reduction in stunting, 14 per cent in wasting, 13 per cent in anaemia, 27 per cent in severe stunting and 21 per cent in severe anaemia, plus reduced mortality in some analyses†. STRONG — this is the best-evidenced child nutrition supplement of the past decade.

Maternal nutrition: multiple micronutrient supplements in pregnancy outperform iron-folic acid alone, with meta-analysis showing roughly 8 to 12 per cent reductions in low birthweight and small-for-gestational-age births and reduced stillbirth in some analyses. WHO's 2020 recommendation permits them in the context of rigorous research, and many countries have adopted them. Balanced energy-protein supplementation in undernourished pregnant women reduces small-for-gestational-age births and stillbirth. MODERATE.

Cash transfers: conditional and unconditional transfers reduce stunting in several randomised and quasi-experimental evaluations, with effect sizes depending on transfer size and duration. MODERATE.

Food fortification of staples. STRONG for the specific micronutrient outcomes.

Immunisation, insecticide-treated nets, oral rehydration salts and zinc for diarrhoea, and antibiotics for pneumonia, all of which prevent the infections that drive wasting and stunting. STRONG.

Deworming: effects on growth are small and contested; Cochrane finds little or no effect on weight, haemoglobin or school performance in mass treatment. CONTESTED.

Water, sanitation and hygiene: the three large randomised trials did not reduce stunting. CONTESTED to negative for stunting, while remaining strongly justified for diarrhoea, cholera and other outcomes. This disagreement between observational and trial evidence is one of the most consequential in global health.

Family planning and birth spacing: short birth intervals are associated with higher stunting, and interventions reduce them. MODERATE.

Girls' education, among the strongest and most consistent predictors in multi-country analyses. MODERATE as a measured intervention.

Treatment. Ready-to-use therapeutic food for uncomplicated severe acute malnutrition in children aged six to 59 months, delivered through outpatient community programmes. The specification is public and local production exists in India, Ethiopia, Nigeria, Kenya, Madagascar, Niger and elsewhere. A full six-to-eight-week treatment course costs roughly US$35 to US$50 (2024), roughly US$0.30 to US$0.50 a sachet at 150 to 200 sachets a child, and UNICEF procures roughly four to five million cartons a year. Simplified protocols reduce this by 25 to 35 per cent. Recovery is roughly 80 to 90 per cent with case fatality under 5

per cent†. The listing status of ready-to-use therapeutic food on the 24th List and the Model List for Children needs checking†.

F-75 and F-100 therapeutic milks for inpatient stabilisation of complicated severe acute malnutrition, with reduced-osmolarity rehydration solution for malnutrition. Off-patent, at dollars a child a day. Listing status needs checking against the 24th List†.

Routine medicines in severe acute malnutrition. A broad-spectrum antibiotic, amoxicillin, for all children with uncomplicated severe acute malnutrition: randomised trials in Malawi and Niger gave discordant results, with the Malawi trial showing reduced mortality and improved recovery and the Niger trial showing no mortality benefit. WHO recommends routine amoxicillin and the evidence is contested. **Amoxicillin is a selected medicine on the 24th List, in section 6.2.1, Access group antibiotics, core list, with severe acute malnutrition among its named first-choice indications**. Off-patent, at cents a course; UNICEF's indicative price for 250 mg dispersible tablets, pack of ten, was US$0.54 in October 2026, about US$0.054 a tablet, and these are indicative prices refreshed against live tenders rather than a fixed price. Vitamin A; zinc, in the therapeutic food, with additional zinc for diarrhoea; folic acid; antimalarials where endemic; measles vaccination on admission; and deworming after stabilisation. **Not iron during the acute phase** — iron is withheld until the recovery phase, because free iron increases infection risk in severely malnourished children. A treatment point that is easy to get wrong.

Oral rehydration salts and zinc for diarrhoea. Off-patent. Oral rehydration salts cost roughly US$0.05 to US$0.20 a sachet and zinc roughly US$0.03 to US$0.10 a tablet (2024)†; UNICEF's indicative price for low-osmolarity oral rehydration salts in a carton of 100 was US$4.80 in October 2026, about US$0.048 a sachet. Oral rehydration salts are among the highest-impact low-cost interventions in medicine. The listing status of both needs checking against the 24th List†.

Supplementary food for moderate acute malnutrition: fortified blended flours such as corn-soy blend plus, or lipid-based supplements, at roughly US$15 to US$30 a treatment course at procurement prices, 2024†.

Treatment of the underlying disease — tuberculosis, HIV, malaria, coeliac disease, congenital heart disease. In adults and older children, undernutrition without food scarcity is usually a symptom of disease.

Refeeding syndrome management in severely malnourished older children and adults: thiamine, phosphate, potassium and magnesium replacement, with slow energy increase. Cheap, and lethal if ignored.

Simple means. This entry is almost entirely simple means, and that is the point.

Breastfeeding. Exclusive for six months, continued to two years with complementary food. Non-exclusively breastfed infants have roughly two to five times the risk of death from diarrhoea and pneumonia, and scaling up breastfeeding could prevent roughly 823,000 child deaths annually†. It requires no product, and what it requires — maternity protection, time, support, and not being undermined by formula marketing — is social, not industrial.

Oral rehydration salts, or the home-made salt-and-sugar solution. The sachets cost cents and are one of the most effective medicines ever devised. The home solution of salt, sugar and clean water works where sachets are unavailable.

Zinc for diarrhoea, which reduces duration by 25 per cent and stool volume by 30 per cent (WHO diarrhoeal disease fact sheet, 7 March 2024), at cents a course.

Complementary food made from locally available ingredients — fermented and germinated cereals, legumes, groundnuts, eggs, small fish eaten whole, dark green leaves, orange-fleshed sweet potato. The measured interventions in WASH Benefits and SHINE that reduced stunting were complementary feeding interventions using local foods plus a lipid-based supplement.

Soaking, germinating and fermenting cereals and legumes, which reduces phytate and raises iron and zinc bioavailability. Traditional, free, measurable.

A mid-upper arm circumference tape. A paper or plastic strip costing cents that identifies severe acute malnutrition and can be used by a mother on her own child. Family MUAC programmes have been shown

to identify cases earlier and at scale with no clinical staff. This is the single best example in the chapter of a simple means replacing an industrial chain.

Measles vaccination and insecticide-treated nets, which prevent the infections that precipitate wasting.

Handwashing with soap, which reduces diarrhoea substantially, even though the water, sanitation and hygiene trials did not show a stunting effect.

Keeping the child feeding during illness, and extra feeding during recovery. Appetite loss during infection and failure to feed up afterwards is a major driver of wasting.

Not giving iron during the acute phase of severe malnutrition.

Ready-to-use therapeutic food made locally. The specification is public, the ingredients are peanut, milk powder, oil, sugar and a micronutrient premix, and local production in Niger, Ethiopia, India and elsewhere has brought cost down and supply closer.

Gaps. Wasting prevalence is a point-in-time snapshot and underestimates annual burden by a factor of roughly two to three, as the Joint Child Malnutrition Estimates report itself states, and incidence data are sparse. WHO's 2022 fact sheet figures and the 2025 Joint Child Malnutrition Estimates are different reference years and are not interchangeable; another dossier in this project prints the 2022 figures alone and unflagged, so the superseded numbers are in circulation. Both stand, unresolved. The cause of kwashiorkor is unknown after seventy years of research. The three large water, sanitation and hygiene randomised trials did not reduce stunting while the observational association is strong — a central unresolved disagreement with major programmatic consequences. Routine amoxicillin in uncomplicated severe acute malnutrition: the Malawi and Niger trials disagree and WHO recommends it. Deworming: Cochrane finds little or no effect on growth and mass deworming programmes continue. How much stunting is reversible after 24 months, and whether adolescent catch-up has functional significance, is contested. The contribution of environmental enteric dysfunction to stunting is not quantified. Attributable mortality of roughly 45 per cent of under-five deaths rests on comparative risk assessment with counterfactual assumptions, the figure is widely used and the uncertainty is wide. Stunting has halted and may be rising, and the reasons — conflict, food prices, climate — are not disentangled. Integrated Food Security Phase Classification famine classifications change monthly and no stable figure can be quoted. Almost all treatment evidence is in children aged six to 59 months; infants under six months with wasting are a large, poorly studied group with no established protocol beyond breastfeeding support, and mortality in that group is high.

> **Depth.** Starts in: protein and energy (shortage). Size: 5 nm†; depth −2.01. First complaint: about 7.4 weeks († weeks to months); time depth 47.10. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. The book names a late stratum. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Vitamin A deficiency

What it is. Not enough vitamin A. The first sign is difficulty seeing in dim light; then the surface of the eye dries, ulcerates and scars, and the child goes blind. It also weakens resistance to infection, so children die of measles and diarrhoea who would otherwise survive.

Measured. Stevens et al., *Lancet Global Health*, 2022, the most recent global micronutrient synthesis, found that 372 million preschool children aged six to 59 months (95% UI 319–425 million), 56 per cent, had at least one of iron, zinc or vitamin A deficiency, and that 1.2 billion non-pregnant women of reproductive age (1.0–1.4 billion), 69 per cent, had at least one of iron, zinc or folate deficiency. The paper does not publish separate per-nutrient counts in the abstract, and where only two of the three biomarkers were measured the third was estimated by regression.

The earlier WHO global estimates, with reference years 1995 to 2005 and published 2009, remain the most widely cited vitamin-A-specific figures: vitamin A deficiency, defined as serum retinol below 0.70 µmol/L, in 190 million preschool children (33.3 per cent) and 19.1 million pregnant women (15.3 per cent); and

night blindness in 5.2 million preschool children (0.9 per cent) and 9.8 million pregnant women (7.8 per cent), with the highest prevalence in Africa and South-East Asia.

Historically roughly 250,000 to 500,000 children a year went blind from vitamin A deficiency, with roughly half dying within 12 months of losing sight†. Those figures date from the 1990s and current numbers are substantially lower but not well measured, which is itself the finding.

Vitamin A deficiency is counted in GBD as a risk factor rather than a cause, and the mortality effect is measured through supplementation trials. The vulnerable window is six to 59 months, with risk peaking after weaning and during measles and diarrhoeal illness, and pregnant and lactating women are the second group. Sub-Saharan Africa and South Asia carry the burden, and the deficiency has essentially disappeared from high-income countries except in malabsorption states and severely restricted diets.

UNICEF reports two-dose annual supplementation coverage of roughly 50 to 70 per cent in priority countries, having fallen from a peak above 70 per cent in the mid-2010s† — coverage is declining, which is a measured programmatic regression.

Where it starts. Inadequate intake of preformed vitamin A — retinol, from liver, eggs, dairy and fish — or of provitamin A carotenoids — beta-carotene, from orange and dark green plant foods — relative to need. Needs rise during growth, pregnancy, lactation and infection.

Bioavailability is the key quantitative point. Conversion of dietary beta-carotene to retinol is inefficient and was revised downward: the current factor is roughly 12:1 by weight for beta-carotene in a mixed diet, and 24:1 for other provitamin A carotenoids, against an older assumed 6:1†. Fat in the meal is required for absorption, so carotenoid-rich diets without fat deliver far less vitamin A than the food composition tables suggest. This is why advice to eat more green vegetables has often underperformed.

Infection depletes it: measles, diarrhoea and respiratory infection increase urinary retinol loss and reduce intake simultaneously. Measles in a vitamin-A-deficient child is the classic route to corneal ulceration and blindness, and the relationship is bidirectional — deficiency worsens measles and measles worsens deficiency. WHO's measles fact sheet of 15 July 2026 records the standing recommendation of two doses of vitamin A for suspected cases under five, with a third dose four to six weeks later if there are eye complications.

Fat malabsorption causes it regardless of intake: cystic fibrosis, cholestasis, coeliac disease, pancreatic insufficiency, short bowel, bariatric surgery. Zinc deficiency impairs vitamin A mobilisation, since zinc is needed for retinol-binding protein synthesis, so the two deficiencies interact. Protein-energy malnutrition reduces retinol-binding protein, so serum retinol falls partly for that reason, which complicates measurement.

Not heritable. Rare monogenic causes of retinol transport defects exist, in *RBP4*, and are vanishingly rare.

The measurement problem is itself a cause of uncertainty: serum retinol is homeostatically controlled until liver stores are nearly exhausted, and falls during infection and inflammation independent of vitamin A status, so serum-retinol-based prevalence estimates are both insensitive to mild deficiency and inflated by concurrent infection.

Not known: current global prevalence, because the authoritative WHO figures use data from 1995 to 2005. Whether the mortality benefit of supplementation, established in trials run in the 1980s and 1990s, still holds in populations with better measles vaccination coverage, lower background mortality and partial food fortification. This is a live and consequential dispute.

Cure status. CURABLE, and the cure is dietary or a cents-worth capsule. This is among the clearest entries in the chapter, with one limit: corneal scarring does not reverse.

Biochemical deficiency and night blindness reverse within days to weeks of adequate vitamin A. Keratomalacia that has perforated or scarred the cornea causes permanent blindness, so the cure is complete only if it comes before that point.

The mortality effect, from the Cochrane review (Imdad et al., 2022; 47 randomised trials, roughly 1,223,856 children aged six to 59 months, 19 countries):

Outcome	Relative risk (95% CI)	Trials / children	GRADE certainty
All-cause mortality	**0.88 (0.83–0.93)**	19 trials / 1,202,382	High
Diarrhoea mortality	0.88 (0.79–0.98)	9 trials / 1,098,538	High
Measles mortality	0.88 (0.69–1.11)	6 studies / 1,088,261	Low, not significant
Diarrhoea incidence	0.85 (0.82–0.87)	15 studies / 77,946	Low
Measles incidence	0.45 (0.30–0.69)	2 studies / 1,982	Low
Night blindness	**0.32 (0.21–0.50)**	2 studies / 22,972	Moderate
Bitot's spots	0.42 (0.33–0.53)	5 studies / 1,063,278	Moderate
Biochemical vitamin A deficiency	0.71 (0.65–0.78)	4 studies / 2,262	Moderate
Respiratory disease incidence	0.99 (0.92–1.06)	11 studies / 27,540	Low, no effect
Vomiting within 48 hours	1.97 (1.44–2.69)	4 studies / 10,541	Moderate, harm

Supplementation reduces all-cause mortality in children aged six to 59 months by about 12 per cent, with high GRADE certainty, and reduces diarrhoea-specific mortality by a similar amount. It does not significantly reduce measles or respiratory deaths, and it reduces measles and diarrhoea incidence. The main adverse effect is vomiting within 48 hours of a large dose.

The dispute: the DEVTA trial in India, with roughly one million children, cluster-randomised and published in 2013, found a mortality reduction of only about 4 per cent, not statistically significant, at a mortality ratio of 0.96. DEVTA is the single largest trial and it is an outlier. Its inclusion pulls the pooled estimate down, and the Cochrane pooled figure of 0.88 includes it. Critics of DEVTA cite incomplete dosing records and lower baseline deficiency, and its authors defend it. This is the central live disagreement in the field, and it determines whether universal supplementation programmes should continue.

Treatment of measles with vitamin A — two large doses on consecutive days — reduces measles mortality substantially in deficient populations. This is a standing WHO recommendation and is distinct from the prophylaxis question.

Prevention. High-dose supplementation every four to six months for children aged six to 59 months. All-cause mortality relative risk 0.88 with high certainty, night blindness 0.32, Bitot's spots 0.42†. The dose is 100,000 IU for infants aged six to 11 months and 200,000 IU for children aged 12 to 59 months. STRONG on the Cochrane evidence; CONTESTED in the light of DEVTA and of falling background mortality. Cost is roughly US$0.02 to US$0.03 a capsule at generic or lowest available acquisition cost, and roughly one to two dollars per child a year delivered, including distribution — among the cheapest mortality-reducing interventions measured anywhere.

Food fortification. Vitamin A fortification of cooking oil, sugar, wheat flour and margarine. Oil is the best vehicle because vitamin A is fat-soluble and oil is centrally processed. Guatemala's sugar fortification programme raised serum retinol measurably and is the longest-running example. MODERATE for biochemical status, MODERATE for clinical outcomes. Roughly 30 countries mandate vitamin A fortification of edible oil, and roughly 25 to 30 fortify sugar or flour with vitamin A†.

Biofortification with orange-fleshed sweet potato and provitamin A maize. Randomised and quasi-experimental trials in Mozambique and Uganda showed that introducing orange-fleshed sweet potato raised serum retinol and reduced the prevalence of low serum retinol in children by roughly 10 to 15 percentage points, with adoption sustained over years†. This is a plant-breeding intervention requiring no supplement chain. MODERATE.

Measles vaccination, which prevents the illness that converts subclinical deficiency into corneal destruction. STRONG. Measles vaccine has been in use about 60 years and costs under one US dollar a child (WHO measles fact sheet, 15 July 2026), and vaccination averted nearly 59 million deaths between 2000 and 2024.

Breastfeeding, which is a reliable vitamin A source for the first six months, and maternal supplementation raises breast milk retinol. STRONG.

Dietary diversification — liver, eggs, dairy, small whole fish, dark green leaves, and orange fruits and vegetables, with fat in the meal. MODERATE: the effect is real and the carotenoid conversion inefficiency of 12:1 limits what plant sources alone achieve.

Postpartum maternal supplementation: WHO no longer recommends routine high-dose maternal supplementation, because trials including large Bangladeshi and Ghanaian trials found no reduction in maternal or infant mortality. Neonatal dosing was likewise tested in three large NEOVITA trials in Ghana, India and Tanzania, with discordant results — benefit in India, none in Ghana or Tanzania — and is not universally recommended. CONTESTED, and reported here because older guidance differs.

Avoiding excess in pregnancy: preformed vitamin A above roughly 10,000 IU a day is teratogenic, so liver and high-dose supplements are restricted in pregnancy. STRONG for the harm.

Treatment. High-dose oral vitamin A as retinyl palmitate capsules for xerophthalmia and for measles in deficient populations: 200,000 IU on day 1, day 2 and day 14, with lower doses by age. Off-patent, at roughly US$0.02 to US$0.03 per 200,000 IU capsule at generic or lowest available acquisition cost, 2024, so a full treatment course costs under 10 US cents†. Retinol's listing status needs checking against the 24th List†.

Eye care for xerophthalmia: topical lubrication, topical antibiotic to prevent secondary bacterial keratitis, and protection of the perforating cornea. Cheap, and the difference between sight and blindness.

Treating the precipitating illness — measles, diarrhoea, pneumonia — and the concurrent protein-energy malnutrition.

Vitamin A as part of severe acute malnutrition protocols, now given in the therapeutic food rather than as a separate high dose in most protocols.

Fat-soluble vitamin replacement in malabsorption, with water-miscible preparations for cholestasis and cystic fibrosis, and monitoring of serum retinol to avoid toxicity.

Managing toxicity: acute hypervitaminosis A — headache, vomiting, raised intracranial pressure, bulging fontanelle in infants — resolves on stopping; chronic toxicity causes bone pain, hepatotoxicity and alopecia.

Simple means. This is one of the entries where the simple means is the cure and the prevention.

Liver, once or twice a week. A small portion of ruminant or poultry liver contains several times a child's weekly vitamin A requirement in preformed, highly bioavailable form. Nothing matches it per unit cost.

Eggs, milk, butter, small whole fish, and fish liver. Preformed retinol, no conversion needed.

Orange-fleshed sweet potato. Trials in Mozambique and Uganda measured roughly 10 to 15 percentage point reductions in low serum retinol prevalence in children after its introduction. It is a crop, propagated by vine cuttings, requiring no factory and no supplement chain. The single best example of a plant-breeding solution to a micronutrient deficiency.

Dark green leaves, mango, papaya, pumpkin and carrot — eaten with fat. The fat is the essential part: absorption of provitamin A carotenoids requires dietary fat, and the conversion ratio is roughly 12:1 by weight, so the quantity needed is large and fat-free preparation wastes most of it.

Red palm oil. Among the richest natural sources of provitamin A carotenoids, widely used in West and Central Africa, and it supplies both the carotenoid and the fat in one ingredient.

Breastfeeding, a reliable vitamin A source for the first six months, free.

Measles vaccination, which prevents the illness that blinds the deficient child, at under one dollar a child.

The capsule itself. At roughly US$0.02 to US$0.03 a dose at generic or lowest available acquisition cost, and roughly one to two dollars per child-year delivered, the supplement is nearly as simple as a food, and it has high-certainty randomised evidence of a 12 per cent reduction in all-cause child mortality.

Not giving high-dose vitamin A to pregnant women, because of teratogenicity above roughly 10,000 IU a day.

Gaps. The authoritative vitamin-A-specific global prevalence figures — 190 million children, 33.3 per cent — use data from 1995 to 2005, and no comparable update exists; Stevens et al. (2022) report combined multi-deficiency figures and do not publish separate vitamin A counts in the abstract. DEVTA, the largest trial, found no significant mortality benefit, roughly 4 per cent, against the Cochrane pooled estimate of 12 per cent with high certainty; sources disagree sharply, and the dispute concerns both DEVTA's conduct and whether older trial results generalise to today's lower-mortality, measles-vaccinated populations. Supplementation coverage is falling, from above 70 per cent to roughly 50 to 70 per cent in priority countries, for programmatic rather than evidential reasons. Serum retinol is a poor biomarker — homeostatically controlled, depressed by inflammation, and dependent on retinol-binding protein which falls in protein-energy malnutrition — so prevalence figures are method-dependent and probably misclassify in both directions. Neonatal and postpartum maternal dosing: the three NEOVITA trials disagreed with each other, WHO withdrew the routine postpartum recommendation, and older national guidance still reflects the previous advice. Current numbers for xerophthalmia and vitamin-A-attributable blindness are not well measured, and the widely quoted 250,000 to 500,000 blinded children a year is from the 1990s. The carotenoid conversion factor was revised from roughly 6:1 to 12:1, which halves the estimated vitamin A supply from plant-based diets in older assessments, so historical dietary adequacy estimates based on food composition tables are unreliable. The interaction with zinc deficiency is established mechanistically and not quantified in programme terms.

> **Depth.** Starts in: retinol. Size: 1.4 nm†; depth −3.17. First complaint: about 6.6 months († body stores last months); time depth 48.32. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book's status: CURABLE. Reading and status agree. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Iodine deficiency disorders

What it is. Not enough iodine to make thyroid hormone. The thyroid swells into a goitre. In a developing fetus and infant the shortage damages the brain permanently, which is the reason iodine deficiency matters more than the swelling.

Measured. Household coverage of iodised salt is nearly 89 per cent globally (Iodine Global Network Annual Report 2025), with West and Central Africa at 74 per cent, the Middle East and North Africa at 80.4 per cent, South Asia at 89.8 per cent and East Asia and the Pacific at 91 per cent.

The monitoring situation, stated by the monitoring body itself, is the finding. Of 171 countries in the WHO iodine database, 44 have one survey, 86 have two to four, 41 have five or more, and 25 have no survey at all; 43 per cent of countries have no coverage data and 34 per cent have data from before 2018.

About 187 million people had goitre from iodine deficiency as of 2010, 2.7 per cent of the world population; iodine deficiency affects roughly two billion people worldwide; and deaths attributed to iodine deficiency were about 2,700 in 2013, up from about 2,100 in 1990†. A goitre is considered endemic when prevalence exceeds 5 per cent.

Pregnancy is the remaining problem even in iodine-sufficient countries. In United States ECHO cohort data, roughly 45 per cent of pregnant participants had inadequate iodine intake, with similar findings reported in the United Kingdom, Norway and Australia. Pregnancy roughly increases iodine requirement by 50 per cent†.

The cognitive effect is measured. Iodine deficiency during development is associated with an average drop of about 12 IQ points in Chinese meta-analytic data†. Introducing salt iodisation in the United States in the 1920s raised IQ by about one standard deviation in the most iodine-deficient quarter of the population (Feyrer, Politi and Weil, analysing United States military test data before and after iodisation) — one of the largest population cognitive effects ever attributed to a single public health measure. Severe deficiency in pregnancy causes cretinism — profound intellectual disability, deaf-mutism, spasticity and stunting — which was endemic in Alpine valleys, the Himalayas, the Andes and inland China and has been largely eliminated by iodisation.

Country data before and after. Norway: before 1950, up to 80 per cent of people in inland areas had goitre; from the 1950s iodine was added to dairy cow feed rather than to salt, and goitre incidence fell. Switzerland was the first country to iodise salt, in 1922, and endemic cretinism and goitre disappeared†. The United States introduced iodised salt in 1924. The United Kingdom has no mandatory iodisation and relies on iodine in milk from fortified cattle feed, which has fallen with changing dairy practices and plant-milk substitution; a 2011 study found almost 70 per cent of teenage girls tested were iodine deficient†. Australia and New Zealand mandated iodised salt in most commercial bread making from October 2009.

Cost: iodine added to salt costs only a few cents a tonne, and salt iodisation programme cost is on the order of US$0.02 to US$0.05 per person a year†. Germany's iodine deficiency costs are estimated at about a billion dollars a year in health care. A United Kingdom model estimates that supplementation for pregnant women saves £199 per woman in health service costs and £4,476 in societal costs — projected savings, not programme costs†.

Where it starts. Low iodine in soil and therefore in local food and water. Iodine is leached from soil by glaciation, flooding and erosion, so mountainous regions and river flood plains are the classic deficient areas — the Alps, Himalayas, Andes, the Great Lakes basin, inland China, Central Asia. Coastal populations with marine food are generally sufficient. This is a geological cause, which is why the disease maps onto terrain rather than onto poverty alone.

Goitrogens add to the effect where intake is marginal: cassava, through linamarin releasing thiocyanate; cruciferous vegetables; millet; soy; and smoking. Cassava is the important one — in parts of Central Africa, high cassava intake with marginal iodine produces goitre and cretinism at iodine concentrations that would otherwise be tolerable.

Selenium and iron deficiency impair thyroid hormone synthesis and the response to iodine, so concurrent deficiencies blunt the benefit of iodisation.

Pregnancy and lactation raise requirement by roughly 50 per cent, and the fetal brain depends entirely on maternal thyroxine in the first trimester, before the fetal thyroid functions. The window for the cognitive damage is the first and second trimester, which is why maternal status before and in early pregnancy is what matters, and why correcting it late does not repair it.

Excess iodine also causes disease: iodine-induced hyperthyroidism, particularly transiently after iodisation programmes begin in previously deficient populations with nodular goitre, and at high chronic intakes, hypothyroidism and autoimmune thyroiditis. Japanese seaweed consumption provides intakes an order of magnitude above recommendations with some increase in subclinical hypothyroidism. The dose-response is U-shaped, which constrains programme design.

Not heritable, though thyroid volume and the tendency to nodule formation are.

Not known: current global and national iodine status, because 43 per cent of countries have no coverage data and 34 per cent have data from before 2018. Whether mild-to-moderate maternal iodine deficiency in otherwise iodine-sufficient countries causes measurable cognitive harm — the observational data suggest it does, and the randomised trials of iodine supplementation in mildly deficient pregnant women in India and Thailand, published in 2021, found no effect on child neurodevelopment at five to six years†, which is a significant negative.

Cure status. The deficiency state: CURABLE by iodine. The goitre regresses partially or fully in children and young adults, less so in long-standing nodular goitre in adults. The brain damage already done: RELIEF ONLY. Cretinism and the IQ loss from fetal and infant deficiency are permanent, and iodine given after the window does not repair it.

Universal salt iodisation is the standing cure at population level, and it has worked. Cretinism has been eliminated from most of the world, household iodised salt coverage is nearly 89 per cent†, and the number of iodine-deficient countries fell from 110 in 1993 to roughly 20 to 25 by the late 2010s†. This is the most successful micronutrient programme in history. The remaining problem is pregnancy, and the countries without mandatory iodisation.

Prevention. Universal salt iodisation. The measure, with the before-and-after data above: Switzerland 1922, the United States 1924, and the global fall from 110 iodine-deficient countries in 1993 to roughly 20 to 25 now, with household coverage near 89 per cent. Cost is a few cents a tonne of salt, or US$0.02 to US$0.05 per person a year in a universal salt iodisation programme†. STRONG — the best-evidenced population fortification programme in existence, and the cheapest. Potassium iodate rather than potassium iodide is used in hot humid climates because it is more stable.

Iodised salt in processed food and bread. Where most salt intake comes from processed food rather than the table, household salt iodisation alone is insufficient, which is why Australia and New Zealand mandated iodised salt in bread from 2009. MODERATE.

Iodine in animal feed, the Norwegian and historical United Kingdom route, delivering iodine through milk. It works, and it is fragile: United Kingdom iodine status fell as dairy practice and plant-milk consumption changed. MODERATE, with the caveat that it is not robust to dietary change.

Iodine supplementation in pregnancy, at 150 µg a day, or iodised salt plus a supplement. WHO recommends iodine supplementation in pregnancy where iodised salt coverage is below 20 per cent. In severely deficient populations, maternal iodine before or in early pregnancy prevents cretinism, from the classic Papua New Guinea and Zaire iodised oil trials: STRONG. In mildly-to-moderately deficient populations, the randomised trials published in 2021 found no effect on child neurodevelopment at five to six years: CONTESTED.

Iodised oil, by injection or oral dose, used historically in remote populations without salt distribution, where a single dose provides iodine for about a year. Largely superseded by salt iodisation. STRONG where salt iodisation is impossible.

Reducing cassava dependence or processing cassava properly — soaking, fermenting and drying removes most of the cyanogenic glycosides. MODERATE in cassava-dependent populations.

Monitoring: median urinary iodine concentration in school-age children, with a target of 100 to 199 µg/L, and in pregnant women, with a target of 150 to 249 µg/L; and salt iodine content at household and production level. This is the part that has broken down, with 43 per cent of countries having no coverage data.

Avoiding excess: monitoring for iodine-induced hyperthyroidism in the early years of a programme in a previously deficient population with nodular goitre. STRONG as a programme safeguard.

Treatment. Iodised salt — the population treatment and prevention in one. Off-patent, at a few cents a tonne of salt, or US$0.02 to US$0.05 per person-year of a salt iodisation programme†. The listing status of iodine and of potassium iodide needs checking against the 24th List†.

Potassium iodide tablets or iodine drops for individuals, at micrograms a day, costing under one dollar a patient-year (2024)†.

Iodised oil, oral or intramuscular, a single dose covering about a year, for remote populations, at roughly US$0.50 to US$2.00 a dose at lowest available acquisition cost†.

Levothyroxine for established hypothyroidism from iodine deficiency and for congenital hypothyroidism. **Levothyroxine is a selected medicine on the 24th List, in section 18.7, thyroid hormones and antithyroid medicines, for hypothyroidism, as oral solid 25, 50 and 100 µg as sodium, first added in 1977**. Off-patent, at US$5 to US$50 a patient-year at generic or lowest available acquisition cost, 2024†.

Goitre: iodine repletion shrinks diffuse goitre in children and young adults. Long-standing multinodular goitre does not regress, and treatment is thyroidectomy or radioiodine, which reduces goitre volume by roughly 40 to 60 per cent over a year and is cheap and effective†. Surgery is reserved for compressive symptoms, suspicion of malignancy, or cosmetic indication.

Iodine-induced hyperthyroidism: thionamides, beta-blockers, and definitive treatment with radioiodine or surgery.

Congenital hypothyroidism: newborn screening and levothyroxine within the first two weeks of life prevents intellectual disability entirely.

Simple means. This entry is the clearest case in the whole chapter of a simple means being both the cure and the prevention.

Iodised salt. A few cents a tonne. It eliminated endemic cretinism from most of the world, reaches nearly 89 per cent of households, and in the United States raised IQ by about one standard deviation in the most deficient quarter of the population. There is no industrial chain to speak of: it is a potassium iodate premix added at the salt works, and small-scale and artisanal salt producers can and do add it.

Seaweed and marine fish. A reliable natural source; a small amount of kelp or dried seaweed contains many times the daily requirement — and can easily contain too much, which is the caution.

Milk, eggs and dairy in countries where cattle feed is iodine-fortified.

Proper cassava processing — soaking, fermenting, sun-drying. Traditional, free, and it removes the goitrogen.

Potassium iodide drops or tablets, under a dollar a year.

A hand around the neck. Goitre is detectable by palpation with no equipment, and goitre prevalence above 5 per cent in schoolchildren defines endemicity. This is how the global programme was monitored before urinary iodine assays, and it still works.

A salt test kit — a spot test for iodine in salt costing cents, usable by anyone, used in household surveys worldwide.

Iodine supplementation in pregnancy where salt coverage is inadequate, at micrograms a day and under a dollar a year, with the caveat that it must come before and during early pregnancy to matter.

Gaps. The monitoring system has largely broken down: 43 per cent of countries have no iodised salt coverage data, 34 per cent have data from before 2018, and 25 countries have never had an iodine status survey. The near-89 per cent household coverage figure is itself therefore uncertain, and the Iodine Global Network report does not date it. There is no current count of iodine-deficient countries or of people with inadequate intake with the authority of the 1990s and 2000s assessments. The 187 million goitre figure is from 2010 and the 2,700 deaths figure from 2013. The randomised trials of iodine supplementation in mildly-to-moderately deficient pregnant women found no effect on child neurodevelopment while observational data associate mild maternal deficiency with lower child IQ — a direct conflict between trial and cohort evidence with major policy consequences for countries like the United Kingdom. Pregnancy iodine status in high-income countries is inadequate in a large minority, roughly 45 per cent in the United States ECHO sample, and the clinical significance is contested. The dose-response is U-shaped and the upper safe limit at population level is not firmly established, particularly in high-seaweed-consumption populations. The interaction with selenium and iron deficiency is established mechanistically and not quantified programmatically. The United Kingdom and several other high-income countries have no mandatory iodisation and declining status, and whether to introduce it is an unresolved policy question. The IQ effect sizes — 12 points in Chinese data, one standard deviation in the most deficient United States quartile — come from very different designs and populations and should not be read as interchangeable estimates of the same quantity.

> **Depth.** Starts in: thyroid hormone (iodine shortage). Size: 1.2 nm†; depth −3.31. First complaint: about 9 months († from conception to birth (fetal brain)); time depth 48.61. One untreated course: no number ([B] permanent).
>
> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Zinc deficiency

What it is. Not enough zinc. Children grow poorly, diarrhoea lasts longer and comes back more often, wounds heal badly and infections are more frequent. There is no good single blood test for it, which is why it is poorly measured.

Measured. About 2.2 billion people are affected, and conservative estimates put the share of the world population at risk at 25 per cent†. Stevens et al., *Lancet Global Health*, 2022, found 372 million preschool children (319–425 million), 56 per cent, with at least one of iron, zinc or vitamin A deficiency, and 1.2 billion non-pregnant women of reproductive age (1.0–1.4 billion), 69 per cent, with at least one of iron, zinc or folate deficiency; per-nutrient counts are not published in the abstract.

Estimated inadequate zinc intake from food supply data, using International Zinc Nutrition Consultative Group methods and FAO food balance sheets, puts roughly 17 per cent of the global population at risk of inadequate intake, with national estimates above 25 to 30 per cent across South Asia and sub-Saharan Africa†.

The claim that zinc deficiency causes stunted growth in one-third of the world's population should be read as an attribution claim, not a measurement. Attributable mortality estimates from GBD and earlier comparative risk assessments range from roughly 100,000 to 450,000 child deaths a year, principally through diarrhoea and pneumonia†; the range reflects different counterfactual assumptions, and recent GBD iterations have reduced or removed zinc as a separate risk factor.

Infants and young children, and pregnant and lactating women, are most affected because requirements are highest relative to intake, with adolescents during growth spurts also at risk. The burden falls on South Asia and sub-Saharan Africa, where cereal-and-legume diets are high in phytate and low in animal-source food, and on soil-zinc-deficient areas — much of South Asia, parts of Turkey, Australia and West Africa have zinc-poor soils, which lowers crop zinc content directly.

Acrodermatitis enteropathica, the monogenic form caused by *SLC39A4* variants, is very rare at roughly 1 in 500,000 births and was uniformly fatal before zinc treatment was discovered in 1973†.

Where it starts. Inadequate intake or absorption relative to requirement.

Phytate is the central quantitative fact. Phytic acid in cereal and legume seeds binds zinc and prevents absorption, and the phytate-to-zinc molar ratio determines bioavailability: ratios above about 15 indicate low bioavailability, roughly 15 per cent absorption, and ratios below about 5 indicate good bioavailability, roughly 50 per cent absorption†. A diet of unrefined cereals and legumes with no animal food can therefore deliver adequate zinc on paper and inadequate zinc in fact — the same problem as with iron, and for the same chemical reason.

Zinc in meat, fish, shellfish, eggs and dairy is absorbed several times better than cereal zinc, and oysters are the richest food source known. Soil zinc deficiency lowers crop zinc content, a geological contributor particularly across the Indo-Gangetic plain.

Diarrhoea causes substantial zinc loss, so diarrhoea causes zinc deficiency and zinc deficiency prolongs diarrhoea — a measured vicious circle, and the reason zinc is given as diarrhoea treatment.

Malabsorption: coeliac disease, Crohn's disease, short bowel, cystic fibrosis, chronic pancreatitis, bariatric surgery. Increased losses: sickle cell disease through urinary loss, chronic kidney disease, cirrhosis, diuretics, burns, dialysis. High requirements: pregnancy, lactation, infancy, adolescence, recovery from severe malnutrition.

Interactions: high-dose iron supplements reduce zinc absorption, and high-dose zinc reduces copper absorption and can cause copper deficiency anaemia and myelopathy — a real iatrogenic harm, seen with denture adhesives and with long-term high-dose zinc self-medication.

Heritability does not apply to the acquired deficiency. Acrodermatitis enteropathica is autosomal recessive, from *SLC39A4* encoding the ZIP4 zinc transporter, with heritability 1.0 for the genotype.

Not known: how much zinc deficiency there actually is, because there is no reliable biomarker. Serum or plasma zinc is the usual measure and it is insensitive — homeostatically controlled, falling with infection and inflammation, falling after a meal, varying diurnally, and not tracking tissue stores. Every global prevalence figure for zinc deficiency is therefore derived from dietary intake modelling from food supply data, not from measured status. This is the central epistemic problem in this entry and it should be stated plainly.

Cure status. CURABLE by diet or by a cents-worth tablet. The deficiency state corrects within days to weeks. Acrodermatitis enteropathica is CONTROLLABLE by lifelong oral zinc: before 1973 it was fatal in infancy, and with zinc, affected individuals are normal. One of the cleanest nutrient-cures-disease stories in medicine — with the standing note that the zinc must continue.

Zinc for acute diarrhoea in children is the best-evidenced use. WHO's diarrhoeal disease fact sheet, printed 7 March 2024, states that **zinc reduces episode duration by 25 per cent and stool volume by 30 per cent**, with a course of 10 to 14 days. The Cochrane review of oral zinc for treating diarrhoea in children reports that in children over six months of age zinc shortened the duration of diarrhoea, with diarrhoea lasting beyond day seven less likely and a mean reduction in duration of roughly 10 to 12 hours in healthy well-nourished children, with larger effects in zinc-deficient and malnourished populations. The two figures describe different populations and are routinely quoted interchangeably. In infants under six months zinc shows no benefit and possible harm, and WHO's recommendation applies from six months. Vomiting is increased by zinc treatment, a consistent adverse effect. WHO and UNICEF recommend 20 mg a day for 10 to 14 days, and 10 mg for infants aged two to six months, for every child with diarrhoea, alongside oral rehydration salts.

Zinc for pneumonia prevention: the Cochrane review in children aged two to 59 months found a modest reduction in incidence, with a small effect size, and the source consulted gives none.

Growth: zinc supplementation in deficient children produces a small but consistent increase in linear growth — meta-analyses give roughly 0.3 to 0.4 cm additional height over supplementation periods of months, and a height-for-age z-score gain of roughly 0.1 to 0.2 standard deviations†. Small, replicated.

Zinc for the common cold: meta-analyses of zinc lozenges report reduced duration of roughly one to two days in adults, and the evidence is heterogeneous, formulation-dependent and contested.

Prevention. Zinc fortification of staple foods, usually as zinc oxide or zinc sulphate alongside iron and folic acid in wheat and maize flour. It raises intake measurably, and effects on functional outcomes are less well demonstrated than for iodine or folic acid. MODERATE.

Biofortification with zinc wheat and zinc rice. HarvestPlus zinc wheat has been released in Pakistan and India and zinc rice in Bangladesh, and randomised efficacy trials of zinc biofortified wheat in Pakistani households (BiZiFED2) showed increased plasma zinc and some functional benefits†. MODERATE — a plant-breeding intervention requiring no supplement chain, with trial evidence accumulating.

Small-quantity lipid-based nutrient supplements, which contain zinc: the individual-participant-data meta-analysis of 14 trials found a 14 per cent reduction in wasting, 12 per cent in stunting and 13 per cent in anaemia†. STRONG for the package.

Agronomic zinc fertilisation in zinc-deficient soils raises grain zinc content and yield simultaneously, and has been deployed at scale in Turkey, where zinc fertiliser use rose from near zero to hundreds of thousands of tonnes a year with measured increases in crop zinc. MODERATE.

Dietary diversification with animal-source foods, and reducing phytate by soaking, germinating, fermenting and leavening. MODERATE — metabolic studies are clear and population outcome data are limited.

Preventive zinc supplementation in children in deficient populations reduces diarrhoea incidence by roughly 10 to 20 per cent and pneumonia incidence modestly in meta-analyses†. MODERATE.

Zinc with oral rehydration salts for every episode of childhood diarrhoea — prevention of the next episode as well as treatment of this one, since zinc reduces diarrhoea incidence over the following two to three months. STRONG.

Avoiding excess: high-dose zinc causes copper deficiency, and upper intake levels exist for this reason. STRONG for the harm.

Treatment. Zinc sulphate, acetate or gluconate, oral, 20 mg elemental zinc daily for 10 to 14 days, for childhood diarrhoea, alongside oral rehydration salts. Off-patent, at roughly US$0.03 to US$0.10 a dispersible tablet at generic or lowest available acquisition cost, so a full 10-to-14-day course costs roughly

US$0.30 to US$1.40 in 2024, with co-packaged oral-rehydration-salts-and-zinc kits at roughly US$0.50 to US$1.00†. The listing status of zinc sulphate, including the co-packaged form on the Model List for Children, needs checking against the 24th List†.

Oral rehydration salts, the essential partner, off-patent at US$0.05 to US$0.20 a sachet (2024)†; UNICEF's indicative price for a carton of 100 low-osmolarity sachets was US$4.80 in October 2026, about US$0.048 a sachet, printed as indicative and dated rather than as a price. Listing status needs checking against the 24th List†.

Therapeutic zinc in severe acute malnutrition, included in the micronutrient premix of ready-to-use therapeutic food and in F-75 and F-100 therapeutic milks.

Lifelong zinc for acrodermatitis enteropathica, at roughly 1 to 3 mg/kg a day elemental zinc, at tens of dollars a patient-year†. Curative while continued.

Zinc in malabsorption states, sickle cell disease, and chronic liver and kidney disease, with monitoring and attention to copper status.

Zinc acetate in Wilson disease is a different use: it blocks copper absorption. Off-patent; listing status needs checking against the 24th List†.

What not to do: give high-dose zinc long-term without monitoring copper; give zinc to infants under six months for diarrhoea; or give zinc and high-dose iron together expecting full absorption of both.

Simple means. Zinc tablets with oral rehydration salts for childhood diarrhoea. Roughly US$0.30 to US$1.40 for a full course at generic or lowest available acquisition cost. It is oral, dispersible, no cold chain, usable by a caregiver at home. Together with oral rehydration salts this is among the cheapest life-saving combinations in medicine.

Animal-source food — meat, offal, fish, shellfish, eggs, dairy, insects. Zinc from these is absorbed several times better than cereal zinc, and they also reduce the inhibitory effect of phytate in the same meal.

Soaking, germinating, fermenting and leavening cereals and legumes. Phytase activity degrades phytate and raises zinc absorption substantially — the difference between roughly 15 and roughly 50 per cent absorption depending on the phytate-to-zinc ratio achieved. Sourdough leavening, injera fermentation, idli and dosa fermentation, and sprouting all do this. Traditional practice, free, chemically measurable.

Not taking high-dose iron supplements at the same meal as zinc-containing food.

Zinc-biofortified wheat and rice. A seed, not a supplement chain.

Agronomic zinc fertiliser in zinc-deficient soils, which raises both crop zinc and yield, so the farmer has an independent reason to use it.

Oysters and small whole fish where available, the richest natural sources.

Breastfeeding. Breast milk zinc is highly bioavailable, and exclusive breastfeeding covers requirements for the first six months.

Handwashing and clean water — fewer diarrhoea episodes means less zinc loss.

Gaps. There is no reliable biomarker for zinc status. Plasma zinc is insensitive, falls with inflammation and after meals, and does not reflect tissue stores. All global prevalence figures are modelled from food supply data rather than measured, and the 2.2 billion affected and 25 per cent at risk figures should be read accordingly. The claim that zinc deficiency causes stunting in one-third of the world's population is an attribution estimate from older literature and is not a measurement; the supplementation trials show growth effects of roughly 0.1 to 0.2 standard deviations in height-for-age, which is small. Attributable child mortality estimates range from roughly 100,000 to 450,000 a year depending on counterfactual assumptions, and recent GBD iterations have changed how zinc is handled as a risk factor. The reported effect on diarrhoea duration differs between populations — roughly 10 to 12 hours in well-nourished children against roughly 25 per cent duration reduction in deficient populations — and the two are not contradictory and are routinely quoted interchangeably. Zinc gives no benefit and possible harm in infants under six months, which is not always reflected in programme guidance. Vomiting is increased by

therapeutic zinc, which reduces adherence and is under-reported in advocacy material. The effect of zinc on pneumonia prevention is small and the Cochrane review consulted gives no effect size. Zinc for the common cold is contested, formulation-dependent and heterogeneous. Fortification and biofortification have demonstrated effects on intake and plasma zinc, and demonstrated effects on stunting, diarrhoea and mortality at programme scale are thin. The interaction with copper means population-wide high-dose approaches carry a real harm, and the safe upper limit at population level is not firmly established.

> **Depth.** Starts in: a zinc-dependent molecule. Size: 1 nm†; depth −3.48. First complaint: about 5 weeks († weeks to months); time depth 46.75. One untreated course: no number.
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> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book's status: CURABLE, with CONTROLLABLE for a named stratum. Reading and status agree. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Rickets and vitamin D deficiency

What it is. Not enough vitamin D, or not enough calcium, so growing bone does not mineralise. Legs bow, the wrists and ribs swell at the growth plates, and children are slow to walk. In adults the same process softens already-formed bone, which is osteomalacia.

Measured. Nutritional rickets is a disease of specific populations, not of latitude alone. Reported incidence: United Kingdom roughly 7.5 to 24 per 100,000 children a year in South Asian, African and Middle Eastern communities, against near zero in the white British population; Denmark roughly 2.9 per 100,000 a year overall, with a relative risk of roughly 60 in children of immigrant origin compared with ethnic Danes; Australia roughly 4.9 per 100,000 a year, concentrated in dark-skinned and veiled populations; and Canada roughly 2.9 per 100,000 a year on national paediatric surveillance, with over 90 per cent of cases in breastfed infants not given vitamin D supplements.

Nigeria, Bangladesh, Tibet, Mongolia, Yemen, Turkey and Ethiopia report far higher rates, with calcium-deficiency rickets — adequate vitamin D and very low dietary calcium — the dominant form in Nigeria and The Gambia, and vitamin D deficiency rickets dominant in Mongolia, Tibet and parts of the Middle East and South Asia, where prevalence in some surveys has exceeded 30 to 70 per cent of young children.

Vitamin D deficiency, defined as serum 25-hydroxyvitamin D below 30 nmol/L, the threshold used in the 2016 Global Consensus on nutritional rickets, affects roughly 5 to 20 per cent of the general population in high-income countries, with much higher figures in specific groups — up to 50 to 80 per cent in veiled women, dark-skinned populations at high latitude, nursing-home residents and people with limited outdoor exposure. Insufficiency, below 50 nmol/L, affects roughly 30 to 60 per cent of populations in Europe and North America in winter, depending on the threshold chosen.

Rickets presents from about three months to two years in the vitamin D deficiency form, and later — 18 months to four years, and again in adolescence — in the calcium deficiency form. Osteomalacia is an adult and elderly disease.

The geographic paradox is that rickets is common at high latitude and in sunny countries where clothing, indoor living, air pollution and skin pigmentation limit UVB exposure: Mongolia, Tibet, the Gulf, and parts of North Africa and South Asia have among the highest reported rates.

Rickets itself rarely kills, and hypocalcaemic seizures, dilated cardiomyopathy and cardiac arrest from vitamin D deficiency in infancy are documented causes of infant death and are entirely preventable. Rickets admissions in England rose several-fold between the 1990s and the 2010s, and the condition is now described as re-emerging in several high-income countries.

Where it starts. Two distinct causes, and distinguishing them matters for treatment. Vitamin D deficiency — inadequate cutaneous synthesis plus inadequate intake. Dietary calcium deficiency — adequate vitamin D but calcium intake far below requirement, typical of maize- and cassava-based diets with little dairy, and the dominant form in Nigeria and The Gambia. Giving vitamin D alone does not cure the calcium form.

Cutaneous synthesis is the main source and it is highly constrained. UVB wavelengths of 290 to 315 nm are required, and above roughly 35 to 37 degrees of latitude there is effectively no cutaneous synthesis in

winter — the vitamin D winter lasts roughly November to March in northern Europe. Melanin absorbs UVB, and deeply pigmented skin requires roughly three to ten times the exposure of pale skin for the same synthesis. Clothing and veiling block synthesis entirely in covered areas. Sunscreen at correct application thickness blocks most synthesis, though real-world application reduces it less than laboratory studies suggest. Glass blocks UVB, so indoor sunlight does not work. Cutaneous synthetic capacity falls by roughly 50 to 75 per cent between young adulthood and old age†. Air pollution attenuates UVB measurably and is a documented contributor in South Asian cities. Synthesis occurs around solar noon, and morning and evening sun at temperate latitudes produces little.

Dietary sources are few: oily fish, cod liver oil, egg yolk, UV-exposed mushrooms, liver and fortified foods. Unfortified diets essentially cannot supply adequate vitamin D, which is why fortification and supplementation exist.

Breast milk is low in vitamin D, roughly 20 to 80 IU/L, so exclusively breastfed infants require supplementation unless the mother is on high-dose supplementation. This is the single commonest cause of nutritional rickets in high-income countries — over 90 per cent of Canadian surveillance cases were breastfed infants without supplements — and it is one of the few places in this chapter where breastfeeding alone is insufficient and a supplement is required.

Maternal vitamin D deficiency produces deficient neonates, because fetal stores depend on maternal status. Malabsorption — coeliac disease, Crohn's disease, cystic fibrosis, cholestasis, bariatric surgery — causes it. Drugs accelerate vitamin D catabolism: anticonvulsants (phenytoin, phenobarbital, carbamazepine), rifampicin, glucocorticoids, antiretrovirals. Chronic kidney disease impairs 1-alpha-hydroxylation and causes renal rickets and osteodystrophy, which requires active vitamin D analogues rather than cholecalciferol.

Genetic forms must be distinguished because they do not respond to ordinary doses. X-linked hypophosphataemic rickets, from *PHEX*, at roughly 1 in 20,000, is now treated with burosumab, an anti-FGF23 antibody far more effective than phosphate and active vitamin D and costing on the order of US$200,000 to US$400,000 a patient-year at lowest available acquisition cost†. Vitamin D-dependent rickets type 1, from *CYP27B1* 1-alpha-hydroxylase deficiency, is treated with calcitriol. Type 2, from a *VDR* receptor defect, needs very high-dose calcium and calcitriol. Hereditary hypophosphatasia, from *ALPL*, is treated with asfotase alfa.

Serum 25-hydroxyvitamin D concentration is heritable at roughly 0.2 to 0.5 in twin studies, with *GC*, *CYP2R1*, *DHCR7* and *CYP24A1* as the main loci†. Nutritional rickets itself is environmental.

Not known: what serum 25-hydroxyvitamin D concentration people actually need. The thresholds differ between authorities — the United States Institute of Medicine set 50 nmol/L as sufficient for bone health in 97.5 per cent of the population, the Endocrine Society prefers above 75 nmol/L, and the 2016 Global Consensus on nutritional rickets uses below 30 nmol/L as deficiency, 30 to 50 as insufficiency and above 50 as sufficiency. These are not reconciled, and the entire vitamin D deficiency prevalence literature depends on which is chosen.

Cure status. Nutritional rickets and adult osteomalacia: CURABLE. Genetic forms, X-linked hypophosphataemia and vitamin D-dependent rickets: CONTROLLABLE. Established fixed deformity: RELIEF ONLY, with corrective osteotomy.

Nutritional rickets heals completely with vitamin D and calcium. Biochemical healing — alkaline phosphatase, calcium, phosphate, parathyroid hormone — occurs over weeks; radiographic healing over one to three months; and bone deformity in young children remodels and usually corrects fully without surgery if treated before the deformity becomes fixed. Established severe deformity in older children may require corrective osteotomy, so the cure is complete only if it comes early enough.

Hypocalcaemic seizures and cardiomyopathy reverse with calcium and vitamin D.

Calcium-deficiency rickets requires calcium, and vitamin D alone will not cure it. This is the commonest treatment error in the African literature.

The genetic forms are controllable rather than curable: X-linked hypophosphataemia responds well to burosumab and requires it indefinitely, and vitamin D-dependent rickets requires lifelong calcitriol.

Adult osteomalacia heals with repletion, with resolution of bone pain and proximal myopathy, over months.

Prevention. Universal infant vitamin D supplementation. The measure that works, and the near-universal recommendation: 400 IU (10 μg) daily from birth for all breastfed infants, and for formula-fed infants taking less than roughly one litre of fortified formula a day. Where implemented and adhered to, nutritional rickets becomes rare: Finland had very high rickets rates in the early twentieth century and has had near-universal infant supplementation plus food fortification since, and rickets is now almost absent. Adherence is the problem — supplementation rates among breastfed infants are roughly 20 to 60 per cent in surveys in Canada, the United States and the United Kingdom, and over 90 per cent of Canadian rickets surveillance cases were unsupplemented breastfed infants. Cost is roughly one to five US dollars per infant-year for vitamin D drops (2024)†. STRONG.

Pregnancy supplementation at 400 to 1,000 IU a day, higher in deficient women, raises neonatal 25-hydroxyvitamin D and reduces neonatal hypocalcaemia. The MAVIDOS trial found no effect on neonatal bone mineral content overall and a benefit in winter-born infants. MODERATE.

Food fortification. Mandatory or widespread vitamin D fortification of milk, in the United States and Canada from the 1930s and 1940s; of margarine, mandatory in the United Kingdom from the 1940s until deregulation; and more recently of a wider range of foods in Finland, from 2003 onward, for fluid milks and fat spreads. **The Finnish fortification policy produced a measured population rise in mean serum 25-hydroxyvitamin D of roughly 20 nmol/L, and reduced the prevalence of concentrations below 50 nmol/L from roughly 55 per cent to roughly 9 per cent between the 2000 and 2011 national health surveys**†. This is the clearest before-and-after fortification dataset for vitamin D. STRONG. United States and Canadian milk fortification effectively eliminated classical nutritional rickets in the mid-twentieth century: STRONG, from historical before-and-after data. Overall: STRONG for biochemical status and for classical rickets; CONTESTED for the wider non-skeletal claims.

Calcium adequacy, the other half, and the limiting nutrient in much of sub-Saharan Africa. STRONG for calcium-deficiency rickets.

Sunlight exposure. Effective and free, and constrained by latitude, season, pigmentation, clothing, air pollution and skin cancer risk. The 2016 Global Consensus declined to give a quantitative sun exposure recommendation because the required dose varies so widely and because of skin cancer risk. MODERATE — mechanistically certain, not quantifiable as a prescription.

Targeted supplementation of high-risk groups: dark-skinned and veiled individuals at high latitude, nursing-home and housebound people, people on anticonvulsants, those with malabsorption, and people with obesity, in whom vitamin D is sequestered in adipose tissue and serum concentrations are lower for the same intake. STRONG.

What vitamin D does not prevent, by randomised trial — stated because it determines how much to spend. VITAL, with 25,871 participants on 2,000 IU a day for 5.3 years, found no reduction in cancer incidence or major cardiovascular events. D2d, with 2,423 participants with prediabetes on 4,000 IU a day, found no significant reduction in progression to type 2 diabetes overall†. Multiple trials and meta-analyses find no reduction in fracture risk from vitamin D alone in community-dwelling adults; the fracture benefit is seen with vitamin D plus calcium in institutionalised and deficient populations. On falls the effect is inconsistent, and high intermittent doses — 500,000 IU annually, 60,000 IU monthly — increased falls and fractures in two randomised trials†, an important harm. On respiratory infection, meta-analyses show a small reduction concentrated in deficient individuals receiving daily rather than bolus dosing, the largest trials have been null, and the effect is CONTESTED. So vitamin D prevents rickets and osteomalacia, which is a large and certain benefit in the deficient; the wider claims have mostly not survived randomised testing.

Treatment. Cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2), with calcium. The 2016 Global Consensus on the Prevention and Management of Nutritional Rickets recommends, for treatment: infants

under three months, 2,000 IU a day for at least three months; three to 12 months, 2,000 IU a day; 12 months to 12 years, 3,000 to 6,000 IU a day; and over 12 years, 6,000 IU a day — for a minimum of three months, followed by maintenance of 400 to 600 IU a day, together with oral calcium 500 mg a day in all cases, because the healing bone takes up calcium rapidly and hypocalcaemia can otherwise be precipitated. Single high-dose therapy of 50,000 to 600,000 IU is an alternative where adherence is a problem, and doses above 300,000 IU risk hypercalcaemia. Off-patent, at roughly one to ten US dollars a patient-year for cholecalciferol at preventive doses, and roughly US$2 to US$20 for a full treatment course at generic or lowest available acquisition cost, 2024† — among the cheapest cures in medicine. The listing status of ergocalciferol, cholecalciferol and calcium needs checking against the 24th List†.

Calcium — carbonate, lactate, gluconate, or dietary. Off-patent, at US$5 to US$30 a patient-year at generic or lowest available acquisition cost, 2024†. For calcium-deficiency rickets, calcium is the treatment and vitamin D is adjunctive. Listing status needs checking against the 24th List†.

Intravenous calcium for hypocalcaemic seizures or cardiomyopathy, an emergency, at cents an ampoule; UNICEF's indicative price for calcium gluconate was printed at 10.66 and at US$5.01 on different catalogue pages in October 2026, which is why these are given as indicative and dated rather than as a price. Listing status needs checking against the 24th List†.

Active vitamin D analogues — alfacalcidol or calcitriol — for renal rickets, 1-alpha-hydroxylase deficiency and vitamin D receptor defects. Not for nutritional rickets. Off-patent, at US$50 to US$400 a patient-year at generic or lowest available acquisition cost, 2024†. Calcitriol's listing status needs checking against the 24th List†.

Phosphate and active vitamin D, or burosumab, for X-linked hypophosphataemia. Burosumab is patented at roughly US$200,000 to US$400,000 a patient-year at lowest available acquisition cost, 2024†; its listing status needs checking against the 24th List†. The price-to-effect contrast with nutritional rickets — cured for under US$20 at generic or lowest available acquisition cost, 2024 — is one of the widest in this chapter.

Orthopaedic correction for fixed deformity after biochemical healing. Treatment of the underlying malabsorption or drug cause, with higher doses and water-miscible preparations in malabsorption.

Monitoring: alkaline phosphatase, calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D, and wrist or knee radiographs for healing. A falling alkaline phosphatase is the cheapest marker of response.

Simple means. This entry, with iodine deficiency and vitamin A deficiency, is one where the simple means is the cure.

Sunlight. Free, and the evolved source. The constraints are quantitative and must be stated: UVB at 290 to 315 nm, around solar noon, on uncovered skin, outdoors because glass blocks it, with roughly three to ten times longer exposure needed for deeply pigmented skin, and effectively no synthesis above roughly 35 to 37 degrees of latitude in winter. The 2016 Global Consensus declined to give a numerical sun prescription for those reasons and because of skin cancer risk, so sunlight is reported here as an effective means, not as a dosing instruction.

Vitamin D drops for infants, 400 IU a day, at roughly one to five dollars per infant-year. This single measure, where adhered to, makes nutritional rickets rare. Over 90 per cent of Canadian surveillance cases were unsupplemented breastfed infants, so the gap is adherence, not cost or technology.

Cod liver oil. The historical cure, identified in the 1920s, and still among the cheapest and most concentrated natural sources. A teaspoon supplies several times the daily requirement.

Oily fish — sardines, mackerel, herring, salmon — including small fish eaten whole with bones, which supply vitamin D and calcium together.

Egg yolk, liver, and UV-exposed mushrooms. Mushrooms exposed to sunlight generate substantial vitamin D2, a free household intervention.

Dietary calcium: dairy, small whole fish with bones, ground eggshell — used as a calcium source in several low-income settings and measurably effective — dark green leaves, calcium-set tofu, and traditionally nixtamalised maize, lime-treated, which raises the calcium content of the staple substantially.

Nixtamalisation is an ancient Mesoamerican process using wood ash or lime, and it is one of the best examples of a traditional food technology solving a nutritional deficiency.

Fortified milk and margarine. The cost per person per year of fortification is cents, and Finland's programme moved mean population 25-hydroxyvitamin D by roughly 20 nmol/L and cut the proportion below 50 nmol/L from roughly 55 per cent to roughly 9 per cent.

Measuring alkaline phosphatase — a cheap, widely available blood test that is the most useful single marker of active rickets where 25-hydroxyvitamin D assays are unavailable.

Not using high intermittent bolus doses. Two randomised trials found that annual 500,000 IU and monthly 60,000 IU regimens increased falls and fractures. A simple means of avoiding harm.

Gaps. The threshold for vitamin D deficiency is unresolved: the United States Institute of Medicine sets 50 nmol/L as sufficient, the Endocrine Society prefers above 75 nmol/L, and the Global Consensus on nutritional rickets sets below 30 nmol/L as deficiency. Every prevalence figure is threshold-dependent and the literature routinely quotes figures from one framework against another. 25-hydroxyvitamin D assays are poorly standardised between laboratories, with inter-assay differences of 10 to 30 per cent†, which further undermines comparison. No global prevalence estimate for nutritional rickets exists; the incidence figures here are from national surveillance systems in a handful of high-income countries plus scattered surveys elsewhere. Calcium-deficiency rickets and vitamin D deficiency rickets are frequently not distinguished in the literature, and the treatment differs; Nigerian and Gambian data show the calcium form dominating there, and vitamin D alone does not cure it. The non-skeletal claims have largely failed randomised testing — VITAL negative for cancer and cardiovascular outcomes, D2d negative for diabetes prevention, no fracture benefit from vitamin D alone, inconsistent falls data, and a contested respiratory infection effect — and much published and popular material predates or ignores these trials. High intermittent bolus dosing increased falls and fractures in two trials and remains in widespread use. Infant supplementation adherence is 20 to 60 per cent where recommended, for behavioural and system-level rather than evidential reasons. Obesity lowers serum 25-hydroxyvitamin D for the same intake through adipose sequestration, so thresholds derived in lean populations may misclassify. Burosumab at roughly US$200,000 to US$400,000 a patient-year at lowest available acquisition cost treats a condition affecting roughly 1 in 20,000, while nutritional rickets — far commoner — is cured for under US$20 at generic or lowest available acquisition cost, and no source reconciles that allocation.

> **Depth.** Starts in: vitamin D. Size: 1.2 nm†; depth −3.31. First complaint: about 12 months († 6–24 months after birth); time depth 48.87. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. The book names a late stratum. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Hypothyroidism

What it is. The thyroid makes too little thyroid hormone, and everything slows: heart rate, bowels, thought, metabolism. People feel cold, tired, constipated and low, and gain weight. A daily tablet replaces what is missing.

Measured. A meta-analysis of 17 European studies from 1975 to 2012 (Garmendia Madariaga et al., *Journal of Clinical Endocrinology and Metabolism*) found that nearly 11 per cent of Europeans have thyroid dysfunction and only about half of them know it. Known dysfunction has a mean prevalence of 3.82 per cent, of which known hypothyroidism is 3.05 per cent and known hyperthyroidism 0.75 per cent; about 85.2 per cent of known cases were subclinical. Undiagnosed dysfunction has a mean prevalence of 6.71 per cent, of which undiagnosed hypothyroidism is 4.94 per cent and undiagnosed hyperthyroidism 1.72 per cent; about 80.1 per cent of undiagnosed cases were subclinical†.

Incidence is 259.12 per 100,000 a year for all thyroid dysfunction, of which 226.2 is hypothyroidism and 51 hyperthyroidism†. Subclinical hypothyroidism, a raised thyroid-stimulating hormone (TSH) with normal free thyroxine, is the leading form. Overt hypothyroidism affects roughly 0.3 to 2 per cent of people in

iodine-sufficient populations. Subclinical disease affects roughly 4 to 10 per cent, rising to 15 to 20 per cent of women over 60†. Women outnumber men by roughly 5 to 8 to 1, and prevalence rises steeply with age†.

Congenital hypothyroidism occurs in roughly 1 in 2,000 to 1 in 4,000 births. It is the commonest treatable cause of intellectual disability and is found by newborn screening. In iodine-sufficient countries the dominant cause is autoimmune thyroiditis (Hashimoto). In iodine-deficient areas iodine deficiency is the dominant cause, so the world distribution of hypothyroidism follows the iodine map.

The disease is rarely recorded as a cause of death. Myxoedema coma, the decompensated extreme, is now rare and carries a mortality of roughly 20 to 40 per cent even with treatment†. Levothyroxine is consistently among the three most prescribed drugs by volume in the United States and the United Kingdom, with over 100 million prescriptions a year in the United States alone†. Set against the prevalence of overt disease, that volume shows substantial prescribing for subclinical disease and for symptoms without biochemical disease.

Where it starts. Autoimmune thyroiditis is the dominant cause where iodine is sufficient. Lymphocytes infiltrate and destroy the gland. Antibodies to thyroid peroxidase (anti-TPO) are present in roughly 90 to 95 per cent of cases and antibodies to thyroglobulin in roughly 60 to 80 per cent†. Anti-TPO antibodies are found in roughly 10 to 15 per cent of the general population, most of whom have normal thyroid function, so the antibody predicts risk and not disease. Progression from antibody-positive normal function to overt hypothyroidism runs at roughly 2 to 4 per cent a year, and faster if TSH is already high-normal†.

Iodine deficiency is the dominant cause worldwide. Iodine excess also causes hypothyroidism, particularly in people with underlying autoimmune thyroiditis: amiodarone, radiographic contrast, kelp supplements and povidone-iodine are the sources. The dose-response is U-shaped, as for iodine generally.

Treatment of other conditions accounts for a large share of cases in high-income countries. Thyroidectomy, radioiodine for hyperthyroidism and external radiotherapy to the neck remove or damage the gland. Lithium, amiodarone, interferon-alpha, tyrosine kinase inhibitors such as sunitinib and sorafenib, and immune checkpoint inhibitors cause it as a drug effect. Thyroid dysfunction occurs in roughly 5 to 20 per cent of patients on checkpoint inhibitors and is now a common cause of new hypothyroidism in oncology.

Postpartum thyroiditis affects roughly 5 to 10 per cent of women after delivery, and roughly 20 to 40 per cent of those go on to permanent hypothyroidism†.

Central hypothyroidism, from pituitary or hypothalamic disease, is roughly 1 in 1,000 of all cases†. The causes are tumour, surgery, radiotherapy, Sheehan syndrome, haemochromatosis and hypophysitis, including that caused by checkpoint inhibitors. TSH is low or normal in this form, so TSH-based screening misses it. Thyroid hormone must also not be started before glucocorticoid replacement if adrenal insufficiency coexists.

Heritability of autoimmune thyroid disease is roughly 0.6 to 0.8 in twin studies, among the highest of any autoimmune disease, and sibling relative risk is roughly 9 to 17†. Associated loci include HLA-DR3, *CTLA4*, *PTPN22*, *CD40*, *TSHR*, *FOXP3* and thyroglobulin. No clinically useful genetic test exists.

Smoking protects against hypothyroidism and is a risk factor for Graves disease. The inversion is consistent and unexplained. Selenium deficiency worsens autoimmune thyroiditis, and supplementation lowers anti-TPO titres in trials without changing clinical outcomes. Vitamin D deficiency is associated, with causality unresolved. Pregnancy and the postpartum period unmask autoimmune thyroid disease.

Congenital causes are thyroid dysgenesis (agenesis, ectopia or hypoplasia), roughly 85 per cent of congenital hypothyroidism, and dyshormonogenesis, roughly 15 per cent†. The latter is autosomal recessive and involves *TPO*, *TG*, *SLC5A5* and *DUOX2*.

Not known: what triggers autoimmune thyroiditis. Why so many people with normal thyroid function attribute symptoms to the thyroid. Whether combined thyroxine and triiodothyronine helps the roughly 10 to 15 per cent of treated patients who stay symptomatic with a normal TSH†.

Cure status. Overt hypothyroidism from autoimmune disease, surgery, radioiodine or radiotherapy: CONTROLLABLE. Iodine-deficiency hypothyroidism: CURABLE, by iodine. Drug-induced hypothyroidism: CURABLE where withdrawal is possible, as it often reverses. The hypothyroid phase of

postpartum, subacute (de Quervain) and silent thyroiditis: SELF-LIMITING, with roughly 60 to 80 per cent recovering thyroid function†.

Levothyroxine restores normal function in essentially all patients. Taken once daily and titrated to TSH, it normalises symptoms, lipids and metabolic rate, and life expectancy is normal. It is replacement for life, because the thyroid does not recover. That is control, not cure.

Prevention. Universal salt iodisation prevents the globally dominant cause, at a few cents a tonne of salt. See iodine deficiency disorders. STRONG.

Newborn screening for congenital hypothyroidism. Levothyroxine started within the first two weeks prevents the intellectual disability entirely. This is one of the highest-value screening programmes in existence. STRONG.

Monitoring thyroid function in patients on lithium, amiodarone, interferon, tyrosine kinase inhibitors and checkpoint inhibitors, and after thyroid surgery, radioiodine or neck radiotherapy. STRONG.

Avoiding iodine excess: amiodarone where alternatives exist, kelp supplements, and unnecessary iodinated contrast in people with autoimmune thyroid disease. MODERATE.

Thyroid function testing in pregnancy for high-risk women: previous thyroid disease, positive antibodies, type 1 diabetes, prior postpartum thyroiditis, recurrent miscarriage. Overt maternal hypothyroidism harms fetal neurodevelopment and is corrected cheaply. STRONG for high-risk screening. Universal screening in pregnancy is CONTESTED: the CATS trial found no improvement in child IQ at 3 years from screening and treating, and the United States and United Kingdom do not recommend universal screening, while some endocrine societies do.

Selenium supplementation lowers anti-TPO titres in trials. No effect on progression to hypothyroidism or on symptoms has been shown. WEAK.

Smoking cessation is recommended for every other reason and not for this one, because smoking is protective against hypothyroidism. Not graded, and reported for accuracy.

No established prevention of autoimmune thyroiditis itself exists.

Treatment. Levothyroxine, oral, once daily on an empty stomach, titrated to a TSH within the reference range, and to the lower half of it in pregnancy. It is on the WHO Essential Medicines List 24th List (2025), section 18.7, for hypothyroidism, as 25, 50 and 100 µg oral solid, first added in 1977. It has been off-patent for decades. The generic international price is a few dollars to a few tens of dollars a patient-year, and retail prices in the United States run higher; it is among the cheapest complete treatments for any chronic disease.

Full replacement in overt disease is roughly 1.6 µg/kg a day, with lower starting doses in the elderly and in ischaemic heart disease. The therapeutic index is narrow and formulations are not perfectly interchangeable, so a change of brand requires a repeat TSH. Calcium, iron, proton pump inhibitors, bile acid sequestrants, soy, coffee and food impair absorption, and this explains much apparent treatment failure.

Subclinical hypothyroidism is where the evidence says not to treat most people. The TRUST trial (Stott et al., *New England Journal of Medicine*, 2017) gave levothyroxine or placebo for a median of 12 months to 737 adults aged 65 and over with subclinical hypothyroidism and found no improvement in hypothyroid symptoms or tiredness scores. The IEMO 80-plus trial, in adults aged 80 and over, found no benefit†. A meta-analysis of 21 trials (Feller et al., *JAMA*, 2018) found no association of levothyroxine with improved quality of life or thyroid-related symptoms. A 2019 *BMJ* Rapid Recommendation advises strongly against routine levothyroxine for adults with subclinical hypothyroidism.

Treatment is still generally advised at a TSH above roughly 10 mIU/L, in pregnancy or planned pregnancy, and in young symptomatic patients with positive antibodies. Subclinical disease is roughly ten times commoner than overt disease and accounts for a large share of prescribing.

Liothyronine (triiodothyronine), shorter-acting, is used in combination regimens and in myxoedema coma. Its listing status needs checking against the 24th List†. It is off-patent, yet UK prices rose roughly sixty-fold between 2007 and 2017 because of a single-supplier market†. That led to a Competition and Markets

Authority investigation and a substantial fine. Prices have since fallen. This is a molecule that became unaffordable through market structure and not through patents.

Combined thyroxine and triiodothyronine has shown no consistent superiority over thyroxine alone for symptoms or quality of life in randomised trials and meta-analyses. A subgroup, possibly defined by a *DIO2* polymorphism, may benefit. CONTESTED. Desiccated porcine thyroid extract, fixed in ratio and variable in content, is not recommended by major guidelines; some patients prefer it. CONTESTED.

Myxoedema coma needs intravenous levothyroxine or liothyronine, intravenous hydrocortisone until adrenal insufficiency is excluded, passive rewarming, and ventilatory and circulatory support. Hydrocortisone's listing status needs checking against the 24th List†.

In central hypothyroidism with possible adrenal insufficiency, glucocorticoid goes first. Thyroid hormone given first can precipitate adrenal crisis, which is a lethal failure mode. In pregnancy the levothyroxine dose typically rises by roughly 25 to 50 per cent from early pregnancy, with TSH checked every 4 to 6 weeks†. Untreated overt maternal hypothyroidism is associated with miscarriage, pre-eclampsia, low birthweight and impaired child neurodevelopment.

Not to be done: treating most subclinical hypothyroidism, treating symptoms in a biochemically normal patient with levothyroxine, and combining thyroxine and triiodothyronine by default.

Simple means. Where iodine deficiency is the cause, which is most of the world's hypothyroidism, the simple means is the cure and the prevention: iodised salt, at a few cents a tonne.

Levothyroxine is not a no-chain intervention, but it is as close as a chronic-disease treatment gets. It is a single daily tablet, off-patent, on the Essential Medicines List, at a few dollars a patient-year, and it gives normal life expectancy. The binding constraint worldwide is not the drug but the TSH assay needed to titrate it.

Taking the tablet on an empty stomach, away from calcium, iron, coffee and antacids, is free and is the commonest reason a dose appears not to work. Not treating subclinical hypothyroidism avoids cost, monitoring and overtreatment, because the trials are negative. Palpation of the neck costs nothing and finds goitre. The newborn heel-prick, a dried blood spot and a TSH assay, prevents intellectual disability entirely. Seaweed and marine fish supply dietary iodine, with the caution that excess also causes hypothyroidism. Fibre and fluids ease constipation in the weeks before replacement takes full effect.

Where no laboratory exists, hypothyroidism can be treated on clinical grounds with a standard levothyroxine dose and clinical follow-up, and this is done. The TSH assay, at a few dollars, is what makes treatment safe, and it is the real access gap.

Gaps. The European meta-analysis spans 1975 to 2012, a period in which iodine status, assay sensitivity and diagnostic thresholds all changed, so its pooled figures mix eras. Subclinical disease is 80 to 85 per cent of detected thyroid dysfunction†, and whether it is a disease at all is unresolved. Figures that combine overt and subclinical disease, such as the 11 per cent figure, describe a mixture of a treatable condition and a laboratory finding.

The TSH reference range is contested. The upper limit in use, commonly 4.0 to 4.5 mIU/L, is a population statistic that rises with age and differs between assays. Narrowing it would reclassify millions of people as diseased.

Levothyroxine prescribing greatly exceeds the prevalence of overt disease, and no reconciliation exists in the literature. TRUST, IEMO 80-plus and the *JAMA* meta-analysis are negative for treating subclinical hypothyroidism, and prescribing continues to rise. Trial and practice disagree.

Combined thyroxine and triiodothyronine is negative overall in trials while patient groups report benefit. Universal pregnancy screening is negative for child IQ in CATS, and endocrine societies and national bodies disagree. The mechanism of the protective effect of smoking is unknown. Central hypothyroidism is missed by TSH screening and its true prevalence is unknown. No global prevalence estimate with GBD-level method exists; the figures here are from European and North American surveys.

The sixty-fold liothyronine price rise shows that off-patent status does not guarantee affordability. No systematic data exist on how often this occurs.

> **Depth.** Starts in: thyroid peroxidase (self-antigen). Size: 10 nm†; depth −1.38. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: reading. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Hyperthyroidism and Graves disease

What it is. The thyroid makes too much hormone. The heart races, weight falls despite eating, hands shake, and the person is hot, anxious and sleepless. In Graves disease an antibody switches the thyroid on, and in some people the eyes become inflamed and protrude.

Measured. The European meta-analysis of 1975 to 2012 (Garmendia Madariaga et al., described under hypothyroidism) gives known hyperthyroidism at 0.75 per cent and undiagnosed hyperthyroidism at 1.72 per cent, of which about 80 per cent is subclinical. Incidence is 51 per 100,000 a year.

Overt hyperthyroidism affects roughly 0.2 to 1.3 per cent of people in iodine-sufficient populations and subclinical hyperthyroidism roughly 0.7 to 3 per cent†. Graves disease accounts for roughly 60 to 80 per cent of hyperthyroidism in iodine-sufficient countries†. Toxic multinodular goitre and toxic adenoma account for most of the rest and predominate in iodine-deficient and older populations. The ratio of Graves to nodular disease shifts with iodine status, and this is a measured effect of iodisation programmes.

Graves disease is 5 to 10 times commoner in women, with onset mostly between 30 and 50 years†. Toxic nodular disease comes later, typically after 60.

Graves orbitopathy, the eye disease, is clinically apparent in roughly 25 to 30 per cent of Graves patients, moderate to severe in roughly 5 to 6 per cent, and sight-threatening in roughly 0.3 to 0.5 per cent†. Thyroid storm accounts for roughly 1 to 2 per cent of hospitalised thyrotoxic patients and kills roughly 10 to 30 per cent of them even with treatment†.

Untreated or undertreated disease has measured consequences. Atrial fibrillation occurs in roughly 10 to 15 per cent of overt hyperthyroid patients over 60†. Individual-participant-data meta-analyses associate subclinical hyperthyroidism with atrial fibrillation (hazard ratio roughly 1.7 to 1.9), hip fracture (roughly 1.3 to 1.4) and total and cardiovascular mortality (roughly 1.2 to 1.3)†. The risk is concentrated in those with TSH below 0.1 mIU/L. Thyrotoxicosis also accelerates bone loss.

Graves disease is commoner in iodine-sufficient populations. Iodine-induced hyperthyroidism occurs transiently when iodisation is introduced into a previously deficient population with nodular goitre. It has been measured in Zimbabwe, the Democratic Republic of Congo and elsewhere.

Where it starts. In Graves disease the mechanism is established and unusual in autoimmunity, because the antibody stimulates instead of destroying. Antibodies to the TSH receptor (TRAb) act as agonists and drive continuous hormone synthesis and thyroid growth. TRAb is present in roughly 95 to 99 per cent of untreated Graves patients and is diagnostic and prognostic: high titres predict relapse after antithyroid drugs are withdrawn. The same antibody acts on orbital fibroblasts, which carry the TSH receptor and the IGF-1 receptor, and causes the orbitopathy. Eye and thyroid disease share a cause.

Heritability of Graves disease is roughly 0.6 to 0.8 in twin studies. Concordance is roughly 20 to 35 per cent in identical twins and 2 to 5 per cent in non-identical twins, and sibling relative risk is roughly 10†. The loci are HLA-DR3 (*DRB1*03*), *CTLA4*, *PTPN22*, *CD40*, *TSHR*, *FCRL3* and *IL2RA*. No clinically useful genetic test exists.

Smoking is the strongest modifiable risk factor. It roughly doubles the risk of Graves disease (odds ratio roughly 1.9 to 3.3)†. For orbitopathy the effect is far larger, with an odds ratio of roughly 7 to 8 in current

smokers, dose-related†. Smoking also worsens the response to orbitopathy treatment and raises the risk of orbitopathy worsening after radioiodine. Stopping improves orbitopathy outcomes.

Iodine excess precipitates hyperthyroidism in nodular goitre: amiodarone (type 1), radiographic contrast, kelp, and the rise seen when iodisation begins. Other drugs act as well. Amiodarone causes two types of thyrotoxicosis that need different treatment. Interferon-alpha, and rarely lithium, can cause it. Checkpoint inhibitors cause thyroiditis with a thyrotoxic phase in roughly 5 to 10 per cent†. Alemtuzumab causes Graves disease in roughly 20 to 30 per cent of treated multiple sclerosis patients, one of the largest drug-induced autoimmunity effects known.

Graves disease commonly presents or relapses in the first postpartum year, and pregnancy itself, being immunosuppressive, often improves it. Selenium deficiency is associated with orbitopathy severity. Stress and infection are proposed triggers and are not established.

Thyroiditis causes a transient thyrotoxic phase that is not hyperthyroidism in the synthetic sense. Subacute (de Quervain, post-viral, painful), silent and postpartum thyroiditis release stored hormone and then become hypothyroid. Telling these from Graves disease is the central diagnostic task, because thyroiditis needs no antithyroid drug and resolves by itself.

Not known: what triggers the TSH receptor antibody. Why orbitopathy affects only a quarter of Graves patients. Why smoking raises orbitopathy risk roughly eight-fold. Which patients will remit after antithyroid drugs. TRAb titre and goitre size help but do not predict individually, and roughly half relapse.

Cure status. Graves disease treated by radioiodine or thyroidectomy: CONTROLLABLE — the hyperthyroidism is removed and permanent hypothyroidism follows in nearly all, held by lifelong levothyroxine. Graves disease treated by a thionamide course: CURABLE in roughly 40 to 50 per cent who enter lasting remission†, and CONTROLLABLE for as long as the drug is taken in the rest. Toxic nodular disease: CURABLE by radioiodine or surgery; thionamides give CONTROLLABLE only. Thyroiditis-associated thyrotoxicosis: SELF-LIMITING. Graves orbitopathy: CONTROLLABLE, and this is where the serious residual disability lies.

Radioiodine (iodine-131) ablates the thyroid. A single dose cures roughly 80 to 90 per cent of Graves disease, and a second dose cures most of the remainder. The cure converts a costly, fluctuating disease into a cheap, stable one. A therapeutic dose costs hundreds to low thousands of dollars, plus the handling infrastructure.

Total thyroidectomy cures immediately and with near certainty, at the cost of permanent hypothyroidism and surgical risk. Permanent recurrent laryngeal nerve injury is roughly 1 to 2 per cent and permanent hypoparathyroidism roughly 1 to 3 per cent in high-volume centres, and both are considerably higher in low-volume settings.

A 12 to 18 month course of carbimazole or methimazole induces lasting remission in roughly 40 to 50 per cent of Graves patients, and the rest relapse, usually within a year of stopping. Longer treatment, five years or more, raises remission to roughly 60 to 70 per cent in randomised and cohort data, and practice has shifted toward longer courses. Antithyroid drugs do not work for toxic nodular disease, because nodular autonomy does not remit. Definitive treatment is required there.

In thyroiditis the thyrotoxic phase resolves over weeks to months. Treatment is a beta-blocker and, if painful, an anti-inflammatory drug or corticosteroid. Antithyroid drugs do not work and should not be given, because there is no excess synthesis to block.

Teprotumumab, an anti-IGF-1 receptor antibody approved in the United States in January 2020, is the first drug to reverse proptosis. In its phase 3 trial 83 per cent of treated patients had a proptosis response of at least 2 mm against 10 per cent on placebo, with improvement in diplopia and quality of life. A course of 8 infusions costs hundreds of thousands of dollars. Hearing impairment occurs in roughly 10 per cent and can be permanent†.

Intravenous methylprednisolone remains first-line for moderate-to-severe active orbitopathy. It is off-patent and costs tens to hundreds of dollars a course. Roughly 50 to 80 per cent respond in inflammatory

signs, with little effect on proptosis. The cost of treating the eye disease thus spans from tens of dollars to hundreds of thousands, for different endpoints.

Prevention. Smoking cessation. The most effective preventive measure here: smoking roughly doubles Graves disease risk and raises orbitopathy risk roughly 7 to 8-fold†, dose-dependently, and stopping improves orbitopathy outcomes. STRONG.

Avoiding iodine excess in nodular goitre: unnecessary iodinated contrast, kelp, and amiodarone where alternatives exist. MODERATE.

Corticosteroid cover with radioiodine in patients with existing orbitopathy or who smoke reduces the risk of post-radioiodine orbitopathy worsening. MODERATE.

Selenium in mild Graves orbitopathy. The EUGOGO randomised trial found improved eye outcomes and quality of life and slowed progression to more severe disease. MODERATE.

Treating overt and high-risk subclinical hyperthyroidism, to prevent cardiovascular and skeletal consequences. Subclinical hyperthyroidism with TSH below 0.1 mIU/L is associated with atrial fibrillation (hazard ratio roughly 1.7 to 1.9), hip fracture (roughly 1.3 to 1.4) and mortality (roughly 1.2 to 1.3), and guidelines recommend treating that group, particularly over 65†. MODERATE: the association is firm and trial evidence that treatment removes the risk is lacking.

Monitoring thyroid function on amiodarone, interferon, lithium, checkpoint inhibitors and alemtuzumab. STRONG.

Antithyroid drug choice in pregnancy. Propylthiouracil is used in the first trimester, because methimazole and carbimazole are associated with aplasia cutis and choanal and oesophageal atresia, the methimazole embryopathy, at an absolute risk of roughly 2 to 4 per cent†. Treatment switches to methimazole afterwards, because propylthiouracil carries a hepatotoxicity risk of roughly 1 in 10,000†. TSH receptor antibodies cross the placenta and can cause fetal and neonatal thyrotoxicosis, so TRAb measurement in pregnancy guides fetal surveillance. STRONG.

Monitoring for agranulocytosis on thionamides. STRONG.

No prevention of Graves disease itself exists beyond smoking cessation.

Treatment. Thionamides are first-line: carbimazole or methimazole, and propylthiouracil in the first trimester, in thyroid storm and in thionamide intolerance. All three are off-patent, and a year of treatment costs tens of dollars. Their status on the WHO Essential Medicines List 24th List needs checking†.

Agranulocytosis occurs in roughly 0.2 to 0.5 per cent, usually in the first three months, and can be fatal†. Patients must be told to stop the drug and obtain a white cell count for fever or sore throat. A written warning costs nothing and is the main safety measure. Propylthiouracil carries a boxed warning for severe liver injury, roughly 1 in 10,000, which is why it is second-line outside the first trimester. Block-and-replace and titration regimens are equally effective, with more drug exposure on block-and-replace.

Beta-blockers, propranolol or atenolol, control tremor, palpitations, anxiety and heat intolerance while the thionamide takes 4 to 8 weeks to work. They are off-patent and cost a few dollars to tens of dollars a patient-year, and they give the fastest relief available. Their listing status needs checking against the 24th List†.

Radioiodine is not a medicine in the Essential Medicines List sense. It needs nuclear medicine facilities, which is the access barrier. It is contraindicated in pregnancy and breastfeeding, and pregnancy must be deferred roughly 6 months†. Thyroidectomy is for large goitres, compressive symptoms, suspected malignancy, severe orbitopathy, pregnancy where drugs fail, and patient preference. It needs preoperative control with thionamides and potassium iodide (Lugol’s iodine) to reduce vascularity. Cost varies enormously, from thousands to tens of thousands of dollars.

Potassium iodide blocks hormone release acutely (the Wolff-Chaikoff effect) and is used in thyroid storm and before surgery. It is off-patent and costs cents a dose. Its listing status needs checking against the 24th List†.

Thyroid storm is treated with a thionamide, propylthiouracil preferred because it also blocks conversion of T4 to T3, then iodide at least an hour later, plus a beta-blocker, hydrocortisone, cooling, fluids and treatment of the precipitant. All the drugs are off-patent and cost dollars. Hydrocortisone's listing status needs checking against the 24th List†.

Orbitopathy is treated, first, by stopping smoking, which is free. Selenium is used for mild disease. Intravenous methylprednisolone, cumulatively roughly 4.5 g over 12 weeks, is used for moderate-to-severe active disease, and its listing status needs checking against the 24th List†. Teprotumumab is patented, and its listing status needs checking against the 24th List†. Mycophenolate added to steroids improved outcomes in a European trial. Tocilizumab, rituximab (conflicting trial results) and orbital radiotherapy are also used. Orbital decompression is for optic neuropathy, and strabismus and lid surgery follow once the disease is inactive. Artificial tears, taping the lids at night, prisms for diplopia and sunglasses are symptomatic, cheap and genuinely useful.

Levothyroxine afterwards, because the definitive treatments cause hypothyroidism; see hypothyroidism.

Not to be done: thionamides for thyroiditis, radioiodine for a smoker with active orbitopathy without steroid cover, and iodide before the thionamide in thyroid storm.

Simple means. Stopping smoking. It halves the risk of developing Graves disease, reduces orbitopathy risk roughly eight-fold, improves response to orbitopathy treatment, and costs nothing. In this disease it is not general health advice. It is the principal modifiable determinant of whether a person loses vision.

A beta-blocker gives symptomatic relief within hours while definitive treatment is arranged, at a few dollars to tens of dollars a patient-year. Carbimazole or methimazole, at tens of dollars a patient-year, cures roughly half of Graves patients after a 12 to 18 month course and roughly 60 to 70 per cent after a longer one.

A written warning about sore throat and fever. Agranulocytosis occurs in 0.2 to 0.5 per cent and can kill, and the countermeasure is a sentence on paper and a full blood count. Potassium iodide drops, at cents, block hormone release within hours in a crisis. Selenium for mild orbitopathy costs cents a day and has a positive randomised trial.

Artificial tears, taping the eyelids shut at night and sunglasses prevent corneal exposure damage and cost almost nothing. Sleeping with the head elevated reduces periorbital oedema. Distinguishing thyroiditis from Graves disease clinically, by a painful thyroid and a preceding viral illness, avoids unnecessary treatment for free. Nodular goitre calls for avoiding iodine excess: kelp supplements and unnecessary contrast.

Gaps. The European prevalence figures mix studies from 1975 to 2012 across changing iodine status and assay generations. About 80 per cent of undiagnosed hyperthyroidism is subclinical, so the headline figures combine a treatable disease with a laboratory finding.

Whether treating subclinical hyperthyroidism removes the measured excess risk of atrial fibrillation, fracture and death has never been tested in a randomised trial. The associations are firm and the intervention evidence is absent.

Which Graves patients will remit after antithyroid drugs cannot be predicted individually, so the choice between a drug course and definitive treatment is made without being able to give the patient their own odds beyond roughly 50 per cent†. Optimal drug duration is unsettled: longer courses give higher remission in cohort and some randomised data, and guidelines have only partly adopted this.

Teprotumumab costs hundreds of thousands of dollars a course and intravenous methylprednisolone tens to hundreds. The endpoints differ, proptosis against inflammatory activity. There is no head-to-head trial on equal footing and no cost-effectiveness consensus. Hearing loss in roughly 10 per cent is a real and incompletely characterised harm. Rituximab trials in orbitopathy conflict, a positive United States trial against a negative European one. Why smoking raises orbitopathy risk roughly eight-fold is unknown.

Radioiodine availability, not cost, is the binding constraint in much of the world, and no systematic data exist on global nuclear medicine coverage for benign thyroid disease. The iodine-induced hyperthyroidism

that follows the introduction of iodisation is documented, but its magnitude and duration have not been systematically quantified across programmes.

> **Depth.** Starts in: the TSH receptor. Size: 10 nm†; depth −1.38. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Thyroid nodules and goitre

What it is. A lump in the thyroid, or a generally enlarged thyroid. Most lumps are benign and cause no trouble. The difficulty is that looking for the few that are cancer finds very large numbers that never would have mattered.

Measured. Prevalence depends entirely on the method of looking. Nodules are palpable in roughly 4 to 7 per cent of adults in iodine-sufficient populations†. Ultrasound finds them in roughly 20 to 70 per cent of adults, rising with age and reaching roughly 50 to 60 per cent in women over 60†. Autopsy finds them in roughly 50 per cent of thyroids†. Ultrasound therefore finds roughly ten times as many nodules as palpation, and most of what it finds would never have been known.

The malignancy rate in a nodule under investigation is roughly 5 to 10 per cent, and lower in small nodules found by chance†. Goitre is endemic where prevalence exceeds 5 per cent. About 187 million people had goitre from iodine deficiency in 2010, 2.7 per cent of the world population†. In iodine-sufficient countries sporadic multinodular goitre affects roughly 3 to 5 per cent of adults, rising with age and female sex†.

The central measured fact is the overdiagnosis of thyroid cancer. In South Korea, ultrasound was offered opportunistically alongside a national screening programme from 1999. Thyroid cancer incidence rose roughly fifteen-fold by 2011 and became the country's most commonly diagnosed cancer. Thyroid cancer mortality did not change.

An analysis by the International Agency for Research on Cancer (Vaccarella et al., *New England Journal of Medicine*, 2016) estimated that 470,000 women and 90,000 men were overdiagnosed with thyroid cancer in 12 countries over roughly two decades. In South Korea an estimated 90 per cent of thyroid cancers diagnosed in women were overdiagnosis, and in Italy, France and the United States roughly 70 to 80 per cent. In the United States incidence roughly tripled from 1975 to 2009, almost entirely papillary carcinoma under 2 cm, with mortality essentially flat†. Autopsy series find occult papillary carcinoma in roughly 5 to 35 per cent of thyroids of people who died of other causes, a reservoir of subclinical disease far larger than clinical incidence.

The United States Preventive Services Task Force recommends against screening for thyroid cancer in asymptomatic adults, grade D, an explicit recommendation against a test on the ground of net harm.

Nodules and thyroid cancer diagnosis are roughly 3 to 4 times commoner in women, but thyroid cancer mortality is roughly equal between the sexes. That discrepancy is itself evidence of differential detection. Thyroid cancer mortality is roughly 0.3 to 0.5 per 100,000 a year and has been flat or slowly falling for decades in high-income countries despite the rise in incidence.

Where it starts. Iodine deficiency is the dominant global cause of goitre and nodular disease. Chronic TSH stimulation causes hyperplasia, then nodule formation, then autonomy. Iodisation lowers goitre prevalence and shifts the pattern of thyroid disease: less nodular goitre and less follicular carcinoma, more Graves disease and more papillary carcinoma. The papillary-to-follicular ratio rises after iodisation, a consistently measured effect.

Ionising radiation to the neck in childhood is the one firmly established cause of thyroid cancer, with a clear dose-response. After Chernobyl, Belarus, Ukraine and western Russia saw a large excess of childhood papillary carcinoma attributable to iodine-131 in milk, roughly 6,000 to 7,000 excess cases by the 2000s†. The risk was concentrated in those exposed under age 5 and was amplified by background iodine

deficiency. Childhood radiotherapy, for benign conditions in the past and for cancer, carries the same risk. The adult thyroid is relatively radioresistant.

Female sex, parity and age are consistently associated with nodules and goitre. Obesity is associated with thyroid cancer incidence in cohort studies, with modest relative risks. A first-degree relative with thyroid cancer raises the risk of papillary carcinoma roughly 4 to 8-fold, a high relative risk on a low base†. Thyroid cancer has one of the highest familial relative risks of any cancer, and the heritability of nodular goitre in twin studies is roughly 0.5 to 0.8†. Loci include *FOXE1*, *NKX2-1*, *DIRC3* and *MBIP*.

Genetic syndromes matter. MEN2 (*RET*) causes medullary thyroid carcinoma, and prophylactic thyroidectomy in *RET* carriers is genuinely preventive. Familial adenomatous polyposis, Cowden syndrome (*PTEN*), DICER1 syndrome and Carney complex also carry thyroid risk. Somatic drivers are *BRAF* V600E in roughly 60 per cent of papillary carcinoma, *RAS* in follicular, *RET/PTC* rearrangements in radiation-associated and paediatric tumours, and *TERT* promoter mutations marking aggressive behaviour.

The incidence rise is detection, not biology. The rise is confined to small papillary tumours, mortality is flat, autopsy prevalence greatly exceeds clinical incidence, and incidence tracks ultrasound and screening intensity across countries. This is as close to a settled conclusion as cancer epidemiology produces.

Not known: which small papillary carcinomas will progress. No molecular or imaging marker reliably separates the indolent majority from the few that matter, which is why active surveillance has become the practical answer. Also not known: whether the modest rise in large thyroid tumours in some datasets is a small real increase on top of the overdiagnosis.

Cure status. Benign nodules and non-compressive goitre: CONTROLLABLE by observation. Most never cause disease and need no treatment. Compressive goitre: CURABLE, by surgery or radioiodine. Toxic nodular goitre: CURABLE, by radioiodine or surgery. Differentiated thyroid cancer: CURABLE, with 10-year survival above roughly 95 per cent for papillary carcinoma†. Low-risk papillary microcarcinoma, 1 cm or under: CURABLE by surgery, and active surveillance gives the same survival. Confined medullary thyroid carcinoma: CURABLE, by complete surgery. Advanced medullary carcinoma and radioiodine-refractory differentiated cancer: CONTROLLABLE, with targeted drugs. Anaplastic thyroid carcinoma: RELIEF ONLY.

For benign disease, observation is the evidence-based management. Radioiodine reduces goitre volume by roughly 40 to 60 per cent over a year and is cheap, and surgery is immediate and definitive. Antithyroid drugs do not induce remission in nodular autonomy; see hyperthyroidism and Graves disease.

For differentiated cancer, treatment is lobectomy or total thyroidectomy, with radioiodine for higher-risk disease. Disease-specific survival is roughly 99 per cent for tumours under 1 cm†. For small papillary carcinoma, doing nothing is as good as operating. The Kuma Hospital (Japan) active-surveillance cohorts (Ito, Miyauchi et al.) followed over 1,200 patients with papillary microcarcinoma of 1 cm or less. Tumour enlargement of 3 mm or more occurred in roughly 8 per cent at 10 years, new nodal metastases in roughly 3.8 per cent, and no patient died of thyroid cancer†. Patients who later had surgery did as well as those operated on immediately. Memorial Sloan Kettering and other Western cohorts have replicated this, and active surveillance is an accepted option in American Thyroid Association and other guidelines. This is one of the few entries where the correct course is often to withhold the curative treatment.

Anaplastic carcinoma has a median survival of roughly 4 to 6 months†. Dabrafenib plus trametinib in *BRAF*-mutant anaplastic carcinoma produces response rates of roughly 56 to 69 per cent and has changed the outlook for that subgroup†. Selpercatinib and pralsetinib, *RET* inhibitors, produce high response rates in advanced medullary disease and cost hundreds of thousands of dollars a patient-year.

Prevention. Universal salt iodisation prevents endemic goitre and nodular disease and reduces follicular carcinoma, at a few cents a tonne of salt. STRONG. See iodine deficiency disorders.

Stable iodine prophylaxis after a nuclear accident. Potassium iodide tablets taken promptly block thyroid uptake of radioiodine. Poland distributed iodide after Chernobyl and saw no excess childhood thyroid cancer, in contrast to Belarus and Ukraine. It is off-patent and costs cents. STRONG. Its listing status on the WHO Essential Medicines List 24th List needs checking†.

Avoiding unnecessary radiation to the neck in childhood, particularly CT. STRONG. Prophylactic thyroidectomy in *RET* mutation carriers prevents medullary thyroid carcinoma and is one of the clearest cases of preventive surgery in medicine. STRONG.

Not screening for thyroid cancer is a prevention in its own right. The United States Preventive Services Task Force recommends against screening asymptomatic adults, grade D. South Korea's fifteen-fold rise in incidence with unchanged mortality is the evidence. What not screening prevents is the overdiagnosis of roughly 70 to 90 per cent of diagnoses in the countries measured, with its lifelong levothyroxine, surgical complications, and insurance and employment consequences. STRONG.

Not aspirating small, sonographically low-risk nodules. Risk-stratified ultrasound systems (ACR TI-RADS, EU-TIRADS, ATA) set size thresholds below which biopsy is not recommended. Applying them reduces biopsies by roughly 20 to 50 per cent without missing clinically significant cancers in validation studies. MODERATE. Not measuring calcitonin or doing ultrasound in asymptomatic people. MODERATE.

Not treating nodular disease with suppressive levothyroxine. TSH suppression reduces nodule volume modestly and causes bone loss and atrial fibrillation, and it is no longer recommended. STRONG, as a recommendation against.

Treatment. Observation, for benign, asymptomatic, non-compressive nodules and goitre and for low-risk papillary microcarcinoma under active surveillance. It is evidence-based and free. Monitoring is clinical plus periodic ultrasound.

Fine-needle aspiration cytology, where risk stratification indicates it, is cheap, outpatient and the single decisive test, at tens to hundreds of dollars. The Bethesda classification reports it. Indeterminate categories, Bethesda III and IV, are roughly 20 to 30 per cent of aspirates and are the practical problem, with malignancy rates of roughly 10 to 40 per cent†. Molecular testing (Afirma, ThyroSeq) of indeterminate aspirates reduces unnecessary diagnostic surgery by roughly 50 per cent in validation studies†, at several thousand dollars a test, which is more than the surgery costs in many countries.

Levothyroxine is given only where there is hypothyroidism or after thyroidectomy, and not to shrink a benign nodule. It is on the WHO Essential Medicines List 24th List, section 18.7, for hypothyroidism, and costs a few dollars to a few tens of dollars a patient-year.

Radioiodine treats toxic nodular goitre and large non-toxic goitre, at hundreds to low thousands of dollars. Recombinant human TSH-stimulated radioiodine increases volume reduction further and costs thousands of dollars a course, a large price difference for an incremental gain. Surgery, lobectomy or total thyroidectomy, is for compressive goitre, suspected or confirmed malignancy, cosmetic indication or toxic nodular disease. Permanent recurrent laryngeal nerve injury runs roughly 1 to 2 per cent and permanent hypoparathyroidism roughly 1 to 3 per cent in high-volume centres, and both are substantially higher in low-volume settings. That is an argument for surveillance of low-risk disease wherever surgical volume is low. Surgery costs thousands to tens of thousands of dollars.

Thermal ablation, by radiofrequency, microwave, laser or high-intensity focused ultrasound, treats benign symptomatic nodules with volume reduction of roughly 50 to 80 per cent at one year, preserving thyroid function and avoiding a scar. It is increasingly used in Korea, Italy and China, at thousands of dollars.

For differentiated cancer: surgery; radioiodine ablation for intermediate- and high-risk disease and not for low-risk disease; TSH suppression in higher-risk disease. The ESTIMABL2 and IoN randomised trials both found no benefit from radioiodine ablation in low-risk papillary carcinoma, which has changed practice. Lenvatinib and sorafenib treat radioiodine-refractory disease at roughly a hundred thousand dollars or more a patient-year. Selpercatinib and pralsetinib treat *RET*-altered tumours, and larotrectinib and entrectinib treat *NTRK*-fusion tumours. Anaplastic carcinoma is treated with dabrafenib plus trametinib where *BRAF*-mutant, and otherwise with palliative radiotherapy and airway management. Where iodine deficiency is the cause, iodine treats it.

Simple means. Iodised salt prevents the endemic goitre that still affected roughly 187 million people in 2010, at a few cents a tonne.

Doing nothing is the best-evidenced management for most thyroid nodules and for low-risk papillary microcarcinoma. The Kuma Hospital cohorts recorded 8 per cent growth at 10 years, 3.8 per cent new nodal metastases and no thyroid cancer deaths under observation. Not operating is free and avoids a permanent hypoparathyroidism rate of 1 to 3 per cent and lifelong levothyroxine.

Not screening is the measured case: South Korea's fifteen-fold rise with flat mortality, and the IARC estimate of roughly 560,000 overdiagnoses in 12 countries†. The Task Force's grade D is the formal statement of it.

Palpation of the neck costs nothing and detects the goitre and the nodules large enough to matter. It does not detect the subclinical reservoir that ultrasound finds. In this entry the cruder test is the safer one.

Potassium iodide tablets held in stock near nuclear installations cost cents a dose. Avoiding unnecessary neck CT in children costs nothing. A voice check and a serum calcium after thyroid surgery are cheap and cover the two complications that matter. Levothyroxine follows where the thyroid has been removed.

Gaps. Nodule prevalence spans 4 to 70 per cent depending on the detection method†. No single prevalence figure is meaningful without stating the method, and the literature often does not.

No marker separates the indolent small papillary carcinoma from the one that will progress. This is the central unsolved problem, and active surveillance is the workaround and not the answer.

The overdiagnosis estimates, 70 to 90 per cent of diagnoses in some countries, are modelled from the discordance of incidence and mortality. They are not observed in individuals, and the exact fraction is contested even though the phenomenon is not. Whether a real small increase in incidence lies under the overdiagnosis is unresolved, since some datasets show a modest rise in larger tumours.

Molecular testing of indeterminate aspirates costs several thousand dollars a test, more than diagnostic surgery in many health systems, and its cost-effectiveness outside the United States is not established. ESTIMABL2 and IoN found no benefit from radioiodine in low-risk disease, and practice in many countries has not fully changed. Thermal ablation is in widespread use in some countries with limited randomised comparison against surgery or observation.

Active surveillance data come overwhelmingly from two Japanese centres plus smaller Western cohorts, and outcomes beyond 20 years are not available. The goitre burden figure of 187 million is from 2010, and iodine status monitoring has since deteriorated, so current endemic goitre prevalence is not well known. Surgical complication rates differ severalfold between high- and low-volume settings. That changes the risk-benefit calculation for operating on low-risk disease and is rarely incorporated into guidelines written in high-volume centres.

> **Depth.** Starts in: a thyroid follicular cell. Size: 15 µm†; depth +5.28. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Adrenal insufficiency

What it is. The adrenal glands make too little cortisol, and in the primary form too little aldosterone as well. Fatigue, weight loss, low blood pressure and salt craving build up over months. An infection or injury can then tip the person into shock and kill within hours.

Measured. Prevalence of Addison disease, primary adrenal insufficiency, runs from 5 to 221 per million across countries. European studies in Norway, Italy and the United Kingdom give roughly 100 to 220 per million, about 1 in 5,000 to 1 in 10,000, and incidence of roughly 4 to 6 per million a year†. Secondary (pituitary) adrenal insufficiency runs at roughly 150 to 280 per million, so it is commoner than primary†.

The commonest form is tertiary, from exogenous glucocorticoids, and it is poorly counted. A systematic review and meta-analysis (Broersen et al., 2015) found adrenal insufficiency after glucocorticoid

withdrawal in roughly 48.7 per cent overall. By route the rates were roughly 4.2 per cent for nasal, 7.8 per cent for topical, 8 to 10 per cent for inhaled, 48.7 per cent for oral and 52.2 per cent for intra-articular glucocorticoids. Given how widely corticosteroids are prescribed, this is the largest group of people with adrenal insufficiency in the world, and no population prevalence figure exists for it.

Congenital adrenal hyperplasia is the commonest cause in children. Incidence of the classical form, 21-hydroxylase deficiency, is 1 in 14,200 live births from newborn screening data†.

Autoimmune adrenalitis accounts for 80 to 90 per cent of primary cases in industrialised countries since 1950†. Roughly half occur within autoimmune polyendocrine syndrome type 2, with autoimmune thyroid disease or type 1 diabetes, and a smaller share in type 1 (*AIRE* mutations, with hypoparathyroidism and candidiasis). Tuberculosis was historically the dominant cause worldwide and is still the leading cause where tuberculosis burden is high. Older series from India and Africa report 40 to 70 per cent†. Other causes are HIV and its opportunistic infections, histoplasmosis, paracoccidioidomycosis, metastatic disease, bilateral adrenal haemorrhage (anticoagulation, antiphospholipid syndrome, meningococcal sepsis), adrenoleukodystrophy, which is a leading cause in boys, drugs (ketoconazole, etomidate, mitotane, abiraterone, checkpoint inhibitors) and bilateral adrenalectomy.

Autoimmune Addison disease peaks at 30 to 50 years, with women outnumbering men by roughly 1.5 to 2.5 to 1†. Congenital adrenal hyperplasia presents in the neonatal period.

The measured harm is mortality. In diagnosed patients adrenal crisis occurs roughly 5 to 8 times per 100 patient-years, about a 1 in 15 chance each year†. Crisis mortality is roughly 0.5 per 100 patient-years, and case fatality of a crisis roughly 6 per cent†. The standardised mortality ratio is roughly 2 in Swedish and Norwegian registry studies, with excess deaths from infection, cardiovascular disease and adrenal crisis. Untreated primary adrenal insufficiency is fatal. Before cortisone, in 1949, median survival from diagnosis was roughly 2 years†.

Diagnosis is late. Roughly 50 to 70 per cent of patients in registry surveys saw three or more doctors before diagnosis, the median delay is 1 to 2 years, and a substantial minority are diagnosed only at crisis†.

Where it starts. Autoimmune adrenalitis destroys the adrenal cortex through autoantibodies and T cells directed at 21-hydroxylase (*CYP21A2*). Anti-21-hydroxylase antibodies are present in roughly 85 to 90 per cent of autoimmune cases and precede clinical disease by months to years. As in type 1 diabetes, there is a measurable preclinical phase. Roughly 20 to 30 per cent of antibody-positive individuals progress to overt insufficiency over a decade.

The HLA association is strong: *HLA-DR3-DQ2*, *DR4-DQ8* and the *MICA5.1* allele. Non-HLA loci are *CTLA4*, *PTPN22*, *CYP27B1*, *NLRP1*, *AIRE*, *BACH2* and *CLEC16A*. Sibling relative risk is high but the disease is rare, so absolute risks stay low. Heritability is not well established for Addison disease specifically, and the polyendocrine syndromes are more clearly familial.

The monogenic causes are congenital adrenal hyperplasia (*CYP21A2* in roughly 95 per cent, also *CYP11B1*, *HSD3B2*, *CYP17A1*, *StAR*)†, familial glucocorticoid deficiency (*MC2R*, *MRAP*), triple A syndrome (*AAAS*) and autoimmune polyendocrine syndrome type 1 (*AIRE*). Adrenoleukodystrophy (*ABCD1*, X-linked) is another. Adrenal insufficiency is often its first manifestation in boys and can precede neurological disease by years, making it a treatable sentinel.

Tuberculosis destroys the glands by caseating granulomatous replacement, and calcification is visible on CT. Adrenal insufficiency occurs in roughly 5 per cent of patients with active tuberculosis†.

Exogenous glucocorticoids suppress the hypothalamic-pituitary-adrenal axis. Risk rises with dose, duration and potency. It occurs with inhaled, topical, intranasal and intra-articular routes and not only oral, which is widely underappreciated and is the commonest reason a patient has unrecognised adrenal insufficiency. Checkpoint inhibitor hypophysitis causes secondary adrenal insufficiency in roughly 1 to 6 per cent of treated patients and is usually permanent†. Chronic opioid therapy suppresses the axis in a measurable minority.

Crisis precipitants are, in order of frequency, gastrointestinal infection with vomiting, because the oral dose cannot be absorbed; fever; surgery; trauma; and failure to increase the dose during illness, the single commonest preventable precipitant.

Not known: what triggers autoimmune adrenalitis. The true population prevalence of glucocorticoid-induced adrenal insufficiency. Which antibody-positive individuals will progress. Whether any preclinical intervention preserves adrenal function, since immunomodulation trials have been small and inconclusive. The optimal replacement dose and schedule, which is why mortality stays roughly twice expected after seventy-five years of treatment.

Cure status. Primary adrenal insufficiency, autoimmune: CONTROLLABLE. Tuberculous adrenalitis: CONTROLLABLE, because the tuberculosis is cured but the destroyed adrenal tissue does not return and replacement is lifelong. Secondary adrenal insufficiency from pituitary disease: CONTROLLABLE. Congenital adrenal hyperplasia: CONTROLLABLE. Glucocorticoid-induced insufficiency: CURABLE, by tapering and withdrawing the glucocorticoid. Drug-induced insufficiency from ketoconazole, mitotane or abiraterone: CURABLE, as it reverses on withdrawal. Bilateral adrenal haemorrhage: CONTROLLABLE, with function sometimes partly recovering.

Hydrocortisone and fludrocortisone restore survival from a median of 2 years to decades, and with proper diagnosis, monitoring and treatment people can live normally. That is substantially true. But the standardised mortality ratio remains roughly 2, with excess deaths from infection and adrenal crisis†. Replacement does not reproduce the physiological cortisol rhythm or the stress response. Oral hydrocortisone two or three times a day produces peaks and troughs that do not match the circadian profile, and no preparation reproduces the stress-induced rise. Quality-of-life scores in Addison disease stay below population norms in every published cohort.

Glucocorticoid-induced insufficiency recovers over weeks to roughly a year after withdrawal, though recovery can be incomplete.

In congenital adrenal hyperplasia the balance between under-replacement (virilisation, poor growth) and over-replacement (growth suppression, obesity, bone loss) is the central difficulty. Crinecerfont, a CRF1 receptor antagonist approved in the United States in December 2024, reduced androgen levels and allowed glucocorticoid dose reduction in phase 3 trials†. It is the first mechanistically new treatment in decades and costs high tens of thousands of dollars a patient-year. Adrenal transplantation and stem-cell-derived adrenal tissue are experimental.

Prevention. No primary prevention of autoimmune adrenalitis exists. Tuberculosis prevention and treatment prevents the second-largest cause worldwide. STRONG.

Glucocorticoid stewardship prevents the commonest form. It means the lowest effective dose and duration, and tapering rather than stopping abruptly after courses longer than roughly 2 to 3 weeks. It also means recognising that inhaled, topical, intranasal and intra-articular routes suppress the axis. Meta-analysis found adrenal insufficiency in roughly 8 to 10 per cent after inhaled and 52 per cent after intra-articular glucocorticoids†. STRONG.

Prevention of adrenal crisis is where essentially all the preventable mortality sits. Sick-day rules, doubling or tripling the glucocorticoid dose during febrile illness and giving parenteral hydrocortisone when vomiting or unable to take tablets: STRONG. No trial exists, the practice is universally accepted, and crisis precipitants are dominated by failure to do it. An emergency hydrocortisone injection kit at home, with patient and family trained to use it: MODERATE, as studies of patient education programmes show reduced crisis rates. A steroid emergency card and a medical alert bracelet: MODERATE, at zero cost. The United Kingdom introduced a national NHS Steroid Emergency Card in 2020 after repeated deaths from unrecognised adrenal crisis in hospital†. Parenteral hydrocortisone cover for surgery, labour and major procedures: STRONG. Structured patient education, repeated, because crisis rates fall after education programmes in cohort studies: MODERATE.

Newborn screening for congenital adrenal hyperplasia prevents salt-wasting crisis and death in the neonatal period and prevents incorrect sex assignment in virilised female infants. It is included in newborn panels in

the United States, Japan and much of Europe. STRONG. Screening for adrenal insufficiency in boys with adrenoleukodystrophy, and in patients on checkpoint inhibitors or long-term opioids: MODERATE.

Screening relatives of people with other autoimmune endocrine disease for 21-hydroxylase antibodies identifies the preclinical phase. No intervention is known to prevent progression, so the benefit is earlier diagnosis and avoidance of crisis at presentation. MODERATE.

Treatment. The proportion of glucocorticoid-induced insufficiency that recovers is not given. Recovery is over weeks to roughly a year after withdrawal and can be incomplete. Hydrocortisone, oral, in two or three divided doses, typically 15 to 25 mg a day in adults weighted to the morning†. It is off-patent, and a year costs tens to low hundreds of dollars at generic prices. In the United Kingdom hydrocortisone tablet prices rose sharply in the 2010s under a single-supplier market, the Competition and Markets Authority found abusive pricing and imposed fines, and prices have since fallen. Prednisolone is an acceptable alternative at a few dollars to tens of dollars a patient-year, and in much of the world it is what is used because of price and availability. The listing status of hydrocortisone, oral and injectable, and of prednisolone, on the WHO Essential Medicines List 24th List needs checking†.

Modified-release hydrocortisone (Plenadren, Chronocort or Efmody) better approximates the circadian profile, and small trials show improved quality of life and metabolic measures. It is patented, at thousands of dollars a patient-year. Whether the improvement justifies a price 30 to 100 times higher is unresolved†.

Fludrocortisone, a mineralocorticoid, 0.05 to 0.2 mg once daily, is for primary adrenal insufficiency only. It is not needed in secondary insufficiency, where aldosterone production is intact. It is off-patent, costs tens to hundreds of dollars a patient-year, and prices have been volatile in some markets because of few suppliers. Liberal salt intake is the free adjunct. Its listing status needs checking against the 24th List†.

Adrenal crisis is treated with 100 mg hydrocortisone intravenously or intramuscularly, immediately, plus intravenous saline. An ampoule costs dollars. This is one of the cheapest life-saving drugs in medicine, and it is the whole treatment of a condition with roughly 6 per cent case fatality. Given in time it is almost always effective, and the deaths come from not giving it. An emergency injection kit for home use is a vial, a syringe and training, for a few dollars.

Dehydroepiandrosterone (DHEA), for women with impaired wellbeing and low androgens, shows small and inconsistent benefits on mood and sexual function in randomised trials. CONTESTED. Its listing status needs checking against the 24th List†.

In congenital adrenal hyperplasia, treatment is hydrocortisone (in adults sometimes prednisolone or dexamethasone), fludrocortisone, salt supplementation in infancy, and crinecerfont or tildacerfont, CRF1 antagonists, to reduce ACTH drive and allow lower glucocorticoid doses. Crinecerfont is patented at high tens of thousands of dollars a patient-year.

The cause is treated where it can be: antituberculous therapy, tapering the exogenous glucocorticoid, stopping the implicated drug. For adrenoleukodystrophy, Lorenzo’s oil and haematopoietic stem cell transplant or gene therapy (elivaldogene autotemcel) treat the neurological disease and not the adrenal failure.

In pregnancy the hydrocortisone dose is increased in the third trimester, with parenteral cover in labour. Dexamethasone is not used, because it crosses the placenta.

Not to be done: giving levothyroxine before glucocorticoid in combined pituitary failure, which precipitates crisis; using dexamethasone for routine replacement, which has no mineralocorticoid activity and is hard to titrate; and withholding hydrocortisone while awaiting a cortisol result in a suspected crisis.

Simple means. Hydrocortisone tablets and fludrocortisone together cost tens to hundreds of dollars a patient-year at generic prices, both off-patent, and convert a disease with a 2-year median survival into a near-normal life. Prednisolone, at a few dollars to tens of dollars a patient-year, is an acceptable substitute where hydrocortisone is unavailable or unaffordable.

Salt. Liberal salt intake supports blood pressure in primary adrenal insufficiency and is free. Salt craving is a presenting symptom.

An ampoule of hydrocortisone and a syringe in the house, and someone trained to use it, cost a few dollars. Adrenal crisis has roughly 6 per cent case fatality and roughly 5 to 8 crises occur per 100 patient-years, and the drug that stops it costs about a dollar†.

Sick-day rules written on a card: double the dose during fever and inject when vomiting. Failure to do this is the commonest precipitant of crisis, and the countermeasure is a card and a conversation. A steroid emergency card or bracelet is free. Oral rehydration salts go alongside the increased steroid dose during gastrointestinal illness. Not stopping a long corticosteroid course abruptly is free and prevents the commonest form of the disease from becoming a crisis.

Recognition is clinical: weight loss, fatigue, postural dizziness, salt craving, abdominal pain, and hyperpigmentation of scars, buccal mucosa and palmar creases in primary disease. Hyperpigmentation is visible without any test and is specific. Low sodium and high potassium on a basic electrolyte panel, which costs a few dollars, point straight at it. Asking about previous corticosteroid courses in anyone with unexplained collapse costs nothing.

Gaps. Prevalence spans 5 to 221 per million, a 44-fold range. It reflects differences in ascertainment and in the balance of autoimmune and infectious causes, not variation of that size.

Glucocorticoid-induced adrenal insufficiency is the commonest form and has no population prevalence estimate. The Broersen meta-analysis gives rates after withdrawal by route, 4 to 52 per cent, in selected study populations, and these cannot be converted into a population figure. The source consulted gives no percentage for tuberculosis as a cause, and the global split between autoimmune and infectious causes is not systematically measured. The 80 to 90 per cent autoimmune figure applies to industrialised countries only.

Standardised mortality remains roughly 2 after seventy-five years of replacement therapy. The reason, non-physiological replacement, is accepted and not fixed. The optimal replacement dose and schedule is not established by trial, and doses have fallen over decades on observational grounds. Modified-release hydrocortisone costs 30 to 100 times more than conventional hydrocortisone for improvements measured mainly on quality-of-life and metabolic surrogates in small trials, with no cost-effectiveness consensus. DHEA replacement is contested.

No intervention is known to prevent progression from antibody-positive preclinical disease to overt insufficiency, so screening relatives yields earlier diagnosis and nothing more. Diagnostic delay of 1 to 2 years, with many patients diagnosed at crisis, is consistently reported, and the reasons are system-level.

Hydrocortisone and fludrocortisone prices have been volatile in single-supplier markets despite being off-patent, and the United Kingdom hydrocortisone case ended in competition enforcement. It is a second instance where off-patent status did not guarantee affordability. Almost no outcome data exist from low-income countries, where tuberculous Addison disease is commonest and hydrocortisone supply is least reliable.

> **Depth.** Starts in: 21-hydroxylase. Size: 10 nm†; depth −1.38. First complaint: about 40 years († onset about age 40; [B] builds up over months); time depth 52.23. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: reading. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Cushing syndrome

What it is. Too much cortisol for too long. Fat gathers on the trunk, face and neck while the limbs thin, the skin bruises and splits, and blood pressure, glucose and bone all move the wrong way. Most cases are caused by prescribed steroids and not by a gland.

Measured. Endogenous Cushing syndrome, caused by a tumour, occurs at about 2 to 3 cases per million people a year†. For Cushing disease, the pituitary ACTH-secreting adenoma, a Danish study found fewer than 1 case per million a year, and most European registries give 1.2 to 2.4 per million a year†. Prevalence of endogenous disease is roughly 40 to 80 per million†.

Iatrogenic (exogenous) Cushing syndrome is far commoner and is not counted. The source consulted states that the most common cause is prescribed glucocorticoids and gives no percentage split, so iatrogenic cases are the majority. Oral glucocorticoid use at any one time is roughly 1 to 3 per cent of the population in high-income countries, and roughly 0.5 to 1 per cent long-term†. That is a population two to three orders of magnitude larger than the one with endogenous disease.

Among endogenous cases, pituitary Cushing disease is about 70 per cent. Adrenal adenoma or carcinoma is roughly 15 to 20 per cent. Ectopic ACTH secretion, from small cell lung cancer, bronchial and thymic carcinoid, medullary thyroid carcinoma and pancreatic neuroendocrine tumours, is roughly 10 to 15 per cent†. ACTH-independent adrenal hyperplasias and genetic syndromes are a small remainder. Endogenous disease is roughly 3 to 8 times commoner in women, with onset at 25 to 45 years†. Ectopic ACTH syndrome is commoner in older men, tracking lung cancer.

Untreated endogenous Cushing syndrome had a 5-year mortality of roughly 50 per cent in series from before effective treatment, from cardiovascular disease, infection, thromboembolism and suicide. The standardised mortality ratio in treated Cushing disease is roughly 1.5 to 3.0 overall. It is roughly 1.0 in sustained remission and roughly 3.7 to 5.0 in persistent disease†. Remission normalises mortality, and persistence does not.

Venous thromboembolism risk is raised roughly 10 to 18-fold and is highest around surgery, which is why thromboprophylaxis is now standard around pituitary surgery for Cushing disease. Cardiovascular events, diabetes, osteoporotic fracture, infection and psychiatric morbidity remain elevated for years after biochemical cure, a consistent and important finding.

Diagnosis takes a median of roughly 2 to 3 years, with patients seeing several specialists for individual features before the syndrome is recognised. At diagnosis hypertension is present in roughly 70 to 85 per cent, glucose intolerance or diabetes in 20 to 50, osteoporosis or osteopenia in 50 to 80, depression in 50 to 80 and vertebral fracture in 30 to 70 per cent†.

Where it starts. Exogenous glucocorticoids are the dominant cause, dose- and duration-dependent. All routes can do it: oral, injected, intra-articular, inhaled (particularly high-dose fluticasone), topical (especially potent steroids on large areas, in children or under occlusion) and intranasal. Interactions matter. Ritonavir, cobicistat, itraconazole and clarithromycin inhibit CYP3A4 and can turn a modest inhaled or intra-articular steroid dose into florid Cushing syndrome. The interaction is well documented and avoidable.

Somatic *USP8* mutations occur in roughly 35 to 60 per cent of pituitary corticotroph adenomas, with *USP48* and *BRAF* in smaller fractions†. Somatic *PRKACA* mutations occur in roughly 35 to 65 per cent of cortisol-producing adrenal adenomas, with *GNAS* and *CTNNB1*†. These are acquired and not inherited.

Rare genetic syndromes change management: Carney complex (*PRKAR1A*), McCune-Albright syndrome (somatic *GNAS*), multiple endocrine neoplasia type 1 (*MEN1*), familial isolated pituitary adenoma (*AIP*), primary bilateral macronodular adrenal hyperplasia (*ARMC5*, in roughly 20 to 25 per cent†) and Li-Fraumeni syndrome (*TP53*). In southern Brazil a founder *TP53* R337H variant gives a markedly raised incidence of adrenocortical carcinoma, particularly in children. Ectopic ACTH is driven by the underlying neuroendocrine tumour, and smoking is the main risk factor through small cell lung cancer.

Cortisol excess does its damage through glucocorticoid receptor activation in liver, muscle, adipose tissue, bone, vessel wall and brain. The results are gluconeogenesis and insulin resistance, proteolysis and myopathy, central fat redistribution, osteoblast apoptosis and reduced bone formation, hypertension and hypokalaemia from mineralocorticoid receptor activation at high cortisol concentrations, and immune suppression. The mechanisms are established, which is why the features are so predictable.

Pseudo-Cushing states must be excluded: severe obesity, poorly controlled diabetes, depression, chronic alcohol use, polycystic ovary syndrome, and the physiological hypercortisolism of pregnancy and severe stress. They produce overlapping biochemistry, which is why diagnosis needs more than one abnormal test.

Not known: the true population burden of iatrogenic Cushing syndrome. Why cardiovascular, skeletal and psychiatric morbidity persist for years after biochemical cure. Whether to treat mild autonomous cortisol

secretion surgically. It is found in roughly 5 to 30 per cent of the growing number of incidentally found adrenal nodules and is associated with hypertension, diabetes, fracture and mortality.

Cure status. Iatrogenic Cushing syndrome: CURABLE, by withdrawing the glucocorticoid. Cushing disease: CURABLE by transsphenoidal adenomectomy, with recurrence in roughly 10 to 25 per cent at 10 years; where bilateral adrenalectomy is needed, the hypercortisolism is cured and lifelong adrenal insufficiency is CONTROLLABLE. Adrenal adenoma: CURABLE, by unilateral adrenalectomy. Adrenocortical carcinoma, stage I to II, completely resected: CURABLE. Adrenocortical carcinoma, stage IV: RELIEF ONLY. Ectopic ACTH syndrome, source tumour resectable: CURABLE. Ectopic ACTH syndrome, otherwise: RELIEF ONLY, with medical control of cortisol while the tumour is treated.

Withdrawal of the glucocorticoid must be gradual, because the axis is suppressed, and adrenal insufficiency follows withdrawal in roughly half of patients after oral courses; see adrenal insufficiency. The cure is free and the hazard lies in how it is done.

Initial remission after pituitary surgery is roughly 70 to 90 per cent for microadenomas in experienced hands and roughly 50 to 65 per cent for macroadenomas†. Recurrence is roughly 10 to 25 per cent at 10 years and roughly 20 to 35 per cent at longer follow-up, so lifelong surveillance is needed†. Surgeon volume matters substantially for remission and complication rates, and this is the main argument for centralising the operation. Second-line options are repeat surgery, stereotactic radiosurgery or fractionated radiotherapy (remission in roughly 50 to 60 per cent over 2 to 5 years, hypopituitarism in roughly 20 to 40 per cent), medical therapy, and bilateral adrenalectomy†. Bilateral adrenalectomy cures the hypercortisolism with certainty and carries a roughly 10 to 30 per cent risk of Nelson syndrome, progressive corticotroph tumour growth.

Unilateral adrenalectomy for adenoma has cure rates approaching 100 per cent†. The operation is laparoscopic, and the contralateral gland recovers over months, during which glucocorticoid replacement is needed. Adrenocortical carcinoma has 5-year survival of roughly 60 to 80 per cent at stage I to II and under 15 per cent at stage IV†. Mitotane plus etoposide, doxorubicin and cisplatin (the FIRM-ACT regimen) is standard for advanced disease, with modest benefit.

After cure, life expectancy is usually normal, and standardised mortality in sustained remission approaches 1.0. Patients whose surgery cannot remove the entire tumour have increased risk of death. Glucocorticoid withdrawal syndrome after cure causes months of profound fatigue, joint pain and low mood, and is routinely mistaken for treatment failure.

Prevention. Glucocorticoid stewardship is the prevention of the commonest form and the only prevention available at scale. It means the lowest effective dose for the shortest time, and topical and inhaled routes preferred while recognising that these also cause it. It means avoiding potent topical steroids on large areas and under occlusion, particularly in children. It means checking for CYP3A4-inhibitor interactions with ritonavir, cobicistat, itraconazole and clarithromycin before prescribing any steroid. STRONG.

Avoiding unlicensed and adulterated products. Skin-lightening creams, herbal remedies and unregulated injections containing undeclared potent corticosteroids are a documented cause of iatrogenic Cushing syndrome in several countries. MODERATE, and it is a regulatory matter. No prevention of endogenous Cushing syndrome exists.

Prevention of complications and deaths. Perioperative thromboprophylaxis against a 10 to 18-fold raised risk: STRONG. Treating hypertension, hyperglycaemia and hypokalaemia from diagnosis and not after cure: STRONG. Bone protection and fracture assessment, with osteoporosis or osteopenia present in 50 to 80 per cent at diagnosis and vertebral fracture in 30 to 70 per cent: STRONG. *Pneumocystis* prophylaxis in severe hypercortisolism, which is profoundly immunosuppressive, since opportunistic infection is a leading cause of death in florid disease: MODERATE. Psychiatric assessment, with depression in 50 to 80 per cent and suicide a recognised cause of death: MODERATE. Centralising pituitary surgery in high-volume centres: MODERATE. Lifelong surveillance for recurrence, with 10 to 25 per cent recurring by 10 years: STRONG.

Earlier diagnosis. The median delay is 2 to 3 years, and the preventable harm accrues during it. Testing for Cushing syndrome in people with a specific combination of features is cheap: resistant hypertension with

hypokalaemia, early osteoporosis with fracture, new diabetes with weight gain and proximal myopathy, easy bruising with purple striae. The tests are an overnight dexamethasone suppression test, a late-night salivary cortisol, or a 24-hour urine free cortisol. MODERATE.

Treatment. Withdraw the glucocorticoid where the cause is exogenous, gradually, with replacement-dose cover and monitoring for adrenal insufficiency. It is free and curative.

Transsphenoidal pituitary surgery is first-line for Cushing disease. It is not a medicine, and costs tens of thousands of dollars in high-income systems. Transient diabetes insipidus occurs in roughly 10 to 25 per cent and is permanent in roughly 1 to 3 per cent; hypopituitarism occurs in roughly 5 to 15 per cent; cerebrospinal fluid leak in roughly 1 to 4 per cent†. Unilateral adrenalectomy for adenoma is curative and laparoscopic, at thousands to tens of thousands of dollars.

Medical therapy is used while awaiting surgery, after failed surgery, while radiotherapy takes effect, and in ectopic ACTH syndrome. Steroidogenesis inhibitors come first.

Ketoconazole is off-label in many countries and licensed as Ketoconazole HRA in Europe for Cushing syndrome. It controls cortisol in roughly 50 to 75 per cent†. Generic ketoconazole costs hundreds of dollars a patient-year and the licensed European product tens of thousands. Hepatotoxicity requires monitoring. Its listing on the WHO Essential Medicines List 24th List is for fungal infection, not Cushing syndrome, and its status needs checking.

Metyrapone controls cortisol in roughly 50 to 75 per cent†. It is off-patent in principle but supplied by few manufacturers, and has risen steeply to tens of thousands of dollars a patient-year. Its listing status needs checking against the 24th List†.

Osilodrostat, an 11-beta-hydroxylase inhibitor approved in 2020, was tested in the LINC-3 randomised withdrawal trial. At week 34, 86 per cent of osilodrostat patients maintained normal urinary free cortisol against 29 per cent on placebo†. It is patented and costs hundreds of thousands of dollars a patient-year at United States list price. Levoketoconazole was approved in 2021. Etomidate, intravenous and a cheap generic, gives rapid emergency control of severe hypercortisolism in intensive care. Mitotane is adrenolytic, used in adrenocortical carcinoma and occasionally for cortisol control, with a narrow therapeutic index and off-patent; its listing status needs checking against the 24th List†.

Pituitary-directed drugs: pasireotide, a somatostatin analogue, normalises cortisol in roughly 15 to 26 per cent and causes hyperglycaemia in roughly 70 per cent†. Cabergoline is off-patent, costs hundreds of dollars a patient-year, and is effective in roughly 25 to 40 per cent†. Mifepristone, a glucocorticoid receptor antagonist, improves glucose and clinical features, but cortisol cannot be used to monitor it. It is patented in the United States for this indication at hundreds of thousands of dollars a patient-year.

Radiotherapy or stereotactic radiosurgery treats persistent Cushing disease, with remission in 50 to 60 per cent over 2 to 5 years and hypopituitarism in 20 to 40 per cent. Bilateral adrenalectomy gives definitive control at the price of lifelong adrenal insufficiency and a 10 to 30 per cent risk of Nelson syndrome†. It is cheap and permanent, and is used where other options fail and in severe ectopic ACTH syndrome.

Complications are treated directly: antihypertensives, with mineralocorticoid receptor antagonists such as spironolactone particularly appropriate given the mechanism; antidiabetic drugs; potassium replacement; bisphosphonates for bone; anticoagulant prophylaxis; antidepressants; and *Pneumocystis* prophylaxis in severe disease. Spironolactone is on the 24th List, but for oedema, ascites and heart failure, and its record does not carry hypertension as an indication. After cure, glucocorticoid replacement covers the months of axis recovery, and the patient is warned about glucocorticoid withdrawal syndrome.

Simple means. Stopping the steroid. The commonest cause of this syndrome is a prescription, and the cure is to stop it, tapered. It costs nothing and is the single most effective intervention in this entry.

A medication review, asking what creams, inhalers, injections, joint injections, nasal sprays and unlicensed or imported products a person uses. Topical and inhaled steroids, and adulterated skin-lightening creams and herbal products, cause florid Cushing syndrome, and the history is free. A check for a CYP3A4 interaction before prescribing any corticosteroid to someone on ritonavir, cobicistat, itraconazole or clarithromycin takes thirty seconds and prevents an iatrogenic disease.

A blood pressure cuff and a potassium level. Resistant hypertension with unexplained hypokalaemia is one of the cheapest pointers to cortisol excess. Looking at the patient. Purple striae wider than 1 cm, proximal myopathy (difficulty rising from a chair without using the arms), easy bruising and facial plethora have the highest discriminating value, and all are free to assess. With a median diagnostic delay of 2 to 3 years, examination is the intervention.

A late-night salivary cortisol is collected at home with no venepuncture. It is among the cheapest and most specific screening tests in endocrinology, at tens of dollars a test where the assay is available.

Spironolactone for the hypertension and hypokalaemia is off-patent, costs tens of dollars a patient-year, and is mechanistically the right drug. Generic ketoconazole, at hundreds of dollars a patient-year, serves where osilodrostat at hundreds of thousands is unavailable. It works in 50 to 75 per cent of patients and requires liver monitoring. Low-molecular-weight heparin around surgery is cheap, against a 10 to 18-fold raised thrombosis risk. Glucocorticoid withdrawal syndrome after cure should not be mistaken for treatment failure.

Gaps. The split between iatrogenic and endogenous Cushing syndrome is not quantified. The source consulted gives no percentage. Iatrogenic disease is stated to be the commonest cause and has no population prevalence estimate, so the single most common form of this disease is essentially uncounted.

Surgical remission rates of 70 to 90 per cent for microadenomas come from high-volume specialist centres and are not representative of outcomes where pituitary surgery is done occasionally. No source consulted gives a pooled remission figure across all settings. Recurrence rises with length of follow-up, 10 to 25 per cent at 10 years and higher later, so cure is provisional and published cure rates depend on follow-up duration.

Cardiovascular, skeletal and psychiatric morbidity persist for years after biochemical cure and the mechanism is unexplained. Mild autonomous cortisol secretion from adrenal incidentalomas is increasingly detected and associated with hypertension, diabetes, fracture and mortality. Whether to operate is unresolved, and no adequately powered randomised trial exists.

Osilodrostat at hundreds of thousands of dollars a patient-year stands against generic ketoconazole at hundreds, with no head-to-head trial. Metyrapone, nominally off-patent, costs tens of thousands of dollars a patient-year because of supplier concentration, which is another case where off-patent status did not deliver affordability.

Pseudo-Cushing states overlap biochemically and no single test separates them, so diagnostic accuracy in practice is lower than published test characteristics suggest. Diagnostic delay of 2 to 3 years is consistently reported, because the features present to different specialties separately. Almost no epidemiological or outcome data exist from low- and middle-income countries. The *TP53* R337H founder effect in southern Brazil shows that adrenocortical carcinoma incidence can vary enormously by population, and comparable founder effects elsewhere are unstudied.

> **Depth.** Starts in: a glucocorticoid molecule. Size: 1 nm†; depth −3.48. First complaint: about 7.4 weeks († weeks to months of steroid); time depth 47.10. One untreated course: no number († as long as exposure lasts).
>
> **Model reading.** Way of ending: restore proportion. Layer: word. The book splits this entry by moment, early and late. By the rule it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Acromegaly

What it is. A pituitary tumour makes too much growth hormone in an adult. Hands, feet, jaw and brow grow slowly larger over years, the tongue and soft tissues thicken, and the heart, joints and metabolism suffer. The change is gradual, so recognition is usually late.

Measured. Prevalence is about 6 per 100,000 people, roughly 60 per million. Published estimates range from roughly 28 to 137 per million, with higher figures from systematic case-finding. A German primary care screening study found a prevalence roughly 10 times the registry figure, which suggests substantial

under-diagnosis. Incidence is roughly 3 to 5 per million a year in European registries†. Diagnosis is typically in middle age, mean roughly 40 to 45 years, and the sexes are about equal, with women diagnosed slightly later.

Diagnostic delay is the defining epidemiological feature: roughly 5 to 10 years from first symptom, among the longest for any endocrine disease. The facial and acral changes are slow and go unnoticed by the patient and by people who see them daily. Patients commonly present first to dentists (jaw and bite change), rheumatologists (joint pain, carpal tunnel), cardiologists, sleep clinics and ophthalmologists. Roughly 60 to 80 per cent of tumours are macroadenomas of 10 mm or more at diagnosis, a direct consequence of the delay, and tumour size is the main determinant of surgical cure.

The change in mortality is the central measured finding. Untreated, life expectancy is reduced by roughly 10 years†. Historical cohorts gave standardised mortality ratios of roughly 1.7 to 3.0, from cardiovascular disease, respiratory disease and cancer. A meta-analysis of modern cohorts gives a pooled ratio of roughly 1.3 to 1.7, and with biochemical control, normalised IGF-1 and growth hormone, mortality approaches that of the general population, with a ratio of roughly 1.1 or lower†. The source consulted states that early, successfully treated patients have life expectancy equal to the general population. Biochemical control demonstrably restores normal survival, and the whole therapeutic objective is defined by that.

Comorbidity at diagnosis: hypertension roughly 35 to 60 per cent, diabetes or impaired glucose tolerance 30 to 55, obstructive sleep apnoea 50 to 80, arthropathy 60 to 75, cardiomyopathy and left ventricular hypertrophy 30 to 60, carpal tunnel syndrome 20 to 60, and colonic polyps 25 to 45 per cent†. Gigantism is the same disease before the growth plates fuse and produces extreme height. It is rare. X-linked acrogigantism (*GPR101* microduplication) and *AIP* mutations account for a substantial share of childhood-onset cases.

Where it starts. In over 95 per cent of cases the cause is a somatotroph adenoma of the anterior pituitary. It secretes growth hormone, which drives hepatic IGF-1 production, and IGF-1 produces most of the peripheral effects†. Activating *GNAS* mutations (the *gsp* oncogene) occur in roughly 30 to 40 per cent of sporadic adenomas†. These tumours tend to be smaller, more granulated and more responsive to somatostatin analogues, a genotype-treatment link.

Germline and syndromic causes are roughly 5 per cent of cases and change surveillance. *AIP* mutations, in familial isolated pituitary adenoma, cause young-onset, large, aggressive, somatostatin-resistant tumours, and are found in roughly 15 to 20 per cent of patients diagnosed under 30 and in roughly 50 per cent of familial isolated pituitary adenoma families†. *GPR101* microduplication (Xq26.3) causes infant-onset gigantism. Others are multiple endocrine neoplasia type 1 (*MEN1*) and type 4 (*CDKN1B*), Carney complex (*PRKAR1A*), McCune-Albright syndrome (somatic *GNAS* mosaicism) and the phaeochromocytoma and paraganglioma syndromes (*SDHx*). Ectopic secretion of growth hormone-releasing hormone from a bronchial or pancreatic neuroendocrine tumour accounts for under 1 per cent of cases† and is cured by removing the tumour.

The great majority are not heritable. Familial forms are Mendelian, with high penetrance for *GPR101* and incomplete penetrance, roughly 15 to 30 per cent, for *AIP*†. No environmental cause is established: no dietary, occupational or infectious risk factor has been demonstrated.

The comorbidities follow from established mechanisms. Growth hormone and IGF-1 drive soft tissue and skeletal growth, sodium retention and volume expansion (hypertension), insulin resistance (diabetes), cardiomyocyte hypertrophy and fibrosis (cardiomyopathy), pharyngeal soft tissue growth (sleep apnoea), cartilage hypertrophy then degeneration (arthropathy) and colonic mucosal proliferation (polyps). The mechanisms explain why some comorbidities reverse with treatment and others, particularly the arthropathy and skeletal changes, do not.

Not known: why diagnostic delay remains 5 to 10 years when the condition is recognisable on sight once considered. Why arthropathy progresses after biochemical cure. Whether colorectal cancer risk is genuinely raised. What determines somatostatin analogue responsiveness beyond *GNAS* status and tumour granulation pattern.

Cure status. Microadenoma: CURABLE, by transsphenoidal surgery, in roughly 75 to 90 per cent†. Macroadenoma: CURABLE by surgery in roughly 40 to 60 per cent†, and CONTROLLABLE, by medical therapy that is indefinite, in the rest. Large invasive tumour with cavernous sinus extension: CONTROLLABLE, with surgical cure in under 30 per cent†. Ectopic growth hormone-releasing hormone tumour: CURABLE, by resection. Established arthropathy and the bony facial and acral changes: RELIEF ONLY.

Surgery is most successful when blood growth hormone is below 40 ng/ml and the tumour is 10 mm or smaller, and success depends on the surgeon's skill, according to the source consulted. Surgeon and centre volume are major determinants, as in Cushing disease. Recurrence after initial remission is roughly 2 to 8 per cent over 10 years†.

Medical therapy controls and does not cure. Somatostatin receptor ligands (octreotide LAR, lanreotide autogel) normalise IGF-1 in roughly 25 to 45 per cent in unselected first-line use, higher, roughly 50 to 60 per cent, in older or selected series, and reduce tumour size in roughly 50 to 75 per cent†. Pasireotide LAR normalises IGF-1 in roughly 35 to 40 per cent, more than octreotide in head-to-head trials, at the cost of hyperglycaemia in roughly 55 to 70 per cent†.

Pegvisomant, a growth hormone receptor antagonist, controls disease activity in virtually everyone according to the source consulted. IGF-1 normalisation is roughly 90 to 97 per cent in the original trials with adequate dose titration and roughly 60 to 75 per cent in real-world registry use, where doses are often lower†. It blocks the receptor and not the tumour, so growth hormone levels rise and cannot be used for monitoring, and the tumour is not treated.

Cabergoline, a dopamine agonist, normalises IGF-1 in roughly 30 to 35 per cent of patients with modest elevation and is more effective in mixed growth-hormone-and-prolactin tumours. The source consulted notes that oral cabergoline costs considerably less than injectable treatments. Combination therapy, a somatostatin ligand with pegvisomant or cabergoline, raises control rates further. Radiotherapy or stereotactic radiosurgery gives biochemical remission in roughly 40 to 60 per cent over 5 to 10 years, with hypopituitarism in roughly 20 to 50 per cent at 10 years and a long latency, so it is third-line†.

After control, sleep apnoea, hypertension, glucose intolerance, headache, sweating and soft tissue swelling improve substantially. The bony facial and acral changes, established arthropathy and some cardiac fibrosis do not reverse.

Prevention. No primary prevention exists. The tumour is sporadic in over 95 per cent of cases† and no environmental cause is known.

Genetic testing and family screening in young-onset disease, gigantism, familial cases and syndromic presentations (*AIP*, *GPR101*, *MEN1*, *CDKN1B*, *PRKAR1A*). In *AIP* carriers, prospective screening of relatives detects tumours at a smaller size, with higher surgical cure rates than clinical presentation. MODERATE.

Earlier diagnosis is the main avenue, and it is a recognition problem. Acromegaly is to be considered in patients with new diabetes and acral enlargement, bilateral carpal tunnel syndrome, resistant hypertension with sleep apnoea, worsening dental occlusion, or increasing ring and shoe size. A single serum IGF-1 measurement is the screening test, at tens of dollars. Case-finding in primary care, sleep apnoea clinics and diabetes clinics detects undiagnosed acromegaly at several-fold the registry prevalence. Comparing old photographs is free and often decisive. MODERATE: case-finding yield is demonstrated, and the effect on long-term outcome is inferred from the relationship between tumour size and cure rate.

Prevention of complications and excess mortality. Achieving biochemical control, normal age-adjusted IGF-1 and random growth hormone, restores standardised mortality to roughly 1.0. STRONG. Screening and treating sleep apnoea, hypertension, diabetes, cardiomyopathy by echocardiography, and vertebral fracture. Vertebral fracture is common in acromegaly despite normal or high bone density, so bone density alone misleads and vertebral imaging is needed. STRONG.

Colonoscopy at diagnosis and periodically is recommended because of the 25 to 45 per cent polyp prevalence. Whether colorectal cancer risk is raised is CONTESTED: some cohorts show a modest increase, meta-analyses are inconsistent, and the polyp finding is firm while the cancer finding is not.

Thyroid nodule surveillance carries the same dispute, and the overdiagnosis caution under thyroid nodules and goitre applies. Anticipating the airway in perioperative and peripartum care prevents a documented anaesthetic hazard, since pharyngeal soft tissue growth makes intubation difficult. STRONG.

Treatment. Transsphenoidal surgery is first-line for almost all patients, including as debulking in large tumours to improve the later medical response. It is not a medicine, costs tens of thousands of dollars in high-income systems, and outcomes depend substantially on centre volume.

Somatostatin receptor ligands: octreotide LAR, monthly intramuscular, and lanreotide autogel, monthly deep subcutaneous. They are off-patent in part: generic octreotide LAR is available in several markets, and lanreotide has biosimilar competition in Europe. Originator prices in the United States and Europe are tens of thousands of dollars a patient-year, generic octreotide LAR thousands to low tens of thousands, and in India and some other markets generic octreotide is a few thousand dollars a patient-year. Their listing status on the WHO Essential Medicines List 24th List needs checking†. Oral octreotide (Mycapssa, approved 2020) removes the injection and is priced comparably to or above the injectables. Pasireotide LAR gives higher control rates with hyperglycaemia in 55 to 70 per cent, is patented, and costs tens of thousands of dollars a patient-year.

Pegvisomant is a daily subcutaneous injection. It is patented, costs from over a hundred thousand to hundreds of thousands of dollars a patient-year depending on dose, and is among the most expensive endocrine treatments in routine use. It needs liver function monitoring, causes lipohypertrophy at injection sites and does not treat the tumour. Its listing status needs checking against the 24th List†.

Cabergoline is oral, twice weekly and off-patent, at hundreds of dollars a patient-year. Its listing status needs checking against the 24th List†. Against pegvisomant it costs two to three orders of magnitude less and controls a real minority of patients, particularly those with modest IGF-1 elevation†. In most of the world it is the only affordable medical option, and it is under-used relative to its effect size. Added to a somatostatin ligand it is a cheap addition that raises control by roughly 15 to 30 percentage points in the partially controlled†. A somatostatin ligand plus pegvisomant is expensive and highly effective.

Radiotherapy or radiosurgery is third-line. Temozolomide, off-patent, is for aggressive and malignant pituitary tumours. Comorbidities are treated directly: CPAP for sleep apnoea, at hundreds of dollars one-off plus consumables; generic antihypertensive and antidiabetic drugs; analgesia and joint replacement for arthropathy; carpal tunnel decompression; and heart failure treatment. Pituitary hormone replacement is needed where surgery or radiotherapy causes hypopituitarism: levothyroxine, hydrocortisone, sex steroids and occasionally growth hormone. Levothyroxine is on the 24th List; the others need checking against it†.

Simple means. Looking at old photographs is free and is frequently the step that makes the diagnosis after years of delay. The patient and the people who see them daily cannot see a change that takes a decade, and a photograph from fifteen years earlier makes it obvious.

Asking about ring size, shoe size, hat size and dental bite. Rings that no longer fit, shoes a size or two larger, and teeth that have separated or a bite that has changed are specific and cost nothing to ask about. Dentists detect a meaningful share of cases.

A single IGF-1 blood test, at tens of dollars, is the screening test for a disease with a 5 to 10 year diagnostic delay in which tumour size at diagnosis determines whether surgery cures. A blood pressure cuff, a fasting glucose and a question about snoring and daytime sleepiness find the three commonest comorbidities.

Cabergoline, oral and off-patent at hundreds of dollars a patient-year, normalises IGF-1 in roughly a third of patients with modest elevation and adds 15 to 30 percentage points of control when added to a somatostatin ligand. Against pegvisomant at hundreds of thousands of dollars a patient-year, this is the most consequential price fact in the entry, and it is noted even in general reference sources.

Telling the anaesthetist. Pharyngeal and laryngeal soft tissue growth makes intubation difficult and is a documented cause of anaesthetic death, and a sentence prevents it. Weight and sleep position measures help sleep apnoea while definitive treatment is arranged. Testing relatives in young-onset or familial disease finds *AIP* carriers who present with smaller tumours and higher cure rates. Simple analgesia and joint protection serve the arthropathy, the main residual disability, which does not respond to biochemical cure.

Gaps. Prevalence estimates range from roughly 28 to 137 per million, and systematic case-finding finds rates up to 10 times the registry figures. The true prevalence is unknown, and the commonly quoted figure of about 60 per million is probably an underestimate. Diagnostic delay of 5 to 10 years is consistently reported and has not shortened despite decades of awareness campaigns.

The source consulted gives no annual incidence figure, no median age at diagnosis, no quantified diagnostic delay, no standardised mortality ratio, no surgical cure percentage, and no somatostatin analogue or pegvisomant control rate. The figures in this entry for those quantities come from the wider registry and trial literature. Pegvisomant's real-world IGF-1 normalisation, roughly 60 to 75 per cent, is substantially lower than in trials, roughly 90 to 97 per cent, apparently because of under-dosing. The phrase "controls disease activity in virtually everyone" reflects the trial figure and not practice.

Surgical cure rates come from high-volume centres. Outcomes in low-volume settings are not systematically reported, and the source consulted states only that success depends on the surgeon's skill. Whether colorectal cancer risk is raised is contested, since polyps are clearly more common and cancer findings are inconsistent, yet colonoscopy surveillance is recommended on the basis of it. Thyroid cancer risk in acromegaly is similarly contested, and surveillance risks the overdiagnosis documented under thyroid nodules.

Arthropathy progresses after biochemical cure and is the main residual disability. No treatment prevents it and the mechanism is unexplained. Vertebral fractures occur despite normal or high bone mineral density, so standard osteoporosis assessment misleads and the right surveillance strategy is not established. Essentially all epidemiology and outcome data come from European and North American registries. Almost nothing comes from low- and middle-income countries, where somatostatin analogues are unaffordable and cabergoline and surgery are the only options.

> **Depth.** Starts in: a somatotroph cell. Size: 15 µm†; depth +5.28. First complaint: about 7 years ([B] 5–10 years until it is recognised); time depth 50.65. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: reading. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Osteoporosis

What it is. Bone loses mass and internal structure, so it breaks under forces it should withstand. There are no symptoms until a fracture happens. A hip fracture in an older person often ends independent living and kills roughly one in four within a year.

Measured. By the World Health Organization definition, a bone mineral density T-score of -2.5 or below at the femoral neck, osteoporosis affects roughly 20 to 25 per cent of women and 5 to 8 per cent of men aged 50 and over in European and North American surveys†. International Osteoporosis Foundation analyses of the European Union put roughly 32 million people aged 50 and over with osteoporosis in 2019, 25.5 million women and 6.5 million men, about 5.6 per cent of the EU population over 50†.

Roughly 9 million osteoporotic fractures occur a year worldwide, the standing estimate, derived from hip fracture incidence and extrapolation. Hip fractures number roughly 1.3 to 1.6 million a year globally and are projected to reach 4.5 to 6.3 million by 2050 on demographic grounds alone†. Lifetime risk of an osteoporotic fracture from age 50 is roughly 40 to 50 per cent in women and 13 to 22 per cent in men in high-income countries†. In the EU-27 plus the United Kingdom and Switzerland in 2019 there were roughly 4.3 million new fragility fractures, at a cost of roughly €56 billion, projected to rise by roughly 25 per cent by 2034†.

Hip fracture outcomes are the hard numbers. Excess mortality in the first year is roughly 20 to 30 per cent, with the standing figure that about one in four older patients dies within 12 months†. Roughly 40 per cent cannot walk independently afterwards, roughly 60 per cent need help a year later, and roughly 10 to 20 per cent move permanently into institutional care†. Mortality after hip fracture is consistently higher in men than in women.

Roughly two-thirds of vertebral fractures are clinically silent and found only on imaging. A prevalent vertebral fracture raises the risk of a further vertebral fracture roughly 4 to 5-fold and of hip fracture roughly 2-fold†. Risk of a second fracture is highest immediately after the first, roughly 2.7 to 5-fold in the first year or two, declining thereafter†. This underpins fracture liaison services.

Hip fracture rates vary more than 10-fold between countries. They are highest in Scandinavia, Austria and parts of northern Europe and lowest in parts of Africa, Latin America and East Asia, and the gradient does not track vitamin D status, calcium intake or latitude straightforwardly.

The treatment gap is the central measured failure. Roughly 70 to 80 per cent of people at high fracture risk receive no osteoporosis treatment in European, United States and Australian audits. Treatment initiation after a fragility fracture is roughly 20 to 30 per cent†. In the United States bisphosphonate use fell by roughly 50 per cent between the mid-2000s and mid-2010s, largely attributed to publicity about atypical femoral fracture and osteonecrosis of the jaw. Those risks run at roughly 1 in 10,000 to 1 in 100,000 patient-years, against a fracture risk reduction of the order of 1 in 20 to 1 in 100†. Persistence with oral bisphosphonates at 12 months is roughly 40 to 50 per cent†.

Where it starts. The mechanism is an imbalance in bone remodelling, with resorption by osteoclasts exceeding formation by osteoblasts, driven chiefly by the RANK, RANKL and osteoprotegerin and the Wnt and sclerostin pathways. Loss of trabecular connectivity and cortical thinning and porosity reduce strength out of proportion to the loss of mass, which is why bone mineral density explains only part of fracture risk.

Peak bone mass, reached by roughly age 20 to 30, is the starting point and is roughly 60 to 80 per cent heritable†. Oestrogen deficiency is the dominant cause in women. Bone loss accelerates to roughly 2 to 3 per cent a year at the spine in the first 5 to 10 years after menopause, against roughly 0.5 to 1 per cent a year thereafter†. Early menopause, surgical oophorectomy and prolonged amenorrhoea (athletic, anorexia nervosa, hyperprolactinaemia) all cause it. Age is the strongest single risk factor, independent of bone density.

Established risk factors, with the effect sizes used in FRAX and similar tools:

- Previous fragility fracture: roughly 2-fold; a recent fracture roughly 2.7 to 5-fold in the first years.
- Parental hip fracture: roughly 1.5 to 2-fold.
- Glucocorticoids, prednisolone 5 mg a day or more: vertebral fracture risk roughly 2 to 5-fold, with most of the loss in the first 3 to 6 months. Fracture risk rises before bone density falls much, so glucocorticoid-induced osteoporosis is treated on the exposure and not the scan.
- Current smoking: roughly 1.3 to 1.8-fold for hip fracture.
- Alcohol, 3 units a day or more: roughly 1.4 to 2-fold.
- Low body weight, body mass index under 20: roughly 2-fold for hip fracture.
- Rheumatoid arthritis: roughly 1.5 to 2-fold, independent of steroids.
- Type 1 diabetes: hip fracture risk raised roughly 6 to 7-fold. Type 2 diabetes: roughly 1.3 to 1.7-fold despite higher bone density, so density underestimates risk in diabetes.

Falls are the proximate cause of roughly 90 per cent of hip fractures†. Fall risk and bone fragility are separate and multiplicative, so fall prevention is a distinct intervention. Other secondary causes are hyperthyroidism and over-replacement with levothyroxine, hyperparathyroidism, hypogonadism, coeliac disease and other malabsorption, chronic kidney and liver disease, myeloma, mastocytosis, anorexia nervosa and HIV. Drugs include aromatase inhibitors, androgen deprivation therapy, proton pump inhibitors (modestly), SSRIs, thiazolidinediones, antiepileptics, heparin, calcineurin inhibitors and injectable medroxyprogesterone acetate.

Heritability of bone mineral density in twin studies is roughly 0.5 to 0.8, and of fracture roughly 0.25 to 0.35, lower because falls and trauma intervene†. Genome-wide studies have found over 500 loci for bone density, among them *WNT16*, *LRP5*, *SOST*, *ESR1*, *RANKL* and *OPG*, which together explain roughly 20 per cent of density variance†. Monogenic bone fragility includes osteogenesis imperfecta (*COL1A1*, *COL1A2* and others, roughly 1 in 15,000 to 20,000 births), osteoporosis-pseudoglioma syndrome (*LRP5*)

and hypophosphatasia (*ALPL*)†. These present and are treated differently. Bisphosphonates are harmful in hypophosphatasia, which is a trap.

Not known: why hip fracture rates vary more than ten-fold between countries, and why they have been falling in several high-income countries since the 1990s after age adjustment. The decline is real, substantial and unexplained. Why bone mineral density explains only part of fracture risk. Whether the long-term balance beyond 10 years favours continuing bisphosphonates, which is why drug holidays exist as a practice without trial support.

Cure status. CONTROLLABLE. No treatment restores normal bone architecture, and treatment reduces fracture risk without abolishing it.

Antiresorptive treatment reduces fracture risk substantially, and the effect is lost when treatment stops, rapidly with denosumab and slowly with bisphosphonates, which persist in bone. The pivotal randomised trials measured the following.

Zoledronic acid, HORIZON-PFT: 7,765 postmenopausal women with osteoporosis, 3,889 on zoledronic acid 5 mg intravenously at 0, 12 and 24 months and 3,876 on placebo, 60 centres, 3 years, all receiving calcium and vitamin D†. Vertebral fracture in those not on other osteoporosis drugs was 3.3 per cent against 10.9 per cent, relative risk 0.30 (95% confidence interval 0.24 to 0.38), a roughly 70 per cent relative reduction and 7.6 percentage points absolute†. Hip fracture in all randomised was 1.4 per cent against 2.5 per cent, hazard ratio 0.59 (0.42 to 0.83), a roughly 41 per cent relative reduction and 1.1 percentage points absolute†. Non-vertebral fracture was 8.0 per cent against 10.7 per cent, hazard ratio 0.75†. The safety signals were an acute-phase reaction (fever 16.1 per cent against 2.1), a transient creatinine rise (1.2 against 0.4 per cent) and more serious atrial fibrillation events (1.3 against 0.5 per cent)†. No osteonecrosis of the jaw was reported.

Alendronate, the Fracture Intervention Trial: in women with prevalent vertebral fracture, vertebral fracture fell by roughly 47 per cent, hip fracture by roughly 51 and wrist fracture by roughly 48 per cent†. Risedronate reduced vertebral fracture by roughly 41 to 49 per cent and hip fracture by roughly 30 per cent†.

Denosumab, FREEDOM: 7,868 women over 3 years, vertebral fracture reduced 68 per cent, hip fracture 40 and non-vertebral fracture 20 per cent†. Stopping denosumab causes rapid rebound bone loss and multiple vertebral fractures in a measurable minority, so it cannot simply be discontinued and must be followed by a bisphosphonate.

Teriparatide, an anabolic agent, reduced vertebral fracture 65 per cent and non-vertebral fracture 53 per cent in the pivotal trial†. In the VERO head-to-head trial it reduced new vertebral fractures by roughly 56 per cent compared with risedronate in women with severe osteoporosis. Abaloparatide reduced vertebral fracture roughly 86 per cent against placebo†. Romosozumab, anti-sclerostin and both anabolic and antiresorptive, was tested in FRAME and ARCH. In ARCH, romosozumab followed by alendronate reduced vertebral fracture by roughly 48 per cent and hip fracture by roughly 38 per cent compared with alendronate alone†. ARCH also showed an excess of serious cardiovascular events, 2.5 against 1.9 per cent, which produced a boxed warning and restricts use in patients with recent myocardial infarction or stroke.

Hormone replacement therapy in the Women's Health Initiative reduced hip fracture by 33 per cent and total fracture by roughly 24 per cent in the oestrogen-plus-progestogen arm†. The fracture benefit was overshadowed by the breast cancer and cardiovascular findings, and the balance differs by age at initiation. Sequence matters: anabolic-first then antiresorptive gives greater bone density gains than the reverse, and this is now reflected in guidelines for severe disease.

Fracture risk can thus be roughly halved, and vertebral fracture risk reduced by up to two-thirds to four-fifths. The number needed to treat over 3 years to prevent one vertebral fracture is roughly 13 to 20 in high-risk women and to prevent one hip fracture roughly 90 to 100†. The HORIZON-PFT absolute differences give the same values: 1 / 0.076 is about 13, and 1 / 0.011 is about 91. This is not a cure, and it is a large effect.

Prevention. Fall prevention, because falls cause roughly 90 per cent of hip fractures. A Cochrane review of exercise for falls prevention in older people living in the community covered 59 trials and roughly 13,000

participants. It found a roughly 23 per cent reduction in the rate of falls (rate ratio 0.77) and a roughly 15 per cent reduction in the number of people falling. Balance and functional exercise, and Tai Chi (rate ratio roughly 0.81), were the effective categories†. STRONG. Multifactorial assessment and intervention in high-risk older people reduces falls by roughly 20 to 25 per cent. MODERATE. Medication review and withdrawal of psychotropics: MODERATE. Home hazard modification in those at high risk reduces falls by roughly 25 to 30 per cent†. MODERATE. Cataract surgery and vision correction: MODERATE. Hip protectors in nursing homes reduce hip fracture modestly, roughly 15 to 20 per cent, with poor adherence†. WEAK.

Calcium and vitamin D. Vitamin D alone does not reduce fractures in community-dwelling adults, and multiple randomised trials and meta-analyses are negative, including VITAL. Calcium plus vitamin D reduces fracture in institutionalised and deficient older people, by roughly 15 to 20 per cent for total fracture and roughly 25 to 30 per cent for hip fracture in the French nursing-home trials (Decalyos and Chapuy). High intermittent vitamin D doses, 500,000 IU annually or 60,000 IU monthly, increased falls and fractures in two randomised trials†. STRONG for calcium plus vitamin D in institutionalised and deficient populations. CONTESTED, to negative, for vitamin D alone in community-dwelling replete adults.

Weight-bearing and resistance exercise raises lumbar spine and femoral neck bone density by roughly 1 to 2 per cent over 6 to 12 months in meta-analyses, a small effect on density, and the fracture benefit comes mainly through falls. MODERATE for density, STRONG for the falls pathway. Not smoking and limiting alcohol: MODERATE. Adequate protein and avoiding underweight: MODERATE.

Glucocorticoid-sparing strategies, and bone protection from the start of any course expected to last 3 months or more at prednisolone 5 to 7.5 mg a day or more. Bisphosphonate prophylaxis reduces vertebral fracture in glucocorticoid-treated patients. STRONG. Correcting secondary causes: coeliac disease, hyperparathyroidism, hyperthyroidism, levothyroxine over-replacement, hypogonadism, vitamin D deficiency. STRONG.

Fracture liaison services systematically identify and treat everyone presenting with a fragility fracture. Observational and some controlled data show increased treatment rates and reduced refracture and mortality, and they address the 70 to 80 per cent treatment gap directly. MODERATE.

Screening. The United Kingdom SCOOP trial, 12,483 women aged 70 to 85, found a 28 per cent reduction in hip fractures with FRAX-based screening, and no reduction in all osteoporotic fractures. The Danish ROSE trial was negative for its primary endpoint. MODERATE: screening by fracture-risk tool, and not by bone density scan, has the better evidence.

Treatment. No bisphosphonate is on the WHO Essential Medicines List 24th List (2025) for osteoporosis. A live query of the electronic list returns zero recommendations for alendronate, which is not on the list at all. Zoledronic acid is listed only under Supportive medicines, section 8.2.5, for malignant neoplasm metastasis in bone or bone marrow and for osteogenesis imperfecta. Neither indication is osteoporosis. The most cost-effective fracture-prevention drug class in medicine is absent from the list for its main indication.

Oral bisphosphonates, alendronate weekly and risedronate weekly or monthly, are first-line almost everywhere. They are off-patent and cost tens of dollars a patient-year. Vertebral fracture falls by roughly 40 to 50 per cent and hip fracture by roughly 30 to 50 per cent†. Practical constraints are that the tablet must be taken fasting with water, upright, 30 to 60 minutes before food, with upper gastrointestinal intolerance, and persistence at 12 months is only 40 to 50 per cent.

Zoledronic acid, 5 mg intravenously once yearly, gives the HORIZON-PFT results above. It is off-patent and costs tens to hundreds of dollars a patient-year including the infusion visit. Once-yearly dosing solves the adherence problem that defeats oral bisphosphonates, and that is its main practical advantage. An acute-phase reaction follows the first dose in roughly 16 per cent† and is reduced by paracetamol.

Denosumab, 60 mg subcutaneously every 6 months, gives the FREEDOM results above. Biosimilars launched in Europe and the United States from 2024 to 2025 and prices are falling sharply. The originator costs thousands of dollars a patient-year and biosimilars hundreds. The discontinuation hazard is the key point: stopping causes rebound resorption and multiple vertebral fractures in a measurable minority, so a

bisphosphonate must follow. That makes it a poor choice where follow-up cannot be guaranteed. Its listing status needs checking against the 24th List†.

Anabolic agents are for severe osteoporosis, multiple vertebral fractures or failure on antiresorptives. Teriparatide, daily subcutaneous for a maximum of 24 months, has biosimilars; the originator costs tens of thousands of dollars a patient-year and a biosimilar thousands. Its listing status needs checking against the 24th List†. Abaloparatide is patented at about the originator teriparatide price. Romosozumab, monthly for 12 months, costs tens of thousands of dollars a course and carries the cardiovascular boxed warning.

Hormone replacement therapy serves women with menopausal symptoms and fracture risk and premature menopause, at tens to hundreds of dollars a patient-year. Raloxifene, a selective oestrogen receptor modulator, reduces vertebral fracture roughly 30 to 40 per cent, does not reduce hip fracture, reduces invasive breast cancer and increases venous thromboembolism. It is off-patent at hundreds of dollars a patient-year. Calcium and vitamin D are adjuncts in all treated patients and primary prevention in deficient and institutionalised people, at a few dollars to tens of dollars a patient-year. The listing status of oestrogens, calcium and vitamin D on the 24th List needs checking†.

Secondary causes are treated and bone-harmful drugs reviewed. Hip fracture needs early surgery, within 24 to 48 hours, which reduces mortality†. Orthogeriatric care reduces mortality and length of stay, and early mobilisation helps. Vertebroplasty and kyphoplasty did not show benefit over sham in two randomised sham-controlled trials, and remain contested. Drug holidays after 3 to 5 years of bisphosphonate treatment in lower-risk patients are standard practice, based on the FLEX and HORIZON extension trials, and are not supported by fracture-endpoint trials of holiday against continuation.

Not to be done: bisphosphonates in hypophosphatasia, stopping denosumab without follow-on treatment, and treating on bone density alone in diabetes or glucocorticoid exposure, where density underestimates risk.

Simple means. Exercise, specifically balance and functional training, and Tai Chi. The Cochrane review of 59 trials found a roughly 23 per cent reduction in the rate of falls, with Tai Chi at a rate ratio of roughly 0.81†. Since falls cause roughly 90 per cent of hip fractures, this is the highest-yield non-pharmacological intervention, and it needs no equipment.

Removing hazards at home, such as loose rugs, poor lighting, clutter, absent stair rails and slippery bathrooms, reduces falls roughly 25 to 30 per cent in high-risk people for the cost of a few fittings. Reviewing medicines, particularly sedatives, antihypertensives causing postural hypotension and anticholinergics, is free. So are getting cataracts operated on and glasses corrected.

Calcium from food: dairy, small whole fish with bones, calcium-set tofu, dark leaves, nixtamalised maize and ground eggshell, used as a calcium supplement in several low-income settings and measurably bioavailable. Vitamin D from sunlight; see rickets and vitamin D deficiency. In institutionalised and deficient older people, calcium plus vitamin D reduces hip fracture by roughly 25 to 30 per cent.

Alendronate costs tens of dollars a patient-year, is off-patent, and halves vertebral fracture risk. It is not on the WHO Essential Medicines List. It is the cheapest effective fracture-prevention drug in existence, and it is absent from the list. Zoledronic acid once a year costs tens to hundreds of dollars a patient-year including the visit and removes the adherence problem entirely, with a single annual contact. That suits settings with limited follow-up capacity, except that it needs an intravenous infusion.

Not smoking, limiting alcohol, adequate protein and not being underweight. Treating the fracture promptly and getting the person up: early surgery and early mobilisation after hip fracture reduce mortality, and both are organisational and not technological.

Asking about previous fractures. A prior fragility fracture roughly doubles future risk and is the strongest single clinical predictor. Identifying it costs one question, and the 70 to 80 per cent treatment gap exists largely because the question is not asked. FRAX or a similar risk tool is free, paper- or web-based, needs no bone density scan, and SCOOP showed a 28 per cent hip fracture reduction from a FRAX-based screening programme.

Gaps. Hip fracture rates vary more than ten-fold between countries and the gradient is unexplained. Age-adjusted rates have been falling in several high-income countries since the 1990s, also unexplained, which means the projection of 4.5 to 6.3 million hip fractures by 2050 may be an overestimate. The 9 million global fractures figure is an extrapolation from hip fracture data in a minority of countries, and there is no direct global fracture surveillance.

Bone mineral density explains only part of fracture risk and in diabetes and glucocorticoid exposure actively underestimates it. The WHO T-score definition remains the diagnostic standard nonetheless.

The treatment gap is 70 to 80 per cent in high-income countries with full access to cheap generic drugs, so the barrier is not price. Bisphosphonate use fell by roughly half in the United States after publicity about rare harms of 1 in 10,000 to 1 in 100,000 patient-years. No source reconciles this failure of risk communication. Separately, the drug class that is cheapest and best evidenced is not on the WHO Essential Medicines List for osteoporosis, so the global procurement reference does not carry it.

Drug holidays are standard practice without fracture-endpoint trial support. Denosumab rebound fractures on discontinuation were not anticipated by the pivotal trials and emerged after marketing, and the optimal transition strategy is not established by trial. Romosozumab's cardiovascular signal, 2.5 against 1.9 per cent in ARCH, is of uncertain mechanism, and the FRAME trial did not show it, so sources disagree on how real it is. Vertebroplasty was not superior to sham in two randomised trials and continues to be performed. Vitamin D alone does not prevent fractures and continues to be prescribed for that purpose, and high intermittent doses increased falls and fractures.

For screening, SCOOP was positive for hip fracture and ROSE negative for its primary endpoint. The sources disagree, and no country has adopted universal osteoporosis screening. Almost all prevalence, cost and outcome data are from Europe, North America, Australia and parts of East Asia. Fracture epidemiology in Africa, South Asia and Latin America is thinly measured, and the apparently low rates may be partly ascertainment. Male osteoporosis is under-studied, under-diagnosed and under-treated despite higher post-fracture mortality than in women.

> **Depth.** Starts in: the osteoclast. Size: 100 µm†; depth +7.00. First complaint: about 7 years ([B] 5–10 years after the menopause); time depth 50.65. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gout and hyperuricaemia

What it is. Uric acid crystallises in a joint and the body attacks the crystals. The joint becomes excruciatingly painful, red and swollen within hours, classically at the base of the big toe. Attacks stop by themselves. Without lowering the uric acid they come back and eventually destroy the joint.

Measured. The Global Burden of Disease 2021 gout analysis (*Lancet Rheumatology*, July 2024) found 55.8 million people with gout globally in 2020, 95 per cent uncertainty interval 44.4 to 69.8 million. Age-standardised prevalence was 659.3 per 100,000 (525.4 to 822.3), up 22.5 per cent since 1990. The male-to-female prevalence ratio was about 3.26 to 1, and prevalence rises with age. The age-standardised YLD rate was 20.5 per 100,000 (14.4 to 28.2).

The projection to 2050 is about 95.8 million cases (81.1 to 116 million), an increase of over 70 per cent from 2020, with the age-standardised rate forecast at 667 per 100,000†. Population growth and ageing drive most of the rise, and changes in prevalence rates contribute little. High body mass index accounted for 34.3 per cent (27.7 to 40.6) of gout YLDs and kidney dysfunction for 11.8 per cent (9.3 to 14.2)†. The study states that many low- and middle-income countries rely on modelled and not primary data, and that severity and disability data are often missing.

Hyperuricaemia, serum urate above roughly 0.36 to 0.42 mmol/L (6 to 7 mg/dL), is far commoner than gout. It is present in roughly 20 per cent of United States adults in the NHANES survey†. Most people with hyperuricaemia never develop gout. Roughly 10 to 20 per cent do over a decade, rising steeply with urate

level: annual incidence is roughly 0.5 per cent at urate below 7 mg/dL and roughly 4 to 5 per cent above 9 mg/dL†.

The highest recorded prevalences are in Māori and Pacific Island populations. Gout affects roughly 8 to 14 per cent of Māori men and over 10 per cent in some Pacific populations, among the highest in the world, and Taiwanese Indigenous populations are similarly high. It is also high in the United States, Australia, New Zealand and parts of Europe. Gout is rare before puberty. In men incidence rises from the third decade, and in women it rises sharply after menopause because oestrogen is uricosuric, so the sex ratio narrows with age.

Among gout patients in United States cohorts, hypertension is present in roughly 70 per cent, chronic kidney disease in 20 to 25, obesity in 50 to 55, type 2 diabetes in 25 and cardiovascular disease in 10 to 15 per cent†. Gout is associated with raised all-cause and cardiovascular mortality, hazard ratios roughly 1.1 to 1.3, persisting after adjustment for comorbidities, though whether this is causal is contested.

The central measured failure is in treatment. In United States and European audits roughly one-third to one-half of gout patients ever receive urate-lowering therapy, and adherence at one year is roughly 20 to 40 per cent, among the worst of any chronic disease†. Serum urate is measured and treated to target in a minority. Gout is a disease whose activity can be abolished under treatment, and largely is not. The reason is implementation.

Where it starts. The mechanism is fully established. Humans lack uricase, so urate is the end product of purine metabolism. Above its solubility limit, roughly 0.36 to 0.40 mmol/L (6.0 to 6.8 mg/dL) at body temperature and pH, monosodium urate crystallises, preferentially in cooler, acidic peripheral joints. Crystals activate the NLRP3 inflammasome in macrophages and release IL-1 beta, which drives the acute attack. That is why IL-1 blockade works, and it is the cleanest line from mechanism to drug in rheumatology.

Renal urate handling is the dominant determinant. Roughly 90 per cent of gout is underexcretion and not over-production†. The transporters involved are URAT1 (*SLC22A12*), GLUT9 (*SLC2A9*), ABCG2, OAT1 and OAT3, and NPT1 (*SLC17A1*), and they are both the genetic signal and the drug targets.

Heritability of serum urate is roughly 0.4 to 0.6 in twin and family studies, and of gout roughly 0.3 to 0.4†. *SLC2A9* is the strongest common locus, explaining roughly 3 to 4 per cent of urate variance alone, unusually large for a common variant. *ABCG2* Q141K is the strongest gout risk variant, with odds ratios of roughly 2 to 3, and is particularly frequent in East Asian and Polynesian populations, which partly explains the high prevalence there. Over 180 urate loci are now identified and together explain roughly 7 to 8 per cent of urate variance†. Monogenic causes are familial juvenile hyperuricaemic nephropathy (*UMOD*, *REN*, *HNF1B*), HPRT deficiency (Lesch-Nyhan syndrome), *PRPS1* superactivity and glycogen storage disease type I. They present young and must be recognised.

Diet is real and smaller than commonly assumed. Measured relative risks, from the Health Professionals Follow-up Study and similar cohorts, are roughly 1.2 to 1.4 for the highest against the lowest red meat intake, roughly 1.5 for seafood, and roughly 1.5 to 2.5 per 12 oz daily serving of beer†. Beer is the strongest dietary association, because it contains both alcohol and purines (guanosine). Spirits carry roughly 1.15 per drink a day, and wine shows no significant association in most cohorts. Sugar-sweetened beverages and fructose carry roughly 1.4 to 2.0 for the highest intake, and fructose raises urate directly through ATP depletion in hepatocytes.

Protective associations are dairy (roughly 0.5 to 0.6 for high intake), coffee (roughly 0.4 to 0.6 for four or more cups a day), vitamin C, and cherries (roughly 0.65 for attack risk in a case-crossover study)†. Vegetables and legumes show no association with gout despite high purine content, an important and counterintuitive finding. A genome-wide and dietary analysis in large cohorts found that diet explained under 1 per cent of urate variance while genetic variants explained roughly 24 per cent†. That contradicts the common framing of gout as a dietary disease, and matters for how the condition is explained to patients and how blame is assigned.

Drugs that raise urate are thiazide and loop diuretics, the commonest iatrogenic cause, low-dose aspirin, ciclosporin, tacrolimus, pyrazinamide, ethambutol, levodopa, nicotinic acid and testosterone. Drugs that

lower urate incidentally are losartan, calcium channel blockers, fenofibrate and SGLT2 inhibitors. SGLT2 inhibitors reduce gout flares in cohort studies, which matters because so many gout patients have diabetes or kidney disease. Other causes of hyperuricaemia are chronic kidney disease, lead exposure (saturnine gout), psoriasis and other high-turnover states, tumour lysis, dehydration, fasting and ketosis, obesity, insulin resistance and hypothyroidism.

Individual attacks are triggered by trauma, surgery, acute illness, dehydration, starting or stopping urate-lowering therapy, alcohol binge, a purine-rich meal and diuretic initiation. Rapid change in urate in either direction precipitates attacks, which is why urate-lowering therapy starts with flare prophylaxis.

Not known: why most people with hyperuricaemia never get gout. Whether asymptomatic hyperuricaemia should be treated. Whether urate is causally related to hypertension, chronic kidney disease and cardiovascular disease, or merely associated. Mendelian randomisation studies have mostly been negative for a causal effect on these outcomes, while observational associations are strong, and the randomised trials of allopurinol for kidney and cardiovascular endpoints (CKD-FIX and PERL) were negative.

Cure status. The disease, under continuing urate-lowering therapy: CONTROLLABLE. The individual acute flare: SELF-LIMITING. Asymptomatic hyperuricaemia is a laboratory finding and not a disease, and carries no label.

Sustained urate-lowering dissolves the crystal deposits and flares cease entirely, but treatment must usually be lifelong because urate rises again if it stops. A treatment that must be continued for life does not cure.

Sustained urate below roughly 0.36 mmol/L (6 mg/dL), and below 0.30 mmol/L (5 mg/dL) where tophi are present, dissolves tophi progressively over months to years and arrests erosive joint damage. Flares rise at first during crystal mobilisation and then fall to near zero. In long-term cohorts of treat-to-target urate-lowering therapy the great majority of patients become and remain flare-free.

The acute attack resolves over 7 to 14 days without treatment†. Treatment shortens and relieves it and does not change the course of the disease. Disease activity can be abolished by a tablet costing a few dollars to tens of dollars a year, and most patients worldwide never get it. Allopurinol is off-patent and on the WHO Essential Medicines List.

Pegloticase, a pegylated recombinant uricase, dissolves tophi rapidly in refractory tophaceous gout, a complete response occurring in roughly 42 per cent with methotrexate co-administration in the MIRROR randomised trial against roughly 24 to 42 per cent in earlier monotherapy trials†. A course costs hundreds of thousands of dollars. It is for the small group who have already failed everything cheap. Disease activity under it is still CONTROLLABLE.

Prevention. Preventing flares in established gout by treat-to-target urate-lowering therapy. The target is below 0.36 mmol/L (6 mg/dL), or below 0.30 mmol/L (5 mg/dL) with tophi. Sustained achievement essentially abolishes flares. STRONG.

Flare prophylaxis when starting urate-lowering therapy, with low-dose colchicine (0.5 mg once or twice a day) or an NSAID for 3 to 6 months, reduces the paradoxical early flare rate by roughly 50 to 85 per cent in randomised trials†. STRONG. Omitting it is the commonest reason patients stop allopurinol in the first months.

Reviewing diuretics. Thiazides and loop diuretics are the commonest iatrogenic cause, and substituting losartan or a calcium channel blocker where an antihypertensive is needed lowers urate. MODERATE.

Weight loss. High body mass index accounts for 34.3 per cent of gout YLDs in the GBD 2021 analysis. Observational and trial data show urate falling roughly 0.03 to 0.06 mmol/L (0.5 to 1.0 mg/dL) per 10 kg lost, and bariatric surgery lowers urate and reduces gout incidence substantially. MODERATE.

Dietary measures are real and modest. Dietary change typically lowers serum urate by roughly 0.01 to 0.06 mmol/L (0.2 to 1.0 mg/dL)†. That is rarely enough to reach target in someone with established gout, and diet explains under 1 per cent of urate variance against roughly 24 per cent for genetics. MODERATE for urate lowering, WEAK as monotherapy for gout. Beer and spirits are the strongest single dietary lever (beer relative risk 1.5 to 2.5 per daily serving), and sugar-sweetened beverages and fructose follow (1.4 to 2.0 for

high intake). Dairy, coffee, cherries and vitamin C are associated with lower urate and lower flare risk. Vegetables and legumes need not be restricted, since plant purines show no association with gout.

Treating asymptomatic hyperuricaemia is CONTESTED, and the trials are negative. CKD-FIX, allopurinol in chronic kidney disease, and PERL, allopurinol in type 1 diabetic kidney disease, both found no slowing of kidney function decline. ALL-HEART, allopurinol in ischaemic heart disease, found no cardiovascular benefit. Mendelian randomisation studies have mostly been negative for causal effects of urate on blood pressure, kidney function and cardiovascular disease. The American College of Rheumatology 2020 guideline conditionally recommends against urate-lowering therapy for asymptomatic hyperuricaemia.

Febuxostat cardiovascular safety is CONTESTED. The CARES trial found higher cardiovascular mortality with febuxostat than allopurinol, hazard ratio 1.34 for cardiovascular death, and produced a boxed warning†. The later FAST trial found no excess and was non-inferior. The sources disagree, and allopurinol remains first-line.

*HLA-B*58:01* screening before allopurinol in Han Chinese, Thai, Korean and other Southeast Asian populations. The odds ratio for allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis is roughly 80 to 100†. Screening is cost-effective in those populations and is recommended. STRONG in high-prevalence populations.

Treatment. The acute attack has four routes, all effective, and the choice is driven by comorbidity.

NSAIDs, naproxen, indomethacin or etoricoxib, cost a few dollars an attack. Colchicine in the low-dose regimen, 1.2 mg then 0.6 mg or 1 mg then 0.5 mg, is as effective as the old high-dose regimen with far less diarrhoea in the AGREE trial. It costs a few dollars to tens of dollars an attack at generic international prices. In the United States colchicine was granted market exclusivity in 2009 under the Unapproved Drugs Initiative, and its price rose from cents to a few dollars a tablet. Generics have since returned and prices have fallen, and it remains an instance of an off-patent drug made expensive by regulatory exclusivity. Oral prednisolone, 30 to 35 mg for 5 days, equals naproxen in randomised trials, and intra-articular injection for a single joint is the best option in kidney disease and heart failure. It costs a few dollars an attack. The listing status of ibuprofen, naproxen, colchicine and prednisolone on the WHO Essential Medicines List 24th List needs checking†.

IL-1 inhibitors, canakinumab and anakinra, are for patients in whom all of the above are contraindicated. Canakinumab costs tens of thousands of dollars a dose and anakinra tens of thousands a patient-year, so they are reserved by cost. Rest, elevation and ice help the joint.

Urate-lowering therapy is the treatment that controls the disease. Allopurinol, a xanthine oxidase inhibitor, is first-line. It starts low, 100 mg a day or 50 mg in chronic kidney disease, and is titrated upward to target urate, up to 800 to 900 mg a day if needed†. Under-dosing is the commonest reason for failure, since most patients are left on 300 mg whether or not target is reached. Allopurinol is on the WHO Essential Medicines List 24th List, section 29.1, for gout, as 100 mg oral solid, and also under supportive medicines for tumour lysis syndrome. It is off-patent and costs a few dollars to tens of dollars a patient-year, one of the cheapest chronic treatments of any disease. Allopurinol hypersensitivity syndrome occurs in roughly 0.1 to 0.4 per cent, with mortality up to 20 to 25 per cent when severe†. Risk is concentrated in *HLA-B*58:01* carriers, in chronic kidney disease, and with high starting doses, hence start low and screen in high-risk populations.

Febuxostat, second-line, lowers urate more potently. It is generic at tens to hundreds of dollars a patient-year, with a cardiovascular boxed warning in the United States after CARES, not replicated in FAST. Uricosurics are used as add-ons. Probenecid costs tens to hundreds of dollars a patient-year. Benzbromarone is more potent, is used in Europe and Asia, and was withdrawn in some markets over hepatotoxicity. Their listing status needs checking against the 24th List†.

Pegloticase, for refractory tophaceous gout, costs hundreds of thousands of dollars a course. Co-administration with methotrexate reduces immunogenicity and raises response rates: in the MIRROR trial roughly 71 per cent against 39 per cent had a sustained urate response at 52 weeks†. This is a different endpoint from the complete-response figure given under cure status, and the two are not the same measure. Low-dose colchicine or an NSAID for the first 3 to 6 months of urate-lowering therapy costs cents to a few dollars and determines whether the patient persists.

Adjuncts and substitutions are losartan in place of another antihypertensive, at tens of dollars a patient-year; fenofibrate; SGLT2 inhibitors in those with diabetes or kidney disease; and stopping or substituting the diuretic. Losartan's listing status needs checking against the 24th List†. Surgery is for tophus debulking, ulceration, infection or nerve compression, and is rarely needed if urate is controlled.

Nurse-led treat-to-target care is the most effective single intervention in the entry. A randomised trial (Doherty et al., *Lancet*, 2018) tested nurse-led gout care with education and treat-to-target urate lowering. Urate was below 6 mg/dL in 95 per cent of patients at 2 years against 30 per cent with usual general practice care, with fewer flares and resolved tophi. It is a service-design intervention using the same cheap drug.

Simple means. Allopurinol is oral, off-patent, on the Essential Medicines List, costs a few dollars to tens of dollars a patient-year, and abolishes disease activity when titrated to a urate target. The barrier is not cost or supply. It is dose titration and adherence.

A serum urate measurement costs a few dollars and is the entire basis of treat-to-target care. Without it, allopurinol is prescribed at a fixed dose and the target is not reached. The Doherty trial showed 95 per cent against 30 per cent target achievement when someone measures and titrates.

Low-dose colchicine for the first few months of allopurinol costs cents to a few dollars and prevents the early flares that make patients abandon treatment. Rest, elevation and ice to the joint help, and ice reduced pain in a small randomised trial.

Stopping beer and spirits, where that is the pattern, since beer carries the strongest dietary relative risk and wine shows no significant association. Reducing sugar-sweetened drinks and fructose. Coffee, low-fat dairy, cherries and vitamin C are all ordinary food and are associated with lower urate or lower flare risk. Vegetables, legumes, pulses, mushrooms and whole grains need not be restricted. Plant purines show no association with gout, and the traditional purine-restricted diet needlessly removes cheap, nutritious food. Adequate water matters, because dehydration precipitates attacks.

Weight loss lowers urate by roughly 0.03 to 0.06 mmol/L per 10 kg lost, and high body mass index accounts for 34.3 per cent of gout YLDs. Asking what diuretic the person is on and switching a thiazide to losartan or a calcium channel blocker, where an antihypertensive is needed, lowers urate at no extra cost.

Telling the patient that gout is a disease of urate handling, mostly genetic, and controllable with a cheap daily tablet. The GBD data and the genetic findings, diet under 1 per cent of urate variance against roughly 24 per cent for genetics, contradict the widespread framing of gout as self-inflicted. That framing is a documented barrier to patients accepting treatment.

Gaps. The GBD 2021 analysis states that many low- and middle-income countries rely on modelled and not primary data, and that severity and disability data are often missing. The 55.8 million figure carries a 95 per cent uncertainty interval of 44.4 to 69.8 million, and the regional detail is weakest where the Indigenous-population prevalences are highest.

Why most people with hyperuricaemia never develop gout is unknown, and no marker predicts it. For treating asymptomatic hyperuricaemia, CKD-FIX, PERL and ALL-HEART are all negative, and Mendelian randomisation is mostly negative for causality, while observational associations with hypertension, kidney and cardiovascular disease are strong. The associations are probably confounded, and this is not settled. Febuxostat cardiovascular safety stands as CARES positive for harm and FAST negative. The sources disagree, and the boxed warning stands.

Roughly one-third to one-half of gout patients ever receive urate-lowering therapy and one-year adherence is 20 to 40 per cent, for a disease controlled by a drug costing a few dollars to tens of dollars a year. The reason is implementation. The Doherty trial shows it is fixable with nursing time, and almost no health system has done so. Allopurinol is routinely under-dosed, and fixed-dose prescribing without urate measurement is the norm.

The contribution of diet is far smaller than the cultural framing implies, and dietary advice remains the dominant message given to patients in many settings. Pegloticase at hundreds of thousands of dollars a course stands against allopurinol at a few dollars to tens of dollars a patient-year, for the small group in whom cheap treatment has genuinely failed. Much of that is failure of titration and not true refractoriness.

Colchicine's United States price history shows that regulatory exclusivity can make an ancient drug expensive, and no systematic data exist on how often this occurs.

The projected rise to 95.8 million by 2050 assumes current prevalence rates persist. Rising obesity could make it higher and better treatment could make it lower, and neither is modelled. Gout in women, and in chronic kidney disease, is under-studied relative to its burden.

> **Depth.** Starts in: a urate crystal. Size: 10 µm†; depth +4.91. First complaint: about 12 hours ([B] within hours); time depth 42.87. One untreated course: about 8.4 days ([B] an attack stops by itself; † 7–10 days); depth 45.44.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Dyslipidaemia

What it is. Too much of the wrong kind of cholesterol in the blood, most importantly low-density lipoprotein (LDL). It causes no symptoms. Over decades it builds plaque in artery walls, and the plaque causes heart attacks and strokes.

Measured. The World Health Organization reports raised total cholesterol, 5.0 mmol/L or above, in roughly 39 per cent of adults worldwide, 37 per cent of men and 40 per cent of women†. Prevalence is highest in high-income countries, roughly 54 per cent in Europe and 48 per cent in the Americas, against roughly 23 to 30 per cent in Africa and South-East Asia†. The Global Burden of Disease attributes roughly 3.8 to 4.5 million deaths a year and roughly 98 million DALYs to high LDL cholesterol, one of the largest single attributable risk factors for death globally. Almost all of it runs through ischaemic heart disease and ischaemic stroke.

Mean total cholesterol has been falling in high-income Western countries and rising in East and South-East Asia. The NCD Risk Factor Collaboration (*Nature*, 2020) found non-HDL cholesterol fell substantially in north-western Europe, North America and Australasia between 1980 and 2018, and rose in China, Indonesia, Malaysia, Japan and other Asian countries. The highest non-HDL cholesterol levels are now in East and South-East Asia and not the West, a complete reversal of the 1980 pattern.

Familial hypercholesterolaemia (FH), the monogenic form, is the most consequential under-diagnosis in the entry. Heterozygous FH occurs in roughly 1 in 250 to 1 in 311 in general populations, in a meta-analysis of over 11 million people, roughly 30 to 35 million people worldwide and far commoner than the previously assumed 1 in 500†. Homozygous FH occurs in roughly 1 in 300,000 to 1 in 400,000. Founder populations are higher: Afrikaners roughly 1 in 70 to 100, French Canadians roughly 1 in 270, Christian Lebanese roughly 1 in 85 and Ashkenazi Jews roughly 1 in 67, with Finns and South African Indians also affected†.

Fewer than 10 per cent of people with FH are diagnosed worldwide, and under 1 per cent in most low- and middle-income countries. In the best-performing country, the Netherlands, roughly 70 per cent are identified†. Untreated heterozygous FH leads to a coronary event in roughly 50 per cent of men by age 50 and roughly 30 per cent of women by age 60. Untreated homozygous FH causes coronary disease in childhood and death typically before age 20 to 30†. Statin treatment reduces coronary mortality in FH by roughly 75 to 80 per cent in cohort studies, and life expectancy approaches normal if treatment starts in childhood or early adulthood.

Treatment and control gaps are large. In the EUROASPIRE and similar surveys roughly 70 to 80 per cent of patients with established coronary disease do not reach an LDL target below 1.8 mmol/L, and roughly half of high-risk patients in primary care are not on a statin. Statin discontinuation within one year is roughly 25 to 50 per cent†.

Where it starts. The mechanism is established beyond reasonable dispute. LDL and other apolipoprotein-B-containing lipoproteins enter the arterial intima, are retained and modified, and provoke a chronic inflammatory response that produces plaque. The evidence for causality is unusually complete and comes from four independent directions. Observational epidemiology gives a log-linear relationship between

LDL and coronary risk. Mendelian randomisation shows that variants in *HMGCR*, *PCSK9*, *NPC1L1*, *LDLR*, *APOB* and others each lower LDL and lower coronary risk by the amount predicted per unit of LDL, regardless of mechanism. Randomised trials supply the Cholesterol Treatment Trialists' meta-analyses. The monogenic extremes complete it: FH raises LDL and causes premature coronary disease, and loss-of-function *PCSK9* lowers LDL lifelong and confers protection. This convergence is why LDL is treated as causal and not merely associated.

The Cholesterol Treatment Trialists' Collaboration meta-analyses of statin trials found a roughly 21 to 22 per cent proportional reduction in major vascular events per 1 mmol/L (about 39 mg/dL) reduction in LDL cholesterol, and roughly a 10 per cent reduction in all-cause mortality per 1 mmol/L†. The effect was consistent across people with and without diabetes, with and without prior vascular disease, across age and sex, and at all baseline LDL levels studied. The benefit accumulates with duration, smaller in year one and larger thereafter.

In monogenic FH, *LDLR* accounts for roughly 85 to 90 per cent of identified mutations, *APOB* roughly 5 to 10 per cent, gain-of-function *PCSK9* roughly 1 to 3 per cent, and recessive *LDLRAP1* the rest†. Over 2,000 *LDLR* variants are described. Roughly 20 to 40 per cent of people with an FH phenotype have no single-gene mutation but a high LDL polygenic score, the commonest cause of severe hypercholesterolaemia.

Lipoprotein(a), Lp(a), is roughly 70 to 90 per cent genetically determined by the *LPA* gene. It varies more than 1,000-fold between individuals, is not meaningfully altered by diet, exercise or statins, and is causally associated with coronary disease and aortic stenosis by Mendelian randomisation. Roughly 20 per cent of the world's population has Lp(a) above 50 mg/dL, the commonly used risk threshold, with the highest prevalence in people of African and South Asian ancestry. It is the commonest genetic cardiovascular risk factor, and until recently there was nothing to do about it.

Familial combined hyperlipidaemia occurs in roughly 1 in 50 to 100, polygenic, with mixed cholesterol and triglyceride elevation and insulin resistance. Severe hypertriglyceridaemia arises from *LPL*, *APOC2*, *APOA5*, *GPIHBP1* and *LMF1* variants, causing familial chylomicronaemia syndrome, roughly 1 in 1,000,000, and recurrent pancreatitis. Heritability is roughly 0.4 to 0.6 for LDL, 0.5 to 0.6 for HDL and 0.7 to 0.9 for Lp(a)†.

Diet effects are smaller for cholesterol than popularly assumed and larger for clinical events when the whole pattern changes. Metabolic ward studies and meta-regressions measured a roughly 0.03 to 0.05 mmol/L fall in LDL per 1 per cent of energy substituted from saturated to polyunsaturated fat, a substantial dietary change yielding roughly 0.2 to 0.5 mmol/L†. A Cochrane review of reducing saturated fat found a roughly 17 per cent reduction in cardiovascular events, relative risk 0.83, with no clear effect on mortality†. The benefit depended on the replacement: polyunsaturated fat and whole grains yes, refined carbohydrate no. Dietary cholesterol has a small effect on serum LDL in most people, far smaller than saturated and trans fat, which is why dietary cholesterol limits were dropped from several guidelines.

Industrial trans fat raises LDL and lowers HDL and has the largest adverse effect per gram of any dietary fat. The WHO REPLACE programme has driven elimination: by 2023 roughly 53 countries covering roughly 3.7 billion people had best-practice trans fat policies. Denmark's 2003 ban was followed by a measurable fall in cardiovascular mortality†. Soluble fibre, plant sterols and stanols, soy protein and nuts each lowered LDL by roughly 3 to 10 per cent in trials, and combined portfolio dietary patterns by roughly 10 to 30 per cent†. Trans fat elimination, salt reduction and saturated fat replacement are the three population dietary measures with the strongest evidence.

Other determinants are physical inactivity, obesity and insulin resistance (raising triglycerides and lowering HDL), smoking (lowers HDL, oxidises LDL), alcohol (raises triglycerides and HDL), hypothyroidism (raises LDL, and must be excluded before treating), nephrotic syndrome, cholestasis, and drugs: thiazides, beta-blockers, corticosteroids, antiretrovirals, antipsychotics, isotretinoin and ciclosporin.

Not known: whether raising HDL has any benefit. Multiple randomised trials of HDL-raising drugs, niacin in AIM-HIGH and HPS2-THRIVE and the CETP inhibitors torcetrapib, dalcetrapib and evacetrapib, were negative or harmful, while HDL remains strongly inversely associated with risk. Mendelian randomisation is negative for HDL causality. It is one of the clearest cases in medicine of a strong biomarker association that is not causal. Also not known: the optimal LDL target, since trials show benefit down to roughly 0.5

mmol/L with no observed lower threshold and no safety signal†. And whether treating Lp(a) lowers events, since the outcome trials are running now.

Cure status. CONTROLLABLE. No treatment cures the underlying lipoprotein metabolism, and the risk reduction depends on continued treatment.

Statins reduce major vascular events by roughly 21 to 22 per cent per 1 mmol/L of LDL reduction, and the effect accumulates with duration. Stopping returns LDL to baseline within weeks. The lifetime framing is measured: Mendelian randomisation shows that lifelong genetically lower LDL confers roughly three times the risk reduction per 1 mmol/L compared with a statin started in middle age, because the exposure is cumulative. Treatment started late therefore recovers only part of the available benefit. That is the strongest argument for early identification of FH.

Homozygous FH is CONTROLLABLE. Statins work poorly because there is little or no LDL receptor function. Treatment is lipoprotein apheresis every 1 to 2 weeks, lowering LDL by roughly 50 to 70 per cent acutely, lomitapide, evinacumab, and in some cases liver transplantation, which supplies functioning LDL receptors and is rarely appropriate. Transplantation carries lifelong immunosuppression, which keeps it within the rule that a treatment continued for life does not cure.

Gene editing is in early trials. Base editing of *PCSK9* (VERVE-101 and 102) produced durable LDL reductions of roughly 50 to 55 per cent in the highest dose cohorts of its phase 1b study from a single infusion†. It is a potential one-time treatment, with tens of patients so far. In familial chylomicronaemia syndrome, olezarsen and plozasiran, which target APOC3, reduce triglycerides by roughly 70 to 80 per cent and markedly reduce pancreatitis episodes in phase 3 trials†. Volanesorsen was approved in Europe, with thrombocytopenia limiting use. That is control, not cure.

Prevention. Statins for primary prevention in people at raised risk. The Cholesterol Treatment Trialists' meta-analyses show the same proportional benefit, roughly 21 to 22 per cent per 1 mmol/L, in people without prior vascular disease, so absolute benefit tracks baseline risk. STRONG.

Industrial trans fat elimination. Denmark banned industrial trans fat in 2003 and a later analysis found a measurable decline in cardiovascular mortality beyond the secular trend. New York City's restaurant ban was followed by reduced trans fat intake and reduced myocardial infarction and stroke in the restricted counties. By 2023 roughly 53 countries covering 3.7 billion people had best-practice policies†. STRONG.

Replacing saturated with polyunsaturated fat gave a roughly 17 per cent reduction in cardiovascular events in the Cochrane review. MODERATE.

Finland's North Karelia project, the longest-running population cardiovascular prevention programme, combined dietary change, smoking reduction and blood pressure treatment. Coronary heart disease mortality in working-age men in North Karelia fell by roughly 80 to 85 per cent between 1972 and 2014, with roughly two-thirds to four-fifths of the decline attributable to the measured changes in cholesterol, blood pressure and smoking. It is the single most important population prevention dataset in cardiovascular disease. STRONG.

Salt reduction, sugar-sweetened beverage taxes, front-of-pack labelling and marketing restrictions have demonstrated effects on intake and on blood pressure, and smaller effects on lipids specifically. MODERATE overall.

Cascade screening for FH. Testing first-degree relatives of an index case identifies affected individuals with roughly 50 per cent yield per relative, and the Dutch national programme raised FH detection to roughly 70 per cent†. Universal lipid screening in childhood, practised in Slovenia and recommended in some United States guidelines at ages 9 to 11 and 17 to 21, with reverse cascade screening from affected children to parents, identifies families earlier. STRONG for detection. MODERATE for outcomes, since the outcome evidence is cohort-based.

Not smoking: STRONG. Physical activity and weight change have modest lipid effects and substantial cardiovascular effects in trials: MODERATE. Excluding and treating secondary causes, hypothyroidism especially, before attributing hypercholesterolaemia to a primary disorder: STRONG.

Polypill strategies. The TIPS-3, PolyIran and SECURE trials showed that a fixed-dose combination of a statin, antihypertensives and in some cases aspirin reduced cardiovascular events substantially. PolyIran, a cluster-randomised village-based trial, found a roughly 34 per cent reduction in major cardiovascular events, and SECURE a roughly 24 per cent reduction after myocardial infarction†. The polypill is made of generics. STRONG, and it is the most directly relevant finding for low-resource settings.

Treatment. Statins are first-line, and their evidence base is the largest in cardiovascular medicine: atorvastatin, simvastatin, rosuvastatin and pravastatin. All are off-patent. They cost a few dollars to tens of dollars a patient-year at generic international prices, and in many low-income country tenders a few dollars. Their listing on the WHO Essential Medicines List 24th List needs checking, including which statin is the listed medicine and which are alternatives.

The effect is a roughly 21 to 22 per cent reduction in major vascular events and a roughly 10 per cent reduction in all-cause mortality per 1 mmol/L LDL reduction†. High-intensity statins lower LDL by roughly 50 per cent and moderate-intensity by roughly 30 to 40 per cent. Muscle symptoms are the dominant reason for discontinuation, and the randomised evidence is that most statin-attributed muscle symptoms are not caused by the statin. SAMSON, an n-of-1 randomised crossover with placebo and no-tablet periods, found that roughly 90 per cent of the symptom burden occurred equally on placebo, and StatinWISE found no difference in muscle symptoms between statin and placebo periods. Objectively confirmed rhabdomyolysis is roughly 1 to 3 per 100,000 patient-years†. This matters because discontinuation runs at 25 to 50 per cent.

Ezetimibe, a cholesterol absorption inhibitor, lowers LDL by a further roughly 15 to 25 per cent on a statin. IMPROVE-IT found a further 6.4 per cent relative reduction in cardiovascular events on top of simvastatin, consistent with the LDL reduction achieved. It is off-patent and costs tens to hundreds of dollars a patient-year. Its listing status needs checking against the 24th List†.

PCSK9 inhibitors, evolocumab and alirocumab, are monoclonal antibodies given subcutaneously every 2 to 4 weeks. They lower LDL by roughly 50 to 60 per cent on top of a statin. FOURIER (evolocumab) found a 15 per cent reduction in the primary composite endpoint, and ODYSSEY OUTCOMES (alirocumab) a 15 per cent reduction, with a mortality signal in the higher-risk subgroup. They are patented, with biosimilars in development. The United States list price has fallen by more than half since launch in 2015, to thousands of dollars a patient-year, and European prices are of the same order. That is two to three orders of magnitude above a generic statin for an incremental benefit. Their listing status needs checking against the 24th List†.

Inclisiran, a small interfering RNA against PCSK9, is given twice yearly after loading and lowers LDL by roughly 50 per cent. Its cardiovascular outcome trials, ORION-4 and VICTORION-2P, are still running, so its event reduction is inferred from LDL and not demonstrated. It costs thousands of dollars a patient-year. The twice-yearly dosing is its main advantage, and the NHS England population-health agreement for it is a notable procurement model. Bempedoic acid, an oral ACL inhibitor, gave a 13 per cent reduction in major cardiovascular events in statin-intolerant patients in the CLEAR Outcomes trial. It is patented at thousands of dollars a patient-year.

For homozygous FH and refractory cases, lipoprotein apheresis costs tens of thousands to over a hundred thousand dollars a patient-year in high-income settings, lomitapide hundreds of thousands, and evinacumab, an anti-ANGPTL3 antibody lowering LDL by roughly 47 per cent in homozygous FH, hundreds of thousands†.

For hypertriglyceridaemia, fibrates (fenofibrate and gemfibrozil) are off-patent and cost tens of dollars a patient-year, and their listing status needs checking against the 24th List†. The PROMINENT trial of pemafibrate was negative for cardiovascular events despite lowering triglycerides, an important negative for the triglyceride hypothesis. Icosapent ethyl gave a 25 per cent event reduction in REDUCE-IT, though the mineral oil comparator is contested, and STRENGTH with a different omega-3 formulation was negative†. Omega-3 fatty acids in general were negative in most outcome trials (VITAL, ASCEND, OMEMI). Olezarsen and plozasiran are for familial chylomicronaemia.

For Lp(a), nothing currently licensed lowers it meaningfully. Niacin and PCSK9 inhibitors lower it modestly. Pelacarsen (antisense, Lp(a)HORIZON outcome trial), olpasiran, lepodisiran and the oral

muvalaplin lower Lp(a) by roughly 80 to 95 per cent, and the first cardiovascular outcome results are expected from 2026†. Until then Lp(a) is a measurable, common, causal risk factor with no treatment, and care intensifies LDL lowering instead.

The polypill, a fixed-dose combination of a statin with antihypertensives, has all components off-patent and costs tens of dollars a patient-year. With the PolyIran and SECURE event reductions of roughly 34 and 24 per cent, it is the highest-value cardiovascular intervention available in resource-limited settings. Secondary causes are treated first: levothyroxine for hypothyroidism, which is on the 24th List.

Simple means. A generic statin costs a few dollars to tens of dollars a patient-year, is off-patent, and reduced major vascular events by roughly 21 to 22 per cent and all-cause mortality by roughly 10 per cent per 1 mmol/L of LDL lowered in the trial meta-analyses. Set against the 3.8 to 4.5 million annual deaths attributed to high LDL, it is among the highest-value medicines in existence.

The polypill uses generic components at tens of dollars a patient-year. In randomised trials it gave 34 per cent (PolyIran) and 24 per cent (SECURE) event reductions, in village and post-infarction settings. It needs no laboratory and no titration.

Finland's North Karelia project replaced animal and hydrogenated fats with vegetable oils at population scale, alongside smoking reduction and blood pressure treatment. Coronary mortality in working-age men fell roughly 80 to 85 per cent over four decades, with most of the fall attributable to the measured risk factor changes. The mechanism was dietary substitution and not a product.

Eliminating industrial trans fat is a regulatory act costing the public purse almost nothing. It now covers roughly 3.7 billion people, with measured mortality effects in Denmark and New York. It is the cheapest cardiovascular intervention ever implemented. Soluble fibre, legumes, oats, barley, nuts and plant sterols each lowered LDL by roughly 3 to 10 per cent, and combined dietary patterns by roughly 10 to 30 per cent in trials. Not smoking is independently the largest modifiable cardiovascular risk factor. Physical activity has a modest lipid effect and a substantial event effect.

A total cholesterol measurement, or even a family history, finds FH. It affects roughly 1 in 250 to 311 people, fewer than 10 per cent are diagnosed, and untreated it causes coronary events in half of men by 50. Asking whether a parent or sibling had a heart attack before age 55 to 60, and looking for tendon xanthomata and corneal arcus, costs nothing and is the entry point. Cascade testing yields roughly 50 per cent per first-degree relative.

In trials the attribution of muscle aches to statins did not hold. SAMSON and StatinWISE showed that roughly 90 per cent of statin-attributed symptom burden occurs equally on placebo. A structured re-challenge is free and recovers a large benefit.

Gaps. The highest non-HDL cholesterol levels are now in East and South-East Asia and not the West (NCD-RisC, 2020), a complete reversal since 1980. The reasons, dietary transition, measurement, or both, are not fully disentangled.

Fewer than 10 per cent of people with FH are diagnosed worldwide, and under 1 per cent in most low- and middle-income countries, for a condition affecting roughly 1 in 250 to 311 people and treatable with a generic costing a few dollars a year. Roughly 70 to 80 per cent of patients with established coronary disease do not reach LDL targets, and statin discontinuation is 25 to 50 per cent, despite the drugs being among the cheapest in medicine.

HDL-raising has failed in every outcome trial, niacin in AIM-HIGH and HPS2-THRIVE and the CETP inhibitors, while the inverse association remains strong. The biomarker is not a target, and establishing that took two decades and several large trials. Triglyceride lowering has mostly failed too: PROMINENT negative, omega-3 trials largely negative, REDUCE-IT positive with a contested mineral oil comparator, and STRENGTH negative. The sources disagree.

Inclisiran's cardiovascular outcome trials have not reported, so its benefit is inferred from LDL reduction, and it is already in large-scale use under population procurement agreements. Lp(a) is a common, highly heritable, causal risk factor with no licensed treatment, above the risk threshold in roughly 20 per cent of the population, and the outcome trials report from 2026. The optimal LDL target is unknown. Benefit extends

to roughly 0.5 mmol/L with no observed threshold and no safety signal, so guidelines set targets by consensus and not by data.

PCSK9 inhibitors cost two to three orders of magnitude more than a generic statin for an incremental 15 per cent event reduction on top of statins. Cost-effectiveness thresholds vary by country and there is no consensus. Statin-associated muscle symptoms are commonly reported by patients and clinicians, the randomised n-of-1 evidence says most are not drug-attributable, and sources disagree sharply in tone. It is a communication failure with large measured consequences.

GBD attributable-death figures for high LDL depend on counterfactual assumptions and differ between GBD cycles. Almost no trial data exist on statin primary prevention in sub-Saharan Africa or South Asia, where lipid distributions and competing risks differ.

> **Depth.** Starts in: the LDL particle. Size: 25 nm†; depth −0.55. First complaint: about 30 years ([B] over decades; † about 30 years); time depth 51.97. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Metabolic syndrome

What it is. A cluster of findings that tend to occur together: central obesity, raised blood pressure, raised fasting glucose, raised triglycerides and low HDL cholesterol. It is not a disease in itself. It is a label for a pattern that predicts diabetes and cardiovascular disease.

Measured. About 25 per cent of adults in the United States have metabolic syndrome, rising with age and higher among racial and ethnic minority populations. On one analysis roughly 32 per cent of United States adults met the criteria in 2000, and more recent estimates are about 34 per cent†. Globally the figure is about 20 to 25 per cent of the world's adults†. The spread between 25, 32 and 34 per cent reflects the criteria applied and the survey years, and no prevalence figure is interpretable without both.

Five competing definitions are the central measurement problem.

- NCEP ATP III (2001, widely used in the United States): at least 3 of 5 components. These are waist 102 cm or more in men or 88 cm or more in women; triglycerides 150 mg/dL or more; HDL below 40 mg/dL in men or 50 in women; blood pressure 130/85 mmHg or more, or treated hypertension; fasting glucose 110 mg/dL or more.
- IDF (2005, harmonised 2009): waist circumference by population-specific cut points plus any 2 of the other four, with fasting glucose 100 mg/dL or more. The 2009 harmonised statement treats it as 3 or more of the 5 components without requiring central obesity.
- WHO (1999): diabetes, impaired glucose tolerance, impaired fasting glucose or insulin resistance, plus 2 of blood pressure 140/90 mmHg or more, dyslipidaemia, central obesity by waist-hip ratio or body mass index, and microalbuminuria.
- EGIR (1999): insulin resistance, the top 25 per cent of fasting insulin among non-diabetics, plus 2 or more of the other criteria.

The IDF waist cut-points differ by ancestry: 90 cm for men and 80 cm for women of South Asian, Chinese, and South and Central American ancestry, against 94 and 80 cm for Europeans and 102 and 88 cm in the United States criteria. The same person can have the syndrome under one definition and not another.

Prevalence rises steeply with age, roughly 10 per cent in United States adults aged 20 to 29 and roughly 45 to 50 per cent over 60†. Sex differences depend on the criteria, because the waist and HDL thresholds differ by sex.

Predictive value is what the label is for. Metabolic syndrome is associated with roughly a 5-fold increased risk of incident type 2 diabetes in meta-analyses†. For cardiovascular disease it is associated with roughly a 2-fold increase in events and roughly a 1.5-fold increase in all-cause mortality. A meta-analysis of prospective cohorts (Mottillo et al., *Journal of the American College of Cardiology*, 2010) gave relative

risks of 2.35 for cardiovascular disease, 2.40 for cardiovascular mortality, 1.58 for all-cause mortality, 1.99 for myocardial infarction and 2.27 for stroke.

The components predict as well or better individually. The source consulted notes that researchers debate whether the syndrome adds risk beyond the sum of its individual components. Multiple analyses have found that established risk scores (Framingham, SCORE2, QRISK) using the continuous values of the same variables outperform the dichotomous label. This is the central criticism, and it is empirical and not semantic.

Associated conditions are metabolic dysfunction-associated steatotic liver disease, present in roughly 60 to 80 per cent of people with the syndrome†, obstructive sleep apnoea, polycystic ovary syndrome, hyperuricaemia and gout, chronic kidney disease and several cancers.

Where it starts. Insulin resistance and visceral adiposity are the common thread, and the pathway is established even though the construct is disputed. Energy storage exceeds the capacity of subcutaneous adipose tissue, so lipid accumulates in visceral depots, liver, muscle and pancreas (ectopic fat). Visceral adipose tissue is lipolytically active and drains into the portal vein, delivering free fatty acids to the liver. That drives hepatic insulin resistance, gluconeogenesis and overproduction of VLDL, producing raised triglycerides, small dense LDL and low HDL, the atherogenic dyslipidaemia triad.

Insulin resistance with hyperinsulinaemia raises renal sodium reabsorption and sympathetic tone, contributing to hypertension. Adipose tissue inflammation, with macrophage infiltration, TNF-alpha, IL-6 and reduced adiponectin, links the components. The twin cycle described under type 2 diabetes is the same physiology viewed from the diabetes end.

Adiposity is the dominant driver, and visceral and ectopic fat predict the syndrome better than body mass index. Waist circumference and waist-to-height ratio outperform body mass index for this purpose, and the waist-to-height ratio is robust across ancestries.

At any given body mass index or waist circumference, South Asian, East Asian, Hispanic and Middle Eastern populations have more visceral and hepatic fat and more insulin resistance, the thin-fat phenotype. This is why the IDF uses population-specific cut-points, and the biological explanation is unknown.

Physical inactivity contributes independently of adiposity. High intake of sugar-sweetened beverages, refined carbohydrate and ultra-processed food associates with the syndrome. A metabolic-ward crossover trial (Hall) measured higher energy intake on an ultra-processed diet than on an unprocessed one. Fructose specifically raises hepatic de novo lipogenesis and liver fat in controlled feeding studies. Short sleep, sleep fragmentation and obstructive sleep apnoea each associate independently. Low birthweight followed by rapid catch-up growth, and maternal obesity and gestational diabetes, are developmental contributors.

Drugs matter. Metabolic syndrome develops in roughly 30 to 50 per cent of patients on olanzapine and clozapine†. Corticosteroids, antiretrovirals (especially older protease inhibitors, causing lipodystrophy), and the combination of beta-blockers and thiazides also contribute. Smoking raises insulin resistance and central fat distribution despite lowering body weight.

Lipodystrophy syndromes are the extreme natural experiment. Congenital generalised lipodystrophy (*AGPAT2*, *BSCL2*) and familial partial lipodystrophy (*LMNA*, *PPARG*) produce severe insulin resistance, hypertriglyceridaemia, fatty liver and diabetes with little or no subcutaneous fat. They show that the problem is where fat is stored and not simply how much there is, and they are treatable with metreleptin.

Heritability of the individual components is roughly 0.3 to 0.6, and of the syndrome as a construct roughly 0.1 to 0.3 beyond its components†. Over 1,000 loci across the component traits are known and there is no metabolic syndrome gene.

Not known: whether metabolic syndrome is a meaningful entity. The source consulted states the debate plainly, whether it adds risk beyond the sum of its components. The empirical answer from prediction studies is largely no, since continuous risk scores outperform the label, and the construct’s defenders argue it has clinical and communicative value in identifying clustered risk. Also unknown: why the same degree of adiposity produces the syndrome in some people and not others. Roughly 10 to 30 per cent of people with obesity are metabolically healthy by these criteria and roughly 5 to 20 per cent of lean people have the

syndrome†. Longitudinal data suggest most people with metabolically healthy obesity convert over a decade.

Cure status. CONTROLLABLE. The components can resolve under weight loss and the syndrome as defined then disappears, but they return when the weight does, so the state is held and not removed.

In the Diabetes Prevention Program, among participants with metabolic syndrome at baseline, intensive lifestyle intervention reduced the prevalence of metabolic syndrome by roughly 41 per cent and metformin by roughly 17 per cent over roughly 3 years†. The diagnosis was removed in a large fraction of people. Look AHEAD found that intensive lifestyle intervention reduced metabolic syndrome prevalence substantially, alongside roughly 8.6 per cent weight loss at year 1†.

DiRECT and DIADEM-I achieved diabetes remission in 46 and 36 per cent at 12 and 24 months and 61 per cent at 12 months respectively, with diet-based weight loss, which by definition resolves the glucose component. Bariatric surgery resolves metabolic syndrome in roughly 60 to 80 per cent of patients at 1 to 2 years†. In SELECT, semaglutide 2.4 mg reduced major adverse cardiovascular events by 20 per cent in people with overweight or obesity and cardiovascular disease without diabetes, and the component measures all improved.

Weight regain restores the syndrome. As in obesity, the physiology is defended and the condition recurs.

Because the syndrome is a set of threshold crossings, resolving it can mean moving someone from 3 abnormal components to 2 without changing underlying risk much. What matters is whether hard outcomes change. For that the evidence is the diabetes prevention trials, with a 58 per cent risk reduction in the Diabetes Prevention Program, the statin trials at roughly 21 to 22 per cent per 1 mmol/L†, the blood pressure trials, and SELECT. All of them act on components and not on the syndrome.

Severe lipodystrophy: CONTROLLABLE. Metreleptin produces large improvements in triglycerides, glucose and liver fat, a mechanism-matched treatment for the extreme form.

Prevention. Prevention of metabolic syndrome is prevention of its components, and the trial evidence is set out under type 2 diabetes, obesity and dyslipidaemia. The measures with demonstrated effects follow.

Intensive lifestyle intervention in people at risk. The Diabetes Prevention Program randomised 3,234 participants to placebo, metformin or intensive lifestyle change, with average follow-up of 2.8 years. Cumulative incidence of diabetes at 3 years was 28.9 per cent on placebo, 21.7 per cent on metformin and 14.4 per cent on lifestyle intervention. The relative reductions were 58 per cent (95% confidence interval 48 to 66) for lifestyle and 31 per cent (17 to 43) for metformin. The numbers needed to treat for 3 years to prevent one case were 6.9 (5.4 to 9.5) for lifestyle and 13.9 (8.7 to 33.9) for metformin. Both reproduce exactly from the cumulative incidences: 1 / 0.145 is 6.9 and 1 / 0.072 is 13.9. The Finnish Diabetes Prevention Study found a 58 per cent reduction†. The Da Qing study found reduced cardiovascular events, microvascular complications and all-cause mortality, and roughly 1.44 years greater life expectancy at 30 years†. STRONG.

Metformin gave a 31 per cent reduction in incident diabetes in the Diabetes Prevention Program and a roughly 17 per cent reduction in metabolic syndrome prevalence†. It is off-patent and costs a few dollars a patient-year. STRONG. In that program each kilogram lost was associated with roughly 16 per cent lower diabetes risk†. STRONG, for weight loss by any means. Physical activity is effective independently of weight change for insulin sensitivity and blood pressure. STRONG for the components.

Population dietary and fiscal measures. Sugar-sweetened beverage taxes reduced purchases by roughly 10 to 20 per cent in Mexico, Chile, the United Kingdom and United States cities. The United Kingdom Soft Drinks Industry Levy was followed by a roughly 30 per cent reduction in soft drink sugar content through reformulation. Chile’s labelling law reduced purchases of high-in sugary drinks by roughly 24 to 27 per cent†. Industrial trans fat elimination now covers roughly 53 countries and 3.7 billion people†. MODERATE for intake and reformulation. WEAK for demonstrated effect on metabolic syndrome prevalence.

Sleep adequacy and treating obstructive sleep apnoea. CPAP improves blood pressure modestly and insulin sensitivity inconsistently, and the SAVE trial found no reduction in cardiovascular events. CONTESTED for cardiovascular outcomes. STRONG for symptoms. Not smoking: STRONG.

Choosing weight-neutral alternatives to obesogenic drugs where clinically possible, particularly antipsychotics, where metabolic syndrome develops in roughly 30 to 50 per cent on olanzapine and clozapine and metformin co-prescription attenuates weight gain in randomised trials. MODERATE. Treating the components to target and not the label, with statins, antihypertensives, and metformin or GLP-1 agonists for glucose. STRONG for each component.

Treatment. No treatment exists for metabolic syndrome as such. Treatment is of the components, and the drugs and prices are set out under type 2 diabetes, obesity and dyslipidaemia.

Structured lifestyle intervention is the foundation and the comparator in every trial. Its resource requirement is personnel time and not product. Metformin is on the WHO Essential Medicines List 24th List for type 2 diabetes, as 500 mg oral solid for adolescents and adults, first added in 1997. It is off-patent and costs a few dollars a patient-year. A generic statin costs a few dollars to tens of dollars a patient-year and gave a 21 to 22 per cent reduction in major vascular events per 1 mmol/L LDL reduction†. The listing status of statins on the 24th List needs checking†.

Antihypertensives are thiazide-like diuretics, ACE inhibitors, ARBs and calcium channel blockers, all off-patent, at a few dollars to tens of dollars a patient-year. Their listing status needs checking against the 24th List†. ACE inhibitors and ARBs are often preferred in insulin-resistant patients because thiazides and beta-blockers worsen glucose and lipids, though the outcome differences are small. The polypill, with generic components at tens of dollars a patient-year, gave PolyIran and SECURE event reductions of 34 and 24 per cent†. For a clustered-risk population it is the most directly applicable intervention and needs no laboratory.

GLP-1 receptor agonists and tirzepatide are patented, and their effect sizes are given under type 2 diabetes and obesity. United States list prices run to many thousands of dollars a patient-year, direct cash channels lower, and European prices lower again. A published minimum production cost estimate for semaglutide is roughly US$11 to US$57 a patient-year (Barber, Hill et al., 2024). Their listing status on the 24th List needs checking†. SGLT2 inhibitors have originator prices in the thousands of dollars a patient-year in the United States and Indian generics in the tens to low hundreds, with cardiovascular, renal and heart failure benefits. Their listing status needs checking against the 24th List†.

Bariatric and metabolic surgery resolves the syndrome in roughly 60 to 80 per cent, and the Swedish Obese Subjects study measured a mortality reduction of roughly 24 to 30 per cent†. Associated conditions are treated separately. Resmetirom (United States approval 2024) is the first licensed drug for metabolic dysfunction-associated steatohepatitis with fibrosis and costs tens of thousands of dollars a patient-year. CPAP treats sleep apnoea, allopurinol gout, which is on the 24th List, and metformin and combined oral contraceptives polycystic ovary syndrome. Metreleptin for generalised lipodystrophy is mechanism-matched and priced in the hundreds of thousands a patient-year.

Simple means. This section reports what trials measured. It sets out no protocol.

A tape measure. Waist circumference, or waist-to-height ratio, costs cents and adds information that body mass index does not. It is robust across ancestries in a way body mass index is not, and the IDF criteria are built on it. It is the cheapest and most useful measurement in the entry. A blood pressure cuff and a finger-prick glucose detect two of the five components between them.

Diet-based weight loss delivered in primary care. DiRECT and DIADEM-I achieved diabetes remission in 46 and 36 per cent, and 61 per cent, using a formula diet followed by structured food reintroduction, with nurses and dietitians in ordinary practice, and with no drug, device or surgery. In the Diabetes Prevention Program each kilogram lost was associated with roughly 16 per cent lower diabetes risk, and lifestyle intervention reduced metabolic syndrome prevalence by roughly 41 per cent†.

Walking and other physical activity. In Da Qing the exercise arm alone was effective, and at 30 years the intervention groups had fewer cardiovascular events, fewer microvascular complications, lower all-cause mortality and roughly 1.44 years greater life expectancy†.

Metformin costs a few dollars a patient-year, is off-patent, gave a 31 per cent reduction in incident diabetes and a roughly 17 per cent reduction in metabolic syndrome prevalence†. A generic statin gave 21 to 22 per cent fewer major vascular events per 1 mmol/L of LDL lowered. The polypill, generics in one tablet, gave 24 to 34 per cent event reductions in randomised trials†.

Sugar-sweetened beverages. Each daily serving was associated with 13 to 26 per cent higher diabetes risk, taxes reduced purchases by 10 to 20 per cent, and the United Kingdom levy cut soft drink sugar content by roughly 30 per cent through reformulation†. In the Hall crossover trial, an unprocessed diet eaten without restriction produced lower energy intake and some weight loss over two weeks compared with an ultra-processed diet. Sleep, and snoring as a question, matter for sleep apnoea. Not smoking matters. Reviewing obesogenic drugs matters, particularly antipsychotics, where metformin co-prescription attenuates weight gain in randomised trials.

Gaps. Five competing definitions, WHO 1999, EGIR 1999, NCEP ATP III 2001, IDF 2005 and the harmonised 2009 statement, classify different people. No prevalence figure is interpretable without the criteria and the survey year. The figures quoted here, 25, 32 and 34 per cent for the United States and 20 to 25 per cent globally, come from different criteria and periods.

Whether the syndrome adds predictive value beyond its components is disputed. The empirical evidence from prediction studies largely says it does not, since continuous risk scores outperform the dichotomous label. The source consulted gives no numeric relative risks for cardiovascular disease or type 2 diabetes. The figures here, roughly 2-fold for cardiovascular disease and roughly 5-fold for diabetes, come from the wider meta-analytic literature.

Dichotomising five continuous variables discards information, and a person can leave the syndrome by crossing one threshold without materially changing risk. Waist cut-points are population-specific and empirically derived. The biological reason South Asian and East Asian populations have more visceral fat at a given anthropometry is unknown. Metabolically healthy obesity, roughly 10 to 30 per cent of people with obesity, may not be a stable state, and the proportion and determinants are unresolved.

No treatment trial has used metabolic syndrome as an inclusion criterion with hard outcomes as the endpoint. Every effect size in this entry is borrowed from trials of diabetes prevention, lipid lowering, blood pressure lowering or weight loss. CPAP did not reduce cardiovascular events in SAVE despite obstructive sleep apnoea being strongly associated with the syndrome.

Almost all prevalence data come from the United States, Europe and East Asia. African and Latin American data are thinner, and the criteria used there are often the European or United States ones and not the population-specific ones. Whether the label helps or harms patients, by prompting action or by medicalising risk, has not been tested.

> **Depth.** Starts in: a fat cell. Size: 100 µm†; depth +7.00. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Phenylketonuria

What it is. An inherited inability to break down phenylalanine, an amino acid present in all protein. It builds up and poisons the developing brain. Detected at birth and treated by diet, the child develops normally. Undetected, it causes severe permanent intellectual disability.

Measured. Incidence is about 1 in 12,000 newborns overall, with males and females affected equally†. National figures vary enormously. Turkey has 1 in 2,600, the highest documented rate, and Ireland 1 in 4,500†. Finland has 1 in 200,000 and Japan 1 in 125,000, and the source consulted states that Finland and Japan have extremely low rates, fewer than one case in 100,000 births†. Italy, Scotland, the Czech Republic and parts of China, roughly 1 in 11,000 to 17,000, are also high.

For the United States the source consulted gives two figures that conflict: 1 in 10,000 for Caucasians in the text and 1 in 25,000 in its country table. Both stand, and the disagreement is not reconciled.

PKU was the first disorder routinely diagnosed through widespread newborn screening. Robert Guthrie introduced the test in the early 1960s. Ireland started the first national programme in February 1966, followed by Austria in 1966 and England in 1968†. Screening uses a heel-prick blood sample, usually taken 2 to 7 days after birth, and a repeat test around two weeks of age catches missed cases. Methods include the Guthrie bacterial inhibition assay, immunoassays and tandem mass spectrometry. Coverage is near-universal in high-income countries and in much of Latin America, the Middle East and East Asia. It remains absent or very limited across most of sub-Saharan Africa and parts of South and Central Asia, where affected children still present with established intellectual disability.

The outcome contrast is large. Untreated, there is progressive intellectual disability with IQ typically below 50 and often below 30, microcephaly, seizures in roughly 25 per cent, eczema, a musty body odour, hypopigmentation, autistic features and self-injurious behaviour. Institutional care was the historical norm. Treated from the first weeks of life, according to the source consulted, early diagnosis and a strict low-phenylalanine diet can allow normal health and a normal lifespan, and treated people may have no detectable physical, neurological or developmental problems. The window is narrow. The diet must begin within about two weeks of birth, and otherwise permanent intellectual disability is likely even if treatment starts later.

Residual morbidity in treated patients is measured. Even with good control, mood disorders occur at roughly 230 per cent of control rates and dizziness at roughly 180 per cent†. Treated adults have higher rates of anxiety, depression, attention deficit, executive dysfunction and reduced processing speed than the general population, correlating with lifetime phenylalanine exposure. Patients whose diets lack added amino acids may have slightly suboptimal neurocognitive and growth outcomes.

Maternal PKU syndrome arises when maternal phenylalanine is high in an untreated or poorly controlled pregnancy. It is teratogenic, causing microcephaly, congenital heart disease, intrauterine growth restriction and intellectual disability in the infant, with risk rising steeply above maternal phenylalanine of roughly 360 µmol/L†. The infant does not have PKU, and the damage is from maternal exposure. Congenital heart disease exceeds 10 per cent where maternal phenylalanine is above 900 µmol/L in the first trimester†. It is entirely preventable by strict control from before conception.

Dietary adherence falls sharply in adolescence and adulthood, with roughly 50 to 80 per cent of adults in several national cohorts having phenylalanine above target. Many adults were historically told they could stop the diet, and that advice was later reversed.

Where it starts. The cause is biallelic loss-of-function variants in *PAH*, encoding phenylalanine hydroxylase, which converts phenylalanine to tyrosine using the cofactor tetrahydrobiopterin (BH4). Inheritance is autosomal recessive. Over 1,000 *PAH* variants are described, and genotype predicts phenotype reasonably well: residual enzyme activity determines whether the picture is classical PKU, mild PKU or mild hyperphenylalaninaemia not requiring treatment.

High phenylalanine competes with other large neutral amino acids for the LAT1 transporter at the blood-brain barrier, so tyrosine and tryptophan transport into the brain falls, reducing dopamine and serotonin synthesis. Phenylalanine also directly impairs myelination and protein synthesis. The mechanism explains why large neutral amino acid supplementation works as a treatment and why the damage is developmental.

BH4-responsive PKU is a subset, generally with residual enzyme activity, that responds to pharmacological doses of BH4 (sapropterin) with a fall in blood phenylalanine. The response is genotype-linked. BH4 deficiency disorders, roughly 1 to 2 per cent of hyperphenylalaninaemia, arise from *PTS*, *QDPR*, *PCBD1*, *GCH1* and *DNAJC12*†. They cause raised phenylalanine plus deficient dopamine and serotonin synthesis, and diet alone does not treat them. They need BH4 plus neurotransmitter precursors (L-dopa, carbidopa, 5-hydroxytryptophan). Missing the diagnosis means treating the wrong disease, which is why every positive newborn screen requires PKU to be told from BH4 defects.

Carrier frequency is roughly 1 in 50 to 1 in 60 in European populations, consistent with birth incidence†. Carriers are healthy. Incidence varies so much between populations through founder effects and historical

population structure. The high Turkish and Irish rates and the very low Finnish and Japanese rates reflect different *PAH* variant frequencies and not any environmental factor.

Not known: why residual neurocognitive and psychiatric morbidity persists in well-treated patients, whether from early exposure before diagnosis, fluctuations across childhood, tyrosine or neurotransmitter precursor deficiency, or the nutritional adequacy of the diet itself. The optimal phenylalanine target across the lifespan, and whether adults need the same control as children. Current consensus says yes, reversing earlier advice, but the evidence is observational. Whether the *PAH* genotype can set individual treatment intensity.

Cure status. Diagnosed at birth and treated by lifelong diet: CONTROLLABLE. Diagnosed after irreversible damage is established: RELIEF ONLY.

The label is CONTROLLABLE and not curable because the enzyme defect is not corrected. The diet substitutes for it, the normal phenotype lasts exactly as long as the diet does, and a treatment that must be continued for life does not cure.

A phenylalanine-restricted diet begun within about two weeks of birth and maintained prevents the disease. The target blood phenylalanine is 2 to 6 mg/dL (120 to 360 µmol/L), monitored by regular blood tests†. It is not reversible once damage is done. Starting the diet in an older child with established disability improves behaviour and seizures but does not restore cognition. That distinction is the whole justification for newborn screening.

Sapropterin dihydrochloride, synthetic BH4, may be useful in some patients and can lower blood phenylalanine in some people, according to the source consulted. Response rates in trials are roughly 20 to 50 per cent of unselected classical and mild PKU patients, concentrated in those with residual enzyme activity. Responders can liberalise protein intake substantially and some achieve control without a restricted diet.

Pegvaliase, a pegylated phenylalanine ammonia lyase, is an enzyme substitute approved in the United States in 2018 for adults poorly managed on other treatments. It degrades phenylalanine independently of PAH. In phase 3 (PRISM-2), roughly 60 to 70 per cent of patients achieved blood phenylalanine below 600 µmol/L and a substantial proportion reached normal levels on an unrestricted diet. For responders it functionally removes the dietary requirement. Anaphylaxis occurs in roughly 5 to 9 per cent, requiring adrenaline availability and a long induction titration. Gene therapy and mRNA therapy, liver-directed AAV and lentiviral *PAH* gene transfer and *PAH* mRNA, are in early clinical trials, and nothing is approved. Genome editing of *PAH* is preclinical.

Prevention. Newborn screening is the measure and the model for all newborn screening. The test is a heel-prick dried blood spot at 2 to 7 days, with a repeat around two weeks. It converts a disease causing lifelong severe intellectual disability into one with a normal outcome. No randomised trial exists and none was needed, since the before-and-after is unambiguous. The PKU assay costs a few dollars per newborn as part of a multiplex panel, and the full multi-disorder tandem mass spectrometry panel tens of dollars per newborn, depending on the programme. Cost-effectiveness analyses consistently find PKU screening cost-saving, because the lifetime cost of institutional care for one untreated case far exceeds the cost of screening a whole birth cohort. STRONG.

Prevention of maternal PKU syndrome by strict phenylalanine control from before conception through pregnancy. The Maternal PKU Collaborative Study showed that phenylalanine below roughly 360 µmol/L before conception essentially eliminates the excess congenital heart disease and microcephaly. Poor control above 900 µmol/L in the first trimester is associated with congenital heart disease in over 10 per cent of pregnancies†. STRONG. This is the strongest argument for keeping women with PKU in lifelong follow-up and not discharging them in adolescence.

Lifelong dietary control and not stopping in adolescence. Earlier practice allowed relaxation after childhood, and that advice was reversed on observational evidence of neurocognitive and psychiatric morbidity in untreated adults. MODERATE: the evidence is observational, and the reversal of advice is itself evidence of earlier error.

Carrier screening and genetic counselling in high-incidence populations and affected families, with prenatal and preimplantation diagnosis where available and acceptable. STRONG for birth prevalence in known families. Separating BH4 deficiency from PKU on every positive screen, because diet alone does not treat BH4 deficiency and the neurotransmitter deficits progress untreated. STRONG.

Extending newborn screening to countries without it is the largest remaining preventable burden. In populations without screening, PKU still causes the disability it caused everywhere before 1966, and the test costs a few dollars. STRONG.

Treatment. A phenylalanine-restricted diet with a phenylalanine-free amino acid substitute. Natural protein is restricted and the remaining protein requirement is supplied as a phenylalanine-free, tyrosine-enriched amino acid mixture with added vitamins and minerals. Low-protein manufactured foods, bread, pasta and flour substitutes, make the diet practicable. These are medical foods and not listed medicines, and whether any is on the WHO Essential Medicines List 24th List needs checking†. Patent status does not apply, since they are formulated products from a small number of manufacturers.

The amino acid substitute plus prescribed low-protein foods cost thousands to tens of thousands of dollars a patient-year in high-income countries. The dietary treatment is cheap in principle and expensive in practice, because the substitute products are manufactured medical foods with few suppliers. Where they are not reimbursed, families pay, and adherence collapses. Monitoring is by dried blood spot phenylalanine, roughly weekly in infancy and monthly to quarterly later, with a target of 120 to 360 µmol/L. Tyrosine is supplemented where levels are low.

Sapropterin dihydrochloride is for responders, identified by a loading test, and allows substantial liberalisation of protein intake. Generics have entered since the United States and European patents expired around 2020 to 2021†. The originator costs tens to hundreds of thousands of dollars a patient-year, with dose weight-based so that adult costs are at the top of the range, and generic sapropterin tens of thousands. Its listing status needs checking against the 24th List†.

Pegvaliase is a daily subcutaneous injection for adults with inadequate control and allows an unrestricted diet in responders. It is patented and costs hundreds of thousands of dollars a patient-year, among the most expensive long-term treatments in the chapter. Anaphylaxis occurs in roughly 5 to 9 per cent, an adrenaline autoinjector is required, and induction is long. Its listing status needs checking against the 24th List†.

Large neutral amino acid supplementation competes with phenylalanine at the LAT1 transporter and reduces brain phenylalanine without lowering blood levels much. It is used as an adjunct in adults with poor dietary adherence, at thousands of dollars a patient-year. Evidence is limited and it does not replace dietary control in children or in pregnancy. Glycomacropeptide-based medical foods, whey-derived protein naturally very low in phenylalanine and more palatable than amino acid mixtures, improve adherence in trials.

BH4 deficiency disorders are treated with sapropterin plus L-dopa and carbidopa plus 5-hydroxytryptophan, and folinic acid in *QDPR* deficiency. The precursors are off-patent and relatively cheap. Maternal PKU is managed by strict control from before conception, with intensive dietary support and frequent monitoring throughout pregnancy. Follow-up is multidisciplinary for life, with metabolic dietitian, metabolic physician and psychologist, and the service and not the drug determines outcome.

Simple means. The heel-prick test is a few drops of blood on filter paper at 2 to 7 days, costing a few dollars for the PKU assay within a panel. It is the whole difference between a normal life and permanent severe intellectual disability. It was the first newborn screening test ever introduced, and it remains unavailable to a large share of the world’s newborns. No intervention in this chapter has a larger ratio of benefit to cost.

The word simple needs qualifying for the treatment that follows. The diet is food, and the amino acid substitute is a manufactured medical food costing thousands of dollars a patient-year in high-income countries. Breastfeeding is compatible with PKU management and is used together with the substitute under monitoring, since breast milk is relatively low in phenylalanine compared with standard formula. Where manufactured low-protein foods are unaffordable, a low-protein diet can be built from ordinary food, fruit, most vegetables, measured starches, fats and sugars, with careful counting, and this is done.

What cannot be improvised is the amino acid substitute. It supplies the protein, vitamins and minerals that the restricted diet cannot, and without it the child becomes malnourished. That is the honest limit of the simple means here.

Dried blood spot monitoring can be taken at home, posted and processed centrally, at a few dollars a test, and it is what makes the diet work. Aspartame is a phenylalanine-containing dipeptide, and avoiding it costs nothing. Telling women with PKU about pregnancy early and repeatedly is free, and phenylalanine below roughly 360 µmol/L before conception essentially eliminates maternal PKU syndrome. Testing siblings and informing the family is simple: inheritance is autosomal recessive, carrier frequency is roughly 1 in 50 to 60 in European populations, and the risk is 1 in 4 per subsequent pregnancy. The diet is not stopped in adolescence, as once advised. A urine pterin profile and a dihydropteridine reductase assay, both cheap, check for BH4 deficiency on every positive newborn screen.

Gaps. The source consulted gives two conflicting United States incidence figures, 1 in 10,000 for Caucasians in the text and 1 in 25,000 in the country table. The global figure of about 1 in 12,000 and the national figures rest on that source. It gives no response rate for sapropterin, stating only that it may be useful in some patients, so the 20 to 50 per cent figure comes from the wider trial literature. The pegvaliase trial figures, PRISM-2, are also from the wider literature. The source describes PEG-PAL as a separate investigational agent placed on clinical hold in September 2021, with an FDA request for oncogenic risk data in February 2022. Pegvaliase is itself a PEGylated phenylalanine ammonia lyase, and whether the two names refer to one molecular class or to different products is unresolved.

No global estimate exists of how many children are born with undetected PKU in countries without newborn screening. At an incidence of roughly 1 in 12,000 and roughly 130 million annual births, the theoretical global birth burden is roughly 10,000 to 11,000 a year, and the proportion reached by screening is not systematically reported.

Why residual neurocognitive and psychiatric morbidity persists in well-treated patients is unknown, and mood disorders at roughly 230 per cent of control rates are a substantial and unexplained residual. The optimal lifelong phenylalanine target is not established by trial, and the reversal of the earlier advice that diet for life is unnecessary was made on observational grounds. Adult adherence is poor, roughly 50 to 80 per cent above target in several cohorts, for reasons of palatability, cost and loss of paediatric support structures.

The dietary treatment costs thousands to tens of thousands of dollars a patient-year because the amino acid substitutes are manufactured medical foods with few suppliers. There is no generic pathway for medical foods, and reimbursement varies even within high-income countries. It is a structural affordability problem that patent expiry does not solve. Pegvaliase at hundreds of thousands of dollars a patient-year and sapropterin at tens to hundreds of thousands stand against a diet that in principle requires only food plus a nutrient mixture. Long-term outcome data for pegvaliase and for generic sapropterin are limited.

> **Depth.** Starts in: phenylalanine hydroxylase. Size: 10 nm†; depth −1.38. First complaint: about 15 months († from conception to months after birth); time depth 49.07. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. The book names a late stratum. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Cystic fibrosis

What it is. An inherited fault in a chloride channel makes mucus thick and sticky. The lungs become chronically infected and scarred, the pancreas stops delivering digestive enzymes, and most men are infertile. It used to kill in childhood. It now kills in middle age, and new drugs have changed it again.

Measured. Incidence in northern European ancestry is about 1 in 3,000 newborns, and the disease is least common in Africa and Asia†. Other commonly cited figures are roughly 1 in 2,500 to 3,500 in white European populations, 1 in 4,000 to 10,000 in Hispanic populations, 1 in 15,000 to 20,000 in African-

ancestry populations and 1 in 30,000 to 100,000 in East Asian populations†. Ashkenazi Jewish populations are roughly 1 in 2,300 to 3,000, and Amish and Hutterite communities are higher.

Carrier frequency in northern European ancestry is up to about 1 in 25. In the United States it is about 1 in 25 white Americans, 1 in 46 Hispanic Americans, 1 in 65 African Americans and 1 in 90 Asian Americans, and over 10 million Americans carry one mutant allele†.

No authoritative global count of people with CF exists. Registry counts are roughly 40,000 in the United States and roughly 55,000 across the European CF Society Patient Registry countries†. The source consulted gives about 50,000 individuals followed in the United States registry since its inception in 1986, a cumulative figure and not a current population. Modelled worldwide estimates run from roughly 105,000 to 162,000, a range reflecting how little is known about CF in Africa, South Asia and Latin America, where it is under-diagnosed and not absent.

Survival is the central measured fact. Average life expectancy is about 42 to 50 years in the developed world, with a cited median of 40.7 years, and newer treatments have raised estimated median survival to about 65 years in Canada, the United States and the United Kingdom†. These are different quantities that are routinely quoted interchangeably: current median age at death, median survival of a historical cohort, and median predicted survival of a birth cohort. The last is a projection and not an observation.

For context, median survival was under 1 year in the 1930s, roughly 10 years in the 1960s and roughly 30 years by 1990†. Median predicted survival for a child born today in a high-income country with modulator access is in the 60s, a gain of roughly 60 years within a century. Almost all of it came from incremental care, nutrition, airway clearance, antibiotics and centralised specialist care, and from no single breakthrough until the modulators arrived. More adults than children now live with CF in high-income countries, an inversion that occurred around 2014 in the United States and United Kingdom.

Respiratory failure causes roughly 70 to 80 per cent of deaths, and the remainder come from transplant complications, liver disease and CF-related diabetes complications. Pancreatic insufficiency affects roughly 85 per cent†. CF-related diabetes affects roughly 20 per cent of adolescents and 40 to 50 per cent of adults†. CF liver disease with cirrhosis affects roughly 5 to 10 per cent, male infertility roughly 97 to 98 per cent (congenital bilateral absence of the vas deferens), and chronic *Pseudomonas aeruginosa* infection roughly 40 to 50 per cent of adults†. Distal intestinal obstruction syndrome, osteoporosis, sinus disease and nasal polyps are also common.

Where it starts. The cause is biallelic variants in *CFTR*, encoding a cAMP-regulated chloride and bicarbonate channel at the apical membrane of epithelial cells. Inheritance is autosomal recessive. Over 2,100 *CFTR* variants are catalogued, of which roughly 400 to 700 are established as disease-causing†. *F508del* is the commonest, on roughly 70 per cent of alleles in northern European populations and present as at least one allele in roughly 85 to 90 per cent of patients†.

Variant classes determine the mechanism and the drug. Class I is no protein (nonsense and frameshift, for example *G542X* and *W1282X*), class II misfolding and failure to traffic (*F508del*), class III a gating defect (*G551D*), class IV a conductance defect, class V reduced quantity and class VI reduced stability. The modulator drugs are class-specific, which is why genotype determines treatment eligibility.

The lungs fail because loss of CFTR-mediated chloride and bicarbonate secretion dehydrates the airway surface liquid and lowers its pH, impairing mucociliary clearance and antimicrobial peptide function. Mucus stasis permits chronic infection with *Staphylococcus aureus*, then *Haemophilus influenzae*, then *Pseudomonas aeruginosa*, and in some patients *Burkholderia cepacia* complex and non-tuberculous mycobacteria. Neutrophilic inflammation, protease release and bronchiectasis follow.

Heterozygote advantage has been proposed for why the allele is common: resistance to typhoid, since CFTR is the receptor for *Salmonella typhi* entry, to cholera and to tuberculosis. None is established, and drift and founder effects may suffice. Lung disease severity varies widely at identical genotype. Modifiers include *SLC26A9*, *SLC9A3*, *EHF*, *MUC4/MUC20*, *AGTR2* and *TGFB1*, and meconium ileus has its own modifier loci. Modifier effects are modest, and a large part of the variance is environmental: socioeconomic status, air pollution, smoke exposure, adherence, centre of care and age at diagnosis all measurably affect outcome.

CFTR-related disorders are milder variant combinations causing isolated chronic pancreatitis, isolated congenital bilateral absence of the vas deferens, or bronchiectasis or sinusitis without full CF. The boundary is a spectrum, which complicates diagnosis and prevalence counts.

Not known: why lung disease severity varies so much at identical genotype, since the known modifiers explain only part of it. Whether the modulators, which correct the basic defect biochemically, will translate into the normal lifespan the biomarker changes imply, since the oldest treated cohorts have under a decade of follow-up. Whether CF is genuinely rare in Africa and much of Asia or substantially undiagnosed. Carrier frequencies of 1 in 65 and 1 in 90 suggest the disease exists in those populations at rates well above the near-zero figures sometimes reported, and the likeliest explanation is diagnostic absence and not biological absence.

Cure status. CONTROLLABLE. The basic defect can now be corrected pharmacologically in roughly 90 per cent of patients†, without the disease being cured.

CFTR modulators correct the protein defect and change the disease course. Elexacaftor, tezacaftor and ivacaftor (Trikafta, Kaftrio), approved from 2019, are effective in patients with at least one *F508del* allele, roughly 85 to 90 per cent of all patients†. Pulmonary exacerbations decreased by 63 per cent and sweat chloride by 41.8 mmol/L, and the pivotal trials showed an FEV1 improvement of roughly 10 to 14 percentage points against placebo or against tezacaftor and ivacaftor, with weight gain and large improvements in respiratory symptom scores. Ivacaftor alone for gating mutations, roughly 4 to 5 per cent of patients†, for example *G551D*, was the first, approved in 2012. Vanzacaftor, tezacaftor and deutivacaftor (Alyftrek), approved in December 2024, are a once-daily next-generation combination.

Registries show population-level effects since modulator introduction. Lung transplant listings for CF in the United States and several European countries fell by roughly 60 to 80 per cent after 2019 to 2020, the rate of decline in FEV1 across the treated population flattened or reversed, and CF-attributed deaths fell sharply. These are among the clearest population-level drug effects recorded in a genetic disease.

It is not a cure. The modulators must be taken daily for life, and they do not reverse established bronchiectasis or cirrhosis or restore fertility in men. Roughly 10 per cent of patients, those with two class I variants, have no effective modulator at all, and that group is disproportionately of non-European ancestry, which compounds existing inequity. Gene and RNA therapy are the route to a cure, and nothing is approved. Inhaled *CFTR* mRNA, lentiviral and AAV gene transfer, and base and prime editing are in phase 1 to 2. The earlier non-viral trial of the UK Cystic Fibrosis Gene Therapy Consortium showed a small but statistically significant FEV1 benefit, establishing proof of principle without clinical utility.

Median survival after lung transplantation for CF is roughly 8 to 10 years, better than for most other indications, and listings have fallen sharply since modulators. Newborn screening does not cure but changes the trajectory. Screened children have better nutritional status, lung function and survival than those diagnosed clinically, which is why screening is now near-universal in high-income countries.

Prevention. Newborn screening by immunoreactive trypsinogen, with *CFTR* genotyping or sweat testing as the second tier, introduced progressively from the 1980s and now near-universal in high-income countries. Measured effects are earlier diagnosis, median weeks and not years, better growth, better lung function, fewer hospitalisations and improved survival compared with clinical diagnosis, in the Wisconsin randomised trial and multiple cohort comparisons. STRONG.

Carrier screening and genetic counselling. Population carrier screening in people of northern European ancestry is offered in the United States, Australia and parts of Europe, with cascade testing in affected families and prenatal and preimplantation genetic diagnosis. STRONG for birth prevalence where it is implemented and acceptable.

Prevention of infection and cross-infection is a major measured success. Cohorting and then full segregation of patients, introduced after *Burkholderia cepacia* epidemics in the 1990s, reduced transmission of *B. cepacia* and epidemic *Pseudomonas* strains markedly. STRONG. Early eradication of first *Pseudomonas aeruginosa* isolation with inhaled tobramycin or colistin achieved eradication in roughly 65 to 90 per cent in the ELITE and EPIC trials and delayed chronic infection†. STRONG. Routine

and influenza vaccination, and palivizumab in selected infants: MODERATE. Avoiding smoke exposure: active and passive smoking measurably accelerate lung function decline. STRONG.

Prevention of malnutrition produced most of the twentieth-century survival gain. The shift to high-energy, high-fat diets with adequate pancreatic enzyme replacement, from the 1980s, is credited with much of the survival improvement. The 1980s comparison between Toronto and Boston cohorts, with the same care except that Toronto used a high-fat unrestricted diet and Boston a low-fat diet, showed a median survival difference of roughly 9 years in favour of the high-fat approach†. It is one of the clearest natural experiments in CF care. STRONG. Annual screening for CF-related diabetes from age 10 by oral glucose tolerance test. Diabetes develops in 40 to 50 per cent of adults and its onset is associated with preceding lung function and weight decline, so detection and insulin treatment improve both. STRONG. Centralised specialist multidisciplinary care, since outcomes correlate strongly with centre volume and multidisciplinary staffing in registry analyses: MODERATE.

Preventing the inequity means ensuring *CFTR* genotype is determined and non-*F508del* variants are reported properly in populations where CF has historically been assumed absent, because roughly 10 per cent of patients have no effective modulator and they are disproportionately of non-European ancestry.

Treatment. CFTR modulators are the first-line disease-modifying treatment where genotype permits. Elexacaftor, tezacaftor and ivacaftor reduced exacerbations 63 per cent, sweat chloride 41.8 mmol/L and improved FEV1 roughly 10 to 14 points. They are patented, and their listing status on the WHO Essential Medicines List 24th List needs checking†. CFTR modulators generally carry United States list prices of hundreds of thousands of dollars a year. Negotiated prices in England, Scotland, Ireland, Canada, Australia and New Zealand are confidential and substantially lower.

Access is the dominant issue. Several high-income countries took years to reach agreement, and most middle- and low-income countries have no access at all. A published analysis of generic production cost (Hill and colleagues' group, using the method applied to insulin and semaglutide) estimated that the three-drug combination could be manufactured and sold profitably for a few thousand dollars a patient-year at scale. That is a factor of roughly 50 to 70 below United States list price†. Argentina and Ukraine, among others, have pursued or implemented generic or compulsory-licence routes. The estimate is modelled and contested by the manufacturer, and no audited figure exists.

Airway clearance, by physiotherapy, positive expiratory pressure devices, oscillating devices, autogenic drainage and exercise, needs no product for the manual techniques. It is daily, lifelong and time-consuming, historically roughly 1 to 2 hours a day.

Inhaled mucoactive agents. Dornase alfa, recombinant human DNase, improves FEV1 by roughly 5 to 6 per cent and reduces exacerbations by roughly 30 per cent in the pivotal trial†. It is off-patent in few markets and costs tens of thousands of dollars a patient-year. Hypertonic saline, 7 per cent, improves FEV1 modestly and reduced exacerbations by roughly 56 per cent in the Australian trial†. It costs hundreds of dollars a patient-year, and nebulised 7 per cent saline can in principle be prepared from sterile saline and salt at trivial cost. It is the cheap alternative to dornase alfa, with comparable effect sizes. Mannitol dry powder is an alternative. The listing status of dornase alfa and hypertonic saline needs checking against the 24th List†.

Inhaled antibiotics for chronic *Pseudomonas*: tobramycin in alternate months improves FEV1 and reduces exacerbations and hospitalisation, with colistin, aztreonam and levofloxacin as alternatives. Tobramycin and colistin are off-patent. Branded nebuliser solution costs tens of thousands of dollars a patient-year. Generic tobramycin injection used off-label for nebulisation costs hundreds to a few thousand dollars, and this substitution is widely practised in middle-income countries. The listing status of tobramycin, inhaled and injectable, needs checking against the 24th List†.

Azithromycin, long-term three times a week, reduces exacerbations by roughly 35 to 40 per cent in patients with chronic *Pseudomonas*†. It costs tens to low hundreds of dollars a patient-year and is one of the best value-for-money treatments in CF. Azithromycin is on the 24th List, in the Watch group, and the indications recorded there are cholera, enteric fever, gonorrhoea, chlamydial infection, trachoma and yaws; cystic fibrosis is not among them.

Pancreatic enzyme replacement is essential in the 85 per cent with pancreatic insufficiency, since without it fat malabsorption causes malnutrition and death. Pancreatic enzymes are on the 24th List, in gastrointestinal medicines and in medicines for cystic fibrosis, as modified-release capsules of 10,000 lipase, 8,000 amylase and 600 protease, and 25,000, 18,000 and 1,000. The product is old and the formulations proprietary, and United States supply has been subject to shortages and price rises. It costs thousands to tens of thousands of dollars a patient-year in high-income countries and far less where generic porcine pancreatin is available. Fat-soluble vitamins A, D, E and K are cheap, and their listing status needs checking against the 24th List†.

High-energy nutrition, salt supplementation in hot climates and gastrostomy feeding where growth fails. Exacerbations are treated with intravenous antibiotics, typically two agents against *Pseudomonas* for 14 days, with intensified airway clearance. Most of these antibiotics (ceftazidime, meropenem, tobramycin, colistin, piperacillin-tazobactam) are off-patent. CF-related diabetes is treated with insulin and not oral agents, and human insulin is on the 24th List for diabetes types 1 and 2. CF liver disease is treated with ursodeoxycholic acid, which is contested, management of portal hypertension, and transplantation. End-stage lung disease is treated by lung transplantation.

Men are almost universally infertile but produce sperm, so surgical sperm retrieval with ICSI achieves fatherhood. Women are subfertile but often conceive, and pregnancy outcomes have improved markedly with modulators.

Simple means. Airway clearance by breathing technique and percussion. Autogenic drainage, the active cycle of breathing techniques, and manual percussion and postural drainage need no equipment at all and are the foundation of CF care worldwide. Positive expiratory pressure can be generated with a simple device costing a few dollars, or by blowing through a tube into water. Exercise is independently associated with slower lung function decline and better survival in registry analyses, and is also an airway clearance technique.

Nebulised hypertonic saline reduced exacerbations by roughly 56 per cent in a randomised trial and improves FEV1, and the active ingredient is salt. Against dornase alfa at tens of thousands of dollars a patient-year, it is the most consequential cheap substitution in CF care. Azithromycin three times a week costs tens to low hundreds of dollars a patient-year, with roughly 35 to 40 per cent fewer exacerbations. Generic tobramycin injection solution used for nebulisation costs hundreds to a few thousand dollars a patient-year against tens of thousands for the branded inhalation solution, and is standard practice in much of the world.

High-fat, high-energy food. The Toronto-versus-Boston comparison suggests a median survival difference of roughly 9 years attributable largely to the unrestricted high-fat diet with adequate enzyme replacement. The intervention is ordinary food in larger amounts, and the removal of a harmful restriction. Extra salt in hot weather costs nothing: CF causes excessive salt loss in sweat, and supplementation prevents hyponatraemic dehydration. Pancreatic enzymes and fat-soluble vitamins are not free, but generic porcine pancreatin is cheap where available, and without enzyme replacement the high-fat diet does not work.

The sweat test, pilocarpine iontophoresis with chloride measurement, has been the diagnostic test since 1959, costs tens to low hundreds of dollars and needs no genetic analysis. Where newborn screening or genotyping is absent, a sweat test in a child with failure to thrive, chronic cough or recurrent pneumonia is the whole diagnostic pathway. Infection segregation, keeping patients apart at clinic and avoiding social contact between patients, is a free organisational measure that stopped the *Burkholderia cepacia* epidemics. No household smoke, handwashing and nebuliser hygiene complete the list.

Gaps. No authoritative global count of people with CF exists. The source consulted gives no worldwide number, and the registry figure it gives, roughly 50,000 followed since 1986, is cumulative and not current. Modelled global estimates range from roughly 105,000 to 162,000. CF is probably substantially under-diagnosed in Africa, South Asia, the Middle East and Latin America. Carrier frequencies of 1 in 65 and 1 in 90 are inconsistent with the near-zero incidence sometimes reported.

Survival figures conflict within the same source: about 42 to 50 years, a cited median of 40.7 years, and about 65 years with newer treatments. They are different quantities, and the last is a projection. The source gives no specific FEV1 figure for elexacaftor, tezacaftor and ivacaftor, reporting only substantial

improvements, so the 10 to 14 percentage point figure comes from the pivotal trials. It gives no price for the triple combination, only a general range for modulators of hundreds of thousands of dollars a year. Negotiated prices elsewhere are confidential.

Roughly 10 per cent of patients have no effective modulator and are disproportionately of non-European ancestry. The disparity is structural and widening as the rest of the population improves. Modulator long-term outcomes are unknown, since the oldest treated cohorts have under a decade of follow-up, so whether corrected sweat chloride translates into normal lifespan is a projection. Generic production-cost estimates for modulators are modelled and contested by the manufacturer.

Pancreatic enzyme replacement is subject to supply shortages and price rises despite being an old product. Ursodeoxycholic acid for CF liver disease is contested, and Cochrane found insufficient evidence. Whether heterozygote advantage explains the allele frequency is unresolved, and so is why lung disease severity varies so widely at identical genotype.

> **Depth.** Starts in: the CFTR channel. Size: 10 nm†; depth −1.38. First complaint: about 12 months († from conception to early infancy); time depth 48.87. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Lysosomal storage diseases (Gaucher, Fabry, Pompe)

What it is. Lysosomes are the cell's recycling compartments. In these inherited diseases one of their enzymes is missing, so the material it should break down accumulates and progressively damages organs. There are about seventy such diseases. Three are treatable with replacement enzymes and are the examples here.

Measured. The class has roughly 70 distinct diseases, with a combined birth incidence of roughly 1 in 5,000 to 1 in 8,000 live births and as high as 1 in 4,000 in some studies†. Dutch and Australian population-based studies give roughly 1 in 7,700 and 1 in 7,000 respectively†. They are individually rare and collectively not rare.

Gaucher disease is glucocerebrosidase deficiency. Type 1, non-neuronopathic, occurs in roughly 1 in 40,000 to 1 in 60,000 in general populations and roughly 1 in 450 to 900 in Ashkenazi Jewish populations, with a carrier frequency of roughly 1 in 15 to 18, one of the strongest founder effects in medicine†. Type 2, acute neuronopathic and infantile, occurs in roughly 1 in 150,000 and is fatal by age 2 to 4. Type 3, chronic neuronopathic, occurs in roughly 1 in 100,000 and is higher in the Norrbottnian population of northern Sweden. Type 1 is roughly 90 to 95 per cent of cases in Western countries.

Fabry disease is alpha-galactosidase A deficiency, X-linked. Classical incidence is roughly 1 in 40,000 to 1 in 117,000 males on clinical ascertainment, but newborn screening finds roughly 1 in 1,250 to 1 in 7,000, a 10-to-50-fold discrepancy†. Screening detects later-onset and variant forms, including the *IVS4+919G>A* variant, which reaches roughly 1 in 1,250 to 1,600 males in Taiwan. Females are affected, often substantially, through X-inactivation mosaicism, and the old description of female carriers is wrong. Fabry disease accounts for roughly 0.2 to 1 per cent of patients on dialysis and a similar share of young stroke patients in screening studies.

Pompe disease is acid alpha-glucosidase deficiency. Combined incidence is roughly 1 in 40,000, with infantile-onset roughly 1 in 138,000 and late-onset roughly 1 in 57,000 in Dutch data†. Newborn screening in Taiwan, Japan and United States states finds roughly 1 in 15,000 to 30,000, higher than clinical ascertainment because of late-onset and pseudodeficiency variants. Untreated infantile-onset Pompe disease has a median survival of roughly 6 to 8.7 months, with death from cardiorespiratory failure, and virtually none survived beyond 2 years†.

Diagnostic delay has a median of roughly 4 to 7 years for Gaucher, roughly 13 to 16 years for Fabry, one of the longest in medicine and longer in women, and roughly 7 to 12 years for late-onset Pompe†. Patients are typically misdiagnosed with rheumatological, haematological, muscular or psychiatric conditions first.

Cost is the defining economic feature of the class. Enzyme replacement therapy costs hundreds of thousands of dollars a patient-year depending on drug, dose and body weight. These are among the most expensive medicines in continuous long-term use anywhere, and the orphan-drug framework that produced them is the reason they exist and the reason they cost what they do.

Where it starts. Deficiency of a single lysosomal hydrolase, or of a transporter, activator or trafficking protein, causes its substrate to accumulate in lysosomes, with secondary effects on autophagy, inflammation, mitochondrial function and cell signalling. The stored substrate is not merely inert. Much of the pathology comes from the secondary cascade, which is why enzyme replacement reverses some manifestations and not others. All the genotypes are Mendelian.

Gaucher disease arises from *GBA1* variants, autosomal recessive. Glucosylceramide accumulates in macrophages, producing Gaucher cells that infiltrate bone marrow, spleen and liver, with splenomegaly, hepatomegaly, anaemia, thrombocytopenia, bone pain, avascular necrosis and fractures. *N370S* (N409S) is associated with non-neuronopathic type 1 and is the predominant Ashkenazi allele, and *L444P* (L483P) with neuronopathic disease. *GBA1* heterozygosity is the single largest genetic risk factor for Parkinson disease, with odds ratios of roughly 5 to 7, higher for severe variants, and roughly 5 to 10 per cent of Parkinson patients carry a *GBA1* variant†. Patients with Gaucher disease have a markedly raised Parkinson risk, roughly 20 to 30-fold†. This links a rare storage disease to a common neurodegenerative one and has made *GBA1* a major Parkinson drug target.

Fabry disease arises from *GLA* variants, X-linked. Globotriaosylceramide (Gb3) and lyso-Gb3 accumulate in vascular endothelium, podocytes, cardiomyocytes, dorsal root ganglia and autonomic neurons. The result is acroparaesthesia and neuropathic pain, hypohidrosis, angiokeratomas, corneal verticillata, proteinuria progressing to renal failure, left ventricular hypertrophy and arrhythmia, and early stroke. Over 1,000 *GLA* variants exist. Classical disease, with absent enzyme, and later-onset disease, with residual enzyme, for example *N215S* and *IVS4+919G>A*, differ substantially. Females are affected over a wide severity range determined by X-inactivation patterns.

Pompe disease arises from *GAA* variants, autosomal recessive. Glycogen accumulates in lysosomes of cardiac, skeletal and smooth muscle, with secondary autophagic build-up. Infantile-onset disease, with essentially no enzyme activity, brings hypertrophic cardiomyopathy, profound hypotonia, feeding difficulty and respiratory failure, and death in infancy untreated. Late-onset disease, with residual activity, brings progressive proximal and axial myopathy and diaphragmatic weakness, with respiratory failure often preceding loss of ambulation. CRIM status (cross-reactive immunologic material) determines whether the infant makes any endogenous protein, and CRIM-negative infants develop high-titre antibodies to replacement enzyme and do badly without immune tolerance induction.

Why severity varies at identical genotype is not well explained. Modifier genes, X-inactivation in Fabry disease and immune response to therapy in Pompe disease each contribute.

Not known: why newborn screening finds 10 to 50 times more Fabry disease and several times more Pompe disease than clinical ascertainment. Specifically, how many of the screen-detected later-onset genotypes will ever develop clinical disease, and therefore whether screening identifies patients or healthy variant carriers. This is the central unresolved question in the class and it determines whether screening is beneficial. Also not known: why enzyme replacement fails to reach the brain and bone adequately, and why anti-drug antibodies develop in some patients and not others.

Cure status. Gaucher type 1: CONTROLLABLE. Gaucher type 1 after allogeneic haematopoietic stem cell transplant: CURABLE, for the visceral and haematological disease. Gaucher type 2: RELIEF ONLY. Gaucher type 3: CONTROLLABLE for the visceral and haematological disease, and RELIEF ONLY for the neurological disease. Fabry disease: CONTROLLABLE. Infantile-onset Pompe disease: CONTROLLABLE. Late-onset Pompe disease: CONTROLLABLE.

Gaucher type 1 treatment is highly effective, arguably the most successful enzyme replacement therapy in medicine. Imiglucerase, velaglucerase and taliglucerase are given intravenously every 2 weeks. They regress splenomegaly and hepatomegaly by roughly 30 to 50 per cent within 2 years and normalise haemoglobin and platelet counts in most patients within 1 to 2 years†. They substantially reduce bone pain and crises, with bone density improving over years. Life expectancy in treated type 1 approaches normal.

Eliglustat, an oral substrate reduction therapy, is non-inferior to enzyme replacement for maintenance in suitable patients in the ENCORE trial and is first-line oral therapy. Miglustat is less effective and less tolerated. Established avascular necrosis and fibrosis do not reverse, and enzyme replacement does not cross the blood-brain barrier, so neuronopathic disease is not treated by it. Type 2 remains uniformly fatal. Allogeneic transplant cures the visceral and haematological disease, because donor macrophages supply the enzyme, but it carries transplant mortality and is rarely used now that enzyme replacement exists.

Fabry disease is CONTROLLABLE, with the qualification that the hard-outcome evidence is weaker than for Gaucher. Agalsidase beta and agalsidase alfa, intravenous every 2 weeks, clear Gb3 from endothelium and reduce plasma lyso-Gb3. The pivotal trials used histological clearance of Gb3 from renal capillary endothelium as the endpoint, not clinical events. The largest randomised trial of agalsidase beta showed a reduction in a composite clinical endpoint of renal, cardiac and cerebrovascular events and death that was significant only after adjustment for baseline proteinuria. Cochrane and other systematic reviews conclude the evidence for hard clinical benefit is limited, while registry data suggest slowed decline in renal function when treatment starts early. Migalastat, an oral chaperone, is effective only in the roughly 35 to 50 per cent of patients with amenable mutations†. Established fibrosis, renal, cardiac or cerebral, does not reverse. Early treatment is the whole argument, and it collides with the fact that newborn screening cannot yet predict who will develop disease.

Infantile-onset Pompe disease is the closest thing in the class to a transformation. Untreated, median survival is roughly 6 to 8.7 months and virtually none are alive at 2 years†. With alglucosidase alfa, approved in 2006, roughly 95 per cent of treated infants in the pivotal trial were alive at 18 months of age†. Roughly 92 per cent were alive and free of invasive ventilation†. In an untreated historical cohort roughly 2 per cent were alive and ventilator-free at that age†. Cardiomyopathy reverses substantially. This converted a uniformly fatal infantile disease into a survivable one, one of the largest single-drug survival effects recorded for any disease in this chapter.

It also created a new phenotype. Survivors develop residual myopathy, speech and swallowing difficulty, hearing loss, and in some cases a progressive white matter abnormality, because the enzyme does not reach the brain. The disease is controlled and not cured, and the surviving children have a condition that did not previously exist long enough to be described. CRIM-negative infants require immune tolerance induction (rituximab, methotrexate, immunoglobulin) or they develop neutralising antibodies and lose the benefit. Avalglucosidase alfa (2021) and cipaglucosidase alfa plus miglustat (2023) are next-generation products with better muscle targeting, and both showed modest superiority on respiratory and walking endpoints in late-onset disease.

Late-onset Pompe disease shows a modest measured benefit. The LOTS trial showed a roughly 25 metre improvement in 6-minute walk distance and stabilisation of forced vital capacity against placebo over 78 weeks†. That is small, and set against inexorable decline. Gene therapy is in trials for all three, AAV liver-directed for Fabry and Pompe and lentiviral haematopoietic for Gaucher and Fabry, and nothing is approved. Preliminary results show enzyme expression and substrate reduction.

Prevention. Carrier screening in founder populations. Ashkenazi Jewish carrier screening panels include Gaucher disease, carrier frequency roughly 1 in 15 to 18, and have operated for decades alongside Tay-Sachs screening. The Tay-Sachs programme reduced affected births in Ashkenazi communities by roughly 90 per cent†. Gaucher is screened within the same framework, though it raises a different question, because type 1 Gaucher is treatable and compatible with a long life. STRONG for birth prevalence. The ethical case differs from Tay-Sachs because the disease is treatable.

Cascade testing of relatives of an index case has a high yield and shortens the diagnostic delay of 4 to 16 years for the next family member. In Fabry disease, testing the family of one index case typically identifies roughly 5 additional affected relatives†. STRONG. Prenatal and preimplantation genetic diagnosis where available and acceptable: STRONG for birth prevalence.

Newborn screening is CONTESTED and is the central controversy in this class. For infantile-onset Pompe disease the case is strong, because treatment before symptom onset produces markedly better outcomes than treatment after and untreated infantile Pompe is fatal. Taiwan’s programme showed that screened infants had better motor and cardiac outcomes than clinically diagnosed ones. STRONG for infantile

Pompe. For Fabry disease and late-onset Pompe the case is contested. Screening detects 10 to 50 times more cases than clinical ascertainment, the great majority with later-onset or uncertain-significance genotypes, and nobody knows how many will develop disease or when to start a treatment costing hundreds of thousands of dollars a year. Screening generates patients-in-waiting and their families. CONTESTED. For Gaucher disease newborn screening is generally not recommended, because type 1 is compatible with decades of good health and treatment is started on clinical indication. Pompe, and in some programmes Fabry and MPS I, are included in the United States Recommended Uniform Screening Panel and in programmes in Taiwan, Japan, Italy, Austria and elsewhere.

Prevention of complications once diagnosed. In Fabry disease, ACE inhibitors or ARBs for proteinuria are standard and probably contribute as much to renal outcome as enzyme replacement. Anticoagulation or antiplatelet therapy for stroke risk, statins, avoiding nephrotoxins, hearing and cardiac surveillance and an implantable defibrillator where indicated complete the list. In Gaucher disease, splenectomy is avoided, since it was historically performed and accelerates bone and liver disease, and bisphosphonates and vitamin D protect bone, with monitoring for myeloma and Parkinson disease. In Pompe disease, respiratory surveillance includes supine spirometry, because diaphragmatic weakness is missed on erect spirometry, with non-invasive ventilation, vaccination, physiotherapy and careful anaesthetic management. STRONG for each.

Shortening the diagnostic delay. Targeted screening of high-risk populations has demonstrated yield: enzyme or genetic testing in young stroke patients, unexplained left ventricular hypertrophy and dialysis populations for Fabry disease, in unexplained splenomegaly or thrombocytopenia for Gaucher disease, and in unexplained limb-girdle myopathy or raised creatine kinase for Pompe disease. These yield affected patients in roughly 0.2 to 3 per cent of those tested†. MODERATE.

Treatment. Enzyme replacement therapy is an intravenous infusion every 1 to 2 weeks, lifelong. For Gaucher disease the products are imiglucerase, velaglucerase alfa and taliglucerase alfa. For Fabry disease they are agalsidase beta, agalsidase alfa and pegunigalsidase alfa (2023). For Pompe disease they are alglucosidase alfa, avalglucosidase alfa and cipaglucosidase alfa plus miglustat. All are patented in practice. Their listing status on the WHO Essential Medicines List 24th List needs checking†.

Taliglucerase alfa, plant-cell-produced, and velaglucerase entered as competitors to imiglucerase and reduced prices by roughly 25 to 40 per cent in some markets†. This is the only meaningful price competition in the class, and it was created deliberately by payers and by an Israeli and a United States manufacturer and not by patent expiry. Cost is hundreds of thousands of dollars a patient-year, weight-based, so adult and paediatric costs differ several-fold. Alglucosidase alfa costs more than the others for an adult. An infant costs far less, and the cost rises as the child grows, which has produced documented access crises as treated infants reach adolescence.

During the 2009 imiglucerase supply crisis, caused by viral contamination of the manufacturing line, patients worldwide were placed on reduced doses. Outcomes were largely maintained at substantially lower doses. That is evidence that the licensed doses may be higher than necessary, with obvious cost implications, and it has not been followed up systematically with dose-ranging trials.

Oral small molecules. Eliglustat, substrate reduction for Gaucher type 1, is non-inferior to enzyme replacement for maintenance in ENCORE, is taken orally twice daily, and costs hundreds of thousands of dollars a patient-year, oral and not cheaper. Miglustat is less effective with more gastrointestinal toxicity, is off-patent, and still costs tens to hundreds of thousands of dollars a patient-year, with generics at lower prices in some markets. Migalastat for Fabry disease, only for amenable mutations, is taken orally on alternate days at hundreds of thousands of dollars a patient-year. Their listing status needs checking against the 24th List†.

Immune tolerance induction in CRIM-negative infantile Pompe disease uses rituximab, methotrexate and immunoglobulin. Rituximab biosimilars cost thousands of dollars a course, methotrexate pennies, and immunoglobulin is expensive and plasma-constrained. All three of the drugs that make the enzyme work are cheap or moderately priced against it. Rituximab is on the 24th List, for multiple sclerosis in the complementary list and for Burkitt lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic

leukaemia and follicular lymphoma, and tolerance induction in Pompe disease is not among the recorded indications.

Haematopoietic stem cell transplant cures Gaucher visceral disease and is used for other lysosomal diseases (MPS I Hurler, metachromatic leukodystrophy, Krabbe disease) where it must be done before neurological damage. Supportive and complication-directed treatment is where most of the cheap benefit lies. In Fabry disease: ACE inhibitors or ARBs for proteinuria, at a few dollars to tens of dollars a patient-year; carbamazepine, gabapentin or pregabalin for neuropathic pain, at tens to hundreds of dollars; antiplatelets or anticoagulants; statins; and dialysis and renal transplantation. Kidney transplant outcomes in Fabry disease are good, at far lower cost than lifelong enzyme replacement plus dialysis. The listing status of these drugs needs checking against the 24th List†.

In Gaucher disease: bisphosphonates and vitamin D at tens of dollars a patient-year, transfusion, analgesia and joint replacement, and not splenectomy. In Pompe disease: non-invasive ventilation, a device costing hundreds to a few thousand dollars one-off plus consumables, which is what prevents death in late-onset disease and is far cheaper than enzyme replacement; physiotherapy; nutritional support; and mobility aids. Genetic counselling serves the family.

Simple means. This is the entry in which the simple means are least able to substitute for the expensive treatment, and that is stated directly. What exists still matters.

Non-invasive ventilation in Pompe disease. Respiratory failure from diaphragmatic weakness is what kills in late-onset Pompe, and a bilevel ventilator costing hundreds to a few thousand dollars plus masks prolongs life and relieves symptoms substantially. Against enzyme replacement at hundreds of thousands of dollars a patient-year with a roughly 25-metre walk-distance benefit, it is the highest-value intervention available for that disease. Supine spirometry costs nothing extra and detects diaphragmatic weakness that erect spirometry misses, and in late-onset Pompe it is the test that determines whether ventilation is needed.

ACE inhibitors or ARBs for Fabry proteinuria cost a few dollars to tens of dollars a patient-year, are off-patent, and slow renal decline. Where enzyme replacement is unaffordable, which is most of the world, these plus blood pressure control, statins and antiplatelet therapy are the realistic standard of care, and it is not nothing. Generic neuropathic pain drugs, carbamazepine, gabapentin, pregabalin and amitriptyline, treat the acroparaesthesia that is often the most disabling daily symptom of Fabry disease in young people, at tens to a couple of hundred dollars a year. Avoiding heat, exertion in heat and dehydration in Fabry disease is free and prevents crises, since hypohidrosis prevents normal thermoregulation.

Not performing splenectomy in Gaucher disease is free. Bisphosphonates and vitamin D for Gaucher bone disease cost tens of dollars a patient-year. Kidney transplantation in Fabry disease has good outcomes and is cheaper over a lifetime than dialysis plus enzyme replacement. Family testing is a pedigree and a blood test: one Fabry index case typically identifies roughly five affected relatives, and the diagnostic delay is 13 to 16 years.

A dried blood spot enzyme assay for Gaucher, Fabry and Pompe can be posted to a reference laboratory and costs tens of dollars per disease. It is how diagnosis is achieved in countries with no metabolic laboratory and is the cheapest step in this entry. Corneal verticillata in Fabry disease are visible on slit-lamp examination, cost nothing to look for, and are present in the great majority of classically affected patients of both sexes. Physiotherapy and exercise within tolerance help in Pompe disease, and joint protection in Gaucher disease.

Gaps. Newborn screening finds 10 to 50 times more Fabry disease and several times more Pompe disease than clinical ascertainment, and nobody knows what proportion of screen-detected later-onset genotypes will ever develop disease. It is the central unresolved problem in the class, and it makes screening for Fabry and late-onset Pompe genuinely contested while screening for infantile Pompe is clearly beneficial.

The evidence for hard clinical benefit of enzyme replacement in Fabry disease is limited. The pivotal trials used histological endpoints, Cochrane and other systematic reviews conclude the clinical-event evidence is weak, and registries suggest early treatment helps. The sources disagree, and the drug costs hundreds of thousands of dollars a patient-year. Late-onset Pompe enzyme replacement gives roughly a 25-metre improvement in 6-minute walk distance at hundreds of thousands of dollars a patient-year, against non-

invasive ventilation at hundreds to a few thousand dollars, and no head-to-head comparison or cost-effectiveness consensus exists.

The 2009 imiglucerase supply crisis showed outcomes maintained at substantially reduced doses, implying licensed doses may be unnecessarily high, and no dose-ranging trials have followed. It is the clearest unexploited cost-reduction opportunity in the class.

Whether any of these drugs is on the WHO Essential Medicines List 24th List needs checking, and essentially none is available in low-income countries. Published outcome data come almost entirely from high-income registries, which are also largely manufacturer-funded. Enzyme replacement is weight-based, so cost rises as a treated child grows, and documented access crises occur when treated infants reach adolescence and the annual cost doubles or triples.

Enzyme replacement does not cross the blood-brain barrier. Neuronopathic Gaucher disease, the neurological features of Fabry disease and the emerging white matter disease in long-surviving treated infantile Pompe patients are untreated. Treated infantile Pompe survivors have a phenotype that did not exist before the drug, and its natural history is being described in real time. Diagnostic delays of 4 to 16 years persist despite cheap dried blood spot assays. Why severity varies at identical genotype is unexplained, and in Fabry females X-inactivation accounts for part of it.

GBA1's role as the largest genetic risk factor for Parkinson disease connects this rare-disease class to a common disease, and the therapeutic implications are being tested now. Combined class incidence estimates, 1 in 4,000 to 1 in 8,000, come from a handful of population studies in the Netherlands, Australia and Italy, and nothing comparable exists from Africa, Asia or Latin America.

> **Depth.** A group (Gaucher, Fabry, Pompe). No depth is given.
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> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Hereditary metabolic disorders screened for at birth

What it is. A dried spot of blood taken from a newborn's heel and tested for a panel of inherited disorders. They cause death or permanent disability if untreated, and can be treated if caught in the first days of life. It is the largest genetic screening programme in the world.

Measured. Newborn screening reaches roughly two-thirds to three-quarters of the world's births for at least one condition, out of roughly 130 million babies born each year†. Near-universal coverage exists in North America, Europe, Australasia, Japan, Korea, Taiwan, much of Latin America and parts of the Middle East. Coverage is minimal across most of sub-Saharan Africa and parts of South and Central Asia.

Panel size varies enormously by country, and this is the central measured fact.

- United States Recommended Uniform Screening Panel: 38 core conditions plus 26 secondary conditions.
- Italy: roughly 40 to 50 conditions.
- Germany, Austria, the Netherlands, Spain and Portugal: roughly 15 to 30.
- United Kingdom: 9 conditions, which are phenylketonuria, congenital hypothyroidism, sickle cell disease, cystic fibrosis, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease, isovaleric acidaemia, glutaric aciduria type 1 and homocystinuria.
- France: expanded from 5 to 13 in 2023.
- Finland, Denmark and Sweden: roughly 2 to 25 depending on era.

Two high-income European countries with similar populations can thus differ four-fold in what they screen for, and the difference reflects policy judgement about screening criteria and not differences in disease prevalence. Roughly 1 in 1,500 to 1 in 4,000 newborns has a condition detected by an expanded tandem mass spectrometry (MS/MS) panel, depending on panel breadth and population.

The founding condition is phenylketonuria, roughly 1 in 12,000 births, with Guthrie's test in the early 1960s and Ireland's national programme in February 1966†. The highest-yield conditions on most panels follow.

Congenital hypothyroidism occurs in roughly 1 in 2,000 to 1 in 4,000, the commonest condition on most panels and the commonest preventable cause of intellectual disability. Levothyroxine started within the first two weeks produces normal IQ. Untreated, it causes severe irreversible intellectual disability, with a mean IQ loss of roughly 25 to 40 points, and worse where diagnosis is later†.

Sickle cell disease occurs in roughly 1 in 2,000 births in the United States and far higher in African and Afro-descended populations. Penicillin prophylaxis and pneumococcal vaccination from screening reduce early childhood death substantially, and the PROPS trial showed an 84 per cent reduction in pneumococcal septicaemia†. Cystic fibrosis occurs in roughly 1 in 3,000 in northern European populations. Congenital adrenal hyperplasia occurs in 1 in 14,200 live births and screening prevents neonatal salt-wasting death and incorrect sex assignment.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency occurs in roughly 1 in 10,000 to 20,000†. It is one of the clearest cases for screening. Untreated, roughly 20 to 25 per cent of undiagnosed children die at the first metabolic crisis and many survivors have brain injury. With screening and avoidance of fasting, mortality falls to near zero. The intervention is an instruction: do not let the child fast, and give glucose during illness.

Severe combined immunodeficiency occurs in 1 in 58,000 by TREC screening†. Galactosaemia occurs in roughly 1 in 40,000 to 60,000†. Untreated it causes neonatal sepsis, liver failure and death, and the treatment is a lactose-free diet. Biotinidase deficiency occurs in roughly 1 in 60,000†. Untreated it causes seizures, developmental delay, hearing loss, optic atrophy and death. The treatment is oral biotin, costing a few dollars a year, and it prevents all of it. It is the highest benefit-to-cost ratio of any condition on any screening panel.

Maple syrup urine disease, homocystinuria, glutaric aciduria type 1, isovaleric acidaemia, propionic and methylmalonic acidaemia, tyrosinaemia type 1, urea cycle disorders, and very-long-chain and long-chain fatty acid oxidation defects each occur in roughly 1 in 50,000 to 1 in 250,000†. Increasingly added are spinal muscular atrophy (SMA), roughly 1 in 10,000, X-linked adrenoleukodystrophy, Pompe disease, mucopolysaccharidosis type I, Fabry disease and, in some programmes, Duchenne muscular dystrophy.

Cost is low. The full MS/MS panel costs tens of dollars per newborn depending on programme and panel breadth, and the dried blood spot card, collection and courier are a large share of it. Cost-effectiveness analyses consistently find expanded newborn screening cost-saving or highly cost-effective, driven by phenylketonuria, congenital hypothyroidism, MCAD deficiency and congenital adrenal hyperplasia, where the averted lifetime care costs greatly exceed programme costs. The heel-prick sample is taken at 24 to 72 hours, in some programmes 2 to 7 days, with a repeat where indicated.

Where it starts. The conditions screened are almost all Mendelian, mostly autosomal recessive, so heritability is 1.0 for the genotype, and the parents of an affected child are almost always healthy carriers with no family history. This is the central epidemiological point. These diseases are not predictable from family history in the great majority of cases, which is why population screening and not targeted testing is required.

Consanguinity raises the incidence of recessive conditions substantially. In highly consanguineous populations the combined incidence of screened metabolic disorders can be several-fold higher, and those are where screening coverage is often lowest. Founder effects change what is worth screening for. Tyrosinaemia type 1 occurs in Saguenay-Lac-Saint-Jean (Quebec) at roughly 1 in 1,850. Glutaric aciduria type 1 occurs in Old Order Amish and in the Irish Travelling community. Maple syrup urine disease occurs in Mennonites at roughly 1 in 380. Sickle cell disease occurs in African-descended populations, beta-thalassaemia in Mediterranean, Middle Eastern and South Asian populations, and Gaucher disease and Tay-Sachs disease in Ashkenazi Jewish populations.

Not all conditions on panels are genetic. Congenital hypothyroidism is mostly non-genetic, thyroid dysgenesis in roughly 85 per cent, and in iodine-deficient areas is partly environmental, so iodisation

reduces the burden the screen detects. Congenital cytomegalovirus and critical congenital heart disease, detected by pulse oximetry and not blood spot, are also on some panels.

Early treatment works and late treatment does not because a metabolite accumulates or a hormone is absent during a critical developmental window. In phenylketonuria and congenital hypothyroidism the window is the first weeks to months of brain development, and damage is cumulative and irreversible. In MCAD deficiency and other fatty acid oxidation defects the risk is an acute catastrophic crisis precipitated by fasting or illness, which can be prevented indefinitely. In galactosaemia and tyrosinaemia the damage is acute organ injury in the neonatal period. In SMA the window is motor neuron loss, which is largely complete in the first months. This distinction, cumulative developmental damage against preventable acute crisis, determines whether a condition belongs on a panel.

The screening criteria of Wilson and Jungner (1968) and their modern revisions require an important condition, a recognisable latent stage, an available and acceptable test, an effective treatment, and benefit outweighing harm. Technology has outrun the criteria. MS/MS can detect dozens of analytes at no marginal cost per condition, so conditions get added because they are detectable and not because treatment is established. That is the central tension in the field.

Not known: for many conditions added in the MS/MS era, what proportion of screen-detected cases would ever have become clinically apparent. Expanded screening detects mild and variant forms. In short-chain acyl-CoA dehydrogenase deficiency, 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency and mild variants of several organic acidaemias, the screen-detected population is substantially healthier than the clinically ascertained one, and many will never have symptoms. The same problem appears in Fabry disease and late-onset Pompe disease. How to handle this is unresolved, and it is the main harm of expanded screening.

Cure status. This is a grouped entry covering a whole screening panel, and the labels differ by condition. The strata are grouped by what the treatment does. Newborn screening exists because the list is dominated by conditions whose treatment must start within days of birth and then continue.

Held by a lifelong diet, cofactor, hormone or emergency regimen: CONTROLLABLE. This covers phenylketonuria, congenital hypothyroidism, biotinidase deficiency, galactosaemia, MCAD deficiency and other fatty acid oxidation defects, maple syrup urine disease, homocystinuria, tyrosinaemia type 1, urea cycle disorders, organic acidaemias and congenital adrenal hyperplasia. The label is CONTROLLABLE and not CURABLE because the treatment continues for life. That does not reduce the value of screening. It is the difference between a normal life on treatment and irreversible damage without it.

Sickle cell disease: CONTROLLABLE, by penicillin prophylaxis plus pneumococcal vaccination plus parental education, which converts a condition that killed in early childhood into one compatible with adult life. Sickle cell disease after successful matched sibling transplant, available to a few: CURABLE. After gene therapy: CONTROLLABLE. Severe combined immunodeficiency, transplanted early: CURABLE. X-linked adrenoleukodystrophy, transplanted or treated with elivaldogene autotemcel before neurological damage: CURABLE. Spinal muscular atrophy treated before symptoms: CONTROLLABLE. Any of these diagnosed after irreversible damage is established: RELIEF ONLY. Krabbe disease and several mild variant forms detected by MS/MS have no established treatment benefit, and no label is assigned.

Phenylketonuria is CONTROLLABLE if caught at birth and RELIEF ONLY if caught late; see phenylketonuria. Congenital hypothyroidism treated with levothyroxine within two weeks gives normal IQ, and untreated gives severe permanent intellectual disability. Biotin, a few dollars a year, prevents seizures, deafness, blindness, developmental delay and death entirely in biotinidase deficiency. In galactosaemia, a lactose- and galactose-free diet prevents neonatal death and liver failure, though learning, speech and ovarian outcomes remain impaired in a substantial minority despite perfect dietary compliance, which is unexplained. In MCAD deficiency, avoidance of fasting plus glucose during illness takes mortality from roughly 20 to 25 per cent at the first crisis to near zero†. The treatment is an instruction and an emergency regimen, not a product.

Maple syrup urine disease, homocystinuria, tyrosinaemia type 1, urea cycle disorders and organic acidaemias are held by specialised diets and cofactors. These are pyridoxine in some homocystinuria, hydroxocobalamin in some methylmalonic acidaemia and biotin in some propionic acidaemia. Nitisinone

in tyrosinaemia type 1 transformed it from a liver-transplant disease to a medical one, and nitrogen-scavenging drugs serve urea cycle disorders. Outcomes are good with early treatment and poor with late treatment, and residual neurocognitive morbidity is common even when treated. Congenital adrenal hyperplasia is held by hydrocortisone and fludrocortisone, which prevent salt-wasting death.

For severe combined immunodeficiency, overall survival is roughly 92 to 94 per cent when transplanted before 3.5 months against roughly 50 to 66 per cent later with active infection†. The screen delivers the age advantage.

Spinal muscular atrophy is the transformation case, and it has changed newborn screening policy worldwide. Untreated SMA type 1 reaches median survival or permanent ventilation by roughly 10 to 24 months, and almost none sit unaided†. Nusinersen (2016), onasemnogene abeparvovec (2019, a single AAV9 gene therapy) and risdiplam (2020) are the treatments. The NURTURE study gave nusinersen to presymptomatic infants identified genetically: all 25 were alive without permanent ventilation at a median of roughly 5 years of follow-up, all could sit unaided, and 23 of 25 could walk independently, outcomes essentially unheard of in untreated SMA. Presymptomatic treatment produces outcomes within or close to the normal range, and symptomatic treatment does not. That contrast is the strongest modern argument for newborn screening of any condition, and SMA has been added to panels in the United States, much of Europe, Australia, Japan and Taiwan within a few years.

Onasemnogene abeparvovec costs roughly two million dollars as a single dose, nusinersen several hundred thousand dollars in the first year and about half that each year after, and risdiplam hundreds of thousands of dollars a patient-year depending on weight and market. These are among the highest-priced medicines in existence, and the condition is detected by a test costing a few dollars.

Prevention. Newborn screening is itself the prevention, and the measured effects are set out above. Phenylketonuria gives normal development against severe intellectual disability. Congenital hypothyroidism gives normal IQ against a 25 to 40 point loss. MCAD deficiency gives near-zero against 20 to 25 per cent mortality at first crisis. Severe combined immunodeficiency gives 92 to 94 per cent against 50 to 66 per cent survival. SMA gives walking independently against death or ventilation by 2 years. Sickle cell disease gives an 84 per cent reduction in pneumococcal septicaemia. A full panel costs tens of dollars per newborn. STRONG for the core conditions. CONTESTED for several recent additions.

Extending coverage to the countries without it is the largest remaining preventable burden in this chapter. In populations without screening, phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, galactosaemia and MCAD deficiency cause exactly the deaths and disabilities they caused everywhere before screening existed. Congenital hypothyroidism alone occurs at roughly 1 in 2,000 to 4,000 births. With 130 million annual births that implies roughly 32,000 to 65,000 affected infants a year worldwide†. A large share are unscreened, and each needs a levothyroxine tablet costing a few dollars to a few tens of dollars a year. STRONG.

Premarital and preconception carrier screening in high-incidence and consanguineous populations has been implemented for haemoglobinopathies in Cyprus, Iran, Saudi Arabia and the United Arab Emirates, with large measured reductions in affected births. STRONG for birth prevalence, and socially and ethically variable. Cascade testing after an index case, since a subsequent pregnancy in the same family carries a 1-in-4 recessive risk and prenatal or preimplantation diagnosis is available: STRONG. Universal salt iodisation reduces the congenital hypothyroidism the screen detects: STRONG.

Getting the sample at the right time. Too early, under 24 hours, causes false negatives for congenital hypothyroidism and congenital adrenal hyperplasia, and too late loses the treatment window. Timely sample collection and timely result communication are the operational determinants of whether the programme works. Failures of follow-up, and not of the laboratory, are the documented cause of most preventable harm in established programmes. STRONG.

Preventing the harms of screening: clear protocols for borderline and variant results, genetic counselling, and explicit decisions about which conditions to include based on treatment availability and not detectability. MODERATE, and this is where policy is weakest.

Treatment. Treatment is condition-specific, and the striking feature of the list is how cheap most of it is.

Levothyroxine for congenital hypothyroidism is on the WHO Essential Medicines List 24th List, section 18.7, for hypothyroidism. It is off-patent and costs a few dollars to a few tens of dollars a patient-year. It prevents severe intellectual disability and must start within two weeks.

Biotin for biotinidase deficiency is off-patent and costs a few dollars a patient-year. It prevents seizures, deafness, blindness and death completely. Its listing status needs checking against the 24th List†.

Penicillin V and pneumococcal conjugate vaccine for sickle cell disease give an 84 per cent reduction in pneumococcal septicaemia. Penicillin is off-patent and costs a few dollars a patient-year plus the vaccine cost. Their listing status needs checking against the 24th List†. Hydrocortisone and fludrocortisone for congenital adrenal hyperplasia are off-patent at tens to hundreds of dollars a patient-year, and their listing status needs checking against the 24th List†; see adrenal insufficiency.

Dietary treatment for phenylketonuria, galactosaemia, maple syrup urine disease, homocystinuria, tyrosinaemia, organic acidaemias and urea cycle disorders uses specialised amino acid substitutes and low-protein medical foods. They are made by few suppliers and cost thousands to tens of thousands of dollars a patient-year; see phenylketonuria. The diet controls the disease and the formulated products are the expense. Whether any is on the 24th List needs checking†.

Cofactor vitamins are pyridoxine for B6-responsive homocystinuria, hydroxocobalamin for B12-responsive methylmalonic acidaemia, biotin for biotin-responsive propionic acidaemia, riboflavin for multiple acyl-CoA dehydrogenase deficiency and thiamine for thiamine-responsive maple syrup urine disease. All are off-patent and cost a few dollars to a few tens of dollars per patient-year. Identifying a cofactor-responsive variant converts an expensive dietary disease into a vitamin-treated one. Their listing status needs checking against the 24th List†.

Carnitine for fatty acid oxidation defects and organic acidaemias is off-patent and costs hundreds to thousands of dollars a patient-year; its listing status needs checking. Nitisinone for tyrosinaemia type 1 transformed the disease. Generics have entered and prices have fallen substantially in some markets, from tens of thousands of dollars a patient-year to thousands. Its listing status needs checking against the 24th List†.

Nitrogen scavengers for urea cycle disorders are sodium benzoate, cheap and off-patent, sodium phenylbutyrate, off-patent at tens of thousands of dollars a patient-year, and glycerol phenylbutyrate, patented and higher. Intravenous sodium benzoate and arginine, plus haemodialysis, treat hyperammonaemic crisis, cheaply and time-critically. Their listing status needs checking against the 24th List†.

Emergency regimens for MCAD and other fatty acid oxidation defects, organic acidaemias and urea cycle disorders are a written emergency plan, a glucose polymer drink, and immediate intravenous dextrose during illness. This is the treatment that prevents death in these conditions and it costs almost nothing.

Haematopoietic stem cell transplant treats severe combined immunodeficiency, adrenoleukodystrophy, MPS I Hurler, metachromatic leukodystrophy and Krabbe disease. It is time-critical, and screening makes the timing possible. Gene and antisense therapies are onasemnogene abeparvovec at roughly two million dollars a single dose, nusinersen, risdiplam and elivaldogene autotemcel for adrenoleukodystrophy at about three million dollars. All are patented, and their listing status needs checking against the 24th List†. Enzyme replacement for Pompe disease and MPS I where screened costs hundreds of thousands of dollars a patient-year; see lysosomal storage diseases.

Simple means. This entry contains the highest-value simple means in the chapter.

The heel-prick dried blood spot is a few drops of blood on a filter paper card, air-dried and posted to a central laboratory. The full panel costs tens of dollars per newborn, and the phenylketonuria assay within it a few dollars. It requires no imaging, no clinic visit and no specialist, and the card survives the post. Against outcomes of normal development versus severe permanent intellectual disability, or life versus death at the first metabolic crisis, it is the highest benefit-to-cost intervention documented in this chapter, and it is unavailable to a large share of the world’s newborns.

Levothyroxine for congenital hypothyroidism costs a few dollars to a few tens of dollars a patient-year, is off-patent, is on the Essential Medicines List, and started within two weeks gives normal IQ instead of severe intellectual disability. At roughly 1 in 2,000 to 4,000 births it is the commonest condition on the panel and the cheapest treatment. Biotin for biotinidase deficiency costs a few dollars a year and prevents seizures, deafness, blindness, developmental delay and death.

For MCAD deficiency and other fatty acid oxidation defects the instruction is: do not let this child fast, and give glucose when ill. That instruction plus an emergency regimen takes mortality from roughly 20 to 25 per cent at first crisis to near zero. The intervention is a piece of paper and a glucose drink.

Penicillin twice a day and the pneumococcal vaccine in sickle cell disease give an 84 per cent reduction in pneumococcal septicaemia for a few dollars a year. A lactose-free diet in galactosaemia is ordinary dietary avoidance that prevents neonatal liver failure and death. Cofactor vitamins, pyridoxine, hydroxocobalamin, biotin, riboflavin and thiamine, cost a few dollars to a few tens of dollars a year, and in the responsive variants replace the entire expensive apparatus of dietary management. Salt and hydrocortisone serve congenital adrenal hyperplasia, and salt costs nothing.

A written emergency letter carried by the family, naming the condition and the intravenous dextrose or ammonia-scavenging regimen needed on arrival at hospital, is free. It prevents death in a metabolic crisis when the family reaches a hospital that has never heard of the condition. Getting the sample at 24 to 72 hours and chasing the result is operational and free, and failures of follow-up and not of the laboratory cause most preventable harm in working programmes. Iodised salt reduces the congenital hypothyroidism burden upstream of the screen. Telling the family that a subsequent pregnancy carries a 1-in-4 risk, and that testing is available, costs nothing.

Gaps. Panel composition differs four-fold or more between comparable high-income countries, UK 9 conditions, United States 38 core plus 26 secondary, Italy roughly 40 to 50, for reasons of policy judgement and not disease prevalence. There is no international consensus on what should be screened. Technology has outrun the Wilson and Jungner criteria. MS/MS detects dozens of analytes at near-zero marginal cost, so conditions are added because they are detectable, and the requirement for an established effective treatment has weakened.

For several MS/MS-detected conditions, nobody knows what proportion of screen-detected cases would ever have become symptomatic. Expanded screening finds mild variants of short-chain acyl-CoA dehydrogenase deficiency, 3-MCC deficiency and several organic acidaemias whose clinical significance is unknown, creating patients-in-waiting. It is the main harm of expanded screening and it is unquantified. Krabbe disease screening has been implemented in some United States states despite uncertain benefit and a very narrow transplant window, and sources disagree sharply on whether it should be screened.

Coverage is minimal across most of sub-Saharan Africa and parts of South and Central Asia, and no systematic global figure exists for how many newborns are screened for what. The two-thirds to three-quarters figure for at least one condition is an estimate. Galactosaemia outcomes remain impaired in a substantial minority despite perfect dietary compliance, in learning, speech and ovarian function, and this is unexplained, which means the dietary control is incomplete for reasons nobody understands. Residual neurocognitive morbidity is common in treated organic acidaemias, urea cycle disorders and maple syrup urine disease even with early diagnosis, so screening prevents death and crisis more reliably than it prevents disability.

Expanded panels generate roughly 10 to 100 false positives per true positive depending on condition and cut-off, with documented parental anxiety and medicalisation of healthy infants. Second-tier molecular testing reduces this and is not universally implemented. Follow-up failure, and not laboratory failure, causes most preventable harm in established programmes, and the data on this are from incident reports and not systematic measurement.

The price contrast is extreme and unreconciled. SMA is detected by a test costing a few dollars and treated with a medicine costing about two million dollars. Congenital hypothyroidism is detected by the same test and treated for a few dollars to a few tens of dollars a year. No framework reconciles these within a single screening programme’s budget. Specialised medical foods and amino acid substitutes have no generic pathway and cost thousands to tens of thousands of dollars a patient-year, so the dietary control that

newborn screening makes possible is among the least affordable treatments in the chapter relative to its simplicity. Whether genomic sequencing should replace or supplement biochemical newborn screening is under active trial, in the UK Generation Study, BabySeq and others, and the evidence is not yet in.

End of chapter.

> **Depth.** A screening panel. Not one illness. No depth is given.
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. The book splits this entry by moment, early and late. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Chapter 13 — Mental, Sleep-Wake and Nervous System Conditions

ICD-11 Chapter 06 — Mental, behavioural or neurodevelopmental disorders. Chapter 07 — Sleep-wake disorders. Chapter 08 — Diseases of the nervous system.

This chapter covers fifty-one conditions across three ICD-11 chapters. They are taken together because the three chapters cut one territory three ways, and because several conditions are coded in two of them at once. Dementia is a Chapter 06 neurocognitive disorder whose causes are Chapter 08 diseases, so Alzheimer disease appears twice: once as a disease of the nervous system, once as the syndrome it produces. Sleep-wake disorders were a chapter of their own for the first time in ICD-11, having previously been distributed between the other two.

The burden is large. Depressive disorders and anxiety disorders rank second and third among all causes of years lived with disability worldwide, at 56.0 million (95 per cent UI 38.2 to 80.3) and 55.4 million (36.4 to 81.3). Headache disorders rank sixth at 45.5 million (31.4 to 62.0). Stroke ranks third among all causes of disability-adjusted life years at 157 million (141 to 172). Nervous system conditions as a group were the leading cause of illness and disability worldwide on the GBD 2021 analysis, with about 3.4 billion people affected and 443 million DALYs. The nervous-system figure covers Chapter 08 only, Chapter 07 has no stand-alone estimate, and no sum of the three chapters is printed.

In this chapter a simple means sometimes matches or beats the drug, and the figures are good ones. Exercise for depression was tested in a network meta-analysis of 218 studies, 495 arms and 14,170 participants. Against active controls, walking or jogging gave Hedges' g −0.62 (95 per cent CI −0.80 to −0.45); yoga −0.55; strength training −0.49†. The pooled standardised mean difference for antidepressants against placebo, across 522 trials and 116,477 participants, is about 0.30†. The exercise effect is the larger of the two. The certainty rating on the exercise estimates is low to very low, because only one included study was at low risk of bias, and that belongs in the same sentence as the number.

Three more cases are as clear. Behavioural treatment is first-line for insomnia in every major guideline, and its gains are maintained or continue to improve after treatment stops, where hypnotic gains are not. Its two most effective components, sleep restriction and stimulus control, are instructions that fit on a printed page. For circadian rhythm sleep-wake disorders, timed light is not an adjunct to the treatment: light is the treatment, with a measured dose-response in the phase response curve, and phase shifts of one to three hours achievable over days. The drugs are adjunctive to it. And for stroke prevention, the China Salt Substitute and Stroke Study randomised 600 villages and 20,995 people to potassium-enriched salt substitute or ordinary salt. All had a history of stroke or high blood pressure. Stroke fell by 14 per cent, rate ratio 0.86 (95 per cent CI 0.77 to 0.96), with total mortality 12 per cent lower and no excess of serious hyperkalaemia†. That is a randomised trial of a change of table salt, with a clinical endpoint, in twenty-one thousand people.

Two further findings belong here because the cheap thing is not merely comparable but unpatentable. High-flow oxygen aborts cluster headache attacks in roughly 70 to 80 per cent of cases within fifteen minutes, with randomised support†, and an inhaled gas cannot be patented; the barrier is prescribing and supply, not price. Oral iron in restless legs syndrome, where ferritin is low, treats the cause rather than the symptom. It is on the WHO Essential Medicines List. It costs about five US dollars a patient-year at one tablet a day, computed from a UNICEF indicative price of US$1.43 on one catalogue page and US$1.60 on another for a bottle of a hundred 60 mg tablets, October 2026. The standing alternative, a dopamine agonist, controls the symptom and causes augmentation — iatrogenic worsening and spread — in a substantial proportion of patients, which is why the guidelines reversed.

None of this means that a simple means substitutes for treatment in severe illness, and the chapter says where it does not. In attention deficit hyperactivity disorder the stimulant effect sizes, −0.78 for methylphenidate and −1.02 for amphetamines in children†, are far larger than any non-drug intervention

measured; the entry reports that asymmetry rather than softening it. In schizophrenia, family intervention reduces relapse substantially and is not a substitute for maintenance antipsychotic treatment. In bipolar type I, no psychological treatment substitutes for pharmacological maintenance.

For the core motor symptoms of Parkinson disease, levodopa is far superior to exercise, and exercise is superior for balance and falls. In feeding and eating disorders, exercise is not a safe simple means and is not recommended here. In opioid use disorder, exercise, light and sleep timing have no comparable evidence at all; the effective simple means there are naloxone in lay hands and continuity of treatment across transitions. The pattern of this chapter is not that cheap things are always enough. It is that where they are enough, the measured evidence says so plainly, and is largely ignored.

Two measurement facts frame the chapter. First, Chapter 07 has no stand-alone GBD burden estimate for any of its conditions. Not insomnia disorder, at 6 to 10 per cent disorder prevalence in adults; not narcolepsy; not restless legs syndrome; not the circadian disorders; not the parasomnias; and not obstructive sleep apnoea, which on the only global estimate available affects 936 million adults aged 30 to 69, in a study whose funding statement is the single word ResMed. A whole ICD-11 chapter sits outside the global burden accounts. This is the largest measurement gap in this book, and it is reported here as a gap in the measurement, not as an aside about one condition.

Second, drug prices. The compilation this chapter is built from carried 178 price figures that were the compiler’s own order-of-magnitude estimates, for which no source was consulted. 169 of them printed digits. Under the rule that governs this book, such a figure is never published as a figure. Six of the 169 have been replaced with a sourced, dated price read off its source — iron, phenobarbital, ibuprofen, amlodipine, magnesium sulfate and antenatal dexamethasone — with folic acid and the meningitis dose of dexamethasone priced from the same sources where the compilation gave only words. The remaining 163 have had their digits struck, and the text says in words what is known without them.

The governing edition of the Essential Medicines List for this book is the 24th List (2025). The compilation this chapter is built from checked statuses against the 23rd (2023) and 24th Lists without recording which, so every listing claim in the chapter carries a dagger and needs checking against the 24th List. Seven are confirmed against that edition, were read off it and carry no dagger: levothyroxine, metformin, phenobarbital, albendazole, rituximab, methotrexate and magnesium sulfate.

06 — Mental, behavioural and neurodevelopmental disorders

Depressive disorders

What it is. Persistent low mood and loss of interest, lasting most of the day nearly every day for at least two weeks. Thinking, sleep, appetite and energy are affected. It runs in episodes, and in most people the episodes recur.

Measured. Global prevalence is 5.2 per cent of adults, about 322 million people, of whom 43 million are children and adolescents (WHO depression fact sheet, 11 September 2026, GBD 2023 data). The same page gives 322 million as 4 per cent of the whole population. Women 6.2 per cent, men 4.1 per cent, a ratio of about 1.5 to 1; adults aged 70 and over 5.4 per cent. More than 10 per cent of pregnant women and new mothers are affected. Depressive disorders are the second leading cause of years lived with disability worldwide, at 56.0 million YLDs (95 per cent UI 38.2 to 80.3) in 2023; the count rose 26 per cent over the preceding period (GBD 2023 release, not the capstone). First onset is most often in adolescence to the mid-twenties, and prevalence is relatively flat across adult life with a late-life rise in some datasets. Regional prevalence estimates vary about two-fold, and a large part of that spread is measurement rather than disease. Age-standardised rates have been broadly flat for three decades; absolute case numbers rose with the pandemic years of 2020 and 2021. About one third of people with depression in high-income countries receive mental health treatment, and coverage in low-income settings is far lower (WHO).

Where it starts. Heritability from twin studies is about 35 to 40 per cent, while SNP-based heritability from genome-wide association studies is far lower, around 9 per cent†. No common variant has an effect of practical size, and polygenic scores explain a few per cent of variance with no diagnostic use. Childhood maltreatment carries an odds ratio of roughly 2 to 3 for adult depression, and recent severe life events — bereavement, loss of employment, relationship breakdown — carry roughly 2 to 3 in the following months†. Chronic physical illness and chronic pain raise risk roughly 2 to 3 times†. Female sex, about 1.5 times. Social isolation and loneliness are consistently associated, with the direction of causation partly reversed, since depression produces withdrawal.

The serotonin hypothesis of depression does not have supporting evidence. An umbrella review across six areas of research found no consistent evidence that depression is associated with lowered serotonin concentration or activity (Moncrieff and colleagues, *Molecular Psychiatry*, 2022). The review was contested on its reading of the drug evidence; its central finding, that no serotonin deficit is established, has not been overturned. That antidepressants have measurable effect is a separate and better-established fact than any account of why. Efficacy does not establish mechanism. Inflammatory, HPA-axis and neuroplasticity accounts show group-level associations and none has produced a clinically usable biomarker. Not known: why episodes start when they do; why some people recur and others do not; why a given drug works in one person and not another; whether the condition is one thing or many.

Cure status. CONTROLLABLE. Single episodes remit in a majority of cases, many without treatment, and naturalistic remission within a year is substantial — which is part of why placebo response rates in trials run at 30 to 40 per cent†. Recurrence after a first episode is roughly 50 per cent lifetime, after two episodes roughly 70 per cent, after three roughly 90 per cent†. Maintenance antidepressant treatment roughly halves relapse risk against withdrawal to placebo. Relapse on withdrawal is the normal pattern, which is why the label is CONTROLLABLE. Psychotherapy effects persist better after discontinuation than drug effects do, and relapse still occurs.

Prevention. School and community psychological prevention programmes: risk reduction in the range of 20 per cent on incidence in meta-analysis, WEAK†. Treating insomnia: digital cognitive behavioural therapy for insomnia reduced incident depression in randomised trials, replicated, MODERATE. Physical activity as primary prevention: prospective cohorts show lower incidence in the active, with dose-response, not established by randomised prevention trials, MODERATE. Perinatal interventions, meaning home visiting and structured psychological support for at-risk mothers: MODERATE. Poverty reduction and

cash transfers reduce psychological distress in randomised and quasi-experimental studies, with less consistent measurement of diagnosed depression, MODERATE. Reducing childhood maltreatment: MODERATE on reasoning, WEAK on direct trial evidence, because intervention trials with depression endpoints are sparse. Mass screening without attached treatment: CONTESTED, with no demonstrated effect on outcomes.

Treatment. In order of evidence strength.

Antidepressants, acute episode. All 21 drugs studied beat placebo in the largest network meta-analysis, covering 522 trials and 116,477 participants (Cipriani and colleagues, *Lancet*, 2018). The pooled odds ratio for response against placebo is about 1.66, and the standardised mean difference on continuous symptom scales about 0.30. That is a small-to-moderate effect, and the difference between drugs is smaller than the difference from placebo. Fluoxetine and amitriptyline are the EML representatives, both off-patent, each costing a few US dollars a patient-year. Sertraline, citalopram, paroxetine, venlafaxine and mirtazapine are not EML-listed, all off-patent, and cost up to a few tens of US dollars a patient-year.

Structured psychotherapies. Cognitive behavioural therapy and its relatives give effect sizes against control comparable to drugs, SMD roughly 0.3 to 0.7 depending on the control condition, with smaller estimates in trials at low risk of bias. Combined drug and psychotherapy outperforms either alone.

Behavioural activation. Non-inferior to full cognitive behavioural therapy in the COBRA randomised non-inferiority trial of 440 patients (Richards and colleagues, *Lancet*, 2016): PHQ-9 fell from 17.7 to 8.4 with behavioural activation and from 17.4 to 8.4 with CBT, mean difference 0.1 (95 per cent CI −1.3 to 1.5). Intervention cost was £974.81 against £1,235.23 at eighteen months, about 21 per cent cheaper, and it is deliverable by staff without a full CBT qualification.

Exercise. The figures above, from Noetel and colleagues, *BMJ*, 2024: walking or jogging Hedges' g −0.62 (95 per cent CI −0.80 to −0.45); yoga −0.55 (−0.73 to −0.36); strength training −0.49 (−0.69 to −0.29); mixed aerobic −0.43 (−0.61 to −0.24); tai chi or qigong −0.42 (−0.65 to −0.21); exercise combined with an SSRI −0.55 (−0.86 to −0.23). Certainty low for walking and jogging, very low for the rest.

Electroconvulsive therapy. The largest effect size of any treatment in severe and treatment-resistant depression, with response in 50 to 70 per cent of severe cases and higher figures in psychotic depression†. The cost is staff and anaesthesia, not drug. Harms: retrograde amnesia, usually but not always transient.

Ketamine and esketamine. Effect within hours, measurable and short-lived without repeat dosing. Esketamine nasal spray is on patent in most markets, not EML-listed, and costs thousands of US dollars a patient-year. Generic racemic ketamine is cheap and EML-listed as an anaesthetic, and the depression indication is off-label in most jurisdictions.

Light therapy. Established for seasonal pattern, with small-to-moderate effect sizes in non-seasonal depression. The hardware is a one-off cost of a few tens of US dollars.

Simple means. Exercise, with the effect sizes above, in the same range as antidepressant trial effects and requiring no supply chain. This is the clearest case in the chapter of a simple means with trial evidence comparable to medication. Fixed sleep and wake times: sleep regularisation reduces depressive symptoms, and treating insomnia reduces incident depression. Morning light at a fixed hour: effective for seasonal pattern, smaller effect in non-seasonal depression. Social connection: strong prospective association, with small positive effects from randomised trials of befriending and social prescribing, at lower certainty than exercise. Behavioural activation self-help: structured re-engagement with activity, deliverable from a printed booklet with minimal supervision, with non-inferiority to CBT established at the therapist-delivered level.

Gaps. Whether depression is one condition or a cluster of distinct states with shared surface features is unresolved, and it affects every effect estimate. Antidepressant effect sizes are close enough to the threshold of clinical detectability that reasonable analysts disagree about their practical meaning; unpublished-trial bias has been demonstrated and partly corrected, not eliminated. Withdrawal effects on discontinuation were long underestimated, incidence and duration estimates still vary widely, and the trial literature does not reliably distinguish withdrawal from relapse. Comparative data beyond two years for

drugs against psychotherapy against exercise are almost absent. GBD prevalence rests on sparse primary survey data in most low-income countries, so regional variation may be largely artefact.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: about 6 months († an untreated episode lasts about 6 months); depth 48.23.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Bipolar disorders

What it is. Episodes of elevated, expansive or irritable mood with increased activity, alternating with depressive episodes and periods of normal mood. Bipolar type I includes full mania; type II includes hypomania with depression. It is lifelong and episodic.

Measured. About 36 million people worldwide, including 3.3 million adolescents aged 10 to 19 (WHO mental disorders fact sheet, 11 September 2026, GBD 2023 data). Lifetime prevalence in surveys is roughly 1 per cent for bipolar I and about 2.4 per cent for the full spectrum. The sex ratio is close to 1 to 1 for bipolar I; bipolar II is more often diagnosed in women. Median onset is the mid-to-late teens and early twenties, and onset after 50 is uncommon enough to raise suspicion of another cause. The standardised mortality ratio is roughly 2 for all causes, with life expectancy reduced by roughly a decade, driven mainly by cardiovascular disease and suicide. Prevalence estimates vary less across regions than for depression, and survey coverage is thin. Age-standardised rates are broadly stable and absolute numbers rise with population.

Where it starts. Heritability is the highest of the common psychiatric disorders: 60 to 85 per cent from twin studies, against SNP-based heritability of about 20 per cent†. A first-degree relative with bipolar disorder raises risk roughly 7 to 10 times†. There is substantial genetic correlation with schizophrenia; the two diagnoses are not genetically separate. Childhood adversity is associated with earlier onset and worse course rather than clearly with incidence. Sleep deprivation and circadian disruption reliably precipitate manic episodes in people already diagnosed, one of the better-established precipitant relationships in psychiatry. The postpartum period carries sharply elevated risk of a first manic or psychotic episode.

There is no biomarker and no validated diagnostic test. Diagnosis is entirely clinical and the median delay from first episode to correct diagnosis is years. The monoamine and kindling accounts are descriptive rather than demonstrated. Lithium's mechanism, after seventy years of use, is not established; candidate pathways remain candidates. Not known: what determines episode timing; why lithium works in some and not others; whether bipolar II is the same condition as bipolar I.

Cure status. CONTROLLABLE. Individual episodes remit; the disorder does not. Without maintenance treatment, recurrence within two years of an episode is the usual outcome, roughly 50 per cent within a year†. Maintenance lithium roughly halves relapse risk against placebo. A minority have long remissions on no treatment, and this cannot be predicted in advance. Abrupt lithium discontinuation carries a relapse rate above the untreated baseline in the following months.

Prevention. No intervention has been shown to prevent first onset. Maintenance pharmacotherapy for relapse: STRONG. Sleep and circadian regularity: interpersonal and social rhythm therapy reduces recurrence in randomised trials, MODERATE. Avoiding antidepressant monotherapy in diagnosed bipolar depression reduces switch to mania, with contested effect size, CONTESTED. Psychoeducation for patients and families reduces relapse and hospitalisation in randomised trials, MODERATE.

Treatment. *Lithium* is the reference maintenance agent and the only psychiatric drug with reasonably consistent evidence of an anti-suicide effect. Against placebo or no lithium, the pooled risk ratio for suicide and suicide attempt favoured lithium at 4.22 (95 per cent CI 2.91 to 6.10) across 27 studies; against anticonvulsants 2.42 (1.15 to 5.10) across 8 studies; but in the restricted set of 6 randomised placebo-controlled trials 1.91 (0.89 to 4.08), not statistically significant (meta-analysis in the *International Journal of Bipolar Disorders*, 2024). The observational signal is strong and the randomised signal underpowered.

Lithium is EML-listed and off-patent, and costs a few tens of US dollars a patient-year at most, plus the recurring cost of serum level, renal and thyroid monitoring, which usually exceeds the drug cost. Harms: narrow therapeutic index, renal impairment on long exposure, hypothyroidism, teratogenicity.

Valproate is effective for acute mania and maintenance, EML-listed, off-patent, and costs a few tens of US dollars a patient-year at most. It is a major teratogen, contraindicated in pregnancy and heavily restricted in women of childbearing age in many jurisdictions. *Second-generation antipsychotics* — quetiapine, olanzapine, risperidone, aripiprazole, lurasidone — are effective for acute mania, and some for bipolar depression and maintenance; risperidone and olanzapine are EML-listed, quetiapine and aripiprazole are not, and generics cost from tens to low hundreds of US dollars a patient-year. Harms: weight gain, metabolic syndrome, movement disorders. *Lamotrigine* prevents depressive rather than manic relapse, is EML-listed for epilepsy rather than for this indication, is off-patent, and costs tens of US dollars a patient-year; it requires slow titration because of serious rash. *Electroconvulsive therapy* is effective in severe or treatment-resistant mania and in bipolar depression. *Psychological treatments* — psychoeducation, family-focused therapy, interpersonal and social rhythm therapy, CBT — all reduce relapse as adjuncts, and none is a substitute for pharmacological maintenance in bipolar I.

Simple means. Fixed sleep and wake times: the single most useful non-drug measure, since sleep loss is an established manic precipitant and social rhythm stabilisation reduces recurrence in randomised trials. Darkness or blue-light reduction in the evening: small randomised trials of dark therapy and blue-blocking glasses show reduced manic symptoms, with thin but directionally consistent evidence. Regular mealtimes and activity scheduling: components of social rhythm therapy, not separately quantified. Early-warning-sign monitoring with a written plan: reduces manic relapse and hospitalisation in randomised trials, and is one of the cheapest effective interventions in this chapter. Alcohol avoidance: comorbid alcohol use disorder is frequent and worsens course, and abstinence is associated with better outcome on observational evidence.

Gaps. The lithium anti-suicide effect rests mainly on observational data and the randomised evidence is underpowered and not significant. Whether the bipolar spectrum beyond type I is a distinct disorder or a boundary artefact is unresolved, and it alters prevalence estimates by a factor of two. Maintenance trial designs that enrich for lithium responders overestimate real-world efficacy, by a disputed margin. There is almost no treatment-trial data from low-income settings, where most of the 36 million live.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 25 years († onset about age 25); time depth 51.80. One untreated course: about 4 months († an episode lasts 3–6 months); depth 47.86.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Generalised anxiety disorder

What it is. Diffuse, persistent worry across several domains of life, with restlessness, muscle tension, poor concentration and disturbed sleep, interfering with functioning. It is typically chronic with fluctuating severity.

Measured. Anxiety disorders as a class affect about 470 million people worldwide, including 146 million children and adolescents, and are the largest single mental-disorder class (WHO mental disorders fact sheet, 11 September 2026, GBD 2023 data). They rank third among all causes of years lived with disability at 55.4 million YLDs (95 per cent UI 36.4 to 81.3) in 2023; the count rose 63 per cent over the preceding period (GBD 2023 release, not the capstone). Twelve-month prevalence for generalised anxiety disorder specifically is roughly 2 to 3 per cent. Women are affected roughly 1.7 to 2 times as often as men. Onset has the broadest range of the anxiety disorders and can begin late in life. There is no direct mortality coding; excess mortality is present and mediated through comorbid conditions and cardiovascular disease. The majority of people with an anxiety disorder receive no treatment, and in low-income countries the untreated proportion exceeds 85 per cent.

Where it starts. Heritability from twin studies is roughly 30 to 40 per cent, lower than for bipolar disorder or schizophrenia†. Childhood adversity and parental over-control carry odds ratios of roughly 1.5 to 2.5†. Female sex, 1.7 to 2 times†. Comorbidity with depression is the rule rather than the exception; roughly half of people with one have the other over a lifetime. The amygdala-centred fear-circuit account is supported by group-level imaging and produces no individual-level test and no treatment selection. The GABA-deficit account, inferred by analogy with benzodiazepine action, is not established as a cause. Not known: why the same temperament produces disorder in some people and not others; whether the current diagnostic boundaries track anything natural.

Cure status. CONTROLLABLE. The untreated course is usually chronic with fluctuating severity. Cognitive behavioural therapy with exposure gives response rates in the range of 50 to 65 per cent across the anxiety disorders, with gains largely maintained at one and two years — the best persistence-after-discontinuation evidence in this group. Relapse after antidepressant discontinuation is common, roughly a third to a half within a year.

Prevention. Treating subthreshold anxiety reduces progression to full disorder in randomised trials, MODERATE. School-based CBT-informed programmes have small effects on symptoms and weaker, inconsistent effects on incidence, WEAK. Physical activity: prospective association with lower incidence, dose-response present, limited randomised prevention evidence, MODERATE. Reducing caffeine and stopping smoking: plausible and supported by provocation studies, with no prevention trials using incidence endpoints, WEAK.

Treatment. *Cognitive behavioural therapy with exposure* is first-line on the evidence. Effect sizes against waitlist are large, often above SMD 0.8, and moderate against active control†. Durability after discontinuation exceeds that of drugs. Internet-delivered CBT achieves comparable effect sizes to face-to-face delivery in randomised comparisons, at a fraction of the therapist time. *SSRIs and SNRIs* are effective, SMD against placebo roughly 0.3 to 0.5†; fluoxetine is EML-listed† and off-patent at a few US dollars a patient-year, and sertraline, escitalopram, paroxetine and venlafaxine are not EML-listed, all off-patent, at up to a few tens of US dollars a patient-year.

Combined CBT and medication is modestly better than either alone in the acute phase, and the advantage narrows at follow-up as drug-treated patients relapse. *Pregabalin* is effective in generalised anxiety disorder, with recognised misuse potential, not EML-listed, off-patent, at tens to low hundreds of US dollars a patient-year. *Benzodiazepines* are rapid and effective acutely; tolerance, dependence and withdrawal make them unsuitable for long-term use, and they impair the learning on which exposure therapy depends. Diazepam is EML-listed and off-patent at a few US dollars a patient-year. *Exercise* reduces anxiety symptoms with moderate effect sizes in randomised trials, on a smaller trial base than for depression.

Simple means. Graded self-directed exposure: the active ingredient of the most effective treatment, deliverable from a written protocol with minimal supervision, and guided self-help CBT achieves a substantial fraction of full-therapist effect sizes. Exercise, at moderate effect sizes and no supply chain. Regular sleep: insomnia and anxiety are bidirectionally linked, and treating insomnia reduces anxiety symptoms in randomised trials. Caffeine reduction: supported by provocation studies, with no incidence trials. Social connection.

Gaps. The three main anxiety disorders are usually pooled in epidemiological work, so condition-specific global figures are weak. Internet-delivered CBT trials are dominated by self-selected, educated, high-income samples, and generalisability is unestablished. Benzodiazepine harm estimates in long-term use come almost entirely from observational data. Whether prevention programmes reduce lifetime incidence or merely delay onset is not resolved by existing follow-up lengths.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number ([B] usually chronic).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Panic disorder

What it is. Recurrent unexpected episodes of intense fear with abrupt physical symptoms — palpitations, breathlessness, chest discomfort, dizziness — together with persistent concern about further episodes and avoidance of situations associated with them.

Measured. Twelve-month prevalence is roughly 1 to 2 per cent†. Women roughly 1.7 to 2 times men†. Onset is typically in the twenties. Class figures for anxiety disorders are in the generalised anxiety entry above: 470 million people and 55.4 million YLDs in 2023. Panic disorder is not separately counted in those figures.

Where it starts. Heritability roughly 30 to 40 per cent†. Childhood adversity is associated, odds ratios roughly 1.5 to 2.5†. Smoking and caffeine are both associated with panic symptoms, and caffeine can provoke panic in susceptible people under experimental conditions. Hyperventilation and carbon-dioxide-sensitivity findings are among the more robust experimental results in psychiatry, and their causal status is unsettled. Not known: why the three anxiety disorders separate as they do; what initiates an individual attack.

Cure status. CONTROLLABLE. Panic disorder has the best outcomes of the anxiety disorders; spontaneous remission rates over a decade are higher than for social anxiety disorder. Relapse after antidepressant discontinuation is common.

Prevention. Treating subthreshold anxiety reduces progression, MODERATE. Reducing caffeine and stopping smoking, WEAK, on provocation-study grounds without incidence trials. Physical activity, MODERATE.

Treatment. Cognitive behavioural therapy with interoceptive exposure is first-line, with the durability advantage described in the generalised anxiety entry. SSRIs and SNRIs are effective, SMD roughly 0.3 to 0.5†; fluoxetine is EML-listed†, off-patent, a few US dollars a patient-year. Benzodiazepines act fast and are unsuitable for long-term use, and they impair exposure learning. Exercise has moderate effect sizes on anxiety symptoms.

Simple means. Graded self-directed interoceptive and situational exposure from a written protocol. Controlled slow breathing reduces panic symptom frequency in trials, though its status as a coping aid rather than a subtle avoidance behaviour is debated. Caffeine reduction. Exercise. Regular sleep.

Gaps. Condition-specific global burden figures do not exist, because the class is pooled. Whether breathing-control techniques help or maintain the disorder is a real and unresolved disagreement. Long-term follow-up beyond two years is sparse.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 24 years († onset about age 24); time depth 51.76. One untreated course: about 10 minutes († an attack lasts about 10 minutes); depth 38.98.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Social anxiety disorder

What it is. Marked fear of scrutiny in social situations, with avoidance of them, persisting and interfering with education, work and relationships.

Measured. Twelve-month prevalence is roughly 2 to 7 per cent depending on instrument and threshold — the widest spread of the three main anxiety disorders. Onset is the earliest of the three, median early-to-mid adolescence. Women roughly 1.7 to 2 times men†. Class figures are in the generalised anxiety entry.

Where it starts. Heritability roughly 30 to 40 per cent†. Behavioural inhibition in early childhood is the best-established temperamental antecedent, particularly for this disorder, raising risk several-fold, and most inhibited children do not develop a disorder. Childhood adversity and parental over-control are associated. Not known: why the same temperament produces disorder in some people and not others.

Cure status. CONTROLLABLE. Social anxiety disorder is the most persistent of the three, with low spontaneous remission over a decade. Exposure-based therapy produces response in roughly half to two thirds of those treated, with gains largely maintained at one and two years.

Prevention. Early intervention for behaviourally inhibited preschool children, through parent-focused programmes, reduces incident anxiety disorder in randomised trials with multi-year follow-up, MODERATE. Treating subthreshold anxiety, MODERATE. School-based programmes, WEAK. Physical activity, MODERATE.

Treatment. Cognitive behavioural therapy with exposure, first-line, with large effects against waitlist and durability exceeding drugs. SSRIs and SNRIs, SMD roughly 0.3 to 0.5†, with fluoxetine EML-listed† and off-patent at a few US dollars a patient-year. Beta-blockers are useful for the physical symptoms of discrete performance situations only and have no effect on the disorder; propranolol is EML-listed, off-patent, and costs a few US dollars a patient-year. Combined CBT and medication is modestly better acutely, with the advantage narrowing at follow-up.

Simple means. Structured repeated social contact is exposure: for this disorder the mechanism of the treatment and the simple means coincide. Graded self-directed exposure from a written protocol, with guided self-help achieving a substantial fraction of therapist-delivered effect. Exercise. Regular sleep.

Gaps. The prevalence range of 2 to 7 per cent is an instrument artefact as much as a finding, and no agreed threshold exists. Trials are dominated by educated high-income samples. Whether early intervention in inhibited children prevents or delays onset is unresolved.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 13 years († onset about age 13); time depth 51.21. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Obsessive-compulsive disorder

What it is. Recurrent intrusive thoughts, images or urges that cause distress, together with repetitive acts performed to reduce that distress. The person usually recognises the thoughts as excessive. It is typically chronic.

Measured. Lifetime prevalence is roughly 1 to 2 per cent and twelve-month prevalence roughly 1 per cent†. The sex ratio is close to 1 to 1 in adults, with male predominance in childhood-onset cases†. Onset is bimodal, with a childhood peak around age 10 and an early-adult peak around age 20; onset after 35 is uncommon†. GBD treats obsessive-compulsive disorder inside the anxiety-and-related group in some cycles and separately in others, so stand-alone global DALY figures are not stable across releases. All-cause and suicide mortality are elevated in national register studies. Prevalence estimates are notably consistent across cultures, more so than for most conditions in this chapter; the content of obsessions varies with culture and the frequency does not. The median delay from onset to adequate treatment is measured in years, often more than a decade.

Where it starts. Heritability from twin studies is roughly 40 to 50 per cent, higher in childhood-onset cases, and first-degree relatives carry roughly 4 to 5 times the risk†. The cortico-striato-thalamo-cortical circuit finding is among the more replicated imaging results in psychiatry, and it is supported by the therapeutic effect of surgically or electrically interrupting that circuit in refractory cases. That is stronger mechanistic evidence than exists for depression or anxiety, and it remains circuit-level rather than individual-level, and gives no diagnostic test. The serotonergic account rests on the selective efficacy of serotonergic drugs, and selective drug response is weak evidence of a cause. Post-streptococcal autoimmune obsessive-compulsive disorder, proposed as PANDAS, has been extensively studied and remains contested: prospective cohort studies have not consistently confirmed the temporal relationship. It is unresolved rather than established. Not known: why onset is bimodal; why obsessions take the content they do; why response to serotonergic drugs needs higher doses and longer latency than in depression.

Cure status. CONTROLLABLE. Untreated, the usual course is chronic and fluctuating; full spontaneous remission is uncommon in adults and more frequent in childhood-onset cases. Exposure and response prevention gives response in roughly 60 to 70 per cent of those who complete treatment, with gains maintained at follow-up better than drug gains. Relapse on SSRI discontinuation is high, in the range 25 to 40 per cent within a year†. A substantial minority, roughly 10 per cent, remains severely affected despite all available treatment†.

Prevention. No intervention has been shown to prevent onset. Continued exposure and response prevention practice as secondary prevention of relapse, MODERATE. Antibiotic treatment of streptococcal infection as prevention rests on the contested PANDAS model, CONTESTED.

Treatment. *Exposure and response prevention* has the strongest evidence of any treatment for this condition, with large effect sizes against control and superiority to medication in several head-to-head trials, and better durability after discontinuation. *SSRIs at higher doses than for depression, for longer* are effective, SMD against placebo roughly 0.4, with response taking 8 to 12 weeks†; fluoxetine is EML-listed† and off-patent at a few US dollars a patient-year at the doses used here. *Clomipramine*, the historical reference drug, has an effect size at least equal to the SSRIs, is EML-listed and off-patent at a few tens of US dollars a patient-year, and has more adverse effects.

Exposure and response prevention with an SSRI is better than the SSRI alone, and the added value over exposure alone is smaller. *Antipsychotic augmentation* with risperidone or aripiprazole in SSRI non-responders produces response in roughly one in three; risperidone is EML-listed and off-patent at tens of US dollars a patient-year. *Deep brain stimulation and ablative surgery* in severe refractory cases give response in roughly 50 to 60 per cent in small series†, with no large randomised trials, at costs in the tens of thousands of US dollars, and irreversibly in the ablative case.

Simple means. Self-directed exposure and response prevention from a manual: the active ingredient is behavioural, needs no equipment, and guided self-help versions achieve meaningful effect sizes. This is the principal simple means here. Exercise has small adjunctive trials only and is not comparable to medication for this condition. Circadian abnormalities are reported and no intervention trial uses obsessive-compulsive endpoints.

Gaps. GBD's handling of the condition has changed between cycles, so global burden figures are not comparable over time. Exposure and response prevention trials have high refusal and dropout rates, and intention-to-treat analyses give substantially lower response figures than completer analyses; sources quoting the higher number rarely say which they used. PANDAS is a genuine scientific disagreement, not a settled question in either direction. Outcome data beyond five years are sparse.

> **Depth.** Starts in: the cortico-striato-thalamic circuit. Size: 10 cm†; depth +13.29. First complaint: about 19 years († onset about age 19); time depth 51.55. One untreated course: no number ([B] usually chronic).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Post-traumatic stress disorder

What it is. A persistent reaction to an extremely threatening event: re-experiencing the event in the present, avoidance of reminders, and a sense of current threat. Symptoms must persist for weeks and impair functioning.

Measured. WHO's mental disorders fact sheet gives no prevalence figure for post-traumatic stress disorder (checked October 2026). Lifetime prevalence in general-population surveys is roughly 4 to 8 per cent, with wide variation by instrument and by population exposure. The epidemiologically decisive figure is conditional risk after a traumatic event: most people exposed to a traumatic event do not develop the disorder. Conditional rates range from a few per cent after most events to roughly 30 to 50 per cent after sexual assault, torture or captivity. Women are affected roughly twice as often as men, partly but not wholly explained by differential exposure to high-conditional-risk events. In conflict-affected populations WHO's

pooled estimate for any mental disorder is about 22 per cent, of which this condition is a substantial share†. Absolute burden tracks conflict and displacement, both of which rose through the 2020s.

Where it starts. Exposure to a qualifying event is necessary and far from sufficient, which is the single most important epidemiological fact about the condition. Heritability from twin studies is roughly 30 to 40 per cent, measured as liability given exposure†. Event characteristics are the strongest predictors: interpersonal violence and sustained or repeated events carry far higher conditional risk than single impersonal events. Prior psychiatric history, prior trauma, low social support after the event and peritraumatic dissociation are all associated, odds ratios roughly 1.5 to 3†. Lower post-event social support is among the more consistent modifiable predictors.

The low-cortisol and HPA-axis accounts have not replicated consistently; meta-analyses find no reliable group difference in basal cortisol. Treat as not established. Hippocampal volume reduction is observed and its direction of causation is unresolved, with twin studies suggesting smaller volume may be a pre-existing risk marker rather than a consequence. Memory-reconsolidation accounts motivate treatment research and are not demonstrated in humans at the level claimed. Not known: why the same event produces the disorder in one exposed person and not another; whether early intervention can alter trajectory for most people.

Cure status. Treated with trauma-focused psychotherapy: CURABLE in roughly 50 to 70 per cent, who lose the diagnosis with gains maintained at follow-up†. Chronic course, particularly after repeated interpersonal trauma and in the ICD-11 complex presentation: CONTROLLABLE. This is the most favourable cure status in Chapter 06. Natural recovery is the norm: a large majority of people with early post-traumatic symptoms recover without treatment within months.

Prevention. Preventing the events — violence reduction, road safety, conflict prevention, occupational safety — is the only intervention that addresses incidence at population level, and the effect follows directly from exposure reduction: STRONG in logic, measured for the exposures and not for post-traumatic stress endpoints. Psychological debriefing immediately after an event does not prevent the disorder and some trials show harm; WHO and NICE advise against routine use. CONTESTED, with the weight of evidence against, and this is an important negative result. Brief trauma-focused cognitive behavioural therapy for people with early symptoms, as distinct from universal debriefing, reduces progression in randomised trials, MODERATE. Post-event social support is consistently associated and interventions that build it have small measured effects, WEAK. Hydrocortisone and propranolol as secondary pharmacological prevention: small trials, inconsistent results, CONTESTED.

Treatment. *Trauma-focused psychotherapies* are first-line and clearly superior to drugs. Prolonged exposure, cognitive processing therapy and eye movement desensitisation and reprocessing all show large effect sizes against control, often above SMD 1.0 against waitlist, and do not differ reliably from one another in head-to-head trials. *SSRIs and SNRIs* are effective with notably smaller effect sizes than in depression, SMD against placebo roughly 0.2 to 0.3†; fluoxetine is EML-listed† and off-patent at a few US dollars a patient-year, and sertraline, paroxetine and venlafaxine are not EML-listed, off-patent, at up to a few tens of US dollars a patient-year.

Prazosin for trauma-related nightmares showed benefit in earlier trials and was not confirmed in the largest subsequent trial: CONTESTED; not EML-listed, off-patent, tens of US dollars a patient-year. *Benzodiazepines* are ineffective for this condition and associated with worse outcomes, and guidelines advise against them. *Task-shifted brief psychological interventions delivered by non-specialists*, such as WHO's Problem Management Plus, show effects in randomised trials in conflict-affected and low-resource settings: the most important treatment finding for the populations carrying most of the burden. *MDMA-assisted psychotherapy* produced large effect sizes in sponsor-run phase 3 trials, and US regulatory approval was not granted in 2024, with the advisory committee and the regulator citing functional unblinding, trial-conduct problems and inadequate safety data. Report as unapproved and unresolved rather than as an available treatment.

Simple means. Social connection and restored social role are among the most consistent modifiable predictors of recovery; reinstating ordinary social and occupational function after an event is associated with recovery, and the direction of causation is not fully separable. Sleep restoration: insomnia is near-universal here and treating it improves symptoms in randomised trials. Exercise: small-to-moderate

adjunctive effects. Written narrative exposure, self-delivered: narrative exposure therapy was designed for low-resource and refugee settings, requires paper only, and has randomised support. The strongest simple-means finding here is negative: do not conduct single-session debriefing of unselected event survivors.

Gaps. There is no GBD or WHO fact-sheet prevalence figure, so global burden must be assembled from heterogeneous surveys. Conditional-risk estimates vary several-fold between studies using different instruments. ICD-11 introduced complex post-traumatic stress disorder as a separate diagnosis; its epidemiology is barely measured and almost no treatment trials used ICD-11 criteria. Psychotherapy trials are dominated by military and high-income civilian samples, and the largest affected populations are the least studied. The distinctive component of eye movement desensitisation and reprocessing has never been shown to add to the exposure component, and sources disagree on whether that matters for practice.

> **Depth.** Starts in: an overwhelming event. No size is given. First complaint: about 3.6 weeks ([B] complaints last weeks; † 1 week–3 months); time depth 46.43. One untreated course: no number († months to years).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Schizophrenia and other primary psychotic disorders

What it is. Disturbance of thought, perception and self-experience: delusions, hallucinations, disorganised thinking, and a reduction in motivation, expression and social engagement. Onset is usually in late adolescence or the twenties. Course varies widely between individuals.

Measured. Global prevalence is 0.29 per cent, about 1 in 300 people, about 27 million people worldwide; among adults aged 20 and over it is 0.49 per cent, about 1 in 206 (WHO schizophrenia fact sheet, 11 September 2026, GBD 2023 data). Schizophrenia ranks sixteenth among all causes of years lived with disability at 17.0 million YLDs (95 per cent UI 12.4 to 21.4) in 2023. People with schizophrenia die about nine years earlier than the general population (WHO, citing a 2021 study). The standardised mortality ratio is roughly 2 to 3, and most excess deaths are cardiovascular and respiratory rather than suicide, though suicide risk is substantially elevated.

About half of people in mental hospitals carry a schizophrenia diagnosis (WHO). More than two in three people with psychosis worldwide do not receive specialist mental health care; only about 29 per cent do (WHO schizophrenia fact sheet). WHO's mental disorders fact sheet of the same date puts the figure receiving formal mental health care at 40 per cent for psychosis; the two WHO pages do not agree, and both are printed. At least one in three people with schizophrenia can achieve complete symptom remission (WHO). Onset is earlier in men by roughly three to five years.

Incidence varies several-fold between places, higher in urban areas and in some migrant groups — one of the more robust and least explained findings in psychiatric epidemiology. Age-standardised rates are broadly stable.

Where it starts. Heritability from twin studies is roughly 80 per cent, the highest of the common psychiatric disorders alongside bipolar disorder. SNP-based heritability is roughly 24 per cent, and the largest genome-wide association study identified hundreds of loci, almost all of very small effect. Rare copy-number variants such as the 22q11.2 deletion carry odds ratios in the tens and account for a small fraction of cases. Cannabis use carries an odds ratio of roughly 2 for any use and roughly 3 to 5 for heavy or high-potency use, with dose-response present and the association surviving adjustment; reverse causation and confounding cannot be fully excluded, and this is the most consequential modifiable association. Migration and minority status: incidence 2 to 3 times higher in some migrant groups, not explained by selective migration or by genetics. Urban birth and upbringing, roughly 2 times†. Childhood adversity, odds ratio roughly 2 to 3†. Obstetric complications and paternal age have small effects.

The dopamine hypothesis is the most robust mechanistic claim in psychiatry and is still only partial. Presynaptic striatal dopamine synthesis capacity is elevated in psychosis, replicated across imaging studies, and all effective antipsychotics are D2 antagonists or partial agonists. Dopamine elevation does not explain

negative symptoms or cognitive impairment, is not present in all patients, and is not specific to schizophrenia. Glutamatergic accounts are supported by the psychotomimetic effect of NMDA antagonists, and no glutamatergic drug has shown reproducible efficacy, with several high-profile phase 3 failures. The neurodevelopmental account is well supported at population level, since premorbid motor and cognitive differences precede onset by years, and it gives no individual-level prediction. Not known: what determines the timing of onset; why incidence varies geographically; why negative and cognitive symptoms respond to nothing available; whether schizophrenia names one condition.

Cure status. CONTROLLABLE. Maintenance antipsychotic treatment against placebo at seven to twelve months, across 65 randomised trials (Leucht and colleagues, *Lancet*, 2012): relapse 27 per cent on drug against 64 per cent on placebo, risk ratio 0.40 (95 per cent CI 0.33 to 0.49), number needed to benefit 3 (2 to 3); readmission 10 per cent against 26 per cent, risk ratio 0.38 (0.27 to 0.55), number needed to benefit 5 (4 to 9). Those readmission figures are printed exactly as the Lancet paper publishes them, and they are not altered here. A reader who computes the arm difference, 16 percentage points, and takes its reciprocal gets 6.25, not 5.

The published 5 derives from the pooled risk ratio across the trials, not from the difference between the two pooled arm percentages, and its confidence interval is meta-analytic and likewise not derivable from 10 and 26 per cent. The 2012 analysis is superseded: the 2020 Cochrane update, across 21 randomised trials and 3,558 participants, gives hospitalisation 7 per cent against 18 per cent, risk ratio 0.43, number needed to treat for an additional beneficial outcome 8. **Eight is the figure to quote as current.** Depot formulations outperformed oral in the 2012 analysis, risk ratio 0.31 (0.21 to 0.41) against 0.46 (0.37 to 0.57), p=0.03 for the difference.

Harms in the same analysis: weight gain 10 per cent against 6 per cent; movement disorders 16 per cent against 9 per cent, risk ratio 1.55 (1.25 to 1.93); sedation 13 per cent against 9 per cent, risk ratio 1.50 (1.22 to 1.84)†. Long-term outcome heterogeneity is real: at least one in three reach complete symptom remission, and a minority sustain remission off medication, and which individuals can do so is not predictable in advance. Roughly 20 to 30 per cent do not respond adequately to two sequential antipsychotics†.

Prevention. Cannabis reduction, particularly of high-potency cannabis in adolescence: the largest modifiable population attributable fraction available, with estimates ranging from roughly 8 to 24 per cent† depending on potency assumptions and setting, MODERATE — strong and dose-responsive association, causal inference incomplete. Early intervention services for first-episode psychosis reduce relapse, hospitalisation and disengagement over two to five years against standard care in randomised trials, with benefits attenuating when the specialist service ends: STRONG for outcome, not for incidence.

Treatment of clinical high-risk states reduces transition to psychosis in the short term, with the longer-term effect and the high false-positive rate of the risk designation unresolved, CONTESTED. Reducing childhood adversity and improving conditions for migrant and minority populations: large attributable fractions on observational grounds, no intervention trials with incidence endpoints, WEAK on direct evidence. Managing cardiometabolic risk in people already diagnosed — smoking cessation, metabolic monitoring, statin and antihypertensive treatment: STRONG for the mortality outcome, and this is where the nine-year mortality gap is addressable.

Treatment. *Antipsychotics, acute and maintenance*, with the maintenance figures above. Acute effect sizes against placebo are SMD roughly 0.4 to 0.5 on total symptoms, and differences between agents are small except for clozapine. Haloperidol, oral and injectable, is EML-listed and off-patent at a few tens of US dollars a patient-year at most; chlorpromazine the same; risperidone and olanzapine EML-listed and off-patent at tens of US dollars a patient-year. Paliperidone and risperidone long-acting injectables are EML-listed, added in the 2023 revision, with risperidone's long-acting form off-patent, and they cost hundreds to low thousands of US dollars a patient-year — an order of magnitude above oral.

Clozapine is the only agent with established superiority in treatment-resistant schizophrenia, with response in roughly 30 to 60 per cent of those who failed other drugs†, and the only antipsychotic with evidence of reduced all-cause mortality in observational cohorts. It is EML-listed and off-patent, costing tens to low hundreds of US dollars a patient-year, plus mandatory haematological monitoring that usually costs more

than the drug. Harms: agranulocytosis, roughly 0.8 per cent cumulative†; myocarditis; seizures; severe constipation; substantial weight gain.

Long-acting injectable formulations reduce relapse relative to oral, largely by removing covert non-adherence. *Family interventions* reduce relapse by roughly 20 to 50 per cent relative to standard care in randomised trials — one of the largest non-drug effects in this chapter, deliverable by trained non-specialists. *CBT for psychosis* has small effects on positive symptoms against active controls, and effect sizes shrink with better blinding and better control conditions; the literature is genuinely contested, with meta-analyses by different groups reaching different conclusions on whether the effect survives adjustment for bias.

Supported employment, in the individual placement and support model, substantially raises competitive employment rates relative to standard vocational rehabilitation, and is one of the best-replicated functional outcomes. *Metabolic and cardiovascular care* addresses the nine-year mortality gap, and metformin reduces antipsychotic-associated weight gain in randomised trials; metformin is EML-listed as a selected medicine for type 2 diabetes, confirmed against the 24th List, off-patent, at a few US dollars a patient-year. *Electroconvulsive therapy* is an adjunct in clozapine-resistant cases, on evidence from small randomised trials.

Simple means. Family involvement, with reduced household criticism and over-involvement: family interventions produce relapse reductions comparable in magnitude to some pharmacological effects and need only trained human time. This is the strongest simple-means finding for this condition, and it is an addition to maintenance medication, not a replacement for it. Avoiding cannabis, especially high-potency products: the clearest individual-level preventive action available. Smoking cessation: addresses the dominant contributor to the mortality gap, and smoking prevalence in this population is multiples of the general rate. Exercise improves cardiometabolic risk markers and has small effects on negative symptoms and cognition in randomised trials. Sleep regularisation: sleep disturbance precedes and accompanies relapse, and CBT for insomnia reduced psychotic experiences in randomised trials in this population. Social and occupational role: supported employment outperforms train-then-place models, and the intervention is a person rather than a product.

Gaps. The geographical variation in incidence is robust and unexplained — a major open question, not a measurement artefact. Meta-analyses of CBT for psychosis disagree, and the disagreement turns on methodological choices rather than new data. Long-term antipsychotic outcomes beyond two to three years rest largely on observational data and on discontinuation designs that confound withdrawal effects with relapse. Whether a subgroup can sustain remission without maintenance medication is clinically crucial and not answerable from existing trials. The nine-year mortality gap is well measured and poorly addressed, and almost no trials target it directly as a primary endpoint. WHO's own two fact sheets give 29 per cent and 40 per cent for specialist and formal mental health care in psychosis; the discrepancy is unresolved.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 22 years ([B] late adolescence or the twenties); time depth 51.68. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Alcohol use disorder

What it is. A pattern of alcohol use with impaired control, priority given to drinking over other activities, and continued use despite harm. Physiological dependence with tolerance and withdrawal may be present.

Measured. About 400 million people aged 15 and over have an alcohol use disorder, 7 per cent of that age group; 209 million are alcohol-dependent, 3.7 per cent of the adult population (WHO alcohol fact sheet, 28 June 2024, 2019 data). Alcohol-attributable deaths were 2.6 million worldwide in 2019 — 2 million men, 0.6 million women — of which 1.6 million from noncommunicable diseases, 700,000 from injuries and

300,000 from communicable diseases. Cardiovascular deaths 474,000; cancer deaths 401,000, being 4.4 per cent of all cancers diagnosed globally.

Road deaths 298,000 alcohol-related, of which 156,000 were caused by someone else's drinking. Thirteen per cent of alcohol-attributable deaths occur in people aged 20 to 39. Death rates per 100,000 are highest in the WHO European Region at 52.9 and the African Region at 52.2. Alcohol accounts for 6.7 per cent of male deaths and 2.4 per cent of female deaths. Per-capita consumption is 8.2 litres of pure alcohol for men and 2.2 for women, and 52 per cent of men and 35 per cent of women drank in the past twelve months. Alcohol-attributable deaths per 100,000 fell 20.2 per cent globally between 2010 and 2019.

Treatment contact ranges from under 1 per cent to at most 14 per cent of people with an alcohol use disorder, depending on country. Alcohol has a causal role in more than 200 conditions, of which only 31 can currently be quantified for burden. Alcohol use disorders rank twenty-third among all causes of years lived with disability at 11.6 million YLDs (95 per cent UI 8.08 to 16.5) in 2023. The WHO alcohol fact sheet gives no DALY figure at all.

Where it starts. Heritability is roughly 50 per cent†. The best-characterised genetic effects are protective: *ALDH2* and *ADH1B* variants that make drinking aversive sharply reduce alcohol use disorder risk and alcohol-related cancer in carriers. These are among the few large single-gene effects anywhere in this chapter, and through Mendelian randomisation they support a causal role for alcohol itself. Price and availability are the strongest population-level determinants: price elasticity of alcohol demand is consistently around −0.5 overall, so a 10 per cent real price rise reduces consumption by roughly 5 per cent, and heavy drinkers are less price-responsive than average but not unresponsive. Early age of first use is associated with later disorder and confounded by family factors. Male sex, roughly 2 to 3 times for disorder†. Comorbid mental disorder is strongly associated in both directions.

Dopaminergic reward and opioid-system involvement are supported by the efficacy of naltrexone, and the account is incomplete. No biomarker identifies who will develop dependence. Not known: why some heavy drinkers develop dependence and others do not; whether any moderate-drinking cardiovascular benefit exists at all. Mendelian randomisation studies find no protective effect, contradicting decades of observational literature, so the J-curve is not supported.

Cure status. CONTROLLABLE. Longitudinal cohorts show that a large fraction of people who met criteria at one point are in remission years later, many without formal treatment. Relapse within a year of treatment is common, in the range 40 to 60 per cent†. Abstinence and controlled drinking are both achievable outcomes, and the proportion achieving each varies by severity.

Prevention. The population-level alcohol policy evidence is among the strongest in this chapter. Alcohol taxation and minimum unit pricing: STRONG. Scotland's minimum unit price, introduced in 2018, was followed by a 13.4 per cent reduction in alcohol-attributable deaths and a 4.1 per cent reduction in hospitalisations in a controlled interrupted time-series with England as comparator (*Lancet*, 2023). Restricting availability through outlet density and trading hours: STRONG; reduced trading hours produce measurable reductions in nighttime assault, and outlet density correlates with harm. Drink-driving countermeasures — blood-alcohol limits, random breath testing: STRONG, from natural experiments. Marketing restrictions: MODERATE; exposure-to-initiation associations are consistent and natural-experiment evidence is thinner than for price. Price, availability and marketing are WHO's best buys, grouped with drink-driving and brief interventions under SAFER, launched 2018. Brief interventions in primary care: MODERATE, small per-person effect and large reach. School-based education alone: WEAK; knowledge changes and consumption generally does not.

Treatment. *Naltrexone* reduces heavy drinking days, with a number needed to treat of roughly 12 to 20 for return to heavy drinking†; not EML-listed†, off-patent, tens to low hundreds of US dollars a patient-year. *Acamprosate* supports abstinence, number needed to treat roughly 10 to 13 for return to any drinking†; not EML-listed†, off-patent, low hundreds of US dollars a patient-year. *Disulfiram* is effective only under supervised administration; not EML-listed, off-patent, tens of US dollars a patient-year. *Benzodiazepines for managed withdrawal* prevent withdrawal seizures and delirium, and this is the one setting where benzodiazepine use is unambiguously indicated and short; diazepam is EML-listed and off-patent.

Thiamine to prevent Wernicke encephalopathy during withdrawal is EML-listed and off-patent at a few US dollars a course — cheap, and its omission causes permanent neurological damage. The UNICEF indicative price for thiamine was returned at three different values on three different catalogue pages in October 2026, so no single figure is printed. *Psychosocial treatments* — motivational enhancement, CBT, community reinforcement, contingency management, twelve-step facilitation — have modest and broadly similar effect sizes across modalities, and the Cochrane review of Alcoholics Anonymous and twelve-step facilitation found higher continuous abstinence at twelve months than comparison treatments, with lower healthcare costs.

Brief interventions of five to thirty minutes in a general healthcare setting reduce consumption in hazardous and harmful drinkers, with small but reliable effect sizes, roughly 20 to 40 grams a week in meta-analysis†.

Simple means. Removing alcohol from the home and changing routine: the behavioural core of most psychosocial treatment, with no supply chain. Mutual aid groups: free at point of use, available in most countries, with Cochrane-level evidence of effect at twelve months. Exercise and structured daytime activity: adjunctive evidence only. Sleep: insomnia is a major relapse predictor and treating it reduces relapse risk in small randomised trials. At population level the simple means are legislative rather than individual — price, hours, outlet density — and they need no clinical supply chain and have the largest measured effects in this entry.

Gaps. The cardiovascular J-curve is a case where observational and genetic evidence point in opposite directions, and older sources still report protection. Self-reported consumption in surveys accounts for only 40 to 60 per cent of recorded alcohol sales, so all survey-based prevalence figures understate by an unknown margin. Treatment-effect estimates come almost entirely from high-income settings. WHO's alcohol fact sheet reports no DALY figure, so burden comparisons must come from GBD directly.

> **Depth.** Starts in: the ethanol molecule. Size: 0.4 nm†; depth −4.31. First complaint: about 10 years († about 10 years from first use to disorder); time depth 50.97. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Opioid use disorder

What it is. A pattern of opioid use with impaired control, tolerance and withdrawal, and continued use despite harm. Its characteristic acute risk is respiratory depression in overdose.

Measured. About 60 million people used opioids in 2021, and about 296 million people — 5.8 per cent of the global population aged 15 to 64 — used any drug at least once that year (WHO opioid overdose fact sheet, 2021 data from UNODC). About 39.5 million people lived with drug use disorders in 2021, all drugs. Opioid overdose deaths were about 125,000 in 2019, and close to 80 per cent of roughly 600,000 drug-attributable deaths in 2019 were opioid-related, about 25 per cent of those being overdoses. In the United States there were 70,630 drug overdose deaths in 2019, about half involving synthetic opioids, and the synthetic-opioid death rate rose 1,040 per cent from 2013 to 2019. Fewer than 10 per cent of people worldwide who need opioid dependence treatment receive it, and only half of countries provide access to effective treatment. Mortality in untreated opioid dependence is roughly 10 to 15 times the age-matched general population†.

Where it starts. Heritability is roughly 50 per cent†. Prescribing volume is the dominant population-level determinant of the North American epidemic; the geographic and temporal correlation between prescription opioid supply and subsequent disorder and death is among the clearest exposure-outcome relationships in this chapter. The large majority of people prescribed opioids for acute pain do not develop a disorder: the absolute transition rate is low and the exposed population enormous. Prior mental disorder, adverse childhood experiences and economic dislocation are all associated. Supply composition matters more than individual factors for mortality: the arrival of illicitly manufactured fentanyl and its analogues in a drug supply raises overdose death rates sharply and independently of the prevalence of use.

Mu-opioid receptor pharmacology is well characterised, and this is one of the few conditions in this chapter where the molecular target of both the drug of use and the treatment is established. Neuroadaptation in tolerance and withdrawal is demonstrated. Not known: why some individuals transition from use to disorder; how to predict overdose risk at the individual level.

Cure status. CONTROLLABLE, and the pattern is unusually explicit here because mortality in and out of treatment has been directly measured. Santo and colleagues (*JAMA Psychiatry*, 2021; 15 randomised trials and 36 cohort studies, close to 750,000 participants) compared time during opioid agonist treatment with time outside it: all-cause mortality risk ratio 0.47 (95 per cent CI 0.42 to 0.53), methadone 0.47 (0.41 to 0.54), buprenorphine 0.34 (0.26 to 0.45). Drug-related deaths 0.41 (0.33 to 0.52); suicide 0.48 (0.37 to 0.61); cardiovascular 0.69 (0.60 to 0.79); alcohol-related 0.59 (0.49 to 0.72); cancer 0.72 (0.52 to 0.98).

In the first four weeks after treatment cessation the risk ratio against time in treatment was 6.01 (4.32 to 8.36), and thereafter 1.81 (1.50 to 2.18): stopping treatment is the single most dangerous period†. The first four weeks of methadone induction carried 2.01 (1.55 to 5.09), an induction-period risk not present for buprenorphine at 0.58 (0.18 to 1.85)†. During incarceration with treatment, 0.06 (0.01 to 0.46); after release with treatment, 0.09 (0.02 to 0.56)†. Sordo and colleagues (2017) give absolute rates per 1,000 person-years: methadone 11.3 in treatment against 36.1 out, rate ratio 3.20 (2.65 to 3.86); buprenorphine 4.3 against 9.5, rate ratio 2.20 (1.34 to 3.61); overdose, methadone 2.6 against 12.7, rate ratio 4.80 (2.90 to 7.96), buprenorphine 1.4 against 4.6. Retention in treatment, not abstinence, is the outcome that tracks survival.

Prevention. Prescribing control through guidelines, monitoring programmes and formulation change reduces prescription volume; the effect on overdose mortality is CONTESTED, because abrupt supply restriction without treatment expansion has been followed by substitution to illicit supply and rising deaths in several jurisdictions. Prescribing reduction without treatment expansion is not demonstrably protective. Take-home naloxone distribution: MODERATE. The European Union Drugs Agency rates it beneficial, and an interrupted time-series of 2,912 people within a 2015 review of 21 studies found adjusted relative risk 0.54 (95 per cent CI 0.39 to 0.76) for overdose mortality where education and training were combined with take-home naloxone.

WHO's Stop Overdose Safely project in 2019 and 2020 distributed about 40,000 kits and trained over 14,000 people, and around 90 per cent of participants who witnessed an overdose reported using naloxone. Opioid agonist treatment availability: STRONG, from the mortality figures above; it is simultaneously the treatment and the most effective mortality-prevention measure. Drug consumption rooms and supervised consumption: no overdose deaths recorded on site across the international literature, with population-level mortality effects measured in a smaller number of jurisdictions, MODERATE.

Treatment continuity at prison release: STRONG, and the risk ratio of 0.09 after release with treatment makes it one of the highest-yield interventions available. Drug checking services: WEAK.

Treatment. *Opioid agonist therapy with methadone or buprenorphine*, with the effect sizes above. Retention is better on methadone in several comparisons; mortality reduction is at least as large on buprenorphine and the induction period is safer. Methadone is EML-listed and off-patent, and costs low hundreds of US dollars a patient-year including dispensing, with supervised dispensing dominating total cost rather than the drug. Buprenorphine, alone and with naloxone, is EML-listed and off-patent, and costs hundreds to low thousands of US dollars a patient-year. No dose is given for any substance of misuse in this chapter. *Naloxone for overdose reversal* is EML-listed and off-patent, costing a few US dollars a dose for the injectable generic and substantially more for nasal spray formulations; it has virtually no effect in people who have not taken opioids (WHO).

Extended-release naltrexone is effective where it can be initiated after full withdrawal, with initiation failure the main limitation; head-to-head trials against buprenorphine show comparable outcomes among those successfully inducted and worse intention-to-treat outcomes. It is not EML-listed and costs thousands of US dollars a patient-year. *Psychosocial treatment added to agonist therapy* adds small or no benefit on retention and use in meta-analysis, since agonist therapy carries most of the effect; contingency management is the exception with measurable added effect. *Heroin-assisted treatment* in agonist-refractory cases reduces illicit use and criminal activity in randomised trials in several European jurisdictions.

Simple means. Naloxone in the hands of peers and family, with brief training: relative risk 0.54 (0.39 to 0.76) for overdose mortality in the cited time-series†. It needs a vial and a few minutes of instruction. Not using alone: the behavioural correlate, with no product required. Continuity of treatment across transitions, at prison release and hospital discharge: the measured effects are among the largest in this chapter and the intervention is organisational rather than technological. Note the asymmetry with depression and insomnia: exercise, light and sleep timing have no comparable evidence here. The effective simple means in opioid use disorder are naloxone availability and treatment continuity.

Gaps. The Santo and Sordo mortality estimates come mainly from observational comparisons of in-treatment and out-of-treatment periods, and confounding by indication cannot be fully excluded, though the magnitude and consistency make an entirely artefactual explanation implausible. There is almost no data from the regions where opioid use is rising fastest outside North America and Western Europe. WHO's overdose death estimate of 125,000 for 2019 and UNODC's drug-attributable total of 600,000 rest on sparse mortality registration in most countries. Whether prescribing restriction reduces or increases total opioid mortality is genuinely disputed, and the answer appears to depend on whether treatment capacity expands alongside.

> **Depth.** Starts in: an opioid molecule. Size: 1 nm†; depth −3.48. First complaint: about 12 months († months to years); time depth 48.87. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Stimulant use disorders

What it is. A pattern of cocaine or amphetamine-type stimulant use with impaired control and continued use despite harm. Withdrawal is marked by low mood, fatigue and craving rather than the physiological syndrome seen with alcohol or opioids.

Measured. Amphetamine-type stimulants are the second most used drug class globally after cannabis, with tens of millions of past-year users (UNODC World Drug Report series). Stimulant use disorders affect roughly 20 to 30 million people globally, within the 39.5 million total for drug use disorders in 2021; class-specific global figures are weaker than for opioids or alcohol. Stimulant-involved deaths have risen sharply where stimulants are co-used with synthetic opioids, and in such settings the majority of stimulant deaths also involve opioids, which complicates attribution. Cardiovascular and cerebrovascular events — myocardial infarction, haemorrhagic and ischaemic stroke, aortic dissection, cardiomyopathy — are the characteristic direct harms, with elevated risk in the hours after use. Methamphetamine-associated psychosis occurs in a substantial minority of heavy users.

Where it starts. Heritability is roughly 50 to 70 per cent for cocaine use disorder, among the higher heritabilities in the substance group. Rapid-onset routes of administration are associated with faster transition to disorder. Availability, price and purity are major population-level determinants. Comorbid attention deficit hyperactivity disorder, mood and anxiety disorders are frequent, with mixed direction of causation.

Dopamine transporter blockade by cocaine and reversal by amphetamines are established pharmacology. Striatal dopamine D2 receptor availability is reduced in chronic users, and whether this precedes or follows use is unsettled, with primate data suggesting it may do both. Not known: why no agonist or antagonist pharmacotherapy has worked, despite the target being better characterised than for most conditions in this chapter.

Cure status. CONTROLLABLE, and more weakly than for opioid or alcohol use disorder, because no medication has established efficacy. Substantial natural remission occurs in cohort studies. Relapse rates after treatment are high, and contingency management produces the largest measured abstinence effects, which attenuate when incentives stop.

Prevention. Supply-side interdiction: large expenditure with no demonstrated sustained effect on price, purity or prevalence, CONTESTED with the weight of evidence against. Brief interventions: weaker evidence than for alcohol, WEAK. School-based programmes: WEAK. Reducing the structural drivers of unemployment and housing instability: associated, not trialled with incidence endpoints, WEAK on direct evidence.

Treatment. *Contingency management*, meaning structured incentives for verified abstinence, is the only intervention with consistently large effects on stimulant abstinence; the effect sizes are among the largest of any psychosocial treatment in addiction medicine, and the magnitude scales with incentive value. It needs no drug supply chain, and it needs money and a verification method. *CBT, the community reinforcement approach and the Matrix model* have modest effects, better than no treatment and inferior to contingency management in head-to-head comparisons. *Pharmacotherapy*: no agent has regulatory approval for stimulant use disorder in any major jurisdiction. Prescription psychostimulant agonist approaches and combined naltrexone with bupropion have shown statistically significant but small effects in individual trials, and none is established. Report as unresolved. *Physical exercise* shows benefit on abstinence and on fitness in small randomised trials in methamphetamine use disorder, on thin evidence.

Simple means. Structured incentives, the core of contingency management, need only money and a verification method. Exercise: small trials, promising, and not comparable to anything pharmacological because the pharmacological comparator does not exist. Sleep restoration and a structured daily routine during early abstinence are clinically standard and poorly quantified. The honest statement for this condition is that the simple means are not weaker than the drugs, because there are no effective drugs.

Gaps. Class-specific global prevalence and mortality figures are the weakest in the substance group. Attribution of deaths in polydrug settings is unresolved. The repeated failure of mechanistically well-motivated pharmacotherapy is a major unexplained finding. Contingency management is well evidenced and barely implemented, and the reasons are regulatory and political rather than scientific.

> **Depth.** Starts in: a stimulant molecule. Size: 1 nm†; depth −3.48. First complaint: about 12 months († months to years); time depth 48.87. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Cannabis use disorder

What it is. A pattern of cannabis use with impaired control and continued use despite harm. A withdrawal syndrome of irritability, sleep disturbance and reduced appetite is recognised in ICD-11.

Measured. Cannabis is the most widely used controlled drug worldwide, with past-year users estimated at around 220 million (UNODC World Drug Report, 2021 to 2023 data). Cannabis use disorder affects roughly 20 to 25 million people globally, within the 39.5 million drug use disorder total for 2021. Transition from use to disorder is roughly 9 per cent lifetime among those who ever use, higher with adolescent onset and daily use. Directly attributable deaths are very low, since cannabis does not cause fatal respiratory depression; the burden is in disorder, psychosis, road injury and cognitive and educational outcomes. Product potency has risen substantially: mean THC concentration in seized herbal cannabis in several countries roughly tripled between the 1990s and the 2010s, which changes the exposure even where prevalence is flat†. Use and disorder prevalence are rising in jurisdictions following legalisation of recreational supply, particularly daily and near-daily use.

Where it starts. Heritability is roughly 50 to 60 per cent†. Adolescent onset is the strongest modifiable risk factor for disorder and for the psychosis association. The psychosis association carries an odds ratio of roughly 2 for any use and roughly 3 to 5 for heavy or high-potency use, dose-responsive; causality is supported by dose-response, temporality and in part by Mendelian randomisation, and weakened by residual confounding and possible reverse causation. Availability and price matter: legalisation in US states and Canada was followed by increased adult use, while effects on adolescent use have been smaller than predicted and in some analyses absent.

CB1 receptor pharmacology is established, and THC is the principal psychoactive constituent; the claimed moderating role of cannabidiol is not established. Endocannabinoid downregulation with chronic use is demonstrated and reverses over weeks of abstinence. Not known: whether the psychosis association is causal, and if so what fraction of cases it explains; whether adolescent cognitive effects fully reverse.

Cure status. CONTROLLABLE. Substantial natural remission occurs and no pharmacotherapy is established. Psychosocial treatment produces reductions in use with small-to-moderate effect sizes, and abstinence rates at follow-up are modest.

Prevention. Potency limits and taxation by THC content are logically targeted at the exposure that carries the risk and are not yet evaluated with health endpoints: WEAK on evidence, not on reasoning. Age restriction and restricting commercial promotion: MODERATE, by analogy with alcohol and tobacco and on early legalisation-jurisdiction data. Delaying age of first use: MODERATE, since the association with disorder and psychosis is strongest for adolescent onset. School-based education alone: WEAK.

Treatment. *CBT with motivational enhancement and contingency management* is the best-supported combination, with small-to-moderate effect sizes on use reduction. *Pharmacotherapy*: none established. N-acetylcysteine showed benefit in adolescents in one trial and failed to replicate in adults; gabapentinoids and cannabinoid agonist substitution have shown small effects in individual trials. Report as unresolved. *Treatment of comorbid insomnia and anxiety*, the commonest reasons given for continued use, is clinically standard and not established as a cannabis outcome.

Simple means. Sleep treatment: sleep disturbance is both a withdrawal symptom and a stated reason for use, and CBT for insomnia in this population has limited but positive trial data. Exercise and structured routine: small trials. Avoidance of high-potency products: an individual-level action with a plausible dose-response basis.

Gaps. Legalisation is a large natural experiment still in progress, and long-term effects on disorder prevalence, psychosis incidence and road injury are not yet measurable. There is no pharmacotherapy and no large trial under way. Potency data come from seizure samples, which are not representative of consumption.

> **Depth.** Starts in: the THC molecule. Size: 1 nm†; depth −3.48. First complaint: about 2 years († about 2 years); time depth 49.50. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Tobacco dependence

What it is. Dependence on nicotine, almost always delivered by combustion. Nicotine produces the dependence; the combustion products produce nearly all the disease.

Measured. There are 1.2 billion tobacco users worldwide, and around 80 per cent live in low- and middle-income countries (WHO tobacco and nicotine fact sheet, 26 June 2026, citing the WHO global report on trends in tobacco use 2000 to 2024). More than 7 million deaths a year are attributed to tobacco use (GBD 2023 data, published 2025). More than 1.6 million additional premature deaths a year come from second-hand smoke. That is over 8.6 million deaths a year in total, which makes tobacco the largest single preventable cause of death in this chapter by a factor of about three over the next largest, alcohol.

Tobacco causes over 20 types or subtypes of cancer. Global prevalence is falling and absolute user numbers fall more slowly because of population growth. Smoke-free laws are in force in 79 countries covering over a third of the world's population; 68 countries have completely banned tobacco advertising, promotion and sponsorship; 41 countries, covering 12 per cent of the world's population, tax at least 75 per cent of retail price. Over 60 per cent of smokers intend to quit, and cessation services with full or partial cost coverage exist in 31 countries.

Tobacco is the clearest case in this chapter where the burden sits in other chapters — cardiovascular, respiratory, cancer — while the disorder sits in Chapter 06.

Where it starts. Heritability of nicotine dependence is roughly 50 to 60 per cent†. *CHRNA5-A3-B4* variants have replicated effects on cigarettes per day and on lung cancer risk, mediated through consumption, and are among the clearest gene-to-disease pathways in behavioural genetics. *CYP2A6* metabolism rate predicts dependence severity and treatment response. Price is the dominant population-level determinant: price elasticity of cigarette demand is around −0.4 in high-income countries and around −0.5 to −0.8 in low- and middle-income countries, and young people are roughly two to three times more price-responsive than adults. Industry marketing exposure in adolescence is associated with initiation, odds ratios roughly 1.5 to 2†. Almost all initiation occurs before age 25.

Nicotinic acetylcholine receptor upregulation and dopaminergic reinforcement are established; this is one of the best-understood dependences pharmacologically. The disease mechanism — combustion products rather than nicotine — is also established, which is what makes substitution a coherent strategy. Not known: the long-term health profile of non-combusted nicotine delivery at population scale.

Cure status. CONTROLLABLE. The stratum with achieved abstinence at twelve months is roughly 3 to 5 per cent of unassisted quit attempts†. Accumulated organ damage is not fully reversible. Cessation at any age extends life: quitting before 40 avoids about 90 per cent of the excess mortality from continued smoking, and before 30 more than 97 per cent†. Unassisted quit attempts succeed in roughly 3 to 5 per cent per attempt at twelve months, most successful quitters succeed after multiple attempts, and the majority of ex-smokers quit without formal treatment. Relapse is concentrated in the first weeks, and after a year of abstinence it becomes uncommon.

Prevention. The strongest and best-replicated prevention evidence in this chapter. Taxation: STRONG; elasticity −0.4 to −0.8, and WHO's single most cost-effective tobacco measure. Smoke-free legislation: STRONG; comprehensive indoor smoking bans were followed by measurable reductions in acute coronary events in meta-analysis of natural experiments, and they reduce second-hand exposure directly. Large graphic health warnings and plain packaging: MODERATE; Australia's plain packaging of 2012 was followed by accelerated prevalence decline, and 62 per cent of the world's population lives in the 110 countries meeting best practice for graphic warnings. Comprehensive advertising, promotion and sponsorship bans: STRONG. Mass media campaigns: MODERATE; over 2.9 billion people live in the 36 countries that aired a strong campaign in the last two years. Cessation support availability: STRONG for the individual, moderate at population scale. These six are the MPOWER measures under the WHO Framework Convention on Tobacco Control, in force since 2005. The fact sheet gives the number of Parties as 182 countries plus the European Union in one place and 183 in another, and does not reconcile the two.

Treatment. *Varenicline* is the most effective single pharmacotherapy, with roughly two to three times placebo odds of sustained abstinence; EML-listed since 2021†, off-patent, tens to low hundreds of US dollars a course. Earlier neuropsychiatric safety concerns were not confirmed by the EAGLES randomised trial of 2016. *Nicotine replacement therapy* gives roughly 1.5 to 1.8 times placebo odds, and combination therapy of a patch with a short-acting form is better than a single form; EML-listed, off-patent, tens to low hundreds of US dollars a course. *Bupropion*, roughly 1.6 times placebo; EML-listed†, off-patent, tens of US dollars a course.

Cytisine, also called cytisinicline, is comparable to or better than nicotine replacement in randomised trials and far cheaper, and has been manufactured in Eastern Europe for decades; EML-listed since 2021†, off-patent, and costing on the order of a few to a few tens of US dollars a course. It has the best cost-effectiveness ratio of any pharmacotherapy in this chapter. *Behavioural support*, individual, group or telephone, adds roughly 1.4 to 1.8 times to pharmacotherapy, and combined is better than either alone†; counselling and medication together can more than double quit success (WHO). *E-cigarettes for cessation*: a Cochrane living review, high-certainty evidence as of its 2024 update, finds nicotine e-cigarettes produce higher six-month quit rates than nicotine replacement, risk ratio roughly 1.6. Long-term safety at population scale is not established, and youth uptake is a separate and contested policy problem. Both halves belong together.

Financial incentives for cessation are effective in randomised trials, including in pregnancy.

Simple means. Quitting abruptly on a set date, with no product: 3 to 5 per cent per attempt, and repeated attempts raise cumulative success substantially. Free. Brief advice from any health worker, under three

minutes: raises quit rates by roughly 1 to 3 percentage points absolute†, and reach makes the population effect large. Telephone quitlines and text-message support: effective in randomised trials, at near-zero marginal cost. Cytisine is as close to a pharmacotherapy without an industrial supply chain as exists: a plant alkaloid from *Cytisus laburnum*, off-patent, at a few US dollars a course. At population level, price and smoke-free law have the largest measured effects available and require legislation rather than supply.

Gaps. Long-term population health effects of non-combusted nicotine products are unmeasured, and sources disagree sharply on how to weigh youth uptake against adult cessation. Cessation pharmacotherapy trials come overwhelmingly from high-income settings, while 80 per cent of users do not live there. Cytisine's cost-effectiveness advantage is well established and its global availability remains limited — a distribution failure, not an evidence gap.

> **Depth.** Starts in: the nicotine molecule. Size: 0.6 nm†; depth −3.94. First complaint: about 8.6 weeks († weeks to months); time depth 47.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gambling disorder

What it is. Persistent gambling that the person cannot control, which takes priority over other activities and continues despite harm. ICD-11 classifies it with the substance use disorders as a disorder due to addictive behaviours.

Measured. Past-year problem gambling prevalence pooled across countries is roughly 0.5 to 2.0 per cent, depending on instrument and threshold, and figures for any gambling harm are several times higher. Online and mobile gambling availability is the main change in exposure since 2010, and electronic gaming machines and online in-play betting carry the highest harm per participant. Suicidality is substantially elevated, and register studies show elevated suicide mortality. Harm is concentrated: a minority of gamblers generates the majority of industry revenue, which aligns commercial incentive with harm. There is no WHO fact sheet and GBD produces no stand-alone burden estimate, so global figures are weak.

Where it starts. Heritability is roughly 50 to 60 per cent†. Product design is an established determinant: event frequency, near-miss structure, losses disguised as wins and continuous play all increase harm per unit of exposure, demonstrated experimentally. Availability and proximity to venues are associated with prevalence. Comorbidity with substance use disorders, depression and attention deficit hyperactivity disorder is high. Male sex predominates in most, not all, settings.

Reward-circuit activation similar to substance use is observed on imaging, and this motivated the ICD-11 reclassification. Variable-ratio reinforcement schedules explain persistence better than any neurobiological account, and that is behavioural psychology well established since the 1950s. Not known: why a minority of exposed individuals develop the disorder; whether gaming disorder, also in ICD-11, is the same kind of thing.

Cure status. CONTROLLABLE. Substantial natural recovery occurs in cohort studies, as with substance use disorders. CBT produces reductions in gambling and in severity, with moderate short-term effect sizes attenuating by twelve months. Relapse is common.

Prevention. Product modification — reduced stake limits, slower event frequency, removal of losses disguised as wins: MODERATE, on experimental and some jurisdictional evidence, and the measure most directly aimed at the established determinant. Advertising restriction: MODERATE; exposure-to-participation associations are consistent and natural-experiment evidence is emerging from several European jurisdictions. Self-exclusion schemes: MODERATE for those who use them, and uptake is low. Affordability and deposit limits: MODERATE, with mandatory limits outperforming voluntary ones. Availability restriction by venue density and online access: MODERATE. Information and responsible-gambling messaging alone: CONTESTED with the weight of evidence against; knowledge-based measures show little effect on behaviour, mirroring the alcohol and tobacco education findings.

Treatment. *Cognitive behavioural therapy* is the best-supported treatment, with moderate short-term effects. *Motivational interviewing and brief interventions* have small effects and large potential reach. *Opioid antagonists*, naltrexone and nalmefene, reduce gambling severity in randomised trials, with effect sizes comparable to their effect in alcohol use disorder; naltrexone is not EML-listed, is off-patent, and costs tens to low hundreds of US dollars a patient-year. *Gamblers Anonymous and peer support* are widely used on thin trial evidence. *Debt advice and financial counselling* address the proximate harm and are not evaluated as a disorder treatment.

Simple means. Self-exclusion, blocking software and bank gambling blocks: free or near-free, effective for those who engage with them. Removing payment access: the behavioural core of most self-management. Peer support: free at point of use. Exercise, light and sleep have no specific trial evidence for this condition.

Gaps. No GBD estimate and no WHO fact sheet; global burden is genuinely unknown. Prevalence instruments differ enough that cross-country comparison is unreliable. Almost all research funding in this field has industry links, and the literature on responsible-gambling measures is substantially industry-shaped — a conflict-of-interest problem acknowledged in the field itself. Long-term treatment outcomes beyond twelve months are barely measured.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Feeding and eating disorders

This entry reports epidemiology, mortality and treatment outcomes only. It carries no weight thresholds and no body-mass-index figures. It carries no diagnostic weight criteria and no calorie or nutritional target figures. It does not describe compensatory behaviours.

What it is. A class of disorders in which eating behaviour and the person's relationship to eating and to their body are disturbed to the point of damaging physical health or functioning. The class includes anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant or restrictive food intake disorder, pica and rumination-regurgitation disorder.

Measured. About 18 million people worldwide have an eating disorder, including 4.7 million children and adolescents (WHO mental disorders fact sheet, 11 September 2026, GBD 2023 data). Lifetime prevalence in surveys: anorexia nervosa roughly 0.9 to 2 per cent in women and 0.3 per cent in men; bulimia nervosa roughly 1 to 2 per cent; binge eating disorder roughly 2 to 3 per cent, making it the most common of the three. Mortality, from a meta-analysis of 36 studies (Arcelus and colleagues, *Archives of General Psychiatry*, 2011): standardised mortality ratio 5.86 for anorexia nervosa, 1.93 for bulimia nervosa, 1.92 for other specified eating disorders.

For anorexia nervosa, 1.3 of 5.1 deaths per 1,000 person-years were from suicide, roughly a quarter of all deaths in that group. Anorexia nervosa has one of the highest mortality rates of any mental disorder. Onset is predominantly in adolescence and early adulthood, and anorexia nervosa typically begins earlier than bulimia nervosa or binge eating disorder. Women predominate in diagnosed cases at roughly 3 to 1 up to 10 to 1 depending on the disorder, and under-detection in men and boys is documented, so the true ratio is narrower than diagnosed figures suggest.

Prevalence estimates are rising in East Asia, South Asia and the Middle East, consistent with changing exposure rather than changing genes. Treatment access is poor everywhere, and the median delay from onset to first treatment is years.

Where it starts. Heritability from twin studies: anorexia nervosa roughly 50 to 60 per cent, bulimia nervosa roughly 50 per cent, binge eating disorder roughly 40 to 50 per cent†. Genome-wide association study of anorexia nervosa found genetic correlations with metabolic as well as psychiatric traits — a

replicated finding that purely psychological models did not predict, and whose interpretation is unsettled. Dieting behaviour is the strongest prospectively measured behavioural antecedent of onset. Perfectionism and childhood anxiety disorder are prospectively associated. Social media and appearance-focused media exposure are associated in cohort studies, with short-term experimental effects on body dissatisfaction; the effect on disorder incidence is not established. Type 1 diabetes, and competitive sport in appearance-judged disciplines, carry elevated risk.

There is no biomarker and no diagnostic test. The serotonergic and dopaminergic accounts of anorexia nervosa are not established. Many physiological abnormalities found in acute illness are consequences of malnutrition and resolve with nutritional restoration, which has repeatedly led to causal misattribution in this literature. The metabolic genetic correlation is the most interesting unresolved finding in the field. Not known: why onset clusters in adolescence; why anorexia nervosa is so resistant to pharmacological treatment; what maintains the disorder once established.

Cure status. Adolescent-onset anorexia nervosa treated early with family-based treatment: CURABLE in 49.3 per cent at twelve months. Lock and colleagues (*Archives of General Psychiatry*, 2010; 121 patients randomised) reported full remission in 41.8 per cent with family-based treatment against 22.6 per cent with adolescent-focused individual therapy at end of treatment (p=0.055), 39.9 against 18.3 per cent at six months (p=0.029), and 49.3 against 23.2 per cent at twelve months (p=0.024). Adult anorexia nervosa, and the class in general: CONTROLLABLE. Adult outcomes are substantially worse, with long-term follow-up finding roughly half recovered, a quarter improved and a quarter with chronic illness. Bulimia nervosa treated with enhanced cognitive behavioural therapy achieves remission in roughly 30 to 45 per cent at end of treatment, with gains largely maintained†. Binge eating disorder has the best treatment response of the three. Duration of untreated illness is among the strongest predictors of poor outcome, which is what makes the treatment-access gap consequential.

Prevention. Dissonance-based prevention programmes in high-risk young women reduce eating disorder onset in randomised trials with multi-year follow-up, with risk reductions reported around 60 per cent in some trials†: MODERATE, among the better prevention evidence in Chapter 06. Media literacy programmes reduce body dissatisfaction, with incidence effects less established: WEAK. Avoiding school-based weight-focused interventions: programmes that emphasise weight have been associated with increased disordered eating, and that is a documented harm; act on the negative finding. Early detection and rapid treatment access reduce duration of untreated illness, which predicts outcome: MODERATE. Regulating appearance-focused advertising to minors: no outcome trials, WEAK.

Treatment. *Family-based treatment for adolescent anorexia nervosa*, the Maudsley approach, is first-line on the evidence, with the outcome figures above. It is delivered to the family, outpatient, and does not require hospital admission in most cases. *Enhanced cognitive behavioural therapy* is the best-supported treatment for bulimia nervosa and binge eating disorder and the leading option for adult anorexia nervosa, with the remission figures above. *Specialist supportive clinical management and the Maudsley adult anorexia treatment* give comparable outcomes to enhanced CBT in randomised comparison, and no modality is clearly superior in adults.

Medical and nutritional restoration is necessary and prior to psychological work in severe cases: it is the intervention that prevents death, and it requires monitoring for electrolyte disturbance. *Fluoxetine for bulimia nervosa* is the only drug with an approved eating-disorder indication in most jurisdictions and reduces symptom frequency; EML-listed, off-patent, a few US dollars a patient-year. *Lisdexamfetamine for binge eating disorder* is approved in some jurisdictions with moderate effect sizes; not EML-listed, patent status varies, and it costs hundreds to low thousands of US dollars a patient-year. *Pharmacotherapy for anorexia nervosa*: no drug has established efficacy. Olanzapine produces modest weight restoration in randomised trials without improving psychological symptoms. The absence is reported as an absence.

Inpatient and day-patient care is necessary for medical instability, and randomised comparisons find no outcome advantage over well-delivered outpatient care for those who are not medically unstable, at much higher cost.

Simple means. Family involvement: the best-evidenced treatment for adolescent anorexia nervosa is a family intervention with no product, no device and no drug, and its twelve-month remission figures of 49.3

against 23.2 per cent exceed anything pharmacological in this condition, because nothing pharmacological works. A regular structured eating pattern is a core behavioural element of enhanced CBT. Guided self-help CBT for bulimia nervosa and binge eating disorder is delivered from a book with brief support, with trial evidence approaching therapist-delivered CBT in binge eating disorder. Peer and carer support: carer-skills interventions reduce carer distress and improve engagement. Exercise is not a safe simple means in this condition and is not recommended here. This is an exception to the general pattern of the chapter, and it is stated as one.

Gaps. The 18 million figure covers anorexia and bulimia nervosa principally, and binge eating disorder and avoidant or restrictive food intake disorder are poorly captured, so the true class burden is higher than the headline figure. Adult anorexia nervosa has no clearly superior treatment and no effective pharmacotherapy, which is a major unmet need. The metabolic-genetic finding is replicated and unexplained. Mortality estimates come largely from specialist-clinic cohorts in high-income countries, which may overstate or understate population mortality in unknown directions. There is almost no treatment trial data from low- and middle-income settings, where prevalence is rising.

> **Depth.** A class of disorders. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. The book names an early stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Suicide and self-harm

This entry reports epidemiology, population-level risk factors, and the interventions that have measured effect. It does not name, list, describe or compare methods, and it gives no lethality data by method. Means restriction appears as a policy category and is not itemised.

What it is. Death caused by self-directed intentional behaviour, and the non-fatal behaviours related to it. It is an outcome rather than a diagnosis, and it occurs across and outside the diagnostic categories of this chapter.

Measured. WHO's suicide fact sheet of 28 August 2026 gives more than 720,000 deaths a year in its Key Facts and 727,000 in its Overview, on the same page, and both are printed here. The depression fact sheet of 11 September 2026 gives 727,000 for 2021, matching the Overview. Suicide was the third leading cause of death among 15 to 29-year-olds globally in 2021. Seventy-three per cent of global suicides occurred in low- and middle-income countries in 2021. Only 38 countries report having a national suicide prevention strategy. Only about 80 WHO Member States have vital registration data of sufficient quality to estimate suicide rates directly, so the global figure rests on modelling for most of the world's population. The fact sheet states no rate per 100,000 and no male-to-female ratio. Male deaths exceed female deaths in most countries while non-fatal self-harm is more frequent in women — a consistent and only partly explained pattern.

Where it starts. Prior self-harm is the strongest individual predictor: roughly 1.6 per cent of people presenting with self-harm die by suicide within a year, and the cumulative risk continues to rise for years. Mental disorder is present in a large majority of cases in high-income settings, and the fraction is lower in some low- and middle-income settings, where acute stressors account for a larger share and where the availability of a particular means has been shown to shape the national rate. Alcohol use disorder, bipolar disorder, schizophrenia, borderline personality pattern and anorexia nervosa all carry substantially elevated risk; see the individual entries. Economic shock, meaning unemployment and recession, is associated with rate increases in time-series studies. Social isolation, incarceration and recent discharge from psychiatric inpatient care are periods of markedly elevated risk. Access to means at population level is an established determinant of population rates, and it is stated here as a policy category only.

Individual-level prediction does not work. Risk-assessment scales and structured instruments have repeatedly been shown to lack the predictive accuracy needed for clinical allocation, and meta-analyses find positive predictive values too low to be useful. This is a robust negative finding and it has changed

guidelines in several countries. The low-serotonin and low-cholesterol accounts of suicidality have produced no usable clinical tools. Not known: why rates differ so much between countries at similar income levels; why the male-female pattern is so consistent; how to identify the individual at risk.

Cure status. Not applicable as a disease category. For the behaviour: CONTROLLABLE at population level, through the measures below. Risk in an individual fluctuates and is not reliably predictable.

Prevention. Means restriction as a policy category is the best-evidenced suicide prevention measure available. Natural experiments in which access to a means was restricted at national level were followed by reductions in overall suicide rates, not merely substitution. The clearest examples in the global literature are national regulatory restrictions, each followed by a substantial reduction in the total national suicide rate — in Sri Lanka, South Korea and Bangladesh. The finding that matters is that the total rate fell, rather than shifting.

STRONG. What was restricted in each case is not itemised here, and no means is named anywhere in this chapter. Responsible media reporting: adherence to reporting guidelines is followed by measurable reductions in imitative deaths, and non-adherent reporting by increases, MODERATE. Treatment of underlying conditions: opioid agonist therapy reduces suicide mortality, risk ratio 0.48 (95 per cent CI 0.37 to 0.61)†; lithium's anti-suicide effect is strong observationally and underpowered in randomised data, risk ratio 1.91 (0.89 to 4.08) in the randomised placebo-controlled subset†; clozapine is associated with reduced suicide mortality in schizophrenia.

MODERATE depending on condition. Crisis services — helplines, text lines, crisis teams — reduce distress and suicidal ideation during and shortly after contact in evaluation studies, and effects on death rates are not established because the studies are not powered for mortality: MODERATE on proximal outcomes, WEAK on mortality. Follow-up contact after a self-harm presentation, by letter, postcard or call, reduces repeat self-harm in several randomised trials though not consistently across all of them: MODERATE. School-based programmes, including the awareness arm of the European SEYLE cluster-randomised trial, reduced incident suicide attempts: MODERATE.

Alcohol policy: population alcohol consumption and suicide rates move together in time-series studies, MODERATE. Safety planning at emergency department discharge reduced subsequent suicidal behaviour in cohort comparison studies: MODERATE. Universal screening without attached intervention: no demonstrated effect on death rates, CONTESTED.

Treatment. *Dialectical behaviour therapy* reduces self-harm repetition in randomised trials, particularly in borderline pattern, and is among the better-evidenced psychological interventions for this outcome. *Cognitive therapy for suicide attempters* reduces repeat attempts in randomised trials. *Treatment of the underlying condition*: see each entry. *Ketamine* reduces suicidal ideation rapidly in randomised trials, and its effect on suicide death is unmeasured. *Lithium and clozapine*: as above.

Simple means. Social connection: among the most consistently measured protective associations, and brief contact interventions — a letter, a phone call — have randomised support for reducing repeat self-harm and cost almost nothing. Reducing access to means in the home environment, stated as a category. Treating sleep disturbance: insomnia is an independent predictor of suicidal ideation, and treating it reduces ideation in randomised trials. Alcohol reduction. Removing the barriers to help-seeking, including decriminalisation of suicide attempt, which remains a criminal offence in roughly 20 countries: a legislative measure with no supply chain.

Gaps. Vital registration adequate for direct estimation exists for only about 80 Member States, so most of the global figure is modelled. Suicide is under-recorded where it is stigmatised or criminalised, by an unknown and probably large margin. Crisis-line evaluations are not powered for mortality endpoints and probably never will be. The failure of individual-level risk prediction is well established and has no replacement, and services still allocate resources using instruments shown not to work. Why national rates differ several-fold between comparable countries is unexplained. WHO's own Key Facts and Overview give different headline totals on one page.

> **Depth.** An outcome, not a diagnosis [B]. No depth is given.
>
> **Model reading.** Not applied. An outcome, not a diagnosis [B].

Personality disorders

What it is. Enduring patterns of experiencing oneself and relating to others that are inflexible, cause distress or impairment, and are evident across situations and over time. ICD-11 replaced the categorical subtypes with a single diagnosis graded by severity — mild, moderate, severe — plus optional trait qualifiers, retaining borderline pattern as the one named specifier.

Measured. Pooled community prevalence of any personality disorder is roughly 7 to 8 per cent, with a range across studies of 4 to 15 per cent†. Borderline pattern is roughly 1 to 2 per cent in community samples and far higher in clinical populations, around 10 per cent of psychiatric outpatients and 20 per cent of inpatients†. Antisocial pattern is roughly 1 to 3 per cent in community samples with strong male predominance, and much higher in prison populations. The standardised mortality ratio is roughly 2 to 5 depending on pattern, and suicide risk in borderline pattern is substantially elevated, with roughly 5 to 10 per cent dying by suicide in long-term follow-up of clinical cohorts. GBD produces no stand-alone burden estimate and WHO has no fact sheet, so global figures are weak. The condition is diagnosable from late adolescence, and borderline pattern symptoms typically attenuate with age, which is one of the most important findings in this area.

Where it starts. Heritability of personality disorder traits is roughly 40 to 60 per cent†. Childhood maltreatment, particularly sexual and physical abuse and severe neglect, is strongly associated with borderline pattern, with odds ratios in the range 3 to 13 across studies — among the largest environmental effect sizes in Chapter 06†. Causality is supported by dose-response and by prospective cohorts, and weakened by shared genetic liability between parent and child. Disrupted attachment and institutional rearing are associated with severe outcomes, with the Bucharest Early Intervention Project and the Romanian adoptee studies providing quasi-experimental evidence. Antisocial pattern carries additional established associations with prenatal exposures, childhood conduct disorder and lead exposure.

There is no biomarker and no diagnostic test. The categorical subtypes of DSM-IV and ICD-10 had poor construct validity, extensive overlap and poor inter-rater reliability, and ICD-11's shift to a severity dimension reflects the failure of the categorical model rather than its refinement. This is a case where the classification was changed because the old one did not work. Serotonergic and amygdala-reactivity accounts of borderline pattern are group-level associations without clinical application. Not known: whether these are disorders, extremes of normal variation, or scars from developmental adversity; why symptoms attenuate with age.

Cure status. CONTROLLABLE. Prospective follow-up in the McLean Study of Adult Development and the Collaborative Longitudinal Personality Disorders Study found remission from the borderline diagnosis in the large majority of patients over 10 to 16 years, with roughly 85 to 99 per cent achieving remission at some point and relatively low relapse rates after remission. Functional recovery lags symptomatic remission considerably. Antisocial pattern has the least favourable course and the least effective treatment. Dialectical behaviour therapy reduces self-harm and hospitalisation and does not remove the diagnosis.

Prevention. Reducing childhood maltreatment: the largest attributable fraction available. Home-visiting programmes such as the Nurse-Family Partnership reduce child maltreatment in randomised trials, with long-term follow-up showing reduced antisocial outcomes: MODERATE for the intermediate outcome, MODERATE for the disorder endpoint. Early intervention for conduct problems, through parenting programmes such as Incredible Years and Triple P, reduces conduct problems with moderate effect sizes in randomised trials, with long-term effects on adult antisocial pattern less well measured: MODERATE. Lead removal: lead exposure is associated with antisocial behaviour, and the removal of tetraethyl lead from petrol is followed in multiple national time-series by declining violent crime; causal inference is contested and the association robust across countries, CONTESTED. Avoiding institutional rearing of infants: the Bucharest Early Intervention Project randomised institutionalised infants to foster care and found better outcomes, one of the few randomised trials of a rearing environment, MODERATE. Early intervention for emerging borderline pattern in adolescence reduces symptom trajectory in randomised trials: MODERATE.

Treatment. *Dialectical behaviour therapy* for borderline pattern reduces self-harm, suicide attempts and hospitalisation relative to treatment as usual, and is the best-replicated psychological treatment in this area. *Mentalisation-based treatment, transference-focused psychotherapy, schema-focused therapy and structured clinical management* all outperform unstructured treatment as usual, and head-to-head comparisons generally show no clear superiority of one over another. Structure appears to matter more than modality, which is a consistent and practically important finding. *Pharmacotherapy*: no drug is indicated for personality disorder itself in any major guideline. Drugs are used for comorbid conditions. Polypharmacy is common and not evidence-based, and NICE explicitly advises against drug treatment for borderline personality disorder itself. *Treatment of comorbid conditions*: depression, substance use disorder and post-traumatic stress disorder are frequent and treatable. *For antisocial pattern*: no psychological treatment has established efficacy in adults; multisystemic therapy and parenting interventions in childhood and adolescence have evidence, and adult treatment does not.

Simple means. Structured, predictable, consistent care with a written plan: the common factor across all effective treatments, costing staff time and organisational discipline rather than products. Crisis plans agreed in advance reduce emergency presentations. Social and occupational role: functional recovery lags symptom remission, and employment and stable housing are the limiting factors. The strongest simple-means statement for this condition is negative — avoid polypharmacy, avoid unplanned long inpatient admissions, avoid discontinuous care. Each is associated with worse outcomes. Exercise, light and sleep have no specific trial evidence here.

Gaps. No GBD estimate and no WHO fact sheet; global burden is unknown. ICD-11's new severity-based system has almost no epidemiological or treatment-trial literature of its own, because nearly all existing evidence uses the abandoned categorical criteria. Trials are overwhelmingly in borderline pattern in women in high-income countries, and other patterns and other populations are barely studied. The lead-crime association is robust and its causal status genuinely disputed. Whether personality disorder is a valid construct at all remains a live disagreement in the field.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 18 years († onset about age 18); time depth 51.50. One untreated course: no number ([B] a lasting pattern).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Autism spectrum disorder

What it is. A developmental condition present from early childhood, characterised by differences in social communication and interaction, together with restricted, repetitive patterns of behaviour, interests or activities, and often atypical sensory processing. Presentation varies from profound disability requiring lifelong support to differences compatible with independent life.

Measured. About 1 in 127 people worldwide, approximately 0.8 per cent (WHO autism fact sheet, GBD 2021 data). WHO notes this is an average and that reported prevalence varies substantially between studies. GBD 2021 ranked autism spectrum disorder ninth among nervous-system and neurodevelopmental conditions by DALYs. Administratively identified prevalence in high-surveillance settings is considerably higher: the US CDC ADDM Network reported 1 in 31 eight-year-olds for the 2022 surveillance year, published 2025. The gap between that and the global 1 in 127 is a detection and ascertainment difference, not a difference in underlying rate.

The male-to-female diagnosed ratio is roughly 3 to 4 to 1, and the true ratio is narrower, with documented under-recognition in girls and women. WHO gives no figure for co-occurring intellectual developmental disorder; CDC surveillance finds roughly a third of identified children with co-occurring intellectual disability. Co-occurring epilepsy affects roughly 10 to 20 per cent, and attention deficit hyperactivity disorder, anxiety and sleep disorders are all substantially more frequent than in the general population. Mortality is elevated, driven by epilepsy, accidents and, in those without intellectual disability, suicide.

Recorded prevalence has risen steeply over four decades. The evidence attributes most of this to broadened diagnostic criteria, increased awareness and diagnostic substitution from intellectual disability, and whether any true incidence increase underlies it remains unresolved.

Where it starts. Heritability is among the highest measured for any behavioural condition, roughly 80 per cent in large twin and population studies†. Recurrence risk in a younger sibling is roughly 10 to 20 per cent†. Rare de novo variants and copy-number variants of large individual effect are identified in roughly 10 to 20 per cent of cases, and several hundred genes are implicated, most with small effects. Advanced paternal and maternal age carry small effects, odds ratios roughly 1.2 to 1.5†. Extreme prematurity and perinatal complications are associated. Valproate exposure in pregnancy produces an established, substantial increase in risk, and is one of the few established environmental causes. Maternal rubella infection and certain metabolic conditions are established in a small number of cases.

The MMR vaccine does not cause autism. This has been tested in very large cohort and registry studies across multiple countries, including a Danish cohort of over 650,000 children (Hviid and colleagues, *Annals of Internal Medicine*, 2019), which found no increased risk overall, in susceptible subgroups, or in any post-vaccination time window. The original 1998 claim was retracted and its author struck from the medical register. This is settled. Thiomersal and vaccine schedules: no association found in any adequately powered study. The leaky-gut, opioid-excess and secretin hypotheses have been tested and are not supported, and secretin failed in multiple randomised trials. Synaptic and excitation-inhibition imbalance accounts have support from monogenic syndromes and have not yielded a treatment. Not known: how hundreds of genetic variants converge on a common presentation; why the sex ratio is what it is; whether the diagnostic category describes one thing or many; what, if anything, underlies the residual unexplained portion of the prevalence rise.

Cure status. RELIEF ONLY for the core condition. No treatment removes autism, and the stated goal of most current practice is support for function and wellbeing rather than removal of the condition. Early intensive behavioural intervention improves measured adaptive and cognitive outcomes and does not eliminate autism. A small proportion of children diagnosed in early childhood no longer meet criteria later, and whether this is change, misdiagnosis or compensation is disputed. Co-occurring conditions — epilepsy, anxiety, sleep disorder, attention deficit hyperactivity disorder — are separately treatable, and that is where the most reliable gains are.

Prevention. Avoiding valproate in pregnancy: STRONG, an established, large, avoidable risk. Rubella vaccination: STRONG for the rubella-attributable fraction, which is now very small in vaccinated populations. Folate supplementation in early pregnancy: observationally associated with lower risk, no randomised evidence with this endpoint, WEAK. Preventing extreme prematurity: MODERATE for the attributable fraction. No other intervention has demonstrated prevention of autism, and given 80 per cent heritability, large-scale prevention is not a realistic prospect on present knowledge.

Treatment. *Early intensive behavioural intervention and naturalistic developmental behavioural interventions* improve adaptive behaviour and cognitive scores with moderate effect sizes, on variable trial quality with weak control conditions and blinding mostly impossible. The field's own systematic reviews rate certainty as low. *Parent-mediated interventions*: the Preschool Autism Communication Trial showed sustained improvement in symptom severity at six-year follow-up, one of the longest follow-ups in the field, and it is delivered through parents with modest professional input. *Speech-language and occupational support, and augmentative and alternative communication* are standard practice on an evidence base thinner than the practice volume.

Treatment of co-occurring conditions is the highest-yield pharmacological area: epilepsy, sleep disorder with randomised support for melatonin, attention deficit hyperactivity disorder with stimulants effective and with more adverse effects than in non-autistic children, and anxiety with adapted CBT. *Risperidone and aripiprazole for severe irritability and aggression* are effective for that specific target and not for autism itself; risperidone is EML-listed, off-patent, and costs tens of US dollars a patient-year. Harms: substantial weight gain, metabolic effects, sedation, prolactin elevation. *Melatonin for sleep onset problems* has randomised support in autistic children; not EML-listed, off-patent, tens of US dollars a year.

Treatments tested and unsupported: chelation, which is harmful; hyperbaric oxygen; secretin; gluten-free and casein-free diet, which had no effect in controlled trials; stem cell therapy. These are reported because families are actively marketed them.

Simple means. Parent-delivered interventions: the six-year follow-up result above came from an intervention delivered by parents after training, with no supply chain. Sleep timing and routine, with melatonin where needed: sleep problems affect a majority of autistic children, and improving them improves daytime function and family wellbeing. Predictable environment and sensory accommodation reduce distress; standard practice, poorly quantified in trials. Exercise: small randomised trials show improvements in stereotypy and in co-occurring symptoms. Social connection on the autistic person's own terms, including peer community, is associated with better mental health outcomes in observational studies of autistic adults. Augmentative communication: a picture board costs almost nothing and changes outcomes for non-speaking people.

Gaps. The 1-in-127 global and 1-in-31 US-surveillance figures differ by a factor of four; this is ascertainment, and no one can currently say what the true comparable rate is. Almost all intervention research is in children, and autistic adults, who are the majority of autistic people, are barely studied. Trial outcome measures are contested: much of the literature measures reduction in autistic behaviour, which autistic-led research argues is the wrong endpoint, and sources genuinely disagree about what should be measured. Whether any real incidence increase underlies the recorded rise is unresolved. Prevalence data from low- and middle-income countries are very sparse.

> **Depth.** Starts in: the developing brain (in utero). No size is given. First complaint: about 2.5 years († from conception to 18–24 months); time depth 49.70. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Attention deficit hyperactivity disorder

What it is. A developmental condition with persistent inattention, or hyperactivity and impulsivity, or both, beginning in childhood and impairing function across settings. It continues into adulthood in a majority of cases, usually with hyperactivity declining and inattention persisting.

Measured. WHO's mental disorders fact sheet gives no prevalence figure for attention deficit hyperactivity disorder (checked October 2026). Pooled childhood prevalence is roughly 5 to 8 per cent using research criteria, and adult prevalence roughly 2.5 to 3 per cent. Diagnosed prevalence varies several-fold between countries and even between neighbouring regions, far more than symptom-survey prevalence does — a service and threshold effect rather than a disease difference. The male-to-female diagnosed ratio is roughly 2 to 3 to 1 in childhood and closer to parity in adults, and under-recognition in girls is documented. Mortality is elevated, roughly twice all-cause in register studies, driven by accidents, and the relative risk is higher in those diagnosed as adults. Associated outcomes include elevated rates of road traffic collisions, substance use disorder, educational non-completion, unemployment and criminal justice contact. Diagnosis and prescribing have risen steeply over the past two decades, particularly in adults, while symptom prevalence in repeated population surveys has been broadly stable.

Where it starts. Heritability is roughly 70 to 80 per cent, among the highest in Chapter 06, against SNP-based heritability of roughly 20 per cent across many loci of small effect†. Extreme prematurity and very low birth weight carry roughly 2 to 3 times the risk†. Prenatal exposures to maternal smoking and alcohol are associated, and sibling-comparison and genetically informed designs substantially attenuate the maternal smoking association, suggesting much of it is confounded by shared familial liability. The attenuation is reported here, because this is a case where a widely cited risk factor weakened under better designs. Lead exposure is associated, with dose-response. Age relative to classmates matters: children who are youngest in their school year are substantially more likely to be diagnosed, up to roughly 1.3 to 1.8 times in several national studies — a measurement artefact in the diagnostic process, and a well-replicated one.

Dopaminergic and noradrenergic involvement is supported by drug efficacy, and drug efficacy is weak evidence of a cause. The dopamine-transporter-density account produced inconsistent imaging results and no clinical test. Structural imaging differences are small at group level and absent at individual level; there is no brain scan that diagnoses the condition, despite commercial claims. Executive function deficits are measurable, present in only a subset, and not specific. Not known: what the diagnostic boundary corresponds to; why prescribing varies so much between similar places; whether the condition is categorical or the tail of a continuous trait, where the evidence favours the continuum.

Cure status. CONTROLLABLE. Symptoms persist into adulthood in roughly 50 to 65 per cent of childhood cases, with full remission in a minority†. Medication effects are large and present only while the drug is active, and there is no evidence of disease modification. The MTA study's long-term follow-up found that initial group differences in symptom levels had converged by three years and beyond, which is the central and uncomfortable finding in this field. Discontinuation leads to symptom return.

Prevention. Lead removal: MODERATE for the lead-attributable fraction; see the intellectual developmental disorders entry for the magnitude of lead's neurodevelopmental burden. Preventing extreme prematurity: MODERATE. Avoiding alcohol in pregnancy: STRONG for fetal alcohol spectrum disorder, which includes attentional impairment, with a smaller condition-specific fraction. Maternal smoking cessation in pregnancy: CONTESTED for this condition specifically, given the sibling-comparison attenuation, and justified on every other ground. Not diagnosing the youngest children in a school year by comparison with their classmates: STRONG as a measurement finding, because the correction prevents diagnoses. No intervention prevents the condition itself, given 70 to 80 per cent heritability.

Treatment. *Stimulants* have the largest effect sizes of any pharmacotherapy in Chapter 06. A network meta-analysis of 133 double-blind randomised trials covering 14,346 children and adolescents and 10,296 adults (Cortese and colleagues, *Lancet Psychiatry*, 2018) gives standardised mean differences against placebo on clinician-rated core symptoms at about twelve weeks: amphetamines, children −1.02 (95 per cent CI −1.19 to −0.85), adults −0.79 (−0.99 to −0.58); methylphenidate, children −0.78 (−0.93 to −0.62), adults −0.49 (−0.64 to −0.35); atomoxetine, children −0.56 (−0.66 to −0.45), adults −0.45 (−0.58 to −0.32); guanfacine, children −0.67 (−0.85 to −0.50), no adult trials identified; modafinil, children −0.62 (−0.84 to −0.41), adults +0.16 (−0.28 to 0.59), not superior to placebo.

GRADE certainty is moderate for amphetamines and methylphenidate in children and amphetamines in adults, and low for the rest. Methylphenidate is EML-listed, added in 2023 for this indication, off-patent, and costs tens to low hundreds of US dollars a patient-year, higher for extended-release. Dexamfetamine and lisdexamfetamine are not EML-listed, dexamfetamine is off-patent, and they cost from low hundreds to low thousands of US dollars a patient-year. Atomoxetine is not EML-listed, is off-patent, and costs tens to low hundreds of US dollars a patient-year.

Harms: appetite suppression and growth slowing in children, sleep onset delay, small blood pressure and heart rate increases, and diversion or misuse. Cardiovascular event risk in people without pre-existing disease is small in absolute terms. Two things sit oddly together here. Amphetamines have the larger effect size, and methylphenidate is the recommended first line in most guidelines, chiefly on tolerability and long-term safety data.

Behavioural parent training and classroom behavioural intervention improve parent-rated behaviour and parenting, and effects on blinded-rated core symptoms are small and inconsistent: effective for the associated problems, not for the core symptoms. *Combined medication and behavioural treatment* was superior for associated outcomes in the MTA trial and not clearly superior to medication alone for core symptoms, with the advantage fading by three years. *Cognitive training and working memory training* produce near-transfer gains on the trained task and do not transfer to symptoms or academic outcomes in blinded-rated trials: a clear negative result, heavily marketed regardless. *Omega-3 supplementation*: very small effects, SMD around 0.15 to 0.2, barely distinguishable from zero†. *Elimination diets*: effects appear in small trials with unblinded parent ratings and do not survive blinding. *CBT for adults* has moderate effects on functioning and comorbid symptoms as an adjunct to medication.

Simple means. Exercise improves executive function and symptoms with moderate effect sizes in randomised trials, on a small and mostly unblinded trial base, and it is not comparable to stimulant

medication for this condition. The asymmetry is reported plainly: stimulant effect sizes of −0.78 to −1.02 are far larger than any non-drug intervention measured here, and this is one of the places where the chapter's general pattern does not hold. Sleep timing: delayed sleep phase is very common here, and treating sleep improves daytime symptoms in randomised trials. Environmental structure — written routines, external reminders, reduced distraction, broken-down tasks — is clinically standard, free and poorly quantified. Physical activity breaks in school show short-term improvement in classroom behaviour in small randomised trials.

Gaps. No WHO fact sheet and no stable GBD figure, so global burden is poorly characterised. The fading of treatment differences in long-term follow-up is the central unresolved problem and is rarely stated clearly in clinical materials. Trials are short: almost all efficacy data come from weeks to months, while treatment is given for years. Diagnostic variation between countries is several-fold and unexplained by anything except service factors. Adult diagnosis and prescribing are rising rapidly on a far thinner evidence base than the childhood literature.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 7.8 years († from conception to about 7 years); time depth 50.73. One untreated course: no number ([B] into adulthood in most).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Intellectual developmental disorders

What it is. Significantly below-average intellectual functioning and adaptive behaviour, originating during the developmental period. ICD-11 grades it mild, moderate, severe or profound, and recognises provisional and unspecified categories where standardised testing is not possible.

Measured. Pooled global prevalence is roughly 1 to 1.5 per cent, higher in low- and middle-income countries where preventable causes are more frequent. GBD 2021 includes intellectual disability within its nervous-system analysis, and found that controlling lead exposure alone could reduce the intellectual disability burden by 63 per cent — the largest single preventable fraction attributed to any condition in that analysis. Lead exposure overall was associated with more than 3.5 million deaths and more than 71.5 million DALYs globally in 2023, mainly cardiovascular (WHO lead poisoning fact sheet, 10 June 2026, IHME/GBD 2023 data).

Blood lead at 3.5 micrograms per decilitre and above is associated with decreased intelligence, behavioural difficulty and learning problems, and WHO's clinical action threshold is 5 micrograms per decilitre. Children absorb up to four to five times as much lead from an ingested dose as adults. As of January 2024 only 48 per cent of countries had legally binding controls on lead paint. Iodine deficiency remains the leading preventable cause of intellectual impairment worldwide where salt iodisation is incomplete. Mortality is substantially elevated, with life expectancy reduced by roughly twenty years in the severe and profound categories and a large documented excess of deaths from avoidable causes. Down syndrome occurs in roughly 1 in 700 to 1,000 live births globally, with wide variation by maternal age structure and prenatal screening practice.

Where it starts. Unusually for this chapter, much of the aetiology is actually known. *Genetic*: Down syndrome, fragile X syndrome, and several hundred single-gene and copy-number causes, collectively accounting for a substantial and rising fraction of cases as genomic testing improves; fragile X is the commonest inherited cause. *Iodine deficiency in pregnancy*: established, dose-responsive and preventable; severe deficiency causes cretinism and moderate deficiency causes measurable loss of intelligence across the whole exposed population. *Lead exposure*: established, with no identified threshold below which there is no effect, and an attributable fraction of 63 per cent on GBD 2021.

Alcohol in pregnancy: fetal alcohol spectrum disorder, established and dose-responsive with no established safe level. *Perinatal asphyxia and neonatal encephalopathy*: GBD 2021 ranked neonatal encephalopathy second among all nervous-system conditions by DALYs. *Congenital hypothyroidism*: established, and detectable by newborn screening, which prevents the disability entirely if treated promptly.

Phenylketonuria and other inborn errors: established, preventable by newborn screening plus dietary management. *Congenital infections* — rubella, cytomegalovirus, syphilis, Zika — together with neonatal jaundice and kernicterus, meningitis, severe malnutrition and folate-preventable neural tube defects all contribute. Heritability estimates for intelligence in the normal range are high, 50 to 80 per cent in adults†, and they do not transfer to the pathological tail, where single large-effect causes dominate.

For a large fraction of cases the cause is now identified at the molecular or exposure level — a different evidential situation from the rest of Chapter 06. For the remaining idiopathic cases, nothing is known. Not known: why the same genetic condition produces widely different functional outcomes; the mechanism of lead neurotoxicity in detail; whether there is any threshold for lead.

Cure status. Established intellectual disability: RELIEF ONLY. Specific treatable causes caught before damage occurs: CURABLE. Congenital hypothyroidism treated early gives normal development and untreated gives permanent severe disability, so newborn screening plus levothyroxine is one of the highest-yield interventions in all of medicine. Phenylketonuria has the same structure: screening plus dietary management prevents the disability. Iodine deficiency is prevented by supplementation in pregnancy and is not reversed afterwards. Removing lead exposure stops further loss and does not recover lost function. The pattern across this condition is that prevention is curative and treatment is not. That is the central fact.

Prevention. This is the strongest prevention section in the chapter. Universal salt iodisation: STRONG, and the single most cost-effective intellectual-disability prevention measure known. Global household coverage of iodised salt rose from roughly 20 per cent in 1990 to around 88 to 90 per cent by the 2020s, and the number of iodine-deficient countries fell from over 100 to around 20†. Moderate iodine deficiency in pregnancy is associated with deficits of several intelligence points in the offspring, and correction removes this. Lead removal from petrol, paint, pipes, cookware, cosmetics and spices: STRONG.

GBD 2021 attributes 63 per cent of the intellectual disability burden to lead. Tetraethyl lead was eliminated from on-road petrol globally by 2021, after a phase-out that produced measurable population blood-lead declines of roughly 90 per cent in countries that completed it early. Paint controls remain legally binding in only 48 per cent of countries (WHO, January 2024), the largest remaining gap. Folic acid fortification of staple foods for neural tube defects: STRONG. In the United States combined neural tube defect prevalence fell from 10.8 per 10,000 in 1995 to 1996 to 6.9 per 10,000 by the end of 2006, a 36 per cent decline, with affected pregnancies falling from about 4,000 to about 3,000 a year (CDC *MMWR*, 2010).

Randomised trial evidence from the MRC Vitamin Study of 1991 established a roughly 70 per cent reduction in recurrence with periconceptional folic acid, and over 80 countries now mandate fortification. Newborn screening for congenital hypothyroidism, phenylketonuria and other treatable metabolic conditions: STRONG, because it prevents the disability outright. Rubella vaccination: STRONG; congenital rubella syndrome is near-eliminated where coverage is high. Alcohol avoidance in pregnancy: STRONG. Obstetric and neonatal care — skilled birth attendance, resuscitation, management of jaundice, treatment of neonatal infection: STRONG for the neonatal encephalopathy fraction, which GBD ranks second among all nervous-system conditions.

Prevention and prompt treatment of childhood meningitis: STRONG; conjugate vaccines reduced confirmed serogroup A disease by 99 per cent in vaccinated populations in the African meningitis belt (WHO meningitis fact sheet, 29 September 2026). Consanguinity counselling where relevant, and prenatal and preconception genetic counselling: MODERATE.

Treatment. *Early intervention and educational support* improve adaptive function with modest effect sizes, on an evidence base weaker than the practice volume. *Treatment of the specific cause where one exists*: levothyroxine for congenital hypothyroidism, dietary management for phenylketonuria, enzyme replacement for some lysosomal disorders. Levothyroxine is EML-listed as a selected medicine for hypothyroidism, confirmed against the 24th List, off-patent, and costs on the order of a few to a few tens of US dollars a patient-year — and it prevents a lifetime of severe disability. *Treatment of co-occurring conditions*: epilepsy, which is very frequent in the severe and profound categories, sensory impairment and mental disorders. Addressing these produces the most reliable functional gains. *Communication support and augmentative or alternative communication* is standard practice. *Supported employment and supported living* improve participation outcomes. *Antipsychotics for challenging behaviour* are widely

prescribed and not supported by trial evidence for that indication in this population; the largest randomised trial found no benefit over placebo. Over-prescribing in this group is a documented quality-of-care problem in several national audits.

Simple means. Iodised salt: a few cents per person per year, preventing loss of intelligence across whole populations. The single best cost-to-effect ratio in this chapter. Folic-acid-fortified flour: similarly cheap, with the 36 per cent reduction in neural tube defects measured above. Removing lead from the home environment — paint, water pipes, cookware, imported spices and cosmetics: no clinical supply chain, large measured effect. Exclusive breastfeeding and adequate nutrition in the first thousand days: associated with better cognitive outcomes. Newborn examination and a heel-prick blood spot: a card, a lancet and a laboratory. Communication boards: paper and pictures.

Gaps. Prevalence data are poorest exactly where preventable causes are most common. The 63 per cent lead-attributable fraction is a modelled estimate with wide uncertainty, resting on an assumed no-threshold dose-response that is plausible and not directly measurable at low exposures. Adults with intellectual disability have markedly worse health outcomes for avoidable reasons, and the measurement of this exists in only a few countries. Antipsychotic prescribing for challenging behaviour continues at scale against the evidence: an implementation failure, not an evidence gap.

> **Depth.** Many causes. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. The book splits this entry by moment, early and late. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Dementia and neurocognitive disorders

ICD-11 codes dementia in Chapter 06, under neurocognitive disorders, with the underlying aetiology cross-coded to Chapter 08. So Alzheimer disease appears as a nervous-system disease in Chapter 08 and the dementia syndrome it causes appears here. This entry covers the syndrome, its care, the full prevention evidence and the anti-amyloid antibody data.

What it is. Acquired, persistent decline in two or more cognitive domains, severe enough to interfere with independence. It is a syndrome with many causes, and it is progressive in most of them.

Measured. 57 million people were living with dementia worldwide in 2021, and over 60 per cent live in low- and middle-income countries (WHO dementia fact sheet, 3 July 2026, 2021 data). Nearly 10 million new cases a year. Alzheimer disease accounts for 60 to 70 per cent of cases. Dementia is the seventh leading cause of death globally, and WHO's Global Health Estimates for 2023 place Alzheimer's disease and other dementias fifth among all causes of death at 2.1 million. Alzheimer's disease and other dementias rank twenty-second among all causes of years lived with disability at 12.2 million YLDs (95 per cent UI 8.52 to 15.6) in 2023.

The economic cost was US$1.3 trillion in 2019, about half of it attributable to informal carers, who provide about five hours of care a day; 70 per cent of care hours are provided by women. Young-onset dementia, before age 65, accounts for up to 9 per cent of cases. GBD 2021 ranked Alzheimer disease and other dementias fourth among nervous-system conditions by DALYs. Prevalence roughly doubles with every five years of age after 65. Absolute numbers are rising with population ageing, and age-specific incidence has been falling in several high-income countries — roughly 13 per cent per decade in pooled Western cohort analyses — consistent with improving vascular risk and rising education. That is a genuinely encouraging finding and it coexists with rising absolute numbers. The proportion in low- and middle-income countries is rising fastest.

Where it starts. The Lancet Commission on dementia prevention of 2024 identified 14 modifiable risk factors with a combined population attributable fraction of 45 per cent: low education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injury, air pollution, social isolation, high midlife LDL cholesterol with a PAF of 7 per cent,

and untreated vision loss in late life with a PAF of 2 per cent. The last two were added in 2024. GBD 2021 estimates that normalising high fasting plasma glucose alone could reduce the dementia burden by about 15 per cent. Age is the dominant non-modifiable factor. *APOE* ε4 carries roughly three times the risk for one copy and roughly 8 to 12 times for two, the largest common genetic effect in late-onset dementia. Autosomal dominant mutations in *APP*, *PSEN1* and *PSEN2* have near-complete penetrance and account for less than 1 per cent of cases. Heritability of late-onset Alzheimer disease is roughly 60 to 80 per cent in twin studies†, which coexists with the 45 per cent modifiable PAF because the two are not additive.

The amyloid cascade hypothesis has driven the field for three decades. Anti-amyloid antibodies now demonstrate that removing amyloid produces a small slowing of decline, which supports some causal role, while the effect size is far smaller than the hypothesis predicted. Dozens of amyloid-targeting agents failed before two succeeded marginally. The position that holds: amyloid is causally involved, and it is not the whole story and not the main lever. Tau pathology correlates better with clinical severity than amyloid does. The vascular contribution is substantial and under-recognised, and mixed pathology is the rule at autopsy rather than the exception. On the literature's integrity: a widely cited 2006 *Nature* paper on amyloid-beta*56 was retracted in 2024 after image-manipulation findings, and several other papers in the field have been retracted. That did not invalidate the amyloid hypothesis, which rests on genetics and much other work, and it is part of the record. Not known: what initiates the pathology decades before symptoms; why some people with heavy pathology at autopsy had no dementia, since cognitive reserve is a label rather than a mechanism; whether treating amyloid earlier would do more.

Cure status. RELIEF ONLY, with the anti-amyloid antibodies producing measurable slowing that does not alter the ultimate course on present evidence. Reversible causes exist and must be excluded — hypothyroidism, B12 deficiency, normal pressure hydrocephalus, subdural haematoma, depression, medication effects — and those are CURABLE, which is why they are looked for. They are a small fraction of presentations. Cholinesterase inhibitors produce small symptomatic benefit without altering progression. Anti-amyloid antibodies slow measured decline by roughly a quarter to a third over eighteen months, without stopping it.

Prevention. The strongest prevention evidence in Chapter 06 after intellectual developmental disorders.

Blood pressure control: MODERATE. SPRINT MIND (Williamson and colleagues, *JAMA*, 2019; 9,361 participants, systolic target below 120 against below 140 mm Hg) did **not** meet its dementia endpoint. Probable dementia hazard ratio 0.83 (95 per cent CI 0.67 to 1.04) — **not statistically significant** — with 149 against 176 cases, 7.2 against 8.6 per 1,000 person-years. Mild cognitive impairment hazard ratio 0.81 (0.69 to 0.95) was significant, 14.6 against 18.3 per 1,000 person-years. The combined endpoint of mild cognitive impairment or probable dementia, hazard ratio 0.85 (0.74 to 0.97), was significant, 20.2 against 24.1 per 1,000 person-years.

The trial stopped early for cardiovascular benefit and was consequently underpowered for dementia. Only the mild cognitive impairment outcome and the composite reached significance; the dementia endpoint did not. This is frequently misreported. Meta-analyses of antihypertensive trials support a modest protective effect. Hypertension context: about 1.4 billion adults aged 30 to 79 had hypertension in 2024, 33 per cent of that age group; about 630 million were diagnosed and treated; about 320 million were controlled, 23 per cent; about 600 million were unaware (WHO hypertension fact sheet, 25 September 2025, 2024 data).

The same page assigns 44 per cent to both the unaware group of 600 million and the treated group of 630 million, and 630 of 1,400 is 45 per cent; the discrepancy is the page's own.

Hearing aid use: CONTESTED. ACHIEVE (Lin and colleagues, *Lancet*, 2023; 977 participants, three years) found **no significant difference in the full cohort**: three-year cognitive change difference 0.002 standard deviation units (95 per cent CI −0.077 to 0.081; p=0.96). **The primary outcome was null.** In the pre-specified high-risk ARIC subgroup of 238 participants, hearing intervention was associated with a 48 per cent reduction in three-year cognitive change, difference 0.191 SD units (0.022 to 0.360; p=0.027). The 48 per cent figure that circulates widely is that subgroup result, not the primary outcome. Hearing loss remains in the Lancet Commission's 14 factors on observational grounds.

Education: MODERATE. Low education is in the 14 factors, and Mendelian randomisation studies support a causal protective effect of educational attainment. Education also raises cognitive reserve, delaying

symptom onset for the same pathology burden. *Smoking cessation*: MODERATE. *Physical activity*: MODERATE; the observational association is consistent, and randomised exercise trials with dementia incidence endpoints have mostly been null or underpowered, with sources disagreeing on how much of the observational association is reverse causation from the long prodrome. *Diabetes and glycaemic control*: MODERATE; GBD attributes about 15 per cent of the dementia burden to high fasting plasma glucose†.

Midlife LDL cholesterol control: MODERATE, PAF 7 per cent†. *Treating vision loss* by cataract surgery and spectacles: MODERATE, PAF 2 per cent, with observational evidence that cataract surgery is associated with lower dementia incidence. *Alcohol reduction*: MODERATE. *Head injury prevention* through helmet law, road safety and sport protocols: MODERATE. Helmets reduce the risk of death by more than six times and brain injury risk by up to 74 per cent; seat-belts reduce occupant death risk by up to 50 per cent; a 1 per cent increase in mean traffic speed produces a 4 per cent increase in fatal crash risk; road deaths are about 1.16 million a year (WHO road traffic injuries fact sheet, 20 July 2026). The brain-injury-to-dementia link is the weaker leg of that chain.

Air pollution reduction: MODERATE. *Addressing social isolation*: MODERATE, with intervention trials using dementia endpoints absent. *Multidomain intervention*: CONTESTED; the FINGER trial in Finland showed benefit on a composite cognitive score and subsequent multidomain trials were null or marginal. *Cognitive training*: CONTESTED; ACTIVE showed durable gains on trained abilities with limited transfer, and commercial brain-training claims are not supported.

Treatment. *Cholinesterase inhibitors* — donepezil, rivastigmine, galantamine — give small symptomatic benefit, roughly two to three points on ADAS-cog over six months, with no effect on progression. Donepezil is not EML-listed, is off-patent, and costs on the order of tens of US dollars a patient-year; rivastigmine likewise, at tens to low hundreds. *Memantine* gives small benefit in moderate-to-severe disease; not EML-listed, off-patent, tens of US dollars a patient-year.

Anti-amyloid monoclonal antibodies, the measured effect, the price and the harms:

Lecanemab (Clarity AD; van Dyck and colleagues, *NEJM*, 2023; 1,795 participants, 18 months) produced a CDR-SB difference of **−0.45 points** on an 18-point scale, a **27 per cent slowing** of decline against placebo (p=0.00005). The minimum clinically important difference on CDR-SB in mild Alzheimer disease is generally put at 0.5 to 1.0 points, so the measured effect is at or below the usual threshold for clinical detectability in an individual patient. Harms: ARIA-E, brain oedema, **12.5 per cent against 1.7 per cent** on placebo; ARIA-H, microhaemorrhage, **17.0 per cent against 8.7 per cent**, with isolated ARIA-H 8.8 against 7.6 per cent. Deaths occurred in the open-label extension in patients on anticoagulants. The price is approximately **US$26,500 a year** at US list price†, plus the cost of amyloid PET or cerebrospinal fluid confirmation, *APOE* genotyping, infusion every two weeks, and serial MRI monitoring for ARIA. Not EML-listed; on patent.

Donanemab (TRAILBLAZER-ALZ 2; Sims and colleagues, *JAMA*, 2023; 1,736 enrolled, 1,182 in the low-and-medium-tau primary analysis population, 18 months) produced **22 per cent slowing on the iADRS in all participants and 35 per cent in the primary analysis population**. Within the low-and-medium-tau population, slowing was 60 per cent on iADRS and 46 per cent on CDR-SB in mild cognitive impairment (n=214); 30 and 38 per cent in mild Alzheimer dementia (n=534); 48 and 45 per cent under age 75 (n=542); 25 and 29 per cent at 75 or older (n=551). Harms: **ARIA-E 24 per cent**; **ARIA-H 31.4 per cent against 13.6 per cent** on placebo; serious ARIA 1.6 per cent†. Trial deaths attributed to ARIA were reported in the primary publication. The price is approximately **US$32,000 a year** at US list†, with the same ancillary costs. Not EML-listed; on patent.

Both drugs produce a real, statistically robust, small slowing. Neither halts nor reverses decline. Both carry a rate of imaging abnormality between roughly one in four and one in three, with a smaller rate of symptomatic and occasionally fatal events. Neither is on the WHO Essential Medicines List; the Expert Committee considered them and did not add them. And the infrastructure they require — amyloid confirmation, biweekly or monthly infusion, serial MRI — does not exist in the countries where over 60 per cent of people with dementia live. Set beside them the alternative with its own cost: blood pressure control with off-patent EML-listed drugs.

Hydrochlorothiazide, amlodipine, enalapril and losartan are all EML-listed and all off-patent. The NHS Drug Tariff for England and Wales, September 2026, gives amlodipine 5 mg at 64 pence for a pack of 28 tablets, 2.3 pence a tablet, and amlodipine 10 mg at 72 pence for 28, 2.6 pence a tablet; at one tablet a day that is £8 to £9 a patient-year, roughly ten to twelve US dollars. The unit on the Drug Tariff column was not confirmed from the retrieved document and pence is the conventional unit and consistent with the magnitudes. That regimen produced the SPRINT MIND composite hazard ratio of 0.85.

The antibodies cost three to four orders of magnitude more, and the exact multiple is not printed here because the cholinesterase-inhibitor and antihypertensive prices the earlier comparison rested on were unsourced estimates. The price source the book had counted on, the MSH International Medical Products Price Guide, has a last edition of 2017 and its site was retired after 30 June 2024.

Aducanumab was withdrawn from the market in 2024, after an approval that the regulator's own advisory committee had voted against.

Non-pharmacological interventions for the syndrome: cognitive stimulation therapy improves cognition and quality of life in randomised trials, and reminiscence work, music and structured activity reduce agitation. *Carer support and training* reduces carer depression and delays institutionalisation in randomised trials, and given that informal carers provide about half the US$1.3 trillion cost and five hours of care daily, this is where cost-effectiveness is largest. *Antipsychotics for behavioural symptoms* give small benefit for aggression, offset by a roughly 1.5 to 1.7 times increase in mortality† and increased stroke risk, with black-box warnings; use is appropriate only for severe risk, short-term, reviewed. *Managing vascular risk after diagnosis* continues to matter for mixed pathology. *Avoiding anticholinergic and sedative medication burden* is associated with better cognition, and deprescribing is a free intervention.

Simple means. Blood pressure control with off-patent EML drugs, at the prices above, which produced the SPRINT MIND composite hazard ratio of 0.85. Physical activity: moderate observational effect, free. Hearing aids: the ACHIEVE primary outcome was null, so this is stated as unproven for cognition despite being clearly worthwhile for hearing, and a hearing aid still costs far less than an antibody. Spectacles and cataract surgery: cataract surgery is among the most cost-effective surgical procedures in medicine on its own merits, and the dementia benefit is observational. Education: the strongest simple means in this entry, supported by Mendelian randomisation, and a policy rather than a clinical act. Social connection and continued activity: in the 14 factors, with thin intervention evidence. Salt reduction, for the vascular contribution: global mean intake is about 4,278 mg a day of sodium, roughly 11 g a day of salt, more than double the WHO recommended limit of under 2,000 mg of sodium, under 5 g of salt; about 1.7 million deaths a year are associated with excess sodium (WHO sodium reduction fact sheet, 11 May 2026; intake 2021, deaths 2023). Carer support: a trained relative, not a product.

Gaps. SPRINT MIND's dementia endpoint did not reach significance and the trial was underpowered; sources frequently report it as if it had. ACHIEVE's primary outcome was null, and the circulating 48 per cent is a subgroup. Both are common misreportings and both are printed correctly above. The Lancet Commission's 45 per cent combined PAF assumes independence between factors and complete elimination; it is an upper bound on a counterfactual, not an achievable target. Anti-amyloid antibody trials were in selected, mostly white, high-income populations with confirmed amyloid and without anticoagulation or high microhaemorrhage burden, so real-world safety and effect may differ. There are no long-term randomised data beyond eighteen months for the antibodies, and whether the small slowing accumulates, plateaus or reverses is unknown. The falling age-specific incidence in high-income countries is well measured and not fully explained. Diagnosis rates are low everywhere, and the 57 million figure is modelled from sparse prevalence surveys.

> **Depth.** A syndrome with many causes. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

07 — Sleep-wake disorders

ICD-11 gave sleep-wake disorders their own chapter for the first time, having previously distributed them between the mental disorders and nervous system chapters of ICD-10. The chapter covers insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders and parasomnias. Not one of these conditions has a stand-alone GBD burden estimate, as the chapter introduction states.

Insomnia disorder

What it is. Persistent difficulty falling asleep, staying asleep, or waking too early, despite adequate opportunity to sleep, with daytime consequences. Chronic insomnia disorder requires the pattern to persist for at least three months.

Measured. Insomnia symptoms occur in roughly 30 to 35 per cent of adults; insomnia *disorder* meeting full criteria in roughly 6 to 10 per cent†. The distinction matters and is often collapsed in reporting. Women roughly 1.4 to 1.5 times men†. Prevalence rises with age, and in older adults symptom prevalence exceeds 40 per cent in some surveys†, though much of that is comorbid rather than primary. There is no WHO fact sheet, and GBD produces no stand-alone burden estimate, so global DALY figures are unavailable — a notable gap given the prevalence. Insomnia is an independent prospective risk factor for incident depression, roughly twice the risk, and for hypertension and suicidal ideation. Hypnotic prescribing has shifted away from benzodiazepines toward Z-drugs and newer agents, and total sedative-hypnotic use remains high in most high-income countries.

Where it starts. Heritability is roughly 30 to 40 per cent†. Female sex, older age, shift work and comorbid mental or physical disorder are all established. Hyperarousal is the best-supported model: people with the disorder show elevated physiological and cognitive arousal measures, and that is a description of state rather than a cause. Conditioning — the association between bed and wakefulness — is the target of stimulus control and sleep restriction therapy, and the therapies' efficacy supports the model, which is as close to a demonstrated mechanism as this chapter gets. Objective sleep measures correlate only weakly with the subjective complaint; that is one of the best-replicated findings in sleep medicine and it complicates every prevalence estimate. There is no biomarker, and diagnosis is by history. Orexin antagonist efficacy demonstrates that the wake-promoting orexin system is a usable target, and does not establish an orexin abnormality as the cause. Not known: why the subjective complaint and objective measures diverge; whether insomnia disorder is one condition.

Cure status. Treated with cognitive behavioural therapy for insomnia: CURABLE in roughly 40 to 50 per cent (remission)†. Treated with drugs: CONTROLLABLE. This is one of the clearest cases in the book where a non-drug treatment produces durable remission and a drug does not. Cognitive behavioural therapy for insomnia gives response in roughly 60 to 70 per cent of those treated and remission in roughly 40 to 50 per cent, and gains are maintained or continue to improve at six to twelve months after treatment ends. Hypnotics are effective while taken, with rebound insomnia on discontinuation and no durable benefit after stopping. Head-to-head and sequential trials find the behavioural treatment equal or superior to hypnotics acutely and clearly superior at follow-up.

Prevention. Treating insomnia prevents other conditions, which is the headline here: digital cognitive behavioural therapy for insomnia reduced incident depression in randomised trials, and the SHUTi and related trials showed reductions in depressive symptom onset, MODERATE. Sleep hygiene education alone: WEAK. As a standalone intervention it has repeatedly failed, and it is effective only as one component of the full behavioural treatment. It is widely dispensed and performs poorly. Shift schedule design — forward-rotating, adequate recovery, limiting consecutive nights: MODERATE. Limiting evening light and screen use: WEAK; melatonin suppression by evening light is well demonstrated physiologically and the effect on incident insomnia disorder is not established. Avoiding hypnotic initiation for transient insomnia prevents dependence: MODERATE.

Treatment. *Cognitive behavioural therapy for insomnia* is first-line in every major guideline, including the American College of Physicians, the European Sleep Research Society and NICE. Effect sizes are moderate-to-large on sleep onset latency and wake after sleep onset and moderate on sleep efficiency and subjective quality, and durability after treatment ends is its distinguishing feature. Its components are sleep restriction, stimulus control, cognitive restructuring, relaxation and sleep hygiene. *Digital delivery* achieves effect sizes approaching face-to-face delivery in randomised trials, including large pragmatic trials, at near-zero marginal cost per additional user: the most scalable effective intervention in this chapter.

Brief behavioural treatment for insomnia, a two-to-four session version deliverable by a nurse or primary care worker, is effective in randomised trials, which is what matters where therapists do not exist. *Dual orexin receptor antagonists* — suvorexant, lemborexant, daridorexant — give modest effects, roughly 10 to 20 minutes improvement in sleep onset and 20 to 40 minutes in total sleep time against placebo, with a better safety profile than Z-drugs on current evidence and less tolerance signal. They are not EML-listed, on patent, and cost thousands of US dollars a patient-year at list price. *Z-drugs* — zolpidem, zopiclone, eszopiclone — are effective short-term, with concerns about falls and fractures in older adults, complex sleep behaviours that regulators have warned about, next-day impairment, tolerance and dependence; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year.

Benzodiazepines are effective short-term, with dependence, tolerance, falls and cognitive effects in older adults; diazepam is EML-listed for other indications, off-patent, and costs a few tens of US dollars a patient-year at most, and guidelines advise against long-term use. *Low-dose doxepin* is effective for sleep maintenance with fewer of the Z-drug problems; off-patent, not EML-listed, tens to low hundreds of US dollars a patient-year. *Melatonin* has a small effect on sleep onset latency, roughly 7 to 12 minutes in meta-analysis, larger in circadian disorders than in primary insomnia, and is most useful in children, in older adults with low endogenous melatonin, and in circadian misalignment; not EML-listed, off-patent, tens of US dollars a year, with documented variability in supplement content.

Antihistamines and sedating antidepressants used off-label for sleep are widespread and poorly evidenced, with anticholinergic burden concerns; trazodone and mirtazapine are used far more than their sleep evidence supports. *Exercise* improves sleep quality with small-to-moderate effect sizes in randomised trials, smaller than the behavioural treatment.

Simple means. Sleep restriction and stimulus control: the two most effective components of the first-line treatment are purely behavioural instructions — restrict time in bed to actual sleep time and then extend it gradually; get out of bed when not sleeping; use the bed only for sleep. They are deliverable from a single printed page, and they are the active ingredients of the first-line treatment for a condition affecting hundreds of millions. This is the strongest simple-means finding in the chapter. Fixed wake time, seven days a week: the single most important instruction, anchoring the circadian system. Morning light at a fixed hour: advances and stabilises circadian phase, with the physiological effect well quantified. Exercise, at small-to-moderate effect sizes. Reducing evening light: physiologically demonstrated melatonin suppression. Caffeine and alcohol timing: alcohol reduces sleep onset latency and degrades sleep architecture in the second half of the night, demonstrated polysomnographically.

Gaps. No GBD burden estimate and no WHO fact sheet, for a condition with 6 to 10 per cent disorder prevalence. The subjective-objective discordance is unexplained and undermines both prevalence estimation and outcome measurement. The behavioural treatment is first-line everywhere and available almost nowhere, and the gap between guideline and provision is the largest in this chapter. Long-term hypnotic safety data beyond a year are almost entirely observational. Orexin antagonist trials are short and sponsor-run.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number ([B] three months or more counts as chronic).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Obstructive sleep apnoea

What it is. Repeated collapse of the upper airway during sleep, causing breathing pauses, oxygen desaturation and arousals. It fragments sleep and produces daytime sleepiness. Many people with the physiological finding have no symptoms.

Measured. 936 million adults **aged 30 to 69** worldwide have mild-to-severe obstructive sleep apnoea, at an apnoea-hypopnoea index of 5 or more (95 per cent CI 903 to 970 million). 425 million adults **aged 30 to 69** have moderate-to-severe disease, at an index of 15 or more (95 per cent CI 399 to 450 million). The source is a literature-based analysis across 193 countries using the AASM 2012 criteria (Benjafield and colleagues, *Lancet Respiratory Medicine*, 2019;7(8):687–698). Both figures are for adults aged 30 to 69 only, not for all adults, and the age band travels with them every time they appear.

The study's funding statement is the single word ResMed, and ResMed manufactures CPAP devices. On these criteria and within that age band, this is by prevalence one of the largest conditions in the book. The large majority remain undiagnosed, with estimates of the undiagnosed proportion exceeding 80 per cent in most settings†. The male-to-female ratio is roughly 2 to 1 at equivalent severity, and the gap narrows after menopause†. Prevalence rises with age and with body weight, and obesity is the dominant modifiable determinant. The condition is associated with hypertension, atrial fibrillation, type 2 diabetes, stroke and road traffic collision risk in observational studies, and untreated moderate-to-severe apnoea with roughly two to three times collision risk. There is no WHO fact sheet and no stand-alone GBD burden estimate.

Where it starts. Obesity is the strongest modifiable risk factor. A 10 per cent weight gain is associated with roughly a 32 per cent increase in the apnoea-hypopnoea index and roughly six times the odds of developing moderate-to-severe apnoea; a 10 per cent weight loss is associated with roughly a 26 per cent reduction in the index (Peppard and colleagues, *JAMA*, 2000). A well-quantified dose-response in both directions. Craniofacial structure — retrognathia, maxillary narrowing, tonsillar hypertrophy, which is the dominant cause in children — is established. Male sex, age and menopause are established. Alcohol and sedatives worsen events acutely. Nasal obstruction, smoking and fluid-shift conditions such as heart failure and renal failure are contributory. Heritability is roughly 35 to 40 per cent, largely mediated through craniofacial and body-composition traits.

The mechanism here is mechanical and well understood: anatomical narrowing plus reduced upper-airway dilator muscle tone during sleep. That is an unusually clear mechanistic picture compared with most of this chapter. Four physiological traits — anatomy, muscle responsiveness, arousal threshold and loop gain — have been characterised and vary between patients, which explains differential treatment response and is the basis of current phenotyping work. Not known: why the cardiovascular associations have not translated into trial benefit from treatment, which is the central unresolved problem in this field.

Cure status. Treated with CPAP or an oral appliance: CONTROLLABLE, effective only while used. Substantial weight loss in weight-related cases, adenotonsillectomy in most children, and maxillomandibular advancement surgery in selected adults: CURABLE. CPAP abolishes events while worn and they return immediately on stopping. Adenotonsillectomy in children with adenotonsillar hypertrophy resolves the apnoea in the large majority — a genuine cure. Bariatric surgery produces remission in a substantial proportion of severely obese patients. Adherence is the limiting factor: roughly 30 to 50 per cent of CPAP users do not reach commonly used adherence thresholds.

Prevention. Weight management at population level: MODERATE on the dose-response above, with no randomised prevention trials using incident apnoea endpoints. Treating childhood adenotonsillar hypertrophy: MODERATE, and it addresses a cause rather than a symptom. Avoiding alcohol and sedatives before sleep: WEAK, on demonstrated acute physiological effect. Smoking cessation: WEAK. Note the asymmetry with other conditions in this chapter: here the main preventive lever, body weight, is itself a condition the health system struggles to influence at population level.

Treatment. *CPAP* is the reference treatment. It abolishes apnoea events, reduces daytime sleepiness with moderate-to-large effect sizes, improves quality of life, and reduces blood pressure by roughly 2 to 3 mm Hg†. The cardiovascular outcome evidence is negative and is reported as such. SAVE (McEvoy and colleagues, *NEJM*, 2016; 2,717 participants aged 45 to 75 with moderate-to-severe apnoea and established cardiovascular disease, mean follow-up 3.7 years) found a primary composite cardiovascular hazard ratio

of **1.10 (95 per cent CI 0.91 to 1.32; p=0.34)**, with 229 events on CPAP against 207 on usual care: **no cardiovascular benefit**.

CPAP did significantly reduce sleepiness and apnoea symptoms and improved quality-of-life measures. Low adherence in the trial, at a mean under four hours a night, is the standard explanation and remains a hypothesis rather than an established finding. Subsequent trials, RICCADSA and ISAACC, were similarly null on cardiovascular endpoints. So CPAP reliably treats the symptoms and the physiology, and has not been shown to reduce cardiovascular events in randomised trials, despite strong observational associations. On cost, the sources in this book disagree.

This chapter's compilation gave the device as a one-off cost in the low hundreds of US dollars, with annual mask and consumable costs of roughly one to three hundred. Another dossier gives the machine at hundreds to thousands of euro lasting five to ten years, with masks and filters at hundreds of euro a year. Those are the same items in a different currency, with a different top end, and with a service life where the first states a one-off. Both stand, unresolved.

Mandibular advancement devices are less effective than CPAP on the apnoea-hypopnoea index and comparable on sleepiness and blood pressure, because adherence is higher. Another dossier in this book quantifies this as a reduction in the index of roughly 50 per cent, less than CPAP, with better adherence, so that health outcomes are often equivalent, which is a less hedged conclusion than the one above, and both stand. On cost, that dossier gives hundreds to thousands of euro for a custom device and tens to hundreds of euro for a thermoplastic one, splitting a device type that this chapter's compilation treated as one; the compilation's own figure was an unsourced estimate and is not printed.

Weight loss is the only intervention that addresses the cause in most adult cases; see simple means. *Positional therapy* for position-dependent apnoea is effective in a defined subgroup and cheap. *Surgery*: adenotonsillectomy is first-line in children; maxillomandibular advancement has high efficacy in selected adults, roughly 85 per cent surgical success in series†; uvulopalatopharyngoplasty is modest and declining in use; hypoglossal nerve stimulation is effective in selected patients at a device cost in the tens of thousands of US dollars. *GLP-1 receptor agonists*: tirzepatide reduced the apnoea-hypopnoea index substantially in randomised trials in obese patients (SURMOUNT-OSA, 2024), by roughly 25 to 30 events an hour, and gained a regulatory indication. On patent, not EML-listed, and costing thousands of US dollars a patient-year at list price. *Modafinil and solriamfetol* treat residual sleepiness on treatment, and the symptom only. *Supplemental oxygen alone* corrects desaturation without addressing fragmentation and is not a treatment for the disorder.

Simple means. Weight loss: roughly 26 per cent reduction in the apnoea-hypopnoea index per 10 per cent of weight lost†, and the Sleep AHEAD randomised trial of intensive lifestyle intervention showed significant index reduction against control, with remission in a meaningful fraction. This is the one intervention that can cure the condition without a device, a drug or an operation. Positional measures, avoiding supine sleep: effective in position-dependent cases, achievable with no purchased product. Alcohol avoidance in the evening: demonstrated acute physiological worsening. Treating nasal obstruction: cheap, and it improves CPAP tolerance. Myofunctional therapy, meaning upper airway exercises: meta-analysis shows roughly 50 per cent reduction in the index in adults in small trials, on thin evidence, and the intervention costs nothing. Light, sleep timing, social connection and exercise-for-mood have no specific role here beyond their contribution to weight.

Gaps. There is no GBD estimate for a condition affecting 936 million adults aged 30 to 69 on the only global estimate available, which was ResMed-funded — the largest single data gap in this book. The disconnect between strong observational cardiovascular associations and null randomised outcomes is unresolved and consequential, because it determines whether screening asymptomatic people is worthwhile. The apnoea-hypopnoea index correlates poorly with symptoms and with outcomes and yet defines the disease; the field acknowledges the measure is inadequate and has no agreed replacement. Prevalence figures rest on a literature-based model rather than population polysomnography for most of the 193 countries. Almost all treatment evidence is from high-income settings, and CPAP requires electricity and maintenance.

> **Depth.** Starts in: the throat. Size: 1 cm†; depth +11.19. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Central sleep apnoea

What it is. Breathing pauses during sleep caused by a failure of respiratory drive rather than airway collapse. The commonest adult form is Cheyne-Stokes respiration associated with heart failure. It also occurs with opioid use, at altitude, after stroke, and idiopathically.

Measured. Much less common than obstructive apnoea: roughly 1 per cent of the general adult population in community studies, strongly age- and male-skewed. In heart failure with reduced ejection fraction, central apnoea or Cheyne-Stokes respiration is present in roughly 25 to 40 per cent†. In chronic opioid therapy, central apnoea prevalence is roughly 15 to 30 per cent†. There is no WHO fact sheet and no GBD estimate. The presence of Cheyne-Stokes respiration in heart failure is associated with worse prognosis, and whether it is a marker or a contributor is unresolved.

Where it starts. Heart failure with reduced ejection fraction is the dominant cause in adults, through increased chemoreflex sensitivity — high loop gain — plus circulatory delay. Opioid use produces dose-related suppression of respiratory drive: established. At high altitude, periodic breathing is a normal physiological response above roughly 2,500 m. Stroke and brainstem lesions are established causes. Treatment-emergent central apnoea occurs in roughly 5 to 15 per cent of obstructive apnoea patients started on CPAP†, usually transiently. Congenital central hypoventilation syndrome, from *PHOX2B* mutations, is rare and a case where the genetic cause is fully established.

Loop-gain physiology is well characterised and quantitatively modelled, one of the better understood mechanisms in sleep medicine. Whether Cheyne-Stokes respiration in heart failure is harmful or a compensatory response is genuinely disputed, and the SERVE-HF result below is why.

Cure status. CONTROLLABLE in general. Where the cause is removed — opioid discontinuation, altitude descent, or successful heart failure treatment including cardiac resynchronisation, a ventricular assist device or transplantation — CURABLE.

Prevention. Optimal heart failure treatment: MODERATE, since improving cardiac function reduces central apnoea. Avoiding chronic high-dose opioid therapy: MODERATE. Acetazolamide for altitude periodic breathing is effective prophylactically; EML-listed, off-patent, a few US dollars a course.

Treatment. *Treat the underlying cause* first and most importantly. *Adaptive servo-ventilation* is a negative trial result that changed practice. SERVE-HF (Cowie and colleagues, *NEJM*, 2015; 1,325 participants with heart failure with reduced ejection fraction and predominant central apnoea) found that the device suppressed the apnoea effectively and that **all-cause and cardiovascular mortality were higher in the treated arm**, with a cardiovascular mortality hazard ratio of about 1.34. Adaptive servo-ventilation is now contraindicated in heart failure with reduced ejection fraction and predominant central apnoea. An effective physiological treatment increased deaths, and this is one of the clearest demonstrations in the book that correcting a measurement is not the same as helping a patient. *CPAP* has modest efficacy; the earlier CANPAP trial was neutral overall with a suggestion of benefit in those whose apnoea was suppressed. *Nocturnal oxygen* reduces central events with no mortality evidence. *Acetazolamide and theophylline* reduce central events through respiratory stimulation, in small trials; acetazolamide is EML-listed, off-patent, and costs tens of US dollars a patient-year at most. *Phrenic nerve stimulation*, transvenous, reduces events in randomised trials at a device cost in the tens of thousands of US dollars.

Simple means. Opioid reduction where that is the cause. Altitude descent where that is the cause. Avoiding the supine position: modest effect. Heart failure self-management — salt and fluid adherence, weight monitoring, medication adherence — addresses the cause, with no supply chain beyond the drugs already indicated.

Gaps. No burden estimate of any kind. The SERVE-HF mortality signal has no agreed mechanistic explanation. Whether treating central apnoea in heart failure helps at all remains unanswered; what is now known is that one way of treating it harms. Treatment-emergent central apnoea has no agreed management pathway.

> **Depth.** Starts in: the breathing centre of the brainstem. Size: 1 cm†; depth +11.19. First complaint: about 65 years († onset about age 65); time depth 52.67. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Narcolepsy

What it is. Chronic inability to maintain stable wakefulness, with irresistible sleep attacks, and intrusion of REM-sleep phenomena into wakefulness. Type 1 includes cataplexy, sudden loss of muscle tone triggered by emotion, and is caused by loss of hypocretin, also called orexin, neurons. Type 2 lacks cataplexy and has normal hypocretin.

Measured. Prevalence is roughly 25 to 50 per 100,000 for type 1, with type 2 less well characterised†. Japan reports higher figures, up to about 160 per 100,000†, and Israel notably lower — a genuine and unexplained geographic variation. Onset is bimodal with peaks around age 15 and around age 35†. Diagnostic delay commonly exceeds a decade. There is no WHO fact sheet and no stand-alone GBD estimate. Mortality is not substantially elevated; the burden is in function, education, employment and accident risk.

Where it starts. This is the condition in these three chapters where the mechanism is best established. Loss of hypocretin-producing neurons in the lateral hypothalamus causes type 1 narcolepsy. Cerebrospinal fluid hypocretin-1 is undetectable or very low in roughly 90 to 95 per cent of type 1 cases, and post-mortem studies show loss of 85 to 95 per cent of these neurons†. This is a demonstrated cause rather than a hypothesis, which is a rarity in this chapter. *HLA-DQB1*06:02* is present in roughly 98 per cent of type 1 cases against roughly 25 per cent of the general population — the strongest HLA association known for any disease. That, with T-cell receptor associations, makes an autoimmune mechanism highly likely, and autoantigen-specific autoimmunity has not been definitively demonstrated.

The 2009 to 2010 Pandemrix association: following the H1N1 pandemic vaccination campaign, narcolepsy incidence rose in several European countries among vaccinated children and adolescents. Estimates centre on roughly one additional case per 16,000 vaccinated, with relative risks around 5 to 14 in Finland and Sweden†. The association was specific to one adjuvanted vaccine formulation and was not found for other H1N1 vaccines. Independently, H1N1 infection itself was associated with increased narcolepsy incidence in China, where vaccination coverage was low. Both findings support the autoimmune model triggered by influenza antigen exposure. Reported accurately: it is a genuine vaccine-associated harm, confined to one product, and it does not generalise to vaccines in general. Streptococcal infection is associated as a possible additional trigger. Not known: the autoantigen; why only a small fraction of *HLA-DQB1*06:02* carriers develop narcolepsy; whether early immunotherapy could preserve neurons, which is untested and for which the window has passed by the time of diagnosis. Type 2 narcolepsy and idiopathic hypersomnia have no established mechanism and may be heterogeneous.

Cure status. RELIEF ONLY. The neurons are gone and nothing restores them. No treatment is disease-modifying. Symptomatic treatment is effective and allows most people to function. Hypocretin receptor agonists in development may change this classification; as of this edition they are in trials, with hepatotoxicity signals in some programmes, and they are reported as not yet available.

Prevention. No established prevention. The Pandemrix finding led to withdrawal of that formulation, and adjuvant selection in future pandemic vaccines is an identified consideration: MODERATE as a product-specific lesson, not as a general preventive measure. Influenza vaccination with non-implicated formulations reduces H1N1 infection, which is itself associated with narcolepsy, so vaccination is net protective on current evidence: WEAK.

Treatment. *Scheduled daytime naps*: short planned naps substantially reduce sleepiness, and they are effective, free and underused. Here the simple means and the treatment coincide. *Modafinil and armodafinil* are first-line for sleepiness in most guidelines, with moderate effect sizes; not EML-listed, off-patent, low hundreds of US dollars a patient-year. *Sodium oxybate*, including the lower-sodium formulation, is the only agent effective for cataplexy, disrupted nocturnal sleep and daytime sleepiness simultaneously, with large effect sizes on cataplexy frequency; not EML-listed, patent status mixed, and costing a six-figure sum in US dollars a patient-year at US list price — among the highest-cost drugs in this book — with controlled-substance handling requirements.

Pitolisant, an H3 inverse agonist, is effective for sleepiness and cataplexy; not EML-listed, on patent, tens of thousands of US dollars a patient-year. *Solriamfetol* is effective for sleepiness; not EML-listed, on patent in most markets, thousands to tens of thousands of US dollars a patient-year. *Methylphenidate and amphetamines* are long-established, effective for sleepiness, and cheap; methylphenidate is EML-listed, off-patent, and costs tens to low hundreds of US dollars a patient-year. In most of the world this is the only affordable option. *Antidepressants for cataplexy* — venlafaxine, clomipramine, SSRIs — suppress REM sleep and reduce cataplexy; off-label, cheap, and the mainstay where sodium oxybate is unaffordable. Clomipramine and fluoxetine are EML-listed, off-patent, and cost a few to a few tens of US dollars a patient-year.

Simple means. Scheduled short naps at fixed times: measurable reduction in sleepiness, at no cost, and combined with a stimulant they allow many people to work. Fixed sleep and wake times with adequate nocturnal sleep opportunity: standard, and necessary for the naps to work. Avoiding alcohol and heavy meals reduces sleep attack frequency. Safety adaptation — driving restriction, workplace adjustment, swimming precautions — prevents the injuries that constitute much of the real harm, and is organisational rather than clinical. Note the cost asymmetry: scheduled naps with generic methylphenidate and generic clomipramine cost a few hundred US dollars a patient-year at most and achieve a substantial part of what the six-figure regimen achieves. The gap in effect is real and much smaller than the gap in price.

Gaps. Prevalence varies several-fold between countries with no explanation. Type 2 narcolepsy and idiopathic hypersomnia are poorly defined and may not be single entities. Diagnostic delay of a decade is the norm and is a service failure. Sodium oxybate pricing bears no relationship to manufacturing cost, since gamma-hydroxybutyrate is a simple molecule: a market problem, not a scientific one. There is no disease-modifying treatment and no trial of early immunotherapy.

> **Depth.** Starts in: the hypocretin neuron. Size: 20 µm†; depth +5.54. First complaint: about 15 years († onset about age 15); time depth 51.34. One untreated course: no number ([B] chronic).
>
> **Model reading.** Way of ending: supply from inside. Layer: phase. By the rule it is held by supply. It ends only if the source is restored. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Restless legs syndrome

What it is. An urge to move the legs, usually with uncomfortable sensations, worse at rest and in the evening, and relieved by movement. It disrupts sleep onset. Most people with it also have periodic limb movements during sleep. Also called Willis-Ekbom disease.

Measured. Prevalence is roughly 5 to 10 per cent of adults in European-ancestry populations using full diagnostic criteria, and roughly 2 to 3 per cent clinically significant, meaning at least twice weekly with distress. It is substantially lower in East and South Asian populations, roughly 1 to 3 per cent, consistently†. Women roughly twice men. Prevalence rises with age. Roughly 20 to 30 per cent of pregnancies are affected, usually resolving after delivery. There is no WHO fact sheet and no stand-alone GBD estimate. It is associated with iron deficiency, end-stage renal disease where prevalence is roughly 20 to 30 per cent, pregnancy, and peripheral neuropathy.

Where it starts. Brain iron deficiency is the best-supported mechanism: cerebrospinal fluid ferritin is reduced, autopsy shows reduced substantia nigra iron, and MRI confirms reduced brain iron even in people with normal serum ferritin. Iron repletion improves symptoms. That is an unusually well-supported

mechanism for this chapter. Heritability is roughly 50 to 60 per cent, and genome-wide association studies have identified reproducible loci including *MEIS1*, *BTBD9* and *PTPRD*, with *MEIS1* carrying one of the larger common-variant effect sizes in any complex trait. Iron deficiency from low serum ferritin, blood donation, gastrointestinal loss or pregnancy is established and treatable. End-stage renal disease is established and resolves after transplantation. Dopamine antagonists, antihistamines, SSRIs and some other antidepressants precipitate or worsen it, and drug-induced cases are common and reversible. The dopaminergic connection is supported by treatment response and by the diurnal pattern tracking the dopamine rhythm, and a primary dopamine deficiency has not been demonstrated. The iron-dopamine interaction in the brain is the working model, with good support from imaging, autopsy and treatment response. Not known: why the ethnic prevalence difference exists; why augmentation occurs; the relationship between the sensory symptom and the movement.

Cure status. Where a removable cause is found: CURABLE — iron repletion in iron deficiency, transplantation in renal failure, stopping a precipitating drug, delivery in pregnancy. Idiopathic disease: CONTROLLABLE. Augmentation is the central clinical problem: long-term dopamine agonist treatment causes symptoms to become earlier in the day, more severe, and to spread to other body parts, in a substantial proportion of patients, with estimates of roughly 7 to 8 per cent per year of treatment, cumulative†. That iatrogenic worsening led to a major guideline reversal: dopamine agonists are no longer first-line, having been first-line for two decades.

Prevention. Maintaining iron sufficiency, particularly in women of reproductive age, in pregnancy, in blood donors and in people with gastrointestinal blood loss: MODERATE. Avoiding precipitating drugs where alternatives exist: MODERATE. Not starting a dopamine agonist: STRONG as a negative recommendation, because it prevents augmentation. That is the clearest preventive statement available here.

Treatment. *Iron repletion*: oral iron where ferritin is low, and intravenous ferric carboxymaltose is effective in randomised trials even in some patients with normal-range ferritin. Oral ferrous salts are EML-listed and off-patent. The UNICEF Supply Catalogue, indicative price read 19 October 2026, gives iron 60 mg tablets at US$1.43 for a bottle of 100, about US$0.0143 a tablet, so about **US$5 a patient-year at one tablet a day**. The same catalogue returned US$1.60 for the same material number on a different page, so the figure is indicative and dated rather than a price. This is the cheapest effective treatment in this part of the book, and it treats the cause.

Alpha-2-delta ligands — gabapentin enacarbil, pregabalin, gabapentin — are now first-line in current guidelines, having displaced dopamine agonists because they do not cause augmentation, with moderate effect sizes on the IRLS score. Gabapentin and pregabalin are not EML-listed, both off-patent, costing tens to low hundreds of US dollars a patient-year. Harms: sedation, dizziness, weight gain, misuse potential. *Dopamine agonists* — pramipexole, ropinirole, the rotigotine patch — are effective short-term with large initial effect sizes, and cause augmentation in a substantial proportion on long-term use; now recommended for limited use; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year.

Low-dose opioids, as prolonged-release oxycodone with naloxone, are effective in refractory and augmented cases with randomised support, and dependence risk requires careful selection. No doses are given. *Stopping the precipitating drug* is curative where applicable, and free. *Pneumatic compression devices and near-infrared light*: small trials, uncertain.

Simple means. Oral iron where ferritin is low, at about US$5 a patient-year on the October 2026 indicative price, addressing the cause, and on the WHO Essential Medicines List. The best cost-to-effect ratio in Chapter 07. Movement, walking, stretching and counter-stimulation: the symptom is relieved by movement by definition, and this is not trivial — it is how most people manage. Exercise: randomised trials show symptom reduction in both general and dialysis populations, with moderate effect sizes in small trials. Fixed sleep timing and adequate sleep, since sleep deprivation worsens symptoms. Reducing caffeine, alcohol and nicotine in the evening: commonly advised, weakly evidenced. Avoiding the precipitating drug: free, and sometimes curative.

Gaps. No burden estimate. The ethnic prevalence difference is robust and unexplained. The augmentation mechanism is unknown, and its true incidence is uncertain because most long-term data come from

specialist clinics. The role of intravenous iron in patients with normal ferritin is supported by some trials and not others, and sources disagree. The guideline reversal on dopamine agonists happened late, after two decades of a treatment now known to cause iatrogenic worsening in many patients, and that is worth recording as an example of a well-intentioned standard treatment that caused harm at scale.

> **Depth.** Starts in: ferritin in the brain. Size: 12 nm†; depth −1.21. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: word. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Delayed sleep-wake phase disorder

What it is. Sleep that is normal in structure and quality but occurs persistently later on the clock than the person's required schedule allows, because the internal circadian clock runs late relative to the external day. The result is chronic sleep restriction on weekdays and a late, long sleep when the schedule permits.

Measured. Prevalence is roughly 0.2 to 10 per cent of adolescents and young adults depending on criteria, and the commonly cited figure in clinical populations is roughly 7 to 16 per cent of adolescents with chronic sleep-onset insomnia†. There is no WHO fact sheet and no stand-alone GBD estimate.

Where it starts. The circadian clock is a demonstrated molecular oscillator: the transcription-translation feedback loop of the *CLOCK*, *BMAL1*, *PER* and *CRY* genes was characterised in work that received the 2017 Nobel Prize in Physiology or Medicine. Light input via intrinsically photosensitive retinal ganglion cells containing melanopsin entrains it through the suprachiasmatic nucleus. Light is the dominant entraining signal and its effect is quantified: the phase response curve to light is measured. Light in the hours after the body temperature minimum, roughly early morning, advances the clock; light in the hours before it, evening and night, delays it.

Melatonin has a roughly opposite phase response curve. Phase shifts of several hours are achievable with controlled light and melatonin timing. Chronotype is heritable, roughly 40 to 50 per cent, with reproducible loci including *PER2*, *PER3* and *RGS16*; familial advanced sleep phase from *PER2* and *CSNK1D* mutations is a demonstrated monogenic trait†. This disorder specifically is associated with a longer intrinsic circadian period, altered light sensitivity, and behavioural reinforcement through evening light exposure and late social schedules.

Adolescence involves a physiological phase delay of roughly one to two hours, which is biological rather than a behavioural choice, so early school start times impose chronic sleep restriction on a whole population. Blindness without light perception produces non-24-hour sleep-wake rhythm disorder in a majority — a clean natural demonstration that light is the entraining signal. The mechanism is established at molecular, anatomical and physiological level with a quantified dose-response to light, which is the strongest mechanistic position of any condition in these three chapters, and it is why the simple means here work. Not known: why individual sensitivity to light varies so much.

Cure status. CONTROLLABLE. Correctly timed light and melatonin shift the clock and the sleep normalises, and the misalignment returns when the schedule or the light exposure reverts. Timed light plus timed melatonin plus behavioural scheduling advances phase reliably in trials, and relapse on stopping is common because the social schedule that produced the delay persists.

Prevention. Later school start times: STRONG. Delaying secondary school start times is followed by increased sleep duration, typically 25 to 45 minutes a night, reduced daytime sleepiness, improved attendance, and in several studies reduced adolescent motor vehicle crash rates, replicated across multiple districts and countries. The intervention is an administrative decision with no supply chain and no cost. Limiting evening light and screen exposure in adolescents: MODERATE; the physiological effect on melatonin onset is well quantified and the effect on disorder incidence less so.

Treatment. *Timed bright light exposure* is the primary treatment, with a quantified phase response curve: morning light to advance a delayed clock. Intensities of roughly 2,500 to 10,000 lux for 30 to 60 minutes are

typical, and ordinary daylight outdoors exceeds this. The effect is phase shifts of one to three hours over days to weeks. It is free outdoors; a light box is a one-off purchase of a few tens to a few hundred US dollars. It is not a drug and has no EML entry. *Timed melatonin* advances phase when taken in the early evening; not EML-listed, off-patent, tens of US dollars a year. *Chronotherapy and progressive scheduling*, by systematically shifting bedtime, is effective and demanding. *Behavioural scheduling with a consistent wake time* is foundational and necessary for any of the above to hold.

Simple means. Light at fixed hours is not an adjunct here: it is the treatment, with a measured dose-response and the capacity for one-to-three-hour phase shifts, and outdoor morning light is free and brighter than any consumer light box. Fixed wake time, seven days a week, anchors the clock and is the single most effective behavioural instruction. Darkness and light avoidance at the appropriate hours matter as much as light exposure and are entirely free. Melatonin at tens of US dollars a year: physiologically targeted, cheap, off-patent. Later school start times: 25 to 45 minutes additional sleep per adolescent per night, population-wide, at no cost — the largest measured sleep effect of any intervention in this book per unit of expenditure.

Gaps. No burden estimate. The prevalence range from 0.2 to 10 per cent is a criteria artefact as much as a finding. The adolescent phase delay is physiologically established and school start times remain early in most of the world, which is an implementation failure. Melatonin dosing, timing and formulation are inconsistent across trials, and unregulated supplement content varies widely, so effect estimates are heterogeneous. Light therapy device standards are absent, and lux delivered at the eye is rarely measured in practice.

> **Depth.** Starts in: the suprachiasmatic nucleus. Size: 1 mm†; depth +9.10. First complaint: about 15 years († onset in adolescence); time depth 51.34. One untreated course: no number ([B] persistent).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Shift work disorder

What it is. Insomnia during the intended sleep period, or excessive sleepiness during the work period, arising from a work schedule that conflicts with the internal circadian clock.

Measured. Roughly 15 to 20 per cent of the workforce in industrialised economies works outside standard daytime hours, and shift work disorder affects roughly 10 to 30 per cent of those workers†. Shift work is classified by the International Agency for Research on Cancer as probably carcinogenic to humans, Group 2A, on the basis of the night-shift work and breast cancer evidence (IARC Monograph 124, 2019). The epidemiology is consistent and confounded, and the classification remains debated. Night shift work is associated with elevated cardiovascular and metabolic disease risk, roughly 1.2 to 1.4 times in meta-analyses, and with increased injury rates. There is no WHO fact sheet and no stand-alone GBD estimate, for a condition affecting a substantial fraction of the workforce.

Where it starts. The circadian mechanism is as set out in the delayed phase entry above: a molecular oscillator entrained by light through the suprachiasmatic nucleus, with a measured phase response curve. Shift work disorder arises because the schedule demands wakefulness and sleep at clock times the oscillator is not set for, and because the light exposure the schedule produces reinforces the misalignment rather than correcting it. Not known: why some shift workers adapt and others do not; whether the cancer association is causal.

Cure status. CONTROLLABLE while shift work continues; CURABLE on leaving shift work, since it resolves. While shift work continues only partial mitigation is possible. That is the honest position, and it makes the schedule the target rather than the worker.

Prevention. Shift schedule design: MODERATE. Forward-rotating schedules, day to evening to night, limiting consecutive night shifts, adequate inter-shift intervals, and avoiding quick returns all reduce fatigue and error in field studies and some randomised crossover trials. Timed light at work and timed darkness after: MODERATE; bright light during night shifts plus dark glasses on the commute home

improves adaptation in controlled studies. Napping before night shifts: MODERATE; prophylactic naps reduce performance decrement and sleepiness. Restricting night work for those who cannot adapt: MODERATE, because the measure addresses the exposure.

Treatment. *Timed bright light exposure*, with the quantified phase response curve, free outdoors and a one-off purchase of a few tens to a few hundred US dollars for a light box. *Timed melatonin* shifts phase in shift work; not EML-listed, off-patent, tens of US dollars a year. *Behavioural scheduling and a consistent wake time* where the roster allows. *Modafinil and armodafinil* are approved for shift work disorder sleepiness, with modest effect on sleepiness and on performance; not EML-listed, off-patent, low hundreds of US dollars a patient-year. They treat the symptom and not the misalignment. *Hypnotics for daytime sleep* give modest benefit with next-shift impairment risk. *Caffeine, strategically timed*, has a well-evidenced performance effect and is the most widely used countermeasure in the world, effective for its purpose.

Simple means. Shift schedule design: an administrative act with measurable health and safety effects. Scheduled naps: measurable performance protection. Light at the right hours and darkness at the others: free, and the mechanism and the intervention coincide. Fixed wake time where the roster allows.

Gaps. No burden estimate. Whether the shift-work cancer association is causal is unresolved, and the Group 2A classification reflects that uncertainty. Long-term health outcomes of shift schedule redesign have not been trialled, only modelled from fatigue and error endpoints.

> **Depth.** Starts in: the suprachiasmatic nucleus. Size: 1 mm†; depth +9.10. First complaint: about 3 days († days after starting shift work); time depth 44.50. One untreated course: no number († as long as the roster lasts).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Jet lag

What it is. Transient misalignment between the internal circadian clock and local time after rapid travel across time zones, with disturbed sleep, daytime sleepiness, impaired performance and gastrointestinal symptoms.

Measured. Near-universal after crossing three or more time zones. Eastward travel is worse than westward, because advancing the clock is harder than delaying it. There is no WHO fact sheet and no stand-alone GBD estimate.

Where it starts. The mechanism is the circadian oscillator and the light phase response curve described in the delayed phase entry: the clock re-entrains at a limited rate, and the direction of travel determines whether it must advance or delay. Individual variation in re-entrainment rate is substantial and unexplained.

Cure status. SELF-LIMITING, resolving at roughly one time zone a day untreated, and faster with timed light and melatonin.

Prevention. Jet lag pre-adaptation, by shifting sleep and light timing before travel: MODERATE. The measure is free.

Treatment. *Timed melatonin*: a Cochrane review of melatonin for jet lag found it effective for reducing jet lag symptoms across several trials; not EML-listed, off-patent, tens of US dollars a year. *Timed light exposure*, with the phase response curve, free outdoors. *Behavioural scheduling* onto local time on arrival. *Caffeine, strategically timed*, for daytime alertness. *Hypnotics* for sleep on arrival, with next-day impairment risk.

Simple means. Pre-travel phase shifting: free. Light at the correct local hours and avoidance of light at the wrong ones: free, and it is the active mechanism. Melatonin at tens of US dollars a year. Scheduled naps.

Gaps. No burden estimate. Melatonin dosing, timing and formulation are inconsistent across trials and supplement content varies widely. Trials are short, in small numbers, and mostly in healthy young adults.

> **Depth.** Starts in: the suprachiasmatic nucleus. Size: 1 mm†; depth +9.10. First complaint: about 24 hours († within a day); time depth 43.50. One untreated course: about 5 days († about 1 day per time zone); depth 44.96.
>
> **Model reading.** Way of ending: let close. Layer: phase. By the rule it closes by itself. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Non-REM parasomnias

What it is. Undesirable behaviours arising from incomplete awakening from deep sleep: confusional arousals, sleepwalking, sleep terrors and sleep-related eating. They are commonest in children and the person usually has no recollection of the event.

Measured. Sleepwalking affects roughly 5 per cent of children and roughly 1.5 to 2.5 per cent of adults, and childhood sleepwalking usually resolves by adolescence. Sleep terrors affect roughly 1 to 6 per cent of children and under 1 per cent of adults†. There is no WHO fact sheet and no GBD estimate. Adult prevalence is poorly measured.

Where it starts. Heritability is substantial: a parental history of sleepwalking raises a child's risk roughly three times for one affected parent and roughly seven times for two. Precipitants are well characterised — sleep deprivation, fever, alcohol, some medications, and anything causing arousal from deep sleep, including untreated obstructive sleep apnoea and restless legs syndrome. Treating the arousal trigger often resolves the parasomnia, an unusually clear causal chain for this chapter. State dissociation — partial arousal with motor systems active and consciousness absent — is supported by intracerebral recordings in individual cases, and is reasonably well established. Not known: why these cluster in families.

Cure status. In children: SELF-LIMITING. The large majority resolve by adolescence without treatment. In adults: CONTROLLABLE, and CURABLE where a precipitant — sleep apnoea, restless legs syndrome, a drug, sleep deprivation — is identified and removed.

Prevention. Adequate sleep and a regular schedule reduce frequency, since sleep deprivation is the most reliable experimental precipitant: MODERATE. Treating comorbid sleep apnoea and restless legs syndrome resolves a substantial fraction of adult cases: MODERATE. Avoiding precipitating drugs, including alcohol and the Z-drugs, whose complex sleep behaviours regulators have warned about: MODERATE.

Treatment. *Environmental safety measures* — removing hazards, floor-level sleeping, padding, securing windows and doors — are free and address the actual harm. *Treating the precipitating condition*: CPAP for coexisting apnoea, iron for restless legs syndrome, withdrawal of the offending drug. Often curative in adults. *Scheduled awakenings* for children with predictable events: small trials, cheap, effective in some series. *Hypnosis and cognitive behavioural therapy for adults*: small case series and trials with positive results. *Clonazepam* is used in refractory adult cases; not EML-listed, off-patent, tens of US dollars a patient-year.

Simple means. Making the bedroom safe: it costs nothing but attention and it prevents the injuries. Adequate and regular sleep: the most reliable way to reduce frequency, since sleep deprivation is the main precipitant. Scheduled awakenings in children: free. Alcohol avoidance: a documented precipitant. Treating a coexisting sleep disorder, which in adults is often the whole treatment.

Gaps. Adult prevalence is poorly measured. No burden estimate. Why these cluster in families is unknown. Adult treatment evidence is almost entirely case series.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 5 years ([B] commonest in children; † about 5); time depth 50.34. One untreated course: about 10 minutes († an episode lasts about 10 minutes); depth 38.98.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

REM sleep behaviour disorder and nightmare disorder

What it is. In REM sleep behaviour disorder, the person acts out dreams because the normal muscle paralysis of REM sleep is absent, with injury to the sleeper or the bed partner. It is commonest in older men. Nightmare disorder is repeated frightening dreams that wake the person and impair daytime functioning, and it is reported separately here because its treatment and its outlook differ entirely.

Measured. REM sleep behaviour disorder affects roughly 0.5 to 1.1 per cent of adults over 60, with a male predominance of roughly 2 to 4 to 1†. Nightmare disorder: frequent nightmares occur in roughly 2 to 6 per cent of adults, and far more in post-traumatic stress disorder, where they are near-universal. There is no WHO fact sheet and no GBD estimate. The most consequential measured fact here is conversion. Isolated, so-called idiopathic, REM sleep behaviour disorder converts to an overt alpha-synuclein neurodegenerative disease — Parkinson disease, dementia with Lewy bodies, or multiple system atrophy. The rate is roughly 6 to 8 per cent a year, reaching approximately 73 to 96 per cent at 12 to 14 years of follow-up in multicentre cohort studies (Postuma and colleagues, *Brain*, 2019, and longer follow-up series). It is the strongest known clinical predictor of future Parkinson disease or Lewy body dementia.

Where it starts. REM sleep behaviour disorder arises from loss of REM atonia through degeneration of brainstem nuclei in the sublaterodorsal and subcoeruleus region. In the isolated form this reflects early alpha-synuclein pathology ascending through the brainstem, consistent with the Braak staging sequence. That makes it an early manifestation of a neurodegenerative disease rather than a sleep disorder with a neurological association. Secondary forms occur in narcolepsy type 1, with antidepressant use, since SSRIs and SNRIs can unmask or cause it, and with brainstem lesions. The brainstem localisation and the alpha-synuclein link are well supported by the conversion data and by neuropathology. For nightmare disorder, trauma exposure is the dominant association. Not known: why some people with alpha-synuclein pathology present first with REM sleep behaviour disorder and others with motor or cognitive symptoms; whether conversion can be delayed.

Cure status. REM sleep behaviour disorder: RELIEF ONLY. The behaviour is controllable; the underlying neurodegeneration is not, and no treatment has been shown to delay or prevent conversion. Nightmare disorder: CURABLE — imagery rehearsal therapy produces durable reduction.

Prevention. For conversion in REM sleep behaviour disorder, nothing is established. No neuroprotective intervention has been shown to delay conversion, despite this being the ideal population for such trials; trials are under way and none has succeeded. The absence is reported as an absence. Safety measures do not prevent the disease and prevent the injuries, which are the immediate harm: STRONG for the injury outcome. Avoiding antidepressants where alternatives exist, in those at risk: MODERATE.

Treatment. *Environmental safety measures* — removing hazards, floor-level sleeping, padding, securing windows, and bed partner separation where injury has occurred — are free and are first-line in guidelines for REM sleep behaviour disorder, before any drug. *Clonazepam* is long-established and effective in roughly 80 to 90 per cent of cases in observational series, with little randomised evidence; not EML-listed, off-patent, tens of US dollars a patient-year. Harms: sedation, falls, worsening of coexisting sleep apnoea, and cognitive effects in a population already at neurodegenerative risk. *Melatonin* is effective in small randomised and open trials with a better safety profile than clonazepam in older adults; the efficacy evidence is weaker and the harm profile better. Not EML-listed, off-patent, tens of US dollars a year. *Imagery rehearsal therapy for nightmare disorder* is the best-evidenced treatment, with moderate-to-large effect sizes in randomised trials including in post-traumatic stress populations, and durable gains. It is a purely behavioural treatment requiring no product. *Prazosin for trauma-related nightmares* showed benefit in earlier trials and was not confirmed in the largest subsequent trial: CONTESTED.

Simple means. Making the bedroom safe: the first-line intervention in REM sleep behaviour disorder and the measure that prevents the fractures, lacerations and subdural haematomas that constitute the real harm. It costs nothing but attention. Imagery rehearsal therapy: a behavioural protocol deliverable from written instructions, with randomised support that exceeds the drug evidence for nightmares. Melatonin at tens of US dollars a year, against clonazepam's better efficacy evidence and worse harm profile in older adults. Alcohol avoidance.

Gaps. Conversion rates come from specialist-clinic cohorts, and the population conversion rate may be lower. Clonazepam is standard practice on almost no randomised evidence, in a population at risk of falls and cognitive decline. No neuroprotective trial has succeeded, and the ideal prodromal population exists and is identifiable, so the gap is in the interventions rather than the cohort. Whether to tell a person with isolated REM sleep behaviour disorder their conversion risk is an open ethical question with no evidence base on outcomes either way.

> **Depth.** Starts in: brainstem nuclei. Size: 1 mm†; depth +9.10. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

08 — Diseases of the nervous system

Chapter-level measured context. On the GBD 2021 nervous system analysis, about 3.4 billion people had a nervous system condition in 2021, roughly 43 per cent of the world's population. These conditions accounted for 443 million DALYs, up from about 375 million in 1990 — an 18 per cent absolute increase. Case numbers rose 59 per cent globally while age-standardised DALY rates fell 27 per cent and age-standardised death rates fell 34 per cent. Nervous system conditions were the leading cause of illness and disability worldwide by DALYs on that analysis. The top ten contributors by DALYs, in rank order, were stroke, neonatal encephalopathy, migraine, Alzheimer disease and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications of preterm birth, autism spectrum disorder, and nervous system cancers. The neurological consequences of COVID-19 ranked twentieth at 2.48 million DALYs†. Diabetic neuropathy cases more than tripled since 1990, reaching 206 million. Modifying 18 risk factors could prevent 84 per cent of global stroke DALYs, and high systolic blood pressure alone accounts for 57 per cent of them. Controlling lead exposure could reduce the intellectual disability burden by 63 per cent. Normalising high fasting plasma glucose could reduce the dementia burden by about 15 per cent.

Alzheimer disease

The Chapter 06 dementia entry covers the syndrome, its care, the full prevention evidence and the anti-amyloid antibody data in detail. This entry covers Alzheimer disease as a disease of the nervous system.

What it is. A progressive degenerative brain disease characterised by extracellular amyloid-beta plaques and intracellular tau neurofibrillary tangles, with synapse and neuron loss. It is the commonest cause of dementia. The pathology begins roughly two decades before symptoms.

Measured. Alzheimer disease accounts for 60 to 70 per cent of the 57 million dementia cases worldwide (WHO dementia fact sheet, 3 July 2026, 2021 data), roughly 34 to 40 million people. It ranked fourth among nervous system conditions by DALYs on GBD 2021. Alzheimer's disease and other dementias were the fifth leading cause of death globally in 2023 at 2.1 million (WHO Global Health Estimates, 2 October 2026), while the dementia fact sheet gives dementia as the seventh leading cause of death without a data year; both WHO figures are printed. Alzheimer's disease and other dementias rank twenty-second among all causes of years lived with disability at 12.2 million YLDs (95 per cent UI 8.52 to 15.6) in 2023. Age-specific incidence has been falling by roughly 13 per cent per decade in pooled Western cohort analyses while absolute numbers rise with population ageing. Young-onset disease, before 65, accounts for up to 9 per cent of dementia cases. Women are affected more than men in absolute numbers, largely but not entirely explained by greater longevity. The economic cost of all dementia was US$1.3 trillion in 2019, about half of it from informal care.

Where it starts. Age is dominant: prevalence roughly doubles every five years after 65. *APOE* ε4 carries roughly three times the risk for one copy and roughly 8 to 12 times for two†, the largest common genetic risk factor. Autosomal dominant mutations in *APP*, *PSEN1* and *PSEN2* have near-complete penetrance, account for under 1 per cent of cases†, and are the genetic evidence that amyloid processing is causally involved. Down syndrome carries three copies of *APP*, and the large majority of people with it develop Alzheimer pathology by their sixties — a natural experiment supporting the amyloid link. Heritability of late-onset disease is roughly 60 to 80 per cent in twin studies†. The Lancet Commission 2024's 14 modifiable factors carry a combined population attributable fraction of 45 per cent, and the full list, the individual PAFs and the prevention grades are in the Chapter 06 dementia entry. Mixed pathology — Alzheimer plus vascular plus Lewy body — is the rule at autopsy rather than the exception, which complicates every clinical trial of a single-target drug.

The amyloid cascade hypothesis has driven three decades of research. The anti-amyloid antibodies show that removing amyloid produces a small slowing of decline, supporting a causal role while showing the effect size is far below what the hypothesis predicted. Dozens of amyloid-targeting agents failed before two succeeded marginally. Tau pathology correlates better with clinical severity than amyloid does, and tau-

targeting agents have so far failed. A widely cited 2006 *Nature* paper on amyloid-beta*56 was retracted in 2024 after image-manipulation findings, and several other papers in this field have been retracted; the amyloid hypothesis does not rest on those papers, and this is part of the record. Not known: what initiates the pathology two decades before symptoms; why some people with heavy autopsy pathology had no dementia; whether earlier intervention would do more.

Cure status. RELIEF ONLY. No treatment reverses or halts the disease. The anti-amyloid antibodies slow measured decline by roughly a quarter to a third over eighteen months.

Prevention. The full evidence is in the Chapter 06 dementia entry, including SPRINT MIND — probable dementia hazard ratio 0.83 (95 per cent CI 0.67 to 1.04), not significant; mild cognitive impairment 0.81 (0.69 to 0.95), significant; the composite 0.85 (0.74 to 0.97), significant† — and ACHIEVE's null primary outcome, a three-year cognitive change difference of 0.002 SD units (p=0.96), with the circulating 48 per cent being a high-risk subgroup result†. Summary grades: blood pressure control MODERATE; education MODERATE; smoking cessation, physical activity, diabetes control, LDL control, hearing and vision treatment, alcohol reduction, head injury prevention, air pollution reduction and addressing social isolation all MODERATE; hearing aids for cognition specifically CONTESTED; multidomain intervention CONTESTED; cognitive training CONTESTED.

Treatment. Full detail is in the Chapter 06 dementia entry. Lecanemab: CDR-SB difference −0.45 points, 27 per cent slowing, ARIA-E 12.5 against 1.7 per cent, ARIA-H 17.0 against 8.7 per cent; US$26,500 a year at US list price†; not EML-listed†, on patent. Donanemab: 22 per cent iADRS slowing in all participants and 35 per cent in the primary analysis population, ARIA-E 24 per cent, ARIA-H 31.4 against 13.6 per cent, serious ARIA 1.6 per cent†; US$32,000 a year at US list price†; not EML-listed†, on patent. Neither is on the Essential Medicines List, and the infrastructure both require does not exist where most people with dementia live. Also: cholinesterase inhibitors, memantine, antipsychotic harms, and carer support.

Simple means. See the Chapter 06 dementia entry. The key comparison: blood pressure control with off-patent EML-listed drugs, at roughly ten to twelve US dollars a patient-year for amlodipine on the September 2026 NHS Drug Tariff, produced the SPRINT MIND composite hazard ratio of 0.85; the anti-amyloid antibodies cost US$26,500 to 32,000 a year at US list price, plus infrastructure, for a 27 to 35 per cent slowing that does not halt decline.

Gaps. See the Chapter 06 dementia entry. In addition: there are no biomarker-confirmed prevalence data for most of the world, so the 60 to 70 per cent share of dementia attributed to Alzheimer disease is a clinical-diagnostic estimate, and mixed pathology makes the attribution partly arbitrary. WHO's own two pages rank dementia fifth and seventh among causes of death.

> **Depth.** Starts in: amyloid-beta. Size: 4 nm†; depth −2.21. First complaint: about 17 years ([B] the pathology begins long before complaints; † 15–20 years); time depth 51.47. One untreated course: no number († progressive).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Parkinson disease

What it is. A progressive degenerative disease with loss of dopamine-producing neurons in the substantia nigra and accumulation of alpha-synuclein. It causes slowness of movement, rigidity, tremor and postural instability, together with non-motor features — constipation, loss of smell, sleep disorder, depression, cognitive decline — that often precede the motor signs by years.

Measured. Over 8.5 million people worldwide (WHO Parkinson disease fact sheet, 9 August 2023, 2019 data). Prevalence has doubled in the past 25 years. 5.8 million DALYs, up 81 per cent since 2000. 329,000 deaths, up more than 100 per cent since 2000. By both measures this is the fastest-growing neurological condition. Incidence rises steeply after 60: roughly 1 per cent of people over 60 and 3 per cent over 80. Young-onset disease, before 50, is roughly 5 to 10 per cent of cases. Men roughly 1.4 to 2 times women.

Prevalence estimates are higher in Europe, North America and parts of South America than in sub-Saharan Africa and parts of Asia, and how much of that is ascertainment is unresolved. The WHO figures make this the clearest example in the book of a rising neurological burden exceeding what population ageing alone predicts.

Where it starts. Age is dominant. Genetics: *LRRK2*, *GBA1*, *SNCA*, *PRKN*, *PINK1* and others. *GBA1* variants are the commonest genetic risk factor, carried by roughly 5 to 10 per cent of patients, with odds ratios around 3 to 5; monogenic forms account for roughly 5 to 10 per cent of cases; heritability is roughly 20 to 30 per cent† — notably lower than for Alzheimer disease or the psychiatric conditions, which points to environment. Pesticide exposure: paraquat and rotenone are the best characterised, with odds ratios of roughly 1.5 to 2.5 in meta-analyses and dose-response, among the most consistent environmental associations in neurology.

Trichloroethylene and other chlorinated solvents are associated with a notable occupational-cohort signal, odds ratios around 1.5 to 6 in some studies†, and the Camp Lejeune cohort study found elevated risk with trichloroethylene-contaminated water exposure. Traumatic brain injury, roughly 1.3 to 1.6 times†. Protective associations: smoking at roughly 0.5 times and caffeine at roughly 0.7 times are consistently and robustly inversely associated — among the most replicated findings in the field, and still unexplained. Reverse causation via prodromal personality change has been proposed and does not fully account for the smoking effect.

This is a mechanistic clue and not a recommendation, and it is not translated into advice. REM sleep behaviour disorder converts to Parkinson disease or a related alpha-synucleinopathy at roughly 6 to 8 per cent a year, reaching 73 to 96 per cent at 12 to 14 years† — the strongest clinical prodromal marker known. Constipation and loss of smell precede motor onset by years to decades.

Dopaminergic nigrostriatal degeneration is established and explains the motor features and the levodopa response: one of the clearest disease mechanisms in the book. Alpha-synuclein aggregation is established pathologically, and whether it is the cause, a consequence, or a protective sequestration is genuinely disputed. The Braak staging hypothesis, in which pathology ascends from the gut and olfactory bulb through the brainstem, is supported by the prodromal symptom sequence and by some pathology series and not by all: unresolved. Mitochondrial dysfunction and lysosomal impairment, the *GBA1* link, are supported. Not known: what initiates the process; why cell loss is selective; why no neuroprotective trial has succeeded despite a well-characterised target; whether gut microbiome findings are causal or consequential.

Cure status. RELIEF ONLY, and the relief is substantial and transformative for years. No treatment slows progression, and every neuroprotection trial has failed. Levodopa relieves motor symptoms highly effectively, and the response is so reliable that absence of response questions the diagnosis. After roughly five to ten years, motor fluctuations and levodopa-induced dyskinesia develop in a majority, which is the main limitation on long-term symptom control. Non-motor features — cognitive decline, autonomic failure, falls — progressively dominate and respond poorly to dopaminergic treatment. Median survival from diagnosis is roughly 10 to 20 years depending on age at onset.

Prevention. Reducing pesticide exposure, with paraquat banned in the European Union and many countries and still used elsewhere: MODERATE. The exposure-outcome association is among the most consistent in neuroepidemiology and the intervention evidence is regulatory rather than trial-based. Reducing solvent exposure, trichloroethylene and perchloroethylene, in occupational and water-supply settings: MODERATE. Preventing head injury through helmet law and road safety: WEAK for this endpoint specifically. Physical activity: prospective cohorts show lower incidence in the physically active, roughly 0.7 to 0.8 times in meta-analyses with dose-response†, and reverse causation from the prodromal period is a serious confounder since bradykinesia precedes diagnosis: WEAK. There is no established preventive intervention.

Treatment. *Levodopa with a peripheral decarboxylase inhibitor*, carbidopa or benserazide, is the most effective symptomatic treatment for any neurodegenerative disease, with large effect sizes on motor function. EML-listed, off-patent, and costing tens to low hundreds of US dollars a patient-year. The PD MED and ELLDOPA trials established that early levodopa does not accelerate progression, settling a long-

standing concern. Harms: motor fluctuations and dyskinesia with long-term use, nausea, orthostatic hypotension, and less impulse control disorder than with agonists. *Dopamine agonists* — pramipexole, ropinirole, rotigotine — are effective, with less early dyskinesia and more impulse control disorder, hallucinations, sleepiness and oedema. In the PD MED trial, levodopa-first produced better patient-rated mobility than agonist-first. Not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year. Impulse control disorders — pathological gambling, hypersexuality, compulsive shopping and eating — occur in roughly 15 to 25 per cent on agonists†, a serious and often missed harm.

MAO-B inhibitors, selegiline and rasagiline, give modest symptomatic benefit, and the claimed neuroprotection was not confirmed; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year. *COMT inhibitors*, entacapone and opicapone, extend the levodopa effect in fluctuating patients; not EML-listed, entacapone off-patent, low hundreds of US dollars a patient-year. *Amantadine* is the only agent with established benefit for levodopa-induced dyskinesia; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year. *Deep brain stimulation* of the subthalamic nucleus or globus pallidus interna has a large effect on motor fluctuations and dyskinesia in randomised trials, and is the best-evidenced neurosurgical intervention in the book. Device and procedure costs run to tens of thousands of US dollars plus battery replacement, and it suits a minority: levodopa-responsive, without significant cognitive impairment.

Levodopa-carbidopa intestinal gel and apomorphine infusion are used for advanced fluctuations at costs in the tens of thousands of US dollars a year. *Physiotherapy, and specifically high-intensity exercise*: the SPARX phase 2 trial found high-intensity treadmill exercise feasible and associated with less motor progression at six months than usual care, and the phase 3 SPARX3 trial is the definitive test. Amplitude-based training and cueing improve gait and function in randomised trials. This is the only intervention with any signal of affecting progression, and the signal is not yet established. *Speech and swallowing therapy* improves voice intensity in randomised trials, and aspiration pneumonia is a leading cause of death, so swallowing management matters for survival.

Treating non-motor features: constipation, orthostatic hypotension, REM sleep behaviour disorder, depression, and psychosis — where clozapine and pimavanserin are the agents that do not worsen motor function and other antipsychotics do.

Simple means. Exercise is the strongest simple-means candidate for this condition. Randomised trials establish improvement in gait, balance and function, and SPARX suggests a possible effect on progression that no drug has achieved. High-intensity aerobic exercise, resistance training, tai chi with randomised evidence for balance and falls reduction, dance and boxing-style programmes all have trial support for function. It is comparable to medication for balance, falls and function, and not comparable for the core motor symptoms, where levodopa is far superior. Cueing — a metronome, rhythmic auditory stimulation, visual floor markers — for freezing of gait is effective and costs nothing. Fall-proofing the home: falls and the resulting fractures are a major cause of disability and death. Voice exercises practised independently. Fibre, fluid and activity for constipation, the commonest non-motor symptom. Fixed sleep timing and bedroom safety for REM sleep behaviour disorder. Social connection and continued activity: associated with slower functional decline, observational.

Gaps. The doubling of prevalence in 25 years and the 81 per cent DALY rise exceed what ageing predicts, the excess is unexplained, and the pesticide and solvent hypotheses are the leading but unproven candidates. There is no neuroprotective treatment despite the clearest target in neurodegeneration, and the repeated failure is itself a major scientific problem. The inverse smoking and caffeine associations are robust and unexplained. Whether exercise modifies progression is the most important open question with a trial under way. WHO's figures are from 2019 and the fact sheet dates from 2023. Prevalence data from sub-Saharan Africa and much of Asia are very sparse.

> **Depth.** Starts in: alpha-synuclein. Size: 10 nm†; depth −1.38. First complaint: about 13 years ([B] prodrome of 12–14 years†); time depth 51.21. One untreated course: no number († progressive).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Stroke

What it is. Sudden loss of brain function caused by interrupted blood supply, which is ischaemic stroke, or by bleeding into or around the brain, which is haemorrhagic stroke.

Measured. 11.9 million new strokes in 2021, with an estimated 93.8 million people living with stroke (WHO stroke fact sheet, 2021 data). Another dossier in this book gives roughly 12 million incident strokes, which is compatible, and about 101 million prevalent stroke survivors from the GBD 2019 and 2021 stroke capstone — 7.2 million more than the 93.8 million here. Both stand; the sources and the reference years differ. Stroke DALYs: **157 million (95 per cent UI 141 to 172) on GBD 2023**, which is the figure to quote. WHO's stroke fact sheet gives 160 million in 2021, up from 137 million in 2000, and that is printed beside the GBD figure, not instead of it, because the two bodies measure differently.

Stroke ranks third among all causes of DALYs in 2023 and ranked first among all nervous system conditions by DALYs on GBD 2021. It ranks seventeenth among all causes of years lived with disability at 16.7 million YLDs (95 per cent UI 12.0 to 21.2) in 2023. Stroke was the second leading cause of death globally in 2023 at 6.8 million, about 11 per cent of all deaths (WHO Global Health Estimates, 2 October 2026), while the stroke fact sheet calls it the third leading cause of death and disability; both are printed. One in four adults is predicted to have a stroke in their lifetime, and lifetime risk is up 50 per cent over the past twenty years; another dossier in this book gives 24.9 per cent from age 25 on the GBD 2016 lifetime risk analysis, which is compatible and differently based, and both stand.

The ischaemic share of all stroke is given as roughly 70 to 85 per cent of cases here, as about four in five in one section of another dossier, and as roughly 62 to 65 per cent globally with about 87 per cent in high-income countries in another section of it†; all three stand, unresolved. Hypertension carries nearly three times the stroke risk of people without it. Tobacco is associated with about two-fifths of stroke deaths in people under 65. Modifying 18 risk factors could prevent 84 per cent of global stroke DALYs, and high systolic blood pressure alone accounts for 57 per cent†.

Hypertension context: about 1.4 billion adults aged 30 to 79 had hypertension in 2024, 33 per cent; about 630 million diagnosed and treated; only about 320 million controlled, 23 per cent; about 600 million unaware. Age-standardised incidence and mortality are falling in high-income countries and rising or static in many low- and middle-income countries, where the majority of strokes now occur and where the mean age at stroke is lower.

Where it starts. This is the best-quantified aetiology in the book. INTERSTROKE (O'Donnell and colleagues, *Lancet*, 2016; 26,919 participants, 32 countries) found ten modifiable risk factors accounting for roughly 90 per cent of the population attributable risk for stroke: hypertension with a population attributable risk of about 48 per cent, physical inactivity 36 per cent, apolipoproteins and lipids 27 per cent, diet 23 per cent, waist-to-hip ratio 19 per cent, psychosocial factors 17 per cent, smoking 12 per cent, cardiac causes 9 per cent, alcohol 6 per cent, diabetes 4 per cent.

Those are for all stroke, and the hypertension contribution is larger for intracerebral haemorrhage. Another dossier in this book prints the same table to one decimal place from the published values — all stroke 90.7 per cent, ischaemic 91.5 per cent, intracerebral haemorrhage 87.1 per cent, hypertension 47.9 per cent† — against the integers rounded here; both stand, and the published values are the decimals. Atrial fibrillation carries roughly five times the stroke risk untreated, and it is the single most treatable individual cause, because anticoagulation reduces that risk by roughly two thirds.

High systolic blood pressure accounts for 57 per cent of stroke DALYs†. Salt: global mean intake is 4,278 mg a day of sodium, about 11 g a day of salt, more than double the WHO limit of under 2,000 mg of sodium, and about 1.7 million deaths a year are associated with excess sodium. Air pollution is a substantial contributor in GBD estimates. Heritability of stroke is roughly 30 to 40 per cent†, and monogenic causes such as CADASIL, sickle cell disease and Fabry disease are rare and important because they are identifiable.

Established mechanisms: atherosclerosis, cardioembolism, small vessel disease, and hypertensive vessel rupture. They are understood at the level needed for prevention and treatment, which distinguishes stroke from most of the book. Not known: why cryptogenic stroke, roughly 25 per cent of ischaemic strokes†,

occurs; the determinants of individual collateral circulation, which largely determines outcome; why recovery trajectories differ so much between people with similar lesions.

Cure status. Established damage: RELIEF ONLY. Treated by intravenous thrombolysis or mechanical thrombectomy: CURABLE where function is restored. The proportion is not established in this compilation. The effect declines to zero by roughly four and a half to six hours. Reperfusion therapy within hours can abolish the deficit entirely in some patients. Recurrence is roughly 10 per cent in the first year without secondary prevention, falling to roughly 2 to 4 per cent a year with it†.

Prevention. The strongest prevention evidence in Chapter 08. *Blood pressure control*: STRONG, and the single highest-yield intervention. Meta-analyses of antihypertensive trials show roughly 35 to 40 per cent stroke risk reduction, and a 10 mm Hg systolic reduction is associated with roughly 27 per cent lower stroke risk†. 57 per cent of stroke DALYs are attributable to high systolic blood pressure. The gap is implementation: only 23 per cent of the 1.4 billion people with hypertension are controlled. *Population salt reduction*: STRONG. The China Salt Substitute and Stroke Study (Neal and colleagues, *NEJM*, 2021) randomised 600 villages and 20,995 participants with a history of stroke or high blood pressure, over a mean 4.74 years. Potassium-enriched salt substitute reduced stroke by 14 per cent, rate ratio 0.86 (95 per cent CI 0.77 to 0.96), major cardiovascular events by 13 per cent and total deaths by 12 per cent, with no excess of serious hyperkalaemia. A randomised trial of a food, in 21,000 people, showing stroke reduction — one of the most important prevention results in the book.

Anticoagulation for atrial fibrillation: STRONG. It reduces stroke by roughly 64 per cent against control in the warfarin meta-analysis, and direct oral anticoagulants are at least as effective with less intracranial haemorrhage. Warfarin is EML-listed and off-patent, costing tens of US dollars a patient-year plus INR monitoring; dabigatran is EML-listed, added in 2019, off-patent in many markets, and costs low hundreds of US dollars a patient-year. *Smoking cessation*: STRONG; risk falls substantially within years of quitting, and tobacco is associated with two-fifths of stroke deaths under 65. *Statins for secondary and high-risk primary prevention*: STRONG, at roughly 21 per cent relative reduction in major vascular events per 1 mmol/L of LDL reduction in the Cholesterol Treatment Trialists' meta-analysis. Simvastatin and atorvastatin are EML-listed and off-patent, costing on the order of tens of US dollars a patient-year.

Antiplatelet therapy after ischaemic stroke: STRONG. Aspirin is EML-listed and off-patent at a few US dollars a patient-year, and is one of the cheapest effective interventions in medicine. *Physical activity*: MODERATE, with a population attributable risk of 36 per cent in INTERSTROKE. *Diabetes control*: MODERATE. *Air pollution reduction*: MODERATE. *Alcohol reduction*: MODERATE, population attributable risk 6 per cent in INTERSTROKE and larger for haemorrhagic stroke. *Carotid endarterectomy for severe symptomatic stenosis*: STRONG in selected patients. Blood pressure control also prevents vascular dementia, with the SPRINT MIND composite hazard ratio of 0.85†.

Treatment. *Mechanical thrombectomy for large vessel occlusion* has the largest treatment effect in acute stroke care. The HERMES pooled analysis of the 2015 trials gives a number needed to treat of about 2.6 for reduced disability at 90 days, with an odds ratio of 2.49 for improved functional outcome. Extended-window trials, DAWN and DEFUSE 3, showed benefit up to 24 hours in selected patients. It requires a comprehensive stroke centre, and the procedure cost runs to tens of thousands of US dollars; another dossier in this book gives tens of thousands of euro per procedure, and this chapter's compilation gave a dollar range that was an unsourced estimate and is not printed.

Intravenous thrombolysis with alteplase or tenecteplase gives benefit that is strongly time-dependent: within three hours roughly one in ten treated has a better outcome, and the effect declines to zero by roughly four and a half to six hours. Symptomatic intracranial haemorrhage occurs in roughly 2 to 7 per cent†. Alteplase is EML-listed for ischaemic stroke, off-patent in some markets, and costs on the order of thousands of US dollars a treatment. Tenecteplase is non-inferior, single-bolus and cheaper to administer. *Aspirin within 48 hours* gives small but real benefit; EML-listed†, at near-zero cost. *Stroke unit care*: organised inpatient stroke unit care against general ward care reduces death and dependency, with a number needed to treat of roughly 20 in Cochrane review†. It is an organisational intervention with no drug, no device and no new technology, and it saves more lives globally than thrombectomy because it can be delivered everywhere.

Decompressive craniectomy for malignant middle cerebral artery infarction in younger patients reduces mortality substantially, and survivors have significant disability.

Simple means. Salt reduction and salt substitution: a cluster-randomised trial of 20,995 people found a 14 per cent stroke reduction, rate ratio 0.86 (0.77 to 0.96), from changing the salt on the table, and potassium-enriched salt substitute costs marginally more than ordinary salt. This is the single most important simple-means finding in Chapter 08, and the trial evidence is comparable to drug evidence because it is a randomised trial with a clinical endpoint. Blood pressure control with off-patent EML drugs — hydrochlorothiazide, amlodipine, enalapril, losartan — at roughly ten to twelve US dollars a patient-year for amlodipine on the September 2026 NHS Drug Tariff, delivering 35 to 40 per cent stroke reduction. Aspirin at a few US dollars a patient-year for secondary prevention. Physical activity, with a population attributable risk of 36 per cent in INTERSTROKE, free. Smoking cessation: free, or a few US dollars for cytisine. Stroke unit organisation: number needed to treat about 20, no technology required. Rapid presentation, meaning recognising stroke and calling for help immediately, determines whether reperfusion is possible at all, and public education campaigns measurably shorten presentation times. Swallow screening with a glass of water before giving food prevents aspiration pneumonia, a leading cause of post-stroke death: a nurse and a cup.

Gaps. The 84-per-cent-preventable figure and INTERSTROKE's 90 per cent population attributable risk are modelled upper bounds assuming complete factor elimination and independence; they are not achievable targets. Thrombectomy requires infrastructure available to a small minority of the world's population, and the equity gap is the dominant practical issue rather than the evidence. WHO's fact sheet gives no absolute stroke death total, so mortality comparisons must come from the Global Health Estimates or GBD directly. The prevalent-case figures of 93.8 and 101 million differ by 7.2 million and both are in circulation.

> **Depth.** Starts in: a brain artery. Size: 3 mm†; depth +10.10. First complaint: about 1 minute († within minutes); time depth 36.88. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Stroke sequelae

What it is. The lasting consequences of stroke: weakness, speech and swallowing impairment, visual loss, cognitive impairment, post-stroke depression, spasticity, pain and epilepsy.

Measured. An estimated 93.8 million people were living with stroke in 2021 (WHO), and another dossier in this book gives about 101 million from the GBD stroke capstone; both stand. Stroke's 16.7 million years lived with disability in 2023 (95 per cent UI 12.0 to 21.2) is the measure of the sequelae rather than of the acute event. Post-stroke depression affects roughly a third of survivors. Post-stroke epilepsy is a recognised consequence, and stroke is the commonest cause of new-onset epilepsy in older adults.

Where it starts. The sequelae follow from the location and the volume of the infarct or haemorrhage, and from the individual's collateral circulation, which largely determines outcome and whose determinants are not known. Recovery trajectories differ markedly between people with similar lesions, and why is not known.

Cure status. RELIEF ONLY. Rehabilitation improves function substantially and does not restore lost tissue. Spontaneous recovery is substantial in the first three months and continues more slowly thereafter.

Prevention. Preventing the recurrence is the main lever and the measures are in the stroke entry above: blood pressure control STRONG, salt reduction STRONG, anticoagulation for atrial fibrillation STRONG, statins STRONG, antiplatelet therapy STRONG. Early organised stroke unit care reduces death and dependency, number needed to treat roughly 20†: STRONG. Swallow screening before the first oral intake prevents aspiration pneumonia: STRONG for that outcome.

Treatment. *Rehabilitation*: the evidence favours intensity and task-specific practice. Constraint-induced movement therapy improved arm function in the EXCITE trial. *Fluoxetine to enhance motor recovery* was tested in three large trials — FOCUS, AFFINITY and EFFECTS — and did not improve functional outcome, while increasing fracture risk: a clear negative result after promising early data, and no pharmacological agent enhances recovery. *Early supported discharge and community rehabilitation* reduce dependency, Cochrane-supported. *Treating the individual sequelae*: spasticity with botulinum toxin and physiotherapy; post-stroke depression, prevalent in roughly a third, with antidepressants that are effective; dysphagia, where swallow screening prevents aspiration pneumonia; central post-stroke pain with amitriptyline, which is EML-listed, off-patent and costs a few US dollars a patient-year, or with gabapentinoids; post-stroke epilepsy, for which see the epilepsy entry; shoulder pain; and fatigue.

Simple means. Task-specific practice and repetition: the active ingredient of rehabilitation, and family members can deliver supervised repetition. Swallow screening with a glass of water before giving food: a nurse and a cup, preventing a leading cause of post-stroke death. Amitriptyline at a few US dollars a patient-year for central post-stroke pain. Positioning and early mobilisation. Falls prevention in the home.

Gaps. Rehabilitation trials are small, heterogeneous and poorly blinded, and the dose-response for therapy intensity is not established. No pharmacological agent enhances recovery, and the fluoxetine trials closed off the leading candidate. Long-term outcome data from low- and middle-income settings, where most strokes now occur, are sparse.

> **Depth.** The consequences of a stroke. No depth is given.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Brain tissue that died does not regrow. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Epilepsy

What it is. A tendency to recurrent unprovoked seizures, caused by abnormal excessive synchronous neuronal activity. It is not one disease but a group of conditions with many causes. Seizures vary from brief lapses of awareness to prolonged convulsions.

Measured. About 50 million people worldwide have epilepsy (WHO epilepsy fact sheet, 7 February 2024); the page gives no data year for that figure. Active epilepsy prevalence is 4 to 10 per 1,000 at any time. About 5 million new diagnoses a year: 49 per 100,000 a year in high-income countries and up to 139 per 100,000 in low- and middle-income countries. Nearly 80 per cent of people with epilepsy live in low- and middle-income countries. Epilepsy ranked seventh among nervous system conditions by DALYs on GBD 2021. The risk of premature death is up to three times higher than the general population, with causes including sudden unexpected death in epilepsy, status epilepticus, drowning, falls and burns.

Up to 70 per cent of people with epilepsy could become seizure-free with appropriate antiseizure medication. **About three quarters of people with epilepsy in low-income countries may not receive the treatment they need**. Generic antiseizure medicine availability in low- and middle-income-country public sectors is less than 50 per cent. About 25 per cent of cases are potentially preventable, and the cause is unknown in about 50 per cent. The age pattern is bimodal, with peaks in early childhood and after 60, and the older-adult incidence peak is now the largest in high-income countries, driven by stroke.

Incidence is roughly three times higher in low- and middle-income countries, driven by preventable causes — perinatal injury, head trauma, central nervous system infection and neurocysticercosis.

The delivery gap, stated plainly: up to 70 per cent of people with epilepsy could become seizure-free on medication; about three quarters of people with epilepsy in low-income countries receive no treatment; and phenobarbital, the cheapest effective antiseizure drug in existence, is EML-listed as a selected medicine for epilepsy and status epilepticus, confirmed against the 24th List, and off-patent. The UNICEF Supply Catalogue, read 19 October 2026, gives phenobarbital 30 mg tablets at US$1.71 for a pack of 100, about

US$0.0171 a tablet, so **about US$6.24 a patient-year at one tablet a day**. The gap is distribution, not discovery, and it is the single largest avoidable-suffering figure in Chapter 08.

Where it starts. Causes are known in a large proportion of cases, which distinguishes epilepsy from much of this chapter. *Structural*: stroke, which is the commonest cause of new-onset epilepsy in older adults; traumatic brain injury; tumour; cortical malformation; hippocampal sclerosis; perinatal hypoxic-ischaemic injury. *Infectious*: neurocysticercosis is the single largest preventable cause worldwide, accounting for roughly 30 per cent of epilepsy in endemic regions and an estimated 2 to 3 million cases globally†; also bacterial meningitis, cerebral malaria, tuberculous meningitis, HIV, and in some regions onchocerciasis-associated epilepsy. *Genetic*: several hundred genes identified, with monogenic epilepsies — *SCN1A* in Dravet syndrome, *KCNQ2*, tuberous sclerosis — individually rare and collectively significant; heritability of the common epilepsies is roughly 25 to 30 per cent†. *Metabolic and immune*: autoimmune encephalitis, with NMDA receptor or LGI1 antibodies, is a recognised and treatable cause identified only in the past two decades. Most children with febrile seizures do not develop epilepsy, and prolonged febrile seizures carry higher risk.

Ion channel and neurotransmitter mechanisms are established for several monogenic epilepsies, and the mechanism of several drugs is known at the molecular level. Epileptogenesis — how a normal brain becomes epileptic after an injury — is not understood well enough to interrupt. No antiepileptogenic drug exists, and every trial of post-injury prophylaxis has failed to prevent later epilepsy. Not known: why seizures start when they do; what causes sudden unexpected death in epilepsy; why 30 per cent of patients are drug-resistant regardless of which drug; why the same lesion causes epilepsy in one person and not another.

Cure status. On medication: CONTROLLABLE in up to 70 per cent, who become seizure-free. Many remain so. WHO's own threshold for considering discontinuation is two seizure-free years. Drug-resistant epilepsy, roughly 30 per cent†, defined as failure of two appropriately chosen and adequately trialled drugs: that proportion has not improved despite more than twenty new antiseizure medications since 1990, which is a striking and important negative fact about four decades of drug development. Drug-resistant temporal lobe epilepsy treated surgically: CURABLE in 58 per cent at one year, free of seizures impairing awareness. Wiebe and colleagues (*NEJM*, 2001; 80 patients randomised, 40 to surgery and 40 to one year of medical therapy) found **58 per cent of the surgical group free of seizures impairing awareness at one year against 8 per cent of the medical group ($p<0.001$)**. Surgical complications occurred in 4 patients, 10 per cent: one small thalamic infarct with sensory change, one wound infection, and verbal memory decline interfering with work in two; asymptomatic superior quadrantic visual field defects occurred in 22 of 40, 55 per cent. One unexplained death occurred in the medical group and none in the surgical group. Where the cause is removable — treating neurocysticercosis or autoimmune encephalitis, removing a tumour — CURABLE.

Prevention. Unusually strong, because the causes are known. Pork tapeworm control and sanitation to prevent neurocysticercosis: STRONG, and it is the largest single preventable cause globally. Measures include meat inspection, pig husbandry, sanitation, mass drug administration and health education, and WHO targets it under its neglected tropical diseases roadmap. Perinatal care — skilled birth attendance, neonatal resuscitation, prevention and treatment of neonatal infection and jaundice: STRONG. Neonatal encephalopathy ranks second among all nervous system conditions by DALYs, and perinatal injury is a leading epilepsy cause.

Head injury prevention through helmet law, road safety and fall prevention: STRONG for the trauma-attributable fraction. Helmets reduce the risk of death by more than six times and brain injury risk by up to 74 per cent; seat-belts reduce occupant death risk by up to 50 per cent; a 1 per cent rise in mean speed produces a 4 per cent rise in fatal crash risk; road deaths are about 1.16 million a year. Vaccination against meningitis and prompt treatment of central nervous system infection: STRONG. Conjugate vaccine reduced confirmed serogroup A meningococcal disease by 99 per cent in vaccinated populations in the African meningitis belt.

Malaria control: STRONG for the cerebral malaria fraction. Stroke prevention: STRONG, since stroke is the leading cause of new epilepsy in older adults and 57 per cent of stroke DALYs are attributable to high systolic blood pressure. Post-traumatic and post-stroke antiseizure prophylaxis to prevent epilepsy:

CONTESTED, with the evidence against. The drugs prevent early provoked seizures and do not prevent later epilepsy, and the negative result is reported. Avoiding valproate in pregnancy prevents fetal valproate syndrome rather than epilepsy, and it is the most important prescribing-safety measure in this condition.

Treatment. Some people withdraw medication without relapse, and the proportion is not given. *Antiseizure medications*, with up to 70 per cent seizure freedom. First-line choice depends on seizure type, and the SANAD trials established carbamazepine and lamotrigine for focal epilepsy and valproate for generalised epilepsy as reference comparators on effectiveness, with valproate's teratogenicity now restricting its use in women of childbearing potential. Carbamazepine is EML-listed and off-patent, costing tens of US dollars a patient-year. Valproic acid is EML-listed and off-patent, tens of US dollars a patient-year, and is a major teratogen.

Phenobarbital is EML-listed as a selected medicine, confirmed against the 24th List, off-patent, and costs about **US$6.24 a patient-year** on the UNICEF indicative price of US$1.71 per 100 tablets of 30 mg, read 19 October 2026, at one tablet a day. It is the cheapest effective antiseizure drug in existence and still first-line in many low-income settings, with sedation and cognitive effects as the trade-off. Phenytoin is EML-listed and off-patent at tens of US dollars a patient-year at most. Lamotrigine is EML-listed and off-patent, tens to low hundreds of US dollars a patient-year, and is preferred in pregnancy.

Levetiracetam is EML-listed and off-patent, tens to low hundreds of US dollars a patient-year, also preferred in pregnancy, with behavioural adverse effects in a minority. Ethosuximide for childhood absence epilepsy is EML-listed and off-patent, tens to low hundreds of US dollars a patient-year. Diazepam, lorazepam and midazolam for acute seizures and status epilepticus are EML-listed and off-patent at a few US dollars a dose, and buccal or intranasal midazolam can be given by a family member without injection, which matters where no clinician is present. No dose is given for any substance of misuse in this chapter.

Epilepsy surgery, with the Wiebe figures above: 58 against 8 per cent seizure freedom at one year†. Also lesionectomy, hemispherotomy in children, and laser interstitial thermal therapy. The cost runs to tens of thousands of US dollars, and it is available to a very small fraction of those who would benefit. *Ketogenic diet for drug-resistant epilepsy*: a Cochrane review (Martin-McGill and colleagues, 2020; 13 randomised trials, 932 participants, of whom 711 children and 221 adults, follow-up 2 to 16 months), as summarised in *American Family Physician* in 2021.

In children, seizure freedom was 66 per 1,000 on the diet against 21 per 1,000 on usual diet, an absolute risk reduction of 4.5 per cent, number needed to treat 22 (95 per cent CI 7 to 250), on very low quality evidence. In children, a 50 per cent or greater seizure reduction occurred in 453 per 1,000 against 78 per 1,000, an absolute risk reduction of 37.5 per cent, **number needed to treat 3 (95 per cent CI 1 to 5)**, on low quality evidence — a large effect. In adults, no participant became seizure-free across 141 participants in two studies, and a 50 per cent or greater reduction occurred in 144 against 29 per 1,000, not statistically significant.

Adult treatment withdrawal was 461 per 1,000 on the diet against 86 per 1,000 on usual diet, so tolerability is the limiting factor in adults. In children, gastrointestinal adverse effects were no more likely than on usual diet, across 425 participants in five studies. So: substantial benefit for a 50 per cent or greater seizure reduction in children, number needed to treat 3; marginal for seizure freedom, number needed to treat 22; and ineffective and poorly tolerated in adults. It requires dietetic supervision, which is the practical constraint, not the food.

Vagus nerve stimulation and responsive neurostimulation: roughly 50 per cent of patients achieve a 50 per cent or greater seizure reduction, and seizure freedom is rare; device costs run to tens of thousands of US dollars. *Cannabidiol* is effective in Dravet and Lennox-Gastaut syndromes and in tuberous sclerosis in randomised trials, with roughly 20 to 40 per cent median seizure reduction above placebo; not EML-listed†, on patent in pharmaceutical grade, and costing tens of thousands of US dollars a patient-year at list price. *Treating the cause*: albendazole with corticosteroids for neurocysticercosis — albendazole is EML-listed as a selected medicine, confirmed against the 24th List — immunotherapy for autoimmune encephalitis, tumour resection.

Status epilepticus: a benzodiazepine first, then a second-line agent, and the ESETT trial found levetiracetam, fosphenytoin and valproate equivalent as second-line, which matters because it means the cheapest available agent is an acceptable choice.

Simple means. Phenobarbital at US$6.24 a patient-year at the UNICEF Supply Catalogue indicative price, October 2026, in a condition where up to 70 per cent can become seizure-free and roughly three quarters of patients in low-income countries get nothing. The gap here is distribution, not discovery. Sleep regularity: sleep deprivation is a well-established seizure precipitant, and regular adequate sleep reduces seizure frequency. Free. Adherence support: missed doses are a leading cause of breakthrough seizures and status epilepticus, and a pill box and a routine address it. Avoiding alcohol, which lowers the seizure threshold on withdrawal. Safety adaptation: supervised bathing rather than baths, since drowning is a leading cause of epilepsy death; kitchen and fire safety; swimming supervision. These prevent a substantial share of the three-fold excess mortality and cost nothing. Buccal or intranasal midazolam given by a family member for prolonged seizures prevents status epilepticus without a clinician or a needle. Ketogenic diet in children: number needed to treat 3 for a 50 per cent or greater seizure reduction, using food; it needs dietetic supervision and no manufactured product. Pig husbandry and sanitation prevent the largest single cause of epilepsy worldwide, with no clinical supply chain at all.

Gaps. The 50 million figure and the regional incidence difference rest on sparse door-to-door surveys, and WHO's page carries no data year for the 50 million. The drug-resistant proportion has not fallen despite more than twenty new drugs, which is unexplained and rarely stated plainly. There is no antiepileptogenic treatment, and every prophylaxis trial has failed. The mechanism of sudden unexpected death in epilepsy is unknown and it is a leading cause of epilepsy death in young adults. Ketogenic diet evidence is rated low to very low quality by Cochrane, with short follow-up. Surgical candidacy is assessed in a tiny minority of eligible patients even in high-income countries.

> **Depth.** A group with many causes [B]. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Multiple sclerosis

What it is. An immune-mediated disease in which the myelin sheaths of central nervous system axons are attacked, producing scattered areas of inflammation and scarring. It typically begins with attacks that partly recover, the relapsing-remitting form, and in many people later becomes steadily progressive. Symptoms depend on lesion location: vision loss, weakness, numbness, imbalance, bladder dysfunction, fatigue and cognitive impairment.

Measured. Over 1.8 million people have multiple sclerosis worldwide (WHO multiple sclerosis fact sheet, 7 August 2023; the page states no data year for the estimate). The MS International Federation's *Atlas of MS*, third edition, 2020, gives 2.8 million, a figure that is widely used and differs from WHO's by more than 50 per cent. Both are printed and the disagreement is named. Prevalence shows a strong latitude gradient: roughly 100 to 300 per 100,000 in northern Europe, North America, Australia and New Zealand, against under 20 per 100,000 near the equator. Women are affected roughly two to three times as often as men, and the ratio has been rising over decades in multiple registries — a change that must be environmental, since the genome has not changed. Onset is most commonly between 20 and 40 years. Life expectancy is reduced by roughly 7 to 10 years, a gap that has narrowed with treatment†. Recorded prevalence is rising, driven by better ascertainment, longer survival, and probably a true incidence increase in women.

Where it starts. This is one of the clearest aetiological stories in Chapter 08, built in the last decade. Epstein-Barr virus infection is very likely a necessary cause. Bjornevik and colleagues (*Science*, 2022) used serial serum samples from over 10 million US military personnel: seroconversion preceded multiple sclerosis onset, and **Epstein-Barr virus infection was associated with a 32-fold increase in risk, hazard ratio 32.4 (95 per cent CI 4.3 to 245.3)**, with no comparable effect for cytomegalovirus or other viruses, and with seroconversion preceding the first rise in neurofilament light chain.

Among 801 cases, only one was Epstein-Barr-negative at onset†. That is the largest effect size for an environmental exposure anywhere in the book. The virus is necessary and far from sufficient: over 90 per cent of adults are seropositive† and almost none develop multiple sclerosis. *HLA-DRB1*15:01* carries roughly three times the risk and is the strongest genetic factor, with over 200 further loci of small effect and heritability roughly 30 to 50 per cent†. Low vitamin D and low sun exposure: the latitude gradient, migration studies in which risk tracks the country of childhood residence rather than of birth or adulthood, and Mendelian randomisation supporting a causal role for genetically low vitamin D give MODERATE causal evidence — the association is strong and the randomised supplementation trials are negative.

Adolescent obesity carries roughly twice the risk, supported by Mendelian randomisation. Smoking carries roughly 1.5 times the risk and faster progression, and the association with progression is better established than for most exposures. Symptomatic Epstein-Barr infection in adolescence, infectious mononucleosis, carries roughly twice the risk beyond seropositivity alone. Organic solvent exposure interacts with smoking and HLA genotype.

Autoimmune demyelination is established. B cells are centrally involved, demonstrated by the efficacy of anti-CD20 therapy, which was a surprise since T cells had been the assumed driver. The Epstein-Barr link is epidemiologically very strong and its mechanism is not settled, with molecular mimicry between Epstein-Barr nuclear antigen 1 and GlialCAM demonstrated in vitro, and bystander activation and persistence of infected B cells as alternatives. Progression is mechanistically distinct from relapse: anti-inflammatory drugs that abolish relapses do not stop progression. That is the central unsolved problem and it indicates a second process — chronic smouldering inflammation, mitochondrial failure, or age-related repair failure — that is not understood. Not known: what converts Epstein-Barr infection into multiple sclerosis in one in a thousand infected people; what drives progression; why the sex ratio is rising.

Cure status. For relapses: CONTROLLABLE. For progression: RELIEF ONLY. High-efficacy disease-modifying therapies reduce relapse rate by roughly 50 to 70 per cent and new MRI lesions by over 80 per cent†. No treatment stops progression, though some slow it modestly. Autologous haematopoietic stem cell transplantation produces prolonged disease inactivity — no evidence of disease activity for years — in highly selected patients with active relapsing disease, in randomised and observational data, and it is the closest to a cure available; treatment-related mortality is roughly 0.2 to 2 per cent depending on protocol and era†. About 10 to 15 per cent have benign disease with minimal disability after decades, and this is not predictable at onset.

Prevention. Epstein-Barr vaccination: no licensed vaccine exists. If the virus is necessary, vaccination is in principle the most powerful prevention possible for this disease, and candidate vaccines are in early trials. It is the most important prospect and it is currently unavailable. Vitamin D supplementation: CONTESTED. The observational and Mendelian randomisation evidence supports a causal role, and randomised supplementation trials, including VITAL and the multiple sclerosis-specific SOLAR and CHOLINE trials, have not shown reduction in incidence or robust reduction in activity. Both halves are reported. Preventing adolescent obesity: MODERATE, supported by Mendelian randomisation. Smoking cessation and prevention: MODERATE for incidence, MODERATE for slowing progression in diagnosed patients. Sun exposure in childhood and adolescence: MODERATE on the latitude and migration evidence, confounded with vitamin D.

Treatment. *Anti-CD20 monoclonal antibodies* — ocrelizumab, ofatumumab, rituximab — are among the most effective agents, with roughly 50 to 70 per cent relapse reduction against interferon in head-to-head trials, and ocrelizumab showed a modest effect in primary progressive disease, the first agent to do so. Rituximab is widely used off-label with comparable observational effectiveness and is off-patent, available as biosimilars at a small fraction of the originator antibody prices; ocrelizumab costs tens of thousands of US dollars a year at US list price. Rituximab **is** EML-listed as a selected medicine, under section 5.1.2 Medicines for multiple sclerosis, complementary list, confirmed against the 24th List; ocrelizumab is not EML-listed†. Another dossier in this book gives a rituximab price range of tens to thousands of US dollars a patient-year in a sentence whose construction excludes rituximab from that range, so it gives no rituximab price, and a third asserts EML status with no price; this chapter's compilation gave a dollar range for biosimilars that was an unsourced estimate and is not printed. Three dossiers, three treatments of one drug.

Natalizumab gives roughly 68 per cent relapse reduction in the AFFIRM trial, with a risk of progressive multifocal leukoencephalopathy stratified by JC virus serology; not EML-listed, biosimilars emerging, and costing tens of thousands of US dollars a year. *Alemtuzumab and cladribine* have high efficacy and are given as short courses; cladribine is off-patent as a generic injectable used off-label and the oral tablet form is on patent, and neither agent is EML-listed, with the oral form costing tens of thousands of US dollars a year-equivalent and the generic injectable a small fraction of that. *Oral agents* — fingolimod, dimethyl fumarate, teriflunomide, siponimod — have moderate efficacy, roughly 30 to 50 per cent relapse reduction; several are now off-patent, and generics cost thousands of US dollars a patient-year against originator pricing in the tens of thousands; none is EML-listed.

Interferon beta and glatiramer acetate, the original agents, give roughly 30 per cent relapse reduction, are largely superseded, are still used, and are the safest in pregnancy planning; not EML-listed, off-patent, thousands to tens of thousands of US dollars a year. *Corticosteroids for acute relapse* shorten relapse duration with no effect on long-term disability; methylprednisolone and prednisolone are EML-listed, off-patent, and cost on the order of tens of US dollars a course. *Autologous haematopoietic stem cell transplantation*: the MIST randomised trial showed superiority to disease-modifying therapy for disability progression in active relapsing disease, at a one-off cost in the tens to low hundreds of thousands of US dollars, which may be less than a decade of a high-cost antibody.

Symptomatic treatment: fampridine for walking speed; baclofen and tizanidine for spasticity, both EML-listed, off-patent, at tens of US dollars a patient-year; anticholinergics or botulinum toxin for bladder; amitriptyline or gabapentinoids for neuropathic pain; modafinil or amantadine for fatigue. *Exercise and rehabilitation*: randomised trials show improvement in walking, balance, fatigue and quality of life with moderate effect sizes, and exercise does not worsen the disease, contrary to decades of earlier advice — a reversed recommendation worth recording.

Simple means. Exercise: randomised trials establish improvement in fatigue, which is one of the most disabling symptoms and one with no good drug, and in walking and balance. For fatigue specifically, exercise has better evidence than any medication, since the modafinil and amantadine trials have been largely negative. This is a case where a simple means outperforms the drugs for a specific symptom. Smoking cessation: slows progression; free, or a few US dollars with cytisine. Weight management in adolescence: Mendelian-randomisation-supported prevention. Heat management — cooling, avoiding overheating: Uhthoff's phenomenon is well characterised, and a cool shower or a fan restores function temporarily. Free. Sun exposure: the latitude and migration evidence supports it and the supplement trials do not, so sun rather than capsules, with the honest caveat that this is unresolved. Bladder management routines and pelvic floor training reduce infections, which are a leading cause of hospitalisation and death in advanced disease. Vitamin D is cheap and harmless at ordinary doses, with negative trial evidence for multiple sclerosis outcomes, and is not oversold here.

Gaps. WHO says 1.8 million and the MS Atlas says 2.8 million; the sources disagree by more than 50 per cent and both are widely cited. The Epstein-Barr finding is epidemiologically powerful and has produced no intervention, and no licensed vaccine exists. Progression is untreatable and mechanistically unexplained. The rising female-to-male ratio is well documented and unexplained. Vitamin D is a textbook case of observational and randomised evidence disagreeing. Disease-modifying therapy pricing bears no relation to cost of goods, and rituximab demonstrates that an effective treatment can cost a small fraction of the alternatives; access in low- and middle-income countries is minimal. There are no trials in the populations with lowest prevalence, so natural history outside high-prevalence regions is poorly described.

> **Depth.** Starts in: the Epstein-Barr virus. Size: 180 nm†; depth +1.25. First complaint: about 5 years ([B] EBV is almost a necessary condition; † about 5 years after seroconversion); time depth 50.34. One untreated course: about 6 weeks († an attack lasts about 6 weeks); depth 46.90.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Motor neurone disease and amyotrophic lateral sclerosis

What it is. Progressive degeneration of the motor neurons in the brain and spinal cord, causing weakness and wasting that spreads, with loss of speech, swallowing and ultimately breathing. Sensation and usually eye movement are spared. Cognitive and behavioural change of frontotemporal type occurs in a substantial minority.

Measured. WHO has no dedicated fact sheet for motor neurone disease (checked October 2026). Incidence is roughly 1.5 to 2.5 per 100,000 a year in European-ancestry populations and prevalence roughly 4 to 8 per 100,000; prevalence is low relative to incidence because survival is short. Global prevalent cases in GBD estimates are roughly 200,000 to 350,000. Median survival from symptom onset is roughly 2 to 4 years, and roughly 10 per cent survive 10 years. Bulbar-onset disease has shorter survival than limb-onset. Men roughly 1.2 to 1.5 times women. Peak onset is 55 to 75 years. Lifetime risk is roughly 1 in 300 to 1 in 400. Incidence is rising modestly with population ageing, and age-standardised rates are broadly stable.

Where it starts. Roughly 10 per cent of cases are familial, and genetic causes are found in roughly 10 to 15 per cent of apparently sporadic cases†. The *C9orf72* hexanucleotide repeat expansion is the commonest cause in European populations, accounting for roughly 40 per cent of familial and 5 to 10 per cent of sporadic cases, and linking the disease to frontotemporal dementia. *SOD1*, *TARDBP* and *FUS* are the other major genes, and heritability is roughly 40 to 60 per cent†. Age and male sex are established. Smoking is the most consistently replicated environmental risk factor, roughly 1.4 to 1.6 times†. Military service is consistently associated across multiple national cohorts, roughly 1.5 to 2 times, with the cause unidentified†. Physical activity and elite athleticism are associated in several studies, including a well-documented excess in professional footballers, and whether that reflects exercise, head injury, or shared genetic predisposition toward athleticism is genuinely unresolved — and the hypotheses point in opposite directions for advice. Head injury, heavy metals, pesticides and electrical work are reported inconsistently. The Guam and Kii peninsula ALS-parkinsonism-dementia complex, linked to cycad consumption and BMAA, is historically important and declined with dietary change, which supports an environmental cause in that specific setting.

TDP-43 protein mislocalisation and aggregation is present in roughly 97 per cent of cases† and is the defining pathology; established as a hallmark, with a causal role that is probable and not proven. RNA processing failure, protein clearance failure, glutamate excitotoxicity, mitochondrial failure and glial contribution are all supported by evidence, and no single mechanism explains the disease. The riluzole mechanism, glutamate modulation, was the basis for a generation of excitotoxicity-targeted trials that all failed apart from riluzole's own small effect. Not known: what initiates degeneration; why it spreads contiguously; why motor neurons specifically; why the same mutation causes disease at age 40 in one carrier and 70 in another.

Cure status. RELIEF ONLY. This is the clearest RELIEF ONLY designation in Chapter 08. No treatment halts or reverses the disease. Riluzole extends survival by roughly two to three months. Non-invasive ventilation extends survival by roughly seven months in those with preserved bulbar function and improves quality of life — the largest survival effect of any intervention. Multidisciplinary clinic attendance is associated with roughly seven months longer survival in observational studies. Reported reversals are vanishingly rare and generally reflect misdiagnosis of mimics, which is why mimics — multifocal motor neuropathy, myasthenia gravis, cervical myelopathy, inclusion body myositis — must be excluded.

Prevention. No established prevention. Smoking cessation is the only replicated modifiable risk factor: WEAK for this endpoint specifically, and justified on every other ground. Genetic counselling for families with known mutations is not prevention of the disease and enables informed reproductive choice; pre-symptomatic testing is available for *C9orf72* and *SOD1*. Dietary and supplement claims: none supported.

Treatment. *Non-invasive ventilation* has the largest measured survival and quality-of-life benefit: roughly **seven months additional median survival** in randomised trial data (Bourke and colleagues, *Lancet Neurology*, 2006) in patients with preserved bulbar function. The device is a one-off cost in the low thousands of US dollars plus consumables, and it is not a drug. *Multidisciplinary specialist clinic care* is associated with roughly seven months longer survival in observational comparisons, through better nutrition, earlier ventilation and secretion management rather than a new treatment. Organisational.

Riluzole extends median survival by roughly two to three months, about a 9 per cent improvement in one-year survival on Cochrane review†; not EML-listed, off-patent, and costing on the order of hundreds to low thousands of US dollars a patient-year as a generic. *Edaravone* was approved in some jurisdictions on a small trial in a narrowly defined subgroup, where the effect was a 33 per cent slowing of functional decline over six months on the ALSFRS-R, and the European regulator refused the application for insufficient evidence. Sources and regulators disagree. Not EML-listed, on patent in most markets, and costing a six-figure sum in US dollars a patient-year for the intravenous form.

Tofersen, an antisense oligonucleotide for *SOD1*-associated disease, reduces neurofilament light chain substantially; the primary clinical endpoint in the VALOR trial was not met, with suggestive effects in secondary and open-label extension analyses, and it was approved in the United States under accelerated approval on the biomarker. An important precedent and not an established clinical benefit. Not EML-listed, on patent, costing a low six-figure sum in US dollars a year, and applicable to roughly 2 per cent of patients. *The counterexample*: sodium phenylbutyrate with taurursodiol, marketed as Relyvrio, was approved in the United States on a phase 2 trial, failed its phase 3 trial, and was withdrawn from the market in 2024. Recorded.

Gastrostomy feeding maintains nutrition and is associated with survival benefit in observational data, with no randomised trial. *Symptomatic treatment*: saliva management with anticholinergics, botulinum toxin or radiotherapy to the salivary glands; spasticity with baclofen, which is EML-listed, off-patent and costs tens of US dollars a patient-year; cramps; pain; emotional lability with dextromethorphan-quinidine; communication aids, where eye-gaze systems transform participation at costs of thousands to low tens of thousands of US dollars; and palliative care. *Exercise*: moderate exercise does not accelerate decline and improves function modestly in small randomised trials, and the earlier advice to avoid exertion was not evidence-based.

Simple means. Communication: a letter board or alphabet chart costs almost nothing and preserves the ability to communicate for people who lose speech. Low-technology communication should be available before high-technology devices and often outlasts their battery life. Positioning, secretion management and cough assistance, taught to family carers, prevent aspiration and distress. Nutrition maintenance: weight loss predicts shorter survival, and attention to calorie-dense food is free; no numeric targets are given. Breathing position and manual assisted cough: taught, free. Advance care planning ensures the person's choices about ventilation and feeding are known while they can state them: a conversation, documented. Exercise within tolerance does not harm and improves function modestly. The honest statement: simple means here address comfort, communication and dignity rather than survival, and the survival interventions are ventilation and multidisciplinary care, both of which need equipment and staff. No simple means approaches the effect of medication here, because medication's effect is also very small.

Gaps. No WHO fact sheet, and GBD figures for motor neurone disease are among the least precise in Chapter 08. Three regulatory decisions in this field — edaravone, Relyvrio, tofersen — show regulators and evidence diverging in different directions, and one approved drug was withdrawn after phase 3 failure. The athleticism association is unresolved and its two leading explanations imply opposite advice. The military service association is consistent and unexplained. Almost all trials are in European-ancestry populations. Biomarker-based accelerated approval is a precedent whose validity here is unestablished.

> **Depth.** Starts in: the motor neuron. Size: 100 µm†; depth +7.00. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: about 3 years († median survival about 3 years); depth 49.87.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Migraine

What it is. A recurrent headache disorder with attacks of moderate to severe, often one-sided, pulsating headache, worsened by activity and accompanied by nausea and sensitivity to light and sound. About a third of people have aura: transient visual or other neurological symptoms before or during the attack.

Measured. Migraine ranks third in both age-standardised DALYs for neurological disease burden and global DALYs overall, after stroke and neonatal encephalopathy (WHO headache disorders fact sheet, 24 October 2025, citing Global Health Estimates 2021 and GBD 2021). Headache disorders collectively affect approximately 40 per cent of the global population, about 3.1 billion people in 2021, and rank sixth among all causes of years lived with disability at 45.5 million YLDs (95 per cent UI 31.4 to 62.0) in 2023. Migraine prevalence is roughly 14 to 15 per cent globally, about 1.1 billion people; WHO's fact sheet gives no migraine-specific prevalence figure. Attacks usually last 4 to 72 hours, and the headache can last hours to two or three days. Migraine most often begins around puberty and generally affects people aged 35 to 45 — the peak working and caregiving years. Women roughly two to three times men after puberty, and before puberty the rates are similar. Medication-overuse headache may affect up to 5 per cent of some populations, more women than men. Chronic migraine, meaning 15 or more headache days a month, affects roughly 1 to 2 per cent of the population†. Age-standardised rates are broadly stable, and migraine's DALY rank has risen as other conditions have fallen.

Where it starts. Heritability is roughly 40 to 60 per cent, with over 100 loci identified, mostly in genes related to vascular and ion channel function. Familial hemiplegic migraine is monogenic, from *CACNA1A*, *ATP1A2* or *SCN1A*, and demonstrates that ion channel dysfunction can cause migraine. Female sex and hormonal fluctuation: a menstrual association is present in a majority of affected women, and attacks typically improve after menopause and during the later trimesters of pregnancy. Medication overuse: acute treatment taken too frequently converts episodic to chronic migraine, an iatrogenic and reversible cause affecting up to 5 per cent of some populations. Obesity, snoring and sleep apnoea, depression and anxiety are associated with chronic migraine progression. On attack triggers, the evidence is weaker than patient report suggests. Controlled provocation studies confirm nitric oxide donors, CGRP infusion and PACAP as reliable triggers. For dietary triggers, blinded challenge studies have generally failed to confirm chocolate, cheese and red wine, and premonitory-phase food craving may explain the apparent association. The asymmetry between belief and blinded evidence is reported. Sleep disruption, missed meals, stress letdown and menstruation have better support.

Migraine is not a vascular disease in the way it was taught for most of the twentieth century. The vasodilation theory was abandoned; migraine is a disorder of brain excitability and of the trigeminovascular pain system. Cortical spreading depression is established as the mechanism of aura, demonstrated directly in animals and inferred from human imaging. CGRP, calcitonin gene-related peptide, is established as a key mediator: it is released during attacks, infusing it triggers migraine in susceptible people, and blocking it prevents and treats attacks. That is the clearest mechanism-to-drug success story in the book — the mechanism was identified, drugs were designed against it, and they worked. Not known: what initiates an attack; the role of the hypothalamus in the premonitory phase; why attacks recur in cycles; why some people develop chronic migraine.

Cure status. CONTROLLABLE. Individual attacks are SELF-LIMITING, resolving in 4 to 72 hours. Medication-overuse headache is CURABLE by withdrawal of the overused acute medication, and the majority revert to episodic migraine — a genuinely curable iatrogenic condition. Many people's migraine remits with age, particularly after menopause in women. Preventive treatment reduces attack frequency by roughly 50 per cent in responders, does not remove the disorder, and symptoms return on stopping in most.

Prevention. Avoiding medication overuse: STRONG. Limiting acute treatment frequency prevents chronification, and withdrawal reverses it. The clearest preventable cause. Regular sleep and meal timing: MODERATE, on cohort and small trial data. Aerobic exercise: MODERATE; randomised trials show exercise reduces attack frequency, with effect sizes comparable to some preventive drugs. Weight loss in obesity: MODERATE; obesity is associated with chronification and bariatric surgery cohorts show reduced headache days. Treating coexisting sleep apnoea and insomnia: MODERATE. Stress management and relaxation training: MODERATE, with randomised support. Dietary trigger elimination: CONTESTED; blinded challenge studies are largely negative, and elimination diets commonly cause more restriction than benefit.

Treatment. *Acute.* **Triptans** are the reference acute treatment, with two-hour pain freedom in roughly 20 to 40 per cent against roughly 10 per cent on placebo, and a number needed to treat of roughly 3 to 6 for two-hour headache relief†. Sumatriptan is EML-listed and off-patent, costing on the order of tens of US

dollars a year at generic prices for typical use. Contraindicated in established cardiovascular disease. **NSAIDs and aspirin** are effective, with high-dose aspirin and ibuprofen comparable to some triptans in trials. Aspirin and ibuprofen are EML-listed and off-patent; the UNICEF Supply Catalogue gives ibuprofen 400 mg at US$2.23 for a pack, with US$1.43 returned for the same material number on a different page, read 19 October 2026, so the figure is indicative and dated. These are among the cheapest effective treatments in the book. **Paracetamol with an antiemetic** is effective in mild to moderate attacks; both EML-listed, off-patent, a few US dollars a year, with metoclopramide or domperidone treating the nausea and improving absorption. **Gepants** — ubrogepant, rimegepant — and **lasmiditan** are effective acutely and usable where there is a cardiovascular contraindication; not EML-listed, on patent, and costing from hundreds to thousands of US dollars a year depending on use frequency. **Avoiding opioids and butalbital**, which are associated with chronification and poor outcomes, and which guidelines advise against.

Preventive. **Propranolol and metoprolol** give roughly 50 per cent reduction in attack frequency in roughly 40 to 50 per cent of patients; propranolol is EML-listed†, off-patent, and costs a few US dollars a patient-year. **Amitriptyline** is an effective preventive; EML-listed, off-patent, a few US dollars a patient-year. **Topiramate and valproate** are effective, and topiramate reduces monthly migraine days by roughly 1.5 to 2 against placebo; valproate is EML-listed† for epilepsy and is a teratogen; topiramate is not EML-listed, is off-patent, costs tens to low hundreds of US dollars a patient-year, and is also teratogenic with cognitive adverse effects.

Candesartan and flunarizine are effective, cheap and off-patent. **CGRP monoclonal antibodies** — erenumab, fremanezumab, galcanezumab, eptinezumab — reduce monthly migraine days by roughly 1.5 to 2.5 more than placebo; roughly 50 per cent of patients achieve a 50 per cent reduction against roughly 30 per cent on placebo; and they are well tolerated†. Not EML-listed, on patent, and costing thousands to tens of thousands of US dollars a patient-year at list price. The honest comparison: the absolute effect size is similar to propranolol or topiramate, at three to four orders of magnitude the cost.

The exact multiple is not printed here, because both price inputs in the earlier compilation were unsourced estimates. The advantage is tolerability and usability where the cheap drugs are contraindicated or not tolerated, which is a real advantage for many patients and not a larger effect. **Atogepant and rimegepant as preventives** are oral CGRP antagonists with similar effect sizes; on patent, thousands to tens of thousands of US dollars a year. **OnabotulinumtoxinA for chronic migraine** gives roughly two fewer headache days a month than placebo; not EML-listed, on patent in most markets, thousands of US dollars a patient-year.

Non-invasive neuromodulation — external trigeminal, vagus nerve, remote electrical — gives modest effects at a device cost in the hundreds of US dollars. **Riboflavin, magnesium and coenzyme Q10** have small effects in small trials, and are cheap and low-harm; riboflavin reduced attack frequency in a small randomised trial, and replication is limited. **CBT, biofeedback and relaxation** have effect sizes comparable to preventive drugs in meta-analysis with durable benefit, and combination with drug treatment is better than either alone.

Simple means. Aerobic exercise: randomised trials show attack frequency reduction, with at least one trial finding exercise comparable to topiramate and to relaxation training. This is a condition where exercise has trial evidence comparable to a standard preventive medication. Fixed sleep and wake times: schedule regularity reduces attack frequency, and sleep disruption is among the better-supported triggers. Regular meals: missed meals are a supported trigger. Limiting acute medication frequency: prevents the iatrogenic chronic form affecting up to 5 per cent of some populations, and withdrawal cures it. Free. Aspirin or ibuprofen for acute attacks, at indicative pack prices of US$1.43 to 2.23 for ibuprofen 400 mg in October 2026, and propranolol or amitriptyline for prevention at a few US dollars a patient-year, against the CGRP antibodies at thousands to tens of thousands for a similar absolute effect. Relaxation training and biofeedback: meta-analytic effect sizes comparable to drugs, deliverable from recordings or printed instructions. A dark quiet room and sleep during an attack terminates many attacks at no cost. Hydration and caffeine: caffeine has a genuine acute analgesic-adjuvant effect and a genuine withdrawal-headache risk, and both are real.

Gaps. WHO’s fact sheet gives migraine’s DALY rank and no prevalence figure, so the 1.1 billion figure comes from GBD publications rather than the fact sheet. The gap between reported dietary triggers and

blinded challenge results is large and under-communicated to patients. Preventive drug trials are short, typically three to six months, for a lifelong condition. There are no head-to-head trials of CGRP antibodies against cheap generics at adequate doses, so the cost-effectiveness comparison rests on indirect comparison. Migraine's enormous DALY burden attracts a small fraction of the research funding of conditions with lower burden, a well-documented disparity.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 15 years († onset about age 15); time depth 51.34. One untreated course: about 17 hours († an attack lasts 4–72 hours); depth 43.18.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE, with SELF-LIMITING and CURABLE for named strata. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Tension-type headache

What it is. Bilateral, pressing or tightening headache of mild to moderate intensity, without the nausea, throbbing quality or activity-worsening of migraine. It is the most common headache disorder and in most people episodic and brief.

Measured. Headache disorders collectively affect about 40 per cent of the global population, about 3.1 billion people in 2021, and rank sixth among all causes of years lived with disability at 45.5 million YLDs in 2023. WHO gives no overall tension-type headache prevalence figure, and reports that episodic tension-type headache, occurring on fewer than 15 days a month, is reported by more than 70 per cent of some populations. Chronic tension-type headache, 15 or more days a month, affects roughly 1 to 3 per cent of adults. Tension-type headache affects 50 per cent more women than men. It is the most prevalent single neurological disorder by headcount and has a far lower DALY weight per case than migraine, so its DALY total is substantial and its rank lower. Onset is typically in the twenties to forties.

Where it starts. Heritability of the chronic form is roughly 40 per cent, and the episodic form has lower familial aggregation†. Pericranial muscle tenderness is the most consistent clinical finding, and whether it is cause or consequence is unresolved. Central sensitisation is supported for the chronic form: lowered pain thresholds at sites distant from the head suggest a generalised change in pain processing. Medication overuse converts the episodic to the chronic form, as in migraine. Stress, sleep deprivation, poor posture and prolonged static work are commonly reported associations with weak formal evidence. Depression and anxiety are strongly associated with the chronic form, with mixed direction of causation.

The muscle contraction headache model that gave the disorder its original name is not supported, since electromyographic studies did not confirm sustained muscle contraction as the cause. Peripheral nociceptive input from pericranial muscle plus central sensitisation is the current model for the chronic form: a reasonable synthesis rather than a demonstrated mechanism. Not known: whether tension-type headache and migraine are distinct disorders or ends of a continuum — a genuine and long-running disagreement in the field, with the frequent coexistence in individuals and the shared treatment response supporting the continuum view.

Cure status. Episodic form: SELF-LIMITING. Individual attacks resolve in hours, the disorder is intermittent, and most people never seek care. Chronic form: CONTROLLABLE. Chronic form with medication overuse: CURABLE.

Prevention. Avoiding medication overuse: STRONG, and the main preventable cause of the chronic form. Regular sleep: MODERATE. Exercise: MODERATE; randomised trials of exercise show reduced frequency. Workstation and posture modification: WEAK, widely recommended and poorly evidenced. Stress management: MODERATE, with randomised support for relaxation training.

Treatment. *Simple analgesics for acute episodes* — ibuprofen, aspirin, paracetamol, naproxen — are effective, with numbers needed to treat of roughly 5 to 9 for two-hour pain relief†. All are EML-listed and off-patent, and the UNICEF Supply Catalogue gives ibuprofen 400 mg at US$2.23 a pack, with US$1.43 for the same material number on another page, read 19 October 2026. These are the cheapest effective treatments in the book. *Limiting analgesic use to fewer than 15 days a month* prevents the chronic

iatrogenic form. *Amitriptyline* is the best-evidenced preventive for the chronic form, with roughly 30 per cent reduction in headache index against placebo; EML-listed, off-patent, a few US dollars a patient-year.

Mirtazapine and venlafaxine are second-line preventives with some randomised support. *Physiotherapy, manual therapy and exercise* reduce headache frequency in randomised trials, with effect sizes comparable to amitriptyline in some comparisons and better tolerability. *Relaxation training, biofeedback and CBT* have moderate effect sizes in meta-analysis, durable after treatment ends, and combination with amitriptyline outperformed either alone in a randomised trial. *Acupuncture*: Cochrane review found a small benefit over sham and over no treatment for frequent tension-type headache, and interpretation of the sham comparison remains contested.

Botulinum toxin is **not** effective for tension-type headache in randomised trials, in contrast to chronic migraine — a clear negative result worth recording because it is sometimes offered.

Simple means. Exercise and physiotherapy: trial evidence comparable to amitriptyline, with fewer adverse effects. Another condition where a simple means matches the standard drug. Relaxation and biofeedback: meta-analytic effect sizes comparable to drug prevention, durable after treatment stops, deliverable from recordings. Limiting analgesic days: prevents and reverses the chronic form. Free. Regular sleep and adequate hydration. Aspirin or ibuprofen at a few US dollars a year: for the most prevalent neurological disorder in the world, the effective acute treatment costs less than a cup of coffee a month and is on the Essential Medicines List. There is no access case to make here beyond basic analgesic availability.

Gaps. No specific WHO prevalence figure for the world's most common neurological disorder. Whether it is distinct from migraine is unresolved after decades. The chronic form is understudied relative to chronic migraine, with far fewer trials and no modern targeted treatment. Posture and ergonomic advice is universal and essentially unevidenced.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 20 years († onset about age 20); time depth 51.60. One untreated course: about 9 hours († 30 minutes–7 days); depth 42.62.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Cluster headache

What it is. Attacks of extremely severe, strictly one-sided pain around the eye or temple, lasting 15 minutes to 3 hours, with tearing, nasal congestion, eyelid drooping and marked restlessness on the same side. Attacks recur once to eight times daily in bouts lasting weeks to months, often at the same time of year and the same time of night.

Measured. Cluster headache affects fewer than 1 in 1,000 adults and affects six men to each woman (WHO headache disorders fact sheet, 24 October 2025) — the most male-skewed condition in the book. Onset is typically between 20 and 40 years. Roughly 10 to 15 per cent have the chronic form without remission periods. Pain intensity is rated among the most severe in clinical medicine, and suicidal ideation during attacks is frequently reported. Diagnostic delay is long, commonly years, with frequent misdiagnosis as sinus or dental disease and unnecessary procedures. There is no stand-alone GBD estimate: low prevalence and high per-case severity.

Where it starts. Circadian and circannual periodicity is the defining epidemiological feature: attacks cluster at fixed times of day and bouts at fixed times of year. That points to the hypothalamus, and functional imaging shows posterior hypothalamic activation during attacks — among the strongest localisation findings for any headache disorder. Smoking: the great majority of patients are current or former smokers, a much stronger association than in migraine; whether it is causal is unresolved, and stopping smoking does not reliably stop the attacks. Alcohol triggers attacks reliably during a bout and not during remission — a striking, well-described and unexplained pattern. First-degree relatives carry roughly 5 to 18 times the risk, and heritability is present with no major gene identified. Male sex, 6 to 1, and the ratio appears to have narrowed over decades.

Hypothalamic involvement is established by imaging and by the circadian pattern, and the trigeminal-autonomic reflex explains the autonomic features. CGRP is involved: levels rise during attacks, and galcanezumab reduces episodic cluster attacks. Not known: what drives the periodicity; why the male predominance; why alcohol triggers only during bouts; why oxygen works.

Cure status. Individual bouts in the episodic form: SELF-LIMITING, since they remit spontaneously. The disorder itself: CONTROLLABLE. Acute treatment aborts individual attacks highly effectively and preventive treatment shortens bouts, which is control; no treatment prevents future bouts permanently. Spontaneous long-term remission occurs in a minority with age.

Prevention. No established primary prevention. Smoking cessation is justified and does not reliably alter the disorder: WEAK. Alcohol avoidance during a bout prevents individual attacks reliably: STRONG for that narrow outcome, and free. Starting preventive treatment early in a bout shortens the bout: MODERATE.

Treatment. *High-flow oxygen* aborts attacks in roughly 70 to 80 per cent within fifteen minutes, with randomised trial support (Cohen and colleagues, *JAMA*, 2009). It is an inhaled gas, not a drug: there is no patent, no EML entry as such, and a cylinder costs a few US dollars a fill. It is one of the most effective acute treatments in all of neurology, and it is frequently unavailable to patients because of supply and reimbursement rules rather than cost. That is recorded. *Subcutaneous sumatriptan* aborts attacks in roughly 75 per cent within fifteen minutes and is the fastest pharmacological option; sumatriptan is EML-listed and off-patent, and the injectable form costs from low hundreds to low thousands of US dollars a year depending on attack frequency and market. Intranasal zolmitriptan is also effective.

Verapamil is the first-line preventive and reduces attack frequency substantially; not EML-listed, off-patent, tens of US dollars a patient-year at most, and it requires ECG monitoring at higher doses. *Corticosteroid bridging* with prednisolone, or a greater occipital nerve block with steroid, rapidly suppresses attacks while verapamil takes effect; prednisolone is EML-listed, off-patent, a few US dollars a course, and the nerve block is cheap, quick and effective in randomised trials. *Lithium* is an effective preventive, particularly in chronic cluster headache; EML-listed, off-patent, a few tens of US dollars a patient-year at most plus monitoring.

Galcanezumab reduced weekly attack frequency in episodic cluster headache in a randomised trial and failed in chronic cluster headache; not EML-listed, on patent, thousands to tens of thousands of US dollars a patient-year. *Topiramate, melatonin and warfarin* are second-line with weaker evidence, and melatonin at night has small randomised support, costs tens of US dollars a year, and fits the circadian mechanism. *Non-invasive vagus nerve stimulation* gives modest benefit for episodic cluster, at a device cost in the hundreds of US dollars. *Sphenopalatine ganglion stimulation and occipital nerve stimulation* are used for refractory chronic cases at device costs in the tens of thousands of US dollars.

Simple means. Oxygen: the single most striking cost-to-effect ratio in Chapter 08 — 70 to 80 per cent attack abortion from an inhaled gas that costs a few dollars a cylinder and cannot be patented. The barrier is prescribing and supply, not price. Alcohol avoidance during a bout prevents attacks reliably, and it is free. Regular sleep timing: attacks are nocturnally clustered and sleep disruption is implicated, and melatonin at tens of US dollars a year fits the circadian mechanism. Keeping a bout diary identifies the bout pattern, which allows preventive treatment to be started early and stopped when the bout ends. Paper. Greater occipital nerve block: a few US dollars of steroid and local anaesthetic, administered in minutes, with randomised support. Correct and early diagnosis: years of delay and unnecessary sinus and dental procedures are a large part of the measured harm, and the remedy is recognition rather than a product.

Gaps. No burden estimate for a condition with extreme per-case severity. The periodicity is the disorder's most distinctive feature and is unexplained. Oxygen's mechanism is unknown and its availability is poor relative to its efficacy. The 6-to-1 male predominance and its apparent narrowing are unexplained. Chronic cluster headache has fewer effective options and galcanezumab failed in it. Most preventive evidence is from small trials, and verapamil, the first-line agent, has a thin randomised base for its wide use.

> **Depth.** Starts in: the hypothalamus. Size: 1 cm†; depth +11.19. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: about 52 minutes ([B] an attack lasts 15 minutes–3 hours); depth 40.48.

> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Diabetic neuropathy

What it is. Damage to the peripheral nerves from chronic hyperglycaemia, typically beginning in the feet and progressing proximally, causing numbness, tingling, burning pain and loss of protective sensation.

Measured. 206 million cases globally, having more than tripled since 1990 (GBD 2021, *Lancet Neurology*, 2024). It ranked fifth among all nervous system conditions by DALYs on that analysis — higher than meningitis, epilepsy or autism. Roughly 50 per cent of people with diabetes develop neuropathy over their lifetime, and roughly 20 per cent have painful neuropathy. Diabetic neuropathy underlies the majority of diabetic foot ulcers, which precede the majority of non-traumatic lower limb amputations, and amputation and ulcer rates are the measurable downstream harm. It is rising faster than almost any condition in the book, tracking the global diabetes epidemic: 830 million people were living with diabetes in 2022, up from 200 million in 1990, and more than half of all people with diabetes were untreated in 2022 (WHO diabetes fact sheet, 14 November 2024).

Where it starts. Duration and degree of hyperglycaemia are the primary determinants. In type 1 diabetes, intensive glycaemic control reduces neuropathy incidence substantially — roughly 60 to 69 per cent in the DCCT trial†. In type 2 diabetes, intensive glycaemic control produces only a small, non-significant reduction in clinical neuropathy in meta-analysis: a major and under-communicated difference between the two diseases. Additional factors in type 2: height, smoking, hypertension, dyslipidaemia, obesity and alcohol.

Polyol pathway flux, advanced glycation end products, oxidative stress, microvascular ischaemia and impaired nerve regeneration are all implicated. No single mechanism is established, and every mechanism-targeted drug has failed in trials — aldose reductase inhibitors, protein kinase C inhibitors, alpha-lipoic acid and others. The failure is as informative as the hypotheses. Not known: why intensive glycaemic control works in type 1 and barely in type 2, which is the single most important unanswered question here; why some people get painful and others painless neuropathy; why no neuroprotective agent has worked.

Cure status. RELIEF ONLY for established neuropathy. Nerve damage does not reverse. Glycaemic control prevents progression in type 1 and has limited effect in type 2. Curable causes of neuropathy exist and must be excluded in anyone presenting with it: B12 deficiency, where replacement reverses it if treated early; hypothyroidism; leprosy; HIV; vasculitis; and alcohol-related neuropathy with abstinence and thiamine.

Prevention. Glycaemic control in type 1 diabetes: STRONG, roughly 60 to 69 per cent reduction in incidence in DCCT†. Glycaemic control in type 2 diabetes: CONTESTED for neuropathy specifically, since meta-analysis shows a small, non-significant reduction. This contradicts common assumption and is stated plainly. Multifactorial risk management in type 2 — blood pressure, lipids, smoking, weight: MODERATE; the Steno-2 trial showed reduced autonomic neuropathy with multifactorial intervention. Diabetes prevention itself: STRONG. The Diabetes Prevention Program randomised 3,234 participants — 1,082 to placebo, 1,073 to metformin, 1,079 to intensive lifestyle intervention — over an average 2.8 years.

Three-year cumulative diabetes incidence was **28.9 per cent on placebo, 21.7 per cent on metformin and 14.4 per cent on lifestyle intervention**. The published relative reductions are 58 per cent (95 per cent CI 48 to 66) for lifestyle and 31 per cent (17 to 43) for metformin. The published numbers needed to treat for three years are 6.9 (5.4 to 9.5) for lifestyle and 13.9 (8.7 to 33.9) for metformin. Those numbers needed to treat follow exactly from the cumulative incidences: 28.9 minus 14.4 gives 14.5 percentage points and a reciprocal of 6.90, and 28.9 minus 21.7 gives 7.2 points and 13.89, both recomputed.

Preventing diabetes prevents its neuropathy. Annual foot examination and protective footwear: STRONG for the ulcer and amputation outcome — not for the neuropathy, but for the harm the neuropathy causes; structured foot care reduces amputation rates substantially in programme evaluations. Vitamin B12 monitoring in long-term metformin users: MODERATE, because it prevents a reversible cause.

Treatment. *Tricyclic antidepressants*, amitriptyline and nortriptyline, give a number needed to treat of roughly 3 to 5 for 50 per cent pain reduction — the best effect size of any class — with anticholinergic and cardiac limitations in older people. Amitriptyline is EML-listed, off-patent, and costs a few US dollars a patient-year: the most effective and the cheapest option simultaneously. *Gabapentinoids*, gabapentin and pregabalin, give a number needed to treat of roughly 6 to 8†; neither is EML-listed†, both are off-patent, and they cost tens to low hundreds of US dollars a patient-year. Harms: sedation, dizziness, oedema, weight gain, misuse potential, and respiratory depression risk with opioids.

SNRIs, duloxetine and venlafaxine, give a number needed to treat of roughly 5 to 7, and duloxetine has the best evidence in diabetic neuropathy†; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year. *Topical capsaicin 8 per cent patch and topical lidocaine* are useful for localised pain, and the high-concentration capsaicin patch has randomised support; costs vary widely. *Opioids and tramadol* have modest efficacy and substantial harms, and guidelines now place them last or advise against them for chronic neuropathic pain. *Treating the cause*: glycaemic control; B12 replacement, EML-listed†, off-patent, a few US dollars a year; thyroxine; alcohol abstinence with thiamine.

Foot care, offloading and podiatry: for the diabetic foot this is the intervention that prevents amputation, and therapeutic footwear, regular inspection, prompt ulcer treatment and total contact casting have strong evidence for the ulcer outcome. *Exercise*: randomised trials show improved nerve function measures, reduced pain and improved balance. No disease-modifying treatment exists.

Simple means. Amitriptyline at a few US dollars a patient-year with a number needed to treat of 3 to 5: the most effective neuropathic pain drug in the world is also one of the cheapest and is on the Essential Medicines List. For a condition affecting 206 million people, that is the central practical fact. Daily foot inspection, well-fitting shoes, and never walking barefoot prevent the ulcers that cause the amputations: a mirror and a pair of shoes, with a large measured effect on amputation rates in structured foot-care programmes. Exercise: trial evidence for improved nerve function, pain and balance. Free. Vitamin B12 at a few US dollars a year reverses a cause if caught early. Weight loss and diabetes prevention: the Diabetes Prevention Program's 58 per cent reduction came from diet and physical activity, outperforming metformin's 31 per cent — a simple means with trial evidence superior to the medication it was compared against. Balance and falls prevention: loss of proprioception causes falls, and balance training has randomised support.

Gaps. The type 1 and type 2 divergence in glycaemic control's effect on neuropathy is established and poorly communicated. Every mechanism-targeted drug has failed, and the field has no disease-modifying candidate. Pain trial outcomes are subjective and placebo responses large, so effect sizes across the class are modest and may be overstated by publication bias. The 206 million figure tripling since 1990 is a modelled estimate following diabetes prevalence rather than direct neuropathy measurement.

> **Depth.** Starts in: a peripheral nerve. Size: 1 mm†; depth +9.10. First complaint: about 10 years († about 10 years of diabetes); time depth 50.97. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The nerve does not regrow while the sugar stays high. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Chemotherapy-induced peripheral neuropathy

What it is. Damage to the peripheral nerves from neurotoxic cancer drugs, typically beginning in the feet and hands, causing numbness, tingling, burning pain and loss of sensation, and often limiting the dose of the cancer treatment.

Measured. Incidence is roughly 68 per cent within the first month of treatment, roughly 60 per cent at three months, and **roughly 30 per cent persisting at six months or more**, on meta-analysis of platinum, taxane, vinca alkaloid and bortezomib regimens. It is the commonest dose-limiting toxicity of several curative cancer regimens, so it directly limits cancer treatment. There is no WHO fact sheet and no stand-alone GBD estimate.

Where it starts. Cumulative dose of the neurotoxic agent is the dominant determinant. Pre-existing neuropathy, diabetes and specific pharmacogenetic variants increase susceptibility. Platinum agents cause a dorsal root ganglion sensory neuronopathy that can worsen for months after treatment stops, which is called coasting and is a distinctive and clinically important feature. Axonal transport disruption by taxanes, dorsal root ganglion accumulation by platinum agents, and mitochondrial injury are supported mechanisms. Not known: why some patients are affected severely and others not at the same cumulative dose.

Cure status. SELF-LIMITING in roughly 70 per cent, who resolve within months of stopping; RELIEF ONLY in roughly 30 per cent, whose neuropathy persists beyond six months, much of it permanently.

Prevention. Dose limitation and regimen selection: STRONG for the neuropathy outcome, with an obvious trade-off against cancer control. Cryotherapy and compression therapy during taxane infusion: MODERATE; randomised trials show reduced neuropathy incidence with limb cooling or compression, and the means are ice packs or compression stockings. Exercise during chemotherapy: MODERATE; randomised trials show reduced severity. Neuroprotective agents during chemotherapy: CONTESTED to negative. Calcium and magnesium infusions, glutathione, vitamin E and acetyl-L-carnitine have all been tested; none is established, and acetyl-L-carnitine **worsened** outcomes in a randomised trial.

Treatment. *Duloxetine* is the only agent with any support in chemotherapy-induced neuropathic pain, where a randomised trial showed modest benefit; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year. *Tricyclic antidepressants and gabapentinoids* are used on the shared neuropathic pain evidence base; amitriptyline is EML-listed, off-patent, a few US dollars a patient-year. *Exercise*: randomised trials show reduced severity and improved function. *Dose reduction or discontinuation of the offending agent* is the only intervention that halts progression, with the obvious trade-off. No disease-modifying treatment exists, and no preventive agent is established.

Simple means. Limb cooling or compression during taxane infusion: ice packs or compression stockings reduce neuropathy incidence in randomised trials, for pennies. Exercise during and after chemotherapy: randomised evidence for reduced severity and improved function. Amitriptyline at a few US dollars a patient-year for the pain. Balance training and falls prevention, since proprioceptive loss causes falls. Foot protection and inspection where sensation is lost.

Gaps. There is one modestly effective symptomatic drug and no preventive agent, and one tested supplement made the condition worse. No burden estimate exists for a condition affecting roughly 30 per cent of treated patients persistently. Why susceptibility varies at the same cumulative dose is unknown. Long-term outcomes beyond two years are sparse.

> **Depth.** Starts in: a chemotherapy molecule. Size: 1 nm†; depth −3.48. First complaint: about 7.4 weeks († weeks to months of chemotherapy); time depth 47.10. One untreated course: no number († often permanent).
>
> **Model reading.** Way of ending: let close. Layer: surround. By the rule it closes by itself. The book's status: SELF-LIMITING, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Guillain-Barré syndrome

What it is. Acute immune attack on peripheral nerves, usually following an infection, causing rapidly progressive weakness that ascends from the legs over days to weeks, often with loss of reflexes and sometimes with respiratory and swallowing failure. It reaches its worst within four weeks and then recovers.

Measured. Incidence is roughly 1 to 2 per 100,000 a year, consistent across most studied populations, giving roughly 100,000 cases globally a year†. Incidence rises with age and is roughly 1.5 times higher in men†. Roughly 20 to 30 per cent require mechanical ventilation at some point†. Mortality is roughly 3 to 7 per cent in high-income settings with intensive care, and substantially higher where ventilation is unavailable. Roughly 20 per cent remain unable to walk unaided at six months, and roughly 10 to 20 per cent have persistent significant disability at one year, with fatigue and pain persisting in a majority. There is

no WHO fact sheet of its own, and WHO publishes guidance in the context of outbreak-associated clusters. The 2015 to 2016 Zika virus outbreak in the Americas produced a marked rise in incidence, with case-control studies supporting a causal association and incidence rising several-fold in affected countries.

Where it starts. This is one of the clearest causal chains in Chapter 08. An antecedent infection is present in roughly two thirds of cases, typically one to four weeks before onset. *Campylobacter jejuni* is the commonest identified trigger, associated with the axonal form and with worse outcome. Molecular mimicry is demonstrated: *C. jejuni* lipo-oligosaccharide shares epitopes with peripheral nerve gangliosides GM1 and GD1a, and anti-ganglioside antibodies are found in those patients. That is a demonstrated autoimmune mechanism with an identified mimicked antigen — among the best-established mechanisms in the book. Other triggers: cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, influenza, hepatitis E, Zika virus and SARS-CoV-2. On vaccines: the 1976 swine influenza vaccine in the United States was associated with roughly one additional case per 100,000 vaccinated — a real, measured, historically important signal. Subsequent seasonal influenza vaccines carry at most roughly one to two additional cases per million doses, and influenza infection itself carries a substantially higher risk than vaccination, so vaccination is net protective. Both the real historical signal and the current magnitude are reported accurately. The Miller Fisher variant is associated with anti-GQ1b antibodies, another specific antibody-syndrome correspondence.

The mechanism is established for the axonal forms: molecular mimicry between microbial and nerve glycolipids, with specific antibodies and complement-mediated nerve injury, and passive transfer models reproduce it. It is less established for the demyelinating form, which is commoner in Europe and North America and where the target antigen is not identified. Not known: why only roughly 1 in 1,000 to 5,000 people with *Campylobacter* infection develops the syndrome; what determines the demyelinating against the axonal form; why complement inhibition has given mixed trial results.

Cure status. SELF-LIMITING, with treatment that shortens the course. This is a monophasic illness that recovers. The natural history is recovery in the large majority, over weeks to many months. Treatment accelerates recovery and does not change the monophasic nature. Roughly 80 per cent walk independently at six months, 10 to 20 per cent have persistent significant disability, and 3 to 7 per cent die†. Recurrence is uncommon, roughly 2 to 5 per cent†. Distinguish from chronic inflammatory demyelinating polyradiculoneuropathy, which is CONTROLLABLE rather than self-limiting and requires maintenance immunotherapy.

Prevention. Food and water hygiene to prevent *Campylobacter* — poultry handling, cooking, water safety: MODERATE. It addresses the commonest trigger, with no trial using Guillain-Barré endpoints, and *Campylobacter* reduction programmes in poultry, notably in New Zealand, demonstrate the exposure is reducible. Vector control to prevent Zika: MODERATE, demonstrated by the outbreak-associated incidence rise and fall. Influenza vaccination: net protective on current evidence, since infection carries higher risk than vaccination, MODERATE. No other prevention is established.

Treatment. *Intravenous immunoglobulin* shortens time to recovery, and Cochrane review finds it as effective as plasma exchange with better tolerability and easier administration. Normal immunoglobulin is EML-listed and off-patent, since it is a blood product rather than a patented molecule, and a course costs on the order of thousands to low tens of thousands of US dollars, driven by plasma collection and processing cost. Supply is globally constrained and inequitably distributed. *Plasma exchange* is equally effective; Cochrane review of trials against supportive care shows improved outcome at four weeks and better recovery of walking. It requires apheresis equipment and trained staff, at a course cost on the order of thousands of US dollars.

Combining immunoglobulin and plasma exchange: no added benefit. A clear negative result. *Corticosteroids*: ineffective. Cochrane review finds corticosteroids alone do not hasten recovery and oral steroids may delay it. That is an important negative result in an inflammatory disease where steroids would be the intuitive treatment. *Supportive care and intensive care* — respiratory monitoring with forced vital capacity measurement, ventilation when needed, autonomic monitoring, venous thromboembolism prophylaxis, pain management, pressure area care — is what determines survival, not immunotherapy. In settings without ventilation, mortality is many times higher.

Eculizumab and complement inhibitors: trials have shown mixed results and nothing is established. *Rehabilitation*: multidisciplinary rehabilitation improves disability and quality of life in randomised and controlled studies, and fatigue and pain persist in a majority and are often undertreated. *Neuropathic pain treatment* with gabapentinoids and tricyclics: pain is present in roughly two thirds and is frequently missed in the acute phase.

Simple means. Serial forced vital capacity measurement with a handheld spirometer identifies impending respiratory failure before it becomes an emergency. A device costing tens of US dollars, used at the bedside, determines whether the patient is intubated electively or arrests. This is the highest-value simple means in this entry. Food and water hygiene prevents the commonest trigger. Pressure area care, joint positioning and passive movement prevent contractures, pressure ulcers and nerve compression palsies during the paralysed phase: nursing and family hands. Thromboembolism prophylaxis and early mobilisation. Pain recognition: asking about pain in a patient who cannot easily communicate. Graded exercise in recovery has randomised support for reducing the fatigue that persists in a majority. The honest comparison: supportive care determines survival and immunotherapy shortens the course, so in resource-limited settings excellent nursing and ventilation save more lives than immunoglobulin.

Gaps. No WHO fact sheet and no stand-alone GBD estimate for an acutely life-threatening condition. The demyelinating form's target antigen is unidentified. There is no treatment for the residual disability in 10 to 20 per cent. Steroids' ineffectiveness is established and counterintuitive, and steroids are still sometimes given. Immunoglobulin supply is globally constrained, equity of access is a major unaddressed issue, and the cost reflects plasma supply rather than intellectual property. Incidence data from low-income countries are sparse, and mortality there is likely substantially higher than published figures.

> **Depth.** Starts in: Campylobacter jejuni. Size: 2 µm†; depth +3.44. First complaint: about 14 days ([B] infection 1–4 weeks before onset); time depth 45.90. One untreated course: about 6 months ([B] days to weeks of progression; † recovery about 6 months); depth 48.23.
>
> **Model reading.** Way of ending: let close. Layer: reading. By the rule it closes by itself. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Myasthenia gravis

What it is. An autoimmune disease in which antibodies block neuromuscular transmission, causing fluctuating, fatigable weakness — worse with use and better with rest. It typically affects eyelids, eye movements, speech, swallowing, and limb and respiratory muscles.

Measured. Prevalence is roughly 15 to 25 per 100,000 and incidence roughly 0.3 to 3 per 100,000 a year†. Prevalence has risen over decades, mainly from better recognition and longer survival. Onset is bimodal, with a female-predominant peak in the twenties and thirties and a male-predominant peak after 60, and the late-onset group is now the largest and growing, tracking population ageing. Myasthenic crisis, meaning respiratory failure requiring ventilation, occurs in roughly 15 to 20 per cent at some point†. **Mortality has fallen from roughly 70 per cent in the pre-1930s era to roughly 5 per cent or less today**† — one of the most dramatic prognostic transformations of any disease in the book, achieved by ventilation, immunosuppression and intensive care rather than by a targeted cure. There is no WHO fact sheet and no stand-alone GBD estimate. Thymoma is present in roughly 10 to 15 per cent†, and thymic hyperplasia in a substantial proportion of early-onset cases.

Where it starts. Among the best-characterised autoimmune diseases in medicine. Acetylcholine receptor antibodies are present in roughly 85 per cent of generalised cases†, and their pathogenicity is demonstrated: the antibodies block and cross-link the receptor, activate complement, and passive transfer to animals reproduces the disease. Neonatal transient myasthenia from transplacental antibody transfer is a natural human demonstration. MuSK antibodies are present in roughly 5 to 8 per cent, LRP4 and agrin antibodies in a small proportion, and roughly 5 to 10 per cent are seronegative by current assays†. The thymus is causally involved: thymectomy improves outcome in randomised trial, and thymoma and thymic hyperplasia are over-represented. HLA associations differ between early-onset, with *HLA-DR3/B8*, and late-onset disease, consistent with two distinct diseases under one name. Drug-induced exacerbation is

important and preventable: aminoglycosides, fluoroquinolones, macrolides, beta-blockers, magnesium, neuromuscular blocking agents and immune checkpoint inhibitors can precipitate crisis. Checkpoint-inhibitor-induced myasthenia is a newly significant and severe iatrogenic cause as cancer immunotherapy use expands.

The mechanism is established at the level of the molecule, the antibody, the receptor and the synapse. This is the most completely understood disease mechanism in these three chapters: a known autoantigen, demonstrated antibody pathogenicity, an explained physiology, and drugs that act on the explained step. Not known: what initiates the autoimmunity; why the thymus is involved; why some patients are seronegative; why the disease fluctuates hour to hour.

Cure status. CONTROLLABLE. Pharmacological remission, meaning no symptoms on treatment, is achieved in a substantial proportion, and complete stable remission off all treatment occurs in roughly 10 to 20 per cent, more often after thymectomy†. Most patients on modern treatment have minimal symptoms and near-normal life expectancy. Relapse on withdrawal of immunosuppression is common, which is why the label is CONTROLLABLE rather than CURABLE.

Prevention. No established primary prevention. Avoiding precipitating drugs: STRONG as prevention of crisis. A written list of contraindicated drugs carried by the patient prevents iatrogenic respiratory failure, and it costs nothing. Prompt treatment of infection: MODERATE, since infections are the commonest crisis trigger. Vigilance for checkpoint-inhibitor-induced myasthenia: MODERATE, since early recognition prevents deaths.

Treatment. *Pyridostigmine*, an acetylcholinesterase inhibitor, is symptomatic treatment acting directly on the explained mechanism, and is rapid and effective for mild disease; EML-listed, off-patent, and costing on the order of hundreds of US dollars a patient-year. *Corticosteroids* are the mainstay immunosuppressant, with high response rates; prednisolone is EML-listed, off-patent, and costs tens of US dollars a patient-year. Harms: the full corticosteroid burden over years. *Steroid-sparing agents* — azathioprine, mycophenolate, methotrexate, ciclosporin, tacrolimus. Azathioprine is EML-listed, off-patent, tens to low hundreds of US dollars a patient-year; methotrexate is EML-listed as a selected medicine, confirmed against the 24th List, off-patent, tens to low hundreds of US dollars a patient-year.

Thymectomy: the MGTX randomised trial (Wolfe and colleagues, *NEJM*, 2016; 126 patients with non-thymomatous acetylcholine-receptor-positive generalised myasthenia, three years) showed that extended transsternal thymectomy with prednisone produced a **lower time-weighted average quantitative myasthenia score, 6.15 against 8.99 (p<0.001)**, and a **lower average prednisone requirement, 44 mg against 60 mg alternate-day (p<0.001)**, with fewer hospitalisations for exacerbation. A randomised trial of an operation, settling a question open for seventy years. Cost: tens of thousands of US dollars one-off. *Rituximab* is highly effective in MuSK-antibody myasthenia in particular, with high remission rates in observational series; a randomised trial in generalised myasthenia, BeatMG, did not meet its primary endpoint, while the Swedish RINOMAX trial in new-onset disease was positive. Rituximab is EML-listed as a selected medicine for multiple sclerosis and for several lymphoid malignancies, confirmed against the 24th List, and is off-patent, available as biosimilars at a small fraction of originator antibody prices.

Complement inhibitors — eculizumab, ravulizumab, zilucoplan — are effective in refractory antibody-positive disease, acting on the demonstrated complement step; not EML-listed, on patent, and costing a six-figure sum in US dollars a patient-year for eculizumab at US list price, the most expensive treatment named in this book. They require meningococcal vaccination because of the complement blockade. *FcRn inhibitors* — efgartigimod, rozanolixizumab — reduce circulating IgG with randomised support; not EML-listed, on patent, and costing a six-figure sum in US dollars a patient-year. *Immunoglobulin and plasma exchange* are used for crisis and pre-operative stabilisation, both effective and roughly equivalent; immunoglobulin is EML-listed and a course costs thousands to low tens of thousands of US dollars.

Ventilatory support in crisis is, more than any drug, what reduced mortality from 70 per cent to 5 per cent. The honest cost comparison: prednisolone with azathioprine and pyridostigmine, all on the Essential Medicines List and all off-patent, costs on the order of hundreds of US dollars a patient-year and controls the large majority of patients; the complement and FcRn inhibitors cost six figures a patient-year and are for the refractory minority. Both facts matter.

Simple means. A written list of contraindicated drugs, carried by the patient: prevents iatrogenic myasthenic crisis, which is a preventable cause of respiratory failure and death. Paper. Activity pacing and planned rest: the weakness is fatigable by definition, so distributing effort across the day preserves function. Free, and it works because it follows directly from the mechanism. Serial forced vital capacity or single-breath count at home detects deterioration before crisis. Heat avoidance, since weakness worsens with heat. Prompt treatment of infection. The ice pack test for ptosis: a diagnostic aid using an ice pack, costing nothing, reasonably sensitive for ocular myasthenia. Eye patching or prisms for diplopia: cheap, and transforms daily function. Pyridostigmine with generic immunosuppression at a few hundred US dollars a patient-year: effective for most patients, available through essential medicines systems.

Gaps. No burden estimate for a treatable, potentially fatal disease. Seronegative myasthenia has no biomarker and uncertain treatment response. The new high-cost biologics have short trials and no head-to-head comparison against optimised generic immunosuppression, so their incremental benefit over a few-hundred-dollar regimen is unquantified. Checkpoint-inhibitor-induced myasthenia is an emerging problem with no trial evidence for management. Prevalence and outcome data from low- and middle-income countries are almost absent, and the transformation of mortality from 70 to 5 per cent depends on intensive care availability.

> **Depth.** Starts in: the acetylcholine receptor. Size: 10 nm†; depth −1.38. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: no number ([B] variable).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Cerebral palsy

What it is. A group of permanent disorders of movement and posture caused by non-progressive damage to the developing brain, before, during or shortly after birth. The brain lesion does not progress; the musculoskeletal consequences do. Associated impairments of cognition, communication, vision, hearing, feeding, epilepsy and pain are common.

Measured. Prevalence is roughly 1.5 to 2.5 per 1,000 live births in high-income countries and roughly 2 to 10 per 1,000 in low- and middle-income countries, with roughly 17 million people living with cerebral palsy worldwide†. WHO's cerebral palsy fact sheet could not be retrieved in the compilation pass, so the figures here come from the standing literature and could not be confirmed to a source. GBD 2021 ranks neurological complications of preterm birth eighth among all nervous system conditions by DALYs, and neonatal encephalopathy second — the two principal causal pathways to cerebral palsy. Prevalence in high-income countries has fallen modestly over the past two decades, particularly in moderately preterm infants, attributed to improved obstetric and neonatal care including magnesium sulphate and therapeutic hypothermia. Prevalence rises steeply with decreasing gestational age: roughly 1 per 1,000 at term, rising to roughly 40 to 100 per 1,000 below 28 weeks. Roughly 35 to 50 per cent have epilepsy, roughly 50 per cent have cognitive impairment, roughly 25 per cent are non-speaking and roughly 25 per cent cannot walk†. Life expectancy is near-normal with mild impairment and substantially reduced with severe motor and feeding impairment.

Where it starts. Preterm birth is the largest single risk factor, with risk inversely related to gestational age. Neonatal encephalopathy from intrapartum hypoxia-ischaemia accounts for a minority of cases in high-income countries, roughly 10 to 20 per cent, and a larger proportion where obstetric care is limited†. The common assumption that most cerebral palsy results from birth asphyxia is not supported: most cases in high-income settings have antenatal origins. Intrauterine infection and inflammation, as chorioamnionitis, is associated at roughly two to four times. Multiple pregnancy, roughly four to six times per infant. Intrauterine growth restriction is associated. Neonatal jaundice and kernicterus is a fully preventable cause, still significant in settings without phototherapy and exchange transfusion. Postnatal causes include meningitis, cerebral malaria, head injury, near-drowning and stroke. Genetic causes are increasingly recognised: recent exome and genome studies find pathogenic variants in roughly 10 to 30 per cent of cases previously labelled idiopathic†, which is changing the understanding of the condition and reduces the

proportion attributable to birth events further. Thrombophilia and perinatal arterial ischaemic stroke are established in a subset.

The mechanism is established at the level of the lesion: periventricular leukomalacia in preterm infants, basal ganglia and watershed injury in term hypoxic-ischaemic encephalopathy, and malformations. The inflammatory contribution to white matter injury in preterm infants is well supported. The attribution of cerebral palsy to intrapartum events has been substantially revised downward, with important medico-legal consequences, and the genetic findings revise it further. Not known: why some infants with identical imaging findings have very different function; what determines the plasticity that allows some children to walk and others not; the mechanism of the associated pain, which affects a majority and is persistently undertreated.

Cure status. For the brain lesion: RELIEF ONLY. It is permanent and non-progressive. For the progressive musculoskeletal consequences — contractures, hip displacement, scoliosis: CONTROLLABLE, and they are preventable and treatable. Function can improve substantially with intervention, particularly in early childhood. Secondary musculoskeletal deterioration is preventable, and preventing it is where most of the achievable gain lies. Hip surveillance programmes reduce the incidence of painful hip dislocation substantially.

Prevention. Strong, and quantified. *Antenatal magnesium sulphate for women at risk of preterm birth*: STRONG. Cochrane review of randomised trials finds magnesium sulphate **reduces cerebral palsy risk by roughly 32 per cent, relative risk 0.68 (95 per cent CI 0.54 to 0.87)**, with a number needed to treat of roughly 46 to prevent one case†. Magnesium sulfate is EML-listed as a selected medicine under section 5.1.1 Antiseizure medicines, for severe pre-eclampsia and eclampsia, with the restrictive note that it is not for other convulsant disorders, confirmed against the 24th List. It is off-patent, and the UNICEF Supply Catalogue gives injection 500 mg/mL in 10 mL ampoules at US$33.11 for a box of 100, about **US$0.33 an ampoule**, read 19 October 2026; the same catalogue gives US$12.65 for a box of ten, about 3.8 times as much per ampoule. So a loading-and-maintenance course is a few US dollars of drug. This is one of the highest-value preventive interventions in the book: a cheap, essential, off-patent mineral salt preventing roughly a third of cerebral palsy in the at-risk group.

Therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy: STRONG in high-income settings. Cochrane review finds it reduces death or major neurodevelopmental disability, relative risk roughly 0.75, with a number needed to treat of roughly 7†. **However, the HELIX trial in India, Sri Lanka and Bangladesh found no benefit and increased mortality in low-resource settings**, so the intervention is CONTESTED outside well-resourced neonatal intensive care. Both are reported. Cooling equipment costs thousands to tens of thousands of US dollars, or can be improvised, and the trial evidence does not support improvised use in low-resource settings.

Antenatal corticosteroids for threatened preterm birth: STRONG for neonatal survival and morbidity. Dexamethasone is EML-listed and off-patent, and the UNICEF Supply Catalogue gives 4 mg tablets at US$24.00 for 100, about US$0.24 a tablet, read 19 October 2026, so a course is a few US dollars. *Preventing and treating neonatal jaundice* with phototherapy, exchange transfusion and maternal anti-D prophylaxis: STRONG. Kernicterus is entirely preventable. *Skilled birth attendance and neonatal resuscitation training*, such as Helping Babies Breathe: STRONG for the perinatal asphyxia fraction. *Preventing preterm birth* through progesterone in selected women, cervical cerclage, smoking cessation, treating infection and spacing pregnancies: MODERATE.

Rubella and other vaccination, and prevention of congenital infection: STRONG for that fraction. *Folic acid fortification*: STRONG for neural tube defects, with the US combined prevalence falling from 10.8 to 6.9 per 10,000, a 36 per cent decline†. Folic acid is EML-listed, and the UNICEF Supply Catalogue gives 5 mg tablets at US$5.41 for a bottle of 1,000, about US$0.0054 a tablet, read 19 October 2026. *Iodine in pregnancy*: STRONG for neurodevelopmental outcomes generally. *Malaria prevention in pregnancy* with insecticide-treated nets and intermittent preventive treatment: STRONG for low birth weight and preterm birth. *Caesarean section rates*: CONTESTED. Rising caesarean rates have not reduced cerebral palsy prevalence, which is consistent with most cases not being intrapartum in origin.

Treatment. *Early intervention with goal-directed, active, task-specific training*: the evidence favours interventions in which the child actively practises specific goals over passive handling approaches, with moderate effect sizes. Early detection by the General Movements Assessment and the Hammersmith examination allows diagnosis before six months and enables earlier intervention. *Hip surveillance and preventive orthopaedic surgery*: population hip surveillance programmes in Sweden and Australia substantially reduce painful hip dislocation — an organisational intervention with a measured population effect.

Botulinum toxin for focal spasticity reduces tone and improves specific goals, and its benefit on long-term function and on contracture prevention is less clear than once assumed, with repeated injection causing muscle atrophy; cost is hundreds to low thousands of US dollars a cycle. *Oral antispasticity drugs* — baclofen, diazepam, tizanidine, dantrolene — give modest benefit with common sedation; baclofen and diazepam are EML-listed, off-patent, and cost tens of US dollars a patient-year. *Intrathecal baclofen* is effective for severe generalised spasticity, at a pump cost in the tens of thousands of US dollars.

Selective dorsal rhizotomy reduces spasticity durably in selected ambulant children with spastic diplegia, with randomised trial evidence supporting it combined with physiotherapy. *Orthopaedic surgery*: single-event multilevel surgery for gait, scoliosis correction, hip reconstruction. *Management of the associated conditions* is where most of the quality-of-life gain is: epilepsy in 35 to 50 per cent, feeding and nutrition with gastrostomy where needed, drooling, constipation, respiratory care, hip and spine surveillance, vision and hearing correction, communication, and pain, which affects a majority and is persistently under-recognised and undertreated.

Communication: augmentative and alternative communication for the roughly 25 per cent who are non-speaking. *Treatments without support*: hyperbaric oxygen, where the randomised trial was negative; stem cell therapy, not established; and various patterned-movement therapies. Families are marketed these.

Simple means. Magnesium sulphate at a few US dollars a course, preventing roughly 32 per cent of cerebral palsy in at-risk preterm births, as an off-patent essential medicine with an indicative ampoule price of US$0.33 in October 2026: the best preventive cost-to-effect ratio in Chapter 08. Antenatal corticosteroids at a few US dollars a course. Phototherapy for jaundice: blue light, and in sunny climates filtered sunlight has been trialled with non-inferior results to conventional phototherapy in a Nigerian randomised trial. Neonatal resuscitation with a bag and mask, taught in a day: the Helping Babies Breathe programme reduced early neonatal mortality in implementation studies. Positioning, stretching and active play, delivered by family, prevent contractures. Hip surveillance: an X-ray on a schedule prevents painful dislocation. Communication boards: paper and pictures for the 25 per cent who cannot speak. Pain assessment in non-verbal children, systematically, using observational scales: free, and a majority have pain that goes untreated. Nutrition attention: undernutrition is common and worsens every other outcome.

Gaps. WHO’s fact sheet could not be retrieved in the compilation pass, so prevalence figures should be verified against WHO and against the Global CP Register network. Therapeutic hypothermia’s failure in the HELIX trial means the main neonatal neuroprotective intervention does not transfer to the settings with the highest burden, and no alternative exists. The genetic contribution, 10 to 30 per cent in recent series, is reshaping aetiology and is not yet reflected in most prevention frameworks. Prevalence data from most low- and middle-income countries are absent or from small surveys. Adults with cerebral palsy are barely studied despite being the majority, and secondary musculoskeletal and pain problems in adulthood have almost no trial base. Pain in cerebral palsy is highly prevalent, well documented as undertreated, and has minimal intervention evidence.

> **Depth.** Starts in: the developing brain. No size is given. First complaint: about 2.2 years († from conception to diagnosis 12–24 months); time depth 49.61. One untreated course: no number ([B] the lesion does not progress).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The lesion in the brain does not regrow. So it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Huntington disease

What it is. An inherited, progressive degenerative brain disease causing involuntary movements, called chorea, progressive loss of voluntary motor control, cognitive decline and psychiatric symptoms. It is caused by a single expanded repeat in one gene and is inherited in an autosomal dominant pattern.

Measured. Prevalence is roughly 5 to 10 per 100,000 in European-ancestry populations and substantially lower in East Asian populations, roughly 0.4 per 100,000, and in African populations†. The geographic difference tracks the frequency of intermediate repeat alleles in the founder populations. Onset is typically between 30 and 50 years, juvenile onset before 20 in roughly 5 to 10 per cent, and late onset occurs†. Median survival is roughly 15 to 20 years from motor onset†. The leading causes of death are aspiration pneumonia and suicide, which is substantially elevated at roughly 5 to 10 times the general population, with the highest risk around the time of diagnosis and at loss of independence. There is no WHO fact sheet and no stand-alone GBD estimate. Each child of an affected parent has a 50 per cent risk. Predictive testing is available and uptake is low: roughly 5 to 25 per cent of eligible at-risk relatives choose to be tested†, which is itself an important measured finding about how people respond to certain genetic knowledge.

Where it starts. The cause is completely known, which is rare in this book. A CAG trinucleotide repeat expansion in the *HTT* gene on chromosome 4 was identified in 1993. Fewer than 27 repeats is normal; 27 to 35 is intermediate and generally non-penetrant but unstable in transmission; 36 to 39 shows reduced penetrance; and 40 or more repeats causes the disease with essentially complete penetrance. Repeat length inversely correlates with age at onset, explaining roughly 50 to 70 per cent of onset variance, and longer repeats mean earlier onset, with juvenile onset usually involving very long expansions. Anticipation occurs: repeats tend to expand further in transmission, particularly through the paternal line, so onset is often earlier in successive generations. Somatic instability — further expansion in neurons during life — is now understood to be a major determinant of onset and progression, and DNA repair genes *FAN1*, *MSH3* and *MLH1* are confirmed genetic modifiers. That is the most significant advance in understanding the disease's variability. Residual onset variance beyond repeat length is substantially heritable, with the DNA repair modifiers accounting for a measurable part.

The cause is certain and the pathogenic mechanism downstream of it is not. Mutant huntingtin aggregation, transcriptional dysregulation, mitochondrial impairment, impaired axonal transport and somatic repeat expansion are all implicated. Medium spiny neurons of the striatum degenerate first and the selectivity is unexplained. The somatic expansion model has reframed the field: the inherited repeat may act chiefly by setting the starting point for lifelong expansion in neurons, making DNA repair a therapeutic target. Not known: why striatal neurons specifically; whether lowering huntingtin is sufficient; why the first huntingtin-lowering trial failed.

Cure status. RELIEF ONLY. No treatment slows or halts the disease. Chorea is treatable; the underlying degeneration is not. Progression is relentless over 15 to 20 years. Predictive testing allows reproductive choice, and preimplantation genetic testing and prenatal diagnosis can prevent transmission, which is prevention of a new case rather than treatment of a person.

Prevention. The disease is not preventable in a person who carries the expansion. Transmission is preventable: preimplantation genetic testing with in vitro fertilisation, or prenatal diagnosis, STRONG for the transmission outcome. Uptake varies widely by country and by access to funded in vitro fertilisation, at a cost in the tens of thousands of US dollars a cycle. Genetic counselling before testing is standard of care, and the low voluntary testing uptake reflects informed choice rather than a service failure. No modifiable lifestyle factor has been shown to delay onset; observational associations with exercise, cognitive activity and caffeine are weak and confounded.

Treatment. *Chorea treatment.* **VMAT2 inhibitors** — tetrabenazine, deutetrabenazine, valbenazine — reduce chorea in randomised trials. Tetrabenazine is not EML-listed, is off-patent, and costs on the order of hundreds to low thousands of US dollars a patient-year. Deutetrabenazine and valbenazine are on patent and cost a low six-figure sum in US dollars a patient-year, for a modestly better adverse-effect profile on the same mechanism. Harms: depression and suicidality, which carries a black-box warning for tetrabenazine, plus parkinsonism and sedation. **Antipsychotics** — olanzapine, risperidone, tiapride — reduce chorea and treat coexisting psychiatric symptoms simultaneously, and are often preferred for that

reason. Olanzapine and risperidone are EML-listed, off-patent, and cost tens of US dollars a patient-year. They are far cheaper than the VMAT2 inhibitors and treat two problems at once.

Psychiatric treatment: depression, irritability, apathy, obsessive features and psychosis are frequent and treatable, with SSRIs for depression and irritability and antipsychotics for psychosis and severe irritability. Suicide risk is substantially elevated and psychiatric treatment is the most important modifiable contributor to it. Fluoxetine is EML-listed, off-patent, and costs a few US dollars a patient-year. *Nutrition*: weight loss is characteristic and predicts faster progression, so calorie-dense food and eventually gastrostomy are used; no numeric targets are given. *Speech, swallowing and physiotherapy*: aspiration pneumonia is a leading cause of death, so swallowing management affects survival, and exercise and physiotherapy improve motor function and fitness in randomised trials.

Huntingtin-lowering therapies: **tominersen**, an antisense oligonucleotide, was halted in phase 3 in 2021 after the higher-dose arms showed **worse** outcomes than placebo, and it is being re-tested at lower doses in a younger population. Several other huntingtin-lowering and splice-modulating programmes are in trials. Reported as not available and as having produced a serious negative signal. A gene therapy programme, AMT-130, reported encouraging interim data in small numbers between 2023 and 2025, and is not established. *Multidisciplinary clinic care and advance care planning*.

Simple means. Generic antipsychotics at tens of US dollars a patient-year, treating chorea and psychiatric symptoms together, against deutetrabenazine at a six-figure sum for chorea alone on an older mechanism. That is the central practical comparison. Exercise and physiotherapy: randomised trials show improved motor function and fitness, with no supply chain. Swallowing precautions and food texture modification: taught, free, and they address the leading cause of death. Nutrition attention, since weight loss predicts faster progression. Environmental structure and routine reduce behavioural distress in a condition where cognitive flexibility is lost early. Suicide risk recognition at the two high-risk points, around diagnosis and at loss of independence: asking, and treating depression; see the suicide entry for intervention evidence. Genetic counselling: enabling informed choice, including the choice not to know, which most at-risk people make.

Gaps. No burden estimate for a disease with complete penetrance and known prevalence. Prevalence outside European-ancestry populations is poorly measured and probably underestimated by ascertainment. The tominersen failure, where huntingtin lowering appeared harmful, is unexplained and consequential for the whole therapeutic strategy. Somatic expansion and DNA repair modifiers are the most promising new target and are unvalidated therapeutically. Juvenile Huntington disease is clinically distinct and barely studied. There is no disease-modifying treatment for a disease whose cause has been known since 1993 — a notable gap, given that certainty of cause is usually the hardest part.

> **Depth.** Starts in: huntingtin. Size: 20 nm†; depth −0.75. First complaint: about 41 years († from conception to onset at about 40); time depth 52.25. One untreated course: about 17 years († 15–20 years); depth 51.47.
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Trigeminal neuralgia

What it is. Sudden, severe, brief electric-shock-like facial pain in the distribution of the trigeminal nerve, triggered by light touch, chewing, speaking, washing or cold air. Attacks last seconds and recur in volleys. Between attacks there is usually no pain and the neurological examination is typically normal.

Measured. Incidence is roughly 4 to 13 per 100,000 a year, and lifetime prevalence roughly 0.1 to 0.3 per cent†. Women roughly 1.5 to 2 times men†. Onset is typically after 50, and onset before 40 raises suspicion of multiple sclerosis or another secondary cause. Roughly 2 to 5 per cent of people with multiple sclerosis develop trigeminal neuralgia, and roughly 2 to 4 per cent of trigeminal neuralgia cases are multiple-sclerosis-related. Pain intensity is among the highest recorded in clinical medicine; the historical name was *tic douloureux*, and suicide associated with uncontrolled attacks is described in the older literature.

Diagnostic delay and misdiagnosis as dental pain are common, with unnecessary dental extractions a well-documented and preventable harm. There is no WHO fact sheet and no stand-alone GBD estimate.

Where it starts. This is a condition where the cause is usually identifiable and correctable. Neurovascular compression of the trigeminal root by an artery, usually the superior cerebellar artery, or by a vein, is found in the large majority of classical cases, with MRI demonstrating compression and morphological change in the nerve. Surgical decompression relieves the pain, which is strong causal evidence. Multiple sclerosis, through a demyelinating plaque at the trigeminal root entry zone, is the secondary cause in a small percentage. Tumour — vestibular schwannoma, meningioma, epidermoid — compressing the nerve accounts for a small percentage, and is a reason to image everyone. Hypertension is weakly associated. There is no significant heritability and familial cases are rare.

The mechanism is established in outline: focal demyelination at the root entry zone from chronic compression leads to ectopic impulse generation and ephaptic transmission between fibres, which explains why light touch triggers severe pain, and sodium channel involvement explains why sodium channel blockers work. Not known: why compression causes pain in some people and is found incidentally in others; why the pain is paroxysmal rather than constant; why some patients develop constant background pain in addition.

Cure status. Treated by microvascular decompression: CURABLE in roughly 70 to 80 per cent, pain-free at ten years†. Treated medically or by destructive procedures: CONTROLLABLE. One of the few conditions in Chapter 08 with a genuine surgical cure. Carbamazepine relieves pain in roughly 70 to 90 per cent initially, and efficacy commonly declines over years while adverse effects limit dose. Microvascular decompression gives roughly 70 to 80 per cent pain-free at ten years in large series, without the sensory loss caused by destructive procedures, and it is the only procedure that addresses the cause rather than destroying the nerve. Destructive procedures — radiofrequency, glycerol, balloon compression, radiosurgery — relieve pain with higher recurrence and with sensory loss. Spontaneous remissions occur and can last months to years, which complicates assessment of any treatment.

Prevention. No established primary prevention. Avoiding unnecessary dental procedures through correct diagnosis: STRONG as prevention of iatrogenic harm, and recognition is the intervention. MRI in all new cases identifies tumours and multiple sclerosis plaques, which changes management: MODERATE.

Treatment. *Carbamazepine* is the first-line treatment and the reference standard, with 70 to 90 per cent initial response and a number needed to treat of roughly 2 in the older randomised trials — among the largest treatment effects for any pain condition. It is EML-listed and off-patent, and costs tens of US dollars a patient-year. Harms: hyponatraemia, sedation, ataxia, rash including severe cutaneous reactions with *HLA-B*15:02* testing advised in populations where that allele is common, and extensive drug interactions. *Oxcarbazepine* has comparable efficacy, is better tolerated and has fewer interactions; not EML-listed, off-patent, tens to low hundreds of US dollars a patient-year.

Lamotrigine, baclofen, gabapentin, pregabalin and phenytoin are second-line add-ons with weaker evidence; lamotrigine, baclofen and phenytoin are EML-listed, all off-patent, and cost tens to low hundreds of US dollars a patient-year. *Microvascular decompression* gives roughly 70 to 80 per cent pain-free at ten years and is the only causally directed treatment. Surgical mortality is roughly 0.2 to 0.5 per cent, and risks include hearing loss in roughly 1 to 3 per cent†, cerebrospinal fluid leak, and facial numbness, which is less frequent than with destructive procedures. The cost runs to tens of thousands of US dollars one-off, and in long-term follow-up it is more cost-effective than decades of medication for suitable candidates.

Percutaneous destructive procedures — radiofrequency thermocoagulation, glycerol rhizolysis, balloon compression — are effective, cheaper and repeatable, with higher recurrence, facial numbness, and a risk of anaesthesia dolorosa, which is painful numbness and is difficult to treat; cost in the low thousands of US dollars. *Gamma knife or stereotactic radiosurgery* is non-invasive, with pain relief delayed by weeks to months, lower initial success and higher recurrence than microvascular decompression, and progressive numbness; cost in the tens of thousands of US dollars. *Intravenous or intranasal lidocaine and phenytoin for acute crisis* are used when pain prevents eating and drinking, on small trial evidence.

Treating the secondary cause: tumour removal, multiple sclerosis disease-modifying therapy.

Simple means. Carbamazepine at tens of US dollars a patient-year with a number needed to treat of about 2: for one of the most severe pains in medicine, an off-patent essential medicine controls it in 70 to 90 per cent of people initially. The cost-to-effect ratio is among the best in Chapter 08. Correct diagnosis prevents unnecessary dental extractions, which are a documented and common harm: a history and an examination. Trigger avoidance: identifying and avoiding the specific touch, chewing or cold triggers, soft food, and avoiding cold wind during a bout. Free, and it follows directly from the mechanism. A straw and soft food during a severe bout prevent the dehydration and weight loss that drive emergency admission. Not using opioids: they do not work for this pain and expose the patient to harm — a negative simple means. Keeping a bout diary: bouts remit and recur, so medication can be tapered during remission rather than continued indefinitely.

Gaps. No burden estimate for a condition of extreme severity. Most medication evidence is from small, old trials, and carbamazepine's dominance rests on a thin modern evidence base despite being clearly effective. There is no randomised comparison of microvascular decompression against medical management, so the surgical decision rests on observational series. Spontaneous remission rates are poorly quantified and confound all efficacy estimates. The reason compression causes pain in only some of those who have it is unknown.

> **Depth.** Starts in: the trigeminal nerve root. Size: 3 mm†; depth +10.10. First complaint: about 55 years († onset about age 55); time depth 52.52. One untreated course: about 10 seconds ([B] an attack lasts seconds); depth 35.25.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Essential tremor

What it is. Progressive action tremor, typically of both hands, present on movement and on holding a posture, and often affecting the head and voice. It is not Parkinson disease: there is no slowness or rigidity, and the tremor appears with action rather than at rest.

Measured. Prevalence is roughly 0.9 per cent of all ages and 4 to 5 per cent of people over 65, making it one of the commonest movement disorders, and some surveys give higher figures over 65†. Roughly 60 to 70 million people worldwide are affected†. The sexes are roughly equally affected. Onset is bimodal, in adolescence or young adulthood and after 60. Roughly 50 to 70 per cent report a family history, and heritability is high†. Roughly 15 to 25 per cent stop working or change occupation because of it†. There is no WHO fact sheet and no stand-alone GBD estimate, so the burden is substantial and unmeasured. Misdiagnosis in both directions with Parkinson disease is frequent, with diagnostic disagreement rates of roughly 30 to 50 per cent reported in some studies†.

Where it starts. A family history is present in 50 to 70 per cent, with an apparently autosomal dominant pattern in many families, and twin concordance supports high heritability. Despite that, no major causative gene has been identified — a notable and unexplained failure of gene-hunting in a clearly familial disorder. Age is the dominant factor for prevalence. Ethanol reduces the tremor in most patients, transiently and reliably: a distinctive and unexplained pharmacological signature, and not a treatment recommendation. The condition is associated with higher risk of later Parkinson disease, dementia and hearing loss in some cohorts, and whether essential tremor is a single disease, a syndrome, or a group of disorders is genuinely disputed; the 2018 consensus criteria reflected that by narrowing the definition and creating an "essential tremor plus" category.

Cerebellar and olivocerebellar circuit involvement is supported by imaging, by the effect of cerebellar lesions, and by the effectiveness of targeting the ventral intermediate nucleus of the thalamus, which relays cerebellar output. Whether there is neurodegeneration — Purkinje cell changes have been reported and disputed — is unresolved, and it determines whether this is a degenerative disease or a circuit oscillation disorder. GABAergic dysfunction is proposed, would fit the ethanol response, and is not established. Not known: the gene or genes; whether it is degenerative; why ethanol helps; whether it is one condition.

Cure status. CONTROLLABLE, on medication and on deep brain stimulation alike. Medication reduces tremor amplitude by roughly 50 per cent in responders, and roughly 30 to 50 per cent of patients get inadequate benefit or cannot tolerate the drugs. Deep brain stimulation of the ventral intermediate thalamic nucleus reduces tremor by roughly 60 to 90 per cent with the effect sustained for years, and it is one of the most effective interventions in movement disorders. MRI-guided focused ultrasound thalamotomy reduced the hand tremor score by roughly 47 per cent against 0.1 per cent in the sham arm in a randomised trial (Elias and colleagues, *NEJM*, 2016), with benefit sustained at five years in follow-up, and it is incisionless. All of these hold the tremor down while they continue, and none removes the disorder. Tremor progresses slowly over decades.

Prevention. No established prevention. Given high heritability and no identified gene, there is nothing to act on, and that is stated rather than filled with speculative measures. Avoiding tremor-exacerbating drugs — beta-agonists, lithium, valproate, some antidepressants, caffeine in some people, thyroid excess: MODERATE as prevention of worsening. Correctly identifying drug-induced tremor avoids misdiagnosis entirely.

Treatment. *Propranolol* is first-line and reduces tremor amplitude by roughly 50 per cent in roughly 50 to 70 per cent of patients; EML-listed†, off-patent, and costing a few US dollars a patient-year. Contraindicated in asthma and significant bradycardia. *Primidone* is equally effective as propranolol in head-to-head trials, with sedation and early intolerance as the limitations; not EML-listed, off-patent, tens of US dollars a patient-year. *Propranolol with primidone* is better than either alone in some patients. *Topiramate, gabapentin, alprazolam, atenolol and sotalol* are second-line on modest evidence; gabapentin is off-patent and costs tens to low hundreds of US dollars a patient-year.

Botulinum toxin is used for head and voice tremor, where oral drugs are least effective, and hand injection causes weakness; cost hundreds to low thousands of US dollars a cycle. *Deep brain stimulation* of the ventral intermediate thalamic nucleus gives 60 to 90 per cent tremor reduction, allows bilateral treatment, and is adjustable and reversible; cost in the tens of thousands of US dollars plus battery replacements. *MRI-guided focused ultrasound thalamotomy* has randomised sham-controlled evidence: 47 per cent reduction in hand tremor score against 0.1 per cent with sham at three months, sustained at five years†. It is unilateral in most practice, incisionless and **irreversible**, which is the key difference from deep brain stimulation; cost in the tens of thousands of US dollars.

Weighted utensils, wrist weights and adaptive equipment reduce functional impact and are cheap. *Occupational therapy* provides adaptive strategies for writing, eating and drinking.

Simple means. Propranolol at a few US dollars a patient-year: the first-line treatment for one of the commonest movement disorders is an off-patent essential medicine costing a few dollars a year, and for 60 to 70 million people that matters more than the surgical options. Weighted cutlery, weighted wrist bands, non-spill cups and thicker pens reduce the functional impact of tremor directly, cost a few dollars, and are often not offered. Stabilising the arm against the body or a surface when performing fine tasks: mechanical, free and effective. Reducing caffeine where it worsens tremor, and identifying and stopping a tremor-causing drug, which can resolve the problem entirely. Occupational adaptation: changing how a task is done rather than treating the tremor. Exercise: limited evidence specific to this condition, with general benefit on function. No light, sleep timing or social-connection intervention has specific evidence here.

Gaps. No burden estimate for a disorder affecting 4 to 5 per cent of people over 65. No causative gene despite clear familial aggregation. Whether it is degenerative is unresolved and determines how it should be understood. Whether it is one disease is disputed; the 2018 criteria revision acknowledged this and the epidemiological literature predates it, so prevalence figures are not comparable to the current definition. There is no head-to-head randomised comparison of deep brain stimulation against focused ultrasound. Focused ultrasound is irreversible and its long-term adverse effects beyond five years are unknown.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: no number ([B] progressive).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Meningitis sequelae

What it is. Lasting consequences in survivors of meningitis: hearing loss, epilepsy, cognitive and learning impairment, motor deficits, hydrocephalus, visual impairment and behavioural change. Bacterial meningitis causes the great majority of sequelae; viral meningitis usually does not.

Measured. Meningitis ranked sixth among all nervous system conditions by DALYs on GBD 2021 — ahead of epilepsy and autism. Bacterial meningitis kills about 1 in 6, roughly 17 per cent; about 1 in 5 survivors has severe complications; and about 1 in 5 survivors has long-term after-effects (WHO meningitis fact sheet, 29 September 2026; the page states no year for these general figures). In the African meningitis belt surveillance network, covering 24 of 26 countries, 2025 saw 21,526 suspected cases, 971 deaths and a case fatality rate of 4.5 per cent; those are surveillance-network figures, not global totals, and **WHO's fact sheet gives no global annual case or death total**.

Hearing loss is the commonest sequela, affecting roughly 10 to 30 per cent of bacterial meningitis survivors depending on pathogen, with pneumococcal meningitis carrying the highest rate. Sequelae rates are substantially higher in low-income settings, where presentation is later and treatment delayed. Before the MenACV rollout from 2010, serogroup A caused 80 to 85 per cent of epidemics in the African meningitis belt; after mass preventive campaigns, confirmed serogroup A disease fell by **99 per cent** in vaccinated populations, with the last confirmed serogroup A case in 2017 in countries that introduced the vaccine.

The Defeating Meningitis by 2030 roadmap, adopted as WHA73.9 in 2020, targets a 50 per cent reduction in vaccine-preventable bacterial meningitis cases and a 70 per cent reduction in deaths. Men5CV was prequalified in 2023, and Niger ran the first Gavi-supported Men5CV campaign in 2025.

Where it starts. The pathogen determines outcome: *Streptococcus pneumoniae* carries the highest mortality and sequelae rates; *Neisseria meningitidis* lower; *Haemophilus influenzae* type b was historically significant and is now largely vaccine-prevented; Group B *Streptococcus* and *E. coli* affect neonates; *Mycobacterium tuberculosis* carries very high sequelae rates; *Cryptococcus* affects people with HIV. Delay to effective antibiotic is the strongest modifiable determinant of death and sequelae. Age matters: neonates and young children have the highest rates of lasting impairment and older adults the highest mortality. Severity at presentation — coma, seizures, shock — predicts sequelae. Lack of vaccination is the entirely preventable component. HIV, asplenia, complement deficiency, cochlear implants and skull base defects raise susceptibility. Crowding, the dry season and dust in the African meningitis belt are the epidemiological driver of the belt's epidemic pattern.

The host inflammatory response to bacterial components in the subarachnoid space causes much of the brain injury, not the bacteria alone, which is why corticosteroids help in some settings: an inflammation-mediated mechanism with a matching treatment. Cochlear damage from labyrinthitis and from the inflammatory response explains the hearing loss, and the window for cochlear implantation closes as the cochlea ossifies — a mechanism with a direct, time-critical clinical consequence. Not known: why dexamethasone's benefit differs so much between high-income and low-income settings; why cognitive sequelae occur without obvious structural damage.

Cure status. The sequelae do not share one label. Hearing loss: RELIEF ONLY — it can be rehabilitated with hearing aids or cochlear implants and not reversed. Cognitive impairment: RELIEF ONLY — it is permanent. Epilepsy: CONTROLLABLE. Hydrocephalus: CONTROLLABLE, treatable by shunting. The acute illness itself is CURABLE with prompt effective antibiotics. The decisive intervention is prevention and speed, not the treatment of sequelae.

Prevention. Among the strongest in the book, with a 99 per cent figure attached. *Conjugate vaccines*: STRONG. MenACV reduced confirmed serogroup A disease by 99 per cent in vaccinated populations in the African meningitis belt. Hib conjugate vaccine has nearly eliminated *Haemophilus influenzae* type b meningitis where introduced, with reductions above 90 per cent†. Pneumococcal conjugate vaccines have substantially reduced pneumococcal meningitis in vaccinated cohorts, and 2025 coverage for the last pneumococcal dose was 71 per cent globally. Men5CV, prequalified in 2023, covers five serogroups in one

product. *Maternal Group B Streptococcus screening and intrapartum antibiotic prophylaxis*: STRONG for early-onset neonatal disease.

Rapid access to antibiotics: STRONG for both death and sequelae; the determinant is time, and the measures are recognition, transport and pre-referral antibiotics. *Dexamethasone with or before the first antibiotic dose*: CONTESTED by setting. Cochrane review finds dexamethasone reduces hearing loss, relative risk roughly 0.74, and neurological sequelae overall, with the mortality benefit confined to high-income settings, and trials in low-income settings and in HIV-prevalent populations showed no benefit. Dexamethasone is EML-listed and off-patent, and the UNICEF Supply Catalogue gives 4 mg tablets at US$24.00 for 100, about US$0.24 a tablet, read 19 October 2026, so a course is a few US dollars. The setting-dependence is reported.

Chemoprophylaxis for close contacts of meningococcal cases: STRONG. Ciprofloxacin, rifampicin and ceftriaxone are all EML-listed and off-patent, and a course is a few US dollars. *Reactive and preventive mass vaccination campaigns* in the meningitis belt: STRONG. *Hearing screening of all bacterial meningitis survivors before discharge*: STRONG for the sequela outcome, because the window for cochlear implantation before cochlear ossification is weeks to months, and delay forecloses the treatment. *HIV treatment*: STRONG for cryptococcal meningitis prevention. *BCG vaccination*: MODERATE specifically for childhood tuberculous meningitis, where its efficacy is better than for pulmonary tuberculosis.

Treatment. *Acute.* **Prompt empirical antibiotics** — ceftriaxone or cefotaxime, with ampicillin where *Listeria* is a consideration, and vancomycin where pneumococcal resistance is prevalent. All are EML-listed and off-patent, and a course costs on the order of tens of US dollars. Oily chloramphenicol or single-dose ceftriaxone is used in epidemic settings where intravenous therapy is impossible; EML-listed, a few US dollars a dose. **Dexamethasone**: see prevention; it reduces hearing loss and neurological sequelae, with mortality benefit confined to high-income settings. **Supportive care**: airway, fluids, seizure control, management of raised intracranial pressure. *Sequelae.* **Hearing aids and cochlear implantation**: cochlear implantation restores functional hearing in post-meningitis deafness and must be done before cochlear ossification, which can begin within weeks. Time-critical. Implant cost runs to tens of thousands of US dollars plus rehabilitation; hearing aids cost from low hundreds to low thousands. **Antiseizure medication** for post-meningitis epilepsy: see the epilepsy entry; phenobarbital at about US$6.24 a patient-year on the October 2026 UNICEF indicative price. **Ventriculoperitoneal shunting** for hydrocephalus. **Educational support and rehabilitation** for cognitive and motor sequelae. **Physiotherapy and orthotics** for motor deficits; vision rehabilitation.

Simple means. Vaccination: a 99 per cent reduction in confirmed serogroup A meningococcal disease in vaccinated populations. Nothing else in this book matches that figure, and the product is a single injection costing a few US dollars at Gavi prices. Dexamethasone at a few US dollars a course reduces hearing loss, relative risk roughly 0.74, in high-income settings: cheap, on the Essential Medicines List†, and setting-dependent. Pre-referral single-dose antibiotic where transport will be delayed: ceftriaxone or oily chloramphenicol, a few US dollars, given by a health worker before transfer. Hearing screening before discharge: a test costing very little that determines whether a deafened child gets an implant within the window or not. Pure organisation. Recognition and speed: public and health-worker awareness of the presentation is the single determinant of outcome. Contact chemoprophylaxis: a few US dollars, preventing secondary cases. Reducing crowding and dust exposure in the belt during the dry season: the epidemiological driver, and non-clinical.

Gaps. WHO's fact sheet gives no global annual case or death total for meningitis, only African belt surveillance figures, and for a condition ranked sixth by nervous-system DALYs that is a significant gap. Dexamethasone's divergent effect between settings is unexplained and clinically consequential. Sequelae are poorly measured systematically, and the one-in-five figures carry no year and no confidence interval in the WHO source. Follow-up of survivors, including hearing screening, is inconsistent even in high-income settings, so sequelae are both under-detected and under-treated. Tuberculous meningitis has the worst sequelae profile and the thinnest treatment evidence. The Men5CV rollout is early and its population impact is not yet measured.

> **Depth.** The consequences of meningitis. No depth is given.

> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Hearing and tissue that were lost do not regrow. So it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Spinal cord injury consequences

What it is. Permanent loss of motor, sensory and autonomic function below the level of damage to the spinal cord. The consequences extend well beyond paralysis: bladder and bowel dysfunction, pressure injury, spasticity, neuropathic pain, autonomic dysreflexia, respiratory compromise, sexual dysfunction and loss of temperature regulation.

Measured. About 15.4 million people were living with spinal cord injury in 2021 (WHO spinal cord injury fact sheet, 2021 data); the key facts section of the same page rounds this to over 15 million. Over 4.5 million years lived with disability in 2021. WHO gives no annual incidence figure; the standing literature puts global incidence at roughly 250,000 to 500,000 new cases a year. In-hospital mortality is nearly three times higher in low- and middle-income countries than in high-income countries. Unemployment among adults with spinal cord injury exceeds 60 per cent. **Only 5 to 35 per cent of people who need wheelchairs have wheelchair access** (WHO; no year stated), and that single figure accounts for a large share of the global burden. WHO ranks the causes without percentages: traumatic injuries from falls and road traffic crashes lead, followed by violence including self-harm, then work- and sports-related injuries, with non-traumatic causes — tumours, degenerative and vascular conditions — increasing. Historically the age pattern showed a young male peak from trauma, and falls in older adults are now a growing and in some high-income countries dominant cause, shifting the demographic older. The leading causes of death after the first year are respiratory disease, usually pneumonia; sepsis, commonly from pressure injury or a urinary source; and cardiovascular disease.

Where it starts. Road traffic crashes: about 1.16 million road deaths a year, with 20 to 50 million non-fatal injuries (WHO road traffic injuries fact sheet, 20 July 2026). Helmets reduce the risk of death by more than six times and brain injury risk by up to 74 per cent; seat-belts reduce occupant death risk by up to 50 per cent; child restraints give a 71 per cent reduction in infant deaths; every 1 per cent increase in mean speed produces a 4 per cent increase in fatal crash risk and 3 per cent in serious crash risk; pedestrian death risk from car fronts rises 4.5 times going from 50 to 65 km/h. Falls are the leading cause in many high-income countries, especially in older adults with pre-existing cervical spondylosis, where a low-energy fall causes central cord injury; fatal falls number 684,000 a year with 37.3 million non-fatal falls needing medical attention, on WHO's oldest fact sheet, printed 26 April 2021 with no data year stated. Violence, including self-harm, is a cause; no methods are described anywhere in this chapter. Occupational and sports injury: diving into shallow water, rugby and similar collision sports, construction falls. Non-traumatic causes: spinal tumour, abscess, tuberculosis of the spine, which is a major cause in endemic regions, transverse myelitis, spinal cord infarction, and degenerative cervical myelopathy — which is the commonest cause of spinal cord dysfunction in adults worldwide and is surgically treatable if recognised before severe damage.

Primary mechanical injury is followed by a secondary cascade of ischaemia, excitotoxicity, inflammation, oedema and apoptosis over hours to days, well characterised in animal models. Every neuroprotective agent targeting that cascade has failed in human trials, including high-dose methylprednisolone, whose use was standard for years and is no longer recommended because the benefit did not hold and the harms — infection, gastrointestinal bleeding — did. Glial scarring and inhibitory molecules prevent axonal regeneration; established, and it has not yielded a treatment. Not known: how to achieve functional axonal regeneration; why the secondary cascade is unmodifiable in humans despite being modifiable in rodents.

Cure status. For the injury itself: RELIEF ONLY. No treatment restores a severed or crushed cord. For most of the consequences: CONTROLLABLE, and most of the mortality and morbidity after the first year is preventable. Some spontaneous neurological recovery occurs in the first year, more in incomplete injuries. Degenerative cervical myelopathy is the important exception: surgical decompression halts progression and often improves function, and it is the commonest cause of spinal cord dysfunction

worldwide, with delayed recognition the problem. The secondary complications — pressure injury, urinary sepsis, pneumonia, autonomic dysreflexia — are preventable, and they are what kills people.

Prevention. Primary prevention is the whole story here, and it is well quantified. *Road safety law* — helmet laws, seat-belt laws, speed limits, drink-driving limits, motorcycle licensing: STRONG. The WHO effect sizes above are among the best-quantified prevention figures in the book, derived from legislative natural experiments across many countries. *Alcohol policy*: STRONG. There were 298,000 alcohol-related road deaths in 2019, of which 156,000 were caused by someone else's drinking, and random breath testing and lowered legal limits reduce crash deaths.

Fall prevention in older adults: STRONG. Exercise programmes with balance and strength components reduce falls by roughly 20 to 25 per cent in Cochrane review†, and multifactorial assessment, medication review, home hazard removal and vision correction add further. For the growing older-adult share of spinal cord injury this is now the main preventive lever. *Safe water entry and diving education, sports rule changes*: MODERATE; rugby scrum law changes in several countries were followed by reductions in catastrophic cervical injury. *Occupational safety law*, fall protection and scaffolding standards: STRONG.

Violence reduction: MODERATE. *Tuberculosis treatment and control*: STRONG for the spinal tuberculosis fraction in endemic regions. *Early recognition and decompression of degenerative cervical myelopathy*: STRONG for preventing the permanent injury. *Secondary prevention of complications*: see treatment, and this is where the preventable deaths are. *High-dose methylprednisolone is no longer recommended*: the negative result is recorded.

Treatment. *Acute spinal immobilisation, timely surgical decompression and stabilisation*: early decompression within 24 hours is associated with better neurological recovery in prospective cohort studies and one randomised trial signal; the evidence is observational-dominant and consistent. *Specialist spinal injury unit care* is associated with fewer complications and better outcomes than general ward care: organisational, like stroke units. *Bladder management*: intermittent catheterisation is the reference standard, with lower infection and renal damage rates than indwelling catheters. Catheters cost a few US dollars each, and renal failure from poor bladder management was historically the leading cause of death after spinal cord injury and is now largely preventable. Anticholinergics or botulinum toxin are used for detrusor overactivity.

Pressure injury prevention: repositioning schedules, pressure-redistributing cushions and mattresses, daily skin inspection. Pressure injury is a leading cause of hospitalisation, sepsis and death, and is almost entirely preventable by routine. *Bowel management*: a regular routine prevents impaction and autonomic dysreflexia. *Autonomic dysreflexia recognition and management*: a medical emergency triggered by bladder or bowel distension or skin stimulation below the injury level, which can cause stroke and death. The treatment is sitting the person up, removing the trigger, and loosening constrictions — free actions, and recognition is the whole intervention. A card carried by the patient explaining it to emergency staff prevents deaths.

Respiratory care: assisted cough, secretion clearance, vaccination against influenza and pneumococcus, and ventilation for high cervical injuries. Pneumonia is a leading cause of death. *Spasticity management*: baclofen, which is EML-listed, off-patent, and costs tens of US dollars a patient-year; tizanidine; botulinum toxin; intrathecal baclofen. *Neuropathic pain*: amitriptyline, EML-listed, off-patent, a few US dollars a patient-year, and gabapentinoids; pain affects a majority and is frequently undertreated. *Wheelchairs, seating and assistive technology*: only 5 to 35 per cent of people who need wheelchairs have access. A basic appropriate wheelchair costs on the order of a few hundred US dollars, and an inappropriate one causes pressure injury and deformity. This is the largest single gap between need and provision in Chapter 08.

Rehabilitation, vocational rehabilitation and supported employment: unemployment exceeds 60 per cent, and supported employment improves it. *Functional electrical stimulation, epidural stimulation, exoskeletons, brain-computer interfaces*: research-stage for function restoration, with striking individual results in small numbers and no established population benefit, at costs from tens of thousands to hundreds of thousands of US dollars. Reported as not established. *Mental health care*: depression prevalence is high and suicide risk elevated; see the suicide entry for intervention evidence.

Simple means. Repositioning and daily skin inspection prevent the pressure injuries that cause sepsis and death: a schedule, a mirror and a pair of hands, with no supply chain. Intermittent catheterisation with clean technique, at a few US dollars a catheter, prevents the renal failure that was once the leading cause of death. A bowel routine prevents impaction and the autonomic dysreflexia it triggers. An autonomic dysreflexia card: a piece of paper that tells an unfamiliar emergency clinician what to do, and it prevents deaths. Sitting the person up and removing the trigger in dysreflexia: free, and it is the treatment. Assisted cough, taught to a family member, prevents pneumonia. An appropriate wheelchair at a few hundred US dollars: for the 65 to 95 per cent without access† this is the difference between participation and confinement, measured by WHO, and the largest avoidable gap here. Helmets, seat-belts and speed limits: legislation, with the six-fold, 50 per cent and 4-per-cent-per-1-per-cent effect sizes above. Prevention beats everything that follows. Exercise for falls prevention in older adults: roughly 20 to 25 per cent fall reduction, free, and it now addresses the leading cause in high-income countries.

Gaps. WHO gives no incidence figure, so the annual new-case number rests on literature estimates with wide ranges. No percentages are given for causes in the WHO source, only a ranking. The 5-to-35-per-cent wheelchair access figure has no stated year and a very wide range. There is no neuroprotective or regenerative treatment despite decades of work and clear animal-model targets. Early surgery evidence is observational-dominant, and the randomised base is thin for an intervention now widely standard. Outcome data from low- and middle-income countries, where in-hospital mortality is three times higher, are sparse. Long-term outcomes of the growing older, fall-related, non-traumatic population are poorly described, because the literature describes a younger traumatic population.

> **Depth.** Starts in: the spinal cord. Size: 1 cm†; depth +11.19. First complaint: about 1 second († instant (injury)); time depth 33.15. One untreated course: no number ([B] permanent).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The spinal cord does not regrow. So it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

What no longer holds

A reference work that records only what is currently believed passes on retired certainties as though they were live. The claims below were once standing positions in these three chapters. Each was overturned, failed to replicate, or was reversed in guidelines. They are listed because readers will still meet them in older textbooks, in clinical habit, and in current marketing.

Claim	Status
Low serotonin causes depression	**Not supported.** An umbrella review across six areas of research found no consistent evidence (Moncrieff, *Molecular Psychiatry*, 2022). Drug efficacy is a separate and better-established fact.
Low cortisol or HPA-axis dysfunction characterises post-traumatic stress disorder	**Did not replicate** consistently; meta-analyses find no reliable group difference in basal cortisol.
Psychological debriefing prevents post-traumatic stress disorder	**Does not work**; some trials show harm. WHO and NICE advise against routine use.
The MMR vaccine causes autism	**Settled: it does not.** A Danish cohort of over 650,000 children found no increased risk overall, in any subgroup, or in any post-vaccination time window (Hviid, *Annals of Internal Medicine*, 2019). The original paper was retracted.
Secretin, gluten-free and casein-free diet, or chelation treat autism	**Tested and not supported**; chelation is harmful.
Cognitive and working-memory training transfers to ADHD symptoms	**Does not transfer** in blinded-rated trials. Heavily marketed regardless.
Maternal smoking causes ADHD	**Substantially attenuated** in sibling-comparison and genetically informed designs.
Elimination diets treat ADHD	Effects **do not survive blinding**.
Vascular dilation causes migraine	**Abandoned.** Migraine is a disorder of brain excitability and of the

Claim	Status
	trigeminovascular pain system.
Chocolate, cheese and red wine trigger migraine	**Blinded challenge studies largely negative**; premonitory-phase craving may explain the association.
Sustained muscle contraction causes tension-type headache	**Not confirmed** by electromyography. The disorder's original name is a misnomer.
Botulinum toxin helps tension-type headache	**Negative** in randomised trials, unlike chronic migraine.
CPAP reduces cardiovascular events in obstructive sleep apnoea	**Negative.** SAVE hazard ratio 1.10 (95 per cent CI 0.91 to 1.32, p=0.34); RICCADSA and ISAACC similarly null.
Adaptive servo-ventilation helps central apnoea in heart failure	**Increased mortality** (SERVE-HF, *NEJM*, 2015). Now contraindicated in heart failure with reduced ejection fraction and predominant central apnoea.
Dopamine agonists are the right first-line for restless legs syndrome	**Reversed.** Augmentation in roughly 7 to 8 per cent a year† led to a guideline change; alpha-2-delta ligands are now first-line.
Sleep hygiene education alone treats insomnia	**Fails as a standalone intervention**; it works only as a component of cognitive behavioural therapy for insomnia.
Hearing aids slow cognitive decline	**Primary outcome null** (ACHIEVE, *Lancet*, 2023; difference 0.002 SD, p=0.96). The circulating 48 per cent is a high-risk subgroup†.
Intensive blood pressure control prevents dementia	**Primary endpoint not significant** (SPRINT MIND; probable dementia hazard ratio 0.83, 95 per cent CI 0.67 to 1.04). Only mild cognitive impairment and the composite were significant. Frequently misreported.
Aducanumab treats Alzheimer disease	Approved against its own advisory committee's vote; **withdrawn from the market in 2024**.
Amyloid-beta*56 is a key Alzheimer species	**The 2006 paper was retracted in 2024** after image-manipulation findings. The amyloid hypothesis rests on other evidence.
Vitamin D supplementation prevents or treats multiple sclerosis	**Observational and Mendelian signal strong; randomised supplementation trials negative.**
Exercise is harmful in multiple sclerosis	**Reversed.** Exercise improves function and does not worsen the disease.
Fluoxetine improves motor recovery after stroke	**Negative** in FOCUS, AFFINITY and EFFECTS, with increased fracture risk.
High-dose methylprednisolone helps acute spinal cord injury	**No longer recommended.** The benefit did not hold; the harms did.
Intensive glycaemic control prevents neuropathy in type 2 diabetes	**Small and non-significant** in meta-analysis, unlike type 1, where DCCT gave roughly 60 to 69 per cent reduction†.
Acetyl-L-carnitine prevents chemotherapy-induced neuropathy	**Worsened** outcomes in a randomised trial.
Corticosteroids help Guillain-Barré syndrome	**Ineffective**; oral steroids may delay recovery.
Combining immunoglobulin and plasma exchange helps Guillain-Barré syndrome	**No added benefit.**
Huntingtin lowering slows Huntington disease	**Tominersen phase 3 halted**: the higher-dose arms were worse than placebo.
Sodium phenylbutyrate with taurursodiol treats amyotrophic lateral sclerosis	Approved on a phase 2 trial, **failed phase 3, withdrawn from the market in 2024** (Relyvrio).
Therapeutic hypothermia helps neonatal encephalopathy everywhere	**No benefit and increased mortality in low-resource settings** (HELIX trial).
Most cerebral palsy results from birth asphyxia	**Substantially revised downward.** Most high-income cases are antenatal in origin, and 10 to 30 per cent are genetic†.
Antipsychotics help challenging behaviour in intellectual disability	**Not supported** by the largest randomised trial. Over-prescribing is a documented quality-of-care problem.
Drug treatment is indicated for borderline personality disorder itself	**Not supported**; NICE advises against it.
The categorical subtypes of personality disorder are valid	**Abandoned in ICD-11** because of poor construct validity, extensive overlap and poor inter-rater reliability.
Antiseizure drugs after head injury or stroke prevent later epilepsy	**Negative.** They prevent early provoked seizures only.
"Responsible gambling" information changes behaviour	**Little effect**, mirroring the alcohol and tobacco education findings.

Claim	Status
Moderate alcohol protects the heart — the J-curve	**Not supported** by Mendelian randomisation.
Supply-side drug interdiction reduces stimulant prevalence	**No demonstrated sustained effect** on price, purity or prevalence.
Individual-level suicide risk prediction works	**It does not.** Risk-assessment scales lack the predictive accuracy needed for clinical allocation, and meta-analyses find positive predictive values too low to be useful. Guidelines in several countries have changed. Services still use the instruments.
The antipsychotic maintenance readmission number needed to treat is 5	**Superseded.** The 2012 Lancet figure of 5 is correctly published and derives from the pooled risk ratio. The 2020 Cochrane update gives hospitalisation 7 against 18 per cent, risk ratio 0.43, number needed to treat 8, and **8 is the figure to quote as current.**
Pandemrix narcolepsy risk generalises to vaccines in general	**It does not.** The association was real, measured at roughly one additional case per 16,000 vaccinated, and confined to one adjuvanted formulation; other H1N1 vaccines showed no such signal, and H1N1 infection itself was associated with increased narcolepsy incidence.

Two further reversals belong here as method rather than finding. The compilation this chapter was built from carried 178 drug prices that were order-of-magnitude guesses with no source consulted. And the international price source the book had relied on, the MSH International Medical Products Price Guide, turns out to have a last edition of 2017 and a website retired after 30 June 2024. Six of the 169 that printed digits have been replaced here with sourced, dated figures from the UNICEF Supply Catalogue and the NHS Drug Tariff, and two further medicines were priced from the same sources. The remaining 163 are given in words. Where this chapter says a drug costs a few dollars or several thousand, that is the honest extent of what is known, and the reader is not handed a number that was never measured.

Chapter 13 covers 51 named conditions across ICD-11 Chapters 06, 07 and 08: 21 in Chapter 06, 10 in Chapter 07 and 20 in Chapter 08.

Chapter 14 — ICD-11 Chapters 09, 10 and 14: the visual system, the ear, the skin

Fifty entries. Nineteen for the visual system, twelve for the ear and mastoid process, nineteen for the skin.

Glaucoma and age-related macular degeneration each take two entries. Open-angle and angle-closure glaucoma have different mechanisms, different geography and different definitive treatments. Dry and wet macular degeneration differ in cure status, so one label would be false at one end.

The widest gap in the book between what a thing costs and what it returns

This chapter holds the largest price-to-return spreads in the whole book, and they are measured, not inferred.

Cataract surgery at the Aravind Eye Care System in India cost **US$29.02** per operation in total direct and indirect cost in 2013, with the intraocular lens charged separately at **US$12.80 to 96.00**, giving an all-in **US$41 to 125** per case. Aravind's own manufacturing arm, Aurolab, brought the lens itself to **US$3**, against **US$4,000 to 6,000** quoted for a lens in the United States†. At that cost the measured outcomes were a complication rate of **1.5 per cent** and an endophthalmitis rate of **0.02 per cent**, reported at about half the United Kingdom National Health Service complication rate. The volume was **over 700,000 operations** and over 5.7 million outpatient visits in 2023. One cheap operation, performed at industrial scale, with a complication rate reported at about half that of the United Kingdom National Health Service, and a lens that costs a small fraction of the lens price quoted in the United States.

Reading glasses cost **a few US dollars per pair** in low-cost programmes. In the PROSPER randomised trial, 750 tea pickers in Assam given near-vision glasses raised their productivity by **21.7 per cent** overall and **31.6 per cent** among those over fifty, an extra **5.25 kg** of tea a day, with about **90 per cent** still wearing the glasses at three months. Presbyopia accounts for **826 million** people with near vision impairment. Cerumen impaction is on the World Health Organization's list of causes of hearing loss, and the Cochrane review of cerumenolytics found no clear difference between agents, including plain water and saline — so a World Health Organization listed cause of hearing loss is removed outright with water and a rubber bulb. The Epley manoeuvre for benign paroxysmal positional vertigo needs a couch and about two minutes, and cures roughly **80 per cent** of patients in one session†. Ivermectin mass drug administration took scabies prevalence from **32 per cent to under 2 per cent** in Fiji and from **18.7 to 2.3 per cent** in the Solomon Islands, with community impetigo down **60 to 88 per cent**, on two oral doses of a drug that is donated or costs cents.

The other half of the chapter is the half where nothing works, and it is the larger half by burden. Glaucomatous visual field loss has never been recovered by any treatment. Mammalian cochlear hair cells do not regenerate, so presbycusis, noise-induced loss and aminoglycoside or cisplatin ototoxicity are permanent, and hearing aids and cochlear implants substitute rather than repair. Dry macular degeneration has licensed drugs that slow lesion growth on imaging without a demonstrated acuity benefit. An opaque cornea is cleared only by transplantation, which is scarcest where trachoma and keratitis are commonest. Amblyopia after roughly age seven does not respond. Deep burn scarring and contracture are improved and never restored.

The honest figure for the commonest of these is the Early Manifest Glaucoma Trial. Of 255 patients with early glaucoma, 129 were treated immediately and 126 were untreated controls. Mean intraocular pressure fell **25 per cent** in the treated group. At six years, **45 per cent** of treated patients had progressed against **62 per cent** of controls. That is a real effect, and it means nearly half of treated patients progressed anyway.

Control here is partial even when it is achieved, which is why the label is CONTROLLABLE and cannot be raised.

Three structures recur and are worth naming before the entries. First, the binding constraint is rarely money. For cataract, trachoma, scabies and vitamin A it is delivery volume; for glaucoma, diabetic retinopathy and hearing aids it is sustained clinical contact over decades; for amblyopia, retinopathy of prematurity, retinal detachment and burns it is **timing**, a window after which the identical intervention achieves nothing; for pressure ulcers and positional vertigo it is simply whether anyone present knows what to do. Second, a recurring and well-evidenced category of intervention consists of **not doing something** — and those interventions save money as well as harm. Third, provenance in this chapter is uneven by design, and the daggers show it: more than three in four of the chapter's figures carry daggers, and more than four in five in the skin block. The skin block in particular carries a large body of figures with daggers: reported as commonly carried, with the source not opened, because the Global Burden of Disease skin analyses and every Cochrane review were unreachable. Where a World Health Organization page was read off the page, the figure is printed plainly and the page is named with its printed date.

ICD-11 Chapter 09 — Diseases of the visual system

Global totals for vision

At least **2.2 billion** people have a near or distance vision impairment, and at least **1 billion** of those — "almost half" — have an impairment that could have been prevented or is still unaddressed (World Health Organization fact sheet, *Blindness and vision impairment*, 10 February 2026).

The named causes within that figure are cataract **94 million**, uncorrected refractive error **88.4 million**, age-related macular degeneration **8 million**, glaucoma **7.7 million** and diabetic retinopathy **3.9 million**. Those five sum to about **202 million**, not a billion: they are the main causes of distance impairment, not the full count. Presbyopia accounts for a further **826 million** people with near vision impairment. An earlier reading of this page added the near-vision and distance-vision figures into one total and produced a sum larger than its own denominator; the figures above are the published figures and the near and distance counts are not additive.

The Vision Atlas of the International Agency for the Prevention of Blindness gives **1.1 billion** people living with sight loss, projected to **over 1.7 billion by 2050**, and states that **90 per cent** of sight loss is preventable or treatable without attributing that percentage to a named study on the page. The two sets of headline figures differ and both are printed.

Global Burden of Disease 2023 places blindness and vision loss at **23.6 million** years lived with disability (95% uncertainty interval 16.3 to 33.5), the twelfth leading cause of years lived with disability.

Annual global productivity loss from vision impairment is about **US$411 billion** at purchasing power parity, against a **US$25 billion** cost gap to address the unmet need. The component split is **US$43.6 billion** for blindness and **US$367.1 billion** for moderate to severe impairment.

Access is the limiting factor. **One in two** people who need cataract surgery cannot get it, and **two in three** people in low-income countries who need spectacles lack them. Effective cataract surgical coverage — surgery performed and a good visual result obtained — is **44 per cent**, with female coverage 43 and male 45 per cent. Distance vision impairment prevalence is about **four times** higher in low- and middle-income regions than in high-income regions. Unaddressed near vision impairment is **above 80 per cent** in western, eastern and central sub-Saharan Africa and **below 10 per cent** in high-income North America, Australasia, western Europe and Asia-Pacific. The global eye care targets for 2030 and the SPECS 2030 initiative count **800 million** people in need of refractive error services.

Myopia (short-sightedness)

What it is. The eye grows too long from front to back. Light focuses in front of the retina instead of on it, so distant things blur. Near vision stays clear.

Measured. Myopia sits inside the uncorrected refractive error figure of **88.4 million** people with distance vision impairment or blindness from uncorrected refractive error. That figure counts the uncorrected subset, not total myopia prevalence.

Holden and colleagues projected **4.758 billion** people with myopia by 2050, 49.8 per cent of the world population, and **938 million** with high myopia, 9.8 per cent, from 1.406 billion (22.9 per cent) and 163 million (2.7 per cent) in 2000†.

Onset and progression concentrate in school-age children, and progression largely stops in the late teens to early twenties. Prevalence in urban East and Southeast Asia is far above Western levels, with reported school-leaver prevalence of 80 to 90 per cent in parts of China, Taiwan, Singapore and South Korea†. The trend is rising, fastest in East Asia. Children's uncorrected refractive error costs an estimated **6.3 million school years** lost per year and **US$173 billion** in future productivity annually.

Where it starts. Outdoor time is the best-evidenced modifiable factor, and the trial evidence is direct. The Guangzhou Outdoor Activity Longitudinal Trial was cluster-randomised across 12 primary schools, 1,903 grade-1 children, 952 intervention and 951 control, over three years, with one extra 40-minute outdoor class per school day plus encouragement of after-school outdoor activity.

Three-year cumulative incidence of myopia, defined as spherical equivalent of −0.5 D or more, was **30.4 per cent** in the intervention group (259 of 853) against **39.5 per cent** in controls (287 of 726). The absolute difference was **−9.1 per cent**, 95% CI −14.1 to −4.1, p<0.001.

The progression measures were weaker. Change in spherical equivalent refraction over three years was −1.42 D against −1.59 D, a difference of 0.17 D, 95% CI 0.01 to 0.33, p=0.04. Change in axial length was 0.95 mm against 0.98 mm, a difference of −0.03 mm, 95% CI −0.07 to 0.003, **p=0.07, not significant**. Both results belong in the same place: outdoor time cut the number of children who became myopic by about a fifth in relative terms, and its effect on the growth of the eye did not reach significance. Taiwanese school outdoor-time programmes reported similar incidence reductions.

Years of education and near-work intensity associate strongly with myopia, and Mendelian randomisation studies support education as causal. Two myopic parents raise a child's risk roughly two- to threefold. Myopia is highly polygenic; genome-wide studies have found hundreds of loci that together explain a modest fraction of variance.

Genuinely not known: why outdoor time protects. Retinal dopamine release under bright light and the dioptric properties of outdoor scenes are the leading candidates, and neither has been demonstrated as the operative mechanism in humans. The light intensity threshold, the required daily duration, and whether the effect is light or simply the absence of near work are all unresolved. Why the incidence effect in Guangzhou was much clearer than the progression effect is not explained.

Cure status. CONTROLLABLE. The refractive error is fully correctable — spectacles restore normal vision the day they are worn — but no treatment reverses the eye's elongation. Refractive surgery removes the need for spectacles with high predictability and leaves the long eye, and with it the elevated lifetime risk of retinal detachment, myopic maculopathy and glaucoma that comes with axial length. Nothing shortens an eye. Spectacles are worn for life, and the deficit returns in full on the day they are not worn, which is CONTROLLABLE and not CURABLE.

Prevention.

- **Outdoor time, two or more hours a day, school-based.** Reduces myopia incidence by about 9 percentage points absolute over three years. **MODERATE** — consistent across several trials and settings, weaker on progression than on onset, and it costs a timetable change.
- **Low-dose atropine eye drops, 0.01 to 0.05 per cent.** Slows progression; 0.05 per cent was the most effective of the low doses tested in the LAMP study, with roughly half the progression of placebo over one year. **MODERATE** for progression, not for onset.
- **Orthokeratology and peripheral-defocus spectacle or contact lenses.** Slow axial elongation by roughly 30 to 60 per cent in trials†. **MODERATE**.
- **Reduced screen time as a factor independent of reduced outdoor time. CONTESTED**.

Treatment.

1. **Spectacles.** Complete correction of the refractive error. A device, so not on the Essential Medicines List; spectacles appear on the World Health Organization's assistive products list. Cost: see *Simple means*.
2. **Soft contact lenses.** Equivalent optical correction, higher recurring cost, a small keratitis risk.
3. **Low-dose atropine.** Atropine is on the Essential Medicines List as an ophthalmological mydriatic, but the 0.01 to 0.05 per cent myopia-control concentrations are a compounded or newly licensed product and not the listed item. Off-patent as a molecule; bulk atropine costs pennies per millilitre, while licensed myopia-control products are priced far above that.
4. **Refractive surgery.** High predictability for low to moderate myopia. Not listed. Cost in the thousands of US dollars per eye in high-income markets.

Simple means. Spectacles are the clearest case in this chapter of a near-zero-technology fix for a very large burden. Ready-made spectacles are supplied at roughly **a few US dollars per pair** in low-cost programmes. The World Health Organization fact sheet states only that spectacle correction is among the most cost-effective healthcare interventions.

The measured effect on earnings comes from the PROSPER randomised trial: 750 tea pickers in Assam, mostly female, aged 40 to over 50, over three months. Near glasses raised productivity by **21.7 per cent** overall and **31.6 per cent** in workers over fifty, an extra **5.25 kg** of tea per day, with nearly **90 per cent** still wearing the glasses at three months.

Added outdoor time costs nothing at all. It is a change to a school timetable with a measured 9-percentage-point effect on three-year incidence.

Gaps. Holden's projections could not be verified against the journal page. School-leaver prevalence figures for East Asia are widely carried and unsourced here. The LAMP atropine figures and the orthokeratology effect sizes were not verified. The mechanism of the outdoor-time effect is unknown, so the dose — intensity and duration — cannot be specified. Whether childhood myopia control reduces adult retinal detachment or myopic maculopathy has never been measured as an outcome.

> **Depth.** Starts in: the eyeball. Size: 2.4 cm†; depth +11.99. First complaint: about 8 years († onset about age 8); time depth 50.76. One untreated course: no number ([B] progression largely stops in the late teens to early twenties).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Hyperopia and astigmatism

What it is. In hyperopia the eye is too short, so light focuses behind the retina and near vision blurs first. In astigmatism the cornea or lens is not evenly curved, so one axis focuses differently from another and vision is blurred at every distance.

Measured. Both sit inside the **88.4 million** people with distance vision impairment or blindness from uncorrected refractive error. Separate global prevalence figures for hyperopia and for astigmatism were not retrievable.

Hyperopia is normal in infancy and usually reduces with growth (emmetropisation); clinically significant hyperopia then rises again with age as accommodative reserve falls. Astigmatism is present from childhood and is relatively stable. Unlike myopia, neither is reported as rising sharply.

Where it starts. Both are largely determined by the geometry of the growing eye and both are substantially heritable. Uncorrected hyperopia in childhood is a direct cause of amblyopia and of accommodative esotropia. Known risk factors for astigmatism include eyelid pressure, ptosis, and corneal disease including keratoconus and scarring from trachoma or keratitis.

Genuinely not known: why emmetropisation fails in some children and not others. There is no established modifiable risk factor for either condition. That is a sharp contrast with myopia, where an environmental intervention changes incidence.

Cure status. CONTROLLABLE. Fully correctable with spectacles; the underlying eye shape is unchanged. Refractive surgery and toric intraocular lenses remove the spectacle need. Nothing reshapes a short eye.

Prevention. Nothing demonstrably prevents either condition. What is preventable is the consequence: preschool vision screening followed by correction prevents the amblyopia that uncorrected childhood hyperopia and astigmatism cause — **MODERATE**.

Treatment.

1. **Spectacles.** Full correction. A device, not listed.
2. **Contact lenses**, including toric lenses for astigmatism.

3. **Refractive surgery, or a toric intraocular lens at cataract surgery.** Not listed. Cost in the hundreds to thousands of US dollars.

Simple means. Ready-made spectacles correct hyperopia and simple astigmatism at roughly **a few US dollars per pair** in low-cost programmes. The limit is specific: ready-made non-prescription spectacles cannot correct significant or oblique astigmatism, which needs a ground lens. That is the point at which the supply chain stops being simple. The PROSPER productivity result, **+21.7 per cent** overall and **+31.6 per cent** over fifty, is a near-correction result and applies directly here.

Gaps. No global prevalence figure for either condition was obtainable. The share of the 88.4 million uncorrected refractive error burden attributable to hyperopia against astigmatism against myopia is not reported on any source read. Thresholds for correcting childhood hyperopia to prevent amblyopia differ between guidelines.

> **Depth.** Starts in: the eyeball. Size: 2.4 cm†; depth +11.99. First complaint: about 3.8 years († from conception to early childhood); time depth 50.07. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Presbyopia

What it is. The lens stiffens with age and stops changing shape, so the eye cannot focus on close things. It begins around age 40 and affects everyone who lives long enough. Reading glasses correct it completely.

Measured. 826 million people have near vision impairment from presbyopia (World Health Organization fact sheet, *Blindness and vision impairment*, 10 February 2026). That is the single largest cause of vision impairment of any kind in the published breakdown, and it is a modelled estimate.

The condition is universal. Onset is around 40, and by the mid-50s accommodative amplitude is effectively gone†. Unaddressed near vision impairment runs **above 80 per cent** in western, eastern and central sub-Saharan Africa and **below 10 per cent** in high-income North America, Australasia, western Europe and Asia-Pacific. The condition is universal; only its correction is unequally distributed. The burden rises with population ageing.

Where it starts. Age. The lens loses elasticity progressively from childhood, and the loss becomes symptomatic when accommodative amplitude falls below what reading distance requires. Earlier onset is reported with hyperopia, which has less reserve to spare, and in hotter climates and at lower latitudes.

Genuinely not known: whether lens stiffening can be slowed or reversed at all. Proposed pharmacological lens-softening agents have not shown a durable clinical effect. Why onset age varies by several years between individuals and populations is unexplained.

Cure status. CONTROLLABLE. The functional deficit is removed completely and immediately by a pair of reading glasses costing a dollar, which makes this the cheapest full functional correction in medicine. Nothing halts or reverses the lens change itself, and the glasses must be worn for the rest of the person's life — the day they are not worn the deficit is back in full. The asymmetry is worth stating: near-total functional restoration, zero disease modification.

Prevention. Nothing prevents presbyopia. It is a universal consequence of ageing and no intervention has been shown to delay its onset. Claims for eye exercises are **CONTESTED** at best and unsupported by trial evidence.

Treatment.

1. **Reading spectacles, ready-made or prescription.** Complete correction. A device, not listed.
2. **Multifocal or progressive spectacles.** Convenience; the same optical result.
3. **Multifocal contact lenses, monovision.** Lower satisfaction than spectacles in some wearers.

4. **Pilocarpine 1.25 per cent drops.** Pupil-constricting, with a transient effect and dim-light and headache side effects. Pilocarpine is on the Essential Medicines List as an antiglaucoma miotic, with carbachol as a therapeutic equivalent — not for this indication.
5. **Refractive lens exchange, corneal inlays.** Not listed; a surgical cost.

Simple means. This is the strongest simple-means case in the chapter. Ready-made reading glasses need no eye examination beyond a reading card, no prescription, no fitting and no power supply, and one of a handful of stock powers fits most presbyopes. Programme cost is roughly **a few US dollars per pair**.

The earnings effect is measured. PROSPER randomised 750 Assam tea pickers with presbyopia over three months: **+21.7 per cent** productivity overall, **+31.6 per cent** in those over fifty, **+5.25 kg** of tea per day, and about **90 per cent** still wearing the glasses at three months. The World Health Organization names spectacle correction for refractive error, with cataract surgery, as among the most cost-effective health-care interventions.

Gaps. The 826 million figure is a model estimate and its uncertainty interval is not given on the fact sheet. PROSPER measured productivity in piece-rate agricultural work over three months; whether the effect size transfers to other occupations, and whether it persists beyond three months, was not measured. The cost per pair in programme conditions could not be sourced to a programme document.

> **Depth.** Starts in: the lens of the eye. Size: 1 cm†; depth +11.19. First complaint: about 40 years ([B] begins around age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Cataract

What it is. The lens of the eye goes cloudy, so less light gets through and vision dims and blurs. It builds up over years, usually with age. Taking the cloudy lens out and putting a plastic one in restores sight.

Measured. 94 million people have distance vision impairment or blindness from cataract, the largest single cause of distance vision impairment in the published breakdown and a modelled estimate. Cataract remains the leading cause of blindness globally; the fact sheet gives no overall blindness total, so its share cannot be computed from that source.

One in two people worldwide who need cataract surgery cannot get it. Effective cataract surgical coverage — surgery performed and a good visual result obtained — is **44 per cent**, female 43 and male 45 per cent. The disease is strongly age-related and most people with vision impairment and blindness are over 50. Burden is concentrated in low- and middle-income countries, where distance vision impairment prevalence is four times the high-income level. India performed about **8.3 million** cataract operations nationally in 2022–23. Case numbers are rising with ageing and coverage is improving, while the gap persists.

Where it starts.

- **Age** — the dominant factor.
- **Ultraviolet B exposure** — established for cortical cataract.
- **Smoking** — dose-related, established for nuclear cataract.
- **Diabetes** — accelerates onset.
- **Systemic or inhaled corticosteroids** — cause posterior subcapsular cataract, dose- and duration-related.
- **Ocular trauma, uveitis, prior vitrectomy, high myopia** — all established.
- **Congenital cataract** — from intrauterine rubella, galactosaemia and genetic causes. Rubella-related congenital cataract is vaccine-preventable.

Genuinely not known: the molecular sequence that takes lens crystallins from soluble to aggregated is only partly described, and no intervention arrests it. Why identical exposures produce cataract at widely different ages is unexplained. No drug has ever been shown to clear or prevent human cataract.

Cure status. CURABLE. This is the clearest curable entry in the book. The diseased tissue is removed whole and replaced with a functioning artificial substitute, in one operation, usually under local anaesthesia, with vision restored within days and no maintenance treatment afterwards. The disease does not recur in the removed lens.

The outcomes at scale are measured. At the Aravind Eye Care System the complication rate was **1.5 per cent** and the endophthalmitis rate **0.02 per cent**, with the complication rate reported at about **half** the United Kingdom National Health Service rate. Mean operating time was about **6 minutes** at Aravind against **21 minutes** in the United States. Aravind performed **over 700,000 operations** and over 5.7 million outpatient visits in 2023, up from 29,928 operations in 1988 and 180,991 in 2007. Aravind surgeons perform **over 2,000 operations a year** against an Indian average of about 300, and one surgeon can perform **50 operations in a day**.

The limit on cure is access and surgical capacity, not biology. Two qualifications: posterior capsule opacification occurs in a minority and is cleared by laser capsulotomy; and eyes with co-existing glaucoma, macular degeneration or amblyopia do not recover full vision, because the cataract was not the only problem.

Prevention.

- **Smoking cessation** — reduces nuclear cataract risk. **MODERATE**.
- **Ultraviolet-blocking sunglasses and hats** — biologically grounded for cortical cataract; no randomised evidence of incidence reduction. **WEAK**.
- **Rubella vaccination** — prevents congenital rubella cataract. **STRONG** for that cause.
- **Glycaemic control in diabetes** — delays onset. **MODERATE**.
- **Minimising systemic corticosteroid dose and duration. MODERATE**.
- **Antioxidant vitamin supplements** — trials have not shown prevention. **CONTESTED**, effectively negative.

There is no strong primary prevention for age-related cataract. The public health lever is surgical volume.

Treatment.

1. **Small-incision cataract surgery with an intraocular lens.** Manual, sutureless, no phacoemulsification machine needed, and the workhorse of high-volume programmes. The lens is a device and not on the Essential Medicines List; it appears on the World Health Organization's priority medical devices lists. The technique is unpatented. Cost: **US$29.02** total direct and indirect cost per operation to Aravind in 2013, with the lens charged separately at **US$12.80 to 96.00**, giving an all-in **US$41 to 125** per case. Hospital surgical expenses have been reported as low as **US$10 per operation**, with a bilateral procedure in India at **US$41 to 125** against **US$2,410 to 5,243** in the United States. United States Medicare reimbursement for comparison: **US$1,766** to the ambulatory surgery centre plus **US$760** to the surgeon.
2. **Phacoemulsification with a foldable lens.** The high-income standard; faster visual recovery, needs a machine and consumables. Not listed.
3. **Topical antibiotic and corticosteroid drops after surgery.** Several are listed — azithromycin and aciclovir eye preparations, betamethasone. Off-patent. Cents to a few dollars per course.
4. **Intracameral antibiotic prophylaxis.** Reduces endophthalmitis.

There is no medical treatment for cataract. No drops, tablets or diet reverse it.

Simple means. High-volume cataract surgery is the standout case in the book of a cheap intervention removing a very large burden, and its economics are documented.

Aurolab, Aravind's manufacturing arm, cut the intraocular lens price from hundreds of US dollars to **below US$10**, with a current price of **US$3** per lens in 2023, against **US$4,000 to 6,000** quoted for lenses in the

United States. Aurolab production rose from 35,000 lenses in 1992–93 to nearly 600,000; about **60 per cent** of its lenses go to non-governmental organisations in India and other developing countries, and it exports to over 130 countries.

The model's components are organisational rather than technological. Task-shifting to mid-level ophthalmic personnel raised each ophthalmologist's productivity **more than fourfold**; cross-subsidy lets paying patients fund the **50 per cent** of patients treated free or heavily subsidised; the day runs at 65 patients per surgical session with 6-minute operations.

What the chain minimally requires: a sterile operating room, a trained surgeon, an operating microscope, a sterilisable instrument set, and an intraocular lens. That is not nothing. At US$41 to 125 all-in per restored eye at Aravind in India, 2013, it is close to the cheapest restoration of a major lost function available anywhere in medicine.

Gaps. The fact sheet gives no overall global blindness total, so cataract's share of blindness cannot be computed from it. The 94 million figure is a model estimate without a published interval on that page. The Aravind cost figures are from 2013, reported in 2014, and from 2023, and are not directly comparable with each other. Whether Aravind's outcomes transfer to settings without its volume, cross-subsidy and training pipeline is not established by these sources. A 2025 Aravind cost-trend paper covering 2012 to 2023 could not be retrieved and would supersede the 2013 figures.

> **Depth.** Starts in: the lens of the eye. Size: 1 cm†; depth +11.19. First complaint: about 60 years († onset about age 60; [B] builds up over years); time depth 52.60. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Glaucoma — primary open-angle

What it is. The optic nerve is progressively damaged, usually with raised pressure inside the eye. Sight is lost from the edges inwards, painlessly, and the person often does not notice until a great deal is gone. What is lost does not come back.

Measured. 7.7 million people have distance vision impairment or blindness from glaucoma, all types combined, a modelled estimate.

Pooled global glaucoma prevalence in people aged 40 to 80 is **3.54 per cent**, 95% credible interval 2.09 to 5.82. Numbers aged 40 to 80 with glaucoma were **64.3 million in 2013**, projected to **76.0 million in 2020** and **111.8 million in 2040** — a 74 per cent increase on 2013. Open-angle prevalence is highest in **Africa at 4.20 per cent**, 95% credible interval 2.08 to 7.35. Men are more likely than women to have open-angle glaucoma, odds ratio **1.36**, 95% credible interval 1.23 to 1.52. People of African ancestry are more likely than those of European ancestry to have it, adjusted odds ratio **2.80**, 95% credible interval 1.83 to 4.06. Prevalence rises steeply with age in all populations.

Where it starts.

- **Raised intraocular pressure** — the only modifiable risk factor with randomised trial evidence. In the Early Manifest Glaucoma Trial each millimetre of mercury of pressure reduction was associated with reduced progression risk, and the treated group achieved a mean **25 per cent** pressure reduction.
- **Age** — the strongest non-modifiable factor.
- **African ancestry** — adjusted odds ratio 2.80 against European ancestry.
- **Male sex** — odds ratio 1.36.
- **Family history** — a first-degree relative raises risk several-fold.
- **Thin central cornea, large cup-disc ratio, myopia, low ocular perfusion pressure, type 2 diabetes** — all established associations†.

Genuinely not known: why the optic nerve dies. Normal-tension glaucoma progresses at statistically normal pressures and ocular hypertension often never progresses, so pressure is neither necessary nor

sufficient — and pressure is the only thing treatment addresses. No treatment targets the retinal ganglion cell directly, and neuroprotection trials have not produced a usable agent. The African-ancestry excess is not explained by any identified mechanism.

Cure status. CONTROLLABLE. Nothing restores lost visual field. Retinal ganglion cells and their axons do not regenerate in humans, and no treatment has ever recovered a glaucomatous field defect. What treatment does is slow or halt further loss.

The evidence for that control is the Early Manifest Glaucoma Trial: 255 patients aged 50 to 80 with early glaucoma, 129 treated immediately and 126 untreated controls. Mean pressure fell **25 per cent** in the treated group. At six years, **45 per cent** of treated patients had progressed against **62 per cent** of controls, and progression occurred significantly later in treated patients.

Treatment reduced six-year progression by 17 percentage points absolute, and **45 per cent of treated patients still progressed**. Control is partial even when it is achieved, and that is why the label cannot be raised.

Prevention. There is no demonstrated primary prevention for open-angle glaucoma. Nothing is known to stop the disease starting. What is demonstrated is prevention of blindness in people who already have it.

- **Case detection by pressure measurement, optic disc assessment and visual fields, then pressure-lowering treatment.** Reduces six-year progression from 62 to 45 per cent. **MODERATE** — strong trial evidence for the treatment effect, weaker evidence that population screening programmes improve outcomes.
- **Targeted screening of high-risk groups** — African ancestry, family history, age 40 and over. **MODERATE**.
- **Population screening of unselected adults. CONTESTED**; not recommended by most national screening bodies on cost-effectiveness grounds.
- **Exercise, diet and supplements. CONTESTED**; no trial evidence of incidence reduction.

Treatment.

1. **Prostaglandin analogues (latanoprost, travoprost, bimatoprost), topical.** First-line; reduce pressure about **25 to 33 per cent**, once daily†. Latanoprost is on the Essential Medicines List — the list document did not load and the searchable index displayed the ophthalmological section incompletely. Off-patent. Generic latanoprost runs roughly **US$2 to 10 per bottle** in generic markets, a bottle lasting about a month†.
2. **Beta-blockers (timolol 0.25 to 0.5 per cent), topical.** Reduce pressure about **20 to 25 per cent**†. Timolol is on the Essential Medicines List as an antiglaucoma agent. Off-patent. **Under a few US dollars per bottle** generic. Contraindicated in asthma and bradycardia.
3. **Selective laser trabeculoplasty.** The LiGHT trial found laser as first-line gave better disease stability and lower cost than drops over three and six years. One treatment, repeatable, no daily adherence needed. A procedure, not listed.
4. **Carbonic anhydrase inhibitors — topical dorzolamide, oral acetazolamide.** Acetazolamide is listed. Off-patent. Cents per tablet.
5. **Pilocarpine, a miotic.** Listed, with carbachol as therapeutic equivalent. Off-patent, cheap, now largely superseded for this indication.
6. **Trabeculectomy.** For failed medical control; effective, with bleb-related complications. Not listed. A surgical episode.
7. **Minimally invasive glaucoma surgery devices.** Expensive implants with modest additional pressure reduction.

Simple means. Weaker here than anywhere else in the chapter, and that needs saying.

What works with almost no supply chain is **generic timolol drops**, at well a few US dollars a bottle, lowering pressure about 20 to 25 per cent†. That is a genuine low-cost intervention and it is on the Essential Medicines List.

The rest of the chain is not simple. Glaucoma requires detection before symptoms, which requires tonometry, optic disc examination and ideally perimetry; and it requires lifelong adherence and monitoring, which requires a clinic the patient can reach for decades. A one-off encounter achieves nothing. This is the structural opposite of cataract, where a single episode of care ends the problem. Laser trabeculoplasty partly escapes the adherence problem — one session, repeatable, no drops — but needs a laser and an operator.

There is no simple means that substitutes for sustained clinical contact in glaucoma. The minimum chain is a tonometer, a trained examiner, a drug supply that does not run out, and a patient who returns.

Gaps. The 7.7 million figure covers all glaucoma types and cannot be split between open-angle and angle-closure from that source. The prevalence figures cover ages 40 to 80 only and are not whole-population counts. The global pooled open-angle prevalence was not on the abstract read, only the regional maximum. The 2020 and 2040 figures are projections. Normal-tension glaucoma's share varies greatly between populations and no figure was obtainable. Whether population screening is justified is genuinely disputed between expert bodies. Generic drug prices were not sourced to a price database.

> **Depth.** Starts in: the optic nerve head. Size: 1.5 mm†; depth +9.47. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: no number ([B] what is lost does not come back).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Glaucoma — primary angle-closure

What it is. The drainage angle of the eye is blocked by the iris, so pressure rises. It can creep up slowly or shut suddenly. A sudden attack is painful, with a red eye, blurred sight, haloes and vomiting, and it can blind an eye in days.

Measured. Included in the **7.7 million** glaucoma figure and not separable from it. Angle-closure prevalence is highest in **Asia at 1.09 per cent**, 95% credible interval 0.43 to 2.32, in people aged 40 to 80.

Angle-closure is a minority of glaucoma by case count and causes a disproportionate share of glaucoma blindness; it is reported to account for roughly half of glaucoma blindness worldwide despite being much less common than open-angle disease. Prevalence rises with age, with mean age of presentation above 50†. It is more common in women and concentrated in East and South Asia and in Inuit populations.

Where it starts.

- **A shallow anterior chamber, short axial length, thick lens, hyperopia** — the direct structural cause.
- **Asian and Inuit ancestry** — angle-closure prevalence 1.09 per cent in Asia, the highest regional figure.
- **Age** — the lens thickens through life, progressively crowding the angle.
- **Female sex**.
- **Family history**.
- **Pupil dilation** — mydriatic drops, anticholinergics, dim light and prone positioning can precipitate acute closure in a predisposed eye.

Genuinely not known: why only a minority of anatomically narrow angles ever close. Which narrow-angle eyes to treat prophylactically is not settled, and the cost-effectiveness of population angle screening is unresolved.

Cure status. Eyes treated by laser peripheral iridotomy before synechial closure and optic nerve damage: CURABLE. Eyes with extensive peripheral anterior synechiae: CONTROLLABLE. Optic nerve damage already sustained: RELIEF ONLY. The anatomical mechanism can be removed: **laser peripheral iridotomy** makes a hole in the iris, equalises pressure across it and abolishes the pupillary-block mechanism. In an eye treated before synechial closure and optic nerve damage, this removes the risk, which

is closer to a cure than anything available in open-angle disease. Cataract surgery itself relieves angle crowding by removing the thick lens and in many eyes is definitive.

Against that: optic nerve damage already sustained is permanent and unrecoverable, as in open-angle disease, and eyes with extensive peripheral anterior synechiae remain pressure-unstable after iridotomy and need ongoing treatment. Early mechanical intervention is definitive only in the first stratum above.

Prevention.

- **Laser peripheral iridotomy in eyes with occludable angles.** Prevents acute attacks. The Zhongshan Angle Closure Prevention trial found prophylactic iridotomy reduced incident angle-closure disease, while the absolute event rate in untreated fellow eyes was low, which weakened the case for population-wide prophylaxis. **MODERATE**, and genuinely contested at population level.
- **Avoiding precipitating drugs in known narrow angles** — anticholinergics, mydriatics. **MODERATE**.
- **Early cataract surgery in narrow-angle eyes.** The EAGLE trial reported better outcomes from clear-lens extraction than laser iridotomy. **MODERATE**.
- **Opportunistic angle assessment at any eye examination in at-risk populations** — gonioscopy, or the van Herick estimate, which needs no equipment beyond a slit lamp or even a torch. **MODERATE**.

Treatment. For the acute attack, which is an emergency:

1. **Pilocarpine 2 to 4 per cent drops.** Constricts the pupil and pulls the iris from the angle. Listed as an antiglaucoma miotic, with carbachol as equivalent. Off-patent, cents to a few dollars.
2. **Oral or intravenous acetazolamide.** Listed. Off-patent, cents per tablet.
3. **Topical timolol, apraclonidine and a topical steroid.** Timolol listed.
4. **Oral or intravenous hyperosmotic agents, glycerol or mannitol**.
5. **Laser peripheral iridotomy.** Definitive once the eye is clear enough to treat. A procedure, not listed. Requires a laser.

For chronic disease:

6. **Lens extraction.** Increasingly first-line.
7. **Trabeculectomy** for synechially closed angles with uncontrolled pressure.

Simple means. Pilocarpine drops and acetazolamide tablets are the simple means here, and in an acute attack they are sight-saving. Both are off-patent, both are on the Essential Medicines List, both cost cents, and both can be given anywhere a tablet and a dropper bottle can be kept. In a setting with no laser, this combination buys the time needed to move a patient.

Gonioscopy, or the van Herick slit-lamp estimate, costs nothing beyond the examiner's time and identifies the occludable angle before it closes.

What the chain minimally requires for the definitive step is a laser for iridotomy, or an operating theatre for lens extraction. There is no non-industrial substitute for making a hole in an iris. Surgical iridectomy is possible without a laser and needs a theatre.

Gaps. Angle-closure cannot be separated from open-angle disease in the 7.7 million figure. The claim that it causes about half of global glaucoma blindness is widely repeated and could not be sourced. Whether to perform prophylactic iridotomy on screen-detected occludable angles is genuinely disputed, and expert bodies read the Zhongshan result differently. Global case counts outside ages 40 to 80 are not available.

> **Depth.** Starts in: the drainage angle of the eye. Size: 1 mm†; depth +9.10. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: no number ([B] an attack can blind the eye in days).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Age-related macular degeneration — dry (non-neovascular)

What it is. The central part of the retina slowly degenerates, so the middle of vision fades and distorts while the edges stay. Reading and faces go first. The slow form has no restorative treatment.

Measured. Macular degeneration in both forms accounts for **8 million** people with distance vision impairment or blindness, a modelled estimate. The dry form is the large majority by case count, commonly reported as about 80 to 90 per cent of cases, with the wet form the minority but historically the greater cause of rapid severe loss.

A dedicated Global Burden of Disease analysis of macular degeneration with forecasts to 2050 exists and could not be retrieved. The disease is strongly age-related, uncommon before 55 and rising steeply after 75†, with higher reported prevalence in populations of European ancestry. Burden is rising with ageing populations.

Where it starts.

- **Age** — dominant.
- **Smoking** — the strongest modifiable factor; roughly doubles to triples risk, dose-related, and risk falls after cessation.
- **Genetics** — complement factor H Y402H and ARMS2/HTRA1 variants carry large effect sizes, among the largest known for a common complex disease.
- **European ancestry**.
- **Family history**.
- **Hypertension, obesity, low dietary carotenoid intake** — associated, weaker.

Genuinely not known: why drusen form, and why some eyes progress to geographic atrophy while others remain stable for decades. The complement pathway is clearly implicated by genetics, yet complement-inhibiting drugs have produced only modest slowing of atrophy growth and no visual benefit, so the link from genotype to treatable mechanism is incomplete. There is no way to predict which eye will progress.

Cure status. RELIEF ONLY. Nothing restores lost central vision, and until recently nothing slowed it. Complement inhibitors — pegcetacoplan, avacincaptad pegol — have been licensed in some jurisdictions for geographic atrophy on the basis of slowed lesion growth on imaging, without a demonstrated visual acuity benefit. Slowing a measured lesion is not restoration. Supplements slow progression in intermediate disease and restore nothing.

What helps function is magnification, lighting, large print and eccentric-viewing training. These are rehabilitation and not treatment. The World Health Organization states that vision rehabilitation is very effective in improving functioning for people with irreversible vision loss.

Prevention.

- **Smoking cessation.** The single most effective measure; smoking roughly doubles to triples risk. **STRONG** — consistent, dose-related, reversible on cessation.
- **The AREDS2 supplement formulation** — vitamin C, vitamin E, zinc, copper, lutein, zeaxanthin — in people with *intermediate* disease or advanced disease in one eye. Reduced five-year progression to advanced disease by about **25 per cent** relative†. **MODERATE**, and only for that group: it has not been shown to prevent macular degeneration in people without it. Beta-carotene in the original formula raised lung cancer risk in smokers and was removed in AREDS2.
- **Mediterranean-type diet, higher leafy green and fish intake.** Observational only. **WEAK**.
- **Blood pressure control. WEAK**.
- **Sun protection or ultraviolet avoidance for this condition specifically. CONTESTED**; the evidence is much weaker than for cataract and pterygium.

Treatment.

1. **AREDS2 supplements**, for intermediate disease only; about a 25 per cent relative reduction in five-year progression†. Not on the Essential Medicines List. Off-patent as a vitamin and mineral combination. Roughly **US$10 to 30 per month** in retail markets†.
2. **Complement inhibitors for geographic atrophy — pegcetacoplan, avacincaptad pegol.** Slow lesion growth; no acuity benefit demonstrated; monthly or two-monthly intravitreal injections. Not listed, on-patent, in the thousands of US dollars per injection.
3. **Low-vision rehabilitation, magnification, lighting, large print, eccentric viewing training.** Not a medicine. Cheap, and effective for function.
4. **Smoking cessation support** — the only intervention that addresses the cause.

Simple means. This is a condition where simple means do nearly all of the available good, because the industrial options do so little.

- **Smoking cessation.** No supply chain. The largest modifiable effect on incidence.
- **Good task lighting and a hand magnifier.** A magnifier costs a few US dollars and restores reading for many people with moderate central loss. No effect size was sourced here, and the World Health Organization states that rehabilitation is very effective in improving functioning for people with an irreversible vision loss.
- **Large-print and high-contrast materials, and Amsler grid self-monitoring** on a printed sheet, to catch conversion to the wet form early enough for anti-VEGF treatment to matter. Printing cost only.

No simple means slows dry macular degeneration itself beyond stopping smoking and, in intermediate disease, a supplement. The chain for the disease-modifying drugs requires intravitreal injection in a sterile setting, monthly, indefinitely.

Gaps. The 8 million figure covers both forms and cannot be split from that source. The dedicated burden analysis with 2050 forecasts could not be retrieved, so no trend or projection figures are carried. The 80 to 90 per cent dry share is widely reported and unsourced here. The AREDS effect sizes come from reports that could not be read. Whether slowed geographic atrophy lesion growth will ever translate into preserved vision is unresolved, and it is the central dispute in the field.

> **Depth.** Starts in: a pigment-epithelium cell of the retina. Size: 15 µm†; depth +5.28. First complaint: about 75 years († onset about age 75); time depth 52.80. One untreated course: no number ([B] slow).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Retinal cells that died do not regrow. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Age-related macular degeneration — wet (neovascular)

What it is. New leaky blood vessels grow under the central retina, and fluid and blood lift and scar it. Central vision can be lost in weeks, much faster than in the dry form. Injections into the eye can stop it and sometimes recover some sight.

Measured. Included in the **8 million** macular degeneration figure. The wet form is the minority of cases and historically caused the majority of severe rapid central vision loss. Anti-VEGF intravitreal injection is one of the highest-volume procedures in medicine in high-income health systems. Age pattern and geography follow the dry form. Incidence is rising with ageing, while blindness from the wet form has fallen in countries with anti-VEGF access, with reported declines in attributable blindness registrations after its introduction.

Where it starts. The same risk set as the dry form, from which it usually develops: age, smoking at roughly two to three times risk, complement factor H and ARMS2/HTRA1 variants, European ancestry, family history†. The specific step is pathological choroidal neovascularisation driven by vascular endothelial growth factor, which is why blocking that factor works, and works quickly.

Genuinely not known: what triggers conversion from dry to wet in a given eye at a given time. No predictive test exists. Why some eyes become treatment-resistant, and why a proportion develop fibrosis

and atrophy despite perfectly suppressed exudation, is not understood. The long-term consequence of years of VEGF suppression on the retina is not fully characterised, and the CATT five-year data showed substantial net decline despite treatment.

Cure status. CONTROLLABLE. Anti-VEGF injections stop the leakage, usually improve vision initially, and prevent the catastrophic rapid loss that was the natural history. They do not remove the disease: the eye needs repeat injections for years, and stopping usually allows recurrence.

The long-term picture is measured. CATT at five years: of 914 living participants, 647 (71 per cent) had acuity measured at a mean of 5.5 years. Mean visual acuity was **3 letters worse than baseline** and **11 letters worse than at two years**, with half of eyes at 20/40 or better. Treatment converts a disease that blinded rapidly into one that declines slowly under continued treatment. That is a major gain and it is not a cure.

Prevention.

- **Smoking cessation. STRONG**.
- **AREDS2 supplements in intermediate disease, or advanced disease in the fellow eye.** About a 25 per cent relative reduction in five-year progression to advanced disease. **MODERATE**.
- **Amsler grid or other self-monitoring, with prompt presentation on new distortion.** Prevents irreversible loss by getting treatment started early, since outcomes depend heavily on baseline acuity. **MODERATE**. This prevents blindness rather than disease, and it costs a printed sheet.
- **Treating the fellow eye's risk factors** once one eye is affected. **MODERATE**.

Treatment. This is the major documented cost case in the chapter. Both the efficacy comparison and the price gap are measured.

1. **Bevacizumab, intravitreal, repackaged.** In CATT — 1,208 participants, 44 centres — bevacizumab and ranibizumab given on the same schedule had **equivalent effects on visual acuity** at one year, and similar effects at two years. The proportion losing at least 15 letters and the proportion gaining at least 15 letters were the same across groups.

Safety in CATT: serious adverse events were **40 per cent** with bevacizumab against **32 per cent** with ranibizumab. Both figures belong in print, and so does the trial's own observation about them: the events were spread across many unrelated conditions, and **fewer doses were associated with a higher serious-adverse-event rate**, which is not a dose-response pattern. There was no difference in death or in arteriothrombotic events.

At five years, the group originally assigned to ranibizumab for two years had lost 4 **more** letters than the bevacizumab group between years two and five, p=0.008, with no other significant drug or regimen differences.

Bevacizumab is the Essential Medicines List anti-VEGF agent. Off-patent, with biosimilars available. **Cost: tens to hundreds of US dollars per dose**. 2. **Ranibizumab, intravitreal.** Licensed for the indication, with efficacy equivalent to bevacizumab in CATT. Not the listed anti-VEGF entry; bevacizumab is the listed item. Biosimilars now exist. **Cost: thousands of US dollars per dose**. 3. **Aflibercept, intravitreal.** Comparable efficacy with potentially fewer injections; priced in the same range as ranibizumab. Not listed. Biosimilars entering. 4. **Monthly against as-needed dosing.** CATT found monthly slightly better than as-needed, by about half a line on the eye chart, for either drug. 5. **Photodynamic therapy and laser.** Largely superseded.

The price gap, as documented: bevacizumab at about **tens to hundreds of US dollars** per dose against ranibizumab at about **thousands of US dollars** per dose — a ratio of roughly **20- to 40-fold** for drugs that CATT found equivalent in visual outcome. The CATT investigators' conservative estimate of the differential was **US$26,800 per patient per year**, with potential United States Medicare savings of up to **US$3 billion per year**. Bevacizumab is the listed agent, and it is the one that is off-patent and cheap. That the expensive drugs retain large market share is a fact of the field and not a clinical finding.

Simple means. Limited, and the limit should be stated.

- **An Amsler grid on paper** for self-monitoring. It costs a printed sheet, and getting a patient treated weeks rather than months after conversion materially changes the outcome, because final acuity tracks baseline acuity.
- **Repackaged bevacizumab** is the nearest thing to a simple means in the treatment itself. A single vial intended for oncology can be split into many intravitreal doses, which is what brings the per-dose cost to tens to hundreds of US dollars or below. It requires a sterile compounding facility; the historical cluster endophthalmitis outbreaks from poorly controlled repackaging are why this cannot be done casually.
- **Low-vision rehabilitation, magnifiers and lighting** for established loss.

What the chain minimally requires: a sterile procedure room, a trained injector, an operating microscope or slit lamp, cold-chain drug storage, imaging for monitoring, and a patient who returns every 4 to 12 weeks for years. This is not a simple-means condition. The drug can be made cheap; the delivery cannot be made simple.

Gaps. Wet disease cannot be separated from dry in the 8 million figure. CATT's serious-adverse-event finding, 40 against 32 per cent, is a real result with a disputed interpretation, and the trial itself recorded that it did not follow a dose-response pattern; sources genuinely disagree on whether bevacizumab carries excess systemic risk, and both readings are printed. The cost figures are CATT-era United States prices, and biosimilar entry has changed ranibizumab and aflibercept prices since; current figures were not obtainable. Long-term outcomes beyond five years under modern treat-and-extend regimens are not established.

> **Depth.** Starts in: a new vessel under the retina. Size: 100 µm†; depth +7.00. First complaint: about 75 years († onset about age 75); time depth 52.80. One untreated course: about 3.4 weeks ([B] central sight lost in weeks); depth 46.39.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Diabetic retinopathy

What it is. High blood sugar damages the small blood vessels of the retina. They leak, close off, and new fragile vessels grow that bleed and pull the retina away. It is silent until late, which is why screening matters.

Measured. 3.9 million people have distance vision impairment or blindness from diabetic retinopathy, a modelled estimate.

The denominator is **830 million** people with diabetes in 2022, up from 200 million in 1990, and **14 per cent** of adults aged 18 and over, up from 7 per cent in 1990 (World Health Organization fact sheet, *Diabetes*, 14 November 2024). Prevalence is rising faster in low- and middle-income countries. That is the all-ages figure. Other chapters of this book use the International Diabetes Federation figure of **589 million adults aged 20 to 79**† as their denominator, and the two give substantially different global figures; attributable burden computed on one is not comparable with attributable burden computed on the other. Both stand, unresolved.

The diabetes fact sheet gives no figure for how many people with diabetes have retinopathy. Duration of diabetes is the dominant determinant, so retinopathy prevalence rises with years since diagnosis rather than with age alone. The burden is rising, driven by the denominator, and diabetic retinopathy is a leading cause of vision loss in working-age adults in high-income countries. The World Health Organization states that for this condition early detection and timely treatment are crucial to avoid irreversible vision loss.

Where it starts.

- **Duration of diabetes** — the strongest predictor.
- **Glycaemic control.** The Diabetes Control and Complications Trial in type 1 diabetes found intensive control reduced retinopathy onset by about **76 per cent** and progression by about **54 per cent** against

conventional control; the United Kingdom Prospective Diabetes Study in type 2 found intensive control reduced microvascular endpoints by about **25 per cent**†. These are among the largest effect sizes in chronic disease prevention.

- **Blood pressure.** Tight control reduced retinopathy progression in that study.
- **Dyslipidaemia.** Fenofibrate reduced progression in the FIELD and ACCORD-Eye trials.
- **Pregnancy, puberty, renal disease, anaemia** — accelerate progression.
- **Rapid tightening of long-standing poor control** can cause transient early worsening.

Genuinely not known: why some people with decades of poor control never develop sight-threatening retinopathy and others progress quickly with modest hyperglycaemia. Duration and glycated haemoglobin together explain only part of the variance. The relative contributions of neurodegeneration and vascular change, and which comes first, are disputed. There is no test that identifies the patient who will progress.

Cure status. CONTROLLABLE. Treatment prevents further loss and in macular oedema often recovers vision; it does not remove the retinopathy, and photoreceptors already lost do not return.

Panretinal photocoagulation is the clearest result: the Diabetic Retinopathy Study found laser reduced severe vision loss in proliferative retinopathy by about **50 per cent** or more†. That is prevention of blindness in an eye that already has advanced disease — control, not cure. Laser also destroys peripheral retina deliberately, costing peripheral and night vision to save central vision. Anti-VEGF for diabetic macular oedema improves acuity, often substantially, and requires repeated injection. The disease is driven by the underlying diabetes, which is itself CONTROLLABLE and not curable, so the retinopathy cannot be more than controlled.

Prevention. This is one of the strongest prevention stories in the chapter.

- **Glycaemic control.** About **76 per cent** reduction in retinopathy onset and **54 per cent** in progression in type 1; about **25 per cent** reduction in microvascular endpoints in type 2†. **STRONG**.
- **Blood pressure control. MODERATE**.
- **Systematic retinopathy screening with treatment of what is found.** The intervention that converts a silent blinding disease into a managed one. The English diabetic eye screening programme is credited with diabetic retinopathy ceasing to be the leading cause of certifiable blindness in working-age adults in England, for the first time in at least five decades. **STRONG** for blindness prevention. Screening interval annually, or every two years in low-risk screen-negative people.
- **Fenofibrate.** Reduced progression in FIELD and ACCORD-Eye. **MODERATE**.
- **Smoking cessation. MODERATE**.

Treatment.

1. **Panretinal photocoagulation for proliferative retinopathy.** About a 50 per cent or greater reduction in severe vision loss†. A procedure, not listed, and the technique is unpatented. Cost: a laser plus an operator — and **one or a few sessions, then no maintenance**, which makes it far more robust than injections in low-resource settings.
2. **Anti-VEGF injection for diabetic macular oedema.** Superior to laser for central oedema. **Bevacizumab is on the Essential Medicines List**, off-patent, at about **tens to hundreds of US dollars per dose**, against ranibizumab at about **thousands of US dollars per dose**. The DRCR Protocol T comparison found aflibercept better at worse baseline acuity, with the three agents similar at better baseline acuity, and the associated cost-effectiveness analysis found bevacizumab the most cost-effective.
3. **Focal or grid macular laser.** Cheaper, one-off, now second-line for centre-involving oedema.
4. **Intravitreal corticosteroids — triamcinolone, dexamethasone implant.** For anti-VEGF non-responders; cause cataract and raise pressure.
5. **Vitrectomy** for vitreous haemorrhage and tractional detachment.
6. **Glycaemic, blood pressure and lipid control.** Metformin, insulin, ACE inhibitors, statins and amlodipine are all on the Essential Medicines List and all off-patent, at cents per day.

Simple means.

- **Screening with a hand-held or smartphone-based fundus camera, images read remotely or by a trained non-specialist grader.** This is the key low-cost move, because it removes the need for an ophthalmologist at the point of screening. Diagnostic accuracy of smartphone-based and non-mydriatic camera screening is adequate for referral triage, and automated grading systems are licensed in several jurisdictions.
- **Direct ophthalmoscopy through a dilated pupil by a trained health worker.** Needs an ophthalmoscope and tropicamide drops only, with lower sensitivity than photography.
- **Laser photocoagulation** is itself a simple means in an important sense: it requires capital equipment but **no consumables, no cold chain and no repeat visits for years** — one or a few sessions per eye. In a setting that cannot sustain monthly injections for a decade, laser is the intervention that actually works.
- **Glycaemic control with off-patent metformin and insulin**, both listed, at low cost.

The cheap intervention here is finding the disease, and the cheap treatment is laser. Both are available without a pharmaceutical supply chain.

Gaps. No figure exists on the sources read for what proportion of the 830 million people with diabetes have retinopathy, or sight-threatening retinopathy — a notable absence given that the denominator is published. The 3.9 million figure covers vision impairment and blindness only, not retinopathy prevalence. The trial effect sizes could not be verified against their primary reports. Optimal screening intervals differ between national programmes. The real-world performance of automated grading outside validation datasets is not established.

> **Depth.** Starts in: a retinal capillary. Size: 10 µm†; depth +4.91. First complaint: about 10 years († about 10 years of diabetes); time depth 50.97. One untreated course: no number ([B] silent until late).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Trachoma

What it is. A blinding eye disease. Repeated infection with a bacterium, *Chlamydia trachomatis*, is spread by flies, fingers and shared cloths. Years of infection scar the inner eyelid until the lashes turn inwards and scrape the cornea. The scraping blinds, and that blindness is preventable at every stage before it.

ICD-11 codes trachoma in chapter 1, among the infectious diseases, because it is an infection. The full entry is there, under Trachoma, in the chapter on certain infectious or parasitic diseases.

A reader in the eye chapter is sent there for a reason that concerns the eye. The cure status differs by stage. The infection is curable, and so is the in-turned eyelid once it is corrected by surgery. The corneal opacity and blindness already caused are not reversible. One label cannot hide that difference. The entry in chapter 1 states it, with the measured burden, the SAFE strategy, the treatments and the simple means.

Retinitis pigmentosa and inherited retinal dystrophies

What it is. A group of inherited conditions in which the retina's light-sensing cells die off over years. Night vision and the edges of sight usually go first, narrowing to tunnel vision. Most forms have no treatment that stops them.

Measured. No global prevalence figure was retrievable, and inherited retinal dystrophies do not appear as a line in the published cause breakdown. Retinitis pigmentosa prevalence is commonly reported at about **1 in 4,000**, giving on the order of 1.5 to 2 million people worldwide†. Inherited retinal dystrophies are collectively the leading cause of blindness certification in working-age adults in England, having overtaken diabetic retinopathy. Onset ranges from childhood to middle age depending on genotype, and the course is progressive throughout life. Prevalence is higher in populations with high consanguinity.

Where it starts.

- **Single-gene mutations.** Over 280 genes are implicated across inherited retinal dystrophies†. Inheritance is autosomal recessive, autosomal dominant, X-linked or mitochondrial depending on the gene.
- **Consanguinity** — raises the prevalence of recessive forms.

There are no established environmental or lifestyle risk factors for onset. This is a genetic disease in the strict sense.

Genuinely not known: why the same mutation produces very different severity and age of onset between family members. Modifier genes are suspected and largely unidentified. In a substantial minority of patients — commonly cited as around 30 to 40 per cent — no causative mutation is found even on full gene panel testing. Whether photoreceptor death can be slowed by any general measure is unresolved.

Cure status. RELIEF ONLY. For almost all patients nothing stops the degeneration and nothing restores lost vision.

One narrow exception exists. **Voretigene neparvovec**, a gene therapy for biallelic RPE65 mutation-associated retinal dystrophy, improved functional vision on a multi-luminance mobility test in its pivotal trial and is licensed. RPE65 disease is a very small fraction of all inherited retinal dystrophy, the benefit is improvement rather than normalisation, and durability beyond several years is not established. It was priced on licensing at roughly **hundreds of thousands of US dollars per eye**, or hundreds of thousands of US dollars per patient.

Retinal prostheses produced crude light perception; one such product was withdrawn commercially, leaving implanted patients without support. RELIEF ONLY is the honest classification for the condition group, with one licensed gene therapy for one rare genotype.

Prevention.

- **Genetic counselling and carrier testing** in affected families. This prevents transmission rather than disease in an affected person. **STRONG** for that purpose, where available and acceptable.
- **Avoiding consanguineous marriage** reduces recessive disease incidence at population level. **MODERATE**, and a matter of social practice rather than clinical intervention.
- **Vitamin A palmitate** was proposed to slow progression; the evidence is weak, it carries hepatotoxicity risk, and it is contraindicated in ABCA4-related disease where it may accelerate harm†. **CONTESTED**.
- **Sunglasses or blue-light protection.** Plausible, unproven. **WEAK**.

Nothing prevents the disease in a person carrying the mutation.

Treatment.

1. **Low-vision rehabilitation, orientation and mobility training, white cane, screen readers, magnification.** The mainstay for the great majority. Not medicines. The World Health Organization states that rehabilitation is very effective in improving functioning for people with irreversible vision loss.
2. **Voretigene neparvovec** for biallelic RPE65 disease. Not listed, on-patent, about **hundreds of thousands of US dollars per patient**.
3. **Cataract surgery.** Posterior subcapsular cataract is common in retinitis pigmentosa and removing it can give a useful gain.
4. **Treatment of cystoid macular oedema** with carbonic anhydrase inhibitors — acetazolamide, which is listed — or intravitreal steroid.
5. **Genetic diagnosis.** Now the gateway to trial eligibility, and so part of standard management even where no treatment follows.

Simple means. Almost everything that helps these patients is low-technology, because the high-technology options barely exist.

- **A white cane and mobility training.** Transforms independent travel. Negligible cost.
- **Task lighting, high-contrast marking of steps and door frames, magnification.**
- **Screen readers and text-to-speech**, now standard and free on ordinary phones — a substantial functional gain at zero marginal cost.
- **Braille literacy** where appropriate.
- **Genetic counselling**, which needs trained counsellors but no laboratory where a family history is available.

There is no simple means that affects the disease. The minimum chain for the one licensed disease-modifying therapy is genetic sequencing, a subretinal surgical delivery service, and hundreds of thousands of US dollars — which places it outside the reach of almost every patient who has the condition.

Gaps. No global prevalence estimate was obtainable. The 1-in-4,000 figure is widely cited and unsourced here. The proportion of patients with no identified mutation varies by population and panel. Long-term durability of voretigene neparvovec is unknown. Whether the many gene therapies in trial will generalise beyond rare genotypes is unresolved. Sources disagree on whether vitamin A supplementation slows retinitis pigmentosa; both the positive and negative readings exist and neither could be verified.

> **Depth.** Starts in: a photoreceptor protein (single gene). Size: 10 nm†; depth −1.38. First complaint: about 21 years († from conception to first night-blindness at about age 20); time depth 51.63. One untreated course: no number ([B] over years).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Retinal detachment

What it is. The retina peels away from the back of the eye. Floaters, flashes and then a dark curtain across the vision. It blinds the eye within days to weeks if the retina is not put back, and putting it back is a surgical emergency.

Measured. No global prevalence or incidence figure was retrievable, and retinal detachment is not a line in the published cause breakdown. Annual incidence of rhegmatogenous detachment is commonly reported at about **10 to 18 per 100,000** population per year†. There is a peak in the 50s to 70s, with a second younger peak in high myopes and after trauma†. Incidence tracks myopia prevalence and cataract surgery volume, both of which raise risk, so rising myopia in East Asia implies rising detachment incidence.

Where it starts.

- **High myopia** — the major risk factor; risk rises steeply with axial length. This connects directly to the myopia entry: the detachment risk is a consequence of the long eye that spectacles correct optically and do not change.
- **Posterior vitreous detachment** — the usual precipitant, tearing the retina as the vitreous separates.
- **Prior cataract surgery** — raises risk several-fold, more so after capsule rupture.
- **Ocular trauma**.
- **Lattice degeneration, retinal breaks, family history, prior detachment in the fellow eye**.
- **Age**.

Genuinely not known: why most posterior vitreous detachments cause no retinal tear and a few do. Which asymptomatic retinal breaks need prophylactic treatment is unsettled, and prophylactic laser to lattice degeneration has not been shown in randomised trials to prevent detachment.

Cure status. CURABLE. A detached retina is reattached in about **85 to 90 per cent** of cases with one operation, and in over **95 per cent** with more than one†. The anatomical problem is fixed permanently and the eye does not re-detach in most cases.

The qualification that must be stated: visual recovery depends on whether the macula had detached and for how long. A macula-on detachment repaired promptly usually keeps good vision. A macula-off detachment

of some weeks leaves permanent central loss even after perfect anatomical reattachment. The disease is curable and the *timing* determines whether the sight is saved, which makes this a condition where access speed, not technology, decides the outcome.

Prevention.

- **Prompt assessment of new floaters, flashes or a visual field shadow**, so that a retinal tear is found and treated with laser before it detaches. **MODERATE** for preventing detachment in symptomatic patients. It costs a dilated examination.
- **Laser or cryotherapy to a symptomatic retinal tear.** Prevents progression to detachment. **STRONG** for that specific lesion.
- **Prophylactic laser to asymptomatic lattice degeneration. CONTESTED**; not supported by randomised evidence.
- **Myopia control in childhood.** Reduces adult axial length and should therefore reduce lifetime detachment risk, and this has never been demonstrated as an outcome. **WEAK** — mechanistically expected, not measured.
- **Eye protection in hazardous work and sport.** Prevents traumatic detachment. **MODERATE**.

Treatment.

1. **Pars plana vitrectomy with gas or oil tamponade.** The dominant modern operation, with 85 to 90 per cent single-operation success†. A procedure, not listed. Requires a vitrectomy machine and consumables.
2. **Scleral buckle.** A silicone band sutured around the eye, with comparable success and particularly good results in younger phakic patients, and **no machine required** beyond an operating microscope and cryotherapy. Not listed.
3. **Pneumatic retinopexy.** A gas bubble injected in the clinic plus cryotherapy or laser, with head positioning. Lower single-operation success than vitrectomy and by far the lowest-resource option — a needle, a gas cylinder and positioning.
4. **Laser or cryotherapy retinopexy** for a tear without detachment. Cheap, one-off, definitive for that lesion.

Simple means. Partly simple, and worth distinguishing from the rest of the chapter.

- **Dilated fundus examination with an indirect ophthalmoscope** finds the tear. The equipment is a lens and a headset light; the cost is training.
- **Cryotherapy retinopexy** needs a cryoprobe and a gas cylinder, no laser.
- **Pneumatic retinopexy** is the closest thing to a simple-means repair: an intravitreal gas injection, retinopexy, and strict head positioning by the patient. It can be done without a vitrectomy suite.
- **Scleral buckling** needs no vitrectomy machine — sutures, a silicone band, a microscope, cryotherapy.
- **Public and primary-care knowledge that a curtain across the vision is an emergency today, not next month.** This costs a message, and it determines whether the macula is still attached when the patient arrives. Given that macula-off duration decides final vision, it is the highest-value zero-cost intervention in the entry.

What the chain minimally requires: an operating theatre, a microscope, a cryoprobe or laser, and a surgeon trained in retinal repair. There is no non-surgical means of reattaching a retina.

Gaps. No global incidence or prevalence figure was obtainable; the 10 to 18 per 100,000 range is widely cited and unverified. Reattachment success rates vary with case mix and were not sourced to a registry. Whether prophylactic treatment of asymptomatic lesions helps is genuinely disputed. The expected effect of the myopia epidemic on future detachment incidence has not been quantified in any source read.

> **Depth.** Starts in: a retinal tear. Size: 1 mm†; depth +9.10. First complaint: about 1 second († complaints directly after the tear); time depth 33.15. One untreated course: about 8 days ([B] blind within days to weeks); depth 45.39.

> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Amblyopia and strabismus

What it is. In strabismus the two eyes do not point the same way. In amblyopia one eye's vision never develops properly because the brain learned to ignore it in early childhood. Treated young it recovers; left past childhood it does not.

Measured. Neither appears as a line in the published cause breakdown and no global figure was retrievable. Amblyopia prevalence is commonly reported at about **1 to 4 per cent** of children, and strabismus at about **2 to 4 per cent**†.

Age is the critical determinant. Visual development is plastic until roughly age **7 to 8** and treatment response falls steeply after that†. Prevalence is similar across populations; *treated* prevalence is not, and where vision screening and spectacles are unavailable amblyopia is permanent. Amblyopia is a leading cause of monocular vision loss in adults worldwide.

Where it starts.

- **Uncorrected refractive error, especially anisometropia** — unequal refraction between the eyes — and significant hyperopia. The commonest cause, linking directly to the hyperopia entry.
- **Strabismus** — the deviating eye is suppressed.
- **Visual deprivation** — congenital cataract, ptosis, corneal opacity. The most severe and most urgent form.
- **Prematurity, low birth weight, maternal smoking, family history** — associated with strabismus.

Genuinely not known: why some children with significant anisometropia never become amblyopic. The cortical basis of suppression, and why plasticity closes when it does, are not fully described. Whether adult amblyopia can be reopened to treatment is unresolved; current evidence shows small gains at best.

Cure status. Treated within the plastic period: CURABLE. Treated after it closes: RELIEF ONLY.

This is the sharpest age dependency in the book. Within the plastic period, amblyopia is genuinely curable: spectacle correction alone resolves a substantial proportion of cases, and patching or atropine penalisation resolves much of the rest. The eye reaches normal or near-normal acuity and keeps it.

After the critical period closes, no intervention restores normal acuity in an adult amblyopic eye. Strabismus surgery in an adult can realign the eyes — a real functional and social gain, and sometimes it restores binocularity — and it does not restore the amblyopic eye's acuity. The determinant of outcome is therefore the age at which the child is found, which makes screening the whole intervention.

Prevention.

- **Preschool vision screening around age 3 to 5, followed by spectacle correction and amblyopia treatment.** This is the intervention: it converts a permanent monocular disability into a treated condition. **MODERATE**; national screening bodies differ on the optimal age and method, which is why it is not graded STRONG uniformly.
- **Treating congenital cataract and ptosis urgently in infancy.** Prevents deprivation amblyopia. **STRONG**.
- **Correcting significant childhood hyperopia and anisometropia. STRONG**.
- **Photoscreening devices usable by non-specialists** for detection at scale. **MODERATE**.

Treatment.

1. **Spectacle correction alone, given time** — refractive adaptation. This resolves a substantial share of amblyopia before any patching is added, and the Amblyopia Treatment Studies established that spectacles alone should be tried first. A device, not listed.

2. **Patching the better eye.** The Amblyopia Treatment Studies found **2 hours** of daily patching as effective as 6 hours, and part-time as effective as full-time in moderate amblyopia. Cost: an adhesive patch, cents.
3. **Atropine 1 per cent penalisation of the better eye.** As effective as patching in moderate amblyopia, with better adherence in some children. **Atropine is on the Essential Medicines List** as an ophthalmological mydriatic. Off-patent. Cents to a few dollars per bottle, and one bottle lasts months.
4. **Strabismus surgery.** Realigns the eyes, may restore binocularity if performed early, and gives a substantial cosmetic and social benefit at any age. A procedure, not listed.
5. **Botulinum toxin** as an alternative to surgery in selected strabismus.
6. **Prism spectacles** for small deviations and diplopia.

Simple means. This is one of the strongest cheap-intervention entries in the book, and it is underused.

- **A vision chart and a trained screener.** Detecting amblyopia needs a letter or picture chart, an occluder and someone trained for an afternoon. Capital cost: a printed chart.
- **Spectacles** at roughly **a few US dollars per pair** in low-cost programmes — and spectacles alone cure a substantial fraction of amblyopia if given early enough.
- **An adhesive eye patch** costs cents, and 2 hours a day suffices in moderate amblyopia† — a finding that cut treatment burden by two-thirds at no cost.
- **Atropine drops**, listed, off-patent, cents per bottle, as an alternative to patching with equivalent effect in moderate amblyopia.
- **The cover test** for strabismus detection: an occluder and an examiner’s eye. Free.

A chart, a patch, a pair of spectacles and a bottle of atropine — a few US dollars in total — prevent a lifetime of monocular vision loss, and only if applied before about age seven. The binding constraint is not cost, it is finding the child in time. Strabismus surgery is the one component requiring a theatre.

Gaps. No global prevalence figure for either condition was obtainable, and neither appears in the published cause breakdown despite amblyopia being a leading cause of monocular vision loss. The 1 to 4 per cent prevalence figures are widely cited and unverified. The Amblyopia Treatment Studies effect sizes could not be verified against the primary reports. National screening bodies genuinely disagree on whether and when to screen preschool children, and have reached different conclusions from similar evidence. Whether adult amblyopia treatment can work is an open question with small positive trials and no established therapy.

> **Depth.** Starts in: the eyeball. Size: 2.4 cm†; depth +11.99. First complaint: about 3.8 years († from conception to early childhood); time depth 50.07. One untreated course: no number ([B] permanent after childhood).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Dry eye disease

What it is. The tear film does not keep the eye surface wet enough, either from too little tear or from tears that evaporate too fast. The eyes sting, burn, feel gritty and sometimes water paradoxically. It is chronic and it fluctuates.

Measured. No global figure was retrievable. The World Health Organization names dry eye among conditions that do not usually cause vision impairment but are treatable, with treatment relieving symptoms and preventing progression to more severe disease.

Reported prevalence varies enormously with definition, commonly **5 to 50 per cent** of adults depending on whether symptoms, signs or both are required. That spread is the central measurement problem in the condition. Prevalence rises with age and is substantially higher in women, particularly after the menopause, with higher reported prevalence in Asian populations. The trend is reported as rising, attributed to screen use and ageing.

Where it starts.

- **Age**.
- **Female sex and post-menopausal status**.
- **Meibomian gland dysfunction** — the commonest contributor; blocked lid oil glands let the tear film evaporate.
- **Screen use and reduced blink rate**.
- **Low ambient humidity, air conditioning, wind, air travel**.
- **Drugs** — antihistamines, anticholinergics, antidepressants, isotretinoin, diuretics, beta-blockers.
- **Autoimmune disease, especially Sjögren syndrome; graft-versus-host disease**.
- **Contact lens wear; prior refractive or cataract surgery**.
- **Vitamin A deficiency** — causes conjunctival and corneal drying; see that entry.

Genuinely not known: why symptoms and signs correlate so poorly. Many people with severe dryness on examination have no symptoms and the reverse also holds, which undermines both diagnosis and trial endpoints. The relative primacy of inflammation against tear deficiency against lid disease is disputed. Why the condition fluctuates is unexplained.

Cure status. RELIEF ONLY. Treatment relieves symptoms and protects the surface; nothing restores a damaged lacrimal gland or reverses established meibomian gland dropout. Gland loss visible on meibography is permanent, and the condition is managed indefinitely. In vitamin A deficiency dry eye the underlying cause is itself curable by repletion, which is the exception.

Prevention.

- **Avoiding or substituting causative drugs** where clinically possible. **MODERATE**.
- **Blink awareness and regular breaks during screen work**, and lowering screens below eye level to reduce exposed ocular surface area. **WEAK**.
- **Humidification, avoiding direct airflow at the face. MODERATE**.
- **Lid hygiene to prevent meibomian gland dropout. WEAK** for prevention of incident disease.
- **Omega-3 supplementation.** The DREAM trial found **no benefit** over placebo. **CONTESTED**, effectively negative.
- **Vitamin A sufficiency. STRONG** for the deficiency form specifically.

Treatment.

1. **Artificial tears and ocular lubricants.** First-line; relieve symptoms with no disease modification, with preservative-free formulations for frequent use. Not confirmed as a core item in the Essential Medicines List ophthalmological section displayed. Off-patent. A few US dollars per bottle, with preservative-free unit doses considerably more.
2. **Warm compresses and lid massage** for meibomian gland dysfunction. Free; see *Simple means*.
3. **Topical ciclosporin 0.05 per cent.** Reduces inflammation, with a modest effect and slow onset. Ciclosporin is listed as a systemic immunosuppressant and not as the ophthalmic preparation. Off-patent as a molecule; the licensed ophthalmic emulsion is expensive.
4. **Topical lifitegrast.** A similar role, on-patent, expensive.
5. **Punctal plugs.** Block tear drainage, retaining the tears the eye makes. Cheap, reversible, effective in aqueous-deficient disease.
6. **A short course of topical corticosteroid** for flares; betamethasone and other steroids are listed. Off-patent, cents to a few dollars. Not for long-term use.
7. **Autologous serum eye drops and scleral lenses** for severe disease.
8. **Oral doxycycline or azithromycin** for meibomian gland dysfunction and rosacea-associated disease; both listed, both off-patent, cents per day.

Simple means. Unusually good, because the mainstays are physical rather than pharmaceutical.

- **Warm compresses and lid massage.** A clean cloth and warm water, twice daily. This is the primary treatment for meibomian gland dysfunction, which is the commonest cause. Zero supply chain. No measured effect size was sourced.
- **Lid margin cleaning** with a clean cloth or a dilute mild shampoo.
- **Humidity and airflow management** — moving away from a fan or vent, a bowl of water in a dry room.
- **Blink breaks during close work.**
- **Protective wrap-around spectacles or a moisture chamber** reduce evaporation; ordinary sunglasses give part of this effect.
- **Simple artificial tears** at a few dollars a bottle; in severe aqueous deficiency, punctal occlusion is a minor office procedure with a cheap plug.

For the common form, warm water and a cloth are first-line therapy. The industrial chain is needed only for the anti-inflammatory drugs, which deliver modest additional benefit.

Gaps. This is the condition in the chapter with the weakest measurement base. No global prevalence figure exists on the sources read, and published prevalence ranges from about 5 to about 50 per cent depending entirely on case definition† — the sources do not disagree about the data so much as measure different things. Symptoms and signs correlate poorly, which means trial endpoints are contested and effect sizes are hard to compare. Omega-3 evidence is genuinely split: earlier positive observational and small-trial data against the null DREAM result, and the null result is the stronger evidence. No effect size for warm compresses could be sourced. The Essential Medicines List status of ocular lubricants could not be confirmed.

> **Depth.** Starts in: the meibomian gland. Size: 1 mm†; depth +9.10. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number ([B] chronic and variable).
>
> **Model reading.** Way of ending: supply from inside. Layer: mesh. By the rule it is held by supply. It ends only if the source is restored. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Conjunctivitis

What it is. The clear skin over the white of the eye becomes inflamed, so the eye is red, gritty and discharging. Most cases are viral or allergic and settle on their own. A few kinds are dangerous.

Measured. No global figure was retrievable; conjunctivitis is not a line in the published cause breakdown, and the World Health Organization names it among conditions that do not usually cause vision impairment. It is among the commonest reasons for primary-care and emergency eye presentation worldwide.

Neonatal conjunctivitis — ophthalmia neonatorum — from gonococcal or chlamydial infection is the form that blinds, and is the reason for universal neonatal ocular prophylaxis in many countries. Viral and bacterial forms concentrate in children and allergic forms follow atopy. Epidemic viral keratoconjunctivitis occurs in outbreaks, and adenoviral outbreaks are regularly reported in institutions.

Where it starts.

- **Adenovirus** — the commonest infectious cause, highly contagious via hands and shared surfaces.
- **Bacteria** — *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*.
- ***Neisseria gonorrhoeae* and *Chlamydia trachomatis*** — in neonates from the maternal genital tract, and in adults by autoinoculation. Gonococcal conjunctivitis can perforate a cornea within days.
- **Allergens** — seasonal and perennial allergic conjunctivitis.
- **Contact lens wear, poor hand hygiene, crowding, shared towels**.

Genuinely not known: clinical signs do not reliably distinguish viral from bacterial conjunctivitis, which is the direct cause of large-scale unnecessary antibiotic use, and no cheap point-of-care test has entered

routine use. Why some adenoviral infections cause prolonged subepithelial opacities and others resolve cleanly is unexplained.

Cure status. Viral: SELF-LIMITING — resolves in 1 to 3 weeks without treatment and no antiviral is indicated for adenovirus. Simple bacterial: SELF-LIMITING — the Cochrane review of topical antibiotics found most cases resolve without them, with antibiotics modestly speeding resolution. Gonococcal and chlamydial: CURABLE, and treatment is mandatory and urgent, because untreated gonococcal conjunctivitis perforates the cornea. Allergic: RELIEF ONLY — the atopic tendency persists.

The dominant cause is viral, so SELF-LIMITING is the single best answer for conjunctivitis as a whole, with the named exceptions treated as emergencies.

Prevention.

- **Hand hygiene and not sharing towels or face cloths.** Interrupts the main transmission route. **STRONG** for outbreak control. No supply chain beyond soap and water.
- **Neonatal ocular prophylaxis** with tetracycline 1 per cent or erythromycin 0.5 per cent eye ointment at birth. Prevents gonococcal ophthalmia neonatorum. **STRONG**.
- **Antenatal screening and treatment of maternal gonorrhoea and chlamydia. STRONG**.
- **Excluding infected children from school during the contagious phase. MODERATE/CONTESTED** — widely practised, limited evidence of benefit.
- **Allergen avoidance** for allergic forms. **MODERATE**.
- **Contact lens hygiene. MODERATE**.

Treatment.

1. **Nothing, plus hygiene advice and cool compresses**, for viral and most simple bacterial conjunctivitis. **The action is omission.** Cost: zero. This is the evidence-based first option and it is the one most often not taken.
2. **Topical antibiotics — chloramphenicol, tetracycline 1 per cent ointment, fusidic acid, azithromycin drops** — for bacterial conjunctivitis. They shorten illness modestly over placebo. **Azithromycin eye drops and tetracycline eye ointment are on the Essential Medicines List**. Off-patent, cents per tube.
3. **Systemic ceftriaxone plus azithromycin** for gonococcal conjunctivitis — urgent; both listed, both off-patent, low cost.
4. **Oral azithromycin or doxycycline** for adult chlamydial conjunctivitis — both listed, off-patent, under a dollar per course.
5. **Topical antihistamine or mast-cell stabiliser — olopatadine, sodium cromoglicate** — for allergic conjunctivitis. Sodium cromoglicate is off-patent and cheap.
6. **Topical corticosteroid.** Only under ophthalmic supervision, and contraindicated if herpes simplex keratitis is possible, where it can destroy the cornea.

Simple means. Nearly everything here is simple means.

- **Hand washing with soap**, and not sharing towels. The single most effective measure for the infectious forms.
- **Cool compresses and eye toilet with clean water** for symptomatic relief.
- **Not treating.** The action is omission. Withholding antibiotics in self-limiting disease is a zero-cost intervention with a real benefit — less cost, less resistance, the same outcome in most cases. It also saves money directly, since the antibiotic is not bought.
- **Tetracycline 1 per cent eye ointment at birth.** Cents per neonate, and it prevents gonococcal blindness. Listed, off-patent. This is one of the cheapest blindness-prevention interventions that exists.
- **Allergen avoidance and a cold compress** for allergic forms.

What the chain minimally requires: for the dangerous forms, an injectable cephalosporin and the clinical judgement to recognise them. For everything else, soap.

Gaps. No global incidence figure exists on the sources read for one of the commonest eye conditions in the world. The viral, bacterial and allergic proportions are not established and vary by setting and season. Clinical differentiation of viral from bacterial is unreliable and no deployable point-of-care test exists, so antibiotic prescribing rates far exceed bacterial prevalence. The Cochrane antibiotic effect sizes could not be verified. Whether school exclusion achieves anything is disputed.

> **Depth.** Starts in: adenovirus. Size: 90 nm†; depth +0.62. First complaint: about 7.7 days († 5–12 days); time depth 45.36. One untreated course: about 12 days ([B] usually clears by itself; † 1–3 weeks); depth 45.76.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Keratitis and corneal opacity

What it is. Keratitis is inflammation or infection of the cornea, the clear window at the front of the eye.

If it scars, the window goes cloudy and sight is permanently reduced. It can destroy an eye in days.

Measured. Corneal opacity is named as a cause of blindness and no count is given on the World Health Organization fact sheet; no global figure was retrievable. India’s national survey in 2023 found about **880,000** people with avoidable blindness from corneal opacities.

Onchocerciasis contributes. Global Burden of Disease estimated **1.15 million** people with vision loss from onchocerciasis and **14.6 million** with onchocercal skin disease, on 2017 estimates (World Health Organization fact sheet, *Onchocerciasis*, 4 December 2025). **252.3 million** people required preventive treatment in 2024, and **171.6 million** were reached across **26** reporting countries. **More than 99 per cent** of infected people are in Africa and Yemen, with the remaining 1 per cent on the Brazil–Venezuela border, and treatment must continue **10 to 15 years** to stop transmission.

Trachoma contributes about **1.9 million** people with blindness or visual impairment; the end stage of trachoma is corneal opacity.

Microbial keratitis affects all ages, and agricultural trauma concentrates in working-age men in low-income settings. Fungal keratitis is far more common in tropical agricultural regions, while in high-income countries contact-lens-related bacterial keratitis dominates.

Where it starts.

- **Corneal trauma, especially agricultural injury with vegetable matter** — the dominant cause in low-income rural settings, and the entry point for fungal keratitis.
- **Contact lens wear**, especially overnight wear and poor hygiene — the dominant cause in high-income settings; *Pseudomonas* and *Acanthamoeba*.
- **Herpes simplex virus** — recurrent, and a leading infectious cause of corneal blindness in high-income countries.
- **Herpes zoster ophthalmicus**.
- **Vitamin A deficiency** — keratomalacia, in which the cornea melts. See that entry.
- **Measles** — a major historic and continuing cause of corneal blindness in children, acting with vitamin A deficiency. Measles killed **95,000** people in 2024, mostly children under five, down from 780,000 in 2000, and vaccination averted nearly **59 million** deaths between 2000 and 2024 (World Health Organization fact sheet, *Measles*, 15 July 2026). The fact sheet directs two doses of vitamin A to every suspected case under five, and a third dose 4 to 6 weeks later if there are eye complications.
- **Trachoma and onchocerciasis** — as above.
- **Ophthalmia neonatorum** — gonococcal perforation.
- **Topical corticosteroid use in undiagnosed herpetic or fungal keratitis**, and **traditional eye medicines**. The World Health Organization names unsafe traditional medicines and unsafe self-administered topical treatments among preventable causes of vision loss.

Genuinely not known: why some corneal ulcers scar centrally and densely while similar ulcers heal clear. Why herpes simplex reactivates when it does. The optimal role of adjunctive corticosteroid in bacterial keratitis is unsettled — the Steroids for Corneal Ulcers Trial found no overall benefit with a possible benefit in subgroups with worse baseline vision.

Cure status. The infection: CURABLE. The resulting opacity: RELIEF ONLY.

The split is the whole story. Active microbial keratitis is curable — appropriate intensive topical antimicrobials eradicate most bacterial and many fungal infections. The scar they leave is not reversible by any medical means. Established corneal opacity is restored only by **corneal transplantation**, which is genuinely restorative — penetrating and endothelial keratoplasty can return normal vision — and depends on an eye bank, a surgical service and lifelong graft surveillance, with graft survival falling over time, especially in inflamed or vascularised eyes.

Cure the infection early and there is no opacity. Arrive late and the available answer is a transplant that most of the affected world cannot reach.

Prevention. Prevention is overwhelmingly more effective than treatment here.

- **Eye protection in agriculture and industry. MODERATE**, and essentially free.
- **Prompt topical antibiotic prophylaxis after corneal abrasion.** Village-level programmes in Nepal, Bhutan and Myanmar reported large reductions in ulcer incidence after training village health workers to treat corneal abrasions with topical antibiotic ointment. **MODERATE**, and one of the most important cheap interventions in the chapter.
- **Contact lens hygiene; no overnight wear; no tap water. STRONG** for lens-related keratitis.
- **Measles vaccination. STRONG**. The vaccine costs under **a few US dollars per child** and has been in use about sixty years.
- **Vitamin A supplementation** in deficient populations. **STRONG** — see that entry.
- **Neonatal ocular prophylaxis** with tetracycline eye ointment. **STRONG**.
- **The trachoma SAFE strategy, and ivermectin mass administration for onchocerciasis.** 171.6 million people treated for onchocerciasis in 2024; **25.5 million** people now live in areas no longer needing treatment, including more than 16.6 million in Nigeria; and five countries have been verified as having eliminated onchocerciasis transmission — Colombia 2013, Ecuador 2014, Mexico 2015, Guatemala 2016 and Niger 2025, the first in Africa. **STRONG**.
- **Not using topical steroids or traditional eye medicines on an undiagnosed red eye. STRONG**, and the action is omission: it costs nothing but instruction.

Treatment.

1. **Intensive topical antibiotics for bacterial keratitis** — fluoroquinolone monotherapy or fortified cefazolin with gentamicin or tobramycin, hourly initially. Ciprofloxacin and gentamicin eye preparations are listed, with amikacin as therapeutic equivalent to gentamicin. Off-patent, a few dollars per course.
2. **Topical natamycin 5 per cent for fungal keratitis.** The Mycotic Ulcer Treatment Trial found natamycin superior to voriconazole for filamentary fungal keratitis, especially *Fusarium*. Natamycin listed. Off-patent, low tens of US dollars per course.
3. **Topical or oral aciclovir for herpes simplex keratitis. Aciclovir eye ointment is listed**. Off-patent, cents to a few dollars. Oral aciclovir prophylaxis reduces recurrence by about half.
4. **Cycloplegia with atropine** for pain and to prevent synechiae. Atropine listed, off-patent, cents.
5. **Corneal transplantation** for established opacity. Not listed; requires an eye bank. A surgical episode plus tissue.
6. **Therapeutic keratoplasty, cyanoacrylate glue, amniotic membrane** for perforation and melt.

Simple means. Strong, and the village-level prophylaxis finding is the key one.

- **Eye protection** in farm work: goggles, or even spectacles. Negligible cost.

- **Topical antibiotic ointment applied by a trained village health worker to any corneal abrasion.** Reported to reduce corneal ulcer incidence substantially in Nepalese, Bhutanese and Burmese programmes; the effect sizes could not be verified. The inputs are a tube of tetracycline or chloramphenicol ointment, a torch and a half-day of training. This is the cheapest corneal-blindness prevention described in the literature read.
- **Fluorescein strips and a blue torch** to find an epithelial defect. Cents.
- **Tetracycline eye ointment at birth.** Cents per neonate.
- **Measles vaccination and vitamin A** — both covered elsewhere, both listed, both cents to under a dollar.
- **Ivermectin mass administration for onchocerciasis** — donated by the manufacturer, and 171.6 million people were treated in 2024.
- **Instruction not to put traditional eye medicines, breast milk or steroid drops into a painful red eye.** Free, and the World Health Organization names unsafe traditional medicines as a preventable cause of vision loss.

What the chain minimally requires for an established opacity: an eye bank and a corneal surgeon. There is no simple means that clears a scarred cornea.

Gaps. No global figure for corneal opacity or microbial keratitis exists on any source read, despite its being a major blindness cause — the fact sheet names it without a count. Only the India 2023 national survey figure was obtainable. The village abrasion-prophylaxis effect sizes, which matter a great deal for policy, could not be verified. The bacterial and fungal split differs completely between regions and no global breakdown exists. The role of adjunctive steroid in bacterial keratitis is genuinely disputed, with an overall null result and a subgroup signal. The onchocerciasis vision-loss figure is a 2017 Global Burden of Disease estimate carried on a 2025 fact sheet.

> **Depth.** Starts in: a microbe on the injured cornea. Size: 2 µm†; depth +3.44. First complaint: about 2 days († 1–3 days after injury or lens wear); time depth 44.13. One untreated course: about 5 days ([B] can destroy an eye in days); depth 44.96.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Vitamin A deficiency blindness (xerophthalmia, keratomalacia)

What it is. Without enough vitamin A the eye cannot make the pigment it needs to see in dim light, and the surface of the eye dries out. Night blindness comes first, then the cornea softens and can melt away within days. It mostly happens to young children and it is entirely preventable.

Measured. The World Health Organization vitamin A deficiency fact sheet did not load, and the figures below are carried as widely reported and are not verified.

Children affected are commonly reported as about **190 million** preschool children with low serum retinol†. Children going blind annually from vitamin A deficiency are commonly reported as **250,000 to 500,000**, of whom about half die within 12 months of losing their sight†. That figure originates in older estimates and is widely repeated; its current accuracy is uncertain. A 2023 systematic review and modelling analysis of prevalence in low- and middle-income countries exists and could not be retrieved.

The World Health Organization names nutrition-related diseases among preventable causes of vision loss without giving a figure. The affected groups are preschool children and pregnant women, concentrated in sub-Saharan Africa and South Asia, and the trend is falling with supplementation coverage and food fortification.

Where it starts.

- **Dietary vitamin A inadequacy** — the necessary cause: low intake of liver, dairy and eggs, and of provitamin A carotenoids from dark green leaves, orange sweet potato, mango, papaya and carrot.

- **Measles** — depletes vitamin A acutely and precipitates keratomalacia in a marginally deficient child. The measles–vitamin A–corneal melt sequence is the classic route to childhood corneal blindness. The World Health Organization directs two doses of vitamin A to every suspected measles case under five, with a third dose 4 to 6 weeks later if there are eye complications.
- **Diarrhoeal disease and intestinal parasites** — fat malabsorption and loss. Diarrhoeal disease kills **443,832** children under five and **50,851** children aged 5 to 9 each year, with nearly **1.7 billion** childhood episodes annually and no data year stated on the page (World Health Organization fact sheet, *Diarrhoeal disease*, 7 March 2024).
- **Protein-energy malnutrition** — impairs retinol transport.
- **Lack of breastfeeding**.
- **Pregnancy and lactation** raise requirement.

Genuinely not known: why individual susceptibility to corneal involvement varies at similar serum retinol levels. Serum retinol is a poor marker of liver stores, which makes population assessment imprecise. The DEVTA trial in India found no significant mortality benefit from vitamin A supplementation, contradicting earlier trials, and that disagreement has never been fully resolved.

Cure status. The deficiency: CURABLE. Established corneal destruction: RELIEF ONLY.

Night blindness and conjunctival xerosis reverse within **days** of high-dose vitamin A — one of the fastest and cheapest cures in medicine. Bitot's spots and corneal xerosis also resolve. But keratomalacia that has melted the cornea leaves permanent opacity or a destroyed eye, and vitamin A cannot undo it. The window between reversible and irreversible is measured in days, which is why this condition is classified by stage and why supplementation programmes rather than treatment are the answer.

Prevention. This is among the best-evidenced and cheapest preventive interventions in all of medicine, and its central effect size is disputed.

- **High-dose vitamin A supplementation twice yearly for children 6 to 59 months.** The Cochrane review of supplementation in children aged 6 months to 5 years found a reduction in all-cause mortality of about **24 per cent**, and reductions in measles incidence, diarrhoea and night blindness — the Cochrane page did not load. **STRONG**, with the important caveat that the large DEVTA trial found no mortality benefit, so the pooled estimate is disputed. Both readings are printed.
- **Measles vaccination.** Removes the main acute precipitant. **STRONG**; the vaccine costs a few US dollars per child.
- **Food fortification** — vegetable oil, sugar, flour with vitamin A. **STRONG**.
- **Biofortification** — orange-flesh sweet potato, biofortified rice. **MODERATE**.
- **Breastfeeding promotion. STRONG**.
- **Home gardening and dietary diversification** with dark green leaves and orange fruit. **MODERATE**.
- **Vitamin A with measles treatment.** The World Health Organization directs two doses to every child with suspected measles under five, which reduces mortality and corneal complications. **STRONG**.

Treatment.

1. **High-dose oral vitamin A (retinyl palmitate), 200,000 IU on days 1, 2 and 14**, age-adjusted, with 100,000 IU for infants 6 to 11 months. Reverses night blindness and conjunctival and corneal xerosis within days. **Retinol is on the Essential Medicines List** — the list document did not load. Off-patent. **Approximately under one US dollar per capsule**, making a full course a few cents.
2. **Topical antibiotic and cycloplegic** to the affected cornea to prevent secondary bacterial infection of a melting cornea.
3. **Treatment of concurrent measles, diarrhoea and malnutrition.**
4. **Corneal grafting** for a healed scar. Rarely available in the affected settings, with poor outcomes in these eyes.

Simple means. This is arguably the single highest-return simple intervention in the book: a capsule costing about two to five US cents, given twice a year, prevents childhood blindness and reduces child mortality.

- **Twice-yearly high-dose vitamin A capsules** delivered by community health workers or on campaign days. No cold chain, no needle, no clinical skill beyond dosing by age. Cochrane gives about a 24 per cent all-cause mortality reduction†, with the DEVTA null result as the counter-evidence.
- **Dark green leafy vegetables, orange sweet potato, mango and papaya** grown in a household garden. No supply chain at all. Provitamin A carotenoid bioavailability from leaves is lower than from animal sources, so quantity and added fat matter.
- **A small amount of oil or fat with the meal** to permit absorption — a free dietary change with a real effect on bioavailability.
- **Breastfeeding.** Free, and breast milk is a vitamin A source for the infant.
- **Measles vaccination** — a listed vaccine at a few US dollars per child.
- **Two doses of vitamin A to every child with measles** — the World Health Organization protocol, at cents.

Nothing else in this book prevents blindness at a lower unit cost.

Gaps. This entry has the weakest sourcing in the chapter, because the World Health Organization vitamin A deficiency fact sheet, the Cochrane review and the 2023 modelling analysis all failed to load. Every prevalence figure above is unverified. Sources genuinely disagree on the mortality effect: the pooled Cochrane estimate of about a 24 per cent reduction against DEVTA, in about a million children, finding no significant mortality benefit. That disagreement is unresolved and material to policy, and both are printed. The 250,000 to 500,000 children blinded annually derives from older estimates and may substantially overstate the current burden; no current figure was obtainable. Serum retinol is an imprecise measure of status, so prevalence estimates carry large uncertainty.

> **Depth.** Starts in: retinol. Size: 1.4 nm†; depth −3.17. First complaint: about 6.6 months († body stores last months); time depth 48.32. One untreated course: about 3 days ([B] the cornea melts within days); depth 44.50.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. The book names a late stratum. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Retinopathy of prematurity

What it is. In babies born very early the retinal blood vessels have not finished growing. After birth they can grow abnormally, scar and pull the retina off. It is a disease produced by survival — babies who would once have died now live, and some are blinded.

Measured. No count is given on the World Health Organization fact sheet and no global figure was retrievable. Retinopathy of prematurity is a leading cause of childhood blindness worldwide, and is reported to cause blindness or severe visual impairment in roughly **20,000 to 30,000** infants per year†.

By definition it is confined to preterm infants, with risk rising steeply as gestational age and birth weight fall. Preterm birth is the context: **13.4 million** babies were born preterm in 2020, about 1 in 10 of all births, and preterm birth complications killed about **900,000** children in 2019 (World Health Organization fact sheet, *Preterm birth*, 10 May 2023).

The geography is the distinguishing feature. Blindness from retinopathy of prematurity is concentrated in **middle-income** countries — a “third epidemic” — where neonatal intensive care now lets very preterm infants survive and oxygen monitoring and screening have not caught up. In high-income countries with tight oxygen control and universal screening it is rare; in the poorest countries very preterm infants still do not survive. The trend is rising in middle-income countries as neonatal survival improves.

Where it starts.

- **Low gestational age and low birth weight** — the primary determinants.

- **Supplemental oxygen, especially unmonitored or fluctuating high concentrations** — the classic modifiable cause; uncontrolled oxygen produced the first epidemic in the 1940s and 1950s†.
- **Sepsis, blood transfusion, poor postnatal weight gain, hyperglycaemia, intraventricular haemorrhage**.
- **Absence of screening** — not a cause of the disease but the cause of the blindness, since treatable disease goes undetected.

Genuinely not known: the optimal oxygen saturation target, which is genuinely unresolved and where the evidence is in tension. Lower saturation targets reduce retinopathy, and the SUPPORT, BOOST-II and COT trials together suggested lower targets increase mortality. This is a direct trade-off between death and blindness and no target satisfies both. Why some infants with identical exposures progress to stage 5 is unexplained. The role of insulin-like growth factor 1 and the balance of the two phases of the disease are incompletely described.

Cure status. Caught in the treatment window: CURABLE. After detachment: RELIEF ONLY.

Treated at threshold disease, ablation or anti-VEGF causes regression and the great majority of eyes retain useful vision; the CRYO-ROP and ETROP trials established that treatment substantially reduces unfavourable outcomes. That is a cure of the sight-threatening process. Once the retina has detached, at stage 4 to 5, surgery rarely restores useful vision and stage 5 outcomes are very poor†.

The treatment window is narrow — a matter of days to a couple of weeks — which makes this a condition where the entire outcome turns on screening logistics rather than therapeutic power. A baby not examined at the right week is blinded by an omission.

Prevention.

- **Controlled, monitored supplemental oxygen with pulse oximetry, defined saturation targets and alarm limits.** The core preventive measure, and it ended the first epidemic. **STRONG** for reducing retinopathy — and the target itself is **CONTESTED**, because of the mortality trade-off above.
- **Universal screening of all infants meeting gestational age and birth weight criteria, at the correct postnatal timing.** Does not prevent the disease; prevents the blindness. **STRONG** for that outcome.
- **Antenatal corticosteroids, delayed cord clamping, breast milk feeding, sepsis prevention, avoiding unnecessary transfusion, optimising postnatal weight gain. MODERATE**.
- **Preventing preterm birth** — the true primary prevention, and the least tractable.
- **Avoiding unnecessary oxygen in more mature preterm infants. STRONG**, and effectively free. The action is omission.

Treatment.

1. **Laser photocoagulation of the avascular retina.** The long-standing standard. A procedure, not listed, and the technique is unpatented. Cost: a capital laser plus an operator, with **no consumables and no repeat dosing**, and it is definitive. It destroys peripheral retina by design and induces myopia.
2. **Intravitreal anti-VEGF (bevacizumab, ranibizumab).** The BEAT-ROP trial found bevacizumab superior to laser for zone I disease. It avoids peripheral retinal destruction and requires prolonged follow-up for late reactivation, and systemic VEGF suppression in a developing infant raises unresolved concerns about neurodevelopment. **Bevacizumab is on the Essential Medicines List**, off-patent, at about **tens of US dollars to 100 per dose** against ranibizumab at about **thousands of US dollars per dose**. For this indication the dose is a fraction of the adult dose, so the per-infant drug cost from a shared vial is very small.
3. **Cryotherapy** — the original CRYO-ROP intervention, still usable where no laser exists.
4. **Vitrectomy, or lens-sparing vitrectomy**, for stage 4 to 5. Poor outcomes.

Simple means. Mixed, and the division is instructive.

- **A pulse oximeter with a correctly set alarm range.** This is the key cheap item: a pulse oximeter costs tens of US dollars and, used with defined saturation targets, prevents the oxygen-driven disease. The first epidemic ended when oxygen was controlled, before any treatment existed.
- **Written oxygen protocols and trained nursing staff.** Costs training, not equipment, and in middle-income neonatal units this is the documented gap.
- **Screening by indirect ophthalmoscopy with a 20 D or 28 D lens and a speculum**, by a trained examiner at the bedside. No imaging equipment required.
- **Telemedicine screening using a retinal camera**, images graded remotely, where no ophthalmologist is available.
- **Breast milk feeding.** Free, and associated with lower risk.
- **Bevacizumab from a shared vial** brings the drug cost per treated infant to a few US dollars.

What the chain minimally requires: a functioning neonatal unit with oxygen blending and monitoring, a trained examiner visiting on schedule, and a laser or an injection. This condition cannot be addressed at all without a neonatal intensive care service. It is the one condition in the chapter that exists only where a hospital exists.

Gaps. No verified global figure for incidence or for blindness was obtainable; the fact sheet gives no count. The 20,000 to 30,000 annual figure is widely cited and unverified. The optimal oxygen saturation target is a genuine, unresolved conflict between retinopathy risk and mortality risk, with three trials pointing one way and the eye outcomes the other; both are printed. Long-term neurodevelopmental safety of intravitreal anti-VEGF in preterm infants is not established and is actively disputed. Screening criteria calibrated in high-income populations miss larger, more mature babies who develop the disease in middle-income settings, so imported guidelines under-detect.

> **Depth.** Starts in: a retinal vessel. Size: 10 µm†; depth +4.91. First complaint: about 5 weeks († 4–6 weeks after birth); time depth 46.72. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Optic neuritis

What it is. The optic nerve becomes inflamed. Vision in one eye dims or greys over hours to days, colours wash out, and moving the eye hurts. Most people recover much of their sight, and it is often the first sign of a wider disease.

Measured. No global figure was retrievable; optic neuritis is not a line in the published cause breakdown. Annual incidence is commonly reported at about **1 to 5 per 100,000**†. It is typically a disease of ages 20 to 45 and more common in women†, with incidence rising with latitude, mirroring multiple sclerosis.

Conversion to multiple sclerosis is the clinically decisive measure. The Optic Neuritis Treatment Trial followed patients 15 years and reported a cumulative probability of multiple sclerosis of about **50 per cent** overall, about **25 per cent** with a normal baseline brain magnetic resonance image and about **72 per cent** with one or more lesions†. These figures are the clinical backbone of the condition and could not be verified against the primary report.

Where it starts.

- **Multiple sclerosis** — the commonest associated condition; optic neuritis is a frequent first demyelinating event.
- **Myelin oligodendrocyte glycoprotein antibody disease and aquaporin-4-antibody neuromyelitis optica spectrum disorder** — distinct antibody-mediated causes with different prognosis and different treatment, and distinguishing them changes management completely.
- **Female sex, age 20 to 45, higher latitude, low vitamin D, Epstein-Barr virus exposure, smoking, HLA-DRB1*15:01** — the multiple sclerosis risk-factor set†.

- **Infections and post-infectious inflammation** — syphilis, Lyme disease, tuberculosis, viral.
- **Ethambutol, amiodarone and methanol** cause optic neuropathy rather than true neuritis, present similarly, and are reversible only if stopped early.

Genuinely not known: what triggers the attack at the moment it occurs. Why some patients recover to 6/6 and others are left with permanent loss despite similar presentation. Whether early disease-modifying therapy after a first episode changes long-term disability is still debated. Neuromyelitis optica and myelin oligodendrocyte glycoprotein antibody disease were only recently separated from multiple sclerosis, so older incidence and prognosis data conflate distinct diseases.

Cure status. The episode: SELF-LIMITING. The underlying disease: CONTROLLABLE.

The individual attack resolves largely on its own. The Optic Neuritis Treatment Trial established that intravenous methylprednisolone **speeds recovery and does not change visual outcome** at six months or beyond, and that **oral prednisone alone at the dose studied was associated with an increased risk of recurrence**. That is an unusually clear negative result and it defines the treatment of the episode: steroids are given for speed, not for outcome.

Most patients recover good acuity, though many retain measurable deficits in contrast sensitivity, colour vision and the visual field, and the nerve thins permanently. The underlying disease is CONTROLLABLE and not curable. Neuromyelitis optica attacks in particular can leave severe permanent loss, which is why distinguishing it matters.

Prevention.

- **No primary prevention of a first episode is established.**
- **Disease-modifying therapy in diagnosed multiple sclerosis.** Reduces relapse rate, including further optic neuritis. **STRONG** for relapse reduction.
- **Immunosuppression in neuromyelitis optica** — rituximab, eculizumab, satralizumab, azathioprine. Prevents attacks, and this matters more than in multiple sclerosis because the attacks are more destructive. **STRONG** for attack prevention.
- **Avoiding oral prednisone monotherapy after an episode**, which was associated with increased recurrence. **MODERATE**, and the action is omission.
- **Smoking cessation and vitamin D sufficiency. WEAK**, and **CONTESTED** for vitamin D.
- **Stopping ethambutol promptly on any visual symptom**, and dose-limiting by weight and renal function. Prevents irreversible toxic optic neuropathy. **STRONG** for that cause.

Treatment.

1. **Intravenous methylprednisolone 1 g daily for three days**, with or without an oral taper. Speeds recovery and does not improve final outcome. Methylprednisolone and dexamethasone are listed. Off-patent, low tens of US dollars per course.
2. **High-dose oral methylprednisolone** — a bioequivalent alternative to the intravenous route, cheaper and deliverable without infusion.
3. **Plasma exchange** for severe steroid-refractory attacks, especially in neuromyelitis optica.
4. **Aquaporin-4 and myelin oligodendrocyte glycoprotein antibody testing.** Changes diagnosis and treatment; not a treatment but the decisive step.
5. **Disease-modifying therapy for multiple sclerosis** — interferon beta, glatiramer, and the oral and monoclonal agents. Costs range from low hundreds to tens of thousands of US dollars per patient-year.
6. **Rituximab or azathioprine for neuromyelitis optica.** Azathioprine is listed, off-patent and cheap; rituximab is listed as a selected medicine in the complementary list, and biosimilars have reduced its cost.
7. **No treatment.** A defensible option for a typical isolated episode, given that steroids do not change the outcome. The action is omission.

Simple means. Limited for the disease, and two things are genuinely simple and matter greatly.

- **Clinical diagnosis without imaging.** Unilateral subacute vision loss with pain on eye movement, a relative afferent pupillary defect found with a torch, red desaturation tested with any red object, and reduced acuity on a printed chart. A torch, a chart and a red cap identify the condition. No scanner required.
- **Recognising and stopping a causative drug**, above all **ethambutol** in tuberculosis treatment. This costs nothing, requires only that someone asks about vision at each visit, and prevents permanent bilateral blindness. Given the scale of tuberculosis treatment — **10.7 million** new cases in 2024 (World Health Organization fact sheet, *Tuberculosis*, 24 March 2026) — this is the highest-value simple intervention in the entry.
- **High-dose oral steroid instead of intravenous** — equivalent, far cheaper, no infusion service.
- **Not giving low-dose oral prednisone alone**, which was linked to increased recurrence. The action is omission, and it is a free improvement.
- **Explanation**, since most episodes recover substantially.

What the chain minimally requires for proper management: antibody testing and magnetic resonance imaging to separate multiple sclerosis, neuromyelitis optica and myelin oligodendrocyte glycoprotein antibody disease, because their treatments differ and untreated neuromyelitis optica blinds. That is a laboratory and a scanner.

Gaps. No global incidence figure was obtainable. The widely quoted 1 to 5 per 100,000 and the 15-year conversion figures could not be verified against primary sources. Incidence and prognosis data published before the separation of neuromyelitis optica and myelin oligodendrocyte glycoprotein antibody disease conflate three diseases and should not be read as applying to any one of them. Whether very early disease-modifying therapy after a first episode changes long-term disability remains disputed. The proportion of optic neuritis attributable to each of the three diseases varies by population and is not globally established.

> **Depth.** Starts in: a myelin protein. Size: 10 nm†; depth −1.38. First complaint: about 21 hours ([B] hours to days); time depth 43.37. One untreated course: about 7.4 weeks ([B] recovery is largely complete; † weeks to months); depth 47.10.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

ICD-11 Chapter 10 — Diseases of the ear or mastoid process

Global totals for hearing

Over 1.5 billion people live with some degree of hearing loss. Of these, **430 million** have moderate or higher loss in the better ear and need rehabilitation — over 5 per cent of the world population, including **34 million children** (World Health Organization fact sheet, *Deafness and hearing loss*, 3 March 2026; World report on hearing, 3 March 2021). **95.1 million** children aged 5 to 19 live with hearing loss.

Disabling hearing loss is defined as greater than **35 dB** in the better ear.

Projected to 2050: **nearly 2.5 billion** people with some degree of hearing loss, or 1 in 4. The fact sheet attaches **more than 700 million** to two different metrics on the same page — its key facts say that many will require hearing rehabilitation, and its body says that many will have disabling hearing loss, which it equates to 1 in 10 people. That is an internal contradiction in the source and both readings are printed. It also sits oddly against the present-day structure, where the same 430 million are described both as having disabling loss and as needing rehabilitation. The World report on hearing's own series runs 430 million in 2019, 509 million in 2030, 612 million in 2040 and **711 million in 2050**.

Nearly **80 per cent** of people with disabling hearing loss live in low- and middle-income countries, and **over 25 per cent** of people older than 60 are affected. Rehabilitation need by region, in millions: Western Pacific 136.5; South-East Asia 109.4; Americas 62.8; Europe 57.3; Africa 39.7; Eastern Mediterranean 22.1.

Global Burden of Disease 2023 places age-related and other hearing loss at **53.1 million** years lived with disability, 95% uncertainty interval 37.5 to 71.6, the **fifth leading cause** of years lived with disability, which is 5.4 per cent of the all-cause total. Because hearing loss is non-fatal it contributes no years of life lost, so its disability-adjusted life years equal its years lived with disability at **53.1 million**, ranking it fourteenth among causes of disability-adjusted life years. Falls carry the same rounded figure of 53.1 million years lived with disability, with a different uncertainty interval of 38.4 to 72.2, at rank 4; the two adjacent rows of the published table are both correct. Hearing loss is the largest sense-organ contributor to global years lived with disability.

The avoidable share. In children, nearly **60 per cent** of hearing loss is due to avoidable causes. The World Health Organization states that the common adult causes — loud sound and ototoxic medicines — are preventable and gives no percentage. **Over 1 billion** young adults are at risk of permanent avoidable hearing loss from unsafe listening.

The correctable share. Only **17 per cent** of those who could benefit from a hearing aid use one, an **83 per cent** gap, ranging 77 to 83 per cent across regions and **74 to 90 per cent** across income levels. The hearing fact sheet does not report hearing aid need against use.

The economics are on the **fact sheet**, not on the report page. The World report on hearing's own item page carries no headline figures at all, and its launch release carries only the return on investment. The fact sheet (3 March 2026) carries all three figures the chapter needs: the annual global cost of unaddressed hearing loss is **almost US$1 trillion**; the additional investment needed to scale ear and hearing care is **less than US$1.40 per person per year**; and the projected return over ten years is **nearly US$16 per US$1 invested**. The World report on hearing gives the per-capita figure as **US$1.33** and the averted burden as nearly **130 million** disability-adjusted life years, benefiting **1.4 billion** people. On this book's convention the fact sheet's "less than US$1.40", the "almost US$1 trillion" and the "nearly US$16 per US$1" are figures read off their page; the 130 million disability-adjusted life years averted and the 1.4 billion beneficiaries come from the report, whose source is named and was not opened again.

The workforce constraint. **78 per cent** of low-income countries have fewer than one ear, nose and throat specialist per million population, and **93 per cent** have fewer than one audiologist per million. **50 per cent** have one or more teachers for the deaf per million, and **17 per cent** have one or more speech therapists per million. Any workable screening or rehabilitation in those settings must be deliverable without specialists, or it will not happen.

Age-related hearing loss (presbycusis)

What it is. The hair cells of the inner ear die off with age and do not grow back. High notes go first, then speech becomes hard to follow, especially in noise. It is the commonest cause of hearing loss in the world.

Measured. Over 25 per cent of people older than 60 are affected by disabling hearing loss. Presbycusis sits inside the **430 million** people who need rehabilitation, of over 1.5 billion with some degree of hearing loss.

Global Burden of Disease 2023: **53.1 million** years lived with disability, 95% uncertainty interval 37.5 to 71.6, the fifth leading cause, and **53.1 million** disability-adjusted life years, fourteenth†.

Projection: **over 700 million** people needing rehabilitation by 2050 on the fact sheet's key facts, with the same number attached to disabling hearing loss in its body; the World report on hearing's disabling-loss series ends at **711 million in 2050**. Nearly **80 per cent** of people with disabling hearing loss live in low- and middle-income countries. Only **17 per cent** of those who could benefit from a hearing aid use one, an 83 per cent gap, 74 to 90 per cent across income levels. The annual cost of unaddressed hearing loss is almost **US$1 trillion**.

Where it starts.

- **Age** — the defining factor. Cochlear hair cells, spiral ganglion neurons and the stria vascularis all degenerate cumulatively and irreversibly.
- **Cumulative lifetime noise exposure** — adds to, and is largely indistinguishable from, pure ageing at the individual level. The World Health Organization names loud sound exposure among the common adult causes and states that it is preventable.
- **Ototoxic medicines** — named among the common preventable adult causes. See that entry.
- **Smoking** — named among adult causes.
- **Chronic diseases**, including diabetes and cardiovascular disease — named.
- **Genetic susceptibility** — delayed-onset or progressive genetic hearing loss across the life span, named.
- **Male sex; occupational history**.

Genuinely not known: how much of "age-related" loss is intrinsic ageing and how much is accumulated noise and ototoxic injury. The two cannot be separated in an individual, and populations with low lifetime noise exposure show less loss, which suggests the intrinsic component may be smaller than assumed. Why hair cells do not regenerate in mammals when they do in birds and fish is understood descriptively and not therapeutically. Whether hearing loss causes dementia or shares a cause with it is unresolved and important; see *Prevention*.

Cure status. RELIEF ONLY. Nothing restores hearing lost to presbycusis. Mammalian cochlear hair cells do not regenerate, no drug regrows them, and no surgery replaces them.

What exists is substitution. Hearing aids amplify what remains, and cochlear implants bypass dead hair cells by stimulating the auditory nerve directly. Both are genuinely effective prostheses — a cochlear implant can restore open-set speech understanding in a profoundly deaf adult — and neither repairs the ear. Both require the device to be worn and powered, and function stops when the device is removed. This is the symmetrical counterpart to glaucoma: the damage is permanent and the deviation remains, and the label is RELIEF ONLY rather than CONTROLLABLE because there is no disease process being held in check. The loss simply accumulates.

Prevention. Presbycusis itself cannot be prevented, and a substantial part of what is called presbycusis is accumulated preventable injury.

- **Lifetime noise exposure limits** — occupational limits and hearing conservation programmes, which the World Health Organization names among its prevention measures. **STRONG** for the noise-attributable component; see the noise-induced hearing loss entry for the dose-response data.
- **Safe listening in recreational settings. Over 1 billion** young adults are at risk from unsafe listening. **STRONG** mechanistically; the World Health Organization–International Telecommunication Union safe listening standard is the instrument.
- **Rational use of ototoxic medicines** — a named World Health Organization prevention measure. **STRONG**.
- **Smoking cessation, diabetes and blood pressure control. MODERATE**.
- **Hearing aids to prevent cognitive decline.** This is where the evidence is genuinely contested and must be reported as such. The ACHIEVE trial found **no significant effect** of hearing intervention on three-year cognitive decline in the full randomised population, and a substantial effect in the pre-specified higher-risk subgroup. The Lancet Commission on dementia prevention lists hearing loss as a major modifiable risk factor. **CONTESTED**: the observational association is strong, the randomised evidence for the full population is null, and the subgroup effect is real and not confirmatory. Both readings are printed.
- **Nothing prevents the intrinsic ageing component.**

Treatment.

1. **Hearing aids.** The mainstay. They improve hearing-specific quality of life and speech understanding in noise. A device, not on the Essential Medicines List; hearing aids appear on the World Health Organization's priority assistive products list. The access gap: only **17 per cent** of those who would benefit use one, a gap of 74 to 90 per cent across income levels. Device cost ranges from around **US$100 or less** for basic and over-the-counter devices to **US$2,000 to 6,000 per pair** for fitted high-end devices in high-income private markets — the World report on hearing gives the access gap and no price figures.
2. **Cochlear implants.** For severe to profound loss where aids fail. They restore open-set speech perception in most postlingually deafened adults. The World report on hearing describes them as effective and cost-effective and gives **no** access, coverage or cost figures. Reported total cost including surgery and rehabilitation is approximately **US$30,000 to 100,000 per recipient** in high-income systems, with the device a large share. The access gap is severe and the primary source does not quantify it.
3. **Assistive listening devices, personal amplifiers, loop systems, captioning.** The World Health Organization names hearing assistive technology including alerting devices and captioning, and lists bone conduction and middle ear implants among hearing technologies.
4. **Communication training, speech and language therapy, counselling and support, auditory rehabilitation, lip-reading training.** Named as rehabilitation components.
5. **No pharmacological treatment exists.**

Simple means. Better than the access figures suggest, and this is where the 83 per cent gap could be attacked.

- **Communication tactics, which cost nothing.** Facing the person; speaking at normal volume but more slowly and clearly; not shouting; reducing background noise; turning off the television; one speaker at a time; good lighting on the speaker's face so lips can be read. These measurably improve comprehension and they are free.
- **Low-cost and over-the-counter hearing aids and personal sound amplifiers** at around **hundreds of US dollars or less**. The 74 to 90 per cent access gap is substantially a price and service-delivery gap rather than a technology gap.
- **Community-based hearing screening with a whispered-voice test or a free smartphone audiometry application**, usable by a non-specialist. In low-income countries 78 per cent have fewer

than one ear, nose and throat specialist per million and 93 per cent fewer than one audiologist per million, so any workable screening must be deliverable without them.

- **Hearing loops and captioning** in public buildings.
- **Noise reduction in the home and workplace.** Moving away from a noise source costs nothing.

The economics of doing this at scale are measured, and the three headline figures are on the fact sheet. Scaling ear and hearing care to 90 per cent coverage requires an additional **less than US$1.40 per person per year** and returns **nearly US$16 per US$1** over ten years, against an annual global cost of unaddressed hearing loss of **almost US$1 trillion** (World Health Organization fact sheet, *Deafness and hearing loss*, 3 March 2026). The World report on hearing gives the per-capita figure as **US$1.33** and the averted burden as nearly **130 million** disability-adjusted life years, benefiting **1.4 billion** people.

What the chain minimally requires: a hearing aid is a microphone, an amplifier, a receiver and a battery. It is not a simple object and it is a cheap one at scale, and the binding constraint named by the primary source is service delivery and workforce, not manufacture.

Gaps. The World Health Organization figures do not separate presbycusis from other causes within the 430 million, so no condition-specific prevalence exists. The World report on hearing gives the hearing aid access gap and **no device price figures and no cochlear implant access or cost figures at all**; the cost and access numbers above are unverified. The fact sheet attaches “more than 700 million” to two different metrics on the same page, and both readings are printed. Whether treating hearing loss prevents dementia is genuinely unresolved: ACHIEVE was null overall with a positive high-risk subgroup, against strong observational data, and both are printed. The split between intrinsic ageing and accumulated noise is not quantified anywhere read.

> **Depth.** Starts in: an inner-ear hair cell. Size: 30 µm†; depth +5.91. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: no number ([B] irreversible).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Hair cells of the inner ear do not regrow. So it is held, not ended. The book’s status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Noise-induced hearing loss

What it is. Loud sound kills the hair cells of the inner ear. It can happen slowly over years of noisy work, or suddenly from one blast. The damage is permanent, and it is almost entirely preventable.

Measured. Over 1 billion young adults are at risk of permanent, avoidable hearing loss from unsafe listening practices. The World Health Organization names loud noise and work-related ototoxic chemicals among causes acting across the life span, and states that the common adult causes including loud sound exposure are preventable.

Noise-induced loss is counted within the **430 million** needing rehabilitation and the over 1.5 billion with some hearing loss; no separate global count was retrievable. Occupational noise is among the leading occupational disease burdens worldwide, and occupational noise-induced hearing loss is one of the most commonly compensated occupational diseases in countries with compensation schemes.

It begins in working life and in adolescence with recreational exposure, and the notch at 4 kHz is the characteristic early sign†. It concentrates in unregulated industry, mining, construction, agriculture and military service, with recreational exposure global. Occupational exposure is falling in regulated economies while recreational exposure from personal audio devices and entertainment venues is rising, which is the basis of the one-billion-at-risk figure.

Where it starts.

- **Sound energy dose — intensity combined with duration.** The dose-response is the established basis of all noise regulation: permissible exposure halves for each 3 dB increase in level under the equal-energy principle, so 85 dB(A) for 8 hours, 88 dB(A) for 4 hours, 91 dB(A) for 2 hours, and so on. The

commonly applied occupational limit is **85 dB(A) averaged over 8 hours**, and the World Health Organization's recommended recreational limit is **80 dB(A) for 40 hours per week** for adults and **75 dB(A)** for children, under the World Health Organization–International Telecommunication Union safe listening standard — the standard document was not retrievable.

- **Impulse and blast noise** — gunfire, explosions, fireworks. A single exposure above about 140 dB peak can cause immediate permanent loss†.
- **Personal audio devices at high volume for long periods, and entertainment venues** — the basis of the over-one-billion-at-risk figure.
- **Co-exposure to ototoxic chemicals** — solvents including toluene and styrene, and heavy metals, acting synergistically with noise. The World Health Organization names work-related ototoxic chemicals explicitly.
- **Co-exposure to aminoglycosides and cisplatin** — synergistic with noise.
- **Individual susceptibility** — wide and largely unexplained.

Genuinely not known: why susceptibility varies so widely at identical measured dose. "Tough" and "tender" ears are a real observation without a usable predictive test. Whether the equal-energy principle holds at the extremes of very short, very intense exposure is disputed. Whether temporary threshold shift reliably predicts eventual permanent shift is unresolved. No pharmacological otoprotectant is established in humans.

Cure status. RELIEF ONLY. Hair cells lost to noise do not return. There is no treatment that restores noise-induced hearing loss and no licensed otoprotective drug.

One qualification: temporary threshold shift after a single loud exposure recovers over hours to days, and that recovery is genuine. It is not a treatment effect, and repeated temporary shifts produce permanent loss. Sudden severe acoustic trauma is sometimes treated with systemic corticosteroids by analogy with sudden sensorineural hearing loss, on weak evidence. Management is substitution with hearing aids, as for presbycusis.

The significance of this condition is not its treatability — it has none — but that it is the most preventable cause of permanent hearing loss in the chapter.

Prevention. The strongest prevention evidence in this part of the chapter.

- **Engineering noise control at source** — quieter machinery, enclosure, damping, isolation. The top of the hierarchy of controls, and the only approach that does not depend on individual behaviour. **STRONG**.
- **Administrative controls** — limiting exposure time, job rotation, distance from the source. This follows directly from the dose-response: halving exposure time offsets a 3 dB increase in level. **STRONG**.
- **Occupational exposure limits, commonly 85 dB(A) over 8 hours**, with mandatory hearing conservation programmes above an action level. **STRONG**.
- **Hearing protection — earplugs and earmuffs.** Laboratory attenuation of roughly **15 to 30 dB** depending on type and fit, and **real-world attenuation is substantially lower than the labelled rating** because of fit and wear-time failures, which is why protection ranks below engineering control. **STRONG** when worn correctly and consistently, **MODERATE** as actually delivered.
- **Audiometric surveillance** — detects early shift so exposure can be changed before disabling loss. **MODERATE**.
- **Safe listening standards for personal audio devices and venues**, with volume limiting, dose tracking and parental controls; the recommended limits are 80 dB(A) over 40 hours weekly for adults and 75 dB(A) for children†. **MODERATE** — effective where implemented, and adoption is the constraint. The World Health Organization names safe listening strategies among its prevention measures.
- **Controlling solvent and heavy-metal co-exposure. MODERATE**.
- **Avoiding fireworks and gunfire without protection. STRONG**.

Treatment. There is no treatment that restores the loss. What follows is substitution and salvage.

1. **Hearing aids.** As for presbycusis. A device, not listed. Access gap **83 per cent**, 74 to 90 per cent across income levels. **hundreds of US dollars** to **thousands of US dollars per pair**.
2. **Cochlear implants** for profound loss. Not listed. About **US$30,000 to 100,000** per recipient in high-income systems†; the World report on hearing gives no cost or access figure.
3. **Systemic corticosteroids for acute acoustic trauma** — weak evidence, used by analogy. Prednisolone and dexamethasone are listed, off-patent, cents per day.
4. **Tinnitus management**, since tinnitus very commonly accompanies the loss. See that entry.
5. **Removal from further exposure** — the only intervention that changes the trajectory.

Simple means. Unusually strong, and essentially free.

- **Distance.** Sound intensity falls with distance from the source, and stepping back halves exposure quickly. No cost.
- **Time.** Under the equal-energy dose-response, halving exposure duration offsets a 3 dB increase in level. Shortening exposure costs nothing and is quantitatively protective.
- **Turning the volume down.** The over-one-billion-at-risk figure is produced by voluntary exposure. The 80 dB(A) over 40 hours weekly budget for adults, and 75 dB(A) for children, is achieved by a volume setting†.
- **Earplugs.** Foam plugs cost **cents per pair** and attenuate roughly 15 to 30 dB when correctly inserted†. This is the clearest cents-for-permanent-disability trade in the chapter.
- **Fingers in the ears, or hands over the ears**, for unexpected impulse noise. Free, and effective for the seconds it is applied.
- **The arm's-length rule.** If a raised voice is needed to be understood at arm's length, the level is likely above the action level. This requires no meter.
- **Free smartphone sound-level meter applications** to identify hazardous environments, and **smartphone audiometry** for screening where 93 per cent of low-income countries have fewer than one audiologist per million people.

A cents-per-pair earplug, consistently worn, prevents a permanent disability that no money can subsequently repair. There is no other condition in this book with a better ratio.

Gaps. No separate global prevalence or disability-adjusted life year figure for noise-induced hearing loss was obtainable; it is not disaggregated in the World Health Organization or Global Burden of Disease figures read. The safe listening standard document could not be retrieved, so the 80 and 75 dB(A) limits and the 85 dB(A) occupational limit are unverified here. Real-world against laboratory attenuation of hearing protection differs substantially and no measured field figure was obtainable. Individual susceptibility variation is unexplained and unpredictable. Whether temporary threshold shift predicts permanent loss is disputed. No otoprotectant has been established, despite decades of candidates.

> **Depth.** Starts in: an inner-ear hair cell. Size: 30 µm†; depth +5.91. First complaint: about 10 years ([B] over years of noise; † about 10 years); time depth 50.97. One untreated course: no number ([B] permanent).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Hair cells of the inner ear do not regrow. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Otitis media — acute

What it is. Infection of the middle ear, behind the eardrum. The ear hurts, hearing dulls and there is often fever. In young children it is one of the commonest reasons for a doctor visit and an antibiotic prescription. Most cases clear up by themselves.

Measured. Around **200 million** people have preventable or treatable chronic ear infections; that figure is for chronic disease and belongs to the next entry. Global Burden of Disease 2023 records **700 deaths** from

otitis media in 2023. No global prevalence or incidence figure for the acute condition was located on the World Health Organization sources read.

Acute otitis media is among the commonest childhood infections worldwide and the commonest reason for antibiotic prescription in children in high-income countries. Incidence peaks between **6 and 24 months** and falls after age 5 as the Eustachian tube lengthens and angles†. It is universal, while complications and progression to chronic suppurative disease concentrate in low-income settings, in crowded households and in some indigenous populations where rates are among the highest recorded. The World Health Organization names chronic suppurative and chronic non-suppurative otitis media among childhood causes of hearing loss, and nearly **60 per cent** of childhood hearing loss is due to avoidable causes.

Where it starts.

- **Eustachian tube dysfunction** — the anatomical basis. The infant tube is short, horizontal and floppy, which is why incidence peaks under 2†.
- **A preceding viral upper respiratory infection** — the usual trigger.
- **Bacteria** — *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, *Moraxella catarrhalis*.
- **Childcare attendance, crowding, siblings**.
- **Tobacco smoke exposure**.
- **Bottle feeding, especially supine; pacifier use; absence of breastfeeding**.
- **Cleft palate, Down syndrome, immunodeficiency, allergic rhinitis**.
- **Indigenous ancestry in some populations** — among the highest recorded rates.

Genuinely not known: why a minority of children have recurrent disease and progress to chronic suppurative otitis media while most have one or two uneventful episodes. Host factors are suspected and not identified. Which child benefits from antibiotics cannot be determined at the bedside, which is the root of the over-prescription problem. Whether grommets improve long-term language outcomes is genuinely disputed.

Cure status. SELF-LIMITING. Most episodes resolve without treatment. The Cochrane review of antibiotics for acute otitis media in children found **no difference in pain at 24 hours**, a modest benefit at two to three days, and an estimated **number needed to treat of about 20** for one child to have less pain, against a clear increase in diarrhoea, vomiting and rash — the Cochrane Library did not load. Spontaneous resolution is reported in roughly **80 per cent** of cases†.

Antibiotics do cure the bacterial infection where it matters — young infants, bilateral disease, perforation with discharge, systemic illness — and they prevent the complications that make this condition dangerous: mastoiditis, intracranial spread, progression to chronic suppurative disease. So the condition is SELF-LIMITING, with antibiotics for the children who need them. SELF-LIMITING is the label the evidence supports for the condition as a whole, with delayed prescribing as the standard strategy.

Prevention.

- **Pneumococcal conjugate vaccination.** Reduces episodes caused by vaccine serotypes, with a modest reduction in all-cause acute otitis media and replacement by non-vaccine serotypes partly offsetting the gain. **MODERATE**. A listed vaccine. The World Health Organization names immunization as a prevention measure.
- **Influenza vaccination.** Reduces episodes. **MODERATE**.
- **Breastfeeding.** Consistently associated with reduced incidence. **MODERATE**, and free. The World Health Organization names good maternal and childcare practices among prevention measures.
- **Avoiding tobacco smoke exposure. MODERATE**.
- **Avoiding supine bottle feeding, and pacifier use after 6 months. MODERATE**.
- **Reducing crowding and childcare group size. MODERATE**.
- **Xylitol.** Reduced episodes in some trials. **WEAK**.

- **Early and adequate treatment of acute episodes**, which prevents progression to chronic suppurative otitis media and so prevents hearing loss. **MODERATE**. The World Health Organization names identification and management of common ear conditions among prevention measures.

Treatment.

1. **Analgesia — paracetamol or ibuprofen.** The highest-value treatment, because pain is the symptom that matters and antibiotics do not relieve it at 24 hours†. Both are on the Essential Medicines List. Off-patent, cents per dose.
2. **Delayed or no antibiotic prescribing, with safety-net advice**, for children over 2 with mild unilateral disease. **The action is omission.** The Cochrane number needed to treat is about 20 for a pain benefit†. Cost: zero, and it reduces adverse effects and resistance. It also saves the price of the antibiotic.
3. **Amoxicillin**, first-line where antibiotics are indicated — under 6 months, under 2 with bilateral disease, perforation with discharge, systemic illness, or failure to improve. **Amoxicillin is on the Essential Medicines List**, in the Access group of antibiotics, with otitis media named among its first-choice indications. Off-patent. **Well a few US dollars per course** in generic markets: the United Nations Children's Fund indicative price for amoxicillin 250 mg dispersible tablets, read October 2026, was **US$0.54 for a pack of ten**, about **US$0.054 per tablet** — an indicative tender price, not a market price.
4. **Amoxicillin-clavulanate** for treatment failure. Listed. Off-patent, low cost.
5. **Topical analgesic ear drops.** Limited evidence.
6. **Myringotomy** for severe pain or complications.
7. **Tympanostomy tubes (grommets)** for recurrent disease. Reduce episodes in the first year; long-term language benefit is disputed.
8. **Antihistamines and decongestants are not effective.** Cochrane found no benefit and more adverse effects. **The action is omission**, and it is a negative result worth stating.

Simple means.

- **Paracetamol or ibuprofen, and watchful waiting.** This is the evidence-based standard for most children, costs cents, and outperforms antibiotics for the symptom that actually troubles the child.
- **Not prescribing an antibiotic.** The action is omission, and it is a zero-cost intervention with measurable benefit: fewer adverse effects, less resistance, the same outcome in most cases, with a Cochrane number needed to treat of about 20 for pain†. It saves the cost of the drug as well as the harm.
- **Breastfeeding.** Free, and preventive.
- **Removing tobacco smoke from the home.** Free.
- **Keeping the ear dry if the drum has perforated**, and dry mopping rather than syringing. See the chronic otitis media entry, where this is the core intervention.
- **A torch and an otoscope** for diagnosis; pneumatic otoscopy needs only a bulb. Diagnosis is the limiting skill, not the equipment.
- **Amoxicillin** where it is needed: listed, off-patent, under a dollar a course.

What the chain minimally requires: an analgesic, an otoscope, a trained examiner, and access to amoxicillin for the minority who need it. All of that is cheap and on the Essential Medicines List. This is one of the least supply-chain-dependent conditions in the book.

Gaps. No global incidence figure for acute otitis media exists on the sources read, despite its being one of the commonest childhood illnesses. The 700 deaths recorded by Global Burden of Disease almost certainly understate deaths from complications in settings without care. The Cochrane effect sizes for antibiotics, and the roughly 80 per cent spontaneous resolution figure, could not be verified. Whether grommets improve long-term language and educational outcomes is genuinely disputed and guidelines differ. The contribution of pneumococcal vaccination to all-cause otitis media reduction is partly offset by serotype replacement and the net effect is contested.

> **Depth.** Starts in: Streptococcus pneumoniae behind the eardrum. Size: 1 µm†; depth +2.81. First complaint: about 3 days († a few days after a cold); time depth 44.50. One untreated course: about 3 days ([B] most clear by themselves; † 2–3 days); depth 44.50.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Otitis media — chronic suppurative

What it is. A hole in the eardrum with a middle ear that keeps discharging pus, for months or years. It deafens the ear, it smells, and it is the commonest preventable cause of childhood hearing loss in poor countries. Occasionally it kills by spreading into the skull.

Measured. Around **200 million** people have preventable or treatable chronic ear infections — the key figure for this entry. Global Burden of Disease 2023 records **700 deaths** from otitis media in 2023.

The World Health Organization names chronic suppurative otitis media and chronic non-suppurative otitis media among the childhood and adolescent causes of hearing loss, and states that nearly **60 per cent** of childhood hearing loss is due to **avoidable** causes. **95.1 million** children aged 5 to 19 live with hearing loss, and chronic suppurative otitis media is a major contributor in low-income settings. The World report on hearing's 2030 target includes a **20 per cent relative reduction** in chronic ear disease and unaddressed hearing loss in children aged 5 to 9.

It begins in early childhood, often after poorly resolved acute otitis media, and persists for years. It is strongly concentrated in low-income settings, crowded households and certain indigenous populations — Australian Aboriginal, Inuit, Greenlandic and Pacific Island communities report some of the highest prevalences recorded worldwide. The trend is falling where acute otitis media is treated and living conditions improve.

Where it starts.

- **Unresolved or recurrent acute otitis media with persistent perforation** — the direct route.
- **Crowding and large household size**.
- **Poor access to care for the acute episode** — the central determinant of why this is a poverty disease.
- **Lack of breastfeeding; tobacco smoke exposure; poor nutrition**.
- **Water contamination of the middle ear through the perforation.** Swimming and bathing in contaminated water perpetuate discharge, and *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the dominant organisms.
- **Cleft palate, Down syndrome, immunodeficiency**.
- **Indigenous ancestry in specific populations**.

Genuinely not known: why perforations heal in most children and persist in some. Why certain indigenous populations carry such extreme prevalence — whether this is Eustachian tube anatomy, bacterial carriage load, crowding or access — is not resolved. The optimal duration of topical antibiotic treatment is not established. Whether ototopical aminoglycosides cause clinically significant hearing loss through a perforated drum is a long-running dispute that affects what can safely be used in the field.

Cure status. CURABLE. Both components can be cured, and that deserves to be stated clearly.

The discharge: topical antibiotics, particularly topical quinolones, with aural toilet, dry the ear in the large majority of cases, and topical antibiotics are more effective than systemic for resolving discharge.

The perforation: tympanoplasty or myringoplasty closes the drum with reported success rates of roughly **80 to 90 per cent**, and closing it both stops recurrent infection and recovers the conductive component of the hearing loss.

The qualifications: a sensorineural component acquired over years of infection does not recover; cholesteatoma requires mastoid surgery and can recur, needing lifelong surveillance; and in practice most of the 200 million affected people have access to neither drops nor surgery, so the disease persists for

reasons of access rather than biology. This is one of the clearer curable entries in this part of the chapter, in sharp contrast with presbycusis and noise-induced loss, where nothing is recoverable.

Prevention.

- **Prompt and adequate treatment of acute otitis media**, so perforations do not become chronic. **MODERATE**. The World Health Organization names identification and management of common ear conditions among prevention measures.
- **Keeping water out of a perforated ear** — no swimming or diving, and preventing bath and shower water entering. Stops the reinfection cycle. **MODERATE**, and free.
- **Breastfeeding. MODERATE**, free.
- **Pneumococcal and influenza vaccination. MODERATE**. The World Health Organization names immunization.
- **Reducing crowding and tobacco smoke exposure. MODERATE**.
- **School-based ear screening with otoscopy**, which finds the discharging ears that families have stopped regarding as abnormal. **MODERATE**. The 2030 target of a 20 per cent relative reduction in chronic ear disease in children aged 5 to 9 presumes such detection.
- **Nutrition improvement. WEAK**.

Treatment.

1. **Aural toilet — dry mopping or suction — plus topical antibiotic drops, ciprofloxacin or ofloxacin.** The most effective standing treatment. Topical quinolones outperform systemic antibiotics, and outperform topical aminoglycosides for safety, since quinolones are not ototoxic. Ciprofloxacin ear drops are on the Essential Medicines List — the list document did not load. Off-patent. **A few US dollars per bottle** generic.
2. **Topical aminoglycoside drops — gentamicin, neomycin.** Effective and much cheaper, and potentially ototoxic through a perforation. Widely used where quinolones are unavailable, and the risk-benefit is genuinely disputed. Gentamicin is listed. Off-patent, cents to a dollar.
3. **Topical antiseptics — acetic acid (dilute vinegar), boric acid, povidone-iodine.** Cheap alternatives with some evidence of benefit. See *Simple means* — this matters enormously for cost.
4. **Systemic antibiotics** for acute exacerbation, mastoiditis or intracranial complication. Amoxicillin-clavulanate, ciprofloxacin and ceftriaxone are all listed, all off-patent, all low cost.
5. **Tympanoplasty or myringoplasty.** Closes the perforation, about 80 to 90 per cent success, and recovers the conductive loss†. A procedure, not listed. A surgical episode.
6. **Mastoidectomy** for cholesteatoma or complications.
7. **A hearing aid** for residual loss. A device, not listed; access gap 83 per cent.

Simple means. This is one of the best simple-means entries in the book: the core treatment is a cloth, a wick and a cheap liquid.

- **Dry mopping (aural toilet).** A twist of clean cotton wool or a tissue wick, rolled to a point and used to absorb discharge from the canal, repeated until the wick comes out dry, several times daily. It requires no suction apparatus, no power and no clinician, and mothers can be taught it in minutes. Removing the pus is what allows any topical agent to reach the middle ear, and dry mopping alone improves many ears; the effect size could not be verified.
- **Dilute acetic acid (vinegar) or boric acid drops.** Acidifying the ear canal suppresses *Pseudomonas*. Household vinegar diluted with clean water costs effectively nothing and has evidence of benefit.
- **Keeping the ear dry** — no swimming, and a plug of cotton wool and petroleum jelly for bathing. Free, and it breaks the reinfection cycle.
- **Topical ciprofloxacin drops** at roughly **a few US dollars per bottle** where available — listed and off-patent.

- **An otoscope and a trained health worker or teacher** for school screening. 78 per cent of low-income countries have fewer than one ear, nose and throat specialist per million people, so detection must be task-shifted or it will not happen.
- **Teaching the family** that a chronically discharging ear is a treatable disease and not a normal state of childhood. Free, and in high-prevalence communities the perforated, discharging ear is often not recognised as abnormal at all.

The measured economics of acting at scale: scaling ear and hearing care needs an additional **less than US$1.40 per person per year**, with a return of **nearly US$16 per US$1** over ten years (World Health Organization fact sheet, *Deafness and hearing loss*, 3 March 2026), averting nearly **130 million** disability-adjusted life years.

What the chain minimally requires for the definitive repair: an operating microscope and a trained ear surgeon for tympanoplasty. Drying the ear and stopping the discharge — which is what preserves the hearing — needs cotton wool and vinegar.

Gaps. The 200 million figure covers chronic ear infections generally and is not disaggregated into chronic suppurative otitis media, chronic otitis media with effusion and cholesteatoma. No condition-specific global prevalence, and no figure for how much of the 95.1 million children with hearing loss is attributable to it, exists on the sources read. The 700 deaths figure is likely an undercount of complication deaths in settings without care. The safety of ototopical aminoglycosides through a perforation is a genuine long-running dispute, and it determines what can be used where quinolones are unaffordable; both positions exist in the literature. Effect sizes for dry mopping and for acetic acid could not be verified. Tympanoplasty success rates vary widely with case selection and surgeon volume.

> **Depth.** Starts in: a hole in the eardrum. Size: 1 mm†; depth +9.10. First complaint: about 5 weeks († weeks to months after otitis); time depth 46.75. One untreated course: no number ([B] months to years).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Otitis externa

What it is. Infection or inflammation of the ear canal, the tube from the outside to the eardrum. The ear itches, then hurts, often badly, and it may swell shut and discharge. Swimmers and people who poke their ears get it most.

Measured. No global prevalence or incidence figure was retrievable; otitis externa is not quantified on the World Health Organization sources read. Lifetime incidence is commonly reported at about **10 per cent**, and it is among the commonest reasons for ear, nose and throat presentation in primary care.

All ages are affected. Acute diffuse otitis externa peaks in children and young adults, and necrotising otitis externa occurs in older people with diabetes or immunosuppression. It is more common in humid and tropical climates and in swimming populations.

Necrotising otitis externa is the dangerous form: osteomyelitis of the skull base, with substantial mortality if untreated, occurring almost exclusively in diabetic or immunocompromised people, usually caused by *Pseudomonas aeruginosa*.

Where it starts.

- **Water retention in the canal** — swimming, humidity, bathing; it macerates the skin and raises canal pH.
- **Trauma to the canal skin** — cotton buds, fingernails, hairpins, hearing aid moulds, earphones. The combination of removing protective wax and abrading the skin is the classic cause.
- **Removal of cerumen.** Wax is protective, acidic and water-repellent; over-cleaning causes the disease.
- **Bacteria** — *Pseudomonas aeruginosa* and *Staphylococcus aureus* dominate, with fungal otitis externa from *Aspergillus* and *Candida* following prolonged antibiotic drops.

- **Eczema, psoriasis or seborrhoeic dermatitis of the canal** — dermatitis of the canal predisposes to and perpetuates otitis externa.
- **Diabetes and immunosuppression** — for the necrotising form.
- **Hearing aid and earphone use** — occlusion and trauma.

Genuinely not known: why some people have a single episode and others become chronically affected. The relative contributions of infection against primary dermatitis in chronic cases is often undecidable in practice, which means treatment is frequently empirical. Optimal treatment duration is not established, and the threshold for suspecting necrotising disease in a diabetic patient with a painful ear is a clinical judgement without a validated rule.

Cure status. Acute otitis externa: CURABLE. Chronic and recurrent otitis externa: CONTROLLABLE. Necrotising otitis externa: CURABLE. Acute otitis externa resolves with topical treatment in the great majority, typically within **7 to 10 days**†, and the canal returns to normal. Topical treatment achieves clinical cure in around **65 to 80 per cent** at one week, against lower rates with placebo†.

Chronic and recurrent otitis externa, particularly where underlying dermatitis is the driver, behaves as a controllable condition requiring repeated or maintenance treatment. Necrotising otitis externa is curable and requires prolonged systemic antipseudomonal therapy, often for 6 to 12 weeks, with glycaemic control and sometimes surgery, and mortality is appreciable. The label is therefore split by form.

Prevention.

- **Keep the ear canal dry.** Tilting the head to drain after swimming or bathing, drying the outer ear with a towel, and using a hair dryer on a cool low setting at a distance. **MODERATE**, and free.
- **Do not put anything in the ear canal — above all, stop using cotton buds.** The single most effective preventive instruction, and the action is omission. It costs nothing. **MODERATE**.
- **Leave the wax alone.** Cerumen is protective and its removal is a cause of the disease. **MODERATE**, and again the action is omission.
- **Acidifying drops after swimming** — dilute acetic acid, or alcohol-acetic acid preparations — in people with recurrent episodes. **MODERATE**.
- **Earplugs or a swim cap for recurrent swimmers' ear. WEAK**.
- **Treating underlying eczema or seborrhoeic dermatitis of the canal. MODERATE**.
- **Glycaemic control in diabetes**, to prevent the necrotising form. **MODERATE**.
- **Cleaning and drying hearing aid moulds. MODERATE**.

Treatment.

1. **Aural toilet to clear debris, then topical antibiotic with or without corticosteroid.** Topical treatment is the standard and outperforms systemic antibiotics for uncomplicated disease. Topical quinolone drops — ciprofloxacin, ofloxacin — with ciprofloxacin ear preparations on the Essential Medicines List; off-patent; roughly **a few US dollars per bottle**.
2. **Topical aminoglycoside or polymyxin with corticosteroid.** Cheaper; avoid if the drum is perforated because of ototoxicity risk. Gentamicin listed, off-patent, cents to a dollar.
3. **Topical corticosteroid alone** where the process is primarily dermatitis — effective, and it avoids antibiotic use. Betamethasone and hydrocortisone are listed, off-patent, cents per tube.
4. **Topical acetic acid or aluminium acetate.** Antiseptic and astringent; cheap and effective in mild disease.
5. **An ear wick** where the canal is too swollen for drops to enter — a compressed sponge or ribbon gauze that carries the drops in and expands the canal. Cheap and decisive.
6. **Analgesia — paracetamol or ibuprofen.** Both listed, off-patent, cents. Pain can be severe and is often undertreated.
7. **Topical antifungal (clotrimazole)** for otomycosis. Clotrimazole listed, off-patent, cheap.
8. **Systemic antipseudomonal therapy — ciprofloxacin, ceftazidime — for 6 to 12 weeks** in necrotising otitis externa†. Both listed, off-patent.

9. **Oral antibiotics for uncomplicated otitis externa are not indicated.** Topical therapy is superior, and systemic therapy adds adverse effects without benefit. **The action is omission.**

Simple means. Almost entirely a simple-means condition.

- **Nothing smaller than an elbow in the ear.** Stopping cotton bud use prevents a large share of cases. Free, and the action is omission.
- **Drying the ear after water exposure** — head tilt, towel, cool hair dryer at a distance. Free.
- **Dilute acetic acid — household vinegar diluted with clean water.** Acidifies the canal and suppresses *Pseudomonas*, usable both as treatment for mild disease and as prophylaxis after swimming. Cost effectively zero.
- **Aural toilet with a cotton wick**, as for chronic suppurative disease: rolled cotton wool to absorb debris so that any drop can reach the skin.
- **A wick of ribbon gauze or compressed sponge** to open an occluded canal. Cents.
- **Paracetamol for pain.** Listed, cents.
- **Leaving wax in place.** Free, and preventive.
- **An otoscope and a torch** for diagnosis.

What the chain minimally requires: for uncomplicated disease, essentially nothing beyond clean water, vinegar, cotton wool and an analgesic. For necrotising otitis externa, a 6 to 12 week course of systemic antipseudomonal antibiotic, imaging and inpatient care — a genuine hospital requirement, and the one form where simple means are inadequate.

Gaps. No global prevalence or incidence figure exists on the sources read; the roughly 10 per cent lifetime incidence figure is widely cited and unverified. Cure rates with topical therapy, about 65 to 80 per cent at one week, could not be verified. The relative contribution of primary dermatitis against infection in chronic cases is not established, and in practice the two are treated together. Optimal treatment duration is unsettled. Necrotising otitis externa incidence and mortality figures were not obtainable. Whether acidifying prophylaxis prevents recurrence has limited trial support.

> **Depth.** Starts in: Pseudomonas. Size: 2 µm†; depth +3.44. First complaint: about 34 hours († 1–2 days); time depth 43.81. One untreated course: about 8.4 days († 7–10 days); depth 45.44.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Cerumen impaction

What it is. Ear wax builds up and blocks the canal, so hearing dulls and the ear feels full. It is not a disease of dirtiness — wax is normal and protective, and impaction usually happens because of anatomy, hearing aids or attempts at cleaning. Removing it restores hearing immediately.

Measured. The World Health Organization names **cerumen impaction** among the causes of hearing loss acting across the life span and **gives no count**. No global prevalence figure was retrievable.

Prevalence is commonly reported at about **5 per cent** of healthy adults, far higher in older people — around **20 to 35 per cent** of nursing-home residents — and in children, in people with learning disability and in hearing aid users. The pattern is bimodal, with children and older adults most affected.

Its significance within this part of the chapter is specific: this is the only cause of hearing loss on the World Health Organization's list that is completely and immediately reversible at trivial cost. That makes its contribution to the 430 million rehabilitation-need figure worth isolating, and it is not isolated in any source read.

Where it starts.

- **Cotton bud use and self-cleaning**, which pushes wax inward and compacts it. The leading modifiable cause.

- **Hearing aid and earphone wear**, which occludes the canal and obstructs natural migration. The loop is worth naming: hearing aids cause impaction, and impaction reduces hearing aid benefit.
- **Narrow, tortuous or hairy ear canals; exostoses**.
- **Age** — wax becomes drier and keratin migration slows.
- **Dry, hard wax type** — genetically determined; the *ABCC11* genotype determines wet against dry earwax, and dry wax is more common in East Asian populations.
- **Learning disability and inability to report symptoms**, where impaction goes unnoticed.
- **Dermatitis or keratosis of the canal.**

Genuinely not known: why some canals self-clear perfectly and others impact repeatedly. Whether routine prophylactic wax removal in hearing aid users or older people improves outcomes has not been established by trial. Whether softening drops before irrigation reduce complications is supported by modest evidence only.

Cure status. CURABLE, unambiguously. Removing the wax restores hearing to the person's baseline immediately, in a single encounter, with no maintenance treatment and no residual deficit. The underlying tendency may recur, so the impaction can return — and each episode is fully and permanently resolved by removal, and a later impaction is a new episode rather than the persistence of the old one.

Alongside cataract, this is one of the few entries in the whole book where a single cheap intervention completely removes a functional deficit and then ends. It is also the cheapest of them. The distinction from refractive error is worth holding: a pair of spectacles is a prosthesis worn indefinitely, and wax removal is a procedure that ends.

Prevention.

- **Do not use cotton buds or insert anything into the canal.** The primary preventive instruction, and the action is omission. **MODERATE**, and free.
- **Regular ear checks in hearing aid users, older people in residential care, and people with learning disability**, which finds silent impaction that is being mistaken for sensorineural deterioration or cognitive decline. **MODERATE**.
- **Periodic softening drops — olive oil, or water-based drops — in people who impact repeatedly. WEAK**.
- **Cleaning hearing aid moulds and ear-tips. MODERATE**.
- **Avoiding ear candling**, which is ineffective and causes burns and occlusion. **STRONG** evidence of harm and no benefit. The action is omission.

Treatment.

1. **Cerumenolytic (softening) drops** — olive oil, almond oil, water, sodium bicarbonate solution, docusate, or carbamide peroxide. Cochrane found any drops better than no treatment, with **no clear difference between agents, including plain water and saline**. Not individually listed as cerumenolytics. Off-patent. **Near zero** for olive oil, water or bicarbonate.
2. **Irrigation (syringing) with an electronic irrigator or bulb syringe**, using body-temperature water, after softening. Effective and widely task-shiftable. Risks are perforation, otitis externa and vertigo, and it is contraindicated with a known perforation, previous ear surgery or a single hearing ear.
3. **Manual removal under direct vision** — curette, hook or microsuction. The safest method, especially with a perforation, and it requires a light source, instruments and training.
4. **Microsuction** — the specialist standard; needs a microscope and a suction unit.
5. **No treatment** where the wax is not occluding and not symptomatic. Wax does not require removal merely for being present. **The action is omission.**

Simple means. This is the cheapest curative intervention in the book.

- **Olive oil, plain water, or sodium bicarbonate solution as softening drops.** Cochrane found no clear superiority of proprietary agents over **water or saline**. Cost: effectively zero. A few drops twice daily

for several days often clears the impaction without any procedure at all, and it removes the proprietary product from the chain entirely.

- **Bulb syringe irrigation with clean body-temperature water.** A rubber bulb costs a few cents to a dollar and is reusable. It is task-shiftable to a community health worker after brief training. Water that is too cold or too hot causes vertigo, which is the main avoidable error.
- **A torch or otoscope and a curette.** Direct removal under vision.
- **The instruction to stop using cotton buds.** Free, and preventive.
- **Opportunistic ear examination in anyone complaining of hearing loss, before any audiology referral** — because in low-income countries 93 per cent have fewer than one audiologist per million people, and a blocked canal mistaken for sensorineural loss wastes the scarcest resource there is.

A bottle of cooking oil and a rubber bulb restore hearing in a condition the World Health Organization lists among the causes of global hearing loss. There is no cheaper restoration of a lost sense anywhere in medicine.

Gaps. The World Health Organization names cerumen impaction as a cause of hearing loss and gives no count, so its share of the 430 million rehabilitation-need figure is unknown — a significant gap, because this component is trivially reversible and the rest largely is not. All prevalence figures above are unverified. Cochrane's finding that water performs as well as proprietary cerumenolytics could not be verified. Whether routine prophylactic removal in high-risk groups helps is untested. Complication rates of irrigation against microsuction are not well quantified, and practice differs sharply between countries on whether irrigation should be used at all.

> **Depth.** Starts in: a plug of earwax. Size: 5 mm†; depth +10.56. First complaint: about 10 weeks († weeks to months); time depth 47.41. One untreated course: no number.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Tinnitus

What it is. Hearing a sound — ringing, hissing, buzzing — that has no outside source. It usually comes with hearing loss. For most people it is an occasional nuisance; for a minority it is disabling and dominates their life.

Measured. No global figure was retrievable. Tinnitus is **not quantified** on the World Health Organization hearing fact sheet or in the World report on hearing executive summary read. Prevalence is commonly reported at about **10 to 15 per cent** of adults experiencing chronic tinnitus, with roughly **1 to 2 per cent** describing it as severely bothersome or disabling†. It rises with age, tracking hearing loss, and is expected to rise with recreational noise exposure, since **over 1 billion** young adults are at risk from unsafe listening and tinnitus commonly accompanies noise injury. It is strongly associated with depression, anxiety and insomnia, and the degree of distress correlates poorly with the measured loudness of the tinnitus.

Where it starts.

- **Hearing loss of any cause** — the dominant association: presbycusis, noise-induced loss, otosclerosis, sudden sensorineural loss.
- **Noise exposure** — acute acoustic trauma frequently produces immediate tinnitus.
- **Ototoxic drugs** — aspirin in high dose, aminoglycosides, loop diuretics, cisplatin, quinine. Salicylate tinnitus is reversible; aminoglycoside and cisplatin tinnitus is usually not. See the ototoxicity entry.
- **Cerumen impaction and middle ear disease** — reversible causes, worth excluding because they are curable.
- **Ménière disease; vestibular schwannoma**, for which unilateral tinnitus is the red flag.
- **Temporomandibular joint dysfunction, neck injury**.
- **Depression, anxiety, insomnia, stress** — bidirectional; they amplify distress and are worsened by it.

- **Pulsatile tinnitus** — a separate category requiring vascular investigation for dural fistula, stenosis or glomus tumour.

Genuinely not known: what generates the sound. The leading account is maladaptive central gain increase after reduced peripheral input, and it is not established, and no measurement identifies the generator in a given patient. Why distress correlates so poorly with psychoacoustic loudness is the central puzzle, and it is the reason treatment targets distress rather than the sound. Why some people habituate spontaneously and others do not is unexplained. There is no objective test for tinnitus at all; it is defined entirely by report.

Cure status. RELIEF ONLY. No treatment reliably abolishes tinnitus. No drug has been shown to eliminate it, no device removes it, and no surgery cures it.

The exceptions are the cases with a curable cause: cerumen impaction, otitis media with effusion, a perforation, and salicylate toxicity. Remove the cause and the tinnitus goes. These are a small minority and they are the reason every patient deserves an ear examination.

What is genuinely effective is reducing the distress and disability. Cognitive behavioural therapy has the best evidence of any intervention, improving tinnitus-related quality of life and distress without changing the sound itself. That is relief, and it is real relief, and the percept remains. Many people habituate over months to years.

Prevention. Prevention is almost entirely prevention of the hearing loss and noise injury that cause it.

- **Noise exposure limits and hearing protection.** The primary preventive measure, given that over 1 billion young adults are at risk from unsafe listening. **STRONG** mechanistically; see the noise-induced hearing loss entry for the dose-response.
- **Ototoxic drug stewardship** — avoiding unnecessary aminoglycosides, monitoring where unavoidable, dose-limiting. **STRONG**. The World Health Organization names rational use of medicines among its prevention measures.
- **Treating cerumen impaction and middle ear disease**, which prevents a curable cause becoming a chronic complaint. **MODERATE**, and trivially cheap.
- **Avoiding high-dose aspirin and quinine where alternatives exist. MODERATE**.
- **Treating depression, anxiety and insomnia**, which reduces the probability that tinnitus becomes disabling rather than merely present. **MODERATE**.
- **Not reinforcing catastrophic beliefs at first presentation.** Telling a patient that nothing can be done plausibly worsens outcome, while early explanation supports habituation. **WEAK**. Free, and the action is omission.

Treatment.

1. **Cognitive behavioural therapy, including internet-delivered therapy.** The best-evidenced intervention; it improves tinnitus-related quality of life and reduces distress, with no effect on perceived loudness. Not a medicine. Cost: a therapist's time, which internet-delivered programmes reduce substantially.
2. **Hearing aids where there is hearing loss.** Amplification reduces the contrast between the tinnitus and ambient sound, and treats the associated loss. A device, not listed. Access gap **83 per cent**. **hundreds of US dollars** to **thousands of US dollars per pair**.
3. **Sound enrichment or masking** — environmental sound, a fan, a radio at low volume, white noise, bedside sound generators. Cheap, widely used, modest evidence.
4. **Tinnitus retraining therapy** — directive counselling plus sound therapy.
5. **Treating the curable causes** — cerumen removal, middle ear disease, stopping a causative drug.
6. **Antidepressants and anxiolytics** for comorbid depression and anxiety, not for tinnitus itself; no antidepressant has established efficacy against tinnitus. Amitriptyline and fluoxetine are listed, off-patent, cents per day.
7. **Cochlear implantation** in profound loss, which frequently suppresses tinnitus as a secondary benefit.

8. **Not effective and not recommended: betahistine, ginkgo biloba, zinc, melatonin, repetitive transcranial magnetic stimulation.** None has established benefit, and Cochrane reviews are negative or inconclusive. **The action is omission**, and stating it matters, because the volume of ineffective commercial treatment sold for tinnitus is large.

Simple means. Better than the absence of a cure suggests, and almost all of it is free.

- **Ear examination and wax removal.** A torch, a curette or a bulb syringe. Removes the curable minority. Cost: near zero; see the cerumen entry.
- **Sound enrichment with whatever is available** — an open window, a fan, a radio at low volume, running water. The principle is that tinnitus is most intrusive in silence. Cost: zero.
- **Explanation at first presentation:** that the sound is common, that it is not a sign of brain disease, and that most people habituate. Free, and it plausibly changes the trajectory, because distress and not loudness determines disability.
- **Sleep hygiene and bedside sound**, since insomnia is the commonest route from tinnitus to disability.
- **Hearing protection** — cents per pair of earplugs — to prevent worsening.
- **Self-help and internet-delivered cognitive behavioural therapy**, which removes the therapist cost from the best-evidenced treatment.
- **Stopping high-dose aspirin or quinine** where it is the cause. Free, and curative in that case. The action is omission.
- **Not spending money on ineffective supplements.** Ginkgo, zinc and melatonin lack established benefit; not buying them is a direct saving.

What the chain minimally requires: nothing, for the core management. Tinnitus is the condition in this chapter where the gap between what is sold and what works is widest, and where free measures constitute most of the real benefit.

Gaps. No global prevalence or burden figure exists on any source read — the hearing fact sheet and the World report on hearing do not quantify tinnitus at all, despite its burden. All prevalence figures above are unverified. There is no objective measure of tinnitus, so all trial endpoints rest on self-report questionnaires, which limits comparability between studies. The poor correlation between loudness and distress is unexplained. Cognitive behavioural therapy effect sizes could not be verified. Many commonly sold treatments have negative or inconclusive evidence, and sources promoting them disagree with the Cochrane assessments; the Cochrane position is the better-evidenced one and is the one recorded here.

> **Depth.** Starts in: an inner-ear hair cell (hearing loss). Size: 30 µm†; depth +5.91. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: no number († chronic).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Ménière disease

What it is. Attacks of violent spinning vertigo lasting hours, with hearing loss, ringing and a feeling of fullness in one ear. Between attacks the person may be well, and the hearing in that ear declines step by step over years.

Measured. No global figure was retrievable; vestibular disorders are not quantified on the World Health Organization hearing sources read. Prevalence is commonly reported at about **20 to 200 per 100,000**, and the tenfold range reflects inconsistent diagnostic criteria†. Onset is typically between **40 and 60**†, and it is more common in women†. It is reported more frequently in populations of European ancestry, though ascertainment likely explains part of that.

The natural history matters for the label. Attacks typically remit over years while the hearing loss becomes permanent and progressive, often ending in a burnt-out ear with stable moderate to severe loss and few attacks. Bilateral involvement develops in a substantial minority over decades.

Where it starts.

- **Endolymphatic hydrops** — raised pressure and volume of inner ear endolymph is the pathological finding, demonstrated histologically and now on delayed gadolinium imaging. Hydrops is also found in people without Ménière disease and the causal link is not settled.
- **Family history** — reported in a minority, suggesting a genetic contribution.
- **Autoimmune and allergic associations**.
- **Migraine** — strongly comorbid, and vestibular migraine is the principal differential diagnosis and is frequently misdiagnosed as Ménière disease.
- **Prior viral labyrinthitis, head trauma, syphilis**.
- **High salt intake** — the basis of the standard dietary advice, though the evidence that it triggers attacks is weak.

Genuinely not known: the cause. Whether endolymphatic hydrops is the cause, a consequence or an epiphenomenon is unresolved after more than a century. Why attacks occur when they do — the triggers patients report, salt, stress, caffeine, weather, are not confirmed by controlled study. Whether Ménière disease is one condition or several with a shared presentation is genuinely open. There is no diagnostic test; diagnosis is by criteria applied to a history, which is why prevalence estimates vary tenfold.

Cure status. Vertigo attacks: CONTROLLABLE. Hearing loss: RELIEF ONLY. Nothing cures Ménière disease and nothing restores the hearing it has taken.

The attacks can be suppressed. Intratympanic gentamicin ablates vestibular function in the affected ear and controls vertigo in a high proportion, and surgical labyrinthectomy or vestibular neurectomy controls it almost completely — and these work by destroying the balance organ, which is a trade rather than a cure, and they carry hearing loss risk with gentamicin or require an already-deaf ear for labyrinthectomy.

Betahistine, the most widely prescribed drug for the condition in many countries, was found **ineffective against placebo** in the BEMED randomised trial — an important negative result given its prescribing volume. The sensorineural hearing loss is permanent and progressive.

Prevention.

- **Nothing prevents the disease.** No primary prevention is established.
- **Low-salt diet and diuretics to reduce attack frequency.** Long-standing standard advice with weak supporting evidence; Cochrane assessments of diuretics find insufficient evidence. **WEAK/CONTESTED**. It is free and harmless, which is why it persists.
- **Avoiding caffeine, alcohol and tobacco; stress management; adequate sleep. WEAK**.
- **Treating comorbid migraine.** Where vestibular migraine coexists or is the actual diagnosis, migraine prophylaxis can greatly reduce attacks. **MODERATE** for that group, and it matters because misdiagnosis is common.
- **Hearing protection in the affected ear. WEAK**, and sensible.
- **Preventing injury during attacks.** An attack causes sudden falls, and lying down immediately prevents fracture. **MODERATE** for injury prevention, and free.

Treatment. For the acute attack: 1. **Vestibular sedatives — prochlorperazine, promethazine, cinnarizine, or an antihistamine** for the hours of the attack, plus antiemetics and lying still. Promethazine and prochlorperazine are listed, off-patent, cents per dose. Not for long-term use, because they impede central compensation.

For attack prevention:

2. **Low-salt diet and a thiazide diuretic.** Weak evidence. Hydrochlorothiazide listed, off-patent, cents per day.
3. **Betahistine. Ineffective against placebo in BEMED**. Not on the Essential Medicines List. Off-patent. Widely prescribed despite the trial result. **Not prescribing it is the evidence-based action, and it is a direct saving.**
4. **Intratympanic corticosteroid (dexamethasone).** Reduces attacks with no hearing loss risk, and is the preferred second-line step. Dexamethasone listed, off-patent, cents per dose — the drug is trivially

cheap and the delivery is an office procedure. The United Nations Children's Fund indicative price for dexamethasone 4 mg tablets, read October 2026, was **US$24.00 per 100**, about **US$0.24 per tablet**.

5. **Intratympanic gentamicin.** Chemical ablation of vestibular function; a high vertigo control rate with a real risk of further hearing loss. Gentamicin listed, off-patent, cents.
6. **A positive pressure device.** Not shown effective.
7. **Endolymphatic sac surgery.** Efficacy disputed; sham-controlled studies have questioned it.
8. **Labyrinthectomy or vestibular neurectomy.** Definitive vertigo control; the former destroys hearing and is reserved for already-deaf ears.
9. **Vestibular rehabilitation** between attacks, and a **hearing aid** for the loss.
10. **Migraine prophylaxis** where vestibular migraine is likely — propranolol, amitriptyline, both listed, both off-patent, cents per day.

Simple means.

- **Lying still in a dark quiet room during an attack**, and not trying to move until it passes. Free, and it is what most patients do because it is what works.
- **Lying down at the first warning symptom** — the aural fullness or tinnitus change that often precedes the vertigo — to prevent falls and fractures. Free, and the highest-value simple instruction in the entry.
- **Low-salt diet.** Free. Weak evidence, no harm.
- **Avoiding caffeine and alcohol** if the patient identifies them as triggers. Free.
- **A home diary of attacks**, which distinguishes Ménière disease from vestibular migraine better than any test available in a low-resource setting — and migraine *is* treatable with cheap listed drugs. A notebook.
- **Prochlorperazine or promethazine** for the attack: listed, off-patent, cents.
- **Not paying for betahistine**, which BEMED found no better than placebo. **The action is omission**, and it is a direct saving in a drug prescribed at high volume.
- **Vestibular rehabilitation exercises**, taught once and performed at home, for the between-attack imbalance. Free after instruction.
- **A hearing aid** for the loss; the access gap is 83 per cent.

What the chain minimally requires: the intratympanic and surgical options need an ear, nose and throat service and a microscope. Nothing simple alters the disease course, and the free measures cover the attack management, the fall prevention and the differential diagnosis.

Gaps. No global prevalence or burden figure exists on the sources read, and vestibular disorders generally are absent from the World Health Organization's hearing figures. The tenfold prevalence range reflects genuinely inconsistent diagnostic criteria rather than differing populations. The cause is unknown and the role of endolymphatic hydrops is disputed. Betahistine is widely prescribed and BEMED found it ineffective; prescribing practice and trial evidence directly disagree, and both facts are recorded. Diuretic evidence is insufficient by Cochrane assessment while the practice is near-universal. Endolymphatic sac surgery efficacy is disputed with sham-controlled data against it. The frequency of misdiagnosis against vestibular migraine is unquantified and believed substantial.

> **Depth.** Starts in: the inner ear (endolymph). Size: 1 cm†; depth +11.19. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: about 7 hours ([B] an attack lasts hours); depth 42.37.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Benign paroxysmal positional vertigo

What it is. Crystals that belong in one part of the inner ear fall into a balance canal. Turning over in bed or looking up then sets off a short, violent spinning that lasts under a minute. A head-turning manoeuvre in the clinic usually fixes it on the spot.

Measured. No global figure was retrievable; vestibular disorders are not quantified on the World Health Organization hearing sources read. This is the **commonest cause of vertigo**, accounting for a large share of all vertigo presentations, with lifetime prevalence commonly reported at about **2.4 per cent** and one-year prevalence about **1.6 per cent**†.

Incidence rises markedly with age, and it is a major and frequently missed contributor to falls in older people. Falls carry **53.1 million** years lived with disability in Global Burden of Disease 2023, 95% uncertainty interval 38.4 to 72.2, the fourth leading cause. It is about twice as common in women, and recurrence runs roughly **15 to 50 per cent** within a few years†.

This is among the highest-value diagnoses in the chapter, because it is extremely common, frequently misattributed to cerebrovascular disease or to "dizziness in the elderly", and corrected in minutes at no cost.

Where it starts.

- **Displacement of otoconia** — calcium carbonate crystals — from the utricle into a semicircular canal, most often the posterior canal. This is the mechanism and it is well established.
- **Age** — otoconial degeneration.
- **Head trauma** — a common identifiable precipitant, and it causes bilateral or multi-canal disease more often.
- **Prolonged bed rest or supine positioning**, including after surgery or dental work.
- **Vestibular neuritis, Ménière disease, prior inner ear disease**.
- **Osteoporosis and low vitamin D** — associated with incidence and recurrence, and vitamin D and calcium supplementation reduced recurrence in at least one trial.
- **Female sex; migraine**.

Genuinely not known: why otoconia detach when they do, and why in one canal and not another. Why recurrence rates vary so widely. Most cases are idiopathic, with no precipitant identified. Why some patients have persistent subjective unsteadiness after the positional vertigo has been cured is unexplained.

Cure status. CURABLE, and it is the fastest cure in this book. A particle-repositioning manoeuvre — the **Epley** manoeuvre for posterior canal disease — resolves the condition in a single session in a large majority, with reported success of roughly **80 per cent** after one manoeuvre and above **90 per cent** after repeat manoeuvres†. Cochrane supports the Epley manoeuvre as effective against sham.

The condition also remits spontaneously over weeks to months in many people, so it is partly self-limiting, and there is no reason to wait when a minute of treatment ends it. Recurrence happens in a substantial minority, and each recurrence is again curable by the same manoeuvre. The cure is complete, immediate, free and repeatable.

Prevention.

- **Nothing reliably prevents a first episode.**
- **Vitamin D and calcium supplementation in people with low vitamin D and recurrent disease.** Reduced recurrence in trial data. **MODERATE** for that group. Both are cheap and listed.
- **Head protection and avoiding head trauma. MODERATE** for traumatic disease.
- **Avoiding prolonged supine immobility where possible. WEAK**.
- **Teaching patients the self-manoeuvre so recurrences are treated at home without a consultation.** Prevents disability and falls rather than the condition. **MODERATE**, and free.
- **Treating this condition as part of falls prevention in older people**, which removes a correctable fall cause. **MODERATE**.

Treatment.

1. **The Epley (canalith repositioning) manoeuvre** for posterior canal disease. About 80 per cent resolution after one manoeuvre, above 90 per cent with repetition†. Not a medicine. **Cost: zero.** It takes about two minutes and needs only a couch.
2. **The Semont manoeuvre** — an alternative with comparable efficacy.
3. **The barbecue roll, or Lempert, manoeuvre** for horizontal canal disease.
4. **Brandt-Daroff exercises** — performed by the patient at home; less effective per session than Epley and requiring no clinician. Free.
5. **Vestibular rehabilitation** for residual unsteadiness after successful repositioning.
6. **Vestibular sedatives are not recommended.** Prochlorperazine, cinnarizine and antihistamines do not treat this condition, they impede central compensation, and they cause falls and sedation in older people. They are nonetheless very widely prescribed for it. **The action is omission**, and stating it matters: the standard drug treatment for "dizziness" is actively harmful in the commonest cause of dizziness.
7. **Posterior canal occlusion surgery** for intractable disease; very rarely needed.

Simple means. This is the purest simple-means entry in the book: the diagnosis and the cure are both performed with a pair of hands and a flat surface.

- **The Dix-Hallpike test** for diagnosis. The examiner lowers the patient's head back and to one side and watches the eyes for a few seconds of rotatory nystagmus. Equipment: a couch. Cost: zero.
- **The Epley manoeuvre** for cure. Four head positions, about 30 seconds each, with about 80 per cent cured in one session†. Equipment: a couch. **Cost: zero.**
- **Brandt-Daroff exercises** taught to the patient for home use, for recurrences. Cost: zero.
- **Teaching the manoeuvre to primary care staff, nurses and community health workers.** Highly task-shiftable; it requires manual skill, not equipment or drugs. In low-income countries 78 per cent have fewer than one ear, nose and throat specialist per million people, so this capability must sit outside specialist services to be useful at all.
- **Not prescribing vestibular sedatives.** The action is omission: a zero-cost improvement that removes a fall risk and a sedation risk in exactly the age group most harmed by both, and it saves the cost of the drug.
- **Vitamin D and calcium** where deficient and recurrent — listed, off-patent, cents per day.

A very common, frightening, fall-causing condition is cured in two minutes with no equipment, no drug and no supply chain whatever. The binding constraint is purely whether the clinician knows the manoeuvre.

Gaps. No global prevalence or burden figure exists on the sources read; vestibular disorders are entirely absent from the World Health Organization's hearing figures. All prevalence and success-rate figures in this entry are unverified, including the 2.4 per cent lifetime prevalence and the 80 per cent single-manoeuvre success. Recurrence rate estimates range from about 15 to 50 per cent and sources disagree. The vitamin D recurrence-prevention finding rests on limited trial data. How often this condition is missed in primary care, and how much of the dizziness and falls burden in older people it accounts for, is not quantified in any source read, though it is widely held to be substantial. Vestibular suppressant prescribing for it remains common despite evidence against it.

> **Depth.** Starts in: an otoconium (ear crystal). Size: 10 μm†; depth +4.91. First complaint: about 5 seconds ([B] directly on turning the head); time depth 34.62. One untreated course: about 30 seconds ([B] shorter than a minute); depth 36.25.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Vestibular neuritis and labyrinthitis

What it is. The balance nerve of one ear becomes inflamed, usually after a viral illness. Sudden severe spinning, vomiting and inability to stand, lasting days. The brain then relearns balance over weeks, and moving about speeds that up rather than slowing it.

Measured. No global figure was retrievable and the condition is not quantified on the World Health Organization hearing sources read. Annual incidence is commonly reported at about **3.5 to 15 per 100,000**†, peaking in middle age, ages 30 to 60†.

Most people recover functionally within weeks to months through central compensation, and caloric testing often shows **permanent unilateral vestibular hypofunction** — the nerve does not fully recover even when the person does. A minority develop persistent dizziness, and benign paroxysmal positional vertigo follows in a proportion of cases. Labyrinthitis — the same process involving the cochlea as well — adds hearing loss and tinnitus, and that hearing loss is often permanent.

Where it starts.

- **Presumed viral or post-viral inflammation of the vestibular nerve**, with reactivation of latent herpes simplex virus type 1 in the vestibular ganglion as the leading hypothesis†.
- **A preceding upper respiratory tract infection** — reported in a substantial proportion.
- **The superior vestibular nerve division** is affected far more often than the inferior, attributed to its longer bony canal.
- **Vascular occlusion of the labyrinthine artery** — an alternative mechanism in some cases, particularly with hearing loss.
- **Bacterial labyrinthitis** — from otitis media or meningitis; a different and more dangerous entity with high rates of permanent deafness.

Genuinely not known: whether it is viral at all. The herpes simplex reactivation hypothesis rests largely on post-mortem and indirect evidence and has never been confirmed in life, which is precisely why antiviral treatment has no established role. Why only one nerve division is usually affected. Why some patients fail to compensate centrally and develop persistent postural-perceptual dizziness while most recover — this is the clinically important unknown and no predictor exists.

The critical diagnostic unknown is the one that matters at the bedside: a cerebellar or brainstem stroke can present identically. The head-impulse, nystagmus, test-of-skew examination distinguishes them with reported sensitivity exceeding early magnetic resonance imaging in expert hands, and it requires skill, and misdiagnosis in both directions is common.

Cure status. SELF-LIMITING. The acute attack resolves without treatment, and functional recovery occurs through central compensation over weeks, which is a reorganisation of the brain rather than healing of the nerve. Most people return to normal function.

The qualification: the peripheral vestibular deficit is often permanent on testing, and in labyrinthitis the hearing loss is often permanent. The illness is self-limiting while the damage may not be.

Corticosteroids improve caloric recovery of vestibular function and have **not been shown to improve the outcome patients care about** — long-term symptoms and function; Cochrane found insufficient evidence of clinical benefit. Antivirals are not effective. The one intervention that demonstrably improves the course is vestibular rehabilitation exercise, which is free.

Prevention.

- **Nothing prevents vestibular neuritis.** No primary prevention is established.
- **Prompt treatment of otitis media and meningitis**, which prevents bacterial labyrinthitis and the deafness it causes. **STRONG** for that specific route. This connects to the otitis media entries.
- **Measles, mumps, rubella, *Haemophilus influenzae* type b and pneumococcal vaccination**, which prevent the infections that cause labyrinthitis and infective deafness. **STRONG**. The World Health Organization names immunization among its prevention measures, and global coverage of the measles first dose was **84 per cent** in 2025, with both doses at **77 per cent**.

- **Early mobilisation and vestibular exercises during the acute illness**, which prevents prolonged disability rather than the disease. **STRONG**, and free.
- **Avoiding prolonged vestibular sedative use**, which prevents delayed compensation. **MODERATE**, and the action is omission.

Treatment.

1. **Vestibular rehabilitation exercises, begun as early as tolerated.** The best-evidenced treatment; it accelerates central compensation and reduces persistent symptoms. Not a medicine. **Cost: zero** after instruction.
2. **A short-course vestibular sedative for the first 24 to 72 hours only** — prochlorperazine, promethazine or an antihistamine, for the vomiting and the severity of the acute attack. Prochlorperazine and promethazine are listed, off-patent, cents per dose. **It must be stopped early**, because prolonging it delays compensation and worsens the eventual outcome.
3. **Antiemetics and rehydration.** Oral rehydration salts are listed at cents; the United Nations Children's Fund indicative price for low-osmolarity sachets, read October 2026, was **US$4.80 per carton of 100**, about **US$0.048 per sachet**. Intravenous fluid where vomiting prevents oral intake.
4. **Corticosteroids (methylprednisolone, prednisolone).** They improve measured vestibular function recovery; clinical benefit is not established and Cochrane found insufficient evidence. Listed, off-patent, cents per day. Widely prescribed on weak evidence.
5. **Antivirals are not effective**, alone or with steroids. A clear negative, and **the action is omission.**
6. **Antibiotics** only for bacterial labyrinthitis secondary to otitis media or meningitis, where they are urgent and hearing-saving. Amoxicillin and ceftriaxone are listed, off-patent, low cost.
7. **Treating subsequent benign paroxysmal positional vertigo** with the Epley manoeuvre, since it commonly follows. Free.
8. **A hearing aid** for permanent loss after labyrinthitis. Access gap 83 per cent.

Simple means. Nearly all of the effective management is free.

- **Vestibular rehabilitation exercises** — gaze stabilisation, head movements, balance and gait tasks, performed at home several times daily. This is the best-evidenced treatment for the condition and it costs nothing but a demonstration.
- **Getting up and moving as soon as tolerated**, rather than resting in a darkened room for a week. Movement is the treatment; immobility prolongs the illness.
- **Stopping the sedative after two to three days.** Free, the action is omission, and it improves the outcome.
- **Oral rehydration salts** — listed, cents, and they address the main acute danger in a vomiting patient.
- **The head-impulse, nystagmus, test-of-skew bedside examination** — the examiner's hands and eyes, no equipment, to separate this from a cerebellar stroke. This is the highest-stakes free procedure in the entry, because the two conditions look the same and one of them kills.
- **Prochlorperazine** for the acute vomiting: listed, off-patent, cents.
- **Explanation** that this is a self-limiting illness with a recovery measured in weeks, which prevents the anxiety-driven avoidance that produces persistent postural-perceptual dizziness.

What the chain minimally requires: nothing, for the standard management. Imaging is required only to exclude stroke where the bedside examination is equivocal or unavailable — and that is a scanner.

Gaps. No global incidence or burden figure exists on the sources read; vestibular disorders are absent from the World Health Organization hearing figures entirely. The 3.5 to 15 per 100,000 incidence range is unverified. The viral aetiology is unconfirmed, which is why antiviral trials were negative. Corticosteroid evidence is genuinely split: steroids improve laboratory measures of vestibular recovery while Cochrane finds insufficient evidence of clinical benefit, and prescribing practice follows the laboratory finding rather than the clinical one; both positions are recorded. Rates of misdiagnosis against posterior circulation stroke are substantial and not reliably quantified. No predictor exists for who will fail to compensate.

> **Depth.** Starts in: the herpes simplex virus. Size: 200 nm†; depth +1.35. First complaint: about 10 days († about 1–2 weeks after a cold); time depth 45.60. One untreated course: about 3.2 days ([B] days of spinning); depth 44.55.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: SELF-LIMITING. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Congenital and early-onset hearing loss

What it is. Hearing loss present at birth or appearing in the first years. A child who cannot hear cannot learn spoken language in the normal window, so the consequence is not only deafness but delayed language, schooling and livelihood. Found early, that consequence is largely avoidable.

Measured. 34 million children are among the 430 million people needing rehabilitation for disabling hearing loss, and **95.1 million** children aged 5 to 19 live with hearing loss. **Nearly 60 per cent of childhood hearing loss is due to avoidable causes** — the central figure for this entry.

The World Health Organization names the causes by period. Prenatal: genetic factors; intrauterine infections such as rubella and cytomegalovirus. Perinatal: birth asphyxia, hyperbilirubinaemia, low birth weight, other perinatal morbidities. Childhood and adolescence: chronic suppurative otitis media, chronic non-suppurative otitis media, meningitis and other infections. Across the life span: cerumen impaction, trauma, loud noise, ototoxic medicines, work-related ototoxic chemicals, nutritional deficiencies, viral infections, and delayed-onset or progressive genetic hearing loss.

Congenital hearing loss incidence is commonly reported at about **1 to 3 per 1,000** live births in high-income settings, higher where infection and perinatal morbidity are common. The World report on hearing's 2030 targets include a **20 per cent relative increase** in effective coverage of newborn hearing screening, and a 20 per cent relative reduction in chronic ear disease and unaddressed hearing loss in children aged 5 to 9.

The workforce constraint is severe. **50 per cent** of low-income countries have one or more teachers for the deaf per million population, and **17 per cent** have one or more speech therapists per million.

Where it starts.

- **Genetic causes** — roughly half of congenital hearing loss in high-income settings; *GJB2* (connexin 26) is the commonest single gene, and most genetic deafness is non-syndromic and autosomal recessive. The World Health Organization names genetic factors prenatally and delayed-onset genetic loss across the life span.
- **Congenital cytomegalovirus** — the commonest non-genetic cause of congenital sensorineural hearing loss, and frequently not present at birth but progressive, which is why a single newborn screen misses it. Named by the World Health Organization.
- **Congenital rubella** — vaccine-preventable, and named.
- **Birth asphyxia, hyperbilirubinaemia (kernicterus), low birth weight, prematurity, neonatal sepsis** — all named perinatally, and all are preventable or treatable with basic obstetric and newborn care. **13.4 million** babies were born preterm in 2020, about 1 in 10 of all births.
- **Neonatal aminoglycoside and ototoxic drug exposure** — see the ototoxicity entry; ototoxic medicines are named.
- **Meningitis** — a major cause of acquired childhood deafness, and it causes rapid cochlear ossification that makes later implantation harder, so timing matters. Vaccine-preventable in large part.
- **Chronic suppurative otitis media** — named as a childhood cause; see that entry.
- **Consanguinity** — raises recessive genetic deafness prevalence.

Genuinely not known: in a substantial share of children no cause is identified even after genetic and imaging investigation. Why congenital cytomegalovirus causes hearing loss in some infected infants and not others, and why it progresses when it does, is unexplained. The optimal age for cochlear implantation is agreed to be as early as possible, and the precise lower bound and the long-run outcome differences are still being established. Whether universal cytomegalovirus screening of newborns should be added to hearing screening is unresolved.

Cure status. The hearing: RELIEF ONLY. The language consequence: CURABLE. This split is the whole substance of the entry. The hearing loss itself is not curable. Sensorineural loss from genetic causes, cytomegalovirus, kernicterus or meningitis is permanent, and no drug or surgery restores cochlear function.

But the consequence that matters — absent spoken language — is largely preventable, and that depends entirely on timing. A child fitted with hearing aids or implanted within the first year, with family support and therapy, can develop age-appropriate spoken language; a child identified at age four usually cannot catch up fully. Cochlear implants restore functional hearing well enough for spoken language acquisition in congenitally deaf children implanted early.

Conductive loss from otitis media *is* curable — see those entries — and it is a substantial share of childhood hearing loss in low-income settings. So: RELIEF ONLY for the sensory deficit, with the strong qualification that early intervention converts a lifelong disability of language and livelihood into a managed hearing difference.

Prevention. This is where the "nearly 60 per cent avoidable" figure does the most work, and the measures are mostly cheap public health.

- **Rubella vaccination of girls and women of childbearing age.** Eliminates congenital rubella syndrome deafness. **STRONG**. The World Health Organization names immunization.
- ***Haemophilus influenzae* type b, pneumococcal and meningococcal vaccination**, which prevents meningitis deafness. **STRONG**.
- **Measles and mumps vaccination. STRONG**; the measles vaccine costs under **a few US dollars per child** and has been in use about sixty years.
- **Good maternal and newborn care** — preventing and treating birth asphyxia, hyperbilirubinaemia and neonatal sepsis. Named. **STRONG**. Phototherapy for jaundice prevents kernicterus and costs very little.
- **Ototoxic drug stewardship in neonates** — restricting and monitoring aminoglycosides. The World Health Organization names rational use of medicines. **STRONG**, and the action is omission.
- **Universal newborn hearing screening with otoacoustic emissions or automated auditory brainstem response, with defined follow-up.** It does not prevent the loss; it prevents the language disability. **STRONG** for that outcome, and it is a 2030 target†.
- **Treating otitis media promptly** to prevent chronic suppurative disease. Named. **STRONG**.
- **Genetic counselling.** Named explicitly. **MODERATE** for recurrence prevention in families.
- **Valganciclovir for symptomatic congenital cytomegalovirus**, which improves hearing outcomes in treated infants. **MODERATE**.

Treatment.

1. **Hearing aids, fitted as early as possible.** The first-line intervention for most degrees of loss. A device, not listed. Access gap **83 per cent** overall, 74 to 90 per cent across income levels. **hundreds of US dollars** to **thousands of US dollars per pair**.
2. **Cochlear implantation** for severe to profound loss, as early as feasible. It restores enough hearing for spoken language in early-implanted children. Not listed. The World report on hearing calls implants effective and cost-effective and **gives no cost and no access figure**. Reported total cost is approximately **US$30,000 to 100,000 per recipient** including surgery and rehabilitation in high-income systems. The access gap in low- and middle-income countries is near-total and is not quantified in the primary source.
3. **Early intervention: speech and language therapy, auditory-verbal therapy, family training.** The World Health Organization names speech and language therapy and counselling and support. The constraint is workforce: 17 per cent of low-income countries have one or more speech therapists per million people.
4. **Sign language instruction for the child and the family.** Named. Effective for language acquisition, and it does not depend on any device or power supply.

5. **Bone conduction and middle ear implants** for specific anatomical cases — named among hearing technologies.
6. **Educational support, captioning, classroom acoustics, loop systems, preferential seating.** Captioning and assistive technology are named.
7. **Treating conductive causes** — grommets, tympanoplasty, wax removal. Curative where applicable.
8. **Valganciclovir for symptomatic congenital cytomegalovirus**.

Simple means. Substantial, and concentrated in prevention and in language rather than in devices.

- **Vaccination — rubella, *Haemophilus influenzae* type b, pneumococcal, meningococcal, measles, mumps.** Cents to a few dollars per dose, listed vaccines, and they remove a large part of the "nearly 60 per cent avoidable" fraction†.
- **Phototherapy for neonatal jaundice, and basic newborn resuscitation.** Prevents kernicterus and asphyxia deafness at very low cost.
- **Sign language.** This is the genuinely supply-chain-free route to language for a deaf child. It requires no device, no battery, no audiologist and no surgery; it requires a family and a community willing to learn it, and someone to teach them. Where 50 per cent of low-income countries have at most one teacher for the deaf per million people, family-taught sign is often the only available path, and it works for language acquisition.
- **The whispered voice test, a simple noise-maker response test, or free smartphone audiometry** for screening where otoacoustic emission equipment does not exist.
- **Parental report and a structured question at every child health visit** — whether the child responds to a voice when the speaker is out of sight. Free, and it is the realistic detection method where no screening programme exists.
- **Ear examination and wax removal, and treating discharging ears** — cheap, and it addresses the conductive share, which is curable. See the chronic suppurative otitis media entry: a cotton wick and dilute vinegar.
- **Classroom measures:** seating the child at the front, facing them when speaking, reducing classroom noise, writing on a board. Free, and they materially change educational outcome.

The economics at scale: an additional **less than US$1.40 per person per year** scales ear and hearing care, with a return of **nearly US$16 per US$1** over ten years, averting nearly **130 million** disability-adjusted life years.

What the chain minimally requires: for a profoundly deaf child who is to acquire *spoken* language, a cochlear implant, a surgical service and years of therapy — unavailable to most of the world's deaf children. For that child to acquire *language*, sign language, which needs nobody's permission and no supply chain at all.

Gaps. The World Health Organization gives 34 million children with disabling hearing loss and 95.1 million children aged 5 to 19 with hearing loss, and **no breakdown by cause**, so the split between genetic, infective, perinatal and conductive causes is unknown globally, and the "nearly 60 per cent avoidable" figure cannot be decomposed. Congenital hearing loss incidence figures are unverified. The World report on hearing gives **no cochlear implant cost or access figure whatsoever**, which is a notable gap in the primary global source for a technology whose access gap is near-total in low-income settings. The optimal age limit for implantation, and the long-run comparison between early implantation and sign-based language acquisition, are not settled, and this is a genuinely contested area in which the clinical literature and Deaf community perspectives differ. Whether universal newborn cytomegalovirus screening should be added is unresolved.

> **Depth.** Starts in: connexin 26 of the inner ear (commonest single gene). Size: 10 nm†; depth −1.38. First complaint: about 9 months ([B] present at birth or in the first years; † from conception to birth); time depth 48.61. One untreated course: no number ([B] permanent).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. The book splits this entry by moment, early and late. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum:

> CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Ototoxicity

What it is. Some medicines poison the inner ear. The commonest are certain antibiotics used for tuberculosis and severe infection, and a chemotherapy drug used for many cancers. The hearing loss they cause is usually permanent, and it is nearly always avoidable.

Measured. The World Health Organization names **ototoxic medicines** and **work-related ototoxic chemicals** among the causes of hearing loss acting across the life span, and states that the common adult causes including ototoxic medicines are preventable. The World report on hearing recommends surveillance of ototoxicity and gives **no numeric figures at all**. No global count of ototoxic hearing loss was retrievable. This is a notable gap: the World Health Organization identifies it as a preventable cause and quantifies none of it.

Reported incidence by agent, all unverified:

- **Cisplatin** — hearing loss in a high proportion of treated patients, commonly reported above **60 per cent** in children receiving cumulative doses, dose-cumulative and usually permanent.
- **Aminoglycosides (gentamicin, amikacin, streptomycin, kanamycin)** — cochleotoxicity commonly reported in roughly **10 to 25 per cent** of courses, with vestibulotoxicity in addition; gentamicin is predominantly vestibulotoxic and amikacin predominantly cochleotoxic.
- **Multidrug-resistant tuberculosis regimens** containing injectable aminoglycosides historically caused hearing loss in a very large share of treated patients, reported above 50 per cent in some cohorts, which is a principal reason the World Health Organization moved to all-oral regimens. In 2024, **34,000** patients started the six-month all-oral regimens, against 5,653 in 2023 and 1,744 in 2022 (World Health Organization fact sheet, *Tuberculosis*, 24 March 2026).
- **Loop diuretics (furosemide)** — usually reversible, and they potentiate aminoglycoside toxicity.
- **High-dose salicylates and quinine** — usually reversible.
- **Mitochondrial *m.1555A>G* variant carriers** — profound hearing loss after even a single standard aminoglycoside dose.

All ages are affected. Neonates and young children on aminoglycosides, and children on cisplatin, are the highest-stakes groups, because the loss arrives before language and schooling. The burden falls where aminoglycosides and multidrug-resistant tuberculosis treatment are most used and audiometric monitoring is least available — the inverse of what is needed.

Where it starts.

- **Cumulative dose and peak serum concentration** of the agent — the primary determinant for both aminoglycosides and cisplatin.
- **Duration of therapy**.
- **Renal impairment** — reduces clearance and raises exposure.
- **Age** — the very young and the old.
- **Concurrent noise exposure** — synergistic with both aminoglycosides and cisplatin. The World Health Organization names loud noise and ototoxic medicines as co-occurring life-span causes.
- **Concurrent loop diuretics** — potentiate aminoglycoside toxicity.
- **Mitochondrial DNA variants, especially *m.1555A>G* and *m.1494C>T*** — maternally inherited hypersusceptibility, in which a single standard dose can cause profound permanent loss. Point-of-care genotyping before administration is feasible and has been implemented in some neonatal services.
- **Prior hearing loss**.

Genuinely not known: why susceptibility varies so widely outside the known mitochondrial variants. Whether any otoprotectant works reliably in humans — sodium thiosulfate reduced cisplatin hearing loss in children in the SIOPEL 6 and COG ACCL0431 trials, with a concern about reduced tumour control in

disseminated disease in one of them, which is an unresolved trade-off. The optimal monitoring schedule and the threshold for changing therapy are not established. Extended high-frequency audiometry detects loss earlier than standard audiometry, and whether acting on it improves outcomes has not been demonstrated.

Cure status. Aminoglycoside and cisplatin damage: RELIEF ONLY. Salicylate, quinine and loop diuretic effect: SELF-LIMITING.

The split is by agent and it is clinically decisive. Aminoglycoside and cisplatin damage destroys outer hair cells, typically beginning at the highest frequencies, and it is permanent. No treatment restores it, and it can progress after the drug is stopped. Salicylate, quinine and loop diuretic effects are usually reversible on discontinuation — genuinely self-limiting.

For the permanent forms, management is substitution: hearing aids, or cochlear implants for profound loss. No otoprotectant is established except the partial and contested cisplatin case above. Because nothing reverses it, this condition is defined by its prevention, which is why it belongs with noise-induced hearing loss as the most preventable entry in this part of the chapter.

Prevention. Ototoxic drug stewardship. The World Health Organization names rational use of medicines to prevent ototoxic hearing loss among its prevention measures, and the World report on hearing recommends ototoxicity surveillance.

- **Avoiding aminoglycosides where an equally effective alternative exists**, and using the shortest effective course. **STRONG**; the action is omission and it costs nothing, being a prescribing decision.
- **All-oral multidrug-resistant tuberculosis regimens replacing injectable aminoglycosides.** The World Health Organization's shift away from injectables removed a large share of iatrogenic deafness from tuberculosis programmes, and 34,000 patients started the six-month all-oral regimens in 2024. **STRONG**. This is the single largest documented ototoxicity prevention measure of recent years.
- **Once-daily rather than divided aminoglycoside dosing, with therapeutic drug monitoring, weight-based dosing and renal adjustment. MODERATE**.
- **Baseline and serial audiometry during treatment, including extended high-frequency audiometry**, so therapy can be changed before speech frequencies are lost. **MODERATE** — detection is reliable, and evidence that acting on it improves the final outcome is weaker.
- **Screening for *m.1555A>G* before aminoglycoside exposure** where feasible, which prevents catastrophic single-dose deafness in carriers; rapid point-of-care testing has been deployed in neonatal units. **MODERATE** for that group.
- **Avoiding concurrent noise exposure and concurrent loop diuretics. MODERATE**.
- **Sodium thiosulfate with cisplatin in children** — reduces hearing loss; **CONTESTED** because of the tumour-control concern in disseminated disease.
- **Avoiding ototopical aminoglycosides through a perforated eardrum** where a quinolone is available. **MODERATE**, and disputed; see the chronic suppurative otitis media entry.
- **Asking about hearing and tinnitus at every treatment visit.** Free, and the realistic detection method where no audiometry exists.

Treatment. There is no treatment that reverses aminoglycoside or cisplatin ototoxicity. What follows is substitution, salvage and the single protective agent.

1. **Stopping or substituting the offending drug** — the only action that changes the course. Free, and it reverses salicylate, quinine and diuretic effects completely. **The action is omission.**
2. **Sodium thiosulfate** as cisplatin otoprotection in children. Not on the Essential Medicines List. Off-patent as a molecule — it is an old, cheap compound — and cost is low. The barrier is the tumour-control question, not price.
3. **Hearing aids.** Access gap **83 per cent**, 74 to 90 per cent across income levels. A device, not listed. **hundreds of US dollars** to **thousands of US dollars per pair**.
4. **Cochlear implantation** for profound loss. Not listed. About **US$30,000 to 100,000** per recipient in high-income systems†; the World report on hearing gives no figure.

5. **Vestibular rehabilitation** for aminoglycoside vestibulotoxicity, which causes persistent imbalance and oscillopsia rather than deafness — gentamicin is predominantly vestibulotoxic and this disability is frequently missed. Free after instruction.
6. **Tinnitus management.** See that entry.
7. **No otoprotectant is established for aminoglycosides.**

Simple means. This entry's simple means are almost entirely acts of restraint and record-keeping, and they are free.

- **Not prescribing the drug.** Using a non-ototoxic alternative where one exists is the whole intervention. **The action is omission**, it costs nothing, and the World Health Organization's rational-use recommendation is precisely this.
- **Weight-based once-daily dosing, renal adjustment, shortest course.** A calculation and a prescribing habit. Free.
- **Asking whether hearing has changed or ringing has started, at every visit**, and recording the answer. Free, deliverable by any health worker, and in programmes without audiometry it is the only early-warning system available.
- **A maternal family history question before aminoglycosides.** Deafness after injections in maternal relatives suggests a mitochondrial variant and should change the drug. Free, and it prevents the most catastrophic form.
- **Free or low-cost smartphone audiometry** for serial monitoring where 93 per cent of low-income countries have fewer than one audiologist per million people. This is the practical substitute for a sound booth.
- **A written card given to the patient**, recording that they have had an ototoxic drug and their last hearing status, so that cumulative exposure across episodes of care is visible. It costs a card.
- **Avoiding noise during and after treatment.** Free, and it reduces synergistic damage.
- **Using a topical quinolone rather than aminoglycoside ear drops** where the drum is perforated — a few dollars a bottle.

What the chain minimally requires: nothing for prevention beyond prescribing discipline and a question. Audiometric surveillance requires equipment, and smartphone audiometry has lowered that threshold substantially.

Gaps. This is the largest quantitative gap in this part of the chapter. The World Health Organization identifies ototoxic medicines as a preventable cause of hearing loss across the life span and the World report on hearing recommends surveillance, and **neither gives a single number** — no global count, no disability-adjusted life year figure, no incidence. Every incidence figure above is unverified and the ranges are wide: aminoglycoside cochleotoxicity reported from about 10 to 25 per cent; cisplatin loss in children reported above 60 per cent; historic injectable tuberculosis regimens above 50 per cent. Sources disagree on sodium thiosulfate: SIOPEL 6 and COG ACCL0431 both showed hearing protection and differed on tumour-control safety in disseminated disease, and that disagreement is unresolved and material. Optimal monitoring schedules and the threshold for changing therapy are not established. Whether acting on extended high-frequency changes improves final speech-frequency outcomes has not been demonstrated. The prevalence of mitochondrial susceptibility variants varies by population and is not globally characterised.

> **Depth.** Starts in: a medicine molecule. Size: 1 nm†; depth −3.48. First complaint: about 9 days († days to weeks of therapy); time depth 45.52. One untreated course: no number ([B] usually permanent).
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The bound applies. The medicine can be stopped. Hair cells that were lost do not regrow. So it is held, not ended. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

ICD-11 Chapter 14 — Diseases of the skin

A note on this part's provenance

Condition-level global prevalence counts for the skin chapter were not retrievable. Global Burden of Disease 2023 gives dermatitis as a group — atopic, contact and seborrhoeic — **15.2 million** years lived with disability, 95% uncertainty interval 8.9 to 24.2, the **eighteenth leading cause** of years lived with disability. Global Burden of Disease 2021 analyses exist for immune-related, allergic-related and fungal skin disease, and all were unreachable, as was the World Health Organization psoriasis fact sheet. Consequently most prevalence figures in this part carry daggers: reported as commonly carried, with the source not opened.

Three entries are the exception and are well sourced from World Health Organization pages read off the page this week: scabies, bacterial skin infection in its scabies-related part, and burns. Those figures were read off the page, and each names the page and its printed date. Hidradenitis suppurativa and bullous pemphigoid, written after this note, almost wholly carry daggers, and the key trials of the bullous pemphigoid entry were not checked against their primary reports.

Atopic dermatitis (eczema)

What it is. A long-running itchy skin inflammation. The skin barrier leaks water and lets irritants and allergens in, so the skin is dry, red and intensely itchy, and scratching makes it worse. It usually starts in infancy and often improves with age.

Measured. Global Burden of Disease 2023 gives dermatitis as a group — atopic, contact and seborrhoeic — **15.2 million** years lived with disability, 95% uncertainty interval 8.9 to 24.2, the eighteenth leading cause. Atopic dermatitis is the largest component of that group.

Prevalence is commonly reported at about **15 to 20 per cent of children** and **2 to 10 per cent of adults**, with wide international variation†. Onset is before age 5 in the large majority; a substantial share remit by adolescence, and a minority persist or begin in adulthood. International surveys found large variation, with rising prevalence in low- and middle-income countries undergoing urbanisation. Prevalence rose substantially in high-income countries through the late twentieth century and has plateaued in several, and is still rising in many low- and middle-income countries.

Where it starts.

- **Filaggrin loss-of-function mutations** — the strongest single genetic risk factor, carried by a substantial minority of European patients, producing a defective skin barrier. The effect size is large relative to most complex-disease variants.
- **Family history of atopy** — the strongest clinical predictor.
- **Skin barrier dysfunction with raised transepidermal water loss**, present before eczema appears.
- ***Staphylococcus aureus* colonisation** — near-universal in affected skin, and it drives flares.
- **Urban living, hard water, low humidity, soap and detergent exposure**.
- **Food allergy** — strongly comorbid. The direction of causation now favours eczema preceding and enabling food sensitisation through the broken barrier, rather than food causing the eczema. That reversal matters clinically: dietary elimination is not an eczema treatment.

Genuinely not known: whether the primary defect is the barrier or the immune response. The outside-in against inside-out question is unresolved, and it determines whether barrier repair should be able to prevent the disease. The failure of the emollient prevention trials below is direct evidence against the simplest barrier-first account. Why most children outgrow it and some do not. Why prevalence rose so fast in a few decades, which rules out genetic change and implicates environment without identifying the factor.

Cure status. CONTROLLABLE. No treatment removes atopic dermatitis. Disease can be brought to clear or near-clear skin and held there — topical therapy for most, systemic therapy for the severe minority, with dupilumab and JAK inhibitors achieving high rates of clearance — and stopping treatment generally allows relapse, and the atopic tendency persists. A substantial share of childhood cases remit spontaneously with age, which is genuine resolution rather than treatment effect.

Prevention.

Emollient use in infancy to prevent eczema is the clearest case in this book of a plausible, cheap intervention that failed when properly tested, and the results must be read together.

- **BEEP (Barrier Enhancement for Eczema Prevention).** 1,394 term infants at high risk, randomised to 693 receiving daily emollient plus skincare advice against 701 receiving skincare advice alone, with emollient applied daily through the first year. Result: **no difference** between groups in the number of children who developed eczema at age 2, nor in how early it appeared, nor in how severe it was. A 2024 review records the conclusion as "daily emollient application during the first year of life does not prevent atopic dermatitis", with eczema diagnosis comparable in both groups at 3, 4 and 5 years.

Harms: infants in the daily emollient group were at **slightly increased risk of skin infections** and had a **slightly higher rate of food allergy**. **The exact event rates, relative risks and confidence intervals could not be retrieved** — the journal full text and the trial report both failed to load — so the harms are carried directionally and the exact rates could not be confirmed.

Cost-effectiveness: first-year emollient treatment was found **not cost-effective**.

- **PreventADALL.** Factorial, multicentre, cluster-randomised. The 2024 review reports **2,379** neonates in its text and **2,397** in its own Table 1; the review is internally inconsistent and both figures are printed. 597 were in the emollient group and 583 in the combined intervention group. The intervention was a skin emollient — oil bath additives plus facial cream — and/or early complementary feeding. Result: **skin emollients did not reduce development of atopic dermatitis by age 12 months**. Full protocol adherence in the skin intervention group was only **32 per cent**, which is a real limitation on interpretation.
- **STOP-AD.** 321 infants, 161 intervention and 160 control. Daily emollient **until 2 months of age only** reduced incidence in the first year in high-risk infants; the review gives no incidence figures, relative risk or confidence interval. Children with the filaggrin mutation may benefit more than those without.
- **The pooled estimate.** A meta-analysis reports **RR 0.75, 95% CI 0.62 to 1.11** in high-risk populations. **The confidence interval includes 1**, so this does not demonstrate benefit. The 2024 review that prints that interval describes a "significant benefit", which its own printed interval contradicts. Both the description and the interval are recorded here, and the interval is the evidence. Another review found six of nine studies supported early emollient use and three did not, and a third concluded that emollients may be ineffective in healthy infants and may increase food allergy and skin infection risk.

Grade for emollient prevention: CONTESTED. The two largest and best-powered trials were both negative; a small short-duration trial was positive; the pooled estimate's confidence interval crosses one; and there is a signal of harm in skin infection and food allergy. The honest reading is that daily infant emollient does not prevent eczema and may cause harm. Whether a very short early course in filaggrin-mutation carriers helps is open.

Other preventive measures:

- **Exclusive breastfeeding. CONTESTED** for eczema prevention specifically.
- **Early introduction of allergenic foods.** Prevents *food allergy* and not eczema. **STRONG** for food allergy, **not** for eczema.
- **Probiotics in pregnancy and infancy. CONTESTED**, with inconsistent trials.
- **Avoiding soap and detergents; using water softeners.** A trial of water softeners for treatment was negative. **WEAK**.
- **Avoiding tobacco smoke. MODERATE**.

Nothing is established to prevent atopic dermatitis.

Treatment.

1. **Emollients, applied liberally and frequently.** The foundation of *treatment*, in contrast to prevention, where they fail. They reduce dryness, itch and flare frequency, and reduce the topical steroid requirement. Emollients are not a specific Essential Medicines List entry; petroleum jelly and zinc and calamine preparations are listed, with calamine confirmed. Off-patent. **Petroleum jelly and paraffin-based emollients cost a few US dollars per large tub**, and proprietary creams cost many times more for no demonstrated advantage.
2. **Topical corticosteroids**, potency matched to site and severity, used in short bursts or as twice-weekly maintenance to previously affected sites. The most effective and most cost-effective anti-inflammatory. **Betamethasone and hydrocortisone are on the Essential Medicines List**. Off-patent. **Cents to a few dollars per tube.**
3. **Topical calcineurin inhibitors — tacrolimus, pimecrolimus.** Steroid-sparing, particularly for face and eyelids. Not listed. Off-patent. Considerably more expensive than steroids.
4. **Treating *Staphylococcus aureus* infection** — flucloxacillin or another appropriate oral antibiotic for infected eczema; listed, off-patent, under a dollar a course. Dilute bleach baths: evidence weak.
5. **Wet wrap therapy** for severe flares — emollient and steroid under damp bandaging. Cheap, effective, and it needs no new drug.
6. **A sedating antihistamine at night** for sleep disruption; **non-sedating antihistamines do not help eczema itch**. Chlorphenamine is listed, off-patent, cents.
7. **Narrowband ultraviolet B phototherapy**.
8. **Systemic immunosuppression — ciclosporin, methotrexate, azathioprine, mycophenolate.** Ciclosporin, methotrexate and azathioprine are listed, off-patent, and cost cents to a few dollars per day.
9. **Dupilumab and the JAK inhibitors — upadacitinib, abrocitinib, baricitinib.** High efficacy in severe disease. **Not on the Essential Medicines List**. On-patent. **Tens of thousands of US dollars per patient-year** in high-income markets. The cost gap between step 2 and step 9 is roughly four orders of magnitude.
10. **Dietary elimination is not indicated** without proven food allergy; it risks nutritional harm and does not treat the eczema. **The action is omission.**

Simple means. Strong, and the cheap options do most of the work.

- **Petroleum jelly or plain paraffin ointment** as the emollient. A few dollars per large tub, no refrigeration, indefinite shelf life, and no demonstrated inferiority to proprietary creams for treatment.
- **Topical hydrocortisone or betamethasone**, listed, off-patent, **cents per tube** — the single most effective cheap intervention in the entry.
- **Soap substitution:** washing with an emollient instead of soap, short lukewarm baths, patting dry. Free, and it removes a major irritant exposure.
- **Wet wraps** using ordinary cotton bandages, clean cotton clothing or tubular gauze over emollient. Cheap and effective for severe flares.
- **Cotton clothing, short nails, scratch mitts for infants, keeping the room cool at night.** Free, and they interrupt the itch-scratch cycle.
- **Identifying and removing irritants** — detergents, fragrance, wool, overheating. Free.
- **Not buying the expensive options that do not work:** proprietary emollients at many times the cost of petroleum jelly, non-sedating antihistamines, and dietary elimination without proven allergy. All three are omissions and all three are savings.

What the chain minimally requires: a tub of paraffin and a tube of hydrocortisone. For the severe minority, phototherapy or systemic drugs — and for the refractory few, biologics at tens of thousands per year.

Gaps. No verified global prevalence figure; Global Burden of Disease 2023 gives only the combined dermatitis total and the 2021 allergic-skin analysis was unreachable. All prevalence figures above are

unverified. **The BEEP and PreventADALL exact event rates, relative risks and confidence intervals could not be retrieved** — the journal full texts and the trial report all failed — so only the directional results and the pooled relative risk of 0.75, 95% CI 0.62 to 1.11, are carried, and the event rates could not be confirmed. PreventADALL's own sample size is reported inconsistently, 2,379 against 2,397, within one review. Sources genuinely disagree on emollient prevention: the two large trials are negative, STOP-AD is positive, and the 2024 review describes a "significant benefit" that its own printed confidence interval contradicts; all positions are recorded above. Whether barrier dysfunction or immune dysregulation is primary is unresolved. Long-term safety of JAK inhibitors in eczema is not established.

> **Depth.** Starts in: filaggrin. Size: 5 nm†; depth −2.01. First complaint: about 15 months ([B] begins in infancy); time depth 49.07. One untreated course: no number ([B] often improves).
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Psoriasis

What it is. Skin cells multiply far too fast, piling up as thick red plaques with silvery scale, typically on elbows, knees and scalp. It is an immune disease, not an infection, and it comes with joint disease and heart risk in a substantial minority.

Measured. The World Health Organization psoriasis fact sheet did not load and no global figure was retrievable. Global prevalence is commonly reported at about **60 million** people, and roughly **2 to 3 per cent** of the population in high-income countries, with substantial geographic variation. A Global Burden of Disease 2021 immune-related skin disease analysis exists and was unreachable.

Onset is bimodal, with peaks in the late teens to early thirties and again in the fifties to sixties. Prevalence is reported higher at higher latitudes and in populations of European ancestry, and low in parts of East Asia and in indigenous populations of the Americas and West Africa.

The major measured burden beyond the skin is comorbidity: **psoriatic arthritis** in roughly **20 to 30 per cent** of patients, and elevated cardiovascular, metabolic syndrome, depression and inflammatory bowel disease risk.

Where it starts.

- **Genetic predisposition.** *HLA-C*06:02* is the strongest association, together with *IL23R*, *IL12B* and *TNFAIP3* among more than 60 identified loci†. Family history is present in roughly a third.
- **IL-23 and Th17 axis activation** — the established effector pathway, and the reason IL-17 and IL-23 blockade works so well. This is one of the few conditions in this book where genetics led to a mechanism and the mechanism led to highly effective drugs.
- **Streptococcal pharyngitis** — precipitates guttate psoriasis.
- **Smoking** — dose-related, and strongly associated with palmoplantar pustulosis.
- **Obesity** — associated with incidence and with severity, and weight loss improves disease.
- **Alcohol**.
- **Drugs: beta-blockers, lithium, antimalarials, and corticosteroid withdrawal**.
- **Skin trauma (the Köbner phenomenon); stress; HIV infection**.

Genuinely not known: the antigen, if any, that drives the immune response. Why lesions occur at the sites they do and why they are so symmetrical. Why the disease waxes and wanes. Whether treating skin inflammation reduces the excess cardiovascular risk — an important open question with observational support and no definitive trial. Why some patients develop psoriatic arthritis and most do not, and no predictive test exists.

Cure status. CONTROLLABLE. No treatment removes psoriasis, and the degree of control now achievable is as high as anywhere in this book: IL-17 and IL-23 inhibitors achieve a 90 per cent reduction in disease severity in a majority of treated patients, and complete clearance in a substantial share.

Clearance is not cure. Withdrawal is followed by relapse in most patients, the genetic predisposition remains, and treatment is indefinite. Control can now be near-total for those who can access the drugs, and the access gap is the binding constraint, since originator biologics cost tens of thousands of US dollars per patient-year.

Prevention.

- **No primary prevention is established.** Nothing prevents psoriasis.
- **Smoking cessation** — reduces incidence and severity. **MODERATE**.
- **Weight loss in overweight patients** — improves severity and treatment response. **MODERATE**.
- **Treating streptococcal throat infection** — may prevent guttate flares. **WEAK**.
- **Avoiding precipitating drugs** where alternatives exist, notably beta-blockers and lithium. **MODERATE**, and the action is omission.
- **Avoiding abrupt systemic corticosteroid withdrawal**, which can precipitate generalised pustular psoriasis. **MODERATE**, and important: systemic steroids should generally not be used for psoriasis at all.
- **Alcohol reduction. WEAK**.
- **Managing cardiovascular risk factors.** Prevents the comorbidity that causes the excess mortality rather than the skin disease. **STRONG** for cardiovascular outcomes.

Treatment.

1. **Topical corticosteroids**, alone or with a vitamin D analogue. First-line for mild to moderate disease. **Betamethasone is on the Essential Medicines List**. Off-patent. **Cents to a few dollars per tube.**
2. **Topical vitamin D analogues — calcipotriol.** Listed, with calcitriol as therapeutic equivalent. Off-patent. Low tens of US dollars per tube generic. The combination of calcipotriol and betamethasone is more effective than either alone.
3. **Coal tar, dithranol, salicylic acid.** Old, cheap, effective and messy, and largely displaced in high-income practice by convenience rather than by efficacy. Off-patent, very low cost.
4. **Narrowband ultraviolet B phototherapy** — effective for extensive plaque and guttate disease. Not a medicine. Capital equipment, low running cost. See *Simple means* for the sunlight alternative.
5. **Methotrexate**, oral weekly. The standard cheap systemic agent. **Listed**. Off-patent. **A few US dollars per month**. It requires blood monitoring and is teratogenic.
6. **Ciclosporin** — rapid acting, for short courses. **Listed.** Off-patent, low cost. Nephrotoxic with prolonged use.
7. **Acitretin** — an oral retinoid, teratogenic for years after stopping. Off-patent.
8. **Apremilast**, oral.
9. **Biologics: TNF inhibitors (adalimumab, etanercept, infliximab), IL-17 inhibitors (secukinumab, ixekizumab), IL-23 inhibitors (guselkumab, risankizumab), IL-12/23 (ustekinumab).** The most effective treatments, with a 90 per cent severity reduction in a majority on the IL-17 and IL-23 agents†. **Adalimumab is on the Essential Medicines List as a selected medicine**, in the complementary list, with psoriasis among its indications and including quality-assured biosimilars; **infliximab is listed only as a therapeutic equivalent to adalimumab** and not as a selected medicine in its own right. Adalimumab, etanercept and infliximab have biosimilars; the IL-17 and IL-23 agents are on-patent. Originator biologics cost **tens of thousands of US dollars per patient-year**, and **biosimilar adalimumab has fallen to a small fraction of the originator price** in competitive markets. That price collapse is the most important access development in this entry.
10. **Systemic corticosteroids — avoid.** Risk of rebound and pustular flare on withdrawal. **The action is omission.**

Simple means. Better than might be expected, because sunlight and tar are genuinely effective.

- **Sunlight.** Natural ultraviolet exposure improves psoriasis in most patients, and this is the oldest and cheapest effective treatment there is. Free. The limits are latitude, season, burn risk and skin cancer risk with cumulative exposure.
- **Climatotherapy** — the documented effectiveness of sun-and-saltwater regimens.
- **Topical hydrocortisone or betamethasone** — listed, off-patent, cents per tube.
- **Coal tar preparations and salicylic acid ointment** — very cheap, off-patent, effective, and still among the better value treatments despite being displaced by convenience.
- **Emollients and scale removal** — petroleum jelly, a few dollars a tub, softens plaque and reduces scale and cracking.
- **Salt water bathing and sunlight together**, where available. Free.
- **Methotrexate** for severe disease: listed, off-patent, **a few dollars a month**. This is the key point for access — effective systemic treatment for severe psoriasis costs a few dollars monthly, not tens of thousands yearly. It needs blood monitoring, which is the real constraint.
- **Smoking cessation and weight loss.** Free, and they improve disease and comorbidity together.

What the chain minimally requires: for most patients, a cheap steroid, an emollient and sunlight. For severe disease, methotrexate plus a laboratory for monitoring. Only the refractory minority need biologics.

Gaps. No verified global prevalence figure — the World Health Organization fact sheet did not load and the Global Burden of Disease 2021 immune-skin analysis was unreachable. The commonly cited 60 million and 2 to 3 per cent figures are unverified. Psoriatic arthritis prevalence estimates range widely and depend on case definition. Whether treating skin inflammation reduces cardiovascular events is unresolved and is the most consequential open question in the field. Biologic prices vary by an order of magnitude between originator and biosimilar and between markets, and no current price source was obtainable. Comparative long-term safety of the newer biologics is not established. No predictor exists for who develops psoriatic arthritis.

> **Depth.** Starts in: a keratinocyte. Size: 15 µm†; depth +5.28. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number († recurring).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Acne vulgaris

What it is. Blocked, inflamed oil glands in the skin, mostly on the face, chest and back. Blackheads, spots and cysts. It affects most adolescents to some degree and can leave permanent scars and lasting psychological harm.

Measured. No global figure was retrievable. Acne is commonly reported to affect roughly **85 per cent of people aged 12 to 24** at some point, with clinically significant acne in a smaller share, and it is consistently among the most prevalent skin diseases in Global Burden of Disease analyses.

Onset is around puberty, with a peak in mid to late adolescence and resolution in the early twenties for most; **adult female acne**, persisting or beginning after 25, is common†. It is universal, with reported severity differences likely reflecting diagnosis and treatment access.

Acne causes little physical disability and substantial **psychological morbidity** — depression, anxiety, social withdrawal and suicidal ideation are measurably increased, and this is the principal reason it carries real burden. Scarring is permanent in a significant minority, which is what makes early treatment a disfigurement-prevention measure.

Where it starts. Four established mechanisms act together: androgen-driven sebum production, which is why it starts at puberty; follicular hyperkeratinisation, the blocked pore; *Cutibacterium acnes* colonisation of the blocked follicle, which is not an infection in the ordinary sense because the organism is a normal commensal; and inflammation, present early, including in clinically uninvolved skin.

Risk factors:

- **Genetics and family history** — substantial heritability.
- **Androgen excess** — polycystic ovary syndrome, congenital adrenal hyperplasia. Acne with hirsutism and irregular periods should prompt endocrine assessment.
- **High glycaemic load diet and dairy** — associated in observational and some trial data. The evidence is real and modest, and far weaker than popular belief holds.
- **Drugs: corticosteroids, anabolic steroids, lithium, isoniazid, some progestogens, EGFR inhibitors**.
- **Mechanical occlusion and friction** — helmets, straps, masks.

Genuinely not known: why severity varies so widely at the same hormonal stage. Why some people scar heavily and others not at all, with no predictor. The role of diet is genuinely unsettled — the association is consistent, the effect size is small, and dietary trials are hard to blind. Whether *Cutibacterium acnes* strain type matters. Chocolate and greasy food, the two things most often blamed, have no established causal role.

Cure status. Standard topical and oral therapies: CONTROLLABLE — they control acne while they are used and it returns when they stop. A single adequate course of isotretinoin: CURABLE in roughly 70 to 80 per cent, the complement of relapse in roughly 20 to 30 per cent†.

Isotretinoin is the exception and deserves naming as such. A single adequate course over several months produces prolonged or permanent remission in a majority of patients, with relapse rates commonly reported around **20 to 30 per cent** needing a second course†. That is durable remission after a finite treatment, which is unusual in this book. Against that: isotretinoin is severely teratogenic, requiring pregnancy prevention programmes, and carries mucocutaneous, hepatic and lipid effects, with a contested association with depression.

Acne also remits spontaneously in most people by the mid-twenties, so a large part of the natural history is self-limiting. The label is split between isotretinoin and the other treatments, and the usual spontaneous resolution with age is noted.

Scarring, once established, is not curable by any of these treatments and is only partially improved by resurfacing procedures. That is why treating before scars form matters.

Prevention.

- **Early effective treatment to prevent scarring.** The real preventive goal; acne itself is not preventable. **STRONG** for scar prevention.
- **Avoiding causative drugs** where possible. **MODERATE**.
- **Low glycaemic load diet. CONTESTED**; some trial support, small effect.
- **Reducing dairy intake. CONTESTED**, observational.
- **Not scrubbing, not picking, avoiding comedogenic and occlusive cosmetics. WEAK**, free, and the action is omission.
- **Avoiding mechanical occlusion** where practical. **WEAK**.
- **Nothing prevents acne.** It is a normal consequence of pubertal androgens in predisposed people.

Treatment.

1. **Benzoyl peroxide, topical.** Antibacterial and comedolytic, available over the counter, and it **does not generate antibiotic resistance**, which is why it is the backbone of modern regimens and why it should be combined with any topical antibiotic. **Benzoyl peroxide is on the Essential Medicines List**. Off-patent. **A few US dollars per tube, and often less.**
2. **Topical retinoids — tretinoin, adapalene.** They target the blocked follicle; first-line and essential for comedonal acne, and adapalene is available without prescription in several countries. Essential Medicines List status not confirmed in the sections displayed. Off-patent, low cost generic.
3. **A fixed combination of topical retinoid plus benzoyl peroxide, or clindamycin plus benzoyl peroxide.** More effective than monotherapy.

4. **Topical antibiotics (clindamycin, erythromycin) — never as monotherapy**, because of resistance. Listed as systemic agents; topical status not confirmed. Off-patent, cheap.
5. **Oral tetracyclines — doxycycline, lymecycline, minocycline** — for moderate to severe inflammatory acne, for a limited course of around three months with a topical retinoid and benzoyl peroxide. **Doxycycline is listed**, off-patent, and costs **cents per day**. Not in pregnancy or under 12.
6. **Combined oral contraceptives and anti-androgens (spironolactone, cyproterone acetate)** — effective in women. Combined oral contraceptives and spironolactone are listed, off-patent, cents per day; spironolactone is listed under diuretics and heart failure, not for this indication.
7. **Oral isotretinoin** — the most effective treatment, with durable remission in a majority. **Not** on the Essential Medicines List. Off-patent. **Low tens of US dollars per month generic**, though monitoring and pregnancy prevention programme requirements add substantially.
8. **Intralesional corticosteroid** for individual nodules.
9. **Scar treatment** — resurfacing, microneedling, subcision, fillers. Partial improvement only, not restorative. Expensive and rarely available.

Simple means. Good, and the single best-value agent is cheap and listed.

- **Benzoyl peroxide.** A few dollars a tube, listed, off-patent, available without a prescription in most places, effective as monotherapy for mild acne, and resistance-proof. This is the highest-value simple intervention in the entry.
- **Washing gently twice daily with a mild cleanser, and not scrubbing.** Free. Scrubbing and harsh antiseptics make acne worse, so part of the free advice is stopping harmful practices.
- **Not picking or squeezing** — directly reduces scarring. Free, and the action is omission.
- **Avoiding occlusive and oil-based cosmetics and hair products.** Free.
- **Doxycycline** for inflammatory acne: listed, off-patent, cents per day.
- **Sun protection**, since several acne treatments cause photosensitivity and post-inflammatory pigmentation is worsened by sun — particularly important in darker skin, where pigmentation is often the patient's main concern.
- **Explanation** that acne is not caused by poor hygiene, chocolate or greasy food. Free, and it removes blame and futile restriction.
- **Early treatment**, since the scars are what is permanent. The cost of a tube of benzoyl peroxide against a lifetime of facial scarring is the relevant comparison.

What the chain minimally requires: a tube of benzoyl peroxide. For severe nodular acne, isotretinoin plus laboratory monitoring and pregnancy prevention — a genuine clinical service requirement.

Gaps. No verified global prevalence or burden figure; condition-level Global Burden of Disease skin data were unobtainable. The widely cited 85 per cent of 12 to 24 year olds figure is unverified. Diet evidence is genuinely contested: a consistent observational association with high glycaemic load and dairy, small trial effects, and strong popular overstatement; all positions are recorded. Isotretinoin relapse rates vary with cumulative dose and are disputed. The association between isotretinoin and depression is contested, with large cohort studies not supporting a causal link while case reports and regulatory warnings persist; both exist. No predictor of scarring exists. Psychological burden is widely documented and not quantified in any source read.

> **Depth.** Starts in: the sebaceous follicle. Size: 1 mm†; depth +9.10. First complaint: about 13 years ([B] begins at puberty); time depth 51.21. One untreated course: about 10 years († about 10 years); depth 50.97.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Contact dermatitis (irritant and allergic)

What it is. Skin inflammation caused by something touching it — either a direct chemical injury, which is irritant contact dermatitis, or an immune reaction to a specific substance, which is allergic contact dermatitis. Remove the cause and it clears; keep contact and it does not.

Measured. Counted within the dermatitis group at **15.2 million** years lived with disability, 95% uncertainty interval 8.9 to 24.2, the eighteenth leading cause. Contact dermatitis is not separately quantified in any source read.

It is consistently reported as the commonest occupational skin disease and among the commonest occupational diseases overall, accounting for a large share of occupational disease claims in countries with reporting systems. Irritant disease is roughly **80 per cent** of occupational contact dermatitis, with allergic disease the remainder.

Occupational cases predominate in working age, with hand eczema in healthcare, cleaning, catering, hairdressing, construction and agriculture. A substantial share of affected workers change or lose their job, which is the measured economic burden. Nickel allergy prevalence fell in Europe after regulation of nickel release in consumer items — a documented regulatory effect.

Where it starts. Irritant: cumulative exposure to water (wet work), soaps and detergents, solvents, oils, acids and alkalis, friction, and low humidity. Wet work — prolonged or repeated hand wetting and glove occlusion — is the dominant occupational cause. There is no immune memory; it is dose-dependent injury.

Allergic: delayed hypersensitivity to a specific allergen. The commonest, from patch-test series:

- **Nickel** — the most frequent positive patch test worldwide; jewellery, fasteners, coins, mobile devices.
- **Fragrance mix and balsam of Peru.**
- **Preservatives: methylisothiazolinone**, which caused a documented European epidemic after its introduction into leave-on cosmetics, **formaldehyde releasers, parabens.**
- **Rubber accelerators (thiurams, carbamates) and latex** — gloves.
- **Chromate** — cement; the cause of construction workers' hand dermatitis, reduced by adding ferrous sulfate to cement, another documented regulatory success.
- **Hair dyes — para-phenylenediamine**, with black henna tattoos as a sensitising route.
- **Topical medicaments** — neomycin, and corticosteroids themselves.
- **Plants** — poison ivy and oak (urushiol), Compositae.

Risk factors: atopic dermatitis raises irritant contact dermatitis risk substantially; female sex, reflecting exposure; and existing barrier damage, which enables sensitisation.

Genuinely not known: why only some exposed people become sensitised to a given allergen. Why some sensitised people react at tiny exposures and others need large ones. Whether irritant damage is a necessary precursor to sensitisation in most cases. Why a minority have persistent post-occupational dermatitis that continues for years after all exposure stops — this is the clinically important unknown, and it undermines the assumption that removal always resolves the disease.

Cure status. CURABLE. Both forms resolve completely when the causative exposure is removed and the skin is allowed to heal, with no residual deficit and no treatment needed thereafter. That makes this one of the clearest curable entries in this part of the chapter.

Two qualifications. **Allergic sensitisation is lifelong**: the dermatitis is cured, the allergy is not, and re-exposure reproduces it, which is why identification of the allergen is the treatment. **Persistent post-occupational dermatitis** occurs in a minority, continuing after exposure ceases, and in those patients the condition behaves as controllable.

Where the exposure cannot be removed, because it is the person's livelihood, the cure is theoretically available and practically not, which is the core difficulty of occupational skin disease.

Prevention. This is the strongest prevention entry in this part of the chapter and much of it is regulatory.

- **Substitution of the allergen or irritant at source** — the top of the hierarchy of controls. **STRONG**. The documented effects: **nickel release regulation** in the European Union reduced nickel allergy prevalence; **adding ferrous sulfate to cement** to reduce hexavalent chromate largely eliminated cement chromate dermatitis in construction workers; **restriction of methylisothiazolinone** in leave-on cosmetics reversed a European epidemic of sensitisation. These are among the clearest demonstrations in this book that regulation measurably removes disease.
- **Reducing wet work; avoiding unnecessary hand washing; using lukewarm water. MODERATE**.
- **Gloves appropriate to the exposure, worn for the shortest necessary time, with cotton liners.** Gloves themselves cause occlusion dermatitis and rubber allergy, so glove use is not automatically protective. **MODERATE**.
- **Emollients and barrier creams.** Emollients after work have reasonable support; **barrier creams are much weaker than their name implies and may increase irritant penetration**. **MODERATE** for emollients, **WEAK/CONTESTED** for barrier creams.
- **Alcohol-based hand rub in preference to repeated soap-and-water washing** in healthcare — less irritant than detergent washing, contrary to common belief. **MODERATE**.
- **Pre-employment counselling for atopic individuals entering wet-work trades. MODERATE**.
- **Skin surveillance programmes in exposed workforces. MODERATE**.
- **Patch testing to identify the allergen.** Not prevention of disease but prevention of recurrence, and without it avoidance is guesswork. **STRONG** for recurrence prevention.

Treatment.

1. **Identifying and removing the cause.** The definitive treatment; everything else is adjunctive. Cost: an occupational history, and patch testing where the allergen is not obvious.
2. **Patch testing** — the only way to identify an allergen. Not a medicine. It requires a standard allergen series and three clinic visits; the capital cost is modest and the series is reusable.
3. **Topical corticosteroids**, potency matched to site. First-line anti-inflammatory. **Betamethasone and hydrocortisone are listed**. Off-patent. **Cents to a few dollars per tube.**
4. **Emollients**, frequently and after every wash. Off-patent; petroleum jelly a few dollars a tub.
5. **Topical calcineurin inhibitors** for facial and eyelid disease, steroid-sparing. Not listed.
6. **Potassium permanganate soaks or wet dressings** for acutely weeping dermatitis. Very cheap.
7. **Oral prednisolone**, a short course, for severe acute widespread dermatitis — for example extensive poison ivy. Listed, off-patent, cents per day.
8. **Treating secondary bacterial infection** — flucloxacillin, listed, off-patent, under a dollar a course.
9. **Alitretinoin** for severe chronic hand eczema. Expensive.
10. **Phototherapy** for chronic hand dermatitis.
11. **Job modification or change** — sometimes the only effective measure, with major economic consequences for the worker.

Simple means. Very strong, and almost entirely behavioural and organisational.

- **Finding and removing the cause.** Free. An occupational and hobby history, plus the distribution of the rash, identifies the culprit in many cases without any test.
- **Reducing hand washing frequency and using lukewarm rather than hot water.** Free, and the action is omission.
- **Removing rings before wet work**, since they trap water and detergent against the skin. Free.
- **Cotton glove liners** inside occlusive gloves, and limiting glove wearing time. Cents.
- **Petroleum jelly or paraffin ointment** as an emollient, applied after every wash and overnight under cotton gloves. A few dollars a tub, and the mainstay of hand eczema care.
- **Topical hydrocortisone** — listed, off-patent, cents per tube.
- **Potassium permanganate or saline soaks** for weeping dermatitis. Pennies.

- **Replacing nickel jewellery, or coating fasteners with clear nail varnish**, for nickel allergy. Near zero cost.
- **Choosing fragrance-free and preservative-reduced products.** No extra cost in principle.
- **At population level, regulation.** The nickel-release limits, cement ferrous sulfate addition and methylisothiazolinone restriction each removed a large disease burden at essentially no healthcare cost at all. This is the cheapest intervention per case prevented in the whole chapter, and it requires no clinical contact whatever.

What the chain minimally requires: for allergen identification where the cause is not obvious, a patch test series and a clinic — otherwise nothing but soap discipline, paraffin and a cheap steroid.

Gaps. Contact dermatitis is not separately quantified in Global Burden of Disease or World Health Organization sources read; only the combined dermatitis total is available. The roughly 80 per cent irritant share of occupational cases is unverified. Patch test positive-allergen frequencies come from clinic series, which are selected populations and not population prevalence. **The effect sizes of the nickel, chromate and methylisothiazolinone regulatory interventions are documented in the literature and could not be verified here** — they are among the most important numbers in this part of the chapter and should be retrieved. Barrier cream efficacy is genuinely disputed, with some evidence of harm. Why persistent post-occupational dermatitis occurs is unknown and its frequency is not established. The proportion of affected workers who lose their jobs varies widely between studies.

> **Depth.** Starts in: the substance on the skin (nickel, soap, solvent). Size: 1 nm†; depth −3.48. First complaint: about 2 days († 1–3 days after contact in the allergic form); time depth 44.13. One untreated course: about 3 weeks († clears in 2–4 weeks once contact stops); depth 46.27.
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Urticaria (hives)

What it is. Itchy raised weals that come up and fade within a day, often with deeper swelling of lips or eyelids. Most episodes are short-lived. In the chronic form they keep appearing for months or years and no cause is ever found.

Measured. No global figure was retrievable, and a Global Burden of Disease 2021 allergic-related skin disease analysis exists and was unreachable. Lifetime prevalence of any urticaria is commonly reported at about **20 per cent**, and point prevalence of chronic spontaneous urticaria at roughly **0.5 to 1 per cent**†.

Chronic spontaneous urticaria peaks in ages 20 to 40 and is about twice as common in women†. It remits spontaneously within one year in roughly **half** of patients, and persists more than five years in a substantial minority. Sleep disruption and quality-of-life impairment are measurably severe — comparable to ischaemic heart disease in some quality-of-life studies — which is disproportionate to how the condition is usually regarded.

Where it starts.

- **Mast cell degranulation with histamine release** — the final common mechanism for all forms.
- **Acute urticaria:** viral infection is the commonest trigger, especially in children, and also drugs, foods and insect stings.
- **Chronic spontaneous urticaria:** autoimmune in a substantial share, with IgG autoantibodies against IgE or its receptor, demonstrated by the autologous serum skin test and by basophil activation, and associated with autoimmune thyroid disease. **No external trigger is found in the majority**, and that is the defining feature.
- **Chronic inducible urticaria:** physical triggers reproducibly provoke weals — dermographism, cold, heat, delayed pressure, solar, vibratory, and cholinergic from heat, exercise or stress.

- **Drugs:** NSAIDs and aspirin exacerbate existing urticaria in roughly a third of chronic patients, which is pharmacological rather than allergic. ACE inhibitors cause bradykinin-mediated angio-oedema, a different mechanism that does **not** respond to antihistamines.
- **Food** — a genuine cause of acute urticaria in true IgE food allergy, and rarely the cause of chronic urticaria, contrary to widespread belief; extensive dietary investigation in chronic urticaria is usually unrewarding.

Genuinely not known: why chronic spontaneous urticaria starts, and why it stops. In most patients no cause is identified despite full investigation, and extensive testing is therefore not recommended — a rare instance where the evidence-based action is to **not** investigate. Why it remits after months or years in most people is unexplained. Why some patients need fourfold antihistamine doses and others respond to standard doses is unknown.

Cure status. Acute: SELF-LIMITING. Chronic: CONTROLLABLE.

Acute urticaria resolves within days to six weeks by definition, and antihistamines only shorten the symptom while it runs its course. Chronic urticaria is controllable: antihistamines, and omalizumab for refractory disease, suppress the weals effectively, and symptoms return when treatment stops. No treatment removes the underlying tendency. Chronic spontaneous urticaria also remits spontaneously, in roughly half within a year, so a large share of patients are eventually free of it without any treatment having cured it.

Prevention.

- **Avoiding an identified trigger** where one genuinely exists — a specific food in IgE allergy, a drug, a physical stimulus. **STRONG** where identified, which is a minority of chronic cases.
- **Avoiding NSAIDs and aspirin in chronic urticaria**, which prevents exacerbation in about a third. **MODERATE**, free, and the action is omission.
- **Stopping an ACE inhibitor** in ACE-inhibitor angio-oedema. **STRONG**, free, and the action is omission.
- **Avoiding overheating, tight clothing, hot showers and alcohol**, which lower the weal threshold non-specifically. **WEAK**, free.
- **Treating any identified infection or thyroid autoimmunity. WEAK**; treating thyroid disease does not reliably improve the urticaria.
- **Not pursuing extensive allergy testing or elimination diets in chronic spontaneous urticaria** — a prevention of harm and cost, since they rarely help and elimination diets risk nutritional damage. **MODERATE**, the action is omission, and it is a saving.
- **Nothing prevents chronic spontaneous urticaria.**

Treatment.

1. **Second-generation non-sedating H1 antihistamines — cetirizine, loratadine, fexofenadine, desloratadine — at standard dose, increased up to fourfold if needed.** First-line, and the fourfold updosing step is guideline-endorsed and effective in many who fail standard doses. **Loratadine and cetirizine are on the Essential Medicines List** — the list document did not load. Off-patent. **Cents per tablet** generic, among the cheapest effective treatments in this part of the chapter.
2. **Sedating first-generation antihistamines (chlorphenamine, hydroxyzine)** at night only; not preferred because of sedation and anticholinergic effects. Chlorphenamine listed, off-patent, cents.
3. **Omalizumab (anti-IgE)** for antihistamine-refractory chronic spontaneous urticaria. Highly effective. **Omalizumab is not on the Essential Medicines List in any form — not as a selected medicine and not as a therapeutic equivalent**. On-patent, with biosimilars emerging. **Thousands of US dollars per patient-year**.
4. **Ciclosporin** for refractory disease — effective and far cheaper than omalizumab. **Listed**, off-patent, low cost. It requires blood pressure and renal monitoring.
5. **A short course of oral corticosteroid** for a severe flare only, and **not for maintenance**, because of cumulative harm. Prednisolone listed, off-patent, cents per day.
6. **Montelukast** as an add-on — weak evidence.

7. **Adrenaline (epinephrine) intramuscularly** for urticaria with anaphylaxis or airway angio-oedema. **Listed**, off-patent, low cost, and life-saving. Adrenaline does **not** work for bradykinin-mediated ACE-inhibitor angio-oedema.
8. **Not indicated:** routine extensive allergy testing, elimination diets, and antihistamine creams. **The action is omission.**

Simple means. Good, and the first-line drug is already nearly free.

- **Generic cetirizine or loratadine** at **cents per tablet**, listed and off-patent, controls most urticaria. Fourfold updosing costs four times almost nothing.
- **Cool compresses, cool showers, loose cotton clothing, keeping the room cool.** Free, and it genuinely reduces weal formation because heat lowers the threshold.
- **Calamine lotion** for symptomatic relief — **listed**, off-patent, pennies.
- **Stopping NSAIDs and aspirin.** Free, the action is omission, and it is effective in about a third of chronic patients.
- **Stopping an ACE inhibitor** in angio-oedema. Free, and definitive.
- **A symptom and exposure diary.** A notebook. It identifies the physical triggers in inducible urticaria better than any laboratory test, and it also demonstrates to the patient that no food is responsible — which is often the main therapeutic gain.
- **Explanation:** that it is not usually an allergy, that extensive testing will not help, that it is not dangerous unless the airway is involved, and that it usually goes away in time. Free, and it prevents years of futile dietary restriction.
- **Not paying for allergy test panels or elimination diets.** The action is omission and it is a direct saving.
- **Knowing when it is dangerous:** lip, tongue or throat swelling, or breathing difficulty, means immediate care. Free knowledge that prevents death.

What the chain minimally requires: a cheap antihistamine. Only the refractory minority need ciclosporin with monitoring, or omalizumab at thousands per year.

Gaps. No verified global prevalence or burden figure; the Global Burden of Disease 2021 allergic-skin analysis was unreachable and no World Health Organization source quantifies urticaria. All prevalence figures above are unverified. The autoimmune share of chronic spontaneous urticaria is estimated differently across studies depending on the assay used. Remission rates vary substantially between cohorts. The evidence base for fourfold antihistamine updosing is accepted in guidelines and rests on limited trial data. Montelukast add-on evidence is weak and sources disagree. Popular belief and the evidence diverge sharply on food as a cause of chronic urticaria; the evidence position is recorded here.

> **Depth.** Starts in: the mast cell. Size: 15 µm†; depth +5.28. First complaint: about 1 hour († an hour after a trigger); time depth 40.61. One untreated course: about 3 days ([B] a weal goes within a day; † an episode lasts days); depth 44.50.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Rosacea

What it is. Persistent redness of the central face, with flushing, visible small blood vessels, and often spots that look like acne. In some people the nose thickens over years. It affects fair-skinned adults most and runs a relapsing course.

Measured. No global figure was retrievable. Prevalence is commonly reported at around **5 per cent** of adults globally, with much higher figures in northern European populations and lower reported figures in Asian and African populations — although under-recognition in darker skin is a known problem and likely explains part of that difference.

Onset is typically between **30 and 50** and it is rare before 20†. It is more commonly diagnosed in women, and **phymatous rosacea (rhinophyma) occurs almost exclusively in men**. Associations are reported with cardiovascular risk factors, inflammatory bowel disease, migraine and depression.

Ocular rosacea affects a substantial share — commonly reported around **50 per cent** — and causes dry eye, blepharitis, meibomian gland dysfunction and, rarely, corneal damage. This connects directly to the dry eye and keratitis entries earlier in this chapter.

Where it starts.

- **Neurovascular dysregulation** — abnormal vasodilatation and flushing responses, the earliest feature.
- **Innate immune activation** — raised cathelicidin and kallikrein-5 in affected skin†.
- ***Demodex folliculorum*** mite density is increased in rosacea skin, and anti-Demodex treatment with ivermectin is effective — and whether the mite is cause or consequence is **not established**.
- **Fair skin, Fitzpatrick types I to II; northern European ancestry; family history**.
- **Cumulative ultraviolet exposure**.
- **Trigger factors that provoke flushing episodes rather than cause the disease:** heat, sun, hot drinks, spicy food, alcohol and especially red wine, exercise, emotional stress, cold wind, and topical corticosteroids.
- **Topical corticosteroid use on the face** — causes steroid-induced rosacea and perioral dermatitis, and worsens existing rosacea. An important iatrogenic cause, and the reason facial steroids must be used cautiously.
- ***Helicobacter pylori* and small intestinal bacterial overgrowth** — associations reported, causal role **CONTESTED**.

Genuinely not known: the cause. Whether the vascular, immune and microbial findings are one process or several. Whether *Demodex* is causal. Why rhinophyma affects men almost exclusively. Whether rosacea subtypes are stages of one disease or distinct conditions — the classification was revised from subtypes to a phenotype-based approach precisely because this is unresolved.

Cure status. CONTROLLABLE. No treatment cures rosacea. Inflammatory papules and pustules respond well and can be cleared; background **erythema and telangiectasia respond poorly to drugs** and need laser or light treatment, which improves and does not remove them; and **rhinophyma is permanent** and requires surgical reduction. Relapse after stopping treatment is the rule, so maintenance is usually required. The fixed vascular and phymatous changes are not reversible medically at all.

Prevention.

- **Sun protection — daily broad-spectrum sunscreen, hats, shade.** The most consistently recommended preventive measure; cumulative ultraviolet exposure drives the vascular change. **MODERATE**.
- **Identifying and avoiding personal flush triggers** — heat, hot drinks, alcohol, spicy food, extremes of temperature. Reduces flare frequency. **MODERATE**, and free.
- **Avoiding topical corticosteroids on the face.** Prevents steroid-induced rosacea and prevents worsening. **STRONG**, free, and the action is omission.
- **Gentle skin care — a mild non-soap cleanser, no astringents, no abrasive scrubs, no alcohol-containing toners. MODERATE**, and free.
- **Early treatment to prevent progression to rhinophyma** — plausible and **not demonstrated**; there is no trial evidence that treating papulopustular disease prevents phymatous change. **WEAK**.
- **Nothing prevents the disease itself.**

Treatment.

1. **Topical ivermectin 1 per cent.** Among the most effective topical agents for papulopustular rosacea. **Ivermectin is on the Essential Medicines List**, listed as a 3 mg tablet under intestinal anthelminthics,

antifilarials and medicines for ectoparasitic infections; the topical cream's status was not confirmed. Off-patent as a molecule. The licensed cream is priced far above the bulk cost of the drug.

2. **Topical metronidazole 0.75 to 1 per cent.** Long-standing first-line, effective for papulopustular disease. **Metronidazole is listed** in oral and intravenous form. Off-patent, low cost generic.
3. **Topical azelaic acid 15 to 20 per cent.** Comparable efficacy to metronidazole. Off-patent, low cost.
4. **Oral tetracyclines — doxycycline**, including the sub-antimicrobial 40 mg modified-release dose, which is anti-inflammatory without antibiotic selection pressure. **Doxycycline is listed**, off-patent, and the standard generic costs **cents per day**.
5. **Oral isotretinoin, low dose**, for severe or refractory papulopustular disease. Not listed. Off-patent. Teratogenic.
6. **Topical brimonidine or oxymetazoline** for transient erythema reduction; the effect lasts hours and rebound erythema occurs.
7. **Vascular laser or intense pulsed light** for telangiectasia and fixed erythema — the only effective treatment for these features. Not listed. Expensive, repeated sessions, rarely available.
8. **Surgical or laser reduction of rhinophyma** — the only treatment for established phymatous change.
9. **Ocular rosacea:** lid hygiene, warm compresses, artificial tears, oral doxycycline, topical ciclosporin. The lid hygiene measures in the dry eye entry apply directly and are free.

Simple means. Reasonable, and the behavioural measures carry real weight because flushing drives the disease.

- **Trigger identification with a simple diary**, then avoidance. A notebook. Triggers are individual, and identifying them is more useful than any test.
- **Sun protection:** a wide-brimmed hat and shade cost nothing; sunscreen is a few dollars a bottle. This is the main preventive measure.
- **Gentle cleansing with a mild non-soap cleanser, lukewarm water, no scrubbing, no alcohol-based toners.** Free, and it stops a common aggravating practice.
- **Stopping topical steroids on the face.** Free, the action is omission, and in steroid-induced rosacea it is curative — with a withdrawal flare to warn the patient about.
- **Cool compresses and cool drinks** during flushing, and avoiding hot drinks, alcohol and spicy food where they are personal triggers. Free.
- **Generic topical metronidazole and oral doxycycline** — both cheap, both with listed parent molecules, both effective for the papulopustular component.
- **Lid hygiene for ocular rosacea:** warm compresses with a clean cloth and lid margin cleaning, twice daily. Free, and it is the primary treatment for the eye involvement.
- **Green-tinted cosmetic camouflage** for fixed redness — cheap, and it addresses the feature that drugs do not.

What the chain minimally requires: for erythema and telangiectasia, a vascular laser; for rhinophyma, surgery. These are the components with no simple substitute. The inflammatory component is manageable with cents-per-day generics.

Gaps. No verified global prevalence figure. The 5 per cent figure is unverified. Prevalence in darker skin is probably substantially underestimated because erythema is harder to see, and this is a recognised measurement problem rather than a true difference. The role of *Demodex* is unresolved despite effective anti-Demodex treatment. Whether treating early disease prevents rhinophyma has never been tested. The *Helicobacter pylori* association is contested. Reported ocular involvement rates vary widely depending on how carefully the eyes are examined. The topical ivermectin price gap between bulk drug and licensed cream could not be quantified.

> **Depth.** Starts in: a small facial blood vessel. Size: 100 µm†; depth +7.00. First complaint: about 35 years († onset about age 35); time depth 52.11. One untreated course: no number ([B] recurring).

> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Vitiligo

What it is. The cells that make skin pigment are destroyed, leaving sharply defined white patches that spread unpredictably. It does no physical harm. In many societies it carries severe social stigma, which is the real burden.

Measured. No global figure was retrievable. Prevalence is commonly reported at about **0.5 to 2 per cent** of the world population, with remarkable consistency across populations and ethnicities. Onset is before age 30 in about half and can begin at any age†. It affects men and women about equally, though women present more often.

Prevalence is broadly similar worldwide, and **visibility and therefore stigma are far greater in darker skin**, with reported burden highest in South Asia and parts of Africa. The measured burden is almost entirely psychosocial — depression, anxiety, social and marital discrimination, and in some settings documented effects on employment and marriage prospects. In parts of South Asia vitiligo has historically been confused with leprosy, compounding the stigma.

Where it starts.

- **Autoimmune destruction of melanocytes** — the established mechanism; CD8+ T cells targeting melanocyte antigens, with interferon-gamma and CXCL10 signalling, which is why JAK inhibitors work†.
- **Genetic predisposition** — over 50 susceptibility loci identified, including *HLA*, *TYR*, *NLRP1* and *PTPN22*; family history in roughly a fifth†.
- **Other autoimmune disease** — autoimmune thyroid disease is substantially more common in vitiligo patients, and thyroid function testing is standard; also type 1 diabetes, pernicious anaemia, alopecia areata, Addison disease†.
- **The Köbner phenomenon** — new patches appear at sites of skin trauma, friction or pressure.
- **Chemical depigmentation** — phenolic compounds, including some hair dyes and occupational chemicals, can trigger it.
- **Emotional stress** — commonly reported by patients as preceding onset or spread; **CONTESTED** as a cause.

Genuinely not known: why melanocytes are targeted, and why in the distribution they are. Why it spreads in bursts and then stops for years. Why segmental vitiligo behaves completely differently from the generalised form — stabilising early and responding to grafting — and whether it is a different disease. No test predicts who will progress. Whether stress is causal or merely remembered is unresolved.

Cure status. CONTROLLABLE. Repigmentation is genuinely achievable in many patients, which deserves emphasis because vitiligo is widely believed to be untreatable. Narrowband ultraviolet B with topical therapy produces substantial repigmentation in a large share of patients, and topical and oral JAK inhibitors — ruxolitinib cream, ritlecitinib — have produced high repigmentation rates in trials and are now licensed.

Against that: the face and neck respond well while **hands, feet and areas with white hair respond poorly or not at all**; repigmentation takes months; and relapse after stopping treatment is common, so maintenance is needed. The autoimmune predisposition remains.

Surgical melanocyte grafting can be definitive in stable **segmental** vitiligo — the one subgroup approaching cure. Depigmentation of the remaining normal skin with monobenzone is an option in very extensive disease, and that is an irreversible alternative endpoint rather than a cure.

Prevention.

- **No primary prevention is established.** Nothing prevents vitiligo.
- **Avoiding skin trauma, friction and pressure** at affected and at-risk sites, given the Köbner phenomenon — including avoiding tight clothing and aggressive scrubbing. **MODERATE**, and free.
- **Avoiding phenolic depigmenting chemicals** — occupational, and some hair dyes. **MODERATE**.
- **Sun protection of depigmented patches**, which have no melanin protection and burn readily, and sunburn can itself trigger spread. **STRONG** for burn prevention, **MODERATE** for preventing spread.
- **Early treatment of active spreading disease to arrest progression** — short courses of systemic corticosteroid or JAK inhibition can halt rapid spread. **MODERATE**.
- **Screening for and treating associated autoimmune thyroid disease** — this does not affect the vitiligo and prevents a separate treatable disease. **STRONG** for that purpose.

Treatment.

1. **Topical corticosteroids** — first-line for limited disease, particularly in children. **Betamethasone and hydrocortisone are listed**. Off-patent. **Cents to a few dollars per tube.** Facial use requires caution and periodic breaks.
2. **Topical calcineurin inhibitors — tacrolimus, pimecrolimus** — preferred for face, eyelids and children, with comparable efficacy to steroids on the face without atrophy. Not listed. Off-patent. Higher cost than steroids.
3. **Narrowband ultraviolet B phototherapy, two to three times weekly for months.** The most effective widely available treatment for generalised vitiligo. Not a medicine. Capital equipment, low running cost; the constraint is attendance two to three times weekly for many months.
4. **Topical JAK inhibitor — ruxolitinib cream; and oral ritlecitinib**. **Not listed.** On-patent. **Thousands of US dollars per patient-year**.
5. **Combining phototherapy with a topical agent** — more effective than either alone.
6. **A short-course systemic corticosteroid, as an oral mini-pulse**, to arrest rapidly spreading disease. Prednisolone and dexamethasone listed, off-patent, cents.
7. **Surgical melanocyte transfer — punch, split-thickness or suction blister grafting, melanocyte-keratinocyte suspension** — for stable disease, especially segmental. Can be definitive.
8. **Depigmentation with monobenzone** for very extensive disease. Irreversible.
9. **Cosmetic camouflage, self-tanning preparations containing dihydroxyacetone, medical tattooing.** These address the actual complaint directly and immediately.
10. **Psychological support.** Given that the burden is overwhelmingly psychosocial, this is not an adjunct but a core treatment.

Simple means. Substantial, and they target the real burden.

- **Sunlight.** Natural ultraviolet with a topical agent produces repigmentation, and in settings without phototherapy cabinets this is the available route — with careful, graduated exposure, because depigmented skin burns readily and burning can worsen the disease. Free.
- **Sun protection of the patches** — hat, clothing, shade, and sunscreen where affordable. It prevents painful burns and reduces contrast between affected and normal skin by stopping the normal skin from tanning darker. Free to cheap, and the contrast reduction matters cosmetically more than it sounds.
- **Topical hydrocortisone or betamethasone** — listed, off-patent, **cents per tube** — for limited disease.
- **Cosmetic camouflage:** ordinary foundation or concealer matched to the normal skin, and **self-tanning lotion** containing dihydroxyacetone, which stains the depigmented skin brown for several days and is cheap, needs no prescription and works immediately regardless of disease activity. For the patient whose complaint is appearance, this is often the most useful single measure available.
- **Avoiding trauma and friction** to affected areas. Free.

- **Explanation:** that it is not infectious, not leprosy, not contagious, not caused by diet, and does no physical harm. Free — and in high-stigma settings this is the intervention with the largest effect on the patient's actual life.
- **Family and community education, and support groups.** Free, and they address the discrimination directly.
- **Thyroid function testing** where available — cheap, and it finds a treatable associated disease.

What the chain minimally requires for repigmentation: either a phototherapy cabinet with months of twice-weekly attendance, or sunlight plus a topical agent, or JAK inhibitors at thousands per year. For the stigma, nothing but words and cheap cosmetics.

Gaps. No verified global prevalence figure; the Global Burden of Disease 2021 immune-skin analysis was unreachable. The 0.5 to 2 per cent range is unverified. Whether psychological stress triggers onset or spread is contested — consistently reported by patients, not demonstrated in controlled study. Repigmentation rates with phototherapy and with JAK inhibitors vary widely by body site and could not be verified. Relapse rates after stopping treatment are not well established. Whether segmental vitiligo is the same disease as generalised vitiligo is unresolved. The psychosocial burden is extensively documented qualitatively and not quantified in any source read, and it is the principal burden of the condition.

> **Depth.** Starts in: a melanocyte antigen. Size: 10 nm†; depth −1.38. First complaint: about 20 years († onset about age 20); time depth 51.60. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Alopecia areata

What it is. The immune system attacks hair follicles, so hair falls out in sharply defined round patches. It can regrow by itself, and it can also progress to loss of all scalp or all body hair. The hair follicle is not destroyed, which is why regrowth remains possible for years.

Measured. No global figure was retrievable. Lifetime risk is commonly reported at about **2 per cent**, with point prevalence around **0.1 to 0.2 per cent**†. It can begin at any age, with onset before 30 in a majority, and childhood onset carries a worse prognosis†. Incidence is roughly equal between the sexes and prevalence is broadly similar worldwide.

Most patients have limited patchy disease. **Alopecia totalis**, all scalp hair, and **alopecia universalis**, all body hair, affect a minority — commonly reported around **5 to 10 per cent** of cases — and carry a much poorer prognosis†. Spontaneous regrowth within a year occurs in a substantial share of limited patchy disease, commonly reported at around **50 per cent or more**, and recurrence over a lifetime is the rule†.

The burden is entirely psychosocial and severe — depression, anxiety and quality-of-life impairment comparable to that in serious physical disease.

Where it starts.

- **Autoimmune attack on the hair follicle**, with collapse of follicular immune privilege. CD8+ T cells and the JAK-STAT and interferon-gamma pathway are the established effectors, which is why JAK inhibitors work and why they were a mechanistically predicted success.
- **Genetic predisposition** — *HLA* associations, *IL2/IL21*, *CTLA4*, *ULBP3/6*; family history in roughly a fifth, and high concordance in identical twins.
- **Associated autoimmune disease** — autoimmune thyroid disease, vitiligo, type 1 diabetes, coeliac disease, pernicious anaemia†.
- **Down syndrome** — substantially increased prevalence.
- **Atopy** — associated with earlier onset and worse prognosis.
- **Psychological stress** — frequently reported by patients as preceding onset; **CONTESTED** as a cause.
- **Vitamin D deficiency** — associated; causal role not established.

Genuinely not known: the trigger. Why the attack is patchy and why patches appear where they do. Why it remits spontaneously and then recurs. Why some patients progress to universalis and most do not, with no predictive test. Whether stress is causal. The follicle itself survives, which is why hair can regrow after decades — and why the follicle is spared destruction while being attacked is not explained.

Cure status. CONTROLLABLE. No treatment removes the disease, and two facts must be stated together. Spontaneous regrowth is common in limited patchy disease — around half or more within a year — so a substantial share of patients recover without treatment. That is self-limiting behaviour within a relapsing condition.

JAK inhibitors produce substantial regrowth in severe disease, including alopecia totalis and universalis that was previously untreatable: baricitinib, ritlecitinib and deuruxolitinib are licensed, with a large share of treated patients achieving major scalp hair regrowth. That is a genuine therapeutic advance. Relapse on stopping is usual, so treatment is indefinite, and the cost is tens of thousands of US dollars per patient-year.

Prevention.

- **Nothing prevents alopecia areata.** No primary prevention is established.
- **Treating associated autoimmune disease.** This does not prevent or improve the alopecia and it finds separate treatable conditions. **STRONG** for that purpose; thyroid function testing is standard.
- **Correcting iron and vitamin D deficiency** where present. **WEAK/CONTESTED** for the alopecia itself.
- **Avoiding unnecessary systemic corticosteroid courses for limited disease**, which prevents iatrogenic harm in a condition that often remits on its own and relapses after steroids anyway. **MODERATE**, and the action is omission.
- **Scalp sun protection in extensive loss**, which prevents sunburn and reduces cumulative ultraviolet skin cancer risk on a newly exposed scalp. **MODERATE**, cheap.
- **Eye protection where eyelashes are lost.** Lashes protect the eye from dust, and spectacles substitute. **MODERATE**, and it links to the dry eye entry.
- **Nasal protection where nasal hair is lost** in universalis.

Treatment.

1. **Topical corticosteroids, potent or very potent.** First-line for limited patchy disease and in children. **Betamethasone is listed**. Off-patent. **Cents to a few dollars per tube.**
2. **Intralesional corticosteroid injection (triamcinolone acetonide)** — the most effective treatment for limited patchy disease, injected into the patch every 4 to 6 weeks†. Triamcinolone and dexamethasone are listed, off-patent. **The drug costs cents per treatment**; it needs a needle and a clinician. This is the best value treatment in the entry.
3. **Topical minoxidil 5 per cent** — adjunctive, modest effect alone†. Off-patent, cheap.
4. **Topical immunotherapy — diphencyprone or squaric acid dibutyl ester** — which deliberately induces a contact allergy on the scalp; effective in extensive disease, cheap, and it needs specialist handling and causes an intentional dermatitis. Not listed.
5. **Topical or intralesional therapy plus a short systemic corticosteroid course** for rapidly progressive disease; relapse on withdrawal is common. Prednisolone listed, off-patent, cents.
6. **JAK inhibitors — baricitinib, ritlecitinib, deuruxolitinib** — for severe disease, with substantial regrowth in a large share. **Not listed.** On-patent. **Tens of thousands of US dollars per patient-year**. They require monitoring, and relapse follows stopping.
7. **Methotrexate, ciclosporin, azathioprine** — used in severe disease; all three are **listed**, all off-patent, all costing **cents to a few dollars per day**. The evidence is weaker than for JAK inhibitors and the cost difference is three to four orders of magnitude, which matters enormously for access.
8. **Wigs, hair-pieces, scalp micropigmentation, eyebrow tattooing, false eyelashes.** These address the actual complaint. Not medicines.
9. **Psychological support.** Core, not adjunctive, given the burden is psychosocial.

10. **Watchful waiting** — entirely appropriate for limited patchy disease given frequent spontaneous regrowth. **The action is omission.**

Simple means. Reasonable, and the highest-value option is a cheap injection.

- **Watchful waiting with explanation.** Free, and correct for limited disease, where around half or more regrow within a year. The explanation — that the follicle is not dead, that regrowth is common, that it is not infectious and not caused by anything the patient did — is itself the main intervention for many.
- **Intralesional triamcinolone.** The drug costs cents per session and it is the most effective treatment for patchy disease. The requirement is a needle, a syringe and a trained injector, and it is highly task-shiftable.
- **Topical betamethasone** — listed, off-patent, cents per tube.
- **Topical minoxidil** — off-patent and cheap.
- **Head covering: a cap, scarf, head-wrap or wig.** Immediate, cheap, and it addresses the presenting complaint directly and completely. In many settings a headscarf is both culturally unremarkable and entirely sufficient.
- **Scalp sun protection** — a hat. Free, and it prevents burns and long-term skin damage on a newly exposed scalp.
- **Spectacles where eyelashes are lost**, to keep dust out of the eyes.
- **Eyebrow pencil and cosmetic measures.** Cheap, and eyebrow loss is often more distressing than scalp loss because it alters facial expression.
- **Support groups and peer contact.** Free, and effective against the isolation that constitutes the burden.
- **Cheap immunosuppressants — methotrexate** at a few dollars a month — where severe disease needs systemic treatment and JAK inhibitors are unaffordable, which is almost everywhere.

What the chain minimally requires: a needle and a vial of triamcinolone for patchy disease. For severe disease, either a JAK inhibitor at tens of thousands per year, or methotrexate with blood monitoring at a few dollars a month.

Gaps. No verified global prevalence figure; the Global Burden of Disease 2021 immune-skin analysis was unreachable. All prevalence figures above are unverified, including the 2 per cent lifetime risk, the 5 to 10 per cent totalis and universalis share, and the 50 per cent spontaneous regrowth rate — this last varies substantially between sources and depends heavily on disease extent at presentation. Whether stress triggers onset is contested. JAK inhibitor regrowth rates and long-term safety could not be verified, and durability beyond a few years is unknown. Evidence for methotrexate and ciclosporin in severe disease is weaker than for JAK inhibitors, which creates a genuine problem: the affordable options are the less well evidenced ones, and no head-to-head comparison exists. The psychosocial burden is extensively documented and not quantified in any source read.

> **Depth.** Starts in: a hair-follicle antigen. Size: 10 nm†; depth −1.38. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: about 12 months ([B] limited patches often regrow within a year); depth 48.87.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Fungal skin infections (tinea and cutaneous candidiasis)

What it is. Fungi growing in the dead outer layer of skin, hair or nails. Ringworm on the body, athlete's foot between the toes, jock itch in the groin, scalp ringworm in children, and thrush in warm moist skin folds. Itchy, scaly, and usually easy to clear.

Measured. Fungal skin disease has high global prevalence, and the Global Burden of Disease 2021 fungal skin analyses were unreachable, so no condition-level global count was retrievable. Fungal skin diseases are consistently among the **most prevalent diseases of any kind** in Global Burden of Disease analyses,

with prevalence commonly reported in the **hundreds of millions to over a billion** people, and tinea pedis alone affecting a very large share of adults.

Tinea capitis, of the scalp, is predominantly a disease of children, especially in sub-Saharan Africa; tinea pedis and onychomycosis rise with age; candidal intertrigo concentrates in infants, older people, people with obesity and people with diabetes. Tinea capitis prevalence in school surveys in parts of sub-Saharan Africa has been reported very high, frequently tens of per cent of schoolchildren.

Terbinafine-resistant *Trichophyton indotineae* has emerged and spread internationally from South Asia, causing extensive treatment-refractory tinea — a significant recent development.

Where it starts.

- **Dermatophyte fungi** — *Trichophyton*, *Microsporum* and *Epidermophyton* species — invading keratin. *T. rubrum* is the commonest cause of tinea pedis and corporis worldwide.
- ***Candida albicans*** and related yeasts for candidal intertrigo and thrush — commensals that overgrow in warm, moist, occluded skin.
- **Warmth, moisture, occlusion and sweating** — the key modifiable conditions: occlusive footwear, shared showers, prolonged glove wear, skin folds in obesity.
- **Direct contact** — person to person, as in tinea capitis in households and schools; animal to person, as with *M. canis* from cats and dogs; and via soil.
- **Shared items** — combs, clippers, hats, towels, barbers' tools, bedding and shared bathroom floors. Barbering is a documented transmission route for tinea capitis.
- **Diabetes, obesity, immunosuppression, and topical corticosteroid use on an undiagnosed rash.** The last produces *tinea incognito*, where steroids suppress the inflammation, allow the fungus to spread, and make the diagnosis much harder.
- **Crowding and limited access to washing facilities**.

Genuinely not known: why some people are repeatedly and extensively affected while household contacts with identical exposure are not — host susceptibility to dermatophytes is poorly characterised. Why *T. rubrum* causes chronic, barely inflamed infection while zoophilic species cause florid inflammation. The drivers of *T. indotineae* resistance emergence — unregulated topical steroid-antifungal combination use in South Asia is the leading explanation and is not established. Whether treating asymptomatic carriers of tinea capitis prevents community transmission is unresolved.

Cure status. CURABLE, and cheaply. Topical antifungals cure the great majority of tinea corporis, cruris and pedis, and candidal intertrigo, with cure rates commonly reported at **70 to 90 per cent** for a two- to four-week course†. Treatment stops and the infection does not return unless reinfection occurs.

Qualifications. **Tinea capitis requires oral treatment** — topicals do not penetrate the hair shaft — and oral griseofulvin or terbinafine cures it. **Onychomycosis**, of the nail, requires months of oral treatment with cure rates well below those for skin, commonly reported around **50 to 70 per cent** mycological cure with relapse common†; it is the least curable form. Reinfection is common where the predisposing conditions persist, so the episode is cured while the tendency is not. *T. indotineae* is terbinafine-resistant and requires itraconazole, often prolonged.

Prevention. Nearly all free, and effective.

- **Keeping skin dry — drying carefully between the toes and in skin folds after washing. MODERATE**, and free.
- **Footwear measures — breathable shoes, changing socks, alternating shoes, sandals in communal showers, going barefoot where safe. MODERATE**.
- **Not sharing towels, combs, clippers, hats or bedding; sterilising barbers' clippers. MODERATE** for tinea capitis.
- **Treating household contacts and pets.** The animal source is frequently the reservoir, and treating the child without the cat guarantees recurrence. **MODERATE**.
- **Screening and treating in schools where tinea capitis is prevalent. MODERATE**.

- **Washing and drying clothing and bedding at adequate temperature. MODERATE**.
- **Avoiding topical corticosteroids on an undiagnosed scaly rash**, which prevents tinea incognito and extensive spread. **STRONG**, free, and the action is omission.
- **Avoiding unregulated steroid-antifungal combination creams**, implicated in resistance emergence. **MODERATE/CONTESTED** as a resistance measure, **STRONG** as good practice.
- **Glycaemic control in diabetes. MODERATE**.
- **Access to soap and washing water. MODERATE**, and a structural prerequisite.

Treatment.

1. **Topical azoles — miconazole, clotrimazole, ketoconazole**, twice daily for two to four weeks, continued a week beyond clearance. First-line for tinea corporis, cruris, pedis and candidal intertrigo. **Miconazole and clotrimazole are on the Essential Medicines List** — the list document did not load and the index showed the dermatological section incompletely. Off-patent. **Well a few US dollars to a few US dollars per tube.**
2. **Topical terbinafine** — slightly higher cure rates and shorter courses than azoles for dermatophytes, and not effective against *Candida*. Off-patent, low cost.
3. **Topical selenium sulfide or ketoconazole shampoo** — for pityriasis versicolor, and as an adjunct in tinea capitis to reduce shedding and transmission. Selenium sulfide is listed. Off-patent, cheap.
4. **Oral griseofulvin** — the long-standing treatment for tinea capitis, particularly for *Microsporum*; it requires six to eight weeks and absorption improves with fatty food. **Listed**. Off-patent. **Low cost, a few US dollars per course**.
5. **Oral terbinafine** — shorter courses than griseofulvin for *Trichophyton* tinea capitis, and the standard for onychomycosis. **Listed**. Off-patent, low cost.
6. **Oral itraconazole or fluconazole** — alternatives, and **itraconazole is the agent for terbinafine-resistant *T. indotineae***. Fluconazole is listed, off-patent, cheap.
7. **Oral or topical nystatin** for candidal infection — listed, off-patent, very cheap.
8. **Treating the reservoir** — household contacts, pets, footwear and shared items. Without this, recurrence is near-certain.
9. **Avoid combination steroid-antifungal creams** as routine therapy. **The action is omission.**

Simple means. One of the best simple-means entries in this part of the chapter: a cheap tube cures a very common disease.

- **Topical clotrimazole or miconazole** at **well under a dollar to a few dollars per tube**, listed and off-patent, curing 70 to 90 per cent of common tinea†. Available without prescription in most countries. This is the key cheap-intervention-large-burden combination in the entry.
- **Keeping the skin dry.** Drying carefully between the toes and in skin folds, letting skin folds air, using a cloth rather than leaving moisture. Free, and both preventive and therapeutic.
- **Sunlight and air exposure** to affected skin fold areas. Free.
- **Changing and washing socks and clothing; alternating footwear so shoes dry out; sandals or bare feet where practical.** Free to very cheap, and it removes the warm moist occlusion the fungus requires.
- **Not sharing combs, towels, hats and clippers; cleaning barbers' clippers between customers.** Free, and it interrupts tinea capitis transmission at the point where it mostly happens.
- **Selenium sulfide or ketoconazole shampoo** — cheap, listed, and it reduces shedding and transmission from a child with tinea capitis while oral treatment works.
- **Treating the household and the pet.** Costs another tube.
- **Oral griseofulvin for tinea capitis** at a few dollars a course — listed, off-patent. This is the one form needing an oral drug, and it is still cheap.
- **Not using steroid creams on an undiagnosed scaly itchy rash.** Free, the action is omission, and it prevents extensive tinea incognito.

- **Soap and water.** The structural prerequisite, and where it is absent these infections persist regardless of what else is done.

What the chain minimally requires: a tube of clotrimazole. For scalp and nail disease, an oral antifungal — still cheap and listed, and needing a several-week supply and, for nails, months.

Gaps. No condition-level global prevalence figure was retrievable — both Global Burden of Disease 2021 fungal skin analyses were unreachable, and this is one of the most prevalent disease groups in the world, so the gap is material. All prevalence figures above are unverified. Cure rates, 70 to 90 per cent topical for skin and 50 to 70 per cent for nails, are widely cited and unverified. The prevalence and geographic spread of terbinafine-resistant *T. indotineae* is changing rapidly and no reliable figure exists. Whether topical steroid-antifungal combination misuse caused that resistance is a plausible and unproven explanation. Whether school screening and treating asymptomatic tinea capitis carriers reduces community prevalence is unresolved. The Essential Medicines List status of individual topical antifungals could not be confirmed because the list document did not load.

> **Depth.** Starts in: a fungal cell. Size: 5 µm†; depth +4.28. First complaint: about 7.5 days († 4–14 days); time depth 45.33. One untreated course: no number.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Bacterial skin infections (impetigo and cellulitis)

What it is. Impetigo is a contagious crusted infection of the top layer of skin, mostly in children. Cellulitis is a deeper, spreading infection of the skin and the tissue under it, with redness, heat, swelling and fever. Cellulitis can become dangerous.

Measured. No global figure was retrievable for impetigo or cellulitis as such. Impetigo is commonly reported to affect roughly **140 million** people at any one time, with the great majority of cases in children in low- and middle-income countries.

The scabies link is the best-evidenced figure in the entry. Scabies affects **at least 200 million** people at any one time (World Health Organization fact sheet, *Scabies*, 31 May 2023), and scabies mass drug administration trials consistently reduced community impetigo prevalence by **60 to 88 per cent** across three studies in Fiji and the Solomon Islands, which quantifies how much impetigo is scabies-driven in those settings. In Fiji, skin and soft tissue infection **hospitalisations fell 17 per cent** in the year after ivermectin mass administration integrated with lymphatic filariasis control, in a population of about 135,000.

Cellulitis incidence in high-income settings is commonly reported at about **200 per 100,000** person-years, and it is a frequent cause of hospital admission†. Impetigo concentrates in children aged 2 to 5; cellulitis rises with age, obesity, lymphoedema and diabetes†.

The downstream burden is the most consequential measured link in the entry. *Streptococcus pyogenes* skin infection contributes to acute post-streptococcal glomerulonephritis — **acute renal damage appears in up to 10 per cent** of children with scabies in resource-poor settings and can persist for years — and the World Health Organization notes growing evidence that *S. pyogenes* impetigo contributes to rheumatic fever and rheumatic heart disease.

Where it starts.

- ***Staphylococcus aureus*** and ***Streptococcus pyogenes*** — the two causative organisms for both conditions.
- **A break in the skin** — the necessary condition. The commonest breaches are scabies excoriations, quantified above, insect bites, eczema, tinea pedis fissures, cuts, abrasions and burns.
- **Scabies** — the dominant precursor of impetigo in endemic settings; scratching breaches the skin and mite activity affects local immunity.

- **Crowding, shared bedding, limited water and soap, hot humid climate**.
- **For cellulitis specifically:** lymphoedema and chronic oedema, the strongest risk factor and the driver of recurrence; obesity; diabetes; venous insufficiency and leg ulcers; tinea pedis as the portal of entry; and previous cellulitis, which carries a high recurrence rate.
- **Intravenous drug use**.
- **Atopic dermatitis** — *S. aureus* colonisation and barrier breach.

Genuinely not known: why cellulitis recurs so readily in some people. Lymphatic damage from the first episode predisposing to the next is the leading account, and it is a vicious cycle without a clear entry point for interruption beyond oedema control. Why some *S. pyogenes* strains cause glomerulonephritis or rheumatic sequelae and others do not. How much of the global rheumatic heart disease burden originates in skin rather than throat infection — an open question with real implications, and the scabies mass administration impetigo reductions are the natural experiment that might answer it. Diagnosis of cellulitis is clinical and frequently wrong; misdiagnosis rates against venous eczema, lymphoedema and gout are substantial.

Cure status. CURABLE. Both are curable with antibiotics.

Impetigo is also substantially self-limiting — it resolves without treatment in most cases over two to three weeks — and treatment speeds resolution and, importantly, reduces transmission. Topical antibiotics are at least as effective as oral for limited impetigo.

Cellulitis resolves with appropriate antibiotics in the great majority. Untreated, it can progress to abscess, necrotising infection, bacteraemia and death — so it is curable and it is also the entry in this part of the chapter most capable of killing.

Qualifications: recurrence is common in cellulitis where the predisposing oedema persists; and antibiotic prophylaxis reduces recurrence only while it is taken — the PATCH I trial found penicillin prophylaxis reduced recurrence, with the benefit diminishing after stopping.

Prevention.

- **Treating scabies, including by mass drug administration.** The best-quantified preventive measure in this entry: scabies mass administration reduced community impetigo prevalence by **60 to 88 per cent** in three studies, and reduced skin and soft tissue infection hospitalisations by **17 per cent** in one Fijian population. **STRONG**.
- **Soap, water and washing. MODERATE** for impetigo.
- **Treating the entry portal** — tinea pedis, eczema, insect bites, wounds. **MODERATE** for cellulitis; treating athlete's foot prevents leg cellulitis.
- **Oedema and lymphoedema control — compression, elevation, exercise, skin care.** The key measure for preventing recurrent cellulitis. **MODERATE**. This links directly to the venous leg ulcer entry.
- **Emollients to maintain skin integrity in dry or oedematous legs. MODERATE**.
- **Weight reduction; glycaemic control. MODERATE**.
- **Antibiotic prophylaxis with low-dose penicillin for recurrent cellulitis**, which reduces recurrence while taken. **MODERATE**, with the benefit ending on discontinuation.
- **Not sharing towels and bedding; keeping nails short; covering impetigo lesions; excluding from school until crusted or treated. MODERATE** for transmission.
- **Prompt wound cleaning. MODERATE**, free.

Treatment. For impetigo:

1. **Topical antibiotic — mupirocin or fusidic acid** — for limited disease, at least as effective as oral antibiotics. Mupirocin is listed. Off-patent. A few US dollars per tube.
2. **Topical antiseptics — povidone-iodine, chlorhexidine, hydrogen peroxide** — cheap alternatives with evidence of benefit. Very low cost.

3. **Oral antibiotics — flucloxacillin, cephalexin or amoxicillin-clavulanate** for extensive or bullous impetigo; all listed, all off-patent, **a few US dollars to a few dollars per course**.
4. **Treating concurrent scabies.** Without this, impetigo recurs.

For cellulitis:

5. **Oral flucloxacillin, cephalexin or penicillin** for uncomplicated cellulitis, typically five to seven days. **Listed**, off-patent, **a few US dollars to a few dollars per course**. Oral is as effective as intravenous for most uncomplicated cases, which matters for cost and admission avoidance.
6. **Intravenous antibiotics** for systemic illness, rapid spread or failure of oral therapy. Listed agents, off-patent.
7. **Elevation of the affected limb**, which reduces oedema and speeds resolution. Free, and routinely under-used.
8. **Marking the edge of the erythema** to track progression objectively. A pen.
9. **Analgesia** — paracetamol, ibuprofen; listed, off-patent, cents.
10. **Surgical drainage** for abscess; **urgent surgical exploration** for suspected necrotising infection, which is a surgical emergency and not an antibiotic problem.
11. **Treating the predisposing cause** — tinea pedis, ulcer, oedema. Without this, recurrence follows.

Simple means. Strong, and the scabies link makes it exceptional value.

- **Soap and water, and washing.** Free to near-free, and it addresses impetigo directly.
- **Treating scabies with permethrin or ivermectin.** The measured effect on impetigo is a **60 to 88 per cent** community reduction. Ivermectin is donated or very low cost in mass administration programmes, at roughly a few US cents per dose. This is the highest-leverage cheap intervention in the entry: treating a mite removes most of the bacterial skin infection in endemic settings, and with it part of the glomerulonephritis and possibly the rheumatic heart disease burden.
- **Topical antiseptics — povidone-iodine, dilute chlorhexidine, or even clean water and soap with crust removal** — for limited impetigo. Pennies.
- **Covering lesions, keeping nails short, not sharing towels or bedding.** Free.
- **Limb elevation** for cellulitis. Free, effective and under-used.
- **Compression and oedema control** for recurrent leg cellulitis — a bandage, costed in the venous ulcer entry. Cheap, and it attacks the cause of recurrence rather than each episode.
- **Treating athlete's foot** with a tube of clotrimazole under a dollar, which closes the portal of entry for leg cellulitis.
- **A pen to mark the erythema margin**, so progression or improvement is objective. Cents.
- **Oral flucloxacillin or penicillin** — listed, off-patent, under a dollar a course. A life-threatening infection treated for the price of a loaf of bread.
- **Knowing the danger signs** — pain out of proportion, rapid spread, skin necrosis, systemic illness — which indicate necrotising infection needing surgery. Free knowledge that saves lives.

What the chain minimally requires: soap, an antiseptic, and a cheap oral antibiotic. For necrotising infection, an operating theatre urgently.

Gaps. No verified global prevalence figure for impetigo or cellulitis; no World Health Organization or Global Burden of Disease source read quantifies them. The roughly 140 million impetigo figure and the roughly 200 per 100,000 cellulitis incidence are unverified. The scabies mass administration impetigo reductions are well sourced and the source reports **no confidence intervals** for any of those figures, which limits their precision. How much global rheumatic heart disease originates in skin rather than throat infection is unknown and potentially large. Cellulitis is frequently misdiagnosed and no source read quantifies the misdiagnosis rate. The duration of benefit of antibiotic prophylaxis after stopping is not established. Topical against oral treatment for impetigo is settled in favour of topical for limited disease, and prescribing practice does not follow it.

> **Depth.** Starts in: Staphylococcus aureus or Streptococcus pyogenes. Size: 1 µm†; depth +2.81. First complaint: about 3.2 days († 1–10 days); time depth 44.55. One untreated course: about 8.4 days († 7–10 days); depth 45.44.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Scabies

What it is. A mite burrows into the top layer of skin and lays eggs. The body reacts with ferocious itching, worst at night, and a rash in the finger webs, wrists, waist and genitals. It spreads by prolonged skin contact and runs through households.

ICD-11 codes scabies in chapter 1, among the infectious and parasitic diseases, because it is an infestation passed from person to person. The full entry is there, under Scabies, in the chapter on certain infectious or parasitic diseases.

A reader in the skin chapter is sent there because scabies is met here first, as itch, rash and the impetigo that follows scratching, and the whole condition is in one place there. That entry carries the burden figures, the population-scale results of mass drug administration in Fiji and the Solomon Islands, the treatments and their listing, and the simple means. The infestation is CURABLE, and the entry in chapter 1 says how, and for whom.

Seborrhoeic dermatitis

What it is. Scaly, greasy, slightly red patches where the skin is oiliest — scalp, eyebrows, sides of the nose, chest. Dandruff is its mild form. It is driven by a normal skin yeast and it comes and goes for life.

Measured. Counted within the dermatitis group at **15.2 million** years lived with disability, 95% uncertainty interval 8.9 to 24.2; seborrhoeic dermatitis is not separately quantified in any source read. Prevalence is commonly reported at about **3 to 5 per cent** for seborrhoeic dermatitis proper, while **dandruff, its mild form, affects up to half of adults**.

The age pattern is trimodal: infantile cradle cap in the first months, then onset after puberty with a peak in the thirties and forties. It is more common in men, consistent with androgen-driven sebum production. It is substantially more common and more severe in **HIV infection**, reported in a large share of people with advanced HIV, where it can be the presenting sign, and in **Parkinson disease** and other conditions with increased sebum.

Where it starts.

- ***Malassezia*** yeasts — normal skin commensals, metabolising sebum triglycerides into free fatty acids that irritate the skin. This is the established driver, and it explains why antifungals work. It is **not an infection**; the organism is present on everyone.
- **Sebum production.** The disease occurs only in sebaceous areas and tracks androgen activity, which is why it starts at puberty and affects men more.
- **Individual susceptibility to *Malassezia* metabolites** — the key variable, since everyone carries the yeast.
- **Immunosuppression, especially HIV**.
- **Neurological disease — Parkinson disease, stroke, facial nerve palsy**.
- **Cold dry weather; stress; fatigue** — reported to worsen it.
- **Some drugs**, including those that alter sebum or dopamine signalling.

Genuinely not known: why only some people react to a universal commensal. Why it is associated with Parkinson disease — whether through sebum changes from reduced dopaminergic activity or something else. Why it remits in childhood between the infantile and post-pubertal phases. Why infantile seborrhoeic dermatitis resolves spontaneously and permanently while the adult form does not.

Cure status. Adults: CONTROLLABLE. Infants: SELF-LIMITING.

Infantile seborrhoeic dermatitis, cradle cap, resolves spontaneously within weeks to months and does not recur in childhood; treatment is for appearance and comfort only.

Adult seborrhoeic dermatitis is controllable. Topical antifungals and anti-inflammatories clear it reliably and quickly, and it returns within weeks of stopping, because the yeast and the sebum remain. Maintenance treatment, typically once or twice weekly, keeps it suppressed. Nothing eliminates the predisposition, and control is easy, cheap and reliable, which makes this one of the more satisfactory entries in this part of the chapter.

Prevention.

- **Regular use of an antifungal or medicated shampoo as maintenance**, once or twice weekly, which prevents relapse. **STRONG** for relapse prevention. This is prevention of flares rather than of the condition.
- **Nothing prevents the condition itself.**
- **Avoiding harsh soaps, hot water and alcohol-containing products on affected skin. WEAK**, free.
- **Avoiding heavy occlusive hair oils and pomades** on an affected scalp. **WEAK**.
- **Managing HIV with antiretroviral therapy**, which improves seborrhoeic dermatitis along with immune function. **STRONG** in that group.
- **Sunlight exposure** — reported to improve it, consistent with ultraviolet suppressing *Malassezia*. **WEAK**.
- Poor hygiene does **not** cause it, and excessive washing does not prevent it. Correcting that belief is useful and free.

Treatment.

1. **Topical antifungal shampoos and creams — ketoconazole 2 per cent, ciclopirox, selenium sulfide, zinc pyrithione.** First-line and effective. **Selenium sulfide is listed**; topical ketoconazole's status could not be confirmed from the index displayed. Off-patent. **A few US dollars per bottle**, and one bottle lasts months at maintenance frequency.
2. **Topical corticosteroids**, mild to moderate potency, for short courses to settle inflammation and itch. **Hydrocortisone and betamethasone are listed**. Off-patent. **Cents to a few dollars per tube.** Not for prolonged facial use, because of atrophy and steroid-induced rosacea.
3. **Topical calcineurin inhibitors — tacrolimus, pimecrolimus** — steroid-sparing for the face and useful for maintenance. Not listed. Higher cost.
4. **Coal tar shampoo and salicylic acid** — keratolytic and antiscaling; old, cheap, effective. Off-patent, very low cost.
5. **Oral antifungal (itraconazole, fluconazole)** for severe or widespread disease. Fluconazole listed, off-patent, cheap.
6. **Emollients and oil to soften scale** before removal.
7. **Infantile disease:** softening with an emollient or plain vegetable oil, gentle brushing, mild shampoo. **Treatment is optional**, because it resolves anyway. **The action is omission.**
8. **Antiretroviral therapy** where HIV-associated.

Simple means. Very strong — almost everything effective is cheap and available without prescription.

- **An antifungal or medicated shampoo** — ketoconazole, selenium sulfide or zinc pyrithione — at **a few dollars a bottle**, lasting months on once- or twice-weekly maintenance. This is the whole treatment for most patients, needs no prescription in most countries, and is the key cheap intervention in the entry.
- **Using the shampoo on the face and chest, not just the scalp**, left on a few minutes before rinsing. A free extension of an existing cheap product to the other affected sites.
- **Coal tar or salicylic acid shampoo** — among the cheapest effective options.
- **Plain vegetable oil or petroleum jelly** to soften scale before gentle removal, particularly for cradle cap and for thick scalp scale. Pennies.

- **Soft brushing of softened scale** in infants, with a soft brush or cloth. Free.
- **Sunlight.** Free, and reported to improve it.
- **Topical hydrocortisone** — listed, off-patent, cents per tube, for flares.
- **Avoiding harsh soaps, very hot water and alcohol-based toners** on affected skin. Free.
- **Explanation:** that it is not caused by poor hygiene, is not contagious, is not an infection to be eradicated, and that maintenance rather than cure is the realistic goal. Free, and it prevents both over-washing and disappointment.
- **For infants: doing little or nothing**, because it resolves on its own. The action is omission, and it is free.

What the chain minimally requires: a bottle of medicated shampoo. No component of this condition's management requires an industrial supply chain beyond that, except for the severe minority needing an oral antifungal, itself a cheap listed generic.

Gaps. Not separately quantified in Global Burden of Disease or World Health Organization sources read; only the combined dermatitis total is available. The 3 to 5 per cent prevalence figure and the "up to half of adults" dandruff figure are unverified. The relationship to *Malassezia* is established and why susceptibility varies is unknown. The association with Parkinson disease is documented and unexplained. Prevalence in HIV is reported as substantially elevated and no verified figure was obtainable. Comparative efficacy between the various antifungal shampoos is not well established and differences are probably small. Optimal maintenance frequency has not been determined by trial. The Essential Medicines List status of topical ketoconazole could not be confirmed.

> **Depth.** Starts in: Malassezia yeast. Size: 5 µm†; depth +4.28. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number ([B] comes and goes for life).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Pressure ulcers (decubitus ulcers)

What it is. Skin and the tissue beneath it die because the weight of the body has pressed on them too long and cut off the blood supply. They form over bony points — heel, hip, buttock, base of the spine — in people who cannot move themselves. Almost all of them are preventable.

Measured. No global figure was retrievable. Hospital point prevalence is commonly reported at roughly **5 to 15 per cent** of inpatients in high-income settings, with higher figures in intensive care and in long-term care. The affected are overwhelmingly older people, and people of any age with spinal cord injury or immobility.

Pressure ulcer treatment is consistently reported as a major health system cost, with national cost estimates in the billions of US dollars for individual high-income countries, and treatment costing many times prevention. Pressure ulcers are associated with substantially increased mortality, though much of that reflects the underlying illness and immobility rather than the ulcer itself.

A measurement problem bears on all of these figures: pressure ulcer rates are used as a care-quality indicator, which creates reporting incentives and makes between-institution comparison unreliable.

Where it starts.

- **Sustained pressure over a bony prominence** — the necessary cause. Tissue tolerance is a function of pressure magnitude and duration together: high pressure for a short time or low pressure for a long time both cause damage.
- **Shear and friction** — sliding down a bed, or being dragged rather than lifted. Shear damages deeper tissue at lower pressures.
- **Immobility** — the dominant clinical risk factor: unconsciousness, sedation, anaesthesia, spinal cord injury, severe frailty, restraint.

- **Moisture — incontinence and sweat** — macerates skin and lowers its tolerance.
- **Malnutrition and low protein intake; dehydration**.
- **Impaired sensation**, where the person does not feel the discomfort that would normally prompt movement: spinal cord injury, diabetic neuropathy, stroke.
- **Poor perfusion** — shock, vasopressors, peripheral arterial disease, anaemia, smoking.
- **Age and thin skin; previous pressure ulcer; device-related pressure** from oxygen tubing, casts, catheters, cervical collars.

Genuinely not known: the exact pressure-time threshold for tissue damage in an individual, which is why risk scores perform only moderately. Why some immobile patients never develop ulcers. **Deep tissue injury** begins at the bone-muscle interface and may be invisible at the skin surface for days, so the moment of injury cannot be identified. Whether the widely used risk assessment scales improve outcomes over clinical judgement is **genuinely unresolved** — Cochrane assessments have found insufficient evidence that structured risk assessment reduces ulcer incidence. And the optimal repositioning interval has never been established by adequate trial: the traditional two-hourly figure is convention, not evidence.

Cure status. Superficial ulcers, stages 1 to 2: CURABLE. Deep ulcers, stages 3 to 4: RELIEF ONLY. Superficial ulcers, affecting epidermis and dermis, heal completely when pressure is removed, often within weeks, with no residual deficit.

Deep ulcers, through subcutaneous fat to muscle, tendon or bone, heal by **scar contraction rather than tissue regeneration**, take months, frequently do not heal at all in frail or malnourished people, and recur readily at the same site because scar tissue tolerates pressure poorly. Surgical flap closure can close them and has a substantial recurrence rate.

The decisive point: healing requires that the pressure be removed. No dressing, drug or nutritional supplement heals an ulcer that is still being sat or lain on. This is why the condition is, functionally, a nursing and positioning problem rather than a pharmaceutical one.

Prevention. This is the entry where prevention most dominates treatment, and it is almost entirely non-pharmaceutical.

- **Repositioning on a schedule.** The foundation of prevention. The conventional two-hourly interval is **convention rather than established evidence**, and the optimal frequency is unknown. **STRONG** as a principle, **uncertain** as to interval. Cost: staff time only.
- **Pressure-redistributing support surfaces.** Higher-specification foam mattresses reduce incidence compared with standard hospital foam, and this is one of the better-evidenced interventions. Alternating-pressure and air-fluidised surfaces for higher risk. **STRONG** for high-specification foam, **MODERATE** for the more expensive dynamic surfaces, whose added benefit over good foam is less clear.
- **Heel offloading** — suspending the heels off the surface with a pillow or a purpose-made device. Heels are a common ulcer site and almost completely protected by this. **STRONG**, and the pillow version is free.
- **Daily skin inspection, especially over bony points and under devices. STRONG**, and free.
- **Keeping skin clean and dry; prompt management of incontinence; barrier preparations. MODERATE**.
- **Nutritional support — adequate protein and energy, and correcting dehydration. MODERATE**.
- **Prophylactic silicone foam dressings over high-risk bony points**, which reduced incidence in trials. **MODERATE**.
- **Correct manual handling — lifting rather than dragging**, to avoid shear. **MODERATE**, free.
- **Early mobilisation wherever possible. STRONG**, free.
- **Avoiding massage over bony prominences and avoiding doughnut ring cushions** — both traditional practices that cause harm. **MODERATE**, free improvements, and the action is omission.

- **Structured risk assessment scales (Braden, Waterlow, Norton)** — widely mandated; **CONTESTED**, with insufficient evidence that they reduce incidence over clinical judgement.

Treatment.

1. **Pressure relief — complete offloading of the ulcer site.** The treatment. Nothing else works without it. Cost: positioning, pillows, staff time, a support surface.
2. **Wound cleansing with water or saline**. Near-zero cost.
3. **Debridement of dead tissue** — sharp, autolytic under a moisture-retaining dressing, or larval. Necessary for deep ulcers. **Dry stable heel eschar is generally left alone.**
4. **Moist wound dressings** — hydrocolloid, foam, hydrogel, alginate. The evidence that any one dressing type outperforms another is **weak**; the principle of maintaining a moist wound environment is better supported than any specific product. Not listed. Off-patent. Cost varies widely; see *Simple means*.
5. **Nutritional support with adequate protein**, and correcting anaemia.
6. **Treating infection** — systemic antibiotics only for cellulitis, osteomyelitis or sepsis, and **not** for colonised wounds; topical antiseptics and antibiotics are not routinely indicated. Listed agents, off-patent, low cost.
7. **Negative pressure wound therapy** for deep cavity wounds, which reduces volume; evidence for improved healing is moderate. Expensive, requiring equipment and consumables.
8. **Surgical flap reconstruction** for stage 4 ulcers, with substantial recurrence rates†.
9. **Analgesia** — paracetamol, ibuprofen, and opioids for dressing changes. Listed, off-patent, cents. Pressure ulcer pain is routinely undertreated.
10. **Not useful:** routine systemic antibiotics, antiseptic soaks on healing tissue, doughnut cushions, massage of bony prominences. **The action is omission in each case.**

Simple means. Almost everything that works is simple, and that is the central fact about this condition.

- **Turning the person.** Free. It is the single most effective intervention in existence for this disease, and it requires no equipment, no drug and no supply chain — only someone to do it, and the knowledge that it must be done.
- **Pillows and rolled blankets** to redistribute pressure, offload heels, and position at 30 degrees rather than directly on the hip. Free or near-free, and heel offloading with a pillow is close to fully protective for a common ulcer site.
- **Daily skin inspection** by a family member or carer, with instruction on what non-blanching redness looks like. Free, and it catches stage 1 damage while it is still fully reversible.
- **Keeping the skin clean and dry; prompt changing after incontinence; petroleum jelly or zinc oxide as a barrier.** Pennies. **Calamine and zinc preparations are listed**.
- **Lifting rather than dragging** when moving someone. Free, and it prevents shear injury.
- **Adequate food and water, with protein.** The cost of food.
- **Clean cloth dressings with petroleum jelly** to keep a superficial wound moist and non-adherent, where manufactured dressings are unavailable. Near-zero cost, and it delivers the one dressing principle that is actually evidence-supported — moisture retention — without any proprietary product.
- **Saline or clean boiled water for cleansing.** Near-zero cost; saline can be made from salt and boiled water.
- **Honey or sugar dressings** where nothing else exists — both have antimicrobial and debriding properties and a long history of use, with modest evidence.
- **Family and carer training.** The highest-value intervention of all in home care settings, because the person who turns the patient at three in the morning is a relative, not a nurse.

A disease that costs health systems billions is prevented by moving people and looking at their skin. The binding constraint is staffing, attention and knowledge — not money or technology.

Gaps. No global prevalence or burden figure exists on the sources read. All prevalence figures above are unverified, and hospital prevalence figures are distorted by the condition's use as a quality indicator. **The optimal repositioning interval has never been established** — two-hourly is convention, and this is a remarkable evidence gap for the world's most commonly recommended nursing intervention. Whether structured risk assessment scales reduce incidence is genuinely unresolved, with Cochrane finding insufficient evidence against near-universal mandated use. Comparative dressing evidence is weak and the large commercial literature does not resolve it. Deep tissue injury cannot be detected at onset. The added benefit of expensive dynamic support surfaces over good-quality foam is unclear. Honey and sugar dressing evidence is modest and contested.

> **Depth.** Starts in: the skin over a bony point. Size: 3 cm†; depth +12.19. First complaint: about 6 hours († hours of unrelieved pressure); time depth 42.24. One untreated course: about 3 weeks ([B] superficial ulcers heal within weeks); depth 46.27.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Venous leg ulcers

What it is. A shallow, often large open sore on the lower leg, usually near the ankle, caused by blood pooling in damaged leg veins. They weep, they ache, they last months or years, and they come back. Compression bandaging heals most of them.

Measured. No global figure was retrievable; venous leg ulcers are not quantified on any World Health Organization or Global Burden of Disease source read. Point prevalence is commonly reported at roughly **0.1 to 0.3 per cent** of the general adult population, rising to around **1 to 3 per cent** in people over 80†. The condition is strongly age-related, with a mean age at presentation in the seventies, and it is more common in women.

Duration and recurrence are the defining measured features: a large share have been open for **more than six months** at presentation, and recurrence after healing is commonly reported at **25 to 50 per cent within a year** without continued compression†.

Venous ulcers consume a very large share of community nursing time in high-income health systems, and the dominant cost is nursing visits rather than materials. Venous disease accounts for the majority of all leg ulcers, commonly reported around **70 per cent**, with arterial, mixed, diabetic and other causes making up the rest.

Where it starts.

- **Chronic venous hypertension** — the necessary cause. Incompetent valves in superficial, deep or perforating veins, or venous outflow obstruction, mean that venous pressure in the leg stays high on standing and walking.
- **Previous deep vein thrombosis** — post-thrombotic syndrome.
- **Varicose veins and superficial venous incompetence**.
- **Calf muscle pump failure** — immobility, ankle stiffness, obesity. The calf pump is what normally lowers venous pressure during walking, so its failure is central.
- **Obesity**.
- **Age; prolonged standing occupations; previous leg fracture or surgery; family history**.

Genuinely not known: why skin ulcerates in some people with severe venous hypertension and not others with equivalent haemodynamics. The microvascular mechanism connecting venous pressure to skin breakdown is incompletely described — leucocyte trapping, fibrin cuffs and pericapillary fibrin are described without a settled causal sequence. Why some ulcers remain open for years despite optimal compression, and no predictor identifies them in advance. Whether the many adjunctive agents and dressings add anything to compression is largely unresolved.

Cure status. The ulcer: CURABLE in roughly 65 to 70 per cent at 24 weeks with adequate compression†. Venous hypertension after healing: CONTROLLABLE, with lifelong compression hosiery.

Venous ulcers heal, and compression is what heals them. Reported healing with adequate compression is roughly **65 to 70 per cent at 24 weeks**, against substantially lower rates without it†. The Cochrane review of compression for venous leg ulcers **could not be retrieved** — the Cochrane Library did not load — and it is the standard reference; its conclusions as commonly reported are that compression heals more ulcers than no compression, that multi-component systems outperform single-component, and that systems containing an elastic component outperform inelastic ones.

The qualification that defines the condition: the venous hypertension remains, so recurrence is **25 to 50 per cent within a year** without continued compression†. The ulcer is cured; the disease is not. Lifelong compression hosiery after healing is therefore part of the control.

Correcting superficial venous incompetence by surgery or endovenous ablation reduces recurrence — the ESCHAR trial found surgery plus compression reduced 12-month recurrence substantially compared with compression alone, and the EVRA trial found early endovenous ablation shortened healing time. That is the nearest thing to curing the underlying disease.

Prevention.

- **Compression hosiery after healing** — the principal measure against recurrence, which is the main preventable event. **STRONG**.
- **Treating superficial venous incompetence** — surgery or endovenous ablation reduces recurrence and speeds healing. **MODERATE**.
- **Leg elevation above heart level when resting. MODERATE**, free.
- **Walking and ankle exercises** to work the calf pump. **MODERATE**, free.
- **Weight reduction. MODERATE**.
- **Skin care — emollients for venous eczema, avoiding trauma, treating tinea pedis. MODERATE**, cheap.
- **Preventing and properly treating deep vein thrombosis**, including anticoagulation and compression, which prevents post-thrombotic syndrome. **STRONG** for that pathway.
- **Pentoxifylline as an adjunct to compression** — improves healing in Cochrane assessment. **MODERATE**. Off-patent and cheap.
- **Treating any arterial component** — and, critically, **measuring the ankle-brachial pressure index before applying compression**, because compression on a severely ischaemic leg causes necrosis. **STRONG** as a safety measure.

Treatment.

1. **Graduated compression — multi-component bandaging, typically four-layer, achieving around 40 mmHg at the ankle.** The treatment. Reported healing roughly **65 to 70 per cent at 24 weeks**†. Multi-component systems outperform single-component, and elastic outperforms inelastic. A device, not listed. Off-patent. **Bandage materials are inexpensive — on the order of a few US dollars to low tens of dollars per application, reusable in part — while the dominant cost is the nurse's time.**
2. **Ankle-brachial pressure index measurement before compression** — a Doppler probe and a blood pressure cuff. A mandatory safety step.
3. **A simple non-adherent dressing under the compression.** The dressing choice makes little difference; **compression is the active component** and no dressing type has demonstrated superiority. This is an important cost finding: expensive dressings add cost without demonstrated benefit.
4. **Emollients for surrounding venous eczema; topical corticosteroid** for active eczema. Betamethasone and hydrocortisone listed, off-patent, cents.
5. **Pentoxifylline** as an adjunct, which improves healing. Off-patent, low cost. Not listed.
6. **Early endovenous ablation or surgery for superficial incompetence**.

7. **Debridement** of slough where present; **larval therapy** as an option.
8. **Antibiotics only for clinical infection** — not for colonisation, malodour or slow healing. Routine antibiotic use is common, unhelpful and drives resistance. **The action is omission.**
9. **Analgesia** — listed agents, cents. Venous ulcer pain is substantial and under-treated.
10. **Pneumatic compression** where bandaging is not tolerated.
11. **Skin grafting** for large or refractory ulcers.
12. **Not useful:** most proprietary advanced dressings, honey as a primary agent, topical antiseptics on granulating tissue, and antibiotics without infection.

Simple means. Strong, and the active ingredient is a bandage.

- **Compression bandaging.** The single intervention that heals these ulcers, achieving roughly 65 to 70 per cent healing at 24 weeks†. The materials are **inexpensive cotton wadding, crepe and elastic bandage** — a few dollars to low tens of dollars per application — and the skill is learnable by a trained non-specialist or a family member. Where four-layer kits are unavailable, **two-layer crepe-and-elastic bandaging or reusable inelastic wraps** deliver compression at low cost.
- **Leg elevation above heart level** whenever resting, and raising the foot of the bed. Free, and it directly reverses the venous hypertension that causes the ulcer.
- **Walking and ankle flexion exercises** to activate the calf pump. Free, and mechanistically targeted at the actual defect.
- **A simple non-adherent dressing — even clean gauze with petroleum jelly** — under the compression. Since dressing type makes little difference and compression is the active component, this is where large savings are available without losing effectiveness.
- **Washing the leg with clean water and soap**, and emollient to the surrounding skin. Pennies.
- **Reusable compression wraps and hosiery** after healing, which prevent the 25 to 50 per cent annual recurrence†. Cheap relative to repeated ulcer episodes.
- **Treating tinea pedis** with a tube of clotrimazole under a dollar, which removes a portal for cellulitis in an already-compromised leg.
- **Training the patient or a family member to apply compression**, where nurse visits are the dominant cost. This is the main route to affordability.
- **Not buying expensive dressings or antibiotics that do not help.** The action is omission and it is a direct and substantial saving.

What the chain minimally requires: bandage material, and a Doppler probe plus cuff to check the ankle-brachial index before compressing. That safety check is the one genuine equipment requirement, and skipping it on an ischaemic leg causes harm.

Gaps. No global prevalence or burden figure exists on the sources read. All prevalence figures above are unverified. **The Cochrane compression review could not be retrieved**, so the compression effect sizes — the central numbers of this entry — are carried as commonly reported rather than verified, and should be retrieved. Healing rates and recurrence rates vary widely between studies and populations. Comparative evidence between compression systems is moderate and between dressings is weak. The ESCHAR and EVRA effect sizes are unverified. Whether patient-applied compression achieves the same results as nurse-applied is not well established, and this matters greatly for cost. The proportion of leg ulcers that are purely venous against mixed arterial-venous differs between series.

> **Depth.** Starts in: a vein valve. Size: 5 mm†; depth +10.56. First complaint: about 65 years († onset about age 65); time depth 52.67. One untreated course: no number ([B] months to years).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The ulcer heals. The vein valve stays weak, so it comes back. So it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Diabetic foot ulcers

What it is. An open sore on the foot of someone with diabetes. Nerve damage means they cannot feel the injury, and poor circulation means it will not heal. It is the commonest reason for amputation of a leg anywhere in the world outside of accidents.

Measured. The denominator is **830 million** people with diabetes in 2022, up from 200 million in 1990, and **14 per cent** of adults aged 18 and over, up from 7 per cent, rising faster in low- and middle-income countries. That is the World Health Organization all-ages figure; other chapters of this book use the International Diabetes Federation figure of **589 million adults aged 20 to 79**†, and the two give substantially different global figures, so attributable burden computed on one is not comparable with attributable burden computed on the other. Both stand, unresolved.

The World Health Organization diabetes fact sheet names lower limb amputation and foot ulcers as consequences and **gives no figures for either**.

Lifetime incidence of foot ulceration in people with diabetes is commonly reported at roughly **19 to 34 per cent**, with annual incidence around **2 per cent**†. Diabetes is commonly reported as the cause of a large majority of non-traumatic lower limb amputations, and an amputation is commonly cited as occurring somewhere in the world every 20 to 30 seconds as a consequence of diabetes†.

Five-year mortality after a diabetic foot ulcer is commonly reported at around **30 per cent**, and substantially higher after major amputation — figures comparable to or worse than many cancers. That is the figure that most changes how the condition should be regarded. Recurrence runs roughly **40 per cent within a year** of healing and around **60 per cent within three years**†.

Where it starts. Three components, usually combined:

- **Peripheral neuropathy** — loss of protective sensation. The person does not feel the blister, the stone in the shoe or the burn. This is the necessary precondition in the large majority.
- **Peripheral arterial disease** — impairs healing and determines whether the ulcer progresses to amputation. Present in a large share.
- **Repetitive mechanical stress** — walking on an insensate, often deformed foot, with high plantar pressures under the metatarsal heads.

Additional factors:

- **Foot deformity** — clawed toes, Charcot neuroarthropathy, prominent metatarsal heads, limited ankle motion.
- **Previous ulcer or amputation** — the strongest single predictor of a new ulcer.
- **Callus and nail pathology.** Callus concentrates pressure, and untreated callus is a direct precursor.
- **Poor glycaemic control; duration of diabetes; smoking; chronic kidney disease, especially dialysis; visual impairment**, which prevents the person seeing their own feet and links this entry directly to the vision chapter; and **inability to reach the feet** from obesity or arthritis.
- **Barefoot walking and ill-fitting footwear**.
- **Infection** — not a cause of the ulcer but the main driver of progression to amputation.

Genuinely not known: why some people with severe neuropathy never ulcerate. Why Charcot neuroarthropathy develops in a few. The relative contribution of neuropathy against ischaemia in a given patient is often hard to determine and it determines treatment. Whether intensive glycaemic control prevents ulceration — it clearly reduces neuropathy progression, and direct ulcer-prevention trial evidence is weaker than assumed. Optimal offloading adherence cannot be achieved reliably, and the reason people remove removable devices is behavioural and poorly addressed.

Cure status. The ulcer: CURABLE — total contact casting heals roughly 80 to 90 per cent of neuropathic plantar ulcers within 6 to 12 weeks†. The foot at risk: CONTROLLABLE — recurrence is around 40 per cent at one year and 60 per cent at three years†.

Ulcers heal when pressure is removed and perfusion is adequate. **Total contact casting** heals roughly **80 to 90 per cent** of neuropathic plantar ulcers within 6 to 12 weeks, and it is the most effective offloading method†. Revascularisation heals ischaemic ulcers that would not otherwise heal.

But recurrence is around **40 per cent at one year and 60 per cent at three years**†, because the neuropathy, the deformity and the pressure distribution are unchanged. The ulcer is curable; the foot at risk remains at risk for life. The condition is better regarded as a lifelong remission-and-relapse state with each episode curable. Where perfusion cannot be restored or infection reaches bone, the outcome is amputation, which is not a cure but a loss.

The label is split, with the recurrence and mortality figures attached, because treating the ulcer and ignoring the foot guarantees the next one.

Prevention. This is one of the strongest prevention-against-treatment contrasts in the book.

- **Annual foot screening — testing sensation with a 10 g monofilament, palpating pulses, inspecting for deformity and callus — and risk stratification.** It identifies the at-risk foot before it ulcerates. **STRONG**. The monofilament costs a few US dollars and lasts for hundreds of examinations.
- **Structured patient education: daily foot inspection, never walking barefoot, checking footwear before putting it on, checking water temperature, not using corn plasters or cutting one's own callus. MODERATE**, and free.
- **Therapeutic footwear and custom insoles that reduce plantar pressure**, for people with neuropathy and deformity, and particularly after a healed ulcer. Reduces recurrence. **STRONG** for recurrence prevention, and the measured effect is larger where the footwear is demonstrated to reduce plantar pressure.
- **Regular podiatric callus and nail care. MODERATE**.
- **Integrated multidisciplinary foot care services.** The introduction of such services is consistently associated with substantial reductions in major amputation rates. **STRONG**. This is an organisational intervention, not a technology.
- **Glycaemic control** — reduces neuropathy progression; direct ulcer prevention evidence weaker. **MODERATE**.
- **Smoking cessation. STRONG** for the arterial component.
- **Treating tinea pedis and onychomycosis**, which removes portals of infection. **MODERATE**, and it costs a dollar.
- **Home skin temperature monitoring** to detect pre-ulcerative inflammation, which reduced ulceration in trials. **MODERATE**.
- **Correcting visual impairment** so the person can see their own feet. Cataract surgery and spectacles are, indirectly, diabetic foot interventions.

Treatment.

1. **Offloading — a total contact cast or non-removable walker.** The most effective treatment: **80 to 90 per cent** healing of neuropathic plantar ulcers in 6 to 12 weeks†. **Non-removable devices outperform removable ones principally because they cannot be removed** — an adherence effect, which is an important and uncomfortable finding. A device, not listed. Materials are plaster or fibreglass casting and felt, at **low tens of US dollars per cast**.
2. **Vascular assessment and revascularisation** where ischaemia is limiting — angioplasty or bypass. It determines limb salvage. Expensive, requiring vascular services.
3. **Debridement of callus and necrotic tissue**, repeated. Sharp debridement is standard and cheap.
4. **Infection management:** oral antibiotics for mild soft tissue infection; broader and often intravenous therapy for deep infection; imaging and bone biopsy for suspected osteomyelitis, treated with prolonged antibiotics or surgical resection. Amoxicillin-clavulanate, flucloxacillin, clindamycin, ciprofloxacin and metronidazole are all **listed**, all off-patent, and cost **a few US dollars to a few dollars per course**.

5. **Simple non-adherent dressings.** As with venous ulcers, **no dressing type has demonstrated superiority**, and offloading is the active component.
6. **Glycaemic optimisation** — metformin and insulin, both listed, both off-patent, at cents to a few dollars per day. Metformin is listed as a 500 mg oral solid for type 2 diabetes; human short-acting and intermediate-acting insulin are listed medicines, while the named analogues — degludec, detemir, glargine, aspart, glulisine, lispro — are listed only as therapeutic equivalents to the two analogue class entries, not as selected medicines in their own right.
7. **Negative pressure wound therapy** for post-surgical foot wounds.
8. **Surgical correction of deformity; Achilles tendon lengthening** to reduce forefoot pressure in selected cases.
9. **Amputation** when the limb is unsalvageable or infection is life-threatening. A failure endpoint.
10. **Not useful or not supported:** topical growth factors and most advanced biologics in routine use, hyperbaric oxygen as a general measure, where the evidence is contested, and antibiotics for uninfected ulcers. **The action is omission.**

Simple means. Strong, and concentrated almost entirely in prevention, which is where the amputations are actually prevented.

- **A 10 g monofilament.** A few US dollars, reusable for hundreds of examinations, and it identifies the insensate foot — the single precondition for almost all diabetic foot ulceration. This is one of the highest-value diagnostic items in the entire book.
- **Looking at the feet.** Free. At every clinic visit, shoes and socks off. The commonest reason ulcers are found late is that nobody looked.
- **Teaching daily self-inspection**, using a mirror or a family member where the person cannot see or reach their feet. Free.
- **Never walking barefoot, and shaking out shoes before putting them on.** Free, and it prevents puncture and foreign-body injuries that an insensate foot cannot detect.
- **Checking bath water with a hand or elbow, not a foot.** Free, and it prevents scald burns, a classic and entirely avoidable injury in neuropathy.
- **Properly fitting footwear with a deep toe box**, and simple felt or foam padding to offload a pressure point. Cheap, and locally makeable: **cushioned insoles cut from closed-cell foam, and felt deflective padding**, deliver pressure redistribution without manufactured orthotics.
- **Removing callus regularly** — with a file, or by a trained worker, and never with corn plasters or a blade by the patient. Cheap.
- **Total contact casting with plaster of Paris and felt** — materials cost low tens of US dollars, it heals 80 to 90 per cent of neuropathic plantar ulcers†, and the skill is learnable. Where casting is impossible, **crutches, a wheelchair or enforced bed rest** achieve offloading for free, if adherence can be obtained.
- **Clean water and soap, simple gauze dressings, and petroleum jelly**, since dressing type does not determine the outcome.
- **Cheap oral antibiotics** for infection — listed generics, under a dollar a course.
- **Treating athlete's foot** with a tube of clotrimazole under a dollar.
- **Correcting the person's eyesight** so they can see their feet — spectacles at a few dollars.
- **Organising a foot care team**, which costs coordination rather than equipment and is consistently associated with large falls in major amputation rates.

A monofilament, a pair of shoes that fit, and the habit of looking at the feet prevent a large share of the world's non-traumatic amputations. What the chain minimally requires for the ischaemic foot is vascular imaging and revascularisation, and that is the component with no cheap substitute.

Gaps. The diabetes fact sheet names foot ulcers and amputation as consequences and **gives no figure for either**, despite giving the 830 million denominator — a striking gap. All the figures in *Measured* above are unverified: lifetime ulcer incidence, the amputation frequency claim, five-year mortality and recurrence

rates are all widely cited and were not verifiable here. The five-year mortality figure in particular is consequential and deserves primary sourcing. Whether intensive glycaemic control prevents ulceration, as opposed to slowing neuropathy, is not well established. Hyperbaric oxygen evidence is contested. Comparative dressing evidence is weak. The effect sizes of multidisciplinary foot services on amputation rates come largely from before-and-after service evaluations rather than randomised trials, so confounding by secular trend cannot be excluded.

> **Depth.** Starts in: a peripheral nerve of the foot. Size: 1 mm†; depth +9.10. First complaint: about 10 years († about 10 years of diabetes); time depth 50.97. One untreated course: about 9 weeks ([B] heals in 6 to 12 weeks in a cast†); depth 47.27.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The ulcer heals. The numb foot stays at risk. So it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Chronic wounds

What it is. Any break in the skin that fails to heal in the expected time — conventionally taken as four to six weeks — and which stays open for months or years. The main types are venous, pressure, diabetic foot and arterial, and they share the feature that healing is blocked by something that must be identified and removed.

Measured. No global figure was retrievable. Chronic wounds are not a single ICD-11 entity and are not quantified as a group on any World Health Organization or Global Burden of Disease source read. Prevalence is commonly reported at roughly **1 to 2 per cent** of the population in high-income countries over a lifetime, with point prevalence around **0.2 to 1 per cent** rising steeply with age†.

Chronic wound care is consistently reported to consume on the order of **2 to 4 per cent of total health expenditure** in high-income health systems, with **nursing time, not materials, as the dominant component**. Venous ulcers are the largest group, commonly around 70 per cent of leg ulcers, followed by diabetic foot, pressure and arterial ulcers. The burden is rising with population ageing, diabetes prevalence and obesity.

Where it starts. Healing fails because of an identifiable, usually persisting, cause. The established blockers:

- **A continuing mechanical cause** — pressure not relieved, venous hypertension not compressed, plantar pressure not offloaded. The commonest reason a wound does not heal, and the most frequently overlooked.
- **Ischaemia** — peripheral arterial disease. A wound cannot heal without perfusion, and no dressing substitutes for blood supply.
- **Infection and high bacterial burden**, including biofilm.
- **Necrotic tissue and slough**, which mechanically obstruct healing.
- **Oedema.**
- **Malnutrition** — insufficient protein, energy, vitamin C, zinc.
- **Diabetes and hyperglycaemia.**
- **Immunosuppression; systemic corticosteroids; chemotherapy.**
- **Smoking.**
- **Repeated trauma; self-inflicted or factitious injury.**
- **An unrecognised different diagnosis.** This matters: a non-healing wound may be **pyoderma gangrenosum**, a **vasculitic ulcer**, a **malignancy** including squamous cell carcinoma in a long-standing scar or ulcer, **calciphylaxis**, or an atypical infection — mycobacterial, deep fungal, cutaneous leishmaniasis, **Buruli ulcer**. Several of these are made worse by debridement and compression, and pyoderma gangrenosum in particular is characteristically worsened by surgical debridement. **Any wound not healing as expected should be biopsied.**

Genuinely not known: why biofilm impedes healing and how to eradicate it clinically — no anti-biofilm agent has established clinical benefit. Why some wounds remain static for years despite correction of every identifiable factor. Whether the many adjunctive therapies — growth factors, skin substitutes, electrical stimulation, ultrasound, hyperbaric oxygen — add anything beyond standard care is largely unresolved, and the commercial literature is substantial and of poor quality.

Cure status. CURABLE where the cause is correctable; RELIEF ONLY where it is not.

Chronic wounds are not a disease but a failure state. When the blocking factor is identified and corrected, most heal — compression heals venous ulcers, offloading heals neuropathic ulcers, pressure relief heals pressure ulcers, revascularisation heals ischaemic ulcers.

Where the cause cannot be corrected — unreconstructable arterial disease, continuing unavoidable pressure, profound immobility, terminal illness — the honest classification is RELIEF ONLY, and the goal becomes symptom control, odour and exudate management, and avoiding futile aggressive treatment. Nothing applied to the surface of a wound heals it if the cause remains active.

Prevention.

- **Identifying and treating the specific cause** — venous disease, diabetes, pressure, arterial disease. The whole of prevention. **STRONG**.
- **Compression hosiery in chronic venous insufficiency. STRONG** for venous ulcer prevention.
- **Pressure redistribution and repositioning in immobility. STRONG**.
- **Diabetic foot screening and protective footwear. STRONG**.
- **Smoking cessation. STRONG** for arterial disease.
- **Nutritional adequacy — protein, energy, vitamin C, zinc. MODERATE**.
- **Glycaemic control. MODERATE**.
- **Early skin care and emollients on fragile at-risk skin. MODERATE**.
- **Prompt, correct treatment of acute wounds** — cleaning, closure where appropriate, and not applying harmful traditional remedies. **MODERATE**.
- **Biopsy of any wound not healing as expected**, which prevents months of wrong treatment and diagnoses malignancy and pyoderma gangrenosum. **STRONG**, and the cost is a punch biopsy.
- **Avoiding harmful practices** — strong antiseptics on granulating tissue, routine antibiotics for colonisation, and debridement of pyoderma gangrenosum. **MODERATE**, free improvements, and the action is omission.

Treatment. The standing approach, in order of evidence:

1. **Correct the cause.** Compression, offloading, pressure relief, revascularisation, glycaemic control, nutrition. Everything below is secondary to this.
2. **Debridement** of necrotic tissue and slough — sharp, autolytic, larval or mechanical. Cheap. Contraindicated in pyoderma gangrenosum and in dry stable heel eschar.
3. **Cleansing with clean water or saline.** Cochrane found **no evidence that any particular cleansing solution outperforms water**. Near-zero cost.
4. **A moist wound dressing.** The principle of moisture retention is supported; **no specific dressing type has demonstrated superiority over another**. This is the single most important cost finding in wound care. Not listed. Off-patent. Cost ranges from pennies to tens of dollars per dressing for no demonstrated difference in healing.
5. **Infection management** — systemic antibiotics for clinical infection only, and **not for colonisation, malodour or slow healing**. Listed generics, off-patent, under a dollar to a few dollars per course.
6. **Topical antimicrobials — iodine, silver, honey** — for heavy bacterial burden. The evidence is modest, and **silver dressings in particular have not demonstrated healing benefit proportional to their cost**. **Not using them is the evidence-based action and it is a direct saving.**
7. **Pain management** — listed analgesics, cents. Chronic wound pain is severe and routinely under-treated, particularly at dressing changes.

8. **Nutritional support.**
9. **Negative pressure wound therapy** for deep cavity and post-surgical wounds — moderate evidence. Equipment and consumables.
10. **Skin grafting and flap reconstruction** for large or refractory wounds.
11. **Biopsy** where the diagnosis is uncertain or healing stalls.
12. **Palliative wound care** where the cause is uncorrectable — odour control with metronidazole, exudate management, comfort. A legitimate and under-used goal.
13. **Weak or unproven adjuncts:** growth factors, bioengineered skin substitutes, electrical and ultrasound stimulation, and hyperbaric oxygen in general use.

Simple means. Very strong, and the evidence actively supports the cheap options.

- **Clean water for cleansing.** Cochrane found no solution superior to water. Potable, or boiled and cooled water, or saline made from salt and boiled water. Near-zero cost, and it replaces every proprietary wound cleanser. **The action is omission as much as substitution**: the proprietary cleanser is simply not bought.
- **Clean cloth or gauze with petroleum jelly** as a non-adherent moisture-retaining dressing. Since no dressing type has demonstrated superiority, this delivers the one supported principle — moisture retention — at pennies per dressing. Boiled and sun-dried cotton cloth is a serviceable dressing material where gauze is unavailable.
- **Compression bandaging** with crepe and elastic bandage for venous wounds — a few dollars to low tens of dollars per application, reusable in part.
- **Pillows, repositioning and heel offloading** for pressure wounds — free.
- **Plaster-and-felt total contact casting, or crutches and bed rest**, for neuropathic foot wounds.
- **Honey or sugar dressings** where nothing manufactured is available — both have antimicrobial and osmotic debriding action and a long documented history, with modest trial evidence. Sugar is available everywhere.
- **Larval (maggot) therapy** for debridement — effective, and produced without an industrial pharmaceutical chain.
- **Elevation, exercise and walking** for venous and oedematous wounds. Free.
- **Adequate food, with protein.** The cost of food.
- **Metronidazole for malodour** in fungating and palliative wounds. Metronidazole is listed and off-patent, and odour control transforms the patient's social life. The form and use are a clinician's decision and are not given here.
- **Not spending on what does not work:** silver and advanced dressings, antiseptic cleansers, antibiotics for colonisation, and most adjunctive devices. In a condition consuming 2 to 4 per cent of health expenditure†, with nursing time as the dominant cost, this is where the money actually is. **Not using silver dressings is an omission that saves money with no loss of healing.**
- **Training patients and families to redress their own wounds**, since nursing visits are the main cost.

What the chain minimally requires: clean water, a cloth, a bandage, and the correct identification of why the wound is not healing. For ischaemia, vascular surgery — the one component with no simple substitute.

Gaps. Chronic wounds are not a defined ICD-11 entity, so there is no coherent global burden figure and none was obtainable. All the figures in *Measured*, including the 2 to 4 per cent of health expenditure claim, are unverified and derive largely from high-income health-system analyses that may not generalise. **The Cochrane reviews on cleansing solutions and on dressing comparisons could not be retrieved**, so the central negative findings — water is as good as any cleanser, no dressing type is superior — are carried as commonly reported rather than verified. These are the most economically consequential findings in the entry and should be retrieved. The commercial wound care literature is large, of variable quality, and systematically favours the products being sold; good sources and marketing claims disagree sharply, and the Cochrane position is recorded here. Biofilm's clinical significance is unresolved. Hyperbaric oxygen is genuinely contested.

> **Depth.** A collective name for several kinds of wound. No depth is given.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Hidradenitis suppurativa

What it is. Recurrent painful boils and abscesses in the armpits, groin, under the breasts and around the buttocks. They join into tunnels under the skin and discharge. It scars badly.

It is not an infection and it is not caused by poor hygiene. Both beliefs are common, and both are wrong.

Measured. No global figure exists. Prevalence is commonly reported at 0.05 to 1 per cent†, a twenty-fold spread. Both ends are printed because neither can be discounted.

Onset is usually in the twenties and thirties, after puberty. It is about three times commoner in women.

The measured failure in this condition is delay. Seven to ten years commonly pass between first symptom and diagnosis, among the longest for any skin disease. Repeated misdiagnosis as recurrent boils is the proximate reason.

Quality-of-life impairment is consistently among the worst of any skin disease, exceeding psoriasis and eczema, driven by pain, discharge and the sites involved. Associations with obesity, smoking, metabolic syndrome, Crohn disease, spondyloarthropathy, depression and suicidality are all strong.

Where it starts. A hair follicle occludes and ruptures in skin bearing apocrine glands, and inflammation spreads into the dermis and forms sinus tracts. The apocrine gland is affected second, not first.

Smoking is the strongest modifiable association and is present in a large majority of patients. Obesity is associated with both incidence and severity, through friction and moisture in skin folds and through metabolic inflammation. About a third of cases are familial, with gamma-secretase mutations in a small subset. Perimenstrual flares indicate a hormonal influence. Lithium is implicated.

It is not caused by shaving, deodorant or washing habits. Stating that is clinically useful, because patients are routinely told otherwise.

Genuinely not known. What initiates the occlusion. Why these sites and not other hair-bearing ones. Why it begins after puberty and often settles after the menopause. Whether the bacteria cultured from lesions have any causal role at all — antibiotics help, but they may be working as anti-inflammatories, and the question is open. That matters, because the courses are months long.

Cure status. CONTROLLABLE.

No medical treatment cures it. Adalimumab and secukinumab are licensed and produce a clinically meaningful response in around half of patients on a defined measure for adalimumab, and relapse follows withdrawal.

Wide surgical excision of an affected area can be definitive for that area, with low recurrence inside the excised field, though disease can appear at new sites. That is locally curative, not systemically so.

Scarring and sinus tracts, once formed, are permanent. Only surgery removes them. This is why a seven-to-ten-year delay costs so much.

Prevention. No primary prevention of the disease is established.

Smoking cessation is the most important modifiable factor and improves severity. MODERATE, and free. Weight reduction improves severity and flare frequency in observational and bariatric cohorts. MODERATE.

Reducing friction — loose clothing, avoiding tight seams and waistbands, keeping folds dry. WEAK, free.

Early diagnosis and early effective treatment, to prevent the permanent scarring. MODERATE on principle; no trial has tested whether early treatment prevents progression.

Screening for and treating depression, given the measured suicidality. STRONG for that purpose.

What does not help: antiseptic washes, hair removal and stopping deodorant. All three follow from the mistaken belief that this is an infection or a hygiene problem.

Treatment. Topical clindamycin for mild localised disease.

Oral doxycycline or lymecycline for three months or more in mild to moderate disease. Doxycycline is on the Essential Medicines List, off-patent, and costs cents a day. It is the first-line systemic treatment and much the cheapest.

Clindamycin with rifampicin for ten weeks in moderate disease. Both are listed and off-patent, though rifampicin's use here sits against tuberculosis stewardship.

In women, spironolactone, combined oral contraceptives or metformin. All three are listed, off-patent, and cost cents a day.

Intralesional corticosteroid for a single inflamed nodule gives rapid relief for a drug cost of cents.

Adalimumab, with about half achieving a defined response. It is on the Essential Medicines List, and biosimilar prices have fallen to a fraction of the originator's in competitive markets. That combination — listed, and biosimilar — is the most consequential access fact in this entry. Secukinumab is licensed, not listed, and expensive.

Incision and drainage relieves acute pain but recurs at the same site and does not alter the disease. Deroofing a tract is more durable. Deroofing and wide local excision remove established tracts, and recurrence inside the excised field is low.

Pain management is the dominant unmet need and is routinely under-treated. Paracetamol, ibuprofen and amitriptyline are all listed, off-patent, and cost cents.

Simple means. Correct diagnosis and explanation is free and, given a delay measured in years, the highest-value single action. Telling someone this is a named inflammatory disease — not recurrent boils, not an infection, not a consequence of being unclean — changes their care and their self-regard at once.

Doxycycline at cents a day. Spironolactone, a combined oral contraceptive or metformin in women, all at cents a day. Smoking cessation, free. Weight reduction, free. Loose cotton clothing and avoiding tight waistbands, free. Keeping folds dry with a cloth, pennies. Warm compresses for an acutely inflamed nodule, free. Absorbent gauze or clean cloth for discharge and odour, which is often the most socially disabling problem, pennies. Metronidazole gel for malodour, cents. Adequate analgesia, cents, and routinely omitted. Peer support, free.

What the chain minimally requires: for established tunnels and scarring, an operating theatre and a surgeon who knows the condition. There is no simple substitute for excising a tract. Everything before that point is cheap generics.

Gaps. No verified global prevalence. The 0.05 to 1 per cent range is a twenty-fold spread and both ends stand. The diagnostic delay figures are unverified. The adalimumab response rate is unverified. Whether bacteria play a causal role is unresolved, and it determines whether months of antibiotics are antimicrobial treatment or anti-inflammatory treatment. Whether early treatment prevents scarring has never been tested.

> **Depth.** Starts in: the hair follicle. Size: 1 mm†; depth +9.10. First complaint: about 20 years († onset about age 20); time depth 51.60. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Bullous pemphigoid

What it is. An autoimmune disease of older people. The body attacks the layer anchoring the skin's surface to what lies beneath, and large tense blisters form on itchy red skin.

It is not contagious. Treatment controls it, and in many people it eventually burns out.

Measured. Annual incidence is commonly reported at 4 to 22 per million in European studies, and is rising in several countries†. The rise is attributed to population ageing and to wider use of the drugs that trigger it.

The defining feature is age. Incidence climbs steeply, most patients are over seventy, and in those over ninety it is many times the population average.

One-year mortality is substantial: commonly between 20 and 40 per cent in European cohorts†, far above age-matched controls. Deaths are mostly from infection, cardiovascular events and the complications of immunosuppression, not from the skin disease.

Whether that figure is caused by the disease or the treatment is unresolved; see Gaps.

It is the commonest autoimmune blistering disease in most populations. Data from outside Europe are sparse.

Where it starts. Autoantibodies form against BP180 and BP230, proteins anchoring the epidermis to the basement membrane. Complement activates, eosinophils arrive, and the skin splits at the junction.

Age is the dominant risk factor. Neurological disease is a consistent and striking association — dementia, Parkinson disease, stroke, multiple sclerosis — with substantial reported odds ratios. Shared BP180 expression in neural tissue is offered as the explanation and is not established.

Drugs are the key modifiable cause. Gliptins carry a well-documented several-fold increased risk; spironolactone, furosemide, some antibiotics and checkpoint inhibitors are also implicated. Drug-associated cases may remit on withdrawal, which makes the drug history potentially curative.

Burns, radiotherapy, ultraviolet exposure, surgery and trauma can localise the disease.

Genuinely not known. Why tolerance to BP180 is lost, and why in late life. The basis of the neurological association. Why gliptins trigger it. Why the disease frequently remits permanently when other autoimmune diseases do not. And the central unresolved question: whether the high mortality is caused by the disease, by the immunosuppression used against it, or by the frailty of the population. The answer determines whether treatment should be more aggressive or less.

Cure status. Drug-induced: CURABLE — withdrawing the implicated drug can produce resolution, which is why the drug history is the most important part of the assessment.

Idiopathic: CONTROLLABLE. Treatment stops new blistering in most patients within weeks. And unusually among autoimmune diseases, a share achieve lasting drug-free remission after one to several years, and the proportion is not given.

Against both: the one-year mortality of 20 to 40 per cent† is the dominant clinical fact. The disease is controllable. The patient often is not saved.

Prevention. Nothing prevents idiopathic bullous pemphigoid.

Avoiding or withdrawing implicated drugs, above all gliptins in older patients with diabetes, is the only meaningful primary prevention, and it is a prescribing decision. MODERATE.

Reviewing and withdrawing the implicated drug at diagnosis may resolve the disease without immunosuppression at all. STRONG where a drug cause exists, and free.

Using topical rather than systemic corticosteroid where feasible. The Joly trial found potent topical corticosteroid gave better survival than oral prednisolone in extensive disease. This is prevention of iatrogenic death and it is among the most important findings in the entry. The grade is MODERATE here, not STRONG, because this entry could not open that trial.

Infection prevention and prompt treatment during immunosuppression, since infection is a leading cause of death. STRONG. Bone, gastric and glycaemic protection during corticosteroid therapy. STRONG for preventing treatment harm. Protecting fragile skin from friction and shear. MODERATE, free.

Treatment. Potent topical corticosteroid applied to the whole body surface is first-line even in extensive disease, and gave better survival than oral corticosteroid in the Joly trial. Betamethasone is on the Essential Medicines List. The drug is cheap; the constraint is the labour of applying it daily to a frail elderly person, which usually needs a carer or nurse.

Oral prednisolone, tapered, is effective but carried greater mortality than topical treatment in that trial. It is listed, off-patent, and costs cents a day.

Doxycycline is the key affordable and safer option. The BLISTER trial found it non-inferior to oral prednisolone for short-term blister control, with significantly fewer serious adverse events. It is listed, off-patent, and costs cents a day.

Azathioprine, methotrexate and mycophenolate spare corticosteroid; the first two are listed and off-patent. Nicotinamide with tetracycline is an old, cheap, low-toxicity combination. Dapsone is listed and cheap. Rituximab is used in refractory disease, is listed, and biosimilars have cut its cost substantially. Omalizumab and dupilumab are emerging options, not listed, and expensive.

Withdrawing the causative drug is free and potentially definitive.

Simple means. Better than expected for an autoimmune blistering disease, because the two best-evidenced treatments are both cheap generics.

Taking a drug history and stopping a gliptin or other implicated drug. Free, and in drug-induced cases it can resolve the disease entirely. The single highest-value action.

Doxycycline at cents a day, non-inferior to prednisolone for short-term control with fewer serious adverse events. For a frail elderly population in a low-resource setting this is close to ideal: oral, cheap, available, and safer than the alternative.

Topical corticosteroid, a few dollars a tube, associated with better survival than oral steroids. Prednisolone at cents a day where topical application is impractical. Emollients for the itch, a few dollars. Non-adherent dressings of clean cloth with petroleum jelly for eroded areas, pennies, since dressing type does not determine outcome.

Leaving intact blisters alone, because the roof acts as a biological dressing. Free, and it reduces infection and pain. Where a large tense blister needs decompressing, that is a clinical procedure and not a household one. Protecting skin from shear, careful lifting, soft bedding, repositioning. Free. Short nails to limit scratching. Free. Watching for infection and treating it promptly, since infection is a leading cause of death.

What the chain minimally requires: a diagnosis. Confirmation needs a skin biopsy with direct immunofluorescence, and therefore a histopathology laboratory. That is the one genuine infrastructure requirement, because the differential includes conditions treated completely differently. Where it is unavailable, clinical diagnosis plus doxycycline is a defensible and cheap course.

Gaps. No verified global incidence or prevalence; no WHO or burden source quantifies bullous disorders. The 4 to 22 per million range is unverified and almost entirely European. One-year mortality is carried as a single unsourced range of about 20 to 40 per cent. Whether that width reflects disagreement between sources or the spread within one is not established here. Whether that mortality is caused by the disease, the treatment or the population's frailty is unresolved, and it is the question that should set how aggressively to treat. The Joly survival finding and the BLISTER non-inferiority result are both central to this entry and neither could be verified against its primary report.

> **Depth.** Starts in: the BP180 protein. Size: 10 nm†; depth −1.38. First complaint: about 75 years († onset about age 75); time depth 52.80. One untreated course: about 4.2 years ([B] passes in many; † 3–6 years); depth 50.19.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Burns and their skin consequences

What it is. Injury to the skin from heat, chemicals, electricity or radiation. Shallow burns heal. Deep ones destroy the layer that regenerates skin, and heal only by scarring or by grafting.

The lasting problems are thick contracting scars that pull joints out of position, disfigurement, and itch.

Measured. About 180,000 deaths a year, mostly in lower- and middle-income countries.

No global count of non-fatal burns is given. Country figures: over a million people moderately or severely burned each year in India; nearly 173,000 children in Bangladesh; over 410,000 burn injuries in the United States in 2008, about 40,000 needing hospital admission.

Almost two-thirds of burn deaths occur in the African and South-East Asia regions. Child burn death rates are over seven times higher in lower- and middle-income countries. Burn incidence requiring medical care is nearly twenty times higher in the Western Pacific than in the Americas.

Burns are the fifth commonest cause of non-fatal childhood injury.

And the figure that defines the skin consequence: among burned children in Bangladesh, Colombia, Egypt and Pakistan, 17 per cent have a temporary disability and 18 per cent a permanent one.

In community surveys in Bangladesh and Ethiopia, 80 to 90 per cent of burns happen at home.

A 2014 systematic review found a mean healthcare cost of US$88,218 per burn patient, with a range from US$704 to US$717,306. South Africa spends an estimated US$26 million a year treating burns from kerosene cookstove incidents.

Where it starts. Open fires, unsafe cookstoves and cooking at floor level, which is why most burns in surveyed populations happen at home. Kerosene appliances. Hot liquid scalds, the commonest mechanism in young children. Loose clothing near open flames.

Age under five, where crawling and reaching combine with thinner skin that burns deeper at lower temperatures and shorter exposure. Female sex and domestic kitchen exposure. Occupational exposure to fire, scalds, chemicals and electricity.

Epilepsy, neuropathy, intoxication and impaired mobility, all of which prevent escape from the heat source. Diabetic neuropathy and leprosy-related sensory loss cause unnoticed contact burns.

Acid violence. Crowding, poverty and lack of electricity.

Genuinely not known. Why some people form thick and keloid scars and others heal flat after comparable burns. Ancestry and site are associated, with darker skin at higher keloid risk, but no predictor is clinically usable. The mechanism of post-burn itch, which is severe, prolonged and poorly treatable. The optimal timing of excision and grafting. And why a superficial burn sometimes deepens over the first forty-eight hours, or whether anything prevents it.

Cure status. Superficial and superficial partial thickness: CURABLE. They heal completely within one to three weeks from surviving epidermal appendages, with normal or near-normal skin and no scar.

Deep partial and full thickness: RELIEF ONLY for the consequences. The regenerating layer is destroyed. The wound heals by contraction and scar, or it is grafted. Grafting closes the wound and saves life and limb, which is a major achievement — but grafted skin is not normal skin. It lacks normal sweat glands, hair and sensation, it looks different, and the donor site scars too.

Thick scars and contractures are the permanent consequence. Pressure garments, silicone, splinting, physiotherapy, steroid injection, laser and surgical release improve them and do not restore them. A released contracture tends to recur, and often needs repeated surgery through a child’s growth.

That split is where the 18 per cent permanent disability figure in burned children comes from.

Prevention. One thing must be said first: WHO states that prevention and care would substantially reduce burn deaths and disability, and gives no quantified effect size for any preventive measure. The grades below reflect that absence.

Raised cooking surfaces, cooking separated from living and sleeping areas, enclosed stoves, stable cookware. This addresses the majority of burns that happen at home. MODERATE on mechanism; effect size not quantified.

Replacing kerosene appliances and open fires with safer stoves or electricity. MODERATE. Hot water temperature limits, which prevent bath scalds. MODERATE in high-income settings. Keeping hot liquids, kettle cords and matches out of reach, and supervising children in kitchens. MODERATE, free. Smoke alarms and an escape plan. MODERATE where there is electricity. Flame-resistant nightwear. MODERATE. Occupational guarding and protective equipment. MODERATE. Regulation of fireworks, acid sales and appliance standards. MODERATE.

Treating epilepsy, which reduces burns from seizures near fires. MODERATE; anticonvulsants cost cents a day.

And first aid education — cool running water immediately. This prevents depth, and therefore prevents the disability that constitutes the burden. MODERATE, on the depth evidence; the population effect of teaching it has not been quantified.

Treatment. Immediate cooling with cool running water for twenty minutes, within the first three hours. It reduces burn depth, pain and the need for grafting. The cost is water.

Fluid resuscitation for burns over about 10 to 20 per cent of body surface, with oral rehydration solution usable where intravenous access is unavailable. Both are listed, off-patent, and cost cents to a few dollars.

Analgesia. This is a severely painful injury and pain control is routinely inadequate. Paracetamol, ibuprofen, morphine and ketamine are all listed, off-patent and low cost.

Wound cleansing and debridement. Topical antimicrobial dressing, though silver sulfadiazine may delay healing and the evidence favours simple non-adherent or paraffin gauze for superficial burns. Tetanus prophylaxis, listed, cents.

Early excision and skin grafting for deep burns — the definitive treatment, requiring an operating theatre. Escharotomy for circumferential full thickness burns compromising circulation or breathing, performed with a scalpel.

Nutritional support, since burn hypermetabolism demands high protein and energy. Antibiotics for infection only, not prophylactically.

Scar management: pressure garments, silicone sheeting, massage, splinting, sustained physiotherapy, intralesional corticosteroid and surgical release. Itch management, often inadequate. Physiotherapy and occupational therapy from day one, which determines whether a contracture forms at all. Psychological support.

Simple means. Exceptionally strong at the point of injury, because the single most effective burn intervention is water.

Cool running water for twenty minutes, immediately. It reduces depth, pain and the need for grafting. It costs nothing and needs no training beyond knowing to do it. And it must happen in the first minutes, which makes it public knowledge rather than a health service. Given that most burns happen at home and that 18 per cent of burned children in four countries are left permanently disabled, teaching this one instruction is among the highest-value free interventions in this book.

Stop, drop and roll; smothering flames with a blanket; removing smouldering clothing and jewellery. Free.

Not applying ice, toothpaste, oil, butter, eggs, mud or ash. Ice deepens the injury; the rest introduce infection. Free, and widely needed as instruction.

Covering the burn with a clean cloth or cling film for transport, pennies. Oral rehydration solution where intravenous fluids are unavailable, cents, addressing the main early cause of death in a large burn. Paraffin gauze or clean cloth with petroleum jelly as a non-adherent dressing, cheap, and the evidence does not favour expensive alternatives. Honey as a burn dressing where manufactured dressings are unavailable.

Splinting in the anti-contracture position with locally made splints, and daily range-of-movement exercises from the start. This is the measure that prevents contracture, and it needs a piece of plastic or plaster and a trained family member, not a surgeon. Preventing a contracture is far cheaper and far more effective than releasing one later.

Pressure therapy with elastic bandage or locally sewn garments for thick scars.

What the chain minimally requires: for a deep burn, an operating theatre, a surgeon and a graft. There is no simple substitute for replacing destroyed skin.

Gaps. The source states about 180,000 annual deaths†. There is no global count of non-fatal burns, and no numeric disability-burden value, although the mortality figure exists. WHO quantifies no preventive effect size at all, which is why every prevention grade in this entry rests on mechanism rather than on a measured reduction. Why some people scar thickly and others do not is unknown and unpredictable. The mechanism of post-burn itch is unexplained. The optimal timing of excision and grafting is debated.

End of chapter.

> **Depth.** Starts in: the skin. Size: 2 mm†; depth +9.73. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 17 days ([B] superficial burns heal; † 2–3 weeks); depth 46.09.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

ICD-11 Chapters 11 and 12 — The Circulatory System and the Respiratory System

Thirty-five entries. Twenty-one circulatory, fourteen respiratory. Heart failure is two entries, so the entries cover thirty-four conditions.

Introduction

These two chapters carry a large share of measured death. Cardiovascular disease killed 19.8 million people in 2022, about 32 per cent of all deaths, of which 85 per cent were heart attack and stroke. The Global Burden of Disease study gives 19.2 million for 2023 and 626 million people living with cardiovascular disease, against 311 million in 1990. Ischaemic heart disease is the first cause of death in the world at 9.5 million, and the first cause of lost healthy life at 193 million disability-adjusted life years. Chronic obstructive pulmonary disease is third at 3.4 million, pneumonia fourth at 2.7 million. Against that, the therapy that carries almost all of the measured benefit is old, off-patent and costs a few euro a year.

Five interventions in this chapter pair a measured mortality benefit with a low price, and the first is a drug that keeps running out. Benzathine benzylpenicillin, given by intramuscular injection every three to four weeks, reduces recurrence of rheumatic fever by 80 to 90 per cent and holds back the valve disease that affects 54.8 million people. A vial costs a fraction of a euro and a patient-year costs a few euro. It has been on the market since the 1950s, it is on the WHO Essential Medicines List, it is off-patent, and it has suffered repeated global supply shortages because the margin is too small to hold manufacturers in the market. Next comes aspirin: one chewed 300 mg tablet at the onset of a myocardial infarction reduces 35-day vascular mortality by 23 per cent, for a cost under one cent. Then oral amoxicillin for childhood pneumonia, which reduces child pneumonia mortality by 35 to 42 per cent when delivered by a trained community health worker, and which is as effective as injectable penicillin even in severe disease. Then dexamethasone, under five euro a course, with a number needed to treat of about eight for mortality in ventilated COVID-19 pneumonia. Then spironolactone, five to thirty euro a patient-year, with a number needed to treat of nine over two years in severe heart failure with reduced ejection fraction.

Rank	Intervention	Measured benefit	Cost
1	Benzathine benzylpenicillin, secondary prophylaxis	Rheumatic fever recurrence down 80–90 per cent; prevents the valve disease affecting 54.8 million people	Under one euro per injection; a few euro per patient-year. UNICEF indicative price October 2026: US$29.49 per box of 50 vials of 2.4 million IU, so about US$0.59 a vial
2	Aspirin, 300 mg chewed in acute myocardial infarction	23 per cent reduction in 35-day vascular mortality, ISIS-2	Under one cent a dose
3	Oral amoxicillin, childhood pneumonia	Child pneumonia mortality down 35–42 per cent; oral as effective as injectable even in severe disease	UNICEF indicative price October 2026: US$0.54 for ten 250 mg dispersible tablets, about US$0.054 a tablet
4	Dexamethasone, ventilated COVID-19 pneumonia and severe community-acquired pneumonia	NNT about 8 in ventilated patients, 29.3 against 41.4 per cent; NNT about 18 in severe pneumonia, 6.2 against 11.9 per cent	Under five euro a course. UNICEF indicative price October 2026: US$24.00 for 100 tablets of 4 mg, about US$0.24 a tablet
5	Spironolactone, heart failure with reduced ejection fraction	Mortality 35 against 46 per cent, RR 0.70, NNT 9 over 24 months, RALES	a few to tens of euro per patient-year

Equal weight belongs to the things that match those effects and are not drugs at all. Bystander cardiopulmonary resuscitation doubles to triples the chance of surviving a cardiac arrest, requires two hands, and costs nothing; it is performed in 40.2 per cent of out-of-hospital arrests in the United States, so

most of the available benefit is currently unrealised. Prone positioning in severe acute respiratory distress syndrome has a number needed to treat of 6 to prevent one death, and needs four or five people, some pillows and a protocol. Low tidal volume ventilation has a number needed to treat of 11, and is a setting on a machine already in use. A large-bore cannula costing under five euro, pushed through the chest wall, converts a tension pneumothorax from an immediately fatal condition into a survivable one within seconds. A pulse oximeter costing twenty to two hundred euro, applied once to a newborn’s hand and foot, detects critical congenital heart disease with a sensitivity of about 76 per cent, and the American states that mandated the screening recorded roughly a third fewer infant deaths from critical congenital heart disease.

Intervention	Measured benefit	What it requires
Bystander CPR	Doubles to triples survival	Nothing
Prone positioning, severe ARDS	28-day mortality 16.0 against 32.8 per cent, NNT 6	Four or five staff, pillows, a protocol
Low tidal volume ventilation	Mortality 31.0 against 39.8 per cent, NNT 11	A ventilator setting and a tape measure
Needle decompression, tension pneumothorax	Immediately life-saving	A cannula, a few to a few euro
Pulse oximetry screening of newborns	Sensitivity about 76 per cent for critical congenital heart disease, false positives about 0.14 per cent; about a third fewer infant deaths from it in mandating US states	A device, tens to hundreds of euro

A large gap in this chapter’s data has to be stated at the front. Retrieved GBD 2023 tables carry no global burden figure at all — no deaths, no disability- adjusted life years — for seventeen conditions treated here. They are: heart failure as a syndrome; venous thromboembolism; aortic aneurysm; endocarditis; pericarditis; pulmonary hypertension; cardiac arrest; varicose veins and chronic venous insufficiency; arrhythmias other than atrial fibrillation and flutter; bronchiectasis; chronic rhinosinusitis; allergic rhinitis; pleural effusion; pneumothorax; acute respiratory distress syndrome; cystic fibrosis; and sleep-disordered breathing. “No figure” here means none was retrieved in the GBD 2023 tables used, which is a limit of retrieval and not a statement about GBD itself, and several of the seventeen carry modelled prevalence elsewhere in their own entries. Heart failure alone affects about 64 million people. Pulmonary hypertension of all causes is estimated at roughly 1 per cent of the world’s population; chronic rhinosinusitis at about 10 per cent of adults; allergic rhinitis at roughly 400 million people; varicose veins at 20 to 35 per cent of western adults. For several of these the reason is structural rather than accidental. Heart failure is not a GBD level-3 cause. Cardiac arrest is a mode of death counted under its causes, and pleural effusion is a sign rather than a cause. Sleep-disordered breathing sits in ICD-11 chapter 07, in which no condition is a GBD level-3 cause at all. Each affected entry repeats the absence in its own Gaps section, because a reader who opens one entry should not have to come back here to learn that the number does not exist.

The heaviest unresolved question in the chapter is clean cooking, and it must be printed both ways. Household air pollution is attributed 44 per cent of child pneumonia deaths and 22 per cent of adult pneumonia deaths. It is attributed 23 per cent of adult COPD deaths in low- and middle- income countries. Of its own 2.9 million annual deaths, 32 per cent are ischaemic heart disease, which is 12 per cent of all ischaemic heart disease deaths worldwide, and 23 per cent are stroke, which is about 12 per cent of all stroke deaths. Around 2.1 billion people, about a quarter of the world, still cook over open fires or on inefficient stoves, and 923 million people in sub-Saharan Africa lacked access to clean cooking in 2022. Against that: the three large randomised stove-intervention trials all missed their primary endpoints. RESPIRE, in Guatemala, tested chimney stoves and missed its primary childhood pneumonia endpoint, with a reduction in severe pneumonia in per-protocol analysis only. CAPS, in Malawi, randomised cookstoves across 10,750 children and found no reduction in pneumonia. HAPIN randomised liquefied petroleum gas stoves to 3,200 households, verified a 66 per cent reduction in personal fine particulate exposure, and found no effect on birth weight, its primary endpoint. The most-cited explanation is that none of the interventions moved exposure far enough down the steep part of the exposure-response curve. That explanation is plausible and unproven. These results are not reconciled here. The attributable fractions are large and the randomised evidence for the interventions tested is absent, and that is the open question.

Three further disagreements recur across these entries, and each is printed both ways wherever it appears. The salt J-curve. The PURE study reports higher cardiovascular risk at both high and low sodium intake, implying a threshold below which reduction does not help. Cook and colleagues reanalysed the TOHP trials with repeated 24-hour urine collections and found a monotonic relation with no J-curve. The measurement method is itself the contested variable: PURE estimated 24-hour sodium from a single fasting morning urine with the Kawasaki formula. Compression stockings: beneficial in surgical thromboprophylaxis, where Cochrane gives roughly a two-thirds reduction in deep vein thrombosis; null and harmful after stroke in CLOTS-1, which found no benefit and more skin breaks; and null for post-thrombotic syndrome after deep vein thrombosis in the SOX trial. Masks: the 2023 Cochrane review of physical interventions concluded that masks in the community probably make little or no difference to influenza-like illness, a conclusion heavily criticised for pooling heterogeneous trials with low adherence and publicly qualified by Cochrane itself, against observational and mechanistic evidence for source control. One provenance figure belongs here as well. Of the figures in this chapter, 410 were read off their source, 2,120 name a source and year that were not opened again, and 55 carry daggers.

Standing note on the Essential Medicines List. Every statement in this chapter that a medicine is or is not on the WHO Essential Medicines List, and that names no edition, is to be read as carrying a dagger: it was not checked against the 24th List (2025) and needs checking against it. This covers the EML column of every treatment table. Listing claims read from the 24th List are printed plainly.

Both chapters in figures

Circulatory system, totals.

Measure	Figure	Source
CVD deaths, 2022	19.8 million, about 32 per cent of all deaths	WHO fact sheet on cardiovascular diseases, 31 July 2025
CVD deaths, 2023	19.2 million	GBD 2023 CVD Collaborators, JACC 2025
CVD deaths, 1990	13.1 million, a 47 per cent rise to 2023	JACC 2025
People living with CVD, 2023	626 million, against 311 million in 1990	JACC 2025
CVD DALYs, 2023	437 million, the leading cause of DALYs globally; also cited as 436.2 million	JACC 2025
Share of CVD DALYs attributable to modifiable risk factors	79.6 per cent	JACC 2025
Share of CVD deaths from heart attack and stroke	85 per cent	WHO
Share of CVD deaths in low- and middle-income countries	Over three-quarters	WHO
Share of the 18 million premature under-70 noncommunicable deaths of 2021 caused by CVD	At least 38 per cent	WHO

The two totals do not agree and are not the same accounting. WHO gives 19.8 million for 2022 and GBD 19.2 million for 2023, and the two bodies redistribute ill-defined cause-of-death codes differently. Both are printed throughout; neither publishes a reconciliation. The WHO page also contradicts itself on one figure: its Key Facts section gives the low- and middle-income share as “over three quarters” and its body gives “approximately 80 per cent”. GBD 2023 puts total global deaths at 60.04 million (59.05 to 61.24 million) and WHO’s Global Health Estimates put them at 61 million for the same year, so every “share of all deaths” figure depends on which denominator is used.

WHO names six basic medicines that should be available everywhere for cardiovascular disease: aspirin, beta-blockers, calcium channel blockers, ACE inhibitors, diuretics and statins. All six are off-patent. That is the single most important economic fact in this chapter.

Respiratory system, totals.

Condition	Deaths	DALYs and YLDs	Source
COPD	3.4 million, 2023, about 6 per cent of all deaths; 3.6 million on the WHO top-ten page for the same year; 3.72 million (3.36–4.09) for 2021 in GBD 2021	74.9 million DALYs (66.2–86.9), rank 7; 15.0 million YLDs (12.6–17.6), rank 19	WHO COPD fact sheet, 10 June 2026; WHO top ten causes, 2 October 2026; GBD 2023
Asthma	442,000	14.1 million YLDs (8.80–20.3), rank 20	WHO asthma fact sheet, 28 April 2026; GBD 2023
Lower respiratory infections	2,501,300 (2,241,000–2,812,200) in GBD 2023; 2.7 million on the WHO top-ten page	98.7 million DALYs (87.7–112), rank 4	GBD 2023; WHO
Upper respiratory infections	27,100 (6,100–77,300), down 29.4 per cent since 2000	—	GBD 2023
Pneumoconiosis, all types	18,323 (16,041–20,916), 2021	507,425 DALYs, 2017 figure	GBD 2021 pneumoconiosis analysis, Frontiers in Public Health 2025

Two WHO pages give 3.4 and 3.6 million COPD deaths for the same year, 2023, and GBD 2021 gives 3.72 million. All three are printed. COPD is the third leading cause of death worldwide and the seventh leading cause of lost healthy life, and nearly 90 per cent of COPD deaths under the age of 70 occur in low- and middle-income countries.

The two risk-factor studies behind this chapter

Almost every risk-factor section in the circulatory half of this chapter refers back to two case-control studies. They are given here once, in full.

INTERHEART

Yusuf S and colleagues, Lancet 2004;364:937–952. Case-control, 15,152 cases of first myocardial infarction and 14,820 controls, 52 countries. Read in a secondary summary of the paper, not in the Lancet original.

Risk factor	Odds ratio (99% CI)	Population attributable risk
ApoB/ApoA1 ratio, top against bottom quintile	3.25 (2.81–3.76)	49.2 per cent
Current or former smoking	2.04 (1.86–2.25)	35.7 per cent
Psychosocial factors	2.67; confidence interval†	32.5 per cent
Abdominal obesity, top against bottom tertile	1.62; confidence interval†	20.1 per cent
Hypertension	1.91 (1.74–2.10)	18 per cent
Daily fruit and vegetables, protective	0.70 (0.62–0.79)	13.7 per cent
Regular exercise, protective	0.86 (0.76–0.97)	12.2 per cent
Diabetes	2.37 (2.07–2.71)	9.9 per cent
Alcohol intake, protective	0.91 (0.82–1.02)	6.7 per cent

Combined population attributable risk across all nine factors: 90.4 per cent, 99 per cent confidence interval 88.1 to 92.4.

Two confidence intervals carry daggers, and the reason is specific. The secondary source used here printed an interval for psychosocial factors, 2.21 to 2.32, that does not contain its own point estimate of 2.67, and printed the abdominal obesity interval malformed. Both are transcription failures in that source. Neither

malformed interval is reproduced. The point estimates and the attributable risks are consistent across sources and are printed; the two intervals must be taken from the Lancet original, which was not read.

INTERSTROKE

O'Donnell MJ and colleagues, Lancet 2016;388:761–775. Case-control, 26,919 participants, 32 countries. Abstract read at the Glasgow Enlighten record.

Risk factor	Odds ratio (99% CI)	PAR, all stroke
Hypertension, history or BP 140/90 or above	2.98 (2.72–3.28)	47.9 per cent
Regular physical activity, protective	0.60 (0.52–0.70)	35.8 per cent
ApoB/ApoA1 ratio, highest against lowest tertile	1.84 (1.65–2.06)	26.8 per cent, top two tertiles against lowest
Diet, mAHEI highest against lowest tertile, protective	0.60 (0.53–0.67)	23.2 per cent, lowest two against highest
Waist-to-hip ratio, highest against lowest tertile	1.44 (1.27–1.64)	18.6 per cent, top two against lowest
Psychosocial factors	2.20 (1.78–2.72)	17.4 per cent
Current smoking	1.67 (1.49–1.87)	12.4 per cent
Cardiac causes, including atrial fibrillation	3.17 (2.68–3.75)	9.1 per cent
Alcohol, high or heavy episodic against never or former	2.09 (1.64–2.67)	5.8 per cent, current against never or former
Diabetes mellitus	1.16 (1.05–1.30)	3.9 per cent

All rows. Combined attributable risk by stroke type: all stroke 90.7 per cent (95 per cent CI 88.7–92.4); ischaemic stroke 91.5 per cent (89.4–93.2); intracerebral haemorrhage 87.1 per cent (82.2–90.8).

The regional variation inside INTERSTROKE is large and is part of the result. The smoking attributable risk runs from 4.5 per cent in Africa to 18 per cent in western Europe, North America and Australia, and from 16.6 per cent in men to 5.3 per cent in women. Physical inactivity runs from 4.7 per cent in Africa to 59.9 per cent in China. Alcohol gives 10 per cent in men and −0.7 per cent in women. Hypertension was associated with stroke in every region. A higher mAHEI diet score was associated with increased risk in south Asia, a reversal the paper does not explain. ApoB/ApoA1 ratio and atrial fibrillation were associated with ischaemic stroke only, not with intracerebral haemorrhage.

What neither study establishes. Both are case-control. A population attributable risk from a case-control design is the share of cases statistically associated with exposure under the model's assumptions. It is not an experimentally demonstrated preventable fraction. Neither study randomised anything, and the nine or ten factors are correlated, which is why the combined figure exceeds the sum of plausible independent contributions. The 90 per cent figures are widely quoted as "90 per cent of heart attacks and strokes are preventable." That is not what either study measured, and the misreading accompanies these figures wherever they are used.

Chapter 11 — Diseases of the circulatory system

Blood pressure and the arteries of the heart

Hypertension (ICD-11 BA00)

What it is. Blood pressure in the arteries stays high when the person is at rest. It causes no symptoms for years. The pressure itself damages arteries, heart, kidneys, eyes and brain.

Measured. About 1.4 billion adults aged 30 to 79 had hypertension in 2024, 33 per cent of that age group, against 650 million in 1990. Around 600 million, 44 per cent, are unaware; about 630 million, given as 44 per cent, are diagnosed and treated; about 320 million, 23 per cent, have it controlled. Two-thirds live in low- and middle-income countries. An earlier edition of the same WHO page gave 1.28 billion with hypertension, 46 per cent unaware, 42 per cent treated and 21 per cent controlled; the 2025 edition's figures are printed above and both sets circulate. The 2025 page contradicts itself twice: 630 million of 1.4 billion is 45 per cent rather than the 44 per cent printed, and the same 44 per cent is attached to both the 600 million unaware and the 630 million treated.

Hypertensive heart disease caused 1.7 million deaths in 2023 and ranks eighth among all causes of death. It is the fourth leading cause of cardiovascular DALYs in GBD 2023, and thirteenth among all causes of death by age-standardised rate in GBD 2021, at 16.3 per 100,000. High systolic blood pressure is the largest single attributable risk factor for death in the world, about 10.8 million deaths a year, and it heads the GBD 2023 ranking of risks by health loss. Prevalence rises steadily with age and exceeds 60 per cent above age 60 in most populations. Prevalence has fallen in high-income countries since 1990 and risen in sub-Saharan Africa, south Asia and parts of Latin America. Regional prevalence is highest in the Eastern Mediterranean at 38 per cent and lowest in the Western Pacific at 29 per cent. The doubling of the absolute number since 1990 is almost entirely population growth and ageing; the age-standardised prevalence has been roughly flat.

Where it starts. Blood pressure itself is the mechanism, and lowering it carries the benefit: each 10 mmHg of systolic reduction cuts major cardiovascular events by 20 per cent, relative risk 0.80 (95 per cent CI 0.77–0.83), from 123 trials and more than 600,000 participants. INTERHEART gives hypertension an odds ratio of 1.91 for myocardial infarction and an attributable risk of 18 per cent; INTERSTROKE gives 2.98 for stroke and 47.9 per cent, the largest single attributable risk in that study. Dietary sodium, body weight, alcohol, physical inactivity and potassium deficiency are the established contributors. Each kilogram of weight lost lowers systolic pressure by roughly 1 mmHg. Twin and family studies give a heritability of 30 to 50 per cent, and genome-wide association studies have identified over a thousand loci that together explain only a small part of population variance.

For more than 90 per cent of cases no specific cause can be identified; the word "essential" records that. Why sodium raises pressure in some people and not others — salt sensitivity — is not explained at a level that predicts it in an individual, and no available test identifies it. The gap between high twin-study heritability and the small variance explained by identified loci is unresolved. Whether the rise in blood pressure with age is intrinsic or entirely environmental is not settled: some hunter-gatherer and remote populations show little or no age-related rise, but those studies are small, non-randomised, and confounded by diet, weight and activity at once.

Cure status. CONTROLLABLE.

Antihypertensive drugs lower pressure and event rates while they are taken, and pressure returns toward baseline when they stop. No standing treatment removes the condition. The secondary hypertensions are the exception and account for only around 5 to 10 per cent of all cases: primary aldosteronism is cured by adrenalectomy in roughly 30 to 40 per cent, higher for a unilateral adenoma; renal artery stenosis in selected cases; phaeochromocytoma resection; coarctation repair. Marked weight loss and bariatric surgery produce remission off drugs in a substantial minority, but that remission holds while the new weight holds.

Prevention.

Salt reduction — STRONG for blood pressure, STRONG for events where a substitute has been tested, CONTESTED at the extremes of intake. The SSaSS trial randomised 20,995 participants in rural China, 10,504 to a potassium-enriched salt substitute and 10,491 to regular salt. Mean age was 65, half were female, and all had either a prior stroke or were aged 60 and over with high blood pressure. Follow-up was 4.74 years. Stroke 29.14 against 33.65 per 1,000 person-years (p=0.006); major adverse cardiovascular events 49.09 against 56.29 (p<0.001); total mortality 39.28 against 44.61 (p<0.001); serious hyperkalaemia 3.35 against 3.30 (p=0.76, no increase). This is the strongest evidence in existence that a population salt measure lowers death.

The UK salt reduction programme between 2003 and 2011 cut intake by 1.4 g a day, about 15 per cent, from 9.5 to 8.1 g measured by 24-hour urinary sodium. Systolic pressure fell 3.0 mmHg and diastolic 1.4 mmHg across all adults, and 2.7 over 1.1 mmHg in those not on blood-pressure medication after adjustment. Stroke mortality fell 42 per cent and ischaemic heart disease mortality 40 per cent over the same period. The design is an ecological before-and-after analysis, not a trial, and those years also carried large falls in smoking and large rises in statin and antihypertensive prescribing. The 3.0 mmHg is the programme's measured effect; the mortality falls are concurrent and are not apportioned.

Where it is contested: the PURE study reported a J-shaped or U-shaped association with higher cardiovascular risk at both high intake, above 5 g of sodium a day, and low intake, below 3 g, implying a threshold below which reduction does not help. PURE estimated 24-hour sodium from a single fasting morning urine using the Kawasaki formula, which its critics argue systematically misestimates intake at the extremes and generates the J-curve as an artefact. Cook and colleagues reanalysed the TOHP trial data using repeated 24-hour urine collections and found a monotonic relation with no J-curve. The disagreement is unresolved and neither camp has conceded. The measurement method is itself the contested variable. SSaSS stands independent of it: a randomised substitute lowered death in a high-intake population.

WHO's own position, for comparison. Global mean adult sodium intake in 2021 was 4,278 mg a day, about 11 g of salt, against a recommended limit below 2,000 mg of sodium or 5 g of salt. Excess sodium is linked to 1.7 million deaths a year, and the stated return on sodium reduction is at least US$12 for every US$1 invested.

Weight reduction — STRONG. About 1 mmHg systolic per kilogram lost.

Dietary pattern — STRONG. The DASH trial lowered systolic pressure by 5.5 mmHg overall and 11.4 mmHg in hypertensive participants against a control diet; DASH with low sodium lowered it further.

Physical activity — MODERATE. Aerobic training lowers systolic pressure by about 5 to 8 mmHg in hypertensive adults.

Potassium supplementation — MODERATE. About 3 to 5 mmHg systolic in hypertensive adults with low baseline intake.

Alcohol reduction — MODERATE. About 3 to 4 mmHg in heavy drinkers who cut down.

Tobacco control — STRONG for cardiovascular events, WEAK for blood pressure itself. Smoking raises acute but not much chronic pressure; its cardiovascular benefit runs through other pathways.

Population hypertension programmes — STRONG and cost-effective, on evidence from 18 countries. WHO's Global Hearts initiative, launched in September 2016, operates in more than 40 low- and middle-income countries and has 13.5 million people on protocol-based treatment since 2017.

Treatment. Four first-line classes, all off-patent, all on the WHO Essential Medicines List. Pooled and head-to-head trials show no large difference in event reduction between them at equivalent blood-pressure reduction; the reduction itself carries the benefit.

Drug	EML	Off-patent	Generic cost per patient-year
Hydrochlorothiazide or chlorthalidone, thiazide	yes	yes	€2–15 at MSH international prices, year not stated in the source
Amlodipine, calcium channel	yes	yes	€3–20. NHS Drug Tariff September 2026: £0.64

Drug	EML	Off-patent	Generic cost per patient-year
blocker			for 28 tablets of 5 mg, about £0.023 a tablet
Enalapril, lisinopril or ramipril, ACE inhibitor	yes	yes	a few to tens of euro
Losartan or telmisartan, angiotensin receptor blocker	yes	yes	a few to tens of euro
Bisoprolol, atenolol or metoprolol, beta blocker	yes	yes	a few to tens of euro
Spironolactone, for resistant hypertension	yes, sections 16 and 12.4	yes	a few to tens of euro

Effect sizes per 10 mmHg systolic reduction, from 123 trials and over 600,000 participants:

Outcome	Relative risk (95% CI)	Reduction
Major cardiovascular events	0.80 (0.77–0.83)	20 per cent
Coronary heart disease	0.83 (0.78–0.88)	17 per cent
Stroke	0.73 (0.68–0.77)	27 per cent
Heart failure	0.72 (0.67–0.78)	28 per cent
All-cause death	0.87 (0.84–0.91)	13 per cent

Number needed to treat depends entirely on baseline risk. For a 60-year-old at moderate risk it is roughly 100 over five years to prevent one major cardiovascular event; in high-risk secondary prevention, 20 to 30. SPRINT randomised 9,361 participants to a systolic target below 120 against below 140. The primary composite fell with a hazard ratio of 0.75 and all-cause death with 0.73. That gives a number needed to treat of 61 over 3.26 years to prevent one primary outcome event, and 90 to prevent one death, at the cost of more hypotension, syncope and acute kidney injury.

The cheap off-patent drugs are the whole of the therapy. No newer class in hypertension has a demonstrated event-reduction advantage over thiazides, ACE inhibitors, calcium channel blockers and beta blockers at matched blood-pressure reduction. A hypertensive patient can be treated to target for €10 to €40 a year at international generic prices, year not stated in the source.

Simple means. Salt reduction and salt substitution carry the largest measured effect here. A potassium-enriched substitute, typically 75 per cent sodium chloride and 25 per cent potassium chloride, lowered total mortality from 44.61 to 39.28 per 1,000 person-years with no excess serious hyperkalaemia. It needs a potassium chloride supply chain and no pharmaceutical one, and costs little more than salt. Weight loss gives about 1 mmHg systolic per kilogram. Walking and other aerobic exercise give 5 to 8 mmHg in hypertensive adults with no equipment. Cutting heavy drinking gives 3 to 4 mmHg. A diet shifted to fruit, vegetables and less processed food gives the DASH effect, 5.5 mmHg overall and 11.4 mmHg in hypertensive participants. Device-guided slow breathing lowers systolic pressure by about 3 to 5 mmHg in trials, with low evidence quality and inconsistent follow-up.

Measurement is the binding constraint, not medicine. The condition causes no symptoms, so without a cuff it is invisible and untreatable, and about 600 million hypertensive adults are unaware. A mechanical aneroid sphygmomanometer and a stethoscope need no electricity and last for decades. That is the minimum chain.

Gaps. The salt J-curve is unresolved: PURE against the TOHP reanalysis, with the urine-measurement method the contested variable. Both results stand. The UK programme's 42 per cent stroke and 40 per cent ischaemic heart disease mortality declines are routinely cited as salt-policy effects; the ecological design, concurrent with large changes in smoking and statin use, cannot support that attribution, and the 3.0 mmHg is the defensible figure. The optimal blood-pressure target is unsettled. SPRINT supports below 120 systolic and ACCORD-BP found no benefit in diabetes. SPRINT excluded diabetes and used unattended automated measurement, which reads several mmHg lower than conventional office measurement, so SPRINT's 120 is not the same quantity as a clinic 120. Guidelines differ, with ACC/AHA at below 130 and ESC/ESH at below 140 for many groups. WHO's own page gives treatment goals of below 130/80 for those with cardiovascular disease, diabetes, chronic kidney disease or high cardiovascular risk and below 140/90 for most others. Salt sensitivity cannot be predicted in an individual by any available test. The

heritability gap is unexplained. Global prevalence rests on national survey coverage that is thin in sub-Saharan Africa and parts of Asia, and the headline figure carries wide model uncertainty that is not usually printed. Whether the age-related rise in pressure is intrinsic is not resolved. Two editions of the same WHO fact sheet carry different headline figures — 1.28 billion and 1.4 billion — and the page contradicts itself on the treated percentage.

> **Depth.** Starts in: the arteriole and artery wall. Size: 1 mm†; depth +9.10. First complaint: about 45 years († onset about age 45; [B] years without complaints); time depth 52.34. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Ischaemic heart disease and myocardial infarction (ICD-11 BA40–BA4Z)

What it is. The arteries feeding the heart muscle narrow with fatty, fibrous plaque. When flow falls short of demand the muscle hurts. When a plaque ruptures and a clot blocks the artery the muscle dies, and that is a myocardial infarction. It is the largest single cause of death in the world.

Measured. Deaths in 2023: 9.5 million, 16 per cent of all deaths, rank 1 of all causes, on WHO's Global Health Estimates; 8.91 million on GBD 2023. The two disagree by about 600,000 and both are printed. DALYs in 2023: 193 million (176–209), rank 1 of all causes globally; GBD 2021 gave 188.3 million, rank 2 behind COVID-19 that year. YLDs in 2023: 10.0 million (7.26–13.5), rank 25. Age-standardised death rate in GBD 2021: 108.7 per 100,000, rank 1. About 240 million people are affected. WHO's top-ten page records the 9.5 million as 3.0 million higher than in 2000.

Deaths rise steeply from age 50. The median age of a first infarction is roughly 65 in men and 72 in women in high-income countries, and about a decade earlier in south Asia. Age-standardised rates are highest in eastern Europe, central Asia and the Middle East and lowest in high-income Asia-Pacific, Andean Latin America and western Europe; absolute numbers are dominated by China and India. Age-standardised mortality has fallen sharply in high-income countries since 1980, roughly 50 to 70 per cent, while absolute global deaths have risen with population growth and ageing. Of that high-income decline, the IMPACT model analyses attribute roughly half to risk-factor change, chiefly smoking and cholesterol, and roughly half to treatment.

Where it starts. INTERHEART is the reference study, and the full table sits at the front of this chapter. Nine factors, combined attributable risk 90.4 per cent (99 per cent CI 88.1–92.4), 52 countries, 15,152 cases. ApoB/ApoA1 ratio carries 49.2 per cent (odds ratio 3.25); smoking 35.7 per cent (2.04); psychosocial factors 32.5 per cent (2.67); abdominal obesity 20.1 per cent (1.62); hypertension 18 per cent (1.91); diabetes 9.9 per cent (2.37). Protective: fruit and vegetables 13.7 per cent (0.70); exercise 12.2 per cent (0.86); alcohol 6.7 per cent (0.91). In INTERHEART the lipid ratio and not blood pressure carries the largest attributable risk, the reverse of INTERSTROKE, where hypertension dominates. The two vascular beds have different dominant exposures, and that is a measured difference rather than an artefact of the two designs.

Further measured contributions. LDL cholesterol is causal and dose-dependent: Mendelian randomisation and the Cholesterol Treatment Trialists' meta-analyses together give a relative risk of 0.78 (0.76–0.80) for major vascular events per 1 mmol/L of LDL reduction, across 26 trials and about 170,000 participants. Lipoprotein(a) is largely genetically set and an independent causal risk factor; roughly 20 per cent of people have elevated levels and no approved therapy lowers it with proven outcome benefit. Ambient air pollution caused an estimated 4.2 million premature deaths in 2019, 89 per cent of them in low- and middle-income countries, and 68 per cent of those deaths were ischaemic heart disease and stroke together. Household air pollution attributes 32 per cent of its 2.9 million annual deaths to ischaemic heart disease, which is 12 per cent of all ischaemic heart disease deaths worldwide and over a million deaths a year.

Why a specific plaque ruptures at a specific moment is not predictable. Most infarctions arise from plaques that were not flow-limiting and would not have been detected as significant stenoses beforehand; angiographic stenosis severity predicts angina well and infarction location poorly. The psychosocial attributable risk of 32.5 per cent is the third largest of the nine and the least mechanistically explained; what

is measured — stress, depression, locus of control, life events — is heterogeneous and self-reported. Roughly 15 to 20 per cent of infarctions occur in people with none of the standard modifiable risk factors at measured thresholds, and that residual is not accounted for. Why age-standardised rates in some high-income countries have plateaued or risen slightly since about 2011, after three decades of decline, is not explained.

Cure status. CONTROLLABLE.

Atherosclerosis is not removed by any standing treatment. Statins and blood-pressure drugs slow progression and reduce events while taken; stopping them returns risk toward baseline. Revascularisation — percutaneous coronary intervention or coronary artery bypass grafting — restores flow past a blockage without removing the disease, and new lesions continue to form. In stable disease, intervention relieves angina but COURAGE, with 2,287 patients, and ISCHEMIA, with 5,179, found no reduction in death or myocardial infarction against optimal medical therapy alone. That is the clearest available evidence that the procedure does not cure the condition.

The exception: primary percutaneous coronary intervention in acute ST-elevation myocardial infarction is genuinely life-saving rather than palliative, and reperfusion within the first hours salvages muscle that would otherwise be lost for good. Meta-analysis against fibrinolysis gives short-term mortality of 7 against 9 per cent with a large reduction in reinfarction and stroke. It cures nothing. It converts a frequently fatal event into a survivable one.

Prevention.

Statins — STRONG. Per 1 mmol/L LDL reduction: major vascular events relative risk 0.78 (0.76–0.80), all-cause mortality 0.90 (0.87–0.93), coronary death 0.80 (99 per cent CI 0.74–0.87). Stroke death 0.96 (0.84–1.09), not significant.

Blood pressure lowering — STRONG. Per 10 mmHg systolic: coronary heart disease relative risk 0.83, a 17 per cent reduction; all-cause death 0.87, 13 per cent.

Smoking cessation — STRONG, and the largest single modifiable effect after diagnosis. The CLARIFY registry followed more than 32,000 patients with stable coronary disease for five years. Quitting after diagnosis gave a 44 per cent lower risk of major adverse cardiovascular events, adjusted hazard ratio 0.56 (95 per cent CI 0.42–0.76, $p<0.001$). Cutting down did not help: adjusted hazard ratio 0.96 (0.74–1.26, $p=0.78$). Each additional year of continued smoking raised risk by about 8 per cent, adjusted hazard ratio 1.08 (1.04–1.12) per year. Of those who eventually quit, 73 per cent did so in the first year after diagnosis. Reduction without cessation produced no measurable benefit, and that is the operative finding.

Tobacco control policy — STRONG. Tobacco kills more than 7 million people a year, with over 1.6 million non-smoker deaths from second-hand smoke, and there are 1.2 billion tobacco users, around 80 per cent of them in low- and middle-income countries. Counselling and medication can more than double quit success, and more than 60 per cent of smokers intend to quit. Tax is the single most effective measure, and 41 countries, covering 12 per cent of the world's population, tax at least 75 per cent of retail price; a 10 per cent price rise reduces consumption by about 4 per cent in high-income and 5 per cent in low- and middle-income countries. Smoke-free laws cover 79 countries and over a third of the world's population, and smoke-free legislation is followed by falls in acute coronary syndrome admissions of roughly 10 to 20 per cent in before-and-after studies, which are ecological designs with widely varying effect sizes.

Polypill — MODERATE. TIPS-3 randomised 5,713 intermediate-risk participants without cardiovascular disease; the polypill plus aspirin reduced cardiovascular events against placebo, with a reported hazard ratio of about 0.69 for that comparison. PolyIran, cluster-randomised across 6,838 participants in Iran, gave a hazard ratio of 0.66 (95 per cent CI 0.55–0.80) for major cardiovascular events with a four-component polypill.

Trans fat elimination — STRONG where enacted. Nearly 60 countries have best-practice trans fat policies in effect, covering 46 per cent of the world's population. WHO's REPLACE programme is stated to have helped protect more than half the global population. One figure needs care: the WHO release states that coronary heart disease is responsible for over 278,000 deaths each year globally in the context of trans fat, and does not present this as the number of deaths attributable to industrially produced trans fat. The widely

circulated figure of 500,000 deaths a year from trans fat comes from earlier WHO communications and should not be conflated with the 278,000.

Clean cooking fuel — STRONG on the attributable fraction, WEAK on randomised prevention evidence. Household air pollution accounts for 12 per cent of all ischaemic heart disease deaths worldwide, with 2.1 billion people still cooking with solid fuels or kerosene. HAPIN randomised liquefied petroleum gas stoves, verified a 66 per cent reduction in fine particulate exposure, and did not show its primary birth-weight benefit; cardiovascular endpoints have not been established by any trial, and the evidence is attributable-fraction modelling. Both must be stated.

Outdoor air quality standards — STRONG on burden, MODERATE on policy effect. In 2019, 99 per cent of the world's population lived above WHO air quality guideline levels, and ambient air pollution caused an estimated 4.2 million premature deaths, 68 per cent of them ischaemic heart disease and stroke. WHO's interim target one, 35 µg/m³, would save around 300,000 deaths a year.

Mediterranean diet — MODERATE. PREDIMED, with 7,447 participants, reported a hazard ratio of about 0.70 for major cardiovascular events. The trial was retracted and republished in 2018 after randomisation irregularities were found at some sites, with similar effect estimates on reanalysis. Any citation must carry the retraction and republication.

Physical activity — STRONG. INTERHEART exercise odds ratio 0.86, attributable risk 12.2 per cent. For scale: 31 per cent of adults, 1.8 billion people, do not meet recommended activity levels, up five percentage points between 2010 and 2022 and projected to reach 35 per cent by 2030; insufficiently active people carry a 20 to 30 per cent higher risk of death.

Vitamin, antioxidant, omega-3 and folate supplementation — CONTESTED to negative. HOPE-2, VITAL, ASCEND, SELECT and Physicians' Health Study II found no cardiovascular benefit for vitamin E, vitamin D, folate or low-dose omega-3 in unselected populations. REDUCE-IT, with 8,179 patients on icosapent ethyl 4 g a day, reported a hazard ratio of 0.75 for the primary composite, but STRENGTH with a different omega-3 formulation was null, and the mineral-oil placebo in REDUCE-IT is disputed as having raised event rates in the control arm. The disagreement is live.

Treatment. Four cheap drugs carry secondary prevention after a myocardial infarction.

Drug	Effect size	EML	Off-patent	Generic cost per patient-year
Aspirin 75–100 mg	Serious vascular events reduced about 19 to 22 per cent in secondary prevention; 6.7 against 8.2 per cent per year, p<0.0001, Antithrombotic Trialists' Collaboration, Lancet 2009. **NNT 67 per year and 33 over two years, recomputed by this book from those rates — see the correction below**	yes	yes	a few euro
Statin, simvastatin 40 mg or atorvastatin 20–80 mg	Per 1 mmol/L LDL reduction: major vascular events RR 0.78, all-cause death 0.90, coronary death 0.80. In 4S, all-cause mortality 8.2 against 11.5 per cent, NNT 30 over 5.4 years to prevent one death	yes	yes	a few to tens of euro
ACE inhibitor, ramipril, enalapril or lisinopril	HOPE, 9,297 patients: primary composite 14.0 against 17.8 per cent, RR 0.78, NNT 26 over five years; all-cause death 10.4 against 12.2 per cent	yes	yes	a few to tens of euro
Beta blocker, metoprolol,	Post-infarction mortality reduced about 20 to 25 per	yes	yes	a few to tens of euro

Drug	Effect size	EML	Off-patent	Generic cost per patient-year
bisoprolol or carvedilol	cent in the pre-reperfusion trials, BHAT, ISIS-1 and Norwegian Timolol; NNT about 40 over two years to prevent one death. Benefit in the modern reperfusion era with preserved ejection fraction is now questioned: REDUCE-AMI, 2024, 5,020 patients, found no benefit after infarction with preserved ejection fraction, hazard ratio 0.96			

A correction, printed in full so the reader can check it. The dossier behind this chapter printed “NNT about 50 over 2 years” for aspirin in secondary prevention, citing the Antithrombotic Trialists’ Collaboration, Lancet 2009. That paper publishes two rates, 6.7 against 8.2 per cent per year, and no number needed to treat at all. The figure of 50 was not read off the paper and is not derivable from it; it was invented. Recomputed from the published rates: the absolute risk difference is 8.2 −6.7 = 1.5 percentage points per year, so the number needed to treat is 1/0.015 = 66.7 per year, which is 33.3 over two years. At the published rates, 50 cannot be reached at either one year or two. The figures printed above — 67 per year, 33 over two years — are this book’s arithmetic on the paper’s published rates, and are labelled as such rather than as figures read off the paper. The 6.7 and 8.2 per cent rates are the paper’s own and are verified.

The polypill combines exactly these drugs and is on the Essential Medicines List. The SECURE trial enrolled 2,499 patients, mean age 76, 31 per cent women, across 113 hospitals in seven European countries, with median follow-up of 3.0 years. The polypill was aspirin 100 mg plus ramipril 2.5, 5 or 10 mg plus atorvastatin 20 or 40 mg, with 91.7 per cent receiving the 40 mg statin dose, against usual care. The primary endpoint of cardiovascular death, non-fatal infarction, non-fatal ischaemic stroke or urgent revascularisation was 9.5 against 12.7 per cent, hazard ratio 0.76 (95 per cent CI 0.60–0.96) — a 24 per cent relative and 3.2 percentage point absolute reduction, giving a number needed to treat of about 31 over three years. The secondary endpoint was 8.2 against 11.7 per cent, hazard ratio 0.70 (0.54–0.90). Cardiovascular mortality fell 33 per cent. The trial missed its enrolment target of 3,200.

Three polypill formulations were added to the Model List in 2023, in section 12.7, fixed-dose combinations for prevention of atherosclerotic cardiovascular disease, all on the core list: aspirin with atorvastatin and ramipril; aspirin with simvastatin, ramipril, atenolol and hydrochlorothiazide at 100, 20, 5, 50 and 12.5 mg; and atorvastatin with perindopril and amlodipine.

Acute myocardial infarction. Primary percutaneous intervention gives short-term mortality of 7 against 9 per cent compared with fibrinolysis, with large reductions in reinfarction and stroke. It requires a catheterisation laboratory, 24-hour staffing and a stent supply chain, and is not available to most of the world’s population. Fibrinolysis with streptokinase, alteplase or tenecteplase needs no catheter laboratory: in ISIS-2 and GISSI, streptokinase reduced 35-day mortality by about 25 per cent against control, and streptokinase plus aspirin by about 42 per cent. Streptokinase is on the Essential Medicines List, off-patent, and costs tens of euro a dose; tenecteplase is far more expensive and easier to give. Aspirin 300 mg chewed at onset reduced 35-day vascular mortality by 23 per cent on its own in ISIS-2, with a number needed to treat of about 40. That is a single tablet costing under one cent, given by anyone, and it is a large absolute mortality benefit for a very low cost. Adding clopidogrel gave a composite of 9.3 against 11.4 per cent in CURE, relative risk 0.80, number needed to treat 48; clopidogrel is on the list†, off-patent, tens of euro a year.

Newer classes, with their measured effect and their price. PCSK9 inhibitors. FOURIER, with 27,564 patients on evolocumab, gave a primary composite hazard ratio of 0.85, 9.8 against 11.3 per cent, and a number needed to treat of about 67 over 2.2 years, with no significant reduction in cardiovascular or all-cause mortality. ODYSSEY OUTCOMES, with 18,924 patients on alirocumab, gave 0.85. These launched at about US$14,000 a year in the United States in 2015, were cut to about US$5,850 in 2018, and now run roughly €4,000 to €7,000 a year in Europe. Neither is on the Essential Medicines List and both are on patent. Cost per event prevented is on the order of €300,000 to €500,000 at those prices, against €100 to

€800 for a statin. Inclisiran, a twice-yearly small interfering RNA, lowers LDL by about 50 per cent; its outcome trial, ORION-4, has not reported, so its effect on events is unmeasured, and it costs €3,000 to €4,500 a year and is not on the list. Ezetimibe: IMPROVE-IT, 18,144 patients, 32.7 against 34.7 per cent, hazard ratio 0.936, number needed to treat 50 over seven years; on the Essential Medicines List as an alternative since 2023†, off-patent, €15 to €60 a year. Colchicine 0.5 mg: COLCOT, 4,745 patients, hazard ratio 0.77; LoDoCo2, 5,522 patients, 0.69. It is off-patent and very cheap at €10 to €50 a year, and is not on the Essential Medicines List for this indication. It has among the most favourable effect-per-euro of any recent addition.

Simple means. Smoking cessation is the largest single effect available and requires no supply chain at all: a 44 per cent reduction in major adverse cardiovascular events after a coronary diagnosis, adjusted hazard ratio 0.56, with reduction short of quitting giving nothing, adjusted hazard ratio 0.96. Aspirin at the onset of chest pain gives about a 23 per cent reduction in 35-day vascular death from one chewed 300 mg tablet, at a cost under one cent. Exercise-based cardiac rehabilitation reduces cardiovascular mortality with a risk ratio of about 0.74 and hospital admissions by about 18 per cent, with no clear effect on all-cause mortality in the most recent Cochrane updates; walking-based programmes need no equipment. Habitual physical activity gives the INTERHEART odds ratio of 0.86 and an attributable risk of 12.2 per cent. Salt substitution gives the SSaSS mortality result, 39.28 against 44.61 per 1,000 person-years in a population with prior stroke or hypertension. A diet shifted to fruit and vegetables gives an odds ratio of 0.70 and an attributable risk of 13.7 per cent. Household air pollution accounts for 12 per cent of all ischaemic heart disease deaths, and randomised outcome evidence for the stove interventions tested is absent. Where the infarction causes cardiac arrest, bystander CPR with no equipment doubles to triples survival.

Weight loss needs stating honestly. It acts through blood pressure, lipids and glucose and improves every intermediate measure, and no independent randomised cardiovascular-outcome benefit was shown in Look AHEAD, which randomised 5,145 patients with type 2 diabetes to intensive lifestyle intervention and was stopped early for futility at a hazard ratio of 0.95.

Gaps. WHO and GBD disagree by about 600,000 deaths a year for this single condition, 9.5 against 8.91 million in 2023. Both are printed. The disagreement lies in cause-of-death redistribution method and neither organisation publishes a reconciliation. Beta blockers after infarction with preserved ejection fraction: the classical 20 to 25 per cent mortality benefit comes from pre-reperfusion trials and REDUCE-AMI found no benefit in the modern era; guidelines have not fully absorbed this, and both are printed. Revascularisation in stable disease: COURAGE and ISCHEMIA found no reduction in death or infarction, and intervention rates remain high — a disagreement between trial evidence and practice, not between trials. PREDIMED was retracted and republished. Omega-3 is unresolved: REDUCE-IT positive, STRENGTH null, the placebo disputed. Lipoprotein(a) is causal, common and has no outcome-proven therapy; Lp(a)HORIZON and olpasiran trials are running, and any benefit figure now would be an estimate rather than a measurement. The psychosocial attributable risk of 32.5 per cent is the least understood of the nine factors, measured heterogeneously and self-reported in a case-control design in which recall after an infarction is a plausible bias. Between 15 and 20 per cent of infarctions occur with no standard risk factor present, and that is unexplained. A population attributable risk from a case-control study is not a demonstrated preventable fraction, and the “90 per cent preventable” reading of INTERHEART misstates what the study measured. Generic prices vary by a factor of ten or more between reference classes for the same molecule, so every price here is an order of magnitude rather than a measurement. The Management Sciences for Health price guide that several of these figures were drawn from published its last edition in 2017 and its website was retired after 30 June 2024. It cannot be used as a current source.

> **Depth.** Starts in: a coronary artery. Size: 3 mm†; depth +10.10. First complaint: about 65 years († first event at about 65); time depth 52.67. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The artery can be opened. The process in the wall goes on. So it is held, not ended. The book’s status: CONTROLLABLE. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Stable angina (ICD-11 BA40.0)

What it is. Chest pain or pressure that comes on with exertion and goes away with rest. It happens when narrowed coronary arteries cannot deliver enough blood for the work the heart is doing. The pattern is stable over months. It is not an infarction.

Measured. No separate global prevalence or death count exists in GBD or WHO sources; angina is counted within ischaemic heart disease, and no angina-specific figure was located. The chapter-level ischaemic heart disease figures apply: 9.5 million deaths on WHO 2023 and 8.91 million on GBD 2023, 193 million DALYs, about 240 million people affected. GBD does model angina as a sequela of ischaemic heart disease with its own disability weight, contributing to the 10.0 million ischaemic heart disease YLDs of 2023, without publishing an angina-specific count. Prevalence of angina in high-income populations is roughly 4 to 7 per cent of men and 5 to 7 per cent of women aged 45 to 64, rising with age. Women report angina at least as often as men and have less obstructive disease on angiography. Incidence of new stable angina has fallen in high-income countries alongside ischaemic heart disease mortality.

Where it starts. The same risk factors as ischaemic heart disease. INTERHEART applies in full: ApoB/ApoA1 ratio 49.2 per cent, smoking 35.7 per cent, psychosocial factors 32.5 per cent, abdominal obesity 20.1 per cent, hypertension 18 per cent, diabetes 9.9 per cent, combined 90.4 per cent.

The relation between measured stenosis and symptoms is weak in both directions. Severe stenoses are often silent, and a substantial proportion of patients with typical angina have no obstructive coronary disease at all — angina or ischaemia with non-obstructive coronary arteries — reported in up to 50 per cent of women undergoing angiography for angina. The proposed mechanisms, coronary microvascular dysfunction and vasospasm, are not measurable in routine practice, and the condition has no established disease-modifying treatment. Why ischaemia produces pain in some people and none in others, particularly the silent ischaemia of diabetes, is not explained.

Cure status. CONTROLLABLE.

Antianginal drugs relieve symptoms while taken. Percutaneous intervention relieves angina better than medical therapy in the short term and does not reduce death or infarction, in COURAGE and ISCHEMIA. The blinded evidence on symptoms is split and both results must be printed. ORBITA randomised 200 patients to intervention against a placebo procedure with sham sedation and angiography, and found no significant difference in exercise time increment, though intervention did improve stress-echocardiographic ischaemia. ORBITA-2, with 301 patients and antianginal drugs withdrawn, did show a significant symptom benefit of intervention over the placebo procedure. Bypass grafting improves survival in specific anatomies — left main disease, and three-vessel disease with reduced ejection fraction — and does not remove atherosclerosis.

Prevention. Identical to ischaemic heart disease, with the same grades: statins STRONG, blood-pressure lowering STRONG, smoking cessation STRONG, physical activity STRONG, diet MODERATE, polypill MODERATE, supplements CONTESTED to negative. The effect sizes and their sources are in that entry.

Treatment. Symptom relief and event prevention are separate tracks. No antianginal drug has been shown to reduce mortality.

Drug	Purpose	Effect	EML	Off-patent	Cost per year
Glyceryl trinitrate, sublingual	Abort an attack	Relief in 1–3 minutes	yes	yes	a few to tens of euro
Beta blocker, bisoprolol, metoprolol, atenolol	First-line prophylaxis	Reduces attack frequency; no mortality benefit in stable angina	yes	yes	a few to tens of euro
Calcium channel blocker, amlodipine, diltiazem, verapamil	First-line alternative	Equivalent symptom control to beta blockers	yes	yes	a few to tens of euro
Long-acting nitrate, isosorbide mononitrate	Add-on	Symptom relief; tolerance develops	yes	yes	a few to tens of euro
Ivabradine	Add-on when heart	SIGNIFY, 19,102	no	partly	hundreds of euro

Drug	Purpose	Effect	EML	Off-patent	Cost per year
	rate is high	patients: no benefit on the primary composite, and an increase in the angina subgroup			
Ranolazine	Add-on	Modest symptom benefit, TERISA	no	yes in some markets	hundreds to thousands of euro
Nicorandil	Add-on	IONA: composite reduced	no	yes	hundreds of euro

All effect figures in this table except where the ischaemic heart disease entry marks them otherwise. Event prevention sits on top: aspirin, a statin and an ACE inhibitor, all on the Essential Medicines List, all off-patent, a few to tens of euro each a year. Revascularisation gives angina relief with no mortality benefit in stable disease; bypass grafting gives a survival benefit in left main and three-vessel disease with impaired ventricular function.

Simple means. Exercise training has been tested against intervention directly: Hambrecht and colleagues randomised 101 patients and reported better event-free survival with training, 88 against 70 per cent at twelve months, at lower cost. That is a small single-centre trial. Smoking cessation gives the 44 per cent reduction in major adverse cardiovascular events after a coronary diagnosis. Pacing exertion and avoiding cold exertion after meals reduces attack frequency, with no trial quantification located. Weight loss, salt reduction and diet shift act as in the ischaemic heart disease entry. Glyceryl trinitrate is the only acute relief and cannot be improvised: it is a cheap, off-patent, listed tablet or spray, and it needs a pharmaceutical chain.

Gaps. No angina-specific global burden figure exists; GBD counts it inside ischaemic heart disease. The blinded evidence on whether intervention relieves angina is split, ORBITA null on exercise time and ORBITA-2 positive on symptoms, and both are printed. Angina without obstructive coronary disease, possibly up to half of angina in women referred for angiography, has no established treatment and no agreed diagnostic standard. Whether the choice of antianginal affects outcome at all beyond symptoms is unresolved, and ivabradine increased events in the angina subgroup of SIGNIFY. Sex differences in presentation and in angiographic findings are documented and unexplained.

> **Depth.** Starts in: a coronary artery. Size: 3 mm†; depth +10.10. First complaint: about 62 years († onset about age 62); time depth 52.63. One untreated course: no number ([B] stable over months).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The artery can be opened. The process in the wall goes on. So it is held, not ended. The book’s status: CONTROLLABLE. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

The failing pump

Heart failure with reduced ejection fraction (ICD-11 BD10–BD1Z)

What it is. The heart muscle pumps too weakly, so blood backs up and the body gets too little. Breathlessness, swollen legs and exhaustion follow. “Reduced ejection fraction” means the left ventricle empties 40 per cent or less of its contents with each beat.

Measured. About 64 million people worldwide have heart failure of all types, from a 2023 review in Cardiac Failure Review. That review does not state the data year or the dataset behind the figure, and the figure is carried with that caveat.

GBD does not publish heart failure as a level-3 cause, so there is no GBD death count and no DALY figure for heart failure as a syndrome. Its burden is distributed across ischaemic heart disease, hypertensive heart disease, cardiomyopathy and valvular disease. For a condition affecting roughly 64 million people, the global mortality burden is not measured directly anywhere.

Heart failure with reduced ejection fraction is roughly 50 per cent of all heart failure, with preserved ejection fraction making up most of the remainder and a mid-range group between. The primary review does not state that split; the 50 per cent comes from registry series — ESC-HF-LT, Get With The Guidelines-HF, the Swedish Heart Failure Registry. Incidence has stabilised worldwide and is apparently declining in developed countries, with no figures given in the source. Lifetime risk from age 40 is roughly 20 per cent. Mortality is roughly 50 per cent at five years after diagnosis across registries, with one-year mortality of about 25 to 30 per cent after a hospitalisation for heart failure; the review states only that heart failure carries high mortality, without rates. Prevalence rises from under 1 per cent below age 50 to over 10 per cent above 80, and is rising from ageing and from improved survival after myocardial infarction.

Where it starts. Ischaemic heart disease is the commonest cause in high-income countries, roughly two-thirds of cases. Hypertension is both a major cause and the most responsive target: per 10 mmHg of systolic reduction, heart failure relative risk is 0.72 (0.67–0.78), a 28 per cent reduction and the largest of the five outcomes in the blood-pressure meta-analysis. Valvular disease, cardiomyopathy both genetic and acquired, myocarditis, alcohol, anthracycline and trastuzumab chemotherapy, uncontrolled tachyarrhythmia, thyroid disease, iron overload and Chagas disease, a leading cause in Latin America, all contribute. Diabetes roughly doubles heart failure risk independent of coronary disease. Up to 30 to 40 per cent of dilated cardiomyopathy is familial, with truncating variants in the titin gene the commonest single finding, about 15 to 25 per cent of familial cases.

Why two people with the same infarct size end up with very different ventricular remodelling is not predictable. The transition from compensated ventricular dysfunction to symptomatic failure has no reliable biomarker of timing. In a substantial proportion of dilated cardiomyopathy no cause is found. Whether modern drug therapy genuinely reverses remodelling or only slows it is argued from surrogate imaging endpoints.

Cure status. CONTROLLABLE.

The four-drug foundation reduces mortality substantially while the ventricular dysfunction persists, and withdrawal is followed by deterioration. TRED-HF randomised 51 patients with recovered dilated cardiomyopathy to withdraw therapy and found 44 per cent relapsed within six months against none in the continuation arm. That is the clearest direct evidence that treatment holds the state rather than removing it.

Genuine cures exist where the cause is removable. Tachycardia-induced cardiomyopathy: ablation or rate control of the causative arrhythmia normalises ejection fraction in the majority. Valvular disease: valve repair or replacement can restore function if done before irreversible remodelling. Alcoholic cardiomyopathy: substantial recovery with sustained abstinence in a large minority. Peripartum cardiomyopathy: ejection fraction recovers in roughly 50 to 70 per cent. Iron overload and thyrotoxic cardiomyopathy are reversible on treating the cause. Heart transplantation removes the failing organ, with median survival after transplant of roughly 12 to 13 years; donor supply limits it to a few thousand procedures a year worldwide and it is not a population-level option.

Prevention.

Blood pressure lowering — STRONG, and the largest effect of any prevention measure here. Per 10 mmHg systolic reduction, heart failure relative risk 0.72 (0.67–0.78), a 28 per cent reduction, from 123 trials and over 600,000 participants.

SGLT2 inhibitors in diabetes — STRONG. EMPA-REG, CANVAS and DECLARE-TIMI 58 showed about a 30 per cent reduction in hospitalisation for heart failure in people with type 2 diabetes and no heart failure at baseline.

Treating myocardial infarction promptly and completely — STRONG, by limiting infarct size.

Statins — MODERATE for preventing heart failure, chiefly by preventing infarction.

Alcohol limitation — MODERATE. *Avoiding and monitoring cardiotoxic chemotherapy — MODERATE*.

Rheumatic fever prevention with penicillin — STRONG where rheumatic valve disease is the dominant cause. *Chagas vector control and screening — STRONG* in endemic Latin America.

Treatment. Four pillars. The first three are off-patent and on the Essential Medicines List; the fourth and the SGLT2 inhibitors are not.

Drug class	Effect size	EML	Off-patent	Cost per patient-year
ACE inhibitor, enalapril, ramipril, lisinopril	SOLVD-Treatment: mortality 35.2 against 39.7 per cent, RR 0.84, NNT 22 over 41 months; CONSENSUS in severe failure: one-year mortality 36 against 52 per cent, NNT 6	yes	yes	a few to tens of euro
Beta blocker, carvedilol, bisoprolol, metoprolol succinate	CIBIS-II: all-cause mortality 11.8 against 17.3 per cent, HR 0.66, NNT 18 over 1.3 years; MERIT-HF 7.2 against 11.0 per cent, NNT 26 over one year; COPERNICUS in severe failure 11.4 against 18.5 per cent, NNT 14. About a 34 per cent relative mortality reduction across the three	yes	yes	a few to tens of euro
Mineralocorticoid receptor antagonist, spironolactone, eplerenone	RALES, spironolactone, severe failure, 1,663 patients: mortality 35 against 46 per cent, RR 0.70, NNT 9 over 24 months, among the lowest in cardiology; EMPHASIS-HF, eplerenone, HR 0.63	yes	yes	a few to tens of euro
Loop diuretic, furosemide	Symptom relief. No mortality trial has ever been done and none will be	yes	yes	a few to tens of euro
Sacubitril/valsartan	PARADIGM-HF, 8,442 patients: primary composite 21.8 against 26.5 per cent, HR 0.80 (0.73–0.87); cardiovascular death 13.3 against 16.5 per cent, HR 0.80; all-cause death HR 0.84. NNT 21 over 27 months for the composite, about 32 for cardiovascular death	yes, added 2023	no; generics emerging in some markets 2025–2026	€1,000–5,000 branded; €300–900 early generic
SGLT2 inhibitor, dapagliflozin, empagliflozin	DAPA-HF, 4,744 patients: composite HR 0.74 (0.65–0.85), 16.3 against 21.2 per cent, NNT 21 over 18 months; all-cause death HR 0.83. EMPEROR-Reduced, 3,730 patients: HR 0.75 (0.65–0.86)	yes, dapagliflozin, 2021 and 2023 for heart failure and chronic kidney disease	no; patents expiring 2025–2028	€400–1,500 branded; €50–200 generic where available
Ivabradine	SHIFT, 6,505 patients with heart rate 70 and above in sinus rhythm: composite HR 0.82, driven by hospitalisation and not death	no	partly	hundreds of euro
Digoxin	DIG, 6,800 patients: no mortality effect, HR 0.99;	yes	yes	a few to tens of euro

Drug class	Effect size	EML	Off-patent	Cost per patient-year
	hospitalisation reduced			
Hydralazine with isosorbide dinitrate	A-HeFT, 1,050 self-identified Black patients: mortality 6.2 against 10.2 per cent, a 43 per cent relative reduction, NNT 25 over ten months	yes, both components	yes	tens of euro
Vericiguat	VICTORIA: HR 0.90, no mortality benefit	no	no	thousands of euro

Devices. An implantable defibrillator for primary prevention of sudden death: SCD-HeFT, 2,521 patients, mortality 22 against 29 per cent, hazard ratio 0.77, number needed to treat 14 over five years; DANISH, 1,116 patients with non-ischaemic cardiomyopathy, found no all-cause mortality benefit, hazard ratio 0.87, p=0.28. Both must be printed: the benefit in non-ischaemic cardiomyopathy is disputed. Device cost tens of thousands of euro plus implantation. Cardiac resynchronisation therapy with left bundle branch block and a wide QRS: COMPANION and CARE-HF, with a mortality reduction of about 36 per cent in CARE-HF and a number needed to treat of 9 over 29 months, at tens of thousands of euro. A left ventricular assist device: REMATCH gave one-year survival of 52 against 25 per cent against medical therapy in transplant-ineligible patients, at hundreds of thousands of euro and upward.

The four cheap pillars together carry the measured mortality benefit in heart failure with reduced ejection fraction. An ACE inhibitor with a beta blocker and spironolactone costs tens of euro a patient-year at generic prices and reduces mortality by well over a third in combination. Adding sacubitril/valsartan and an SGLT2 inhibitor adds a further measured reduction at 20 to 100 times the cost.

Simple means. Exercise training: HF-ACTION randomised 2,331 patients and gave a hazard ratio of 0.93 for all-cause mortality or hospitalisation, p=0.13, not significant unadjusted, and 0.89, p=0.03, after prespecified adjustment, with consistent improvements in exercise capacity and quality of life. The null primary result is printed as it stands. Cochrane reviews of exercise-based rehabilitation report reduced heart-failure-specific hospitalisation and improved quality of life with no clear all-cause mortality benefit.

Salt and fluid restriction is long-standing advice, and the trial evidence is weak and inconsistent. SODIUM-HF randomised 806 patients to below 1,500 mg of sodium a day and found no reduction in death, cardiovascular hospitalisation or emergency visits, hazard ratio 0.89, p=0.53, with a small quality-of-life improvement. Grade CONTESTED. This contradicts decades of standard advice.

Daily weight monitoring to catch fluid accumulation early costs a bathroom scale and is recommended in all guidelines, and the trial evidence of benefit is weak: the telemonitoring trials TIM-HF and BEAT-HF are mostly null. Leg elevation and compression for peripheral oedema are symptomatic with no outcome data. Alcohol abstinence in alcoholic cardiomyopathy gives substantial recovery in a large minority. Smoking cessation has no heart-failure-specific randomised data and the benefit is inferred from coronary disease. Sitting upright during acute breathlessness reduces the work of breathing; universal practice, unquantified.

Furosemide is the one indispensable drug and cannot be improvised. It is cheap, off-patent and on the Essential Medicines List at €2 to €15 a year; the UNICEF indicative price in October 2026 for injection 10 mg/mL in 2 mL ampoules was US$2.05 for a box of ten on one page of the catalogue and US$1.84 on another. Decompensated heart failure cannot be managed without a diuretic, and that requires a pharmaceutical supply chain.

Gaps. GBD publishes no heart failure death count and no DALY figure, because heart failure is not a GBD level-3 cause. The syndrome’s global mortality burden is therefore not measured directly anywhere; it is distributed across other causes. For a condition affecting about 64 million people this is one of the largest holes in the global data, and it is part of the seventeen-condition gap set out in this chapter’s introduction. The 64 million figure comes from a 2023 review that does not state its data year or dataset. The split between reduced and preserved ejection fraction is not given in that review, and the 50 per cent figure comes from registries with selection bias toward hospitalised patients. Defibrillator benefit in non-ischaemic cardiomyopathy is unresolved, SCD-HeFT positive and DANISH null. Sodium restriction is

unresolved, SODIUM-HF null against universal guideline advice. Exercise training's primary endpoint in HF-ACTION was not significant and guidelines recommend it anyway. Whether the four-pillar effect sizes are additive or overlapping is modelled rather than measured: no trial has randomised all four simultaneously against none. Most trial populations are predominantly male, white and under 75, while the median real-world patient is older and carries more comorbidity than any trial cohort.

> **Depth.** Starts in: the heart. Size: 12 cm†; depth +13.46. First complaint: about 70 years († onset about age 70); time depth 52.74. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Heart failure with preserved ejection fraction (ICD-11 BD1Z)

What it is. The heart's pumping fraction looks normal but the stiff ventricle cannot fill properly at normal pressures. The person is breathless and swollen with an ejection fraction of 50 per cent or more. It is now about half of all heart failure.

Measured. Roughly 50 per cent of all heart failure, and rising as a proportion, from registry series. Against the roughly 64 million people with heart failure that implies something of the order of 30 million people, but no source publishes a global count for preserved ejection fraction and the arithmetic is not presented here as a measurement.

No GBD death count and no DALY figure, because heart failure is not a GBD level-3 cause. The age pattern is markedly older than reduced ejection fraction: trial mean age 70 to 75, and a majority female, unlike reduced ejection fraction. Mortality is comparable in most registries, around 50 per cent at five years, with a larger share of deaths non-cardiovascular. Incidence is rising both absolutely and as a share of heart failure, tracking obesity, hypertension, diabetes and ageing.

Where it starts. Hypertension is the dominant antecedent, present in about 80 to 90 per cent of cohorts; per 10 mmHg systolic reduction, heart failure of all types carries a relative risk of 0.72. Obesity, and visceral adiposity in particular, is now regarded as a driver rather than a comorbidity, and the obese phenotype is distinct. Diabetes, chronic kidney disease, atrial fibrillation present in up to 65 per cent, anaemia and sleep-disordered breathing all contribute. Transthyretin cardiac amyloidosis accounts for roughly 10 to 15 per cent of cases in men over 60 referred with left ventricular hypertrophy, and is a recognised and specifically treatable subgroup. The condition is more common in women and the reason is not established.

This is a diagnosis of exclusion with no agreed positive test, and different scoring systems — H2FPEF and HFA-PEFF — classify different people. It is widely held to be several diseases pooled under one label, and the subgroups have not been separated prospectively. Whether diastolic stiffness is the primary lesion or a consequence of systemic extracardiac disease is unresolved. Why almost every drug that works in reduced ejection fraction failed here is unexplained, and that is the central unanswered question in the field.

Cure status. Transthyretin cardiac amyloidosis subgroup, roughly 10 to 15 per cent: CONTROLLABLE. Remaining preserved-ejection-fraction disease: CONTROLLABLE in the sense that SGLT2 inhibitors reduce hospitalisation while taken, and no treatment has been shown to reduce mortality

For decades no treatment reduced mortality. Candesartan in CHARM-Preserved, irbesartan in I-PRESERVE, perindopril in PEP-CHF, spironolactone in TOPCAT and sacubitril/valsartan in PARAGON-HF, hazard ratio 0.87, p=0.06, all failed their primary endpoints. The SGLT2 inhibitors are the first class to succeed, and they reduce hospitalisation and not mortality. No treatment has been shown to reduce mortality in preserved ejection fraction, and that is the honest statement of the evidence.

In the transthyretin amyloidosis subgroup tafamidis is a genuine exception: ATTR-ACT, 441 patients, reduced all-cause mortality from 42.9 to 29.5 per cent, hazard ratio 0.70, and reduced cardiovascular hospitalisation. It costs hundreds of thousands of euro a year, is on patent and is not on the Essential Medicines List. A genuine mortality benefit in a defined subgroup at an extreme price. Rate control or ablation of atrial fibrillation improves symptoms substantially in the large overlap group.

Prevention.

Blood pressure lowering — STRONG, and the main lever. Heart failure relative risk 0.72 per 10 mmHg systolic. SPRINT found a 38 per cent reduction in incident heart failure with intensive targets.

SGLT2 inhibitors in diabetes — STRONG for preventing incident heart failure, about 30 per cent fewer heart failure hospitalisations in EMPA-REG, CANVAS and DECLARE.

Weight management — MODERATE, the grade limited by the absence of outcome trials for prevention. *Physical activity — MODERATE*. *Atrial fibrillation management — MODERATE*.

No trial has ever used heart failure with preserved ejection fraction as the primary prevented endpoint. Every figure above comes from a trial with a different primary purpose.

Treatment.

Drug	Effect size	EML	Off-patent	Cost per patient-year
SGLT2 inhibitor — the only class with a positive primary endpoint	EMPEROR-Preserved, empagliflozin, 5,988 patients with ejection fraction above 40 per cent: composite of cardiovascular death or heart failure hospitalisation 13.8 against 17.1 per cent, HR 0.79 (0.69–0.90), NNT 31 over 26 months, driven by hospitalisation with no significant reduction in cardiovascular death, HR 0.91, or all-cause death. DELIVER, dapagliflozin, 6,263 patients: HR 0.82 (0.73–0.92), same pattern	yes, dapagliflozin	no	hundreds to thousands of euro branded; tens to hundreds of euro generic
Loop diuretic, furosemide	Symptom relief; no outcome trial	yes	yes	a few to tens of euro
Spironolactone	TOPCAT, 3,445 patients: primary endpoint not met overall, HR 0.89, p=0.14; a much larger effect in the Americas than in Russia and Georgia, where event rates were implausibly low and drug-metabolite testing suggested some patients never took the drug. The regional discrepancy is unresolved and the trial is cited both ways	yes	yes	a few to tens of euro
Sacubitril/valsartan	PARAGON-HF, 4,822 patients: HR 0.87 (0.75–1.01), p=0.06, primary endpoint not met; benefit suggested in lower-ejection-fraction and female subgroups	yes	no	thousands of euro
Tafamidis, amyloidosis subgroup only	ATTR-ACT: all-cause mortality 29.5 against 42.9 per cent, HR 0.70	no	no	hundreds of thousands of euro
Candesartan, irbesartan, perindopril, digoxin, nitrates, sildenafil	All failed their trials: CHARM-Preserved, I-PRESERVE, PEP-CHF, the DIG ancillary study, NEAT-HFpEF, RELAX	Most yes; **sildenafil is NOT on the 24th List in any form**	Most yes	a few to tens of euro
Semaglutide, obesity phenotype	STEP-HFpEF, 529 patients: large improvements in symptom score, KCCQ up 7.8 points, and in six-minute walk distance; not powered for mortality	no	no	thousands to tens of thousands of euro

Treatment of the comorbidities — hypertension, atrial fibrillation, obesity, anaemia, sleep apnoea — is the practical substance of care, and all of it uses the cheap off-patent drugs listed in the hypertension and atrial fibrillation entries.

Simple means. Exercise training is the best-evidenced non-drug measure here. Meta-analyses report improvements in peak oxygen uptake of roughly 2.0 to 2.7 mL/kg/min and in six-minute walk distance of about 30 to 60 m, consistently larger relative to drug effects than in reduced ejection fraction. There are no mortality data. Weight loss in obese patients: caloric restriction plus exercise, in a 100-patient trial by Kitzman and colleagues, improved peak oxygen uptake and quality of life, with the combination best, and needs no equipment. Walking is the lowest-cost form of that. A diuretic remains indispensable for congestion and cannot be improvised. Salt reduction is plausible given the hypertension dependence, and SODIUM-HF, in a mixed population, was null: grade CONTESTED. Sleeping propped up, leg elevation and compression for oedema are symptomatic and unquantified.

Gaps. No GBD death count and no DALY figure exist for heart failure as a syndrome, and therefore none for the preserved-ejection-fraction half of it; this entry is part of the seventeen-condition gap in this chapter's introduction. No global prevalence figure for preserved ejection fraction exists either — the 50 per cent share is from registries. No treatment reduces mortality, 25 years after the syndrome was named, and the SGLT2 benefit is hospitalisation only. TOPCAT's regional discrepancy is unresolved and the trial is cited as both positive and negative depending on which population is treated as valid. There is no agreed diagnostic standard, and the H2FPEF and HFA-PEFF scores disagree on who has the condition, which makes prevalence figures and trial populations non-comparable. The hypothesis that this is several diseases has not been tested prospectively. Why every drug class effective in reduced ejection fraction failed here is unexplained. Cardiac amyloidosis is likely still under-diagnosed within these cohorts, and the 10 to 15 per cent figure comes from referral series with selection bias. Sildenafil is not on the 24th Model List in any form, and any statement to the contrary is wrong.

> **Depth.** Starts in: the left ventricle. Size: 10 cm†; depth +13.29. First complaint: about 75 years († onset about age 75); time depth 52.80. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status, given by stratum: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Rhythm

Atrial fibrillation (ICD-11 BC81.3)

What it is. The upper chambers of the heart quiver instead of beating, so the pulse is fast and irregular. Blood pools and can clot, and the clot can travel to the brain. It is the commonest sustained heart rhythm disorder.

Measured. From the GBD 2023 Results Tool, cause category atrial fibrillation and atrial flutter, as analysed in the International Journal of Stroke in 2026: prevalence in 2023, 59,045,058 cases; incidence, 5,021,980 new cases; deaths, 377,258; DALYs, 9,265,726. The burden rose sharply in absolute terms since 1990, which the source states qualitatively without giving the 1990 figures.

In INTERSTROKE, cardiac causes — predominantly atrial fibrillation — carried an odds ratio of 3.17 (2.68–3.75) and an attributable risk of 9.1 per cent for all stroke, and were associated with ischaemic stroke only, not with intracerebral haemorrhage. Lifetime risk from age 55 is roughly one in three in European-ancestry populations. The condition is rare below 50 and prevalence roughly doubles per decade thereafter, exceeding 10 per cent above age 80. Age-standardised rates are highest in high-income North America and western Europe, and part of that is detection intensity rather than true incidence. Atrial fibrillation multiplies stroke risk about fivefold overall and accounts for roughly 20 to 30 per cent of all ischaemic strokes.

Where it starts. Age is the strongest determinant. Hypertension carries an attributable risk for atrial fibrillation of roughly 20 per cent, the largest single modifiable contributor. Each 5 unit rise in body mass index raises risk about 10 to 29 per cent across cohorts. Alcohol is dose-dependent, each additional daily drink raising risk about 8 per cent. The abstinence trial by Voskoboinik and colleagues randomised 140 moderate drinkers with atrial fibrillation. Recurrence was 53 against 73 per cent and the atrial fibrillation

burden was 0.5 against 1.2 per cent of time, with abstinence against continued drinking. That is a randomised result, and the clearest lifestyle effect in the condition. Obstructive sleep apnoea is associated with incidence and with recurrence after ablation. Endurance exercise shows a U-shaped relation: very high-volume endurance athletes carry two- to fivefold higher risk while moderate activity is protective. Hyperthyroidism, valvular disease, heart failure, chronic kidney disease, diabetes and smoking all contribute. Over a hundred genetic loci have been identified, the strongest near PITX2 on 4q25.

What initiates a given episode at a given moment is not predictable. The relation between atrial fibrillation and stroke is not a simple pump-failure story: anticoagulation prevents stroke, and stroke risk does not track fibrillation burden closely, and patients with device-detected subclinical fibrillation have far lower stroke rates than the clinical risk scores predict. NOAH-AFNET 6 and ARTESiA both tested anticoagulation for device-detected subclinical fibrillation with divergent results: NOAH stopped early for futility and bleeding, ARTESiA showed stroke reduction with more major bleeding. Whether atrial fibrillation causes the stroke or marks an atrial myopathy that causes both is an open question with direct treatment consequences.

Cure status. CONTROLLABLE in general. Paroxysmal atrial fibrillation treated by catheter ablation: CURABLE in 75 per cent free of arrhythmia without antiarrhythmic drugs in the second worldwide survey, 2003 to 2006, with success definitions that vary across studies. Atrial fibrillation secondary to hyperthyroidism, to alcohol, or to an accessory pathway or atrial tachycardia driving it: CURABLE by removing the cause.

The ablation figures come from a compilation of the Heart Rhythm Society consensus document and the worldwide surveys. Early studies, per the 2017 consensus: paroxysmal fibrillation, 60 per cent or better single-procedure success and 70 per cent or better with multiple procedures; persistent fibrillation, 30 per cent or less single-procedure and 50 per cent or better with multiple. The first worldwide survey, covering procedures from 1995 to 2002 across 181 centres, gave 52 per cent successful and symptom-free without antiarrhythmic drugs, 75.5 per cent successful including those still on drugs, with 24.3 per cent needing a second procedure and 3.1 per cent a third; it did not report by fibrillation type. The second worldwide survey, covering 2003 to 2006, gave success without antiarrhythmic drugs of 75 per cent for paroxysmal, 65 per cent for persistent and 63 per cent for longstanding persistent fibrillation, with 70 per cent overall without drugs and 80 per cent including drug users. Some centres report 80 to 85 per cent for first ablations and 95 per cent for second procedures, and the compiling source notes that these are not measured consistently and that success definitions, follow-up length and monitoring method vary across all these studies, so the figures are not directly comparable. That caveat belongs with any ablation success rate.

What ablation does and does not do. CABANA, with 2,204 patients randomised to ablation or drug therapy, did not meet its primary composite endpoint, hazard ratio 0.86, p=0.30, though it reduced recurrence and improved quality of life. CASTLE-AF, 363 patients with atrial fibrillation and heart failure, found ablation reduced death or heart failure hospitalisation, hazard ratio 0.62. EAST-AFNET 4, 2,789 patients, found early rhythm control, whether by drugs or ablation, reduced cardiovascular death, stroke or hospitalisation, hazard ratio 0.79. So ablation abolishes the arrhythmia in a majority of paroxysmal cases, which is a cure of the rhythm disorder, while the stroke risk and the anticoagulation decision are not abolished with it: successful ablation does not license stopping anticoagulation in a patient with a high stroke-risk score on current evidence.

Prevention.

Blood pressure control — MODERATE. Hypertension is the largest modifiable contributor, attributable risk about 20 per cent.

Alcohol reduction or abstinence — STRONG for recurrence, and randomised. Recurrence 53 against 73 per cent with abstinence.

Weight loss — MODERATE, with observational support. The LEGACY and ARREST-AF studies, registry and observational designs with structured weight management, reported substantially higher arrhythmia-free survival with 10 per cent or more weight loss.

Treating obstructive sleep apnoea — WEAK. Observational support for reduced recurrence; no adequately powered randomised trial.

Moderate physical activity — MODERATE. *Avoiding extreme endurance training volumes — WEAK*, observational only.

Treatment. Almost all the mortality benefit lies in anticoagulation.

Drug	Effect size	EML	Off-patent	Cost per patient-year
Warfarin	Against placebo or control: stroke reduced about 64 per cent, RR 0.36; all-cause mortality reduced 26 per cent, Hart and colleagues, Annals of Internal Medicine 2007 meta-analysis. NNT about 25 a year in high-risk fibrillation to prevent one stroke	yes	yes	a few to tens of euro for the drug, but INR monitoring costs tens to hundreds of euro a year and is the real constraint
Aspirin	Stroke reduced only about 22 per cent against control; clearly inferior to warfarin and no longer recommended for stroke prevention in atrial fibrillation	yes	yes	a few euro
Apixaban	ARISTOTLE, 18,201 patients, against warfarin: stroke or systemic embolism 1.27 against 1.60 per cent a year, HR 0.79; all-cause mortality HR 0.89; major bleeding HR 0.69; intracranial haemorrhage HR 0.42	yes, added 2019	generics from 2026 in several markets	€500–3,000 branded; €30–150 early generic
Dabigatran	RE-LY, 18,113 patients: 150 mg gave stroke HR 0.66 against warfarin	yes	partly	hundreds to thousands of euro; generic lower
Rivaroxaban	ROCKET-AF, 14,264 patients: HR 0.88, non-inferior	yes	generics available	hundreds to thousands of euro branded; tens to hundreds of euro generic
Beta blocker, rate control	Symptom and rate control; no mortality benefit in atrial fibrillation itself	yes	yes	a few to tens of euro
Digoxin, rate control	Rate control at rest; observational signals of harm at higher serum levels, disputed	yes	yes	a few to tens of euro
Amiodarone, rhythm control	The most effective antiarrhythmic for maintaining sinus rhythm; thyroid, pulmonary, hepatic and ocular toxicity limit long-term use; no mortality benefit	yes	yes	tens of euro
Flecainide, propafenone, sotalol, dronedarone	Rhythm control; contraindicated with structural disease, per the CAST trial	Sotalol and flecainide partly	Mostly yes	tens to hundreds of euro

Rate against rhythm control. AFFIRM, with 4,060 patients, and RACE found no mortality difference between rate control and rhythm control with the drugs of that era. EAST-AFNET 4, in 2020, found early rhythm control better, hazard ratio 0.79. The two results are reconciled by timing and by ablation availability rather than contradicted.

Procedures. Catheter ablation costs €8,000 to €25,000 a procedure in Europe and the United States, year not stated in the source and requires an electrophysiology laboratory; the success rates are above. Left atrial appendage occlusion, in PROTECT-AF and PREVAIL, was non-inferior to warfarin for stroke prevention in selected patients, at tens of thousands of euro. Ablation of the atrioventricular node with pacing gives symptom control for an uncontrollable rate and commits the patient to pacemaker dependence.

Warfarin is the single most important off-patent drug in this condition: stroke reduced about 64 per cent, mortality about 26 per cent, drug cost a few to tens of euro a year. Its constraint is not price but INR monitoring. Where point-of-care INR testing exists, warfarin delivers nearly the whole benefit of a direct oral anticoagulant at a fraction of the price, and the measured advantage of the newer drugs is chiefly in intracranial haemorrhage, hazard ratio 0.42 for apixaban, and in not needing monitoring.

Simple means. Pulse-taking is the cheapest cardiovascular screening test in existence. Atrial fibrillation can be detected by a finger on the wrist — an irregularly irregular pulse — with no equipment at all, and pulse palpation has a sensitivity for atrial fibrillation of roughly 87 to 97 per cent with a specificity of 70 to 81 per cent in screening studies. It detects the condition that causes 20 to 30 per cent of ischaemic strokes.

Alcohol abstinence gives recurrence of 53 against 73 per cent, randomised, and nothing is required but stopping. Weight loss of 10 per cent or more is associated with substantially higher arrhythmia-free survival. Blood pressure control by salt reduction, weight loss and exercise acts as in the hypertension entry. Vagal manoeuvres — Valsalva, cold water to the face — terminate some supraventricular tachycardias and do not terminate atrial fibrillation; that is worth stating plainly, because the error is common.

Anticoagulation cannot be improvised, and that is where this condition needs an industrial chain: warfarin plus INR measurement, or a direct oral anticoagulant. Without it the stroke risk stands. Rate control with a cheap beta blocker relieves symptoms and does nothing for stroke.

Gaps. Prevalence figures depend heavily on detection intensity. Screening with wearables finds large amounts of subclinical fibrillation whose clinical meaning is unsettled — STROKESTOP, mSToPS, Apple Heart, LOOP — and the 59 million figure is a modelled estimate from diagnosed disease. Subclinical device-detected fibrillation is unresolved and directly consequential: NOAH-AFNET 6 and ARTESiA gave divergent answers on whether to anticoagulate. Ablation success rates are not comparably measured; definitions of success, monitoring intensity and follow-up duration all vary, and the compiling source says so explicitly, so a single quoted percentage is not interpretable without its definition. Whether successful ablation permits stopping anticoagulation is not established by trial. CABANA missed its primary endpoint while CASTLE-AF and EAST-AFNET 4 were positive; the populations differ and the field cites selectively. The causal relation between atrial fibrillation and stroke against a shared atrial myopathy is open. Digoxin harm signals are observational and confounded by indication.

> **Depth.** Starts in: the atrium. Size: 5 cm†; depth +12.66. First complaint: about 70 years († onset about age 70); time depth 52.74. One untreated course: no number († often permanent).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Other arrhythmias (ICD-11 BC63–BC9Z)

What it is. Any heartbeat that is too fast, too slow or out of sequence other than atrial fibrillation. Some are harmless extra beats. Others stop the circulation within seconds.

Measured. GBD publishes no separate burden figures for arrhythmias other than atrial fibrillation and flutter. No global prevalence, death or DALY figure exists for supraventricular tachycardia, ventricular tachycardia, heart block or sick sinus syndrome. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Supraventricular tachycardia of the atrioventricular nodal reentrant and accessory-pathway types has a prevalence of roughly 2.25 per 1,000 population and an incidence of 35 per 100,000 person-years, from the Marshfield epidemiology study of 1998. The Wolff-Parkinson-White pattern on an electrocardiogram has

a prevalence of 1 to 3 per 1,000, with a sudden death risk of roughly 0.1 per cent a year in those carrying the pattern and lower in asymptomatic individuals. Pacemaker implantation rates for complete heart block and bradyarrhythmia run roughly 500 to 1,200 per million population a year in high-income countries. Ventricular arrhythmia burden is counted within cardiac arrest and ischaemic heart disease. Nodal reentrant tachycardia presents typically between 20 and 50 and more often in women; accessory-pathway tachycardia presents younger; bradyarrhythmias and heart block rise steeply with age. Pacemaker and ablation rates differ by a factor of 50 or more between high- and low-income countries, which reflects access rather than disease frequency.

Where it starts. Accessory pathways and dual atrioventricular nodal physiology are congenital anatomical variants present from birth. Structural heart disease, and prior infarction scar in particular, is the commonest substrate for sustained ventricular tachycardia. The inherited channelopathies: long QT syndrome, prevalence about 1 in 2,000, with more than fifteen genes of which KCNQ1, KCNH2 and SCN5A are commonest; Brugada syndrome, about 1 in 2,000 and higher in southeast Asia; catecholaminergic polymorphic ventricular tachycardia; short QT syndrome. Drugs that prolong the QT interval make a long and clinically important list. Electrolyte disturbance — low potassium, magnesium or calcium — contributes, as do thyroid disease, caffeine and stimulants, alcohol, fever and sleep deprivation as triggers of benign ectopy and of some tachycardias. Degenerative fibrosis of the conduction system causes most acquired heart block. Infective causes include Chagas disease, Lyme carditis, diphtheria, rheumatic carditis and viral myocarditis.

Why an accessory pathway present since birth conducts dangerously in one person and never in another is not predictable. Risk stratification in asymptomatic Wolff-Parkinson-White, Brugada and long QT syndrome is weak: most sudden deaths in these conditions occur in people who would not have been selected for a defibrillator by current criteria, and most people meeting the criteria never have an event. The timing of a lethal ventricular arrhythmia is unpredictable even with full knowledge of the substrate.

Cure status. Pathway-dependent tachycardias — nodal reentrant tachycardia, accessory pathway, atrial tachycardia, typical atrial flutter, idiopathic outflow-tract ventricular tachycardia: CURABLE. Inherited channelopathies: CONTROLLABLE. Heart block and ventricular arrhythmia on a structural substrate: CONTROLLABLE. Arrhythmia from a reversible cause — electrolytes, thyroid, drug, fever: CURABLE by removing the cause.

Catheter ablation of atrioventricular nodal reentrant tachycardia gives acute success of 96 to 99 per cent, recurrence of 2 to 5 per cent, and a risk of requiring a pacemaker from atrioventricular block under 1 per cent, lower still with modern cryoablation. That is a single procedure that permanently removes the condition. Ablation of an accessory pathway gives acute success of 93 to 98 per cent and recurrence of 3 to 8 per cent, and permanently abolishes both the arrhythmia and the sudden-death risk. Ablation of atrial tachycardia and typical atrial flutter gives acute success above 95 per cent and long-term freedom around 90 per cent, among the most reliably curative procedures in medicine. Idiopathic outflow-tract ventricular tachycardia in a structurally normal heart has an ablation success of 80 to 95 per cent and is usually curative.

A pacemaker for complete heart block is not a cure; it substitutes permanently for the failed conduction system, and it restores normal life expectancy in isolated heart block. A defibrillator is not a cure; it terminates events and leaves the substrate. In the channelopathies beta blockade reduces events in long QT syndrome, with nadolol and propranolol most effective, and a defibrillator terminates them; nothing removes the mutation.

Prevention.

Avoiding QT-prolonging drug combinations — STRONG, and the single most actionable measure; drug-induced torsades de pointes is substantially preventable by prescribing review.

Correcting potassium and magnesium — STRONG.

Beta blockade in diagnosed long QT syndrome — STRONG: cardiac events reduced by roughly 60 to 80 per cent in registry cohorts.

Family screening after a sudden cardiac death in a young person — MODERATE for identifying at-risk relatives; a diagnosis is found in roughly 20 to 50 per cent of first-degree relatives in specialist series.

Avoiding competitive extreme exertion in diagnosed catecholaminergic polymorphic ventricular tachycardia and some long QT genotypes — MODERATE, and the restriction advice has loosened as data accumulated.

Preventing rheumatic fever and Chagas disease — STRONG where these cause conduction disease.

Reducing caffeine, alcohol and stimulants — WEAK for benign ectopy, and CONTESTED: randomised caffeine studies have generally not shown increased ectopy.

Treatment.

Intervention	Effect	EML	Off-patent	Cost
Adenosine, acute termination of supraventricular tachycardia	Terminates nodal reentrant and accessory-pathway tachycardia in about 90 per cent of episodes within seconds	yes	yes	a few to tens of euro a dose
Verapamil or diltiazem	Effective acutely and as prophylaxis; contraindicated in Wolff-Parkinson-White with pre-excited atrial fibrillation	yes	yes	a few to tens of euro a year
Beta blocker	First-line prophylaxis for most supraventricular tachycardia, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and ectopy	yes	yes	a few to tens of euro a year
Amiodarone	The most effective antiarrhythmic; substantial cumulative toxicity; no mortality benefit as primary prophylaxis, since the amiodarone arm of SCD-HeFT was no better than placebo	yes	yes	tens of euro a year
Lidocaine, acute ventricular arrhythmia		yes	yes	a few to tens of euro a dose
Flecainide or propafenone	Effective in structurally normal hearts; increased mortality after myocardial infarction in the CAST trial, a landmark negative result	partly	yes	tens to hundreds of euro a year
Magnesium sulfate, torsades de pointes	First-line and rapidly effective	yes, section 5.1.1, with a restriction to eclampsia and severe pre-eclampsia on the Model List	yes	€1–5 a dose. UNICEF indicative price October 2026: US$33.11 for 100 ampoules of 5 g in 10 mL, about US$0.33 an ampoule
Atropine or isoprenaline, acute bradycardia		yes, atropine	yes	a few to tens of euro a dose
Catheter ablation	Nodal reentrant tachycardia 96–99 per cent, accessory pathway 93–98 per cent, atrial flutter above 95 per cent	n/a	n/a	thousands to tens of thousands of euro a procedure
Pacemaker	Restores normal life expectancy in isolated heart block	n/a	n/a	thousands to tens of thousands of euro device plus implantation
Implantable defibrillator	Terminates ventricular arrhythmia; SCD-HeFT HR 0.77, NNT 14 over five years; DANISH null in non-ischaemic cardiomyopathy	n/a	n/a	tens of thousands of euro

Catheter ablation of accessory pathways and of nodal reentrant tachycardia is one of the clearest genuine cures in all of medicine: a single procedure, success above 95 per cent, permanent, and in the Wolff-Parkinson-White case it removes a sudden-death risk.

Simple means. Vagal manoeuvres for supraventricular tachycardia cost nothing and terminate a frightening arrhythmia in a substantial minority. Standard Valsalva terminates roughly 20 to 40 per cent of episodes, and the modified Valsalva — supine with leg elevation immediately after straining — raised success to 43 against 17 per cent in the randomised REVERT trial of 428 patients. It is a technique rather than a device. It does not work for atrial fibrillation. Carotid sinus massage and cold water immersion of the face, the diving reflex, terminate some supraventricular tachycardias, and the cold-water method is used in infants. Pulse-taking detects both tachy- and bradyarrhythmia with no equipment. Correcting potassium by diet — fruit, vegetables, legumes — reduces ectopy risk where the deficiency is dietary. Stopping the offending drug is free and is the treatment for drug-induced arrhythmia. A precordial thump for witnessed monitored pulseless ventricular tachycardia has success rates under 2 per cent in most series and is no longer recommended except in witnessed monitored arrest with no defibrillator immediately available.

Everything else here needs a supply chain. Adenosine, amiodarone, pacemakers, defibrillators and ablation cannot be improvised. For lethal arrhythmia, bystander CPR is the only no-equipment intervention, and it buys time rather than terminating the rhythm.

Gaps. No global burden figures exist for arrhythmias other than atrial fibrillation and flutter — no prevalence, no deaths, no DALYs — and this entry is part of the seventeen-condition gap in this chapter's introduction. It is a real hole: conditions curable by a single ablation procedure have no measured global prevalence. Risk stratification in asymptomatic Wolff-Parkinson-White, Brugada and long QT syndrome is weak; most events occur outside the criteria and most people inside the criteria never have an event, and guidelines differ substantially between societies. Ablation success rates come largely from specialist-centre series with publication bias toward good results, and population-level success rates are not measured. Caffeine and ectopy is contested: observational association, randomised studies largely null. Pacemaker and ablation rates differ fiftyfold internationally, and whether the low-rate countries carry untreated disease or lower incidence is not measured. Defibrillator benefit in non-ischaemic cardiomyopathy is unresolved, SCD-HeFT against DANISH.

> **Depth.** Starts in: an extra conduction pathway (inborn). Size: 1 mm†; depth +9.10. First complaint: about 15 years († onset about age 15); time depth 51.34. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

The arteries of the brain

Ischaemic stroke (ICD-11 8B11)

What it is. A clot blocks an artery in the brain and the tissue beyond it dies within minutes to hours. The person suddenly loses speech, strength, vision or balance on one side. It is the commonest kind of stroke.

How common a share it is cannot be given as a single number. GBD's stroke series puts ischaemic stroke at roughly 62 to 65 per cent of incident strokes globally and about 87 per cent in high-income countries. A figure of about four in five is widely carried, and another chapter of this book gives roughly 70 to 85 per cent of cases†. Three figures circulate for one quantity and all three stand.

Measured. All stroke deaths in 2023: 6.8 million, about 11 per cent of all deaths and rank 2 of all causes, on WHO's Global Health Estimates; 6.79 million on GBD 2023. The two agree closely here, unlike ischaemic heart disease.

All stroke DALYs in 2023: **157 million, 95 per cent uncertainty interval 141 to 172, rank 3 of all causes globally**, from GBD 2023. A figure of 160 million also circulates and is the WHO figure for 2021; it is named here beside the GBD figure rather than printed instead of it. These are not two measurements of the

same thing disagreeing: they are two different sources with different reference years, and 157 million is the GBD 2023 figure this book uses. Stroke YLDs in 2023: 16.7 million (12.0–21.2), rank 17. The age-standardised death rate for all stroke in GBD 2021 was 87.4 per 100,000, rank 3. Ischaemic stroke is the third leading cause of cardiovascular DALYs in GBD 2023, behind ischaemic heart disease and intracerebral haemorrhage.

Global incident strokes run at roughly 12 million a year. The number of stroke survivors alive is given as about 101 million in the GBD stroke capstone and as 93.8 million on the WHO stroke fact sheet for 2021 data; the two differ by 7.2 million for the same quantity and both stand. Incidence roughly doubles each decade after 55, and a rising share of strokes occurs under 55, especially in low- and middle-income countries. Age-standardised incidence is highest in east Asia, eastern Europe and central Asia, and over 85 per cent of stroke deaths occur in low- and middle-income countries. Age-standardised stroke mortality has fallen substantially since 1990 while absolute numbers have risen. Lifetime risk of stroke from age 25 is 24.9 per cent globally on the GBD 2016 lifetime-risk analysis, which WHO renders as one in four adults.

Where it starts. INTERSTROKE is the reference study and the full table sits at the front of this chapter. The combined attributable risk for ischaemic stroke specifically is 91.5 per cent (95 per cent CI 89.4–93.2). Ranked by attributable risk for all stroke, with the odds ratio in brackets. Hypertension 47.9 per cent (2.98). Physical inactivity 35.8 per cent (0.60 for activity). ApoB/ApoA1 ratio 26.8 per cent (1.84). Diet 23.2 per cent (0.60 for a good diet). Waist-to-hip ratio 18.6 per cent (1.44). Psychosocial factors 17.4 per cent (2.20). Current smoking 12.4 per cent (1.67). Cardiac causes 9.1 per cent (3.17). Alcohol 5.8 per cent (2.09 for heavy intake). Diabetes 3.9 per cent (1.16). This book prints the published one-decimal values; the same table appears elsewhere in the book rounded to integers, and the one-decimal values are the published ones.

The ApoB/ApoA1 ratio and atrial fibrillation were associated with ischaemic stroke in all regions and are the two factors specific to this subtype; neither was associated with intracerebral haemorrhage. Regional variation is large: smoking attributable risk from 4.5 per cent in Africa to 18 per cent in western Europe, North America and Australia; physical inactivity from 4.7 per cent in Africa to 59.9 per cent in China. Waist-to-hip ratio associations were largest in western Europe, North America, Australia and parts of Asia, and larger in women; cardiac causes carried larger odds in women.

Further contributions. Atrial fibrillation multiplies stroke risk about fivefold and causes 20 to 30 per cent of ischaemic strokes. Symptomatic carotid stenosis of 70 per cent or more carries a two-year stroke risk of about 26 per cent untreated, from NASCET. Household air pollution attributes 23 per cent of its 2.9 million annual deaths to stroke, which is about 12 per cent of all stroke deaths worldwide; ambient air pollution’s 4.2 million premature deaths are 68 per cent ischaemic heart disease and stroke together. Sickle cell disease, patent foramen ovale in young cryptogenic stroke, cervical artery dissection, vasculitis, antiphospholipid syndrome and Fabry disease are less common causes.

About 25 per cent of ischaemic strokes remain cryptogenic after full investigation. The higher diet-score risk observed in south Asia in INTERSTROKE is a reversal the paper does not explain. Why the same degree of carotid stenosis causes stroke in one person and not another is not predictable. The mechanism of the psychosocial association is not established and the measurement is self-reported in a case-control design. Why stroke incidence is rising in people under 55 is not explained by the measured risk factors.

Cure status. CONTROLLABLE as a disease state. The deficit already sustained after the acute event: RELIEF ONLY, since it is permanent tissue loss.

Nothing removes the predisposition. Reperfusion within the therapeutic window salvages threatened but not yet dead tissue, which is why the effect size collapses with time. The infarcted tissue does not regenerate; recovery after the acute phase is reorganisation of surviving networks, not repair. Secondary prevention reduces recurrence while taken.

The acute treatments are genuinely effective and strictly time-dependent. Intravenous thrombolysis with alteplase within 4.5 hours has a number needed to treat of about 10 within three hours for an improved modified Rankin outcome, rising to about 20 at three to 4.5 hours, with symptomatic intracranial haemorrhage rising from about 0.4 to about 6 per cent. Mechanical thrombectomy for large-vessel occlusion has a number needed to treat of 2.6 for any reduction in disability and about 5 for functional independence, from the HERMES meta-analysis of five trials — MR CLEAN, ESCAPE, EXTEND-IA,

SWIFT PRIME and REVASCAT — covering 1,287 patients, odds ratio 2.49 for improved functional outcome. That is among the lowest numbers needed to treat of any procedure in medicine. It requires a catheter suite, an interventional team and imaging within hours, and is therefore unavailable to most of the world's population.

Prevention.

Blood pressure lowering — STRONG, and the largest single lever. Per 10 mmHg systolic reduction, stroke relative risk 0.73 (0.68–0.77), a 27 per cent reduction. Hypertension carries the largest INTERSTROKE attributable risk at 47.9 per cent.

Salt reduction and salt substitution — STRONG, with randomised mortality evidence. SSaSS, in 20,995 participants with prior stroke or hypertension over 4.74 years: stroke 29.14 against 33.65 per 1,000 person-years ($p=0.006$), major cardiovascular events 49.09 against 56.29 ($p<0.001$), total mortality 39.28 against 44.61 ($p<0.001$), no excess hyperkalaemia. The UK programme cut salt by 1.4 g a day with systolic pressure down 3.0 mmHg, and stroke mortality fell 42 per cent over the same period — ecological, and not attributable. CONTESTED at low intakes: the PURE J-curve against the TOHP reanalysis, with the urine-measurement method the contested variable. See the hypertension entry.

Anticoagulation in atrial fibrillation — STRONG. Warfarin reduces stroke about 64 per cent and mortality 26 per cent, number needed to treat about 25 a year in high-risk fibrillation. This is the highest-yield single prevention action available for ischaemic stroke.

Statins — STRONG, with one qualification that is usually dropped. Per 1 mmol/L LDL reduction, major vascular events relative risk 0.78; for more against less intensive therapy, ischaemic stroke reduced 16 per cent (95 per cent CI 5–26). The same meta-analysis found no significant reduction in stroke death, relative risk 0.96 (0.84–1.09), because statins slightly raise haemorrhagic stroke risk. Both are printed.

Physical activity — STRONG. INTERSTROKE odds ratio 0.60 for regular activity, attributable risk 35.8 per cent, the second largest in the study.

Diet — STRONG. INTERSTROKE mAHEI odds ratio 0.60, attributable risk 23.2 per cent.

Smoking cessation — STRONG. INTERSTROKE smoking attributable risk 12.4 per cent, odds ratio 1.67; cessation after a coronary diagnosis gives a 44 per cent reduction in major adverse cardiovascular events.

Carotid endarterectomy for symptomatic stenosis of 70 per cent or more — STRONG. NASCET gave two-year ipsilateral stroke of 9 against 26 per cent, number needed to treat 6 over two years. For asymptomatic stenosis the benefit is much smaller and now CONTESTED given improved medical therapy; ACST-2 has reported and CREST-2 is running.

Polypill — MODERATE. The SECURE primary endpoint, which includes non-fatal ischaemic stroke, gave a hazard ratio of 0.76, and the aspirin, simvastatin, ramipril, atenolol and hydrochlorothiazide polypill on the Essential Medicines List is indicated for cerebral ischaemic stroke.

Clean cooking and air quality — STRONG on attributable burden, WEAK on randomised prevention evidence. Household air pollution accounts for about 12 per cent of stroke deaths; the randomised stove trials missed their primary endpoints.

Patent foramen ovale closure in young cryptogenic stroke — MODERATE. CLOSE, REDUCE and the long-term RESPECT follow-up found recurrent stroke reduced with hazard ratios around 0.2 to 0.4 in selected patients under 60, with atrial fibrillation increased.

Treatment. Acute:

Intervention	Effect size	EML	Off-patent	Cost
Aspirin 160–300 mg within 48 hours	IST and CAST: death or dependency reduced, about 9 fewer deaths or recurrent strokes per 1,000 treated, NNT about 100	yes	yes	Under under one euro a dose
Alteplase, intravenous thrombolysis within 4.5 hours	NNT about 10 within three hours, about 20 at three to 4.5 hours for improved outcome; symptomatic	yes	yes; tenecteplase is on patent in most markets	hundreds of euro a dose for generic alteplase; tenecteplase higher

Intervention	Effect size	EML	Off-patent	Cost
	intracranial haemorrhage about 6 against 0.4 per cent			
Mechanical thrombectomy	NNT 2.6 for reduced disability, about 5 for functional independence, HERMES, 1,287 patients, OR 2.49	n/a	n/a	tens of thousands of euro a procedure
Stroke unit care	Death or dependency reduced by about 20 per cent, odds ratio about 0.79, against a general ward, from the Stroke Unit Trialists Collaboration Cochrane review. NNT about 20. Requires organisation and nursing, not technology	n/a	n/a	Organisational
Decompressive craniectomy for malignant middle cerebral artery infarction	DESTINY, DECIMAL and HAMLET pooled: mortality 22 against 71 per cent, with increased survival at severe disability	n/a	n/a	Surgical

Secondary prevention is an antiplatelet — aspirin, or clopidogrel, or aspirin with dipyridamole — plus a statin and an antihypertensive, all on the Essential Medicines List, all off-patent, together tens of euro a patient-year. Short-course dual antiplatelet therapy after minor stroke or transient ischaemic attack, in CHANCE and POINT, reduced recurrent stroke with hazard ratios around 0.68 to 0.75, with the benefit confined to the first three weeks. Anticoagulation replaces antiplatelet therapy where atrial fibrillation is present.

Stroke unit care is the intervention with the largest population-level benefit and the lowest technology requirement. It needs trained nursing, swallow assessment, early mobilisation and organised protocols, not a catheter laboratory. In most of the world it is the realistic intervention, and its effect applies to every stroke patient rather than to the 10 to 20 per cent who arrive inside a reperfusion window.

Simple means. Salt substitution is the cheapest proven stroke-prevention commodity in existence: SSaSS gave stroke of 29.14 against 33.65 per 1,000 person-years and total mortality of 39.28 against 44.61 in a population including prior-stroke patients. Physical activity gives an odds ratio of 0.60 and an attributable risk of 35.8 per cent, up to 59.9 per cent in China, and the activity is walking. Smoking cessation gives 12.4 per cent. Weight and waist reduction gives 18.6 per cent. A diet shifted to fruit, vegetables, fish and legumes gives 23.2 per cent. Cutting heavy drinking gives 5.8 per cent. Pulse palpation to find atrial fibrillation needs no equipment and is about 87 to 97 per cent sensitive; finding atrial fibrillation and anticoagulating prevents about 64 per cent of the strokes it would cause. Blood pressure measurement with a mechanical cuff is the single most useful piece of low-technology equipment in stroke prevention, by way of the 47.9 per cent attributable risk.

Aspirin within 48 hours of an ischaemic stroke gives about 9 fewer deaths or recurrent strokes per 1,000 treated, one tablet, under one euro. It must not be given before haemorrhage is excluded, and that needs a scanner. The scanner is the binding constraint, not the aspirin.

Positioning, swallow assessment and early mobilisation are nursing practice rather than equipment, and they are the core of stroke unit care. Withholding oral intake until swallow is assessed prevents aspiration pneumonia, a leading cause of post-stroke death. One qualification: AVERT, with 2,104 patients, found that very early and very high-dose mobilisation was worse than usual early care, odds ratio 0.73 for a favourable outcome, so earlier and more is not simply better. Rehabilitation by repetitive task practice with no devices improves function, with modest and dose-dependent effect sizes.

Gaps. About 25 per cent of ischaemic strokes are cryptogenic after full workup. Statins reduce ischaemic stroke and slightly increase haemorrhagic stroke, and the Cholesterol Treatment Trialists' meta-analysis found no reduction in stroke death at all, relative risk 0.96; this is routinely omitted when statins are described as stroke prevention, and it is printed here. Carotid intervention for asymptomatic stenosis is contested, since modern medical therapy may have erased the surgical benefit, and CREST-2 is designed to answer it and has not reported. Thrombolysis beyond 4.5 hours and in mild deficits remains debated, and

the alteplase evidence has been publicly disputed over trial-level reanalysis. The INTERSTROKE diet reversal in south Asia is unexplained. Rising incidence under 55 is unexplained by measured risk factors. Global incidence figures depend on registries that barely exist across much of Africa and south Asia, and the 12 million figure carries wide model uncertainty. AVERT contradicts the instruction to mobilise as early and as much as possible. The number of stroke survivors is given as 101 million in one source and 93.8 million in another, and both stand. The ischaemic share of all strokes is given as 62 to 65 per cent globally, as about four in five, and as 70 to 85 per cent, in three different places; all three stand. A population attributable risk from a case-control design is not a demonstrated preventable fraction.

> **Depth.** Starts in: a brain artery. Size: 3 mm†; depth +10.10. First complaint: about 1 minute ([B] within minutes; † about 1 minute); time depth 36.88. One untreated course: no number († recovery takes months).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The artery can be opened. The process in the wall goes on. So it is held, not ended. The book's status: CONTROLLABLE, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Haemorrhagic stroke — intracerebral haemorrhage (ICD-11 8B00)

What it is. A small artery deep in the brain bursts and blood presses into the tissue. Headache, vomiting and loss of consciousness come on within minutes. It kills a much higher proportion of those affected than clot-caused stroke.

Measured. Intracerebral haemorrhage is the second leading cause of cardiovascular DALYs in GBD 2023, which ranks it above ischaemic stroke in third place, because it kills younger. GBD does not publish a separate death count for it in the retrieved tables; it falls within the 6.79 million GBD 2023 and 6.8 million WHO 2023 all-stroke deaths.

The haemorrhage share of all stroke is roughly 28 per cent of incident strokes globally, far higher in east and southeast Asia and sub-Saharan Africa, up to 35 to 40 per cent, and about 10 to 15 per cent in high-income western countries. Case fatality at 30 days is 35 to 52 per cent, with roughly half of deaths in the first two days — three to four times the case fatality of ischaemic stroke. The mean age at onset is younger than for ischaemic stroke, and the burden in people aged 40 to 60 is substantial, which is why the DALY rank exceeds the share of deaths. More than 80 per cent of cases occur in low- and middle-income countries, and incidence in east Asia is roughly double that in western Europe. Age-standardised incidence has fallen in high-income countries and risen or stayed flat elsewhere.

Where it starts. INTERSTROKE gives a combined attributable risk for intracerebral haemorrhage of 87.1 per cent (95 per cent CI 82.2–90.8). The factors associated with haemorrhage specifically are hypertension, physical activity, diet, waist-to-hip ratio, psychosocial factors, cardiac causes and alcohol. The ApoB/ApoA1 ratio and atrial fibrillation were not associated with haemorrhage; they were specific to ischaemic stroke. That is a measured difference between the subtypes and it matters: the lipid pathway is not the haemorrhage pathway.

Hypertension is the dominant cause, with an INTERSTROKE odds ratio of 2.98 for all stroke and an attributable risk of 47.9 per cent, and the hypertension odds ratio for haemorrhage specifically is higher than for ischaemic stroke in the published subtype analysis. Alcohol has a stronger association with haemorrhage than with ischaemic stroke; heavy or heavy episodic drinking carries an odds ratio of 2.09 for all stroke and higher for haemorrhage. Cerebral amyloid angiopathy causes most lobar haemorrhage in people over 70 and is the second major pathology after hypertensive small-vessel disease. Anticoagulation raises haemorrhage risk roughly seven- to tenfold with warfarin, and the direct oral anticoagulants roughly halve that against warfarin, with apixaban's intracranial haemorrhage hazard ratio of 0.42 in ARISTOTLE. Antiplatelet therapy raises the risk modestly. Statins are associated with a small increase, which is part of why the Cholesterol Treatment Trialists' meta-analysis found no reduction in stroke death. Arteriovenous malformations, cavernous malformations, moyamoya, cocaine and sympathomimetics, thrombocytopenia, haemophilia and sickle cell disease all contribute. Low LDL and low total cholesterol are associated with higher haemorrhage risk in observational data, the inverse of the ischaemic relation.

Which hypertensive person's deep perforating artery will rupture, and when, is not predictable. Why the haemorrhage-to-ischaemic ratio is so much higher in east Asia and sub-Saharan Africa than in western Europe is not explained by measured risk-factor differences alone. Whether the observational association between low cholesterol and haemorrhage is causal or confounded is unresolved, and it has direct consequences for intensive lipid lowering. Cerebral amyloid angiopathy cannot be diagnosed definitively without pathology.

Cure status. The acute haemorrhage: RELIEF ONLY. The underlying predisposition: CONTROLLABLE. An arteriovenous malformation, an aneurysm or a cavernous malformation as the bleeding source: CURABLE by obliteration or resection.

No treatment has been shown to improve functional outcome after intracerebral haemorrhage, and the major trials are negative or equivocal. STICH and STICH II found no benefit of early surgical evacuation of supratentorial haemorrhage over initial conservative treatment. INTERACT2, with 2,839 patients randomised to intensive blood-pressure lowering to below 140 systolic, did not significantly reduce death or major disability, odds ratio 0.87, p=0.06, with a favourable ordinal shift on secondary analysis. ATACH-2, with 1,000 patients and more intensive lowering, found no benefit and more renal adverse events. Recombinant factor VIIa reduced haematoma growth and did not improve outcome in the FAST trial. TICH-2, with 2,325 patients on tranexamic acid, found no difference in functional outcome, adjusted odds ratio 0.88, p=0.11, though haematoma expansion and early death were reduced. INTERACT3, in 2023, tested a care bundle of blood-pressure lowering with glucose, temperature and coagulation management across 7,036 patients and improved functional outcome, odds ratio 0.86 (0.76–0.97) — the first positive trial, and a bundle of basic care rather than a drug or a device.

Surgical or endovascular obliteration of an arteriovenous malformation or an aneurysm removes that source permanently, as does resection of a cavernous malformation. ARUBA, with 223 patients, found that for unruptured arteriovenous malformations intervention was worse than medical management, hazard ratio 0.27 favouring medical management. Posterior fossa or cerebellar haematoma evacuation is life-saving where brainstem compression is developing, on consensus rather than trial evidence.

Prevention.

Blood pressure lowering — STRONG, and overwhelmingly the main measure. Per 10 mmHg systolic reduction, stroke of all types carries a relative risk of 0.73; the effect on haemorrhage specifically is at least as large as on ischaemic stroke, and hypertension's attributable risk is the largest in INTERSTROKE at 47.9 per cent.

Salt reduction and salt substitution — STRONG. SSaSS reduced total stroke and total mortality in a rural Chinese population where haemorrhage makes up a large share of strokes. That matters: the trial was conducted in exactly the population where haemorrhage is proportionally common.

Alcohol reduction — MODERATE, and relatively more important for haemorrhage than for ischaemic stroke.

Avoiding unnecessary anticoagulation and antiplatelet therapy — STRONG. The absolute increase in haemorrhage risk is the main harm of these drugs, and using a direct oral anticoagulant rather than warfarin where anticoagulation is needed roughly halves it, with an intracranial haemorrhage hazard ratio of 0.42 for apixaban.

Blood pressure lowering after a first haemorrhage — STRONG for recurrence. Recurrence risk is roughly 2 to 4 per cent a year and higher with lobar amyloid haemorrhage, and blood-pressure control reduces it.

Physical activity and diet — MODERATE, both associated with haemorrhage in INTERSTROKE. *Smoking cessation — MODERATE*.

Statins after haemorrhage — CONTESTED. The observational low-cholesterol association and the small trial-level excess make the decision genuinely unresolved, and practice varies.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
INTERACT3 care bundle: blood-pressure lowering with glucose and temperature control and coagulation reversal	Functional outcome improved, odds ratio 0.86 (0.76–0.97) — the only positive trial, and a protocol rather than a product	Components yes	yes	Organisational
Blood pressure lowering: labetalol, nicardipine, urapidil	INTERACT2 odds ratio 0.87, p=0.06, not significant; ATACH-2 null; haematoma expansion reduced	yes, labetalol	yes	a few to tens of euro a dose
Reversal of anticoagulation: vitamin K with prothrombin complex concentrate for warfarin, idarucizumab for dabigatran, andexanet alfa for factor Xa inhibitors	Haematoma expansion reduced; ANNEXA-I showed andexanet reduced expansion with more thrombotic events	Vitamin K yes; prothrombin complex yes; idarucizumab and andexanet no	Vitamin K yes	Vitamin K a few euro; prothrombin complex hundreds to thousands of euro; andexanet tens of thousands of euro a course
Tranexamic acid	TICH-2: no functional benefit, odds ratio 0.88, p=0.11; expansion and early death reduced	yes, sections 10.2 and 22	yes	a few to tens of euro a course
Surgical evacuation	STICH and STICH II: no benefit in supratentorial haemorrhage. Cerebellar haematoma evacuation life-saving on consensus. Minimally invasive evacuation in MISTIE III missed its primary endpoint and suggested benefit with good haematoma clearance	n/a	n/a	Surgical
External ventricular drain for hydrocephalus	Life-saving for obstructive hydrocephalus	n/a	n/a	hundreds to thousands of euro plus neurosurgical care
Stroke unit and neurocritical care	Organised care reduces death or dependency by about 20 per cent across stroke types	n/a	n/a	Organisational

The important point for a reference work: in intracerebral haemorrhage the only positive randomised trial tested a bundle of cheap, basic care. Every expensive product — factor VIIa, surgery in the main trials, andexanet — either failed its functional endpoint or carried offsetting harm. The off-patent components, labetalol, vitamin K, tranexamic acid and prothrombin complex, plus organised nursing, are the therapy.

Simple means. Blood pressure control is the entire prevention programme and is achievable with thiazides, amlodipine and ACE inhibitors at tens of euro a patient-year, plus salt reduction, weight loss and exercise at no cost. Salt substitution, in exactly this population, gave total mortality of 39.28 against 44.61 per 1,000 person-years. Alcohol reduction matters relatively more here than for ischaemic stroke. Head elevation to 30 degrees, airway positioning and withholding oral intake until swallow is assessed are nursing actions requiring no equipment, and they prevent aspiration, a leading cause of death after haemorrhage. Stroke unit organisation gives an odds ratio of about 0.79 for death or dependency from trained nursing and protocol rather than technology. Vitamin K for warfarin-associated haemorrhage costs a few euro is on the Essential Medicines List, is off-patent, and reverses the coagulopathy slowly but effectively. Tranexamic acid costs a few to tens of euro is listed and off-patent, and reduces haematoma expansion with no proven functional benefit.

One negative is critical. Aspirin is beneficial in ischaemic stroke and harmful in haemorrhage, and without imaging the two are not reliably distinguishable at the bedside. That is the hard limit on simple means in

stroke care: the single most consequential decision requires a scanner. The clinical scores — Siriraj, Guy's — have insufficient accuracy to substitute.

Gaps. No treatment improves functional outcome after intracerebral haemorrhage except the INTERACT3 care bundle, and that single positive trial has not been replicated. INTERACT2 at p=0.06 and ATACH-2 null disagree with guideline enthusiasm for intensive acute blood-pressure lowering, and both are printed. TICH-2 reduced early death and not disability, and how to report tranexamic acid is genuinely unclear. The low-cholesterol and haemorrhage association is unresolved and affects whether to give statins after a haemorrhage; practice varies between countries, and SATURN is running. ARUBA found intervention worse than medical management for unruptured arteriovenous malformations and remains disputed on generalisability. GBD publishes no separate death count for intracerebral haemorrhage in the retrieved tables despite ranking it second in cardiovascular DALYs; the burden figure and the death figure come from different granularities. The roughly twofold difference in the haemorrhage proportion between east Asia and western Europe is not explained. Cerebral amyloid angiopathy prevalence is unknown without pathology, and the Boston criteria are imaging proxies.

> **Depth.** Starts in: a small brain artery. Size: 300 µm†; depth +8.00. First complaint: about 3.2 minutes ([B] within minutes); time depth 37.93. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Subarachnoid haemorrhage (ICD-11 8B01)

What it is. An aneurysm on an artery at the base of the brain bursts and blood spreads into the fluid around the brain. The person reports the worst headache of their life, starting in an instant. About a third die before reaching hospital.

Measured. Global incidence is roughly 7.9 per 100,000 person-years, with a meta-analysis range of 6.9 to 9.0 and large regional variation, from a pooled worldwide analysis in JAMA Neurology in 2019. Finland and Japan have incidence roughly twice the global average — Finland historically 15 to 20 per 100,000 and Japan above 20 — and central and south America are among the lowest at about 4. Subarachnoid haemorrhage is roughly 5 per cent of all stroke. Between 8 and 15 per cent die before medical contact, and overall 30-day case fatality is roughly 30 to 40 per cent, falling over recent decades. The mean age at onset is roughly 55, substantially younger than ischaemic stroke, and it is the stroke type with the greatest loss of productive years per case. Incidence is roughly 1.3 to 1.6 times higher in women. Unruptured intracranial aneurysm prevalence in the general population is about 3.2 per cent (95 per cent CI 1.9–5.2), and most never rupture. Age-standardised incidence has fallen roughly 1.7 per cent a year worldwide since 1980, largely tracking falls in smoking and blood pressure. GBD counts subarachnoid haemorrhage within the all-stroke figures and the retrieved tables publish no separate count.

Where it starts. Smoking is the strongest modifiable risk factor, with a relative risk of roughly 2.2 to 3.1. Hypertension carries a relative risk of roughly 2.5. Heavy alcohol use carries roughly 1.5 to 2.1. Female sex and family history contribute, with a first-degree relative raising risk roughly three- to sevenfold. Autosomal dominant polycystic kidney disease carries an aneurysm prevalence of roughly 10 per cent. Connective tissue disorders — vascular Ehlers-Danlos, Marfan syndrome, fibromuscular dysplasia — contribute, as do cocaine and sympathomimetics as acute triggers. Rupture risk depends on size, site and population: the ISUIA and UCAS Japan studies give five-year rupture risks from under 1 per cent for small anterior-circulation aneurysms to over 40 per cent for large posterior-circulation ones.

Why most of the roughly 3.2 per cent of people carrying an aneurysm never bleed, and which will, is not predictable at the individual level; the PHASES score stratifies populations and performs poorly for individuals. Why Finland and Japan have roughly double the global incidence is not explained by known risk factors. Delayed cerebral ischaemia, which causes much of the disability in survivors, was long attributed to large-artery vasospasm, and drugs that relieve angiographic vasospasm, clazosentan among

them, have not reliably improved outcome, so the causal account is now in doubt. The mechanism of nimodipine's benefit is therefore also unclear.

Cure status. The ruptured aneurysm: CURABLE — securing it permanently removes the source of bleeding. The brain injury already sustained: RELIEF ONLY. An unruptured aneurysm: intervention is not automatically beneficial, and the status is CONTROLLABLE by surveillance and risk-factor treatment.

ISAT randomised 2,143 patients to endovascular coiling or neurosurgical clipping: dependency or death at one year was 23.5 per cent with coiling against 30.9 per cent with clipping, an absolute reduction of 7.4 percentage points and a number needed to treat of 14. The survival advantage persisted at ten years, and rebleeding and retreatment were more common after coiling. Securing the aneurysm reduces the rebleed risk from roughly 20 to 30 per cent in the first two weeks, with case fatality around 50 per cent for a rebleed, to very low.

Before rupture the calculation changes. ISUIA and ARUBA caution that treating unruptured lesions can do net harm: ARUBA found medical management superior for unruptured arteriovenous malformations, hazard ratio 0.27, and for small unruptured aneurysms the procedural risk can exceed the natural rupture risk. Both statements belong together: after rupture, securing the aneurysm is curative of the lesion; before rupture, intervention is not automatically beneficial.

Prevention.

Smoking cessation — STRONG, and the single largest modifiable factor. Relative risk 2.2 to 3.1 for current smoking, with risk falling substantially after cessation. The worldwide decline of about 1.7 per cent a year in incidence is attributed chiefly to falling smoking prevalence.

Blood pressure control — STRONG. Relative risk about 2.5 for hypertension; per 10 mmHg systolic reduction, all stroke relative risk 0.73.

Heavy alcohol reduction — MODERATE.

Screening in high-risk groups — MODERATE. Screening first-degree relatives where two or more family members have had a subarachnoid haemorrhage, and screening in polycystic kidney disease, is cost-effective in modelling. Screening with only one affected relative is CONTESTED.

Preventive treatment of an incidentally found aneurysm — CONTESTED. It depends on size, site and age; the procedural risk is real, roughly 3 to 5 per cent morbidity for coiling and higher for clipping, and for small anterior aneurysms in older patients the natural risk may be lower.

Population screening — not recommended, and no body recommends it: a prevalence of 3.2 per cent with low rupture rates means screening would generate large numbers of harmful interventions.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Endovascular coiling	ISAT: death or dependency 23.5 against 30.9 per cent for clipping, NNT 14; more rebleeding and retreatment	n/a	n/a	tens of thousands of euro
Neurosurgical clipping	More durable occlusion; worse one-year functional outcome in ISAT	n/a	n/a	tens of thousands of euro
Nimodipine 60 mg four-hourly for 21 days	The only drug with a proven outcome benefit: poor outcome reduced, relative risk about 0.67, NNT about 13 to prevent one poor outcome, from the Cochrane review and the original Allen and Pickard trials	yes	yes	tens to hundreds of euro for the 21-day course
Tranexamic acid, short course before securing	Rebleeding reduced; the ULTRA trial, 955 patients, found no improvement in functional outcome, odds ratio 0.86	yes	yes	a few to tens of euro
Clazosentan	Relieves angiographic vasospasm;	no	no	High; not standard

Intervention	Effect size	EML	Off-patent	Cost
	CONSCIOUS-2 and CONSCIOUS-3 did not improve functional outcome			
External ventricular drain for hydrocephalus	Life-saving for acute hydrocephalus, present in about 20 to 30 per cent	n/a	n/a	hundreds to thousands of euro plus care
Neurocritical care, euvolaemia, blood-pressure management	Organisational; part of standard care	n/a	n/a	Organisational

Nimodipine is the key fact. The only drug shown to improve outcome in subarachnoid haemorrhage is a cheap, off-patent, Essential Medicines List calcium channel blocker at tens to hundreds of euro for the full 21-day course, with a number needed to treat of about 13. Every expensive agent aimed at vasospasm has failed on functional outcome.

Simple means. Smoking cessation carries a relative risk of 2.2 to 3.1, is the largest modifiable factor, drives the falling worldwide incidence, and costs nothing. Blood pressure control carries a relative risk of about 2.5 and is achievable with tens of euro a year of generic drugs plus salt reduction, weight loss and exercise. Heavy alcohol reduction carries 1.5 to 2.1. Recognition is free and it is the rate-limiting step: a sudden worst-ever headache, often with neck stiffness, vomiting or brief loss of consciousness, warrants immediate transfer. A substantial proportion of cases are missed at first contact, and the warning or sentinel headache that precedes a major bleed in perhaps 10 to 40 per cent of cases is the single best opportunity to intervene. Nimodipine is cheap, listed, off-patent and oral, with a number needed to treat of about 13; it needs a pharmaceutical chain and no technology. Nursing care — airway positioning, euvolaemia, bowel care, avoiding hypotension — is organisational.

The hard limit is severe. Securing an aneurysm requires either neurosurgery or an endovascular suite, and there is no simple-means substitute. Without one, the rebleed risk of 20 to 30 per cent in the first two weeks stands, with roughly 50 per cent case fatality per rebleed. Diagnosis also requires computed tomography, or lumbar puncture where the scan is negative. In subarachnoid haemorrhage the whole of definitive care depends on an industrial chain, and the only measures that need no chain are prevention and recognition.

Gaps. GBD publishes no separate burden figure for subarachnoid haemorrhage in the retrieved tables. Incidence estimates rest on registries concentrated in Europe, Japan and North America, and the 7.9 per 100,000 global figure extrapolates heavily. The Finland and Japan excess, roughly twofold, is unexplained. The vasospasm theory of delayed cerebral ischaemia is in doubt: drugs that relieve vasospasm do not improve outcome, while nimodipine improves outcome possibly without acting mainly on vasospasm, so the mechanism of the only effective drug is unclear. Individual rupture prediction is not possible, and PHASES stratifies groups rather than people. Whether to treat small unruptured aneurysms is unresolved, and the two large natural-history studies, ISUIA and UCAS Japan, give different rupture rates for comparable lesions. Screening thresholds for family history differ between guidelines on one against two affected relatives. Pre-hospital deaths, 8 to 15 per cent, are poorly captured, so case fatality depends on whether the denominator includes them, and that alone explains much of the 30 to 50 per cent range in the literature†.

> **Depth.** Starts in: the aneurysm. Size: 7 mm†; depth +10.87. First complaint: about 1 second ([B] in an instant); time depth 33.15. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

The peripheral arteries and the veins

Peripheral arterial disease (ICD-11 BD40–BD4Z)

What it is. The arteries to the legs narrow, so walking causes cramping pain in the calves that stops with rest. In advanced cases the tissue dies and the limb is lost. It marks the same disease as in the heart arteries.

Measured. About 122 million people worldwide were affected in 2023, from the GBD 2023 cardiovascular collaborators, and that figure is specifically for lower-extremity disease. No global death count and no DALY figure for peripheral arterial disease is published in the retrieved GBD 2023 tables.

An earlier estimate gives 236 million people aged 25 and over in 2015, of whom roughly two-thirds in low- and middle-income countries. That is nearly double the 2023 GBD figure, because it used a different case definition — an ankle-brachial index of 0.90 or below, including asymptomatic disease — rather than GBD's symptomatic definition. Both are printed with their definitions, because they are not measuring the same thing.

Prevalence rises from under 5 per cent at age 50 to over 20 per cent above 80. Roughly 1 to 3 per cent of patients a year progress to critical limb ischaemia, and one-year mortality after a major amputation is 20 to 50 per cent. Cardiovascular mortality runs roughly two to three times that of people without the condition, and most people with it die of coronary or cerebrovascular disease rather than of their legs. The highest absolute numbers are in south and east Asia, and the strongest risk-factor gradient is smoking. Absolute numbers are rising with ageing and diabetes.

Where it starts. Smoking is the dominant risk factor, with an odds ratio of roughly 2 to 4, stronger here than for coronary disease, and roughly 80 per cent of patients are current or former smokers. Diabetes carries an odds ratio of roughly 2 to 4 and also shifts the disease distally and multiplies amputation risk. Hypertension, dyslipidaemia, chronic kidney disease, age and male sex all contribute, as do homocysteine, C-reactive protein and lipoprotein(a). The INTERHEART and INTERSTROKE factors apply as the same atherosclerotic substrate, and neither study used peripheral arterial disease as an endpoint, so there is no INTERHEART-equivalent attributable-risk table for it.

Why atherosclerosis is distributed to the legs in one person and to the coronaries in another is not explained, though smoking and diabetes shift it toward the limbs. Most of the disease is asymptomatic or atypical: in population screening only about 10 to 30 per cent of people with an abnormal ankle-brachial index have classical claudication, and the natural history of the asymptomatic majority is poorly characterised. Why some patients with severe stenosis walk normally through collateral development while others with less disease lose a limb is not predictable.

Cure status. CONTROLLABLE.

No treatment removes the atherosclerosis. Revascularisation restores flow and relieves symptoms, restenosis is common, and the underlying disease progresses. In claudication, supervised exercise therapy matches or exceeds endovascular revascularisation for walking distance at one year — the CLEVER trial found supervised exercise improved peak walking time more than stenting — which is direct evidence that the procedure is not curing anything. For critical limb ischaemia revascularisation is limb-saving, and BEST-CLI, with 1,830 patients, found surgical bypass with a vein graft superior to endovascular therapy for the primary composite in the subgroup with adequate vein. Amputation removes the affected part; it does not cure the disease.

Prevention.

Smoking cessation — STRONG, and the single most important measure for both incidence and limb outcomes. Continued smoking after diagnosis is associated with far higher amputation and graft-failure rates, and cessation improves graft patency and walking distance. In coronary disease, cessation gave a 44 per cent reduction in major adverse cardiovascular events while reduction short of cessation gave nothing.

Foot care and footwear in diabetes — STRONG for amputation prevention. Structured foot care programmes reduce amputation rates by roughly 50 to 85 per cent in before-and-after and cohort studies.

Diabetes prevention and control — STRONG for limb outcomes; glycaemic control reduces amputation risk, though its effect on incidence of the arterial disease itself is more modest.

Statins — STRONG. In the Heart Protection Study subgroup, simvastatin reduced major vascular events by about 24 per cent; the Cholesterol Treatment Trialists' figure is a relative risk of 0.78 per 1 mmol/L of LDL reduction overall.

Blood pressure lowering — STRONG for cardiovascular events. *Physical activity — MODERATE*.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Supervised exercise therapy	The first-line treatment for claudication: maximal walking distance increased by roughly 50 to 200 per cent, with Cochrane giving about a five-minute increase in treadmill walking time; CLEVER found it superior to stenting for peak walking time	n/a	n/a	Supervision cost only
Statin	Heart Protection Study subgroup: major vascular events down about 24 per cent; walking distance also improves	yes	yes	a few to tens of euro
Antiplatelet, aspirin or clopidogrel	CAPRIE subgroup: clopidogrel better than aspirin, relative risk reduction about 24 per cent in that subgroup. Aspirin’s benefit in asymptomatic disease is not established; the AAA and POPADAD trials were null	yes, both	yes, both	a few to tens of euro
ACE inhibitor	HOPE subgroup: event reduction consistent with the main trial	yes	yes	a few to tens of euro
Cilostazol	Walking distance increased by roughly 40 to 50 per cent against placebo, per Cochrane; contraindicated in heart failure	no	yes	tens to hundreds of euro
Rivaroxaban 2.5 mg twice daily with aspirin	VOYAGER PAD, 6,564 patients after revascularisation: composite hazard ratio 0.85, with more major bleeding; the COMPASS subgroup was similar	yes, rivaroxaban	generics available	hundreds to thousands of euro branded; tens to hundreds of euro generic
Endovascular revascularisation	Relieves symptoms; no better than supervised exercise for claudication walking distance at one year, per CLEVER	n/a	n/a	thousands to tens of thousands of euro
Surgical bypass	BEST-CLI: superior to endovascular therapy in critical limb ischaemia with adequate vein conduit	n/a	n/a	tens of thousands of euro
Amputation	Limb removal where revascularisation fails; one-year mortality after major amputation 20 to 50 per cent	n/a	n/a	Surgical

Simple means. Walking is the first-line treatment for the commonest presentation. Structured walking — walk until claudication pain is moderate, rest, repeat, for 30 to 45 minutes three times a week — increases maximal walking distance by roughly 50 to 200 per cent and matches stenting at one year. It requires nothing but a programme and supervision. Home-based programmes with structured coaching also work, less well than supervised ones.

Foot inspection and footwear is the highest-yield no-technology intervention here. Daily foot inspection, properly fitted shoes and prompt treatment of ulcers reduce amputation by roughly 50 to 85 per cent in structured programmes. It needs eyes, a mirror, and shoes that fit.

Smoking cessation has the largest single effect on limb outcomes and costs nothing. Ankle-brachial index measurement needs only a blood-pressure cuff and a Doppler probe; with a cuff alone, palpation of foot

pulses gives a rough screen with poor sensitivity, roughly 70 per cent. Weight loss, blood pressure control and diet act as in the hypertension and ischaemic heart disease entries. Keeping the limb warm, avoiding trauma and positioning the leg dependent at night reduces rest pain in critical ischaemia; symptomatic and unquantified.

The hard limit: critical limb ischaemia needs revascularisation or amputation. There is no simple-means substitute, and untreated critical limb ischaemia leads to limb loss or death.

Gaps. The two prevalence figures differ nearly twofold — 122 million in GBD 2023 against 236 million in the 2019 Lancet Global Health analysis — because of different case definitions, symptomatic against ankle-brachial index. Neither is wrong and they are not comparable; both are printed with their definitions. No global death or DALY figure for peripheral arterial disease exists in the retrieved GBD 2023 tables. No INTERHEART- or INTERSTROKE-equivalent attributable-risk study exists for this condition; risk factors are inferred from coronary studies and from disease-specific cohorts. The natural history of asymptomatic disease, which is most of it, is poorly characterised. Aspirin in asymptomatic disease: the AAA and POPADAD trials were null, against widespread practice. Revascularisation against exercise for claudication: CLEVER favours exercise, and revascularisation rates remain high and rising, so evidence and practice disagree. Amputation rates vary several-fold between countries and between regions within countries at similar disease prevalence, which is an access and practice signal rather than a disease signal.

> **Depth.** Starts in: a leg artery. Size: 6 mm†; depth +10.73. First complaint: about 65 years († onset about age 65); time depth 52.67. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The artery can be opened. The process in the wall goes on. So it is held, not ended. The book’s status: CONTROLLABLE. Reading and status agree. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Aortic aneurysm (ICD-11 BD50–BD5Z)

What it is. The wall of the body’s main artery stretches and balloons out. It gives no symptoms while it grows. If it tears or bursts, most people die within minutes to hours.

Measured. No global prevalence, death or DALY figure for aortic aneurysm is published in the retrieved GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all. GBD 2019 reported roughly 172,000 deaths worldwide, with an age-standardised death rate of about 2.2 per 100,000, and that is an earlier round.

Abdominal aortic aneurysm prevalence in men aged 65 to 74 is 1.3 to 3.3 per cent in modern screening programmes, down from 4 to 8 per cent in the screening trials of the 1990s. The prevalence has fallen by roughly half in two decades, tracking the fall in smoking. Prevalence in women is roughly one-sixth to one-quarter that in men. Rupture case fatality is roughly 80 to 90 per cent overall including pre-hospital deaths, and 30-day mortality after emergency repair of a ruptured aneurysm is roughly 30 to 50 per cent against 1 to 5 per cent for elective repair. Annual rupture risk by diameter: under 1 per cent at 4.0 to 4.9 cm, about 1 to 3 per cent at 5.0 to 5.9 cm, about 10 to 20 per cent above 6.0 cm, and over 30 per cent above 7 cm. Acute aortic dissection has an incidence of roughly 3 to 6 per 100,000 person-years, and untreated type A dissection mortality rises about 1 to 2 per cent an hour in the first 48 hours. The condition is rare before 55 and incidence rises steeply with age. Incidence and mortality are falling in high-income countries, attributed mainly to reduced smoking.

Where it starts. Smoking is the overwhelming risk factor for abdominal aortic aneurysm, with an odds ratio of roughly 5 and a strong dose and duration relation; it is the strongest smoking association of any cardiovascular condition. Male sex gives four- to sixfold higher prevalence. Age, hypertension — strongest for thoracic aneurysm and dissection — and family history, with a first-degree relative raising risk roughly two- to fourfold, all contribute. Atherosclerosis and dyslipidaemia contribute, with a weaker relation than for coronary disease, and statins do not reliably slow aneurysm growth. Diabetes is inversely associated with abdominal aortic aneurysm, a consistent and unexplained finding with an odds ratio of roughly 0.7 to 0.8. Connective tissue disease dominates thoracic aneurysm in the young: Marfan syndrome and FBN1, Loeys-Dietz and TGFBR1 or TGFBR2, vascular Ehlers-Danlos and COL3A1, bicuspid aortic valve,

Turner syndrome. Inflammatory and infective causes include Takayasu arteritis, giant cell arteritis, syphilitic aortitis and mycotic aneurysm.

Why aneurysms grow in bursts rather than steadily is not explained, and growth is not reliably predictable from diameter or risk factors. No drug has been shown to slow aneurysm growth: beta blockers in the propranolol trial, doxycycline in N-TA³CT, ACE inhibitors, statins and macrolides have all failed or given inconsistent results. The inverse association with diabetes is reproducible and unexplained. Why women have fewer aneurysms but rupture at smaller diameters is not understood, and the current size thresholds for repair were derived largely in men.

Cure status. An aneurysm above the repair threshold: CURABLE by repair. An aneurysm below the repair threshold: RELIEF ONLY — no medical treatment exists at all, and the only management is surveillance. The underlying aortopathy: RELIEF ONLY — the risk of a further aneurysm elsewhere remains.

Open surgical repair replaces the segment with a graft and is durable, with low reintervention rates. Endovascular repair carries a trade-off that must be stated honestly: EVAR-1, with 1,252 patients, found lower 30-day mortality, 1.8 against 4.3 per cent, and no long-term survival advantage, with higher aneurysm-related and all-cause mortality than open repair by eight years, driven by late rupture and endograft failure. The less invasive procedure traded early survival for late failure, and lifelong imaging surveillance is required after it.

Elective repair below 5.5 cm gives no benefit. The UK Small Aneurysm Trial, with 1,090 patients at 4.0 to 5.5 cm, and ADAM, with 1,136 patients, both found no survival advantage from early repair against surveillance. That is why the threshold is 5.5 cm in men, and it is trial-derived rather than arbitrary. Acute type A aortic dissection requires emergency surgery; mortality without it is roughly 50 per cent at 48 hours.

Prevention.

Smoking cessation — STRONG, and by far the dominant measure. An odds ratio of about 5 for current smoking; the roughly 50 per cent fall in screened prevalence over two decades tracks the fall in smoking, and continued smoking accelerates growth of an existing aneurysm.

Screening men aged 65 for abdominal aortic aneurysm — STRONG, with randomised mortality evidence. Four randomised trials — MASS, Viborg, Chichester and Western Australia — pooled give aneurysm-related mortality reduced by roughly 35 to 45 per cent, odds ratio about 0.60, in men invited to a single ultrasound scan. MASS showed persistent benefit at thirteen years. The number needed to screen is roughly 200 to 700 men to prevent one aneurysm death, depending on prevalence. Screening women is not recommended: prevalence is too low for net benefit and no trial shows benefit.

Blood pressure control — STRONG for thoracic aneurysm and dissection, where hypertension is the leading modifiable factor; per 10 mmHg systolic reduction, major cardiovascular events relative risk 0.80.

Screening first-degree relatives — MODERATE.

Beta blockade in Marfan syndrome — MODERATE. Losartan against atenolol trials showed similar aortic root growth rates, and a meta-analysis suggested both slow it.

No drug prevents or slows sporadic aneurysm growth. This is a genuine therapeutic void. Doxycycline, in N-TA³CT with 261 patients, did not slow growth and if anything growth was slightly faster.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Surveillance ultrasound	The entire management below threshold, because no treatment exists	n/a	n/a	tens to hundreds of euro a scan
Open surgical repair	Durable; elective 30-day mortality 4.3 per cent in EVAR-1; better long-term survival than endovascular repair beyond eight years	n/a	n/a	tens of thousands of euro
Endovascular repair	30-day mortality 1.8 against 4.3	n/a	n/a	tens of thousands

Intervention	Effect size	EML	Off-patent	Cost
	per cent for open repair; no long-term survival advantage and worse beyond eight years; lifelong surveillance required			of euro graft cost dominating
Emergency repair of rupture	30-day mortality 30 to 50 per cent, against 80 to 90 per cent overall case fatality without repair	n/a	n/a	Surgical
Blood pressure and heart rate control in dissection: labetalol, esmolol, then oral agents	Reduces propagation; standard care	yes, labetalol	yes	a few to tens of euro
Beta blocker or losartan in Marfan syndrome	Slows aortic root growth; similar between agents	yes, both	yes, both	a few to tens of euro a year
Statins, doxycycline, ACE inhibitors, macrolides for growth	All failed to slow growth	—	—	—

Simple means. Smoking cessation has a dominant effect, with an odds ratio of about 5, costs nothing, and also slows growth of an existing aneurysm. Blood pressure control is dominant for thoracic disease, with generic drugs at tens of euro a year plus salt reduction, weight loss and exercise. Abdominal palpation can feel a pulsatile mass in thinner patients, with poor sensitivity, roughly 30 to 40 per cent for aneurysms under 5 cm and better above, and it cannot be relied on to exclude an aneurysm. It costs nothing and occasionally finds one. Ultrasound screening requires a machine and an operator, and that is a modest chain: a single scan in a 65-year-old man reduces aneurysm mortality by roughly 35 to 45 per cent, and portable handheld ultrasound now brings this within reach of primary care in many settings.

The hard limit, stated plainly: there is no medical treatment for an aortic aneurysm at all, cheap or expensive. Below the threshold the management is watching; above it, major vascular surgery or an endograft. No simple means exists for the aneurysm itself, and the chain minimally requires ultrasound for detection and a vascular surgical service with anaesthesia, blood transfusion and intensive care for repair. Rupture without that chain is almost always fatal.

Gaps. No GBD 2023 global burden figure for aortic aneurysm exists in the retrieved tables, and the roughly 172,000 deaths figure comes from an earlier round; this entry is part of the seventeen-condition gap set out in this chapter’s introduction. No drug slows aneurysm growth, and multiple trials have failed; that is a complete therapeutic void. Endovascular against open repair: early survival favours endovascular and long-term survival favours open, guidelines and practice have not fully resolved it, and practice has shifted heavily toward endovascular repair on the early figures. Repair thresholds in women are not evidence-based: the 5.5 cm threshold was derived in male cohorts, women rupture at smaller diameters, and the correct threshold is unknown. The inverse diabetes association is reproducible and unexplained. Screening is cost-effective in high-smoking-prevalence populations, and as smoking falls so does screening yield and so does cost-effectiveness; several programmes are reconsidering thresholds, and that is an active policy disagreement. Pre-hospital rupture deaths are inconsistently captured, so case fatality figures range from 65 to 90 per cent depending on the denominator†, and sources disagree for that reason.

> **Depth.** Starts in: the aorta. Size: 2.5 cm†; depth +12.03. First complaint: about 70 years († onset about age 70); time depth 52.74. One untreated course: no number ([B] grows without complaints).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Deep vein thrombosis and pulmonary embolism — venous thromboembolism (ICD-11 BD71, BB00)

What it is. A clot forms in a deep vein, usually in the leg. A piece can break off and lodge in the lungs, blocking blood flow there. The leg clot causes pain and swelling; the lung clot can kill within hours.

Measured. No global prevalence, incidence, death or DALY figure for venous thromboembolism is published in the retrieved GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all, and it is consequential, because the figures that circulate instead are model outputs.

Incidence in high-income populations is 1 to 2 per 1,000 person-years for all venous thromboembolism, roughly two-thirds deep vein thrombosis and one-third pulmonary embolism, from the Worcester, Olmsted County and Tromsø population studies. Estimated annual events run at roughly 10 million worldwide, with 300,000 to 500,000 related deaths a year in Europe and roughly 100,000 in the United States, from the International Society on Thrombosis and Haemostasis and modelling estimates. Those are model-based and not measured, and they should never be presented as measured counts. Case fatality of untreated pulmonary embolism is roughly 25 to 30 per cent; with anticoagulation, roughly 2 to 8 per cent at 30 days. Hospital-acquired venous thromboembolism accounts for roughly 50 to 60 per cent of all cases, a large and partly preventable fraction. Recurrence after an unprovoked event off anticoagulation is roughly 10 per cent in the first year and 30 per cent at ten years, and much lower after a provoked event with a transient cause removed. Post-thrombotic syndrome develops in 20 to 50 per cent after a proximal deep vein thrombosis, and severe forms in roughly 5 to 10 per cent. Incidence rises sharply with age, from about 1 per 10,000 under 40 to about 1 per 100 above 80. Reported incidence is substantially lower in east Asian and African populations, partly genuine through lower factor V Leiden prevalence and partly under-detection.

Where it starts. Virchow's triad — stasis, endothelial injury, hypercoagulability. Measured contributions: major orthopaedic surgery without prophylaxis carries deep vein thrombosis rates of 40 to 60 per cent on screening venography, from the historical trials that established prophylaxis. Active cancer raises risk roughly four- to sevenfold, with pancreatic, brain, gastric and lung cancers highest. Pregnancy and the puerperium raise it roughly four- to fivefold, highest in the first six weeks postpartum. Combined oral contraceptives raise it roughly two- to fourfold, with the absolute risk remaining low at about 1 per 1,000 a year, and third-generation progestins somewhat higher than second. Oral hormone replacement therapy raises it roughly twofold, transdermal much less. Factor V Leiden raises it three- to eightfold heterozygous and roughly 50- to 80-fold homozygous, with a prevalence of about 5 per cent in European-ancestry populations and near zero in African and east Asian. Prothrombin G20210A raises it roughly threefold heterozygous. Antiphospholipid syndrome and antithrombin, protein C and protein S deficiency carry higher relative risks and are much rarer. Obesity raises it roughly two- to threefold; long-haul travel over eight hours roughly two- to threefold; previous venous thromboembolism is the strongest single predictor; and hospitalisation itself, with or without surgery, contributes.

Why a given person with a given risk factor clots on a given day is not predictable, and most people with factor V Leiden never have an event. Roughly 30 to 50 per cent of cases are unprovoked with no identifiable trigger, and in that group the decision on how long to anticoagulate rests on recurrence models — DASH, HERDOO2, Vienna — that perform moderately and are not individually reliable. Whether thrombophilia testing changes outcomes is not established, and most guidelines now advise against routine testing. Why some patients develop post-thrombotic syndrome and others do not is unexplained.

Cure status. A provoked event with a removable cause: CURABLE. Unprovoked and recurrent disease: CONTROLLABLE. Chronic thromboembolic pulmonary hypertension in operable cases: CURABLE by pulmonary endarterectomy.

A clot treated with anticoagulation resolves or organises, and after a provoked event with the provocation removed, three months of anticoagulation is sufficient and recurrence risk falls to roughly 1 to 3 per cent a year; the condition is gone. After an unprovoked event, recurrence after stopping is roughly 10 per cent in year one and 30 per cent at ten years, so anticoagulation holds the state rather than curing it, and extended therapy is often indefinite. EINSTEIN-CHOICE and AMPLIFY-EXT showed low-dose extended therapy with a direct oral anticoagulant reduces recurrence by roughly 80 per cent with little excess bleeding.

Chronic thromboembolic pulmonary hypertension develops in roughly 3 per cent after a pulmonary embolism, and pulmonary endarterectomy is genuinely curative in operable cases, with large and durable falls in pulmonary vascular resistance and normalisation of function in many patients. That is one of the real surgical cures in this chapter.

Prevention.

Pharmacological thromboprophylaxis in hospital — STRONG, and the single largest preventable fraction. Low-molecular-weight heparin reduces deep vein thrombosis after major orthopaedic surgery from 40 to 60 per cent down to roughly 10 to 20 per cent on screening. It reduces symptomatic events by roughly 50 to 70 per cent across surgical and medical populations. Hospital-acquired cases are 50 to 60 per cent of the total, so this is a very large lever.

Early mobilisation after surgery and illness — MODERATE, and it costs nothing.

Graduated compression stockings — the grade splits by population, and all three results must be printed. MODERATE in surgical prophylaxis: Cochrane gives roughly a two-thirds reduction in deep vein thrombosis risk when added to other measures in surgical patients, odds ratio about 0.35. CONTESTED to negative after stroke: CLOTS-1, with 2,518 stroke patients, found no benefit from thigh-length stockings and increased skin breaks, 5 against 1 per cent. Null for post-thrombotic syndrome after deep vein thrombosis: the SOX trial, 806 patients, found no reduction, 14.2 against 12.7 per cent, against earlier smaller trials that had reported roughly a 50 per cent reduction. The same garment, three different answers in three different populations.

Intermittent pneumatic compression — MODERATE where anticoagulation is contraindicated; CLOTS-3, with 2,876 stroke patients, found it reduced deep vein thrombosis, 8.5 against 12.1 per cent, odds ratio 0.65, and showed a survival signal.

Mechanical plus pharmacological prophylaxis — STRONG in high-risk surgery. *Avoiding unnecessary immobility and central lines — MODERATE*.

Calf exercises and hydration on long flights — WEAK. Compression stockings on long flights reduce asymptomatic deep vein thrombosis substantially, Cochrane odds ratio about 0.10, and symptomatic events are too rare in the trials to measure.

Extended thromboprophylaxis after cancer surgery and in high-risk ambulatory cancer — MODERATE, from AVERT and CASSINI.

Treatment.

Drug or procedure	Effect size	EML	Off-patent	Cost
Low-molecular-weight heparin, enoxaparin or dalteparin	Initial treatment and prophylaxis; symptomatic events reduced about 50 to 70 per cent as prophylaxis	yes, enoxaparin	yes	tens to hundreds of euro a prophylaxis course; hundreds of euro a treatment course
Unfractionated heparin	Where renal failure or reversal matters	yes	yes	a few to tens of euro a course
Warfarin	Long-standing standard; recurrence reduced about 80 to 90 per cent against no treatment	yes	yes	a few to tens of euro a year plus tens to hundreds of euro a year for INR monitoring
Apixaban	AMPLIFY, 5,395 patients: recurrent venous thromboembolism or related death 2.3 against 2.7 per cent against warfarin, non-inferior; major bleeding 0.6 against 1.8 per cent, relative risk 0.31, a large bleeding advantage	yes	generics from 2026 in several markets	€500–3,000 branded; €30–150 generic
Rivaroxaban	EINSTEIN-DVT and EINSTEIN-PE: non-inferior to standard therapy, less major bleeding in pulmonary embolism	yes	generics available	hundreds to thousands of euro branded; tens to hundreds of euro generic

Drug or procedure	Effect size	EML	Off-patent	Cost
Thrombolysis for high-risk pulmonary embolism, alteplase	PEITHO, 1,005 intermediate-risk patients: death or haemodynamic decompensation 2.6 against 5.6 per cent, odds ratio 0.44, with major bleeding 11.5 against 2.4 per cent and stroke 2.4 against 0.2 per cent. Net benefit only in haemodynamically unstable embolism	yes	yes	hundreds of euro a dose
Catheter-directed thrombolysis or thrombectomy	Thrombus burden reduced; ATTRACT, 692 patients, did not reduce post-thrombotic syndrome, 47 against 48 per cent, and increased bleeding	n/a	n/a	thousands to tens of thousands of euro
Inferior vena cava filter	PREPIC: pulmonary embolism reduced and recurrent deep vein thrombosis increased, with no mortality benefit; PREPIC-2 found no benefit added to anticoagulation	n/a	n/a	thousands of euro
Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension	Curative in operable cases	n/a	n/a	tens of thousands of euro
Compression stockings after deep vein thrombosis	The SOX trial, 806 patients: did not prevent post-thrombotic syndrome, 14.2 against 12.7 per cent; earlier smaller trials by Brandjes and by Prandoni reported roughly a 50 per cent reduction. Both are printed — this is a genuine reversal	no	n/a	tens of euro a pair

Simple means. Early mobilisation and walking cost nothing and reduce stasis; they are standard in all post-operative care. Graduated compression stockings cost tens of euro a pair and need no power and no supply chain beyond the garment. They carry three different answers. In surgical prophylaxis, roughly a two-thirds reduction in deep vein thrombosis, Cochrane odds ratio about 0.35. After stroke, no benefit and more skin breaks, in CLOTS-1. After deep vein thrombosis, no prevention of post-thrombotic syndrome, in SOX. All three are printed, and the common claim that stockings prevent post-thrombotic syndrome is contradicted by the largest trial. Calf and ankle exercises during immobility and long travel reduce stasis, with symptomatic event reduction not measurable in the trials. Leg elevation relieves swelling in acute deep vein thrombosis with no effect on outcome. Hydration during travel and illness is plausible and unquantified. Early recognition of pulmonary embolism — sudden breathlessness, chest pain, collapse — costs nothing and is the decisive step, because untreated embolism carries a case fatality of 25 to 30 per cent and treated embolism 2 to 8 per cent.

The hard limit. Venous thromboembolism cannot be treated without anticoagulation, and anticoagulation cannot be improvised. The minimum chain is heparin, warfarin or a direct oral anticoagulant, plus INR measurement for warfarin. Diagnosis also effectively requires D-dimer and either ultrasound for deep vein thrombosis or computed tomographic pulmonary angiography for embolism; the clinical scores, Wells and Geneva, rule out low-risk cases and cannot confirm. In this condition the simple means are all preventive and the treatment requires an industrial chain.

Gaps. No GBD global burden figure for venous thromboembolism exists, and this entry is part of the seventeen-condition gap in this chapter’s introduction. The widely quoted 10 million events and 300,000 to 500,000 European deaths are model-based estimates rather than measurements and should never be presented as measured counts. Compression stockings after deep vein thrombosis: SOX null against earlier positive trials, the guidelines changed and much clinical practice did not. CLOTS-1 after stroke, no benefit and more harm, against the surgical prophylaxis evidence of benefit — the same device, opposite answers in different populations. ATTRACT: catheter-directed thrombolysis did not reduce post-thrombotic syndrome, against strong prior expectation. Duration of anticoagulation after an unprovoked event is

unresolved, the risk-prediction models perform moderately, and practice varies widely. Thrombophilia testing has no evidence that it improves outcomes and is widely performed. Reported incidence in Asian and African populations is much lower, and how much of that is genuine and how much under-diagnosis is not resolved. Most incidence data come from a handful of North American and Scandinavian cohorts.

> **Depth.** Starts in: a deep vein. Size: 1 cm†; depth +11.19. First complaint: about 5.3 days († 2–14 days after surgery); time depth 45.02. One untreated course: no number ([B] lung embolism within hours).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Varicose veins and chronic venous insufficiency (ICD-11 BD74, BD72)

What it is. The valves in the leg veins fail, so blood falls back down and pools. The veins bulge and the lower leg aches, swells, darkens and eventually ulcerates. It is very common and rarely fatal.

Measured. No global prevalence, death or DALY figure for varicose veins or chronic venous insufficiency is published in the retrieved GBD 2023 tables. GBD does model varicose veins as a cause with years lived with disability, and no figure was retrieved. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all, and the burden is almost certainly substantially under-counted in global data.

Visible varicose veins affect roughly 20 to 35 per cent of western adults; the Edinburgh Vein Study found 40 per cent of men and 32 per cent of women with trunk varices, and the Bonn Vein Study was similar. Chronic venous insufficiency with skin changes, CEAP classes C4 to C6, affects roughly 3 to 7 per cent of adults. An active venous leg ulcer affects roughly 0.1 to 0.3 per cent of adults, rising to 1 to 3 per cent above age 70. Venous ulcers account for 60 to 80 per cent of all leg ulcers. With compression, roughly 60 to 70 per cent of venous ulcers heal within 24 weeks, and recurrence at twelve months is 25 to 50 per cent without continued compression. Prevalence rises steadily with age; incidence is higher in women for symptoms and roughly equal or male-predominant for trunk varices depending on the study. Reported prevalence is lower in African, Asian and rural populations, and whether that is genuine or a reporting artefact is not established. Venous ulcer care consumes roughly 1 to 3 per cent of total healthcare budgets in western European estimates, almost entirely nursing time and dressings.

Where it starts. Age and family history: a parent affected roughly doubles risk, and both parents higher. Female sex for symptomatic disease, and each pregnancy raises risk. Prolonged standing occupations carry an odds ratio of roughly 1.5 to 2. Obesity carries roughly 1.5 to 3, stronger for venous insufficiency and ulceration than for simple varices. A previous deep vein thrombosis causes post-thrombotic venous insufficiency in 20 to 50 per cent of proximal cases. Height and male sex contribute for trunk varices. FOXC2 mutations appear in rare syndromic cases, and genome-wide association studies have found common variants with small effects.

Whether valve failure causes vein wall dilatation or the reverse is unresolved — the descending and ascending theories have not been settled, and that is the central mechanistic question. Why some people with extensive varices never develop skin changes while others ulcerate from modest disease is not predictable. Whether standing occupations cause the condition or select for it is confounded. The relation between visible varices and symptoms is weak: many symptomatic legs have no visible varices and many prominent varices are asymptomatic.

Cure status. Varicose veins: CURABLE by ablation of the refluxing vein. Established chronic venous insufficiency with skin damage: CONTROLLABLE. Post-thrombotic venous insufficiency: RELIEF ONLY.

Endovenous thermal ablation by laser or radiofrequency, ultrasound-guided foam sclerotherapy and surgical stripping all abolish the refluxing segment. Occlusion or abolition rates at five years are roughly 85 to 95 per cent for radiofrequency and laser, 70 to 80 per cent for foam sclerotherapy and about 85 per cent for surgical stripping, from the CLASS trial of 798 patients and the EVRA follow-up series. New varices

form elsewhere over years, so the condition recurs in a substantial minority even though the treated vein stays closed.

The EVRA trial, with 450 patients carrying venous ulcers, found early endovenous ablation plus compression healed ulcers faster than compression alone, median 56 against 82 days, with more ulcer-free time over one year. That is the clearest evidence that correcting the reflux changes the disease course rather than just the appearance.

Established skin damage — lipodermatosclerosis, pigmentation — does not reverse. Compression prevents progression and ulceration and does not restore the skin. Post-thrombotic venous insufficiency has no curative treatment; deep venous valve reconstruction and stenting are used in selected cases with limited evidence.

Prevention.

Preventing deep vein thrombosis — STRONG for preventing post-thrombotic venous insufficiency, which affects 20 to 50 per cent after a proximal clot. Hospital thromboprophylaxis is the measure; see the venous thromboembolism entry.

Compression to prevent ulcer recurrence after healing — STRONG. Cochrane finds compression reduces recurrence substantially, against 25 to 50 per cent recurrence at twelve months without it.

Compression after deep vein thrombosis to prevent post-thrombotic syndrome — CONTESTED. The SOX trial, 806 patients, found no reduction, 14.2 against 12.7 per cent; earlier smaller trials reported roughly a 50 per cent reduction. Both are printed.

Weight management — MODERATE. *Exercise, calf muscle pump training — MODERATE* for symptoms and venous function. *Avoiding prolonged static standing, and moving and activating the calf muscles — WEAK*, mostly observational. *Compression during pregnancy — WEAK*: symptoms are reduced and prevention of varices is not established.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Graduated compression, stockings or bandaging	The foundation of all venous care. Cochrane: compression heals more venous ulcers than no compression, relative risk about 1.8; multi-component and elastic systems better than single-layer; 60 to 70 per cent healing by 24 weeks	no	n/a	tens of euro a pair, replaced every three to six months; bandages a few to tens of euro an application
Endovenous thermal ablation, laser or radiofrequency	Five-year occlusion 85 to 95 per cent; EVRA ulcer healing median 56 against 82 days with compression alone	n/a	n/a	hundreds to thousands of euro
Ultrasound-guided foam sclerotherapy	Five-year success 70 to 80 per cent; the cheapest ablative option	Polidocanol and sodium tetradecyl sulfate: no	yes	hundreds of euro
Surgical stripping and ligation	Five-year success about 85 per cent; more post-operative pain than endovenous methods	n/a	n/a	thousands of euro
Pentoxifylline, adjunct for venous ulcers	Cochrane: ulcer healing improved, relative risk 1.70 (1.30–2.24), added to compression	no	yes	tens to hundreds of euro a year
Micronised purified flavonoid fraction or horse chestnut	Oedema and symptoms modestly reduced; Cochrane rates the evidence low to moderate	no	yes	hundreds of euro a year
Aspirin, adjunct for ulcer healing	Small trials positive; the larger ASPiVLU and AVURT trials null	yes	yes	a few euro a year

Intervention	Effect size	EML	Off-patent	Cost
Antibiotics for venous ulcers	No benefit without clinical infection, per Cochrane; routine use is inappropriate	yes	yes	Varies
Skin grafting or bioengineered skin	For large non-healing ulcers; moderate evidence	n/a	n/a	thousands to tens of thousands of euro

Simple means. This is the condition in the chapter where simple means do the most work.

Compression is the single most effective treatment for chronic venous disease, and it is a garment or a bandage. Cochrane finds compression heals substantially more venous ulcers than no compression, relative risk about 1.8, with 60 to 70 per cent healed by 24 weeks, and it reduces recurrence from 25 to 50 per cent at twelve months. It costs tens of euro a pair, or a few to tens of euro an application for bandaging. No electricity, no drug, no procedure. The binding constraints are correct application, since it must be graduated and firm; patient tolerance; and excluding arterial disease first, because full compression on an ischaemic leg causes necrosis, so an ankle-brachial index or at least palpable foot pulses are required before applying it.

Simple non-adherent dressings carry an important economic finding: Cochrane found no dressing type superior to simple low-adherent dressings beneath compression. The expensive advanced dressings have not been shown to outperform cheap ones, and compression is what heals the ulcer.

Leg elevation above heart level for thirty minutes several times daily reduces oedema; standard advice, with the effect on healing not well quantified. Calf-muscle pump exercise, heel raises and walking improve venous return and calf pump function, and small trials show improved healing and reduced symptoms. Weight loss reduces venous pressure and ulcer risk. Skin care and emollients prevent fissuring and cellulitis in lipodermatosclerosis at very little cost. Avoiding prolonged standing and taking movement breaks helps. Foam sclerotherapy is the cheapest ablative option at hundreds of euro and needs only ultrasound and a sclerosant, not a laser or a theatre.

Gaps. No GBD global figure was retrieved for varicose veins or chronic venous insufficiency despite a prevalence of 20 to 35 per cent, and this entry is part of the seventeen-condition gap in this chapter's introduction. Compression after deep vein thrombosis to prevent post-thrombotic syndrome is unresolved: SOX null against earlier positive trials. The descending against ascending theory of valve failure is unsettled, so the basic mechanism is not agreed. Visible varices correlate poorly with symptoms, which makes prevalence figures of limited clinical meaning and treatment indications contested. Lower reported prevalence in African and Asian populations is unresolved as genuine or as detection. Advanced dressings have a large market and no demonstrated advantage over simple dressings under compression. Long-term comparative data beyond five years between endovenous methods and surgery are thin, and recurrence definitions differ between trials. Pentoxifylline has a positive Cochrane result, relative risk 1.70, and is barely used, and that gap between evidence and practice is unexplained.

> **Depth.** Starts in: a vein valve. Size: 5 mm†; depth +10.56. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

The valves, the muscle and the sac

Rheumatic heart disease (ICD-11 BA00–BA0Z, 1B40–1B41)

What it is. A throat infection with group A streptococcus sets off an immune reaction that scars the heart valves. It happens in childhood and the damage shows up years later as a leaking or narrowed valve. It is almost entirely a disease of poverty.

Measured. WHO gives rheumatic heart disease as about 2 per cent of all cardiovascular deaths, which against the WHO total of 19.8 million is roughly 0.4 million deaths. Global prevalence at all ages was 54.8 million in 2021, up from 32.3 million in 1990, from GBD 2021 as cited in a 2025 analysis in Frontiers in Cardiovascular Medicine. More than 11.6 million children and young people aged 5 to 19 are affected.

In ages 5 to 19, from GBD 2021. Age-standardised incidence rose from 77.98 per 100,000 in 1990 to 93.96 in 2021 (95 per cent CI 62.05–134). Age-standardised prevalence rose from 498.49 to 588.46 per 100,000, estimated annual percentage change +0.42. Age-standardised mortality fell from 1.23 to 0.52 per 100,000, estimated annual percentage change −2.71. Prevalence rose most in the 10 to 14 group and mortality fell most in the 5 to 9 group. Women aged 15 to 19 had the highest incidence and prevalence; women have higher prevalence, men higher mortality.

Geography: prevalence is highest in sub-Saharan Africa and south Asia, and low and low-middle sociodemographic index countries carry the greatest burden. Eritrea has the highest incidence at 252.88 per 100,000; the Republic of the Congo the highest prevalence at 1,517.35; Niue the highest mortality at 5.38; Sweden the lowest prevalence at 2.79. Incidence and prevalence are rising and mortality is falling in nearly all regions, with south Asia showing the fastest rise in incidence and prevalence.

The source carries three internal inconsistencies, and they must travel with its figures. Its Discussion describes incidence rising from 1995 to 2015 and then falling from 2015 to 2021, which contradicts the abstract's overall 1990 to 2021 increase. Its Results say incidence was higher in men while its Discussion says significantly higher in females. And its abstract gives a 1990 mortality upper confidence limit of 19.89 where Table 1 gives 1.48.

Where it starts. Untreated group A streptococcal pharyngitis. Roughly 0.3 to 3 per cent of untreated streptococcal sore throats lead to acute rheumatic fever in susceptible populations, and roughly 30 to 50 per cent of acute rheumatic fever episodes leave valve damage. Recurrent streptococcal infection is the main driver of progressive valve damage, each recurrence adding injury. Household crowding, poor housing and limited access to primary care are the dominant determinants, and this is the clearest social-gradient disease in the chapter. Acute rheumatic fever is concentrated in ages 5 to 15. Genetic susceptibility shows HLA class II associations with DR7 and DR4, familial clustering, and monozygotic twin concordance of roughly 44 per cent against 12 per cent dizygotic. Differences between group A streptococcal emm types exist and the relation to rheumatogenicity is disputed. Skin infection, impetigo, as an alternative route to rheumatic fever is proposed in high-burden Indigenous populations and is not established.

Why only a small minority of people with streptococcal pharyngitis develop rheumatic fever is not explained. The autoimmune account — molecular mimicry between streptococcal M protein and cardiac myosin — is well supported and does not predict who will react. Whether specific rheumatogenic strains exist is contested. There is no vaccine, and the historical concern that a vaccine might itself provoke rheumatic autoimmunity has slowed development; several candidates are now in early trials. Why incidence is rising in ages 5 to 19 while mortality falls is not explained in the source.

Cure status. Acute rheumatic fever and streptococcal pharyngitis: CURABLE. Established rheumatic valve disease: CONTROLLABLE.

Penicillin eradicates the infection and, given within nine days of symptom onset, prevents the first episode of rheumatic fever; the original United States military trials showed roughly a 70 to 80 per cent reduction.

For established valve disease, percutaneous balloon mitral valvuloplasty for rheumatic mitral stenosis with suitable anatomy has a procedural success of 80 to 95 per cent, with immediate doubling of valve area and restenosis-free survival of roughly 50 to 70 per cent at ten years. In suitable anatomy it is as effective as open surgery, far cheaper, and performed by catheter. Mitral valve repair in rheumatic disease is less durable than in degenerative disease because the leaflets themselves are scarred, and replacement is often required. Valve replacement relieves the lesion permanently; a mechanical valve commits the patient to lifelong warfarin, and a bioprosthesis to re-operation in ten to fifteen years. The rheumatic process itself is not cured by surgery, and secondary prophylaxis must continue.

Prevention. This is the condition in the chapter with the clearest, cheapest and most neglected prevention.

Secondary prophylaxis with benzathine benzylpenicillin intramuscularly every three to four weeks — STRONG, and the single highest-value intervention here. Cochrane and cohort evidence give a reduction in recurrence of acute rheumatic fever of roughly 80 to 90 per cent against no prophylaxis, with reduced progression of valve disease. Intramuscular administration is clearly superior to oral. Cost: a fraction of a euro per injection and a few euro per patient-year. The UNICEF indicative price in October 2026 for benzathine benzylpenicillin powder for injection, 2.4 million IU, was US$29.49 per box of 50 vials on one page of the catalogue and US$29.12 on another, which works out at about US$0.59 a vial; the single-vial pack with solvent was US$3.01, five times as much per dose. Benzathine benzylpenicillin is on the 24th Model List, in section 6.2.1, the Access group antibiotics, with syphilis as its listed first-choice indication. This is arguably the largest measured mortality and disability benefit per euro in this entire chapter.

Primary prophylaxis: penicillin for streptococcal pharyngitis — STRONG. Treatment within nine days of onset reduces first-episode rheumatic fever by roughly 70 to 80 per cent, and Cochrane confirms that antibiotic treatment of sore throat reduces acute rheumatic fever, relative risk about 0.27.

Housing, crowding reduction and access to primary care — STRONG historically. Rheumatic fever disappeared from western Europe and North America largely before widespread penicillin use, as housing and nutrition improved: the decline began in the 1900s and antibiotics arrived in the 1940s. This is the strongest historical evidence in the chapter that a non-medical measure eliminated a major disease.

Oral penicillin for secondary prophylaxis — MODERATE, clearly inferior to intramuscular, used where injections are refused or unavailable.

Echocardiographic screening of schoolchildren — CONTESTED. It detects large amounts of subclinical borderline disease whose natural history and treatment benefit are not established, and WHO has not recommended population echocardiographic screening.

Vaccine — none exists. Candidates are in early trials.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Benzathine benzylpenicillin intramuscularly, three- to four-weekly, secondary prophylaxis	Recurrence reduced about 80 to 90 per cent; valve progression prevented	yes, section 6.2.1	yes	Under one euro an injection; a few euro a patient-year. UNICEF indicative price October 2026 about US$0.59 a vial in a box of 50
Phenoxymethylpenicillin or benzylpenicillin, acute pharyngitis	First-episode rheumatic fever reduced about 70 to 80 per cent	yes	yes	a few to a few euro a course
Aspirin or naproxen, acute rheumatic fever arthritis	Symptom control; does not alter cardiac outcome	yes	yes	a few to tens of euro a course
Corticosteroids, severe carditis	Cochrane: no clear reduction in cardiac valve damage at one year, relative risk 0.87 — a negative result against long practice	yes	yes	a few to tens of euro a course
Diuretics, ACE inhibitors, beta blockers, for heart failure from valve disease	Symptom and afterload management	yes	yes	tens of euro a year
Warfarin, mechanical valve or atrial fibrillation with mitral stenosis	Essential; stroke prevention	yes	yes	a few to tens of euro a year plus tens to hundreds of euro for INR monitoring
Percutaneous balloon mitral valvuloplasty	Success 80 to 95 per cent; restenosis-free survival 50 to 70 per cent at ten years	n/a	n/a	thousands of euro far cheaper than surgery
Valve repair	Less durable in rheumatic than degenerative disease	n/a	n/a	thousands to tens of thousands of euro

Intervention	Effect size	EML	Off-patent	Cost
Valve replacement, mechanical or bioprosthetic	Relieves the lesion; mechanical commits the patient to lifelong warfarin	n/a	n/a	thousands to tens of thousands of euro; mechanical valve thousands of euro

The central economic fact. A disease affecting 54.8 million people and killing roughly 0.4 million a year is prevented by an injection costing under one euro, given every three to four weeks, reducing recurrence by 80 to 90 per cent. Benzathine penicillin has been on the market since the 1950s, is on the Essential Medicines List†, is off-patent, and has suffered repeated global supply shortages because its margins are too low to attract manufacturers.

Simple means. Benzathine penicillin injections are the model case of a no-industrial-chain intervention with a large mortality benefit. US$0.59 a vial at UNICEF indicative prices, October 2026, an 80 to 90 per cent recurrence reduction, and a requirement of a needle, a syringe and someone trained to inject. No electricity, no laboratory, no refrigeration beyond basic. Treating sore throats with oral penicillin costs a few to a few euro a course and prevents 70 to 80 per cent of first rheumatic fever episodes; the constraint is access to a health worker within nine days, not the drug.

Reducing household crowding and improving housing eliminated rheumatic fever in western Europe and North America before antibiotics, with no medical chain at all. Hand hygiene and respiratory hygiene to reduce streptococcal transmission are plausible and unquantified for this endpoint. Register-based recall for injections is organisational rather than technological: the main cause of secondary prophylaxis failure is missed doses, and a paper register with community health workers raises adherence substantially in programme reports. Auscultation with a stethoscope detects most significant valve lesions, with moderate sensitivity against echocardiography, roughly 40 to 60 per cent for mild disease and better for severe; a stethoscope costs a few euro and needs nothing.

The hard limit: severe valve disease needs valvuloplasty or surgery. Balloon valvuloplasty is the cheap end of that chain at thousands of euro and needs a catheter laboratory, and nothing below that treats a tight mitral valve.

Gaps. The main source carries three internal contradictions — the direction of the incidence trend, the sex difference in incidence, and the 1990 mortality confidence limit — and any figure taken from it must carry them. WHO gives rheumatic heart disease as about 2 per cent of cardiovascular deaths, roughly 0.4 million, and GBD-based analyses give varying counts; no precise global death count was retrieved. Why incidence is rising in ages 5 to 19 while mortality falls is not explained. Echocardiographic screening is contested: it finds large amounts of borderline disease of unknown significance, and no trial shows that treating it helps. Corticosteroids for acute carditis: Cochrane found no benefit, relative risk 0.87, against long-standing practice. There is no vaccine, and the historical safety concern has never been formally resolved. Benzathine penicillin supply shortages recur globally for a sub-euro off-patent drug; that is a market failure rather than a scientific gap, and it is the binding constraint on prevention. Whether skin infection can trigger rheumatic fever is unresolved and matters for prevention strategy in high-burden Indigenous populations. Surveillance in the highest-burden countries is weakest, and the GBD figures for sub-Saharan Africa rest on sparse primary data.

> **Depth.** Starts in: group A streptococcus. Size: 1 µm†; depth +2.81. First complaint: about 17 days († 2–3 weeks after a throat infection; [B] valve damage years later); time depth 46.09. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names a late stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Cardiomyopathies (ICD-11 BC43)

What it is. The heart muscle itself is diseased — stretched thin and weak, abnormally thickened, or stiff and infiltrated. The valves and arteries may be normal. Many forms run in families.

Measured. No global prevalence, death or DALY figure for cardiomyopathy and myocarditis was retrieved from the GBD 2023 tables. GBD groups cardiomyopathy and myocarditis as a cause, and GBD 2019 estimates gave roughly 354,000 deaths globally, which is an earlier round.

Hypertrophic cardiomyopathy has a prevalence of 1 in 500 by classical echocardiographic series, revised to roughly 1 in 200 when genetic carriers are included; it is the commonest inherited cardiac condition. Dilated cardiomyopathy has a prevalence of roughly 1 in 250 to 1 in 2,500 depending on definition, with an incidence of roughly 5 to 7 per 100,000 a year. Arrhythmogenic right ventricular cardiomyopathy runs at roughly 1 in 1,000 to 1 in 5,000. Transthyretin cardiac amyloidosis is present in roughly 10 to 15 per cent of men over 60 with heart failure with preserved ejection fraction and left ventricular hypertrophy, and the wild-type form is far commoner than previously thought. Peripartum cardiomyopathy incidence varies from 1 in 100 pregnancies in Nigeria and 1 in 300 in Haiti to 1 in 1,000 to 4,000 in Europe and North America, a ten- to fortyfold geographic range. Chagas cardiomyopathy: roughly 6 to 7 million people are infected with Trypanosoma cruzi, predominantly in Latin America, of whom 20 to 30 per cent develop cardiomyopathy over decades. Endemic restrictive cardiomyopathy, endomyocardial fibrosis, is a leading cause of heart failure in parts of equatorial Africa and is almost absent from global datasets. Hypertrophic cardiomyopathy is the commonest cause of sudden cardiac death in young athletes in United States series, roughly a third of cases, while in UK and Italian series arrhythmogenic cardiomyopathy and normal-heart sudden death are relatively more prominent. Hypertrophic cardiomyopathy presents from adolescence onward, transthyretin amyloidosis after 60, and peripartum cardiomyopathy in the weeks around delivery.

Where it starts. Hypertrophic cardiomyopathy: autosomal dominant sarcomere gene mutations, with MYH7 and MYBPC3 accounting for roughly 70 per cent of genotype-positive cases, and a pathogenic variant found in roughly 30 to 60 per cent of probands. Dilated cardiomyopathy: 30 to 40 per cent familial, with truncating titin variants the commonest single finding at roughly 15 to 25 per cent of familial cases, and also LMNA with its high arrhythmic risk, MYH7, RBM20, FLNC and DSP. Arrhythmogenic cardiomyopathy: desmosomal genes PKP2, DSG2, DSC2, DSP and JUP. Acquired dilated cardiomyopathy: alcohol, with a threshold of roughly 80 g a day for years; anthracycline and trastuzumab chemotherapy, dose-dependent; viral myocarditis; iron overload from haemochromatosis or transfusion; thyroid disease; cocaine and methamphetamine; uncontrolled tachyarrhythmia; and the peripartum state. Cardiac amyloidosis: wild-type transthyretin misfolding with age, or hereditary TTR variants, of which V122I is carried by roughly 3 to 4 per cent of people of West African ancestry. Chagas disease: vector-borne T. cruzi infection. Endomyocardial fibrosis: cause unknown, with hypotheses including eosinophilia, helminth infection, cerium and magnesium soil content and dietary factors, none established.

Penetrance and expressivity in hypertrophic cardiomyopathy vary widely within the same family carrying the same variant and are not predictable, which is the central unsolved problem for genetic counselling. In 40 to 70 per cent of hypertrophic cardiomyopathy probands no causal variant is found. Risk stratification for sudden death is imperfect: the HCM Risk-SCD model and the United States criteria disagree on a substantial minority of patients, and most sudden deaths occur in people not identified as high risk. The cause of endomyocardial fibrosis, a leading cause of heart failure in parts of Africa, is entirely unknown. Why peripartum cardiomyopathy incidence varies ten- to fortyfold geographically is unexplained. Whether viral myocarditis commonly progresses to dilated cardiomyopathy, and in whom, is not established.

Cure status. Genetic cardiomyopathies — hypertrophic, dilated, arrhythmogenic: CONTROLLABLE. Tachycardia-induced cardiomyopathy: CURABLE. Alcoholic cardiomyopathy: CONTROLLABLE. Iron-overload and thyrotoxic cardiomyopathy: CURABLE on treating the cause. Chagas cardiomyopathy once established: RELIEF ONLY. Cardiac transthyretin amyloidosis: CONTROLLABLE, newly so.

For the genetic forms, no treatment removes the mutation, and treatment reduces symptoms and sudden-death risk. Septal myectomy or alcohol septal ablation for obstructive hypertrophic cardiomyopathy permanently abolishes the outflow gradient; myectomy in experienced centres gives operative mortality under 1 per cent and long-term survival equal to the general population. That is relief of the obstruction rather than cure of the cardiomyopathy, and it is one of the most effective operations in cardiology.

Tachycardia-induced cardiomyopathy: ablation or rate control of the driving arrhythmia normalises ejection fraction in the majority. Alcoholic cardiomyopathy: substantial recovery in a large minority with

sustained abstinence. Peripartum cardiomyopathy: ejection fraction recovers in roughly 50 to 70 per cent, the most reversible of the dilated cardiomyopathies.

Chagas cardiomyopathy once established is RELIEF ONLY. The BENEFIT trial, with 2,854 patients, found benznidazole reduced parasite detection and did not reduce cardiac clinical progression, hazard ratio 0.93. Antiparasitic treatment is effective in acute and early chronic infection and does not reverse established cardiomyopathy.

Cardiac transthyretin amyloidosis has become CONTROLLABLE. Tafamidis reduced all-cause mortality from 42.9 to 29.5 per cent, hazard ratio 0.70, in ATTR-ACT; patisiran, vutrisiran and eplontersen reduce transthyretin production, and HELIOS-B with vutrisiran showed reduced death and cardiovascular events. CRISPR-based TTR knockout is in trials and is the first plausible one-time cure in this group; outcome data are not yet available and no cure should be claimed. Heart transplantation removes the organ, with median post-transplant survival of roughly 12 to 13 years.

Prevention.

Family screening in genetic cardiomyopathy — STRONG for case-finding. Cascade genetic and echocardiographic screening of first-degree relatives identifies affected relatives in roughly 20 to 50 per cent. It prevents sudden death by enabling defibrillator placement and activity modification; it does not prevent the cardiomyopathy.

Alcohol limitation — STRONG for alcoholic cardiomyopathy. For scale: alcohol-attributable deaths worldwide were 2.6 million in 2019, including 474,000 cardiovascular deaths, and alcohol-attributable death rates per 100,000 fell 20.2 per cent globally between 2010 and 2019.

Iron chelation in transfusion-dependent thalassaemia — STRONG; it transformed survival in thalassaemia major, where cardiac iron overload was the leading cause of death.

Chagas vector control, blood-donor screening and treatment of early infection — STRONG. Vector-control programmes in the Southern Cone reduced transmission by over 90 per cent.

Anthracycline dose limitation, dexrazoxane and cardiac monitoring during chemotherapy — MODERATE. Dexrazoxane reduces clinical heart failure, Cochrane relative risk about 0.29.

Avoiding cocaine and methamphetamine — MODERATE.

Pre-participation athletic screening — CONTESTED. The Italian programme with electrocardiography reported reduced sudden death in athletes; United States and Israeli analyses found no benefit, and false-positive rates and costs are substantial. Guidelines differ between countries and the disagreement is unresolved.

Nothing prevents hypertrophic, arrhythmogenic or familial dilated cardiomyopathy.

Treatment. The proportion of alcoholic cardiomyopathy that recovers with sustained abstinence is not given by the sources used here, which describe recovery only as substantial in a large minority.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Beta blocker, for hypertrophic cardiomyopathy symptoms and for dilated cardiomyopathy	Reduces outflow gradient and symptoms in hypertrophic disease; mortality benefit in dilated disease per the heart failure trials, CIBIS-II hazard ratio 0.66	yes	yes	a few to tens of euro
Verapamil or disopyramide, hypertrophic cardiomyopathy	Gradient and symptoms reduced	yes, verapamil	yes	a few to tens of euro
Four-pillar heart failure therapy for dilated cardiomyopathy	As in the heart failure entry: RALES number needed to treat 9, CIBIS-II 18, DAPA-HF	First three yes	First three yes	tens of euro for the three cheap pillars

Intervention	Effect size	EML	Off-patent	Cost per patient-year
	21			
Septal myectomy, obstructive hypertrophic cardiomyopathy	Abolishes the gradient; operative mortality under 1 per cent in expert centres; long-term survival equal to the general population	n/a	n/a	tens of thousands of euro
Alcohol septal ablation, obstructive hypertrophic cardiomyopathy	Comparable gradient reduction; 10 to 20 per cent need a pacemaker for heart block	n/a	n/a	thousands to tens of thousands of euro
Mavacamten, obstructive hypertrophic cardiomyopathy	EXPLORER-HCM, 251 patients: primary functional endpoint met in 37 against 17 per cent; gradient and symptoms improved; no mortality data	no	no	tens of thousands of euro
Implantable defibrillator	Terminates ventricular arrhythmia; SCD-HeFT hazard ratio 0.77, number needed to treat 14 over five years; DANISH null in non-ischaemic cardiomyopathy	n/a	n/a	tens of thousands of euro
Tafamidis, transthyretin amyloidosis	All-cause mortality 29.5 against 42.9 per cent, hazard ratio 0.70, ATTR-ACT	no	no	hundreds of thousands of euro
Patisiran, vutrisiran, eplontersen, transthyretin amyloidosis	Transthyretin reduced; HELIOS-B reduced death and cardiovascular events	no	no	hundreds of thousands of euro
Benznidazole or nifurtimox, Chagas disease	Effective in acute and early chronic infection; BENEFIT found no reduction in cardiac progression once cardiomyopathy is established, hazard ratio 0.93	yes, both	yes	tens to hundreds of euro a course
Iron chelation, deferoxamine or deferasirox	Transformed survival in thalassaemia major	yes; deferiprone is on the 24th List only as a therapeutic equivalent to deferasirox, not as a selected medicine	Deferoxamine yes	hundreds to tens of thousands of euro
Heart transplantation	Median survival 12 to 13 years	n/a	n/a	hundreds of thousands of euro in the first year

The price range inside this one entry runs from a few euro for a beta blocker to hundreds of thousands of euro for an amyloidosis drug. Both are standing treatments in cardiomyopathy.

Simple means. Alcohol abstinence is curative in a large minority of alcoholic cardiomyopathy and costs nothing. Avoiding competitive high-intensity exertion matters in hypertrophic and arrhythmogenic cardiomyopathy, and the advice now differs by disease, so both results are printed. In arrhythmogenic cardiomyopathy exercise restriction is disease-modifying: endurance exercise accelerates structural progression and arrhythmic events in cohort studies — a behavioural measure with a structural effect and no cost. In hypertrophic cardiomyopathy the blanket restriction has loosened: the LIVE-HCM study found no excess event rate in vigorous exercisers.

Family history taking and cascade screening is the highest-yield no-technology action in genetic cardiomyopathy: a pedigree costs nothing and identifies at-risk relatives. Confirming disease requires echocardiography. Auscultation detects the dynamic systolic murmur of obstructive hypertrophic cardiomyopathy — louder on Valsalva and standing, softer on squatting — with a stethoscope, and the manoeuvres cost nothing. Salt and fluid management and weight monitoring act as in the heart failure entry, with SODIUM-HF null on sodium restriction. Vector control for Chagas disease is largely housing and community work: house improvement, wall plastering, roof replacement and insecticide reduced transmission by over 90 per cent in the Southern Cone programmes. The four cheap heart failure pillars — an ACE inhibitor with a beta blocker and spironolactone at tens of euro a patient-year — carry most of the mortality benefit in dilated cardiomyopathy, and they need a pharmaceutical chain, but a very cheap one.

The hard limit. Hypertrophic obstruction, arrhythmic risk and amyloidosis need surgery, devices or very expensive drugs. For a young person at risk of sudden death from cardiomyopathy the only effective intervention is an implantable defibrillator, and there is no simple-means substitute. Bystander CPR and a public defibrillator are the fallback.

Gaps. No GBD 2023 global burden figure for cardiomyopathy was retrieved, and the roughly 354,000 deaths figure comes from an earlier round. Penetrance in genetic cardiomyopathy is unpredictable, and in 40 to 70 per cent of hypertrophic cardiomyopathy probands no variant is found; genetic counselling operates with that uncertainty. Sudden-death risk stratification is imperfect and the European and American criteria disagree for a substantial minority. Athletic pre-participation electrocardiographic screening is unresolved, with Italian data positive and United States and Israeli analyses negative, and large policy consequences. Exercise advice has reversed in hypertrophic cardiomyopathy with LIVE-HCM while remaining restrictive in arrhythmogenic cardiomyopathy; both are printed. The cause of endomyocardial fibrosis is unknown, and it is a leading cause of heart failure in parts of Africa with almost no representation in global data. Peripartum cardiomyopathy incidence varies ten- to fortyfold geographically, unexplained. Defibrillator benefit in non-ischaemic cardiomyopathy is unresolved. BENEFIT was negative for benznidazole in established Chagas cardiomyopathy, against prior expectation. Amyloidosis drug prices of hundreds of thousands of euro a year make the measured mortality benefit inaccessible to the large majority of affected people worldwide, and no generic pathway exists.

> **Depth.** Starts in: a sarcomere protein. Size: 10 nm†; depth −1.38. First complaint: about 35 years († onset about age 35); time depth 52.11. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Congenital heart disease (ICD-11 LA80–LA8Z)

What it is. The heart is formed wrongly before birth — a hole between chambers, a narrowed valve, vessels joined in the wrong place. Some kinds cause no trouble; others are fatal within days unless corrected. It is the commonest serious birth defect.

Measured. Birth prevalence is roughly 9 per 1,000 live births worldwide, with a meta-analysis range of 8 to 9.4, which is roughly 1.35 million affected births a year. Congenital anomalies of all types carried 54.8 million DALYs in 2023, rank 13 of all causes, and congenital heart anomalies are the largest single component; no separate GBD 2023 figure for congenital heart disease was retrieved. Deaths run at roughly 217,000 to 261,000 a year from congenital heart anomalies in GBD 2017 to 2019 estimates, of which about 70 per cent in the first year of life. WHO’s own congenital disorders fact sheet gives 240,000 newborn deaths within 28 days of birth each year from congenital disorders of all types, plus 170,000 deaths of children aged one month to five years. It gives no prevalence figure for cardiac defects. That page also contradicts itself on the low- and middle-income share: Key Facts gives nine in ten and the body gives about 94 per cent.

Severe or critical disease requiring intervention in the first year affects roughly 2 to 3 per 1,000 live births. Reported birth prevalence has risen from about 0.6 per 1,000 in the 1930s to 1950s to about 9 per 1,000

now, almost entirely from improved echocardiographic detection of mild lesions rather than a true increase. In high-income countries over 90 per cent of children now reach adulthood and adults with congenital heart disease outnumber children with it; in low-income countries a large share still die in infancy, and mortality is roughly ten to twenty times higher in low-income than high-income settings. Roughly 90 per cent of children with congenital heart disease are born in regions without adequate access to cardiac surgical care. The commonest lesions are ventricular septal defect at about 30 per cent of all cases, atrial septal defect, patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot, coarctation and transposition of the great arteries.

Where it starts. Roughly 20 to 30 per cent has an identified genetic cause. Trisomy 21, of which 40 to 50 per cent have a cardiac defect, typically an atrioventricular septal defect. The 22q11.2 deletion, with conotruncal defects. Turner syndrome, with coarctation and bicuspid aortic valve. Noonan, Williams, trisomy 13 and trisomy 18. Pre-gestational maternal diabetes raises risk roughly three- to fivefold and is one of the strongest and most modifiable factors. Maternal rubella infection in the first trimester causes congenital rubella syndrome with patent ductus arteriosus and pulmonary artery stenosis, and is essentially eliminated by vaccination where coverage is high. Uncontrolled maternal phenylketonuria carries high risk. Teratogenic drugs: retinoids, thalidomide, lithium, some anticonvulsants including valproate, and ACE inhibitors and angiotensin receptor blockers in pregnancy. Maternal alcohol, with septal defects in the fetal alcohol spectrum; smoking, a modest increase; obesity, roughly 1.15- to 1.4-fold. Folate deficiency: folic acid fortification is associated with roughly 20 to 40 per cent reductions in some conotruncal and septal defects in before-and-after national studies from Canada and Quebec — ecological, and smaller than its effect on neural tube defects. Assisted reproduction gives a modest increase of roughly 1.3- to 1.5-fold, partly confounded. Consanguinity raises risk in populations with high rates, and WHO describes the risk as nearly doubling, without a figure.

In roughly 70 to 80 per cent of cases no cause is identified at all. Most congenital heart disease is sporadic, in families with no history and mothers with no identified exposure. Why a specific structure fails to form is not explained in the individual case. The large majority of the genetic contribution is not single-gene: de novo variants, copy number variation and oligogenic models account for part of it, and much remains unassigned. Whether the rise in reported birth prevalence contains any true increase alongside the detection effect is not resolved.

Cure status. Patent ductus arteriosus, secundum atrial septal defect, ventricular septal defect, coarctation, pulmonary valve stenosis and transposition of the great arteries after an arterial switch: CURABLE. Small ventricular septal defects, roughly 70 to 80 per cent of which close by school age: SELF-LIMITING. Tetralogy of Fallot after repair: CONTROLLABLE. Single-ventricle lesions palliated to a Fontan circulation: CONTROLLABLE. Eisenmenger syndrome: RELIEF ONLY.

This is the chapter’s clearest set of procedural cures. Patent ductus arteriosus closure, by transcatheter device or surgical ligation, has a success rate of roughly 95 to 99 per cent with complete closure and normal life expectancy afterwards, and transcatheter closure in infants and children has largely replaced surgery. That is a complete cure of a potentially fatal lesion by one procedure. Secundum atrial septal defect closure by transcatheter device has a procedural success of 95 to 98 per cent, with normalisation of right heart loading and normal life expectancy if done in childhood or early adulthood. Ventricular septal defect closure, surgical or transcatheter in selected anatomy, has high success, and small defects close spontaneously in roughly 70 to 80 per cent by school age, so many need no treatment at all. Coarctation repair, by surgery in infancy or balloon and stent in older children and adults, relieves the obstruction, and long-term hypertension persists in 25 to 50 per cent, so it is cure of the obstruction and not of the arteriopathy. Pulmonary valve stenosis: balloon valvuloplasty has a success of roughly 85 to 95 per cent and is usually durable and effectively curative. Tetralogy of Fallot repair has early mortality now under 2 per cent in high-income centres with over 90 per cent survival to thirty years, and pulmonary regurgitation leads to re-operation for valve replacement in a large proportion: repaired rather than cured. Transposition of the great arteries treated by arterial switch has operative survival over 95 per cent with excellent long-term function, close to a cure, with lifelong surveillance needed for the coronary anastomoses and the neo-aortic valve.

Not curable: single-ventricle lesions — hypoplastic left heart, tricuspid atresia — are palliated by staged surgery to a Fontan circulation, with roughly 60 to 70 per cent surviving to twenty years and progressive Fontan-associated liver disease, protein-losing enteropathy, arrhythmia and eventual failure; transplantation is the endpoint for many. Eisenmenger syndrome, irreversible pulmonary hypertension from a late-closed shunt, is RELIEF ONLY, and closing the defect at that stage is harmful.

Prevention.

Rubella vaccination — STRONG, and one of the clearest primary preventions of a structural birth defect in existence. Congenital rubella syndrome with its cardiac lesions has been eliminated in the Americas and in much of Europe through vaccination. Rubella coverage in 2025 was 73 per cent globally.

Pulse oximetry screening of newborns — STRONG for detection, not prevention, and it saves lives. Adding pulse oximetry to clinical examination detects critical congenital heart disease with a sensitivity of roughly 76 per cent and a false-positive rate of roughly 0.14 per cent, from a meta-analysis of 229,421 newborns. United States states that mandated screening showed roughly a 33 per cent reduction in infant deaths from critical congenital heart disease. A pulse oximeter costs tens to hundreds of euro and this is the highest-value detection intervention in the entry.

Pre-conception glycaemic control in maternal diabetes — STRONG. Risk falls from the three- to fivefold excess toward baseline with good peri-conceptional control.

Avoiding teratogens in pregnancy — STRONG: retinoids, valproate, lithium, ACE inhibitors and angiotensin receptor blockers. *Alcohol avoidance in pregnancy — STRONG*. *Maternal phenylketonuria dietary control — STRONG*.

Folic acid fortification — MODERATE. Roughly 20 to 40 per cent reductions in some septal and conotruncal defects in national before-and-after studies; these are ecological and the effect is much less certain than for neural tube defects, so the grade is MODERATE rather than STRONG.

Antenatal ultrasound screening — MODERATE for detection; detection rates for major lesions range from under 30 per cent to over 80 per cent between programmes.

Maternal weight management and smoking cessation — MODERATE. *Genetic counselling in consanguineous populations and after an affected child — MODERATE*.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Prostaglandin E1, alprostadil, infusion	Keeps the ductus open in duct-dependent lesions; it is the drug that keeps a newborn alive until surgery and there is no substitute	yes	yes	tens to hundreds of euro a course
Ibuprofen, indomethacin or paracetamol, to close a patent ductus in preterm infants	Pharmacological closure in roughly 70 to 80 per cent of preterm cases; paracetamol comparably effective to ibuprofen in meta-analysis	yes, all three	yes	a few to tens of euro a course
Transcatheter patent ductus closure	Success 95 to 99 per cent, curative	n/a	n/a	thousands of euro device-dominated
Transcatheter atrial septal defect closure	Success 95 to 98 per cent, curative	n/a	n/a	thousands to tens of thousands of euro
Balloon pulmonary valvuloplasty	Success 85 to 95 per cent, usually curative	n/a	n/a	thousands of euro
Surgical closure of a septal defect	High success, curative	n/a	n/a	thousands to tens of thousands of euro depending on country
Tetralogy of Fallot repair	Early mortality under 2 per cent; over 90 per cent survival to thirty years	n/a	n/a	thousands to tens of thousands of euro
Arterial switch for	Operative survival over 95	n/a	n/a	tens of thousands of euro

Intervention	Effect size	EML	Off-patent	Cost
transposition	per cent			
Staged Fontan palliation	60 to 70 per cent survival to twenty years, with progressive complications	n/a	n/a	tens of thousands to hundreds of thousands of euro across stages
Diuretics, ACE inhibitors, digoxin, for heart failure in congenital disease	Symptom management	yes	yes	a few to tens of euro a year
Endocarditis prophylaxis, amoxicillin before dental procedures in high-risk lesions	Indications narrowed sharply in the 2007 and 2008 guidelines; evidence of benefit is weak	yes	yes	a few to a few euro a dose
Pulmonary vasodilators in Eisenmenger syndrome, bosentan or sildenafil	Exercise capacity improved, per BREATHE-5	**Neither bosentan nor sildenafil is on the 24th Model List in any form**	Sildenafil yes	hundreds to tens of thousands of euro a year

Simple means. Pulse oximetry on every newborn is the single highest-value low-technology intervention in this entry and it requires no laboratory, no specialist and almost no training. A device costs tens to hundreds of euro and the measurement is one reading in each foot and hand at 24 hours of age. Sensitivity for critical congenital heart disease is roughly 76 per cent with false positives at 0.14 per cent, and mandated screening was followed by roughly 33 per cent fewer infant deaths from critical disease in United States states.

Clinical examination of the newborn costs nothing: auscultation for murmurs, femoral pulse palpation, where absent or weak femoral pulses indicate coarctation, and observation of colour, feeding and breathing. Its sensitivity alone is poor for critical lesions, which is exactly why pulse oximetry adds so much. Rubella vaccination eliminates congenital rubella syndrome and is on the Essential Medicines List, off-patent, and part of routine immunisation. Pre-conception folic acid costs €1 to €5 a year and is on the Essential Medicines List†; the UNICEF indicative price in October 2026 for folic acid 5 mg was US$5.41 per bottle of 1,000 tablets on one page and US$5.39 on another, about US$0.0054 a tablet. Avoiding alcohol and teratogenic drugs in pregnancy costs nothing. Breastfeeding support and high-calorie feeding for infants who fail to thrive from the work of breathing is nursing and nutritional support with no technology.

The knee-chest position in a tetralogy of Fallot hypoxic spell is a free manoeuvre that raises systemic vascular resistance and aborts the spell. That is a technique that saves lives with nothing but hands.

The hard limit, stated plainly. Most congenital heart disease requiring treatment needs cardiac surgery or interventional catheterisation: a theatre, cardiopulmonary bypass, paediatric anaesthesia, intensive care and trained surgeons. Roughly 90 per cent of affected children are born where that chain does not exist, and mortality is ten to twenty times higher as a result. Prostaglandin E1 keeps a duct-dependent newborn alive but only until surgery; it is a bridge to a chain that must exist. There is no simple-means substitute for cardiac surgery.

Gaps. No GBD 2023 figure for congenital heart disease specifically was retrieved; it sits inside congenital anomalies at 54.8 million DALYs, rank 13. In 70 to 80 per cent of cases no cause is identified. The rise in reported birth prevalence from 0.6 to 9 per 1,000 over eighty years† is attributed to detection, and how much if any is a true increase is unresolved. Antenatal detection rates range from under 30 per cent to over 80 per cent between programmes at similar resource levels, and the reasons are not well characterised. Folic acid's effect on cardiac defects is ecological and much weaker than for neural tube defects, and grades differ between sources. Endocarditis prophylaxis indications were narrowed on weak evidence and the change remains debated, with UK and United States and European guidance differing. Long-term outcome data for Fontan patients beyond thirty years barely exist, since the first cohorts are only now reaching that age. Mortality data from the regions carrying most of the burden are the weakest, so the global death count of roughly 217,000 to 261,000 is a model output rather than a measurement. Surgical outcome figures come overwhelmingly from high-volume high-income centres, and population outcomes in low-income settings

are largely unmeasured. WHO's congenital disorders fact sheet contradicts itself on the low- and middle-income share, nine in ten against 94 per cent, and is dated February 2023.

> **Depth.** Starts in: the embryonic heart tube. Size: 1 mm†; depth +9.10. First complaint: about 9 months († from conception to birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Infective endocarditis (ICD-11 BB40)

What it is. Bacteria settle on a heart valve and build a crumbling mass of infected tissue. Fever drags on for weeks, fragments break off and travel to the brain or limbs, and the valve is destroyed. Untreated it is almost always fatal.

Measured. No global prevalence, death or DALY figure for endocarditis was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all. GBD 2019 estimates gave roughly 66,000 deaths a year globally with incidence up roughly 50 per cent since 1990, and that is an earlier round.

Incidence in high-income countries is roughly 3 to 15 per 100,000 person-years and rising. In-hospital mortality is 15 to 25 per cent and one-year mortality 25 to 40 per cent despite treatment, from the ICE-PCS and EURO-ENDO registries. Roughly 40 to 50 per cent of patients undergo valve surgery during the index admission in high-income series. The microbiology has shifted: Staphylococcus aureus is now the commonest cause in high-income countries at about 25 to 30 per cent, displacing the viridans streptococci, and enterococci are rising with age and healthcare exposure. In low- and middle-income countries rheumatic valve disease remains the dominant substrate and streptococci the dominant organisms, and patients are decades younger. The median age has risen from roughly 40 in the 1960s to 65 to 70 now in high-income countries, tracking the shift from rheumatic to degenerative and prosthetic valve substrate. Injecting drug use accounts for a rising share, with an incidence in that group of roughly 1 to 5 per cent a year, far higher than any other risk group. Prosthetic valve endocarditis runs at roughly 1 per cent in the first year after valve replacement and 0.3 to 0.6 per cent a year thereafter.

Where it starts. A damaged or prosthetic valve plus a bacteraemia; the two together are the requirement. A prosthetic heart valve is the highest single structural risk. Previous endocarditis strongly raises the risk of a further episode. Rheumatic valve disease dominates in low-income settings. Congenital heart disease, especially unrepaired cyanotic lesions and prosthetic material, contributes. Degenerative valve disease — calcific aortic stenosis, mitral annular calcification — is the dominant substrate in ageing high-income populations. Injecting drug use gives right-sided tricuspid endocarditis, usually with S. aureus. Intravascular catheters, haemodialysis and pacemaker and defibrillator leads make healthcare-associated endocarditis roughly 25 to 30 per cent of cases in high-income series.

Poor dental health and dental procedures need care. Dental procedures were long assumed causal, and case-control studies by Strom and colleagues found no significant association between dental procedures and endocarditis, while chewing and tooth-brushing produce bacteraemia far more often than dental visits. That finding is why the prophylaxis guidance was narrowed.

Why a transient bacteraemia, which occurs routinely with chewing and brushing, settles on a valve on one occasion and not the thousands of others is not explained. Whether antibiotic prophylaxis before dental procedures prevents endocarditis has never been tested in a randomised trial and almost certainly never will be, because the event is too rare. The guidance change rests on case-control and ecological data, and the subsequent observation of rising endocarditis incidence after the restriction in some countries, notably England after the 2008 NICE guidance, has been read both as evidence of harm from the change and as part of a longer pre-existing trend. That disagreement is unresolved. The optimal timing of valve surgery is also not settled by adequate trial evidence.

Cure status. CURABLE.

A completed course of appropriate intravenous antibiotics, with valve surgery where indicated, eradicates the infection in the majority of survivors, and relapse rates are roughly 2 to 6 per cent. That is a cure of the infection. But in-hospital mortality is 15 to 25 per cent and one-year mortality 25 to 40 per cent; the valve damage is permanent, and many patients are left with a prosthetic valve that itself carries a renewed endocarditis risk of 0.3 to 0.6 per cent a year. Treatment requires two to six weeks of intravenous antibiotics, which means prolonged hospital admission or an outpatient parenteral service.

The POET trial, with 400 patients, found that switching to oral antibiotics after an initial intravenous period was non-inferior to continued intravenous therapy, with a primary composite of 12.1 against 12.1 per cent — a significant finding for resource-limited settings and for shortening admission. On surgical timing, the EASE trial, with 76 patients, found early surgery reduced the composite of death and embolic events, 3 against 23 per cent, in a selected group, and the evidence base for timing is otherwise observational.

Prevention.

Aseptic technique and prompt removal of intravascular catheters — STRONG for healthcare-associated endocarditis, which is 25 to 30 per cent of cases. *Chlorhexidine skin preparation before vascular access — STRONG* for catheter-related bacteraemia generally. *Treating S. aureus bacteraemia promptly and adequately — STRONG*.

Preventing rheumatic heart disease with benzathine penicillin — STRONG where rheumatic disease is the substrate: a few euro a patient-year for an 80 to 90 per cent reduction in recurrence.

Dental and oral hygiene — MODERATE, and probably more important than procedural prophylaxis given that routine chewing and brushing cause more cumulative bacteraemia than dental visits.

Needle and syringe programmes and opioid agonist therapy in injecting drug use — MODERATE for reducing injection-related bacteraemia, by reducing injection frequency and sharing.

Antibiotic prophylaxis before dental procedures in the highest-risk group — CONTESTED, and both readings must be printed. No randomised trial exists and none is feasible. Indications were narrowed sharply in 2007 and 2008 by the American Heart Association and essentially withdrawn in England by NICE in 2008, then partly reinstated by NICE in 2016. Case-control data found no association between dental procedures and endocarditis; ecological data from England showed rising incidence after the restriction, and that has been interpreted both ways. Current guidance restricts prophylaxis to prosthetic valves, previous endocarditis and some congenital lesions, before dental procedures involving gingival manipulation. Cost: a few to a few euro a dose of amoxicillin.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Benzylpenicillin or amoxicillin with gentamicin, streptococcal and enterococcal disease	Cure in the majority; two- to six-week courses	yes, all	yes	€20–200 a course. UNICEF indicative price October 2026 for amoxicillin 250 mg dispersible: US$0.54 for ten tablets, about US$0.054 a tablet
Flucloxacillin or cloxacillin, methicillin-sensitive S. aureus	The drug of choice, and clearly better than vancomycin for sensitive strains	yes	yes	tens to hundreds of euro a course
Vancomycin, resistant strains or penicillin allergy	Standard for resistant S. aureus; requires level monitoring	yes	yes	hundreds of euro a course
Gentamicin, for synergy	Synergy in enterococcal disease; nephrotoxic, and its role in staphylococcal disease has been withdrawn	yes	yes	tens of euro a course
Ceftriaxone, outpatient streptococcal	Once-daily, which	yes	yes	tens to hundreds of

Intervention	Effect size	EML	Off-patent	Cost
regimens	enables outpatient therapy			euro a course
Rifampicin, prosthetic valve, with others	Biofilm penetration	yes	yes	tens of euro a course
Daptomycin	Alternative for resistant S. aureus and enterococci	no	yes, generics	hundreds to thousands of euro a course
Oral step-down after initial intravenous therapy, the POET regimen	Non-inferior to continued intravenous therapy: 12.1 against 12.1 per cent composite	Component drugs yes	yes	Substantially cheaper; shortens admission
Valve surgery	Indicated for heart failure, uncontrolled infection and large vegetations with embolism; EASE gave a composite of 3 against 23 per cent in a selected group	n/a	n/a	tens of thousands of euro

The antibiotics that cure endocarditis are old, off-patent and on the Essential Medicines List: penicillin, amoxicillin, flucloxacillin, gentamicin, ceftriaxone, vancomycin and rifampicin. A full curative course costs on the order of tens to hundreds of euro in drug terms. The expensive parts are the weeks of hospital admission, the blood cultures, the echocardiography and the surgery.

Simple means. Oral step-down antibiotic therapy is the single most important finding for treating endocarditis where hospital beds and intravenous services are scarce: non-inferior to intravenous therapy in POET, and it converts weeks of admission into oral tablets. Dental and oral hygiene — brushing, and access to basic dental care — is probably more important than procedural prophylaxis given the bacteraemia arithmetic, and costs very little. Benzathine penicillin for rheumatic heart disease prevention costs US$0.59 a vial at UNICEF indicative prices, October 2026 and prevents the valve damage that becomes the endocarditis substrate. Amoxicillin prophylaxis where indicated costs a few to a few euro a dose, is oral, listed and off-patent, with the grade of benefit CONTESTED. Hand hygiene and clean injection practice are free or nearly free and directly address the two fastest-growing risk groups.

The hard limit, stated plainly. Endocarditis cannot be diagnosed without blood cultures and echocardiography, and it cannot be treated without weeks of appropriate antibiotics. The modified Duke criteria depend on both. Clinical suspicion alone — fever with a new murmur, splinter haemorrhages, splenomegaly — identifies candidates and cannot confirm or guide therapy. The minimum chain is a microbiology laboratory able to culture blood, an echocardiography machine, and a reliable supply of intravenous and then oral antibiotics. Without blood cultures, therapy is blind and failure rates rise sharply. There is no simple-means substitute.

Gaps. No GBD 2023 global burden figure for endocarditis was retrieved, and the roughly 66,000 deaths figure comes from an earlier round; this entry is part of the seventeen-condition gap in this chapter's introduction. Whether dental antibiotic prophylaxis works has never been and will never be tested in a randomised trial; the guidance rests on case-control and ecological data, England's rising incidence after restriction is read both ways, and guidelines differ between countries. Optimal timing of valve surgery rests on one small trial of 76 patients and on observational data. Incidence is rising and the reasons are multiple and not apportioned: ageing, more prosthetic valves and devices, more injecting drug use, more healthcare exposure, better detection. Blood-culture-negative endocarditis is 5 to 20 per cent of cases depending on prior antibiotic exposure and on the availability of serology for Coxiella, Bartonella and Tropheryma, and in most of the world those tests do not exist, so the true share is unknown. Mortality figures come from referral centres in registries, and population-based case fatality, especially where surgery is unavailable, is largely unmeasured. The low- and middle-income disease — younger patients, rheumatic substrate, streptococcal organisms — is barely represented in a guideline evidence base built on high-income cohorts.

> **Depth.** Starts in: a bacterium on a heart valve. Size: 1 µm†; depth +2.81. First complaint: about 14 days († about 2 weeks after bacteraemia); time depth 45.90. One untreated course: about 3 months ([B] weeks of fever, fatal if untreated; † about 3 months); depth 47.60.

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Pericarditis (ICD-11 BB20)

What it is. The thin sac around the heart becomes inflamed. It causes sharp chest pain that is worse lying flat and better sitting forward. Most cases settle on their own; a few fill the sac with fluid and squeeze the heart.

Measured. No global prevalence, death or DALY figure for pericarditis was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Incidence is roughly 27.7 per 100,000 person-years in an Italian urban population study, and pericarditis accounts for roughly 0.1 per cent of hospital admissions and 5 per cent of emergency attendances for non-ischaemic chest pain. Recurrence after a first episode is 15 to 30 per cent without colchicine and 10 to 15 per cent with it. Constrictive pericarditis develops in roughly 0.5 to 1 per cent after idiopathic or viral pericarditis, roughly 2 to 5 per cent after immune-mediated causes, and 20 to 30 per cent after tuberculous or purulent pericarditis. In-hospital mortality for acute pericarditis in high-income series is roughly 1.1 per cent, concentrated in those with a bacterial cause or comorbidity. Idiopathic and viral pericarditis peaks in young and middle-aged adults with a male predominance of roughly 1.5 to 1.

Tuberculous pericarditis accounts for roughly 70 to 80 per cent of pericarditis in sub-Saharan Africa and is strongly associated with HIV, with six-month mortality of roughly 17 to 40 per cent; in high-income countries it is under 5 per cent of cases. That is the sharpest geographic divergence in the chapter: the same named condition is a self-limiting viral illness in Europe and a frequently fatal tuberculous one in southern Africa. For scale, tuberculosis caused 1.23 million deaths in 2024 with 10.7 million new cases, and people with HIV are twelve times more likely to develop tuberculosis.

Where it starts. Idiopathic or presumed viral accounts for roughly 80 to 90 per cent of cases in high-income countries: coxsackievirus, echovirus, adenovirus, influenza, Epstein-Barr virus, cytomegalovirus, parvovirus B19, human herpesvirus 6 and SARS-CoV-2. Tuberculosis dominates in sub-Saharan Africa and in HIV-positive populations. Bacterial purulent pericarditis, from S. aureus or S. pneumoniae, is rare and highly lethal, with untreated mortality near 100 per cent. Post-cardiac-injury causes: after myocardial infarction, now rare with reperfusion; after cardiac surgery, with post-pericardiotomy syndrome in 10 to 40 per cent; after catheter ablation or device implantation. Autoimmune causes: systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, familial Mediterranean fever, Still disease. Uraemia in advanced kidney failure and in dialysis patients. Malignancy — lung and breast cancer, lymphoma, mesothelioma — is the commonest cause of a large haemorrhagic effusion. Chest radiotherapy and drugs, including hydralazine, isoniazid, procainamide and immune checkpoint inhibitors, contribute. Hypothyroidism causes effusion without much inflammation.

In the 80 to 90 per cent called idiopathic, no specific cause is ever identified. Viral aetiology is presumed on clinical grounds and rarely confirmed, because pericardial fluid and tissue are seldom sampled in uncomplicated cases, and when they are the yields are low. Why some patients recur repeatedly for years and others never do is not explained, and the recurrent form behaves like an autoinflammatory disease; the success of interleukin-1 blockade supports that, and the mechanism is not established. Why colchicine works is not fully explained. Which patients will progress to constriction cannot be predicted.

Cure status. Acute idiopathic and viral pericarditis, the large majority: SELF-LIMITING. Bacterial and tuberculous pericarditis: CURABLE with appropriate antimicrobial therapy and drainage, and fatal without it. Recurrent pericarditis: CONTROLLABLE. Constrictive pericarditis: CURABLE by pericardiectomy. Tamponade: CURABLE by drainage, for that episode.

Acute idiopathic and viral pericarditis resolves without specific treatment in roughly 70 to 85 per cent, and anti-inflammatory therapy shortens symptoms and reduces recurrence rather than being necessary for resolution. This is one of the few genuinely self-limiting conditions in the chapter.

Recurrent pericarditis is CONTROLLABLE rather than curable, and the interleukin-1 blockers make the point. Colchicine halves recurrence. Anakinra and rilonacept suppress it strongly and recurrence returns on withdrawal: RHAPSODY, with 61 patients on rilonacept, gave a recurrence hazard ratio of 0.04 on treatment, with flares after stopping. That is holding the state.

Constrictive pericarditis is CURABLE by pericardiectomy, with substantial perioperative mortality of 6 to 12 per cent in modern series and higher after radiation, and excellent long-term relief in survivors. Tamponade is relieved immediately and definitively for that episode by pericardiocentesis.

Prevention.

Colchicine to prevent recurrence — STRONG, and the central evidence of this entry. The ICAP trial, 240 patients with a first episode: colchicine added to conventional therapy reduced incessant or recurrent pericarditis from 37.5 to 16.7 per cent, relative risk 0.45, number needed to treat about 5. CORP and CORP-2, in recurrent pericarditis, reduced recurrence from roughly 55 to 24 per cent and from 42 to 22 per cent respectively. Colchicine is off-patent, cheap at tens of euro a course, and on the Essential Medicines List.

Colchicine to prevent post-pericardiotomy syndrome after cardiac surgery — STRONG. The COPPS and COPPS-2 trials reduced the syndrome by roughly half, with COPPS-2 giving 19.4 against 29.4 per cent, relative risk 0.67, number needed to treat 10.

Avoiding corticosteroids in a first episode — MODERATE, and important. Corticosteroid use is associated with increased recurrence in cohort and trial-subgroup data, and steroids are reserved for specific indications. This is a case where a widely available cheap drug makes the condition worse and the evidence says to withhold it.

Tuberculosis control and HIV treatment — STRONG where tuberculous pericarditis dominates.

Adjunctive corticosteroids in tuberculous pericarditis — CONTESTED, with three results to print. The IMPI trial, 1,400 patients: prednisolone did not reduce the primary composite of death, tamponade or constriction; it did reduce constriction and hospitalisation; and it increased HIV-associated malignancy.

Exercise restriction during acute inflammation — WEAK, consensus-based. *Dialysis adequacy — MODERATE* for uraemic pericarditis.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
NSAID, ibuprofen or high-dose aspirin, with gastroprotection	First-line; relieves pain in the large majority within days	yes, both	yes	€2–20 a course. UNICEF indicative price October 2026 for ibuprofen 400 mg: US$2.23 on one page and US$1.43 on another
Colchicine 0.5 mg once or twice daily, three months for a first episode or six for recurrent disease	Recurrence 37.5 down to 16.7 per cent, number needed to treat about 5, ICAP; CORP and CORP-2 similar	yes	yes	tens of euro a course
Corticosteroids, prednisone, low dose	Effective for symptoms and associated with more recurrence; reserved for failure of NSAIDs and colchicine, autoimmune cause, or contraindication	yes	yes	a few to tens of euro a course
Anakinra, interleukin-1 receptor antagonist, recurrent disease	AIRTRIP, 21 patients: recurrence 18 against 90 per cent on placebo	no	no	tens of thousands of euro a year
Rilonacept, recurrent disease	RHAPSODY: recurrence hazard ratio 0.04 on treatment; flares after withdrawal	no	no	€200,000 and above a year, United States list price, year not stated in the source

Intervention	Effect size	EML	Off-patent	Cost
Azathioprine or intravenous immunoglobulin, recurrent, steroid-sparing	Observational support	Azathioprine yes	Azathioprine yes	Azathioprine tens to hundreds of euro a year; immunoglobulin thousands to tens of thousands of euro a course
Antituberculous therapy, tuberculous pericarditis	Curative; a six-month regimen of rifampicin, isoniazid, pyrazinamide and ethambutol	yes, all	yes	tens of euro a full course
Pericardiocentesis, tamponade	Immediately life-saving; relieves tamponade definitively for that episode	n/a	n/a	hundreds to thousands of euro with ultrasound guidance
Pericardial window or pericardiectomy	For recurrent effusion and for constriction; perioperative mortality 6 to 12 per cent for constriction	n/a	n/a	thousands to tens of thousands of euro

Colchicine is the key fact. A plant-derived alkaloid in use for centuries, off-patent, on the Essential Medicines List, costing tens of euro a course, halves recurrence with a number needed to treat of about 5. The interleukin-1 blockers achieve a larger effect at tens of thousands to hundreds of thousands of euro and above a year, and the effect stops when they stop.

Simple means. Sitting forward relieves the pain of pericarditis; it is both a diagnostic feature and free symptom relief. Rest during the acute phase and avoiding strenuous exertion until inflammation settles is consensus. Aspirin or ibuprofen costs a few to tens of euro a course, is on the Essential Medicines List, off-patent, and first-line. Colchicine costs tens of euro a course with a number needed to treat of about 5 for preventing recurrence, and it is a tablet. Withholding corticosteroids in a first episode is a free decision that reduces recurrence.

Pericardiocentesis is one of the few immediately life-saving procedures in this chapter that needs almost no equipment: with a needle, a syringe and ideally ultrasound guidance, tamponade is relieved at the bedside. Historically it was done blind, subxiphoid, with high complication rates; ultrasound guidance reduces complications substantially and is now standard. A handheld ultrasound at thousands to tens of thousands of euro falling, makes it far safer. Auscultation and clinical recognition help: the pericardial friction rub is audible with a stethoscope in roughly a third of cases, and pulsus paradoxus and raised jugular venous pressure identify tamponade clinically with no equipment.

Antituberculous therapy costs tens of euro for a full six-month cure, with all four drugs on the Essential Medicines List and off-patent. In the region where pericarditis is most often fatal, the cure costs tens of euro and the constraint is diagnosis rather than drugs.

The hard limit. Distinguishing viral from tuberculous from malignant pericarditis requires at minimum chest imaging and often pericardial fluid analysis. Constriction requires surgery. An electrocardiogram and a stethoscope identify the syndrome and cannot identify the cause, and the cause determines whether the condition is self-limiting or fatal.

Gaps. No GBD global burden figure for pericarditis was retrieved, and this entry is part of the seventeen-condition gap in this chapter’s introduction. In 80 to 90 per cent of cases no cause is identified and viral aetiology is presumed rather than demonstrated. Tuberculous pericarditis is 70 to 80 per cent of cases in sub-Saharan Africa and under 5 per cent in high-income countries — the same ICD entity with entirely different natural history and lethality — and most guideline evidence comes from the high-income presentation. IMPI gave a split result for steroids in tuberculous pericarditis: no effect on the primary composite, less constriction, more HIV-associated malignancy, and how to act on it is unresolved. Why recurrent pericarditis recurs is unexplained; the interleukin-1 response suggests autoinflammation and the mechanism is not established. Interleukin-1 blocker effects stop on withdrawal and optimal duration is

unknown, and the trials are small at 21 and 61 patients. Incidence figures come essentially from one Italian study extrapolated widely. Progression to constriction cannot be predicted.

> **Depth.** Starts in: a virus. Size: 100 nm†; depth +0.72. First complaint: about 12 days († 1–3 weeks after a virus infection); time depth 45.77. One untreated course: about 12 days ([B] usually clears by itself; † 1–3 weeks); depth 45.77.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Pulmonary hypertension (ICD-11 BB01)

What it is. The pressure in the arteries from the heart to the lungs rises. The right side of the heart has to push against it and eventually fails. Breathlessness on exertion comes first, then swelling and collapse.

Measured. No global prevalence, death or DALY figure for pulmonary hypertension was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all. Estimated global prevalence of pulmonary hypertension of all causes is roughly 1 per cent of the world population and up to 10 per cent of people over 65, from a 2016 review in Lancet Respiratory Medicine; that is a modelled estimate.

Pulmonary arterial hypertension, group 1, is rare: prevalence roughly 15 to 60 per million adults with an incidence of 5 to 10 per million a year, from the REVEAL, French and COMPERA registries. Group 2, from left heart disease, and group 3, from lung disease, together account for roughly 80 per cent or more of all pulmonary hypertension, which is the central epidemiological fact: the common forms are consequences of heart failure and chronic lung disease. Schistosomiasis-associated pulmonary arterial hypertension is probably the commonest cause of group 1 disease worldwide. At least 253.7 million people required preventive treatment for schistosomiasis in 2024, and a few per cent of those infected develop pulmonary hypertension. It is almost absent from the registries, which are European and North American. Chronic thromboembolic pulmonary hypertension has an incidence of roughly 3 to 5 per million a year and develops in roughly 3 per cent of pulmonary embolism survivors. Untreated median survival in pulmonary arterial hypertension was 2.8 years in the 1980s registry; with modern therapy, one-year survival is roughly 85 to 90 per cent and five-year roughly 55 to 65 per cent in registries. Idiopathic disease historically presented in young women with a mean age of about 36 in the early registry; contemporary registries show a mean age of 50 to 65 with a much weaker female predominance, a shift that is not fully explained.

Where it starts. Left heart disease, group 2 — heart failure with reduced or preserved ejection fraction, valve disease — is the commonest cause overall. Lung disease and hypoxia, group 3 — chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, high-altitude residence — is next. Chronic thromboembolic disease, group 4, follows roughly 3 per cent of pulmonary embolisms.

Group 1 causes. Heritable disease: BMPR2 mutations in roughly 70 to 80 per cent of familial cases and 10 to 20 per cent of sporadic idiopathic cases, with penetrance of roughly 20 per cent and lower in men. Connective tissue disease, of which systemic sclerosis is commonest, with pulmonary arterial hypertension in roughly 8 to 12 per cent of scleroderma patients. Congenital heart disease with an uncorrected shunt, giving Eisenmenger syndrome. Schistosomiasis. HIV, with a prevalence of roughly 0.5 per cent, orders of magnitude above background. Portal hypertension. Drugs and toxins: the appetite suppressants aminorex, fenfluramine and dexfenfluramine caused a well-documented epidemic, and dasatinib, interferon, methamphetamine and toxic rapeseed oil have been implicated. Chronic hypoxic pulmonary hypertension occurs in long-term high-altitude residents.

BMPR2 penetrance is roughly 20 per cent, so most carriers never develop disease and the second hit is unknown. Why idiopathic disease overwhelmingly affected young women in the early registries and now presents in older patients of both sexes is unexplained, and it is unclear how much is a change in the disease against a change in who gets investigated. The mechanism linking schistosomiasis to pulmonary vascular remodelling is not established. Whether treating group 2 and group 3 pulmonary hypertension with pulmonary vasodilators helps is not merely unknown but repeatedly shown to be harmful.

Cure status. Pulmonary arterial hypertension: RELIEF ONLY. Chronic thromboembolic pulmonary hypertension in operable cases: CURABLE by pulmonary endarterectomy. Group 2 and group 3 disease where the underlying cause is treatable: CONTROLLABLE.

No treatment removes the vascular remodelling in pulmonary arterial hypertension. Modern therapy improves exercise capacity and haemodynamics and, in combination and in meta-analysis, reduces mortality, and the disease progresses and transplantation remains the endpoint for many, with five-year survival of 55 to 65 per cent on treatment.

Pulmonary endarterectomy for chronic thromboembolic disease is genuinely curative in operable cases: pulmonary vascular resistance falls substantially and often normalises, perioperative mortality in expert centres is 2 to 5 per cent, and long-term survival approaches that of the general population in good surgical candidates. That is the one form of pulmonary hypertension with a surgical cure, and it is systematically under-diagnosed, so all pulmonary hypertension patients should be screened for it. Balloon pulmonary angioplasty treats inoperable distal disease with substantial haemodynamic improvement.

In group 2 and group 3, treating the underlying heart or lung disease is the therapy, and pulmonary vasodilators are not indicated and can worsen outcomes. A correctable congenital shunt closed before irreversible remodelling prevents the condition; once Eisenmenger physiology is established, closure is harmful. Lung or heart-lung transplantation for end-stage disease gives five-year survival of roughly 50 to 60 per cent.

Prevention.

Withdrawal of appetite-suppressant drugs — STRONG, historically demonstrated. The aminorex epidemic in Europe in the 1960s and the fenfluramine epidemic in the 1990s both rose and fell with the drugs' availability. That is a clear, measured prevention by withdrawing a product.

Early repair of congenital shunts — STRONG for preventing Eisenmenger syndrome. *Treating left heart disease and chronic obstructive pulmonary disease — STRONG* for preventing groups 2 and 3.

Schistosomiasis control — MODERATE in endemic areas: praziquantel mass treatment, snail control, water and sanitation. Praziquantel costs under one euro a treatment, is on the Essential Medicines List in sections 6.1.1, 6.1.3 and 6.1.4†, and is off-patent. Coverage in 2024 was 39.6 per cent globally and 61.7 per cent of school-aged children requiring preventive chemotherapy, with at least 93.9 per cent of those needing treatment living in Africa.

Anticoagulation after pulmonary embolism and follow-up for persistent breathlessness — MODERATE for preventing and detecting chronic thromboembolic disease, which develops in about 3 per cent.

Screening in systemic sclerosis — MODERATE. Annual echocardiography and the DETECT algorithm identify disease earlier, and earlier treatment is associated with better survival.

Antiretroviral therapy in HIV — MODERATE. *Oxygen in chronic hypoxaemia — MODERATE* for limiting hypoxic pulmonary vasoconstriction. *Genetic counselling in BMPR2 families — MODERATE* for information rather than prevention, given penetrance of about 20 per cent.

Nothing prevents idiopathic pulmonary arterial hypertension.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Pulmonary endarterectomy, chronic thromboembolic disease	Curative; perioperative mortality 2 to 5 per cent in expert centres	n/a	n/a	tens of thousands of euro
Balloon pulmonary angioplasty, inoperable chronic thromboembolic disease	Substantial haemodynamic improvement	n/a	n/a	tens of thousands of euro across sessions
Sildenafil or tadalafil, phosphodiesterase-5 inhibitor	SUPER-1, sildenafil, 278 patients: six-minute walk distance up 45 m at 20 mg three	**Sildenafil is NOT on the 24th Model List in any form**	yes, and this matters	tens to hundreds of euro for generic sildenafil; branded pulmonary formulations far higher

Intervention	Effect size	EML	Off-patent	Cost per patient-year
	times daily; haemodynamics improved			
Bosentan, ambrisentan or macitentan, endothelin receptor antagonists	BREATHE-1, bosentan: six-minute walk distance up 44 m. SERAPHIN, macitentan, 742 patients: morbidity and mortality composite hazard ratio 0.55, one of the few event-driven positive trials	**Bosentan is NOT on the 24th Model List in any form**	Bosentan: generic available	Generic bosentan thousands of euro; macitentan tens of thousands to hundreds of thousands of euro
Riociguat, soluble guanylate cyclase stimulator	PATENT-1: six-minute walk distance up 36 m. CHEST-1: the only drug approved for inoperable chronic thromboembolic disease, walk distance up 46 m	no	no	tens of thousands of euro
Epoprostenol, intravenous prostacyclin	The only therapy with a demonstrated mortality benefit in a single randomised trial: Barst and colleagues, 1996, 81 patients, 8 deaths in the conventional arm and none in the epoprostenol arm	no	yes, generic epoprostenol exists	€30,000–150,000 including pump and line care
Treprostinil, iloprost, selexipag, prostacyclin pathway	GRIPHON, selexipag, 1,156 patients: morbidity and mortality composite hazard ratio 0.60	no	no	tens of thousands to hundreds of thousands of euro
Upfront combination therapy	AMBITION, 500 patients, ambrisentan with tadalafil against monotherapy: clinical failure hazard ratio 0.50	—	partly	Varies
Sotatercept, activin signalling inhibitor	STELLAR, 323 patients: six-minute walk distance up 40.8 m against placebo; the first new mechanism in years	no	no	€240,000 a year, United States list price, year not stated in the source
Calcium channel blockers, in the 5 to 10 per cent of patients who are acute vasodilator responders	In true responders, long-term survival is substantially better, and nifedipine, diltiazem and amlodipine are the treatment	yes	yes	a few to tens of euro
Diuretics, oxygen, anticoagulation	Supportive; diuretics for right heart failure	yes, furosemide and warfarin	yes	a few to tens of euro
Pulmonary vasodilators in group 2 or group 3 disease	Harmful or neutral. Sildenafil in heart failure with preserved ejection fraction and in pulmonary fibrosis: no benefit; STEP-IPF null; riociguat in group 3, RISE-IIP, was stopped	—	—	—

Intervention	Effect size	EML	Off-patent	Cost per patient-year
	for increased mortality			
Lung or heart-lung transplantation	Five-year survival 50 to 60 per cent	n/a	n/a	hundreds of thousands of euro in the first year

Two cheap, off-patent drugs matter disproportionately. First, calcium channel blockers in the 5 to 10 per cent of patients who are genuine acute vasodilator responders produce substantially better long-term survival at a few to tens of euro a year — and identifying those patients requires right heart catheterisation with acute vasodilator testing. Second, generic sildenafil at tens to hundreds of euro a year delivers the phosphodiesterase-5 inhibitor effect at a fraction of the branded price and is the realistic option in most of the world. Everything else in this entry costs tens of thousands to hundreds of thousands of euro a patient-year.

Simple means. Praziquantel for schistosomiasis is the highest-value simple intervention here, given that schistosomiasis-associated disease may be the commonest form of pulmonary arterial hypertension worldwide. It costs under one euro a treatment, is on the Essential Medicines List, off-patent, and is a single oral dose — and it is mass drug administration rather than individual care.

Avoiding pregnancy is the most consequential piece of free advice in the entry: maternal mortality in pulmonary arterial hypertension is roughly 10 to 25 per cent, and contraception counselling is a free intervention with a very large effect.

Exercise training deserves a direct comparison. Supervised rehabilitation improves six-minute walk distance by roughly 50 to 100 m in randomised trials, which is comparable to or larger than the drug effects of plus 36 to plus 46 m, at a tiny fraction of the cost. A training programme matches a tens of thousands of euro drug on the walk-distance endpoint. It does not replace the drugs for survival, which has not been tested.

Supplemental oxygen in chronic hypoxaemia reduces hypoxic vasoconstriction; see the chronic obstructive pulmonary disease entry for the concentrator-against-cylinder comparison. Diuretics for right heart failure: furosemide at a few to tens of euro a year, listed, off-patent and indispensable for congestion. Avoiding high altitude and unpressurised flight in significant disease is behavioural and free. Recognising the condition — breathlessness on exertion with a loud pulmonary second sound, raised jugular venous pressure and peripheral oedema — needs a stethoscope and the eyes; confirmation requires echocardiography and ultimately right heart catheterisation.

The hard limit, stated plainly. Pulmonary arterial hypertension cannot be diagnosed without echocardiography and right heart catheterisation, and it cannot be treated without drugs costing tens of thousands to hundreds of thousands of euro a year, except generic sildenafil and, in the responder minority, calcium channel blockers. Chronic thromboembolic disease, the one curable form, requires a specialist surgical centre of which there are perhaps a few dozen in the world. For most of the world's patients with pulmonary arterial hypertension, no effective treatment is accessible at any price they can pay.

Gaps. No GBD global burden figure for pulmonary hypertension was retrieved, and this entry is part of the seventeen-condition gap in this chapter's introduction; the figure of 1 per cent of the world population is a modelled estimate from a single review. The registries are European and North American, and if schistosomiasis-associated disease is the commonest form worldwide then the entire evidence base describes a minority of the disease; that is the largest gap in the entry. The age and sex shift in idiopathic disease, from young women to older patients of both sexes, is unexplained. BMPR2 penetrance is about 20 per cent and the second hit is unknown. Almost all trials use six-minute walk distance, a surrogate; only epoprostenol, in an 81-patient trial from 1996, has a mortality benefit from a single randomised trial, and SERAPHIN and GRIPHON used composite morbidity-mortality endpoints, so a mortality benefit for most of these drugs is not demonstrated. Riociguat in group 3 increased mortality in RISE-IIP and sildenafil in pulmonary fibrosis and in heart failure with preserved ejection fraction was null; vasodilators are harmful outside group 1 and that is widely under-appreciated. Chronic thromboembolic disease is systematically under-diagnosed and it is the only curable form. Prices of tens of thousands to hundreds of thousands of euro a year for drugs with surrogate endpoints make cost-effectiveness a live and unresolved dispute in every health system. Exercise training matches the drug effects on walk distance and has never been

compared with drugs on survival. Neither sildenafil nor bosentan is on the 24th Model List in any form, and any claim otherwise is wrong.

> **Depth.** Starts in: a lung arteriole. Size: 100 µm†; depth +7.00. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Cardiac arrest (ICD-11 MC82)

What it is. The heart stops pumping. The person collapses, stops breathing normally and loses consciousness within seconds. Brain damage begins within minutes and death follows unless the circulation is restarted.

Measured. No GBD global cardiac arrest figure exists; it is a mode of death counted under its causes, chiefly ischaemic heart disease. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

In the United States there are more than 350,000 out-of-hospital cardiac arrests a year, and the 2023 American Heart Association statistics report gives over 356,000. Survival to hospital discharge is 9.1 per cent for all emergency-service-treated non-traumatic out-of-hospital arrests in adults, on 2021 United States data. Bystander cardiopulmonary resuscitation is performed in 40.2 per cent of out-of-hospital arrests. Immediate resuscitation can double or triple the chance of survival. One figure needs care: the 436,852 deaths for 2020 on the same page cover any mention of sudden cardiac arrest on a death certificate, not out-of-hospital arrest alone, and the two are frequently conflated.

Global estimates put out-of-hospital incidence at roughly 30 to 97 per 100,000 person-years depending on registry and inclusion criteria, with survival to discharge ranging from under 1 per cent to over 20 per cent between regions and systems — a twentyfold range. In-hospital arrest has an incidence of roughly 1 to 6 per 1,000 hospital admissions, with survival to discharge of roughly 20 to 25 per cent, higher than out-of-hospital because of witnessed onset and immediate response. A shockable initial rhythm — ventricular fibrillation or pulseless ventricular tachycardia — is present in roughly 20 to 25 per cent of out-of-hospital arrests now, down from 60 to 70 per cent in the 1980s. Survival in that group is far higher, roughly 25 to 40 per cent with prompt defibrillation, than in asystole or pulseless electrical activity, at roughly 2 to 5 per cent. Survival falls roughly 7 to 10 per cent for every minute without resuscitation or defibrillation. Neurologically intact survival is roughly 7 to 8 per cent of all emergency-service-treated arrests, slightly below survival to discharge.

Where it starts. Coronary artery disease is the underlying cause in roughly 70 to 80 per cent of adult out-of-hospital arrests, with acute infarction or ischaemia the immediate trigger in a large share. Cardiomyopathy — hypertrophic, dilated, arrhythmogenic — is the dominant cause in the young, as are the inherited channelopathies. Congenital coronary anomalies, myocarditis and aortic stenosis contribute. Non-cardiac causes account for roughly 20 to 35 per cent of out-of-hospital arrests: respiratory arrest, drowning, trauma, haemorrhage, overdose and notably opioids, hypoxia, electrolyte disturbance, pulmonary embolism, tension pneumothorax, hypothermia and anaphylaxis. In children the dominant causes are respiratory — hypoxia from airway obstruction, drowning, asthma, bronchiolitis and sepsis — which is why rescue breaths matter more in paediatric arrest than in adult arrest, and the guidelines differ for that reason. The INTERHEART and INTERSTROKE risk factors apply by way of coronary disease. Sudden arrhythmic death syndrome, with a morphologically normal heart at autopsy, is roughly 4 to 10 per cent of sudden cardiac deaths and higher in the young.

The timing of a cardiac arrest is not predictable even with full knowledge of the coronary anatomy and ejection fraction, and that is the central unsolved problem. Most sudden cardiac deaths occur in people who would not have met criteria for a defibrillator: the majority happen in the large population at moderate risk rather than the small population at high risk, which is why population-level risk stratification has not reduced total sudden death much. Why the proportion of shockable initial rhythms has fallen from 60 to 70 per cent to 20 to 25 per cent over four decades is not fully explained; longer call-to-arrival times, changing

substrate, more beta blockade and more reperfusion are all proposed. In sudden arrhythmic death syndrome no cause is found at all.

Cure status. All-comers, any rhythm, any setting: RELIEF ONLY. Witnessed arrest with a shockable rhythm, bystander resuscitation and early defibrillation: CURABLE.

RELIEF ONLY describes cardiac arrest as it is encountered: 9.1 per cent survive to discharge and 7 to 8 per cent survive neurologically intact, and nothing removes the predisposition. CURABLE describes the witnessed, shockable, bystander-resuscitated, early-defibrillated stratum, where survival reaches 40 to 60 per cent in the best-performing systems and a survivor with an intact brain and a treated cause is cured of the arrest.

The variation between those two is almost entirely in the system rather than the disease. Survival in the favourable subgroup reaches 40 to 60 per cent in Seattle, North Holland and parts of Scandinavia — the same condition, a five- to sixtyfold difference in outcome depending on the response.

Reversing the cause cures it: primary percutaneous intervention for the infarction that caused the arrest, and an implantable defibrillator for a recurring arrhythmic substrate, where the secondary prevention trials AVID, CIDS and CASH reduced mortality roughly 20 to 30 per cent against antiarrhythmic drugs. On temperature, both results must be printed: HACA and the Bernard trial in 2002 showed benefit at 32 to 34 °C, and TTM2, with 1,900 patients in 2021, found hypothermia at 33 °C gave no mortality benefit against normothermia with fever avoidance, hazard ratio 1.04. Practice has shifted to fever avoidance. No neuroprotective drug has ever been shown to work; every trial has failed.

Prevention.

Treating coronary disease — STRONG, and quantitatively the largest lever, since 70 to 80 per cent of arrests arise from it. All the measures in the ischaemic heart disease entry apply: statins at a relative risk of 0.78 per mmol/L of LDL reduction, blood pressure lowering at 0.80 per 10 mmHg, smoking cessation at an adjusted hazard ratio of 0.56.

Bystander resuscitation training at population scale — STRONG. Denmark and Norway roughly doubled or tripled bystander resuscitation rates and survival over ten to fifteen years through mandatory school and driving-licence training plus dispatcher-assisted resuscitation, and Danish survival rose from roughly 3.5 to 10 to 16 per cent. That is the clearest demonstration that cardiac arrest survival is a function of population training rather than technology.

Public access defibrillation — STRONG. The PAD trial, across 993 community units with 19,000 volunteers, found survival doubled with resuscitation plus an automated external defibrillator against resuscitation alone, 30 against 15 survivors. Defibrillation within three to five minutes yields survival of 50 to 70 per cent.

Dispatcher-assisted telephone resuscitation — STRONG. It raises bystander resuscitation rates substantially at essentially no cost, and meta-analyses show improved survival.

Beta blockers after myocardial infarction — STRONG historically, about a 20 to 25 per cent mortality reduction with much of it sudden death, and *questioned in the reperfusion era with preserved ejection fraction*, since REDUCE-AMI was null.

Implantable defibrillator for primary prevention — STRONG in ischaemic cardiomyopathy, CONTESTED in non-ischaemic. SCD-HeFT hazard ratio 0.77, number needed to treat 14 over five years; DANISH null in non-ischaemic cardiomyopathy.

Drowning prevention, opioid overdose response with naloxone, choking first aid — STRONG for the non-cardiac causes. Drowning kills about 300,000 people a year worldwide, with 92 per cent of deaths in low- and middle-income countries.

Family screening after a sudden death in a young person — MODERATE: a diagnosis is found in 20 to 50 per cent of first-degree relatives. *Athletic pre-participation screening — CONTESTED*.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Bystander resuscitation	Doubles to triples survival; performed in only 40.2 per cent of United States arrests	n/a	n/a	Nothing
Early defibrillation	Survival 50 to 70 per cent if within three to five minutes; falls 7 to 10 per cent a minute of delay. PAD trial: survival doubled with a defibrillator added to resuscitation	n/a	n/a	Automated external defibrillator hundreds to thousands of euro
Adrenaline 1 mg intravenously	PARAMEDIC2, 8,014 patients: 30-day survival 3.2 against 2.4 per cent, odds ratio 1.39, a real but small benefit; favourable neurological outcome 2.2 against 1.9 per cent, not significantly different; severe neurological impairment more common among survivors, 31 against 18 per cent. Number needed to treat about 112 for 30-day survival	yes	yes	a few euro a dose
Amiodarone or lidocaine, shock-refractory fibrillation	ALPS, 3,026 patients: survival to admission improved; no significant difference in survival to discharge or neurological outcome	yes, both	yes	a few to tens of euro a dose
Airway management: bag-mask, supraglottic airway, intubation	AIRWAYS-2 and PART: supraglottic airway and tracheal intubation gave broadly similar outcomes, with no clear superiority	n/a	n/a	Bag-mask tens of euro; supraglottic airway a few to tens of euro
Targeted temperature management	HACA and Bernard positive at 32 to 34 °C; TTM2, 1,900 patients, found no benefit of 33 °C over normothermia with fever avoidance, hazard ratio 1.04	n/a	n/a	Cooling device tens of thousands of euro; ice packs and cold saline cost almost nothing
Primary percutaneous intervention after arrest with ST elevation	Strongly beneficial; COACT and TOMAHAWK found no benefit of immediate angiography in arrest without ST elevation	n/a	n/a	thousands to tens of thousands of euro
Extracorporeal resuscitation	ARREST, 30 patients, and Prague OHCA suggested benefit in highly selected refractory arrest; INCEPTION, 134 patients, found no benefit. Unresolved	n/a	n/a	tens of thousands to hundreds of thousands of euro
Secondary prevention defibrillator	AVID, CIDS and CASH: mortality reduced about 20 to 30 per cent against antiarrhythmic drugs	n/a	n/a	tens of thousands of euro
Mechanical chest compression devices	LINC and PARAMEDIC: no better than manual compressions	n/a	n/a	tens of thousands of euro
Sodium bicarbonate, calcium, high-dose adrenaline, vasopressin, atropine	All removed from routine algorithms for lack of benefit	Varies	yes	—

The pattern in that table is striking. The two interventions with by far the largest effects — resuscitation and early defibrillation — are the two that cost almost nothing, and every drug and device added on top has a small, absent or unproven effect. Adrenaline's number needed to treat is about 112 for 30-day survival with no clear neurological benefit; mechanical compression devices, extracorporeal resuscitation beyond selected cases, and almost every drug have failed to improve neurologically intact survival.

Simple means. This is the entry where simple means dominate completely.

Bystander resuscitation with no equipment at all doubles to triples the chance of survival. It requires two hands and the knowledge to use them, and it is performed in only 40.2 per cent of United States out-of-hospital arrests, so the majority of the available benefit is currently unrealised. Compression-only resuscitation is as good as compression plus rescue breathing for adult out-of-hospital arrest of cardiac cause, from the randomised dispatcher trials SOS-KANTO, Rea and Svensson and from meta-analysis; that removes the mouth-to-mouth barrier that deterred bystanders and is why guidelines now teach hands-only resuscitation to the public. For children, drowning and asphyxial arrest, rescue breaths should be included, because the cause is hypoxic. The technique is the centre of the chest, at least 5 cm deep, 100 to 120 compressions a minute, allowing full recoil and minimising interruptions.

Dispatcher-assisted resuscitation over the telephone, where the call-taker talks the bystander through compressions, raises bystander resuscitation rates substantially and improves survival, and it costs nothing beyond training the dispatchers. Population resuscitation training raised Danish survival from roughly 3.5 to 10 to 16 per cent, chiefly through mandatory school and driving-licence training and dispatcher resuscitation. That is a teaching programme rather than a technology.

Recognising cardiac arrest is unresponsiveness and not breathing normally. Agonal gasping is commonly mistaken for breathing and is the main reason bystanders fail to start resuscitation. Teaching that agonal breathing means start compressions is free and changes outcomes.

An automated external defibrillator costs hundreds to thousands of euro and is usable by an untrained person following voice prompts. Defibrillation within three to five minutes gives survival of 50 to 70 per cent against 9.1 per cent overall. It is the one piece of equipment that genuinely changes the outcome and it requires no medical training.

Fever avoidance after resuscitation can be achieved with ice packs, cold fluids, fans and antipyretics; TTM2 found normothermia with fever avoidance equivalent to cooling at 33 °C, so the tens of thousands of euro cooling device is not required by the current evidence. Naloxone for opioid-overdose arrest costs a few to tens of euro a dose, is listed, off-patent, and can be given intranasally or intramuscularly by a bystander; for that subgroup it is the specific cure. Choking first aid — back blows, abdominal thrusts — and drowning rescue are free techniques for the asphyxial causes.

The honest summary: of everything in this entry, the interventions with the largest measured effects require no industrial supply chain at all — recognising the arrest, compressing the chest, and with a single inexpensive device delivering a shock. The twentyfold variation in survival between regions is explained mainly by how many bystanders act and how fast a defibrillator arrives, not by the drugs or the intensive care that follow.

Gaps. No GBD global cardiac arrest figure exists, because the condition is counted under its causes, so global burden is not directly measured; this entry is part of the seventeen-condition gap in this chapter's introduction. Survival ranges from under 1 per cent to over 20 per cent between regions, a twentyfold spread. How much of that is true outcome difference and how much is denominator definition — which arrests are counted, whether unwitnessed and non-attempted resuscitations are included — is unresolved. The Utstein template was created to fix this and compliance remains partial. The 436,852 sudden cardiac arrest deaths for 2020 and the 356,000 out-of-hospital arrests are different quantities and are frequently conflated. Adrenaline improves 30-day survival, 3.2 against 2.4 per cent, without clearly improving neurological outcome, and severe neurological impairment was commoner among survivors, 31 against 18 per cent; whether that is a net benefit is genuinely contested. TTM2 overturned targeted hypothermia; guidelines changed and practice lags, and both are printed. Extracorporeal resuscitation is unresolved: ARREST and Prague positive, INCEPTION null. Immediate angiography in arrest without ST elevation: COACT and TOMAHAWK both null, against prior practice. Why shockable initial rhythms fell from 60 to 70 per cent to 20 to 25 per cent over four decades is unexplained. Most sudden cardiac deaths occur outside any current high-risk criteria, so defibrillator-based prevention cannot address the bulk of the problem, and that structural limit is rarely stated. No neuroprotective drug has ever worked. Registry data from Africa, south Asia and most of Latin America barely exist, and the global incidence range of 30 to 97 per 100,000 rests on high-income registries.

Depth. Starts in: the heart. Size: 12 cm†; depth +13.46. First complaint: about 10 seconds ([B] within seconds); time depth 35.25. One untreated course: about 10 minutes ([B] minutes to death); depth 38.98.

Model reading. Way of ending: restore proportion. Layer: mesh. The book names an early stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Chapter 12 — Diseases of the respiratory system

The obstructed airway

Chronic obstructive pulmonary disease (ICD-11 CA22)

What it is. The airways are permanently narrowed and the air sacs are destroyed, so air cannot be pushed out. Breathlessness builds over years and never fully reverses. Smoke is the main cause — tobacco in rich countries, cooking fires in poor ones.

Measured. Deaths in 2023: about 3.4 million, approximately 6 per cent of all global deaths, the third leading cause of death worldwide and the seventh leading cause of poor health measured in DALYs, from the WHO fact sheet of 10 June 2026 carrying 2023 data. WHO's top-ten causes page, dated 2 October 2026, gives 3.6 million for the same year. GBD 2021 gives 3.72 million (3.36–4.09), rank 4, with an age-standardised death rate of 45.2 per 100,000. All three are printed.

DALYs in 2023: 74.9 million (66.2–86.9), rank 7 of all causes; GBD 2021 gave 79.8 million, rank 6. YLDs in 2023: 15.0 million (12.6–17.6), rank 19. Nearly 90 per cent of deaths in people under 70 occur in low- and middle-income countries.

The WHO fact sheet gives no global prevalence figure at all. GBD 2019 estimated roughly 212 million prevalent cases, and the BOLD study found airflow obstruction at GOLD stage II or worse in roughly 10 per cent of adults over 40 across twelve countries. The condition is rare before 40 and prevalence and mortality rise steeply thereafter. Age-standardised mortality is falling while absolute deaths are roughly flat to rising with ageing, and the condition has moved from rank 4 to rank 3 among causes of death. It is substantially under-diagnosed: roughly 60 to 85 per cent of cases in population studies have no prior diagnosis.

Where it starts. Tobacco smoking accounts for over 70 per cent of cases in high-income countries and 30 to 40 per cent in low- and middle-income countries. That single sentence is the key epidemiological fact: the majority of the disease in poorer countries is not from tobacco.

Household air pollution is named a major risk factor in low- and middle-income countries on the COPD fact sheet, without a quantified share. The household air pollution fact sheet quantifies it: the condition is 19 per cent of the 2.9 million deaths attributed to household air pollution, and household air pollution causes 23 per cent of adult COPD deaths in low- and middle-income countries, with 2.1 billion people still cooking with solid fuels or kerosene. Ambient air pollution: the condition is 14 per cent of the 4.2 million premature deaths attributed to it.

Occupational exposure to dusts, fumes and chemicals is listed as a cause without a quantified contribution on the WHO page; population-attributable estimates put roughly 14 to 15 per cent of the disease down to occupational exposures. Early-life factors matter more than was long assumed: low birthweight, childhood respiratory infections, childhood asthma and impaired lung growth. A substantial proportion of the disease arises from never reaching normal peak lung function rather than from accelerated decline — roughly half of cases in three cohorts had low baseline FEV1 with normal decline, from a 2015 New England Journal of Medicine analysis. That reframes the condition as partly developmental and is a relatively recent finding. Alpha-1 antitrypsin deficiency accounts for roughly 1 to 2 per cent of cases, with PiZZ homozygote prevalence of roughly 1 in 2,000 to 5,000 in European-ancestry populations. Post-tuberculous lung damage is a major contributor in high-incidence countries, with odds ratios of roughly 2 to 4 for airflow obstruction. Asthma, HIV, biomass and coal smoke, and chronic bronchitis in non-smokers all contribute.

Only a minority of smokers develop clinically significant disease — roughly 25 to 50 per cent depending on definition and follow-up† — and why those individuals and not others is not explained by any known genetic or environmental factor. The susceptibility question is the central unsolved problem. The relative contributions of impaired lung growth and accelerated decline are still being apportioned. Whether the exacerbation-prone phenotype is a stable trait or a statistical artefact of regression to the mean is debated.

The non-smoking disease that dominates in low-income countries is far less studied than tobacco disease, and whether it responds the same way to treatment is largely untested.

Cure status. CONTROLLABLE — and more precisely, nothing reverses the airflow obstruction.

By definition the obstruction is not fully reversible, and no drug restores destroyed alveoli or normalises FEV1. Smoking cessation is the only intervention shown to slow the rate of FEV1 decline: the Lung Health Study, with 5,887 participants over eleven years, showed sustained quitters lost FEV1 at roughly half the rate of continuing smokers, about 31 against 62 mL a year in men. It does not recover lost function; it changes the slope.

Long-term oxygen therapy is the only treatment other than smoking cessation shown to prolong survival in hypoxaemic disease. Lung volume reduction surgery in selected upper-lobe-predominant emphysema with low exercise capacity gave a survival benefit in that subgroup in the NETT trial of 1,218 patients, and harm in those with very low FEV1 and homogeneous disease; it removes destroyed tissue to let the remainder work and does not cure. Lung transplantation gives median survival of roughly 6 to 7 years post-transplant and replaces the organ. Alpha-1 antitrypsin augmentation slows emphysema progression on computed tomographic density in the RAPID trial in that 1 to 2 per cent subgroup, and does not reverse disease.

Prevention.

Tobacco control — STRONG, and the dominant measure where tobacco dominates. Smoking accounts for over 70 per cent of high-income-country disease. Tobacco kills more than 7 million people a year with over 1.6 million second-hand-smoke deaths among non-smokers, and there are 1.2 billion tobacco users, around 80 per cent of them in low- and middle-income countries. Counselling and medication can more than double quit success, and cessation services with full or partial cost coverage exist in 31 countries. A 10 per cent price rise reduces consumption by roughly 4 to 5 per cent, and 41 countries covering 12 per cent of the world's population tax at least 75 per cent of retail price. Smoking cessation halves the rate of FEV1 decline.

Clean cooking fuel and improved ventilation — STRONG on attributable burden, WEAK on randomised prevention evidence, and both must be printed. Household air pollution causes 23 per cent of adult COPD deaths in low- and middle-income countries, with 2.1 billion people exposed. Only 78 per cent of the world is projected to have clean cooking access by 2030, leaving about 1.8 billion without, and 923 million people in sub- Saharan Africa lacked access in 2022. Against that: the randomised stove-intervention trials have largely failed to show the expected respiratory benefits. RESPIRE, in Guatemala with chimney stoves, missed its primary pneumonia endpoint; HAPIN, across 3,200 households with liquefied petroleum gas stoves, verified a 66 per cent reduction in fine particulate exposure and missed its primary birth-weight endpoint; CAPS, in Malawi, found no reduction in childhood pneumonia. The most-cited explanation is that the interventions did not reduce exposure far enough to cross the steep part of the exposure-response curve, and that is plausible and unproven. The attributable burden is graded STRONG and the randomised evidence for stove interventions WEAK. This is one of the most important honest disagreements in the chapter.

Outdoor air quality standards — STRONG on burden, MODERATE on policy effect. In 2019, 99 per cent of the world's population lived above WHO guideline levels, and the condition is 14 per cent of the 4.2 million ambient air pollution deaths. Natural-experiment studies — the Dublin coal ban, the Utah Valley steel mill closure, the Beijing Olympics — showed measured falls in respiratory mortality and morbidity; these are quasi-experimental rather than randomised.

Occupational dust and fume control — STRONG, with roughly 14 to 15 per cent of the disease attributable to occupational exposure.

Smoking cessation in established disease — STRONG, and it is the only disease-modifying intervention.

Tuberculosis control — MODERATE in high-incidence settings.

Influenza and pneumococcal vaccination — MODERATE for preventing exacerbations and hospitalisation, not for preventing the disease itself; influenza vaccination reduces exacerbations per Cochrane.

Childhood measures — MODERATE: avoiding second-hand smoke, treating childhood respiratory infection, breastfeeding, reducing preterm birth, all acting on the lung-growth pathway.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Smoking cessation	Halves the rate of FEV1 decline, Lung Health Study; the only disease-modifying therapy	Nicotine replacement, bupropion and varenicline yes	yes	Nicotine replacement hundreds of euro; generic varenicline tens to hundreds of euro
Long-term oxygen therapy, 15 hours a day or more, in chronic hypoxaemia	The MRC trial, 87 hypercapnic patients with arterial oxygen tension 40 to 55 mmHg on more than 15 hours a day: three-year mortality 45.2 against 66.7 per cent without oxygen, **number needed to treat about 5 over three years to prevent one death**. NOTT, 203 patients: continuous oxygen, mean 18 hours a day, against nocturnal-only, 24-month mortality 27 against 41 per cent. This is the largest survival effect of any treatment in this condition. It does not benefit patients with moderate or exertional-only desaturation: the LOTT trial, 738 patients, was null	yes, oxygen	yes	Concentrator hundreds to thousands of euro one-off plus hundreds of euro a year for electricity; cylinders thousands of euro a year
Short-acting bronchodilator, salbutamol or ipratropium	Symptom relief and rescue therapy; short-acting bronchodilators last 4 to 6 hours, and salbutamol is generally available in public primary care in less than two-thirds of low and low-middle income countries	yes, both	yes	tens of euro
Long-acting muscarinic antagonist, tiotropium	UPLIFT, 5,993 patients over four years: exacerbations reduced, relative risk 0.86, and quality of life improved; it did not slow FEV1 decline, which was its primary endpoint	yes, added 2017	yes, generics available	€100–600 generic; branded higher
Long-acting beta-agonist, formoterol or salmeterol	Exacerbations reduced and symptoms improved	yes, formoterol	yes	tens to hundreds of euro
Long-acting beta-agonist with long-acting muscarinic antagonist	Superior to either alone for exacerbations; FLAME found indacaterol with glycopyrronium better than salmeterol with fluticasone, relative risk 0.89	partly	partly	hundreds of euro
Inhaled corticosteroid with long-acting beta-agonist	Exacerbations reduced in the frequent-exacerbator and high-eosinophil phenotype; pneumonia risk increased, TORCH 19.6 against 12.3 per cent. TORCH, 6,112 patients: all-cause mortality 12.6 against 15.2 per cent, p=0.052, missing significance	yes, beclometasone	yes	hundreds of euro
Triple therapy, inhaled corticosteroid with both long-acting bronchodilators	IMPACT, 10,355 patients: exacerbations reduced against dual therapy, all-cause mortality 1.2 against 1.8 per cent against the two bronchodilators. ETHOS, 8,588 patients: mortality 1.3 against 2.1 per cent. These are the first mortality	partly	partly	hundreds to thousands of euro

Intervention	Effect size	EML	Off-patent	Cost per patient-year
	signals in inhaled therapy for this condition, and both are secondary or post-hoc with incomplete vital-status follow-up, so both are contested			
Pulmonary rehabilitation after an exacerbation	Hospital readmissions odds ratio 0.44 (95 per cent CI 0.21–0.91), 8 studies and 810 participants, moderate certainty; mortality odds ratio 0.68 (0.28–1.67), not significant, low certainty; St George's Respiratory Questionnaire quality of life −7.80 points (−12.12 to −3.47), above the 4-point minimal important difference, high certainty; six-minute walk distance plus 62 m (38–86), high certainty. Twenty trials, 1,477 participants, Cochrane 2016. Newer trials showed smaller effects than earlier ones	n/a	n/a	hundreds to thousands of euro a programme
Azithromycin prophylaxis	Exacerbations reduced: 1.48 against 1.83 a year, hazard ratio 0.73, Albert and colleagues, 2011; hearing loss and resistance are the concerns	yes, section 6.2.2, Watch group	yes	tens to hundreds of euro
Roflumilast	Modest exacerbation reduction in severe disease with chronic bronchitis	no	yes	hundreds of euro
Non-invasive ventilation in acute hypercapnic exacerbation	Mortality reduced by roughly 50 per cent and intubation by roughly 60 per cent: Cochrane mortality relative risk 0.54, intubation 0.36, number needed to treat about 10 to prevent one death. One of the largest effects in acute respiratory care	n/a	n/a	Machine thousands of euro reusable for years
Systemic corticosteroids in exacerbation	Recovery shortened and treatment failure reduced, Cochrane odds ratio about 0.48; five days is as good as fourteen, per REDUCE	yes, prednisolone	yes	a few euro a course
Antibiotics in exacerbation	Treatment failure reduced in moderate to severe exacerbations with purulent sputum, per Cochrane	yes, amoxicillin and doxycycline; amoxicillin is listed first-choice for COPD exacerbation	yes	a few to tens of euro a course
Lung volume reduction surgery or endobronchial valves	NETT: survival benefit in the upper-lobe, low-exercise-capacity subgroup; harm in low-FEV1 homogeneous disease	n/a	n/a	tens of thousands of euro
Alpha-1 antitrypsin augmentation	Slows computed tomographic lung density loss, RAPID, in the 1 to 2 per cent deficient subgroup	no	no	tens of thousands to hundreds of thousands of euro
Dupilumab	BOREAS and NOTUS, in type 2 inflammation with eosinophils at 300 or above: exacerbations reduced roughly 30 per cent, rate ratio about 0.70 — the first successful biologic in this condition	no	no	tens of thousands of euro

The two interventions with a proven survival benefit are smoking cessation and oxygen. The first is free and the second costs hundreds to thousands of euro for a concentrator.

Simple means. Pulmonary rehabilitation is the single highest-value non-drug intervention in respiratory medicine, and it requires a trained supervisor and a chair rather than a gymnasium. Quality of life improves 7.8 points against a minimal important difference of 4, six-minute walk distance improves 62 m, both high-certainty, and readmissions fall with an odds ratio of 0.44, moderate certainty. Home-based and community programmes with minimal equipment — walking, sit-to-stand, step-ups, simple weights — achieve comparable results to gym-based programmes in randomised comparisons.

Smoking cessation halves the rate of FEV1 decline, about 31 against 62 mL a year, is the only disease-modifying intervention, and costs nothing in itself. Brief advice from a health worker alone raises quit rates by roughly 2 to 3 percentage points absolute per Cochrane, and combined with pharmacotherapy and support gives sustained quit rates of 10 to 25 per cent.

Breathing retraining is free and teachable in minutes. Pursed-lip breathing reduces dynamic hyperinflation and breathlessness immediately; diaphragmatic and paced breathing are taught in all rehabilitation programmes. Cochrane reviews of breathing exercises find improvements in six-minute walk distance of roughly 35 to 50 m and in dyspnoea scores, with low to moderate certainty. Forward-leaning with arms supported improves diaphragm mechanics and reduces breathlessness measurably.

Oxygen: concentrator against cylinder. A concentrator draws room air and separates nitrogen. It costs hundreds to thousands of euro once, lasts five to ten years, needs mains electricity at roughly 300 to 600 W or hundreds of euro a year, and filter changes; it delivers up to 5 to 10 L a minute continuously and never runs out while the power is on. A cylinder of compressed or liquid oxygen needs no electricity and is portable, and a standard cylinder at 2 L a minute lasts only hours, with the delivery logistics of refilling and transport costing thousands of euro a patient-year and dominating the expense. The MRC trial that proved oxygen prolongs life used a concentrator and provided no portable oxygen, and NOTT's continuous group averaged eighteen hours a day and did use portable systems. For a static patient with reliable electricity a concentrator is far cheaper over time and is the appropriate choice; for settings without reliable power, cylinders are the only option and the recurring cost is high. Solar-powered and battery-buffered concentrators are being deployed in low-resource settings, and outcome data are not yet available. Fifteen hours a day is the threshold at which a survival benefit was demonstrated; below that no survival benefit has been shown, and LOTT found none for moderate desaturation at all.

Clean cooking measures that cost little or nothing — ventilation, chimneys, moving the fire outdoors, cooking with lids, drying fuel — reduce exposure. The randomised stove trials RESPIRE, HAPIN and CAPS did not show the expected respiratory benefit. The attributable burden and the trial failures are reported together.

Exercise and walking are the active ingredient of pulmonary rehabilitation. Weight management matters at both ends: obesity imposes a mechanical load, and low body mass index is an independent predictor of mortality in this condition. Non-invasive ventilation reduces mortality by roughly 50 per cent in acute hypercapnic exacerbation, Cochrane relative risk 0.54, and the machine costs thousands of euro and is reusable for years; it is the most cost-effective piece of respiratory equipment in acute care. The cheap drugs that matter: prednisolone at a few euro an exacerbation course, with five days as good as fourteen; amoxicillin or doxycycline at a few to tens of euro; salbutamol at tens of euro a year — all listed, all off-patent.

Gaps. Two WHO pages give 3.4 and 3.6 million deaths for 2023, and GBD 2021 gives 3.72 million; all three are printed. The WHO fact sheet gives no global prevalence figure. Estimates vary roughly twofold depending on whether spirometric or diagnosed-disease definitions are used, and on whether fixed-ratio or lower-limit-of-normal criteria are applied. The fixed FEV1/FVC below 0.70 criterion over-diagnoses in the elderly and under-diagnoses in the young. That is an unresolved definitional dispute and it changes prevalence substantially. Between 60 and 85 per cent of cases are undiagnosed in population studies, so all prevalence figures are model-dependent. The randomised clean-cooking trials failed while the attributable-burden estimates are large, and that is this chapter's most consequential evidence gap: a measure with a very large estimated burden and no randomised confirmation of benefit. No drug has been shown to slow

FEV1 decline, and UPLIFT missed that endpoint. The mortality signals in IMPACT and ETHOS are secondary endpoints with incomplete vital-status ascertainment and are contested. TORCH missed significance for mortality at p=0.052 and is frequently cited as positive. Inhaled corticosteroids reduce exacerbations and increase pneumonia, TORCH 19.6 against 12.3 per cent, and the net effect by phenotype is still being worked out. The developmental and decline pathways are not yet apportioned, and that changes how prevention should be targeted. Why only 25 to 50 per cent of smokers develop the disease is unknown. Non-tobacco disease, which is the majority in low- and middle-income countries, is far less studied, and treatment-response data in that population are thin; almost all trial evidence comes from tobacco-smoking high-income populations. Pulmonary rehabilitation effects were smaller in newer trials than in older ones, and the mortality and readmission effects were heterogeneous, with I^2 of 59 and 77 per cent.

> **Depth.** Starts in: an air sac of the lung. Size: 200 µm†; depth +7.63. First complaint: about 35 years († about 35 years after starting to smoke); time depth 52.11. One untreated course: no number ([B] never returns in full).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Air sacs that were lost do not regrow. So it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Asthma (ICD-11 CA23)

What it is. The airways tighten, swell and fill with mucus in attacks, then open again. Wheezing, coughing and breathlessness come and go. It usually starts in childhood and most of it can be controlled with an inhaled steroid.

Measured. An estimated 363 million people had asthma in 2023, from the WHO fact sheet of 28 April 2026 carrying GBD 2023 data. Deaths: an estimated 442,000. YLDs in 2023: 14.1 million (8.80–20.3), rank 20 of all causes, against 10.2 million in GBD 2021. Asthma is the most common chronic disease among children, and the fact sheet gives no numerical figure for children. Most asthma deaths occur in low- and lower-middle-income countries, where the condition is often under-diagnosed and under-treated.

The central fact of global asthma care is an availability figure. In 2023, steroid inhalers were available in public primary health care facilities in fewer than half of low- and low-middle-income countries, and bronchodilators in fewer than two-thirds. The cheap drug that prevents death is absent from most public clinics in poor countries.

Onset is usually in childhood and prevalence is highest in children and adolescents, while deaths are concentrated in older adults. Reported prevalence is highest in high-income English-speaking countries, Latin America and parts of Africa, and mortality is inversely distributed — low prevalence and a high death rate in poor countries. Prevalence rose sharply in high-income countries from the 1960s to the 1990s and has plateaued or fallen since, and mortality has fallen substantially in countries with inhaled corticosteroid access, by roughly 50 to 70 per cent from the 1980s peaks in the UK, New Zealand and Australia.

Where it starts. Atopy — sensitisation to inhaled allergens including house dust mite, cat, dog, cockroach, Alternaria, and grass and tree pollen — underlies roughly 70 to 80 per cent of childhood asthma. Twin studies give a heritability of roughly 50 to 60 per cent, with over a hundred genome-wide association loci of which the strongest is at 17q21, around ORMDL3 and GSDMB, and which interacts with early-life rhinovirus infection. Early-life respiratory viral infection with respiratory syncytial virus or rhinovirus bronchiolitis is strongly associated with later asthma; causality is contested, and the MAKI trial of palivizumab prophylaxis in preterm infants reduced later wheeze, which supports a causal role for respiratory syncytial virus. Tobacco smoke exposure including in utero raises childhood asthma risk roughly 1.5- to twofold for maternal smoking in pregnancy. Air pollution: traffic-related pollution and nitrogen dioxide are associated with asthma incidence in children, with roughly 13 per cent of childhood asthma incidence attributed to traffic pollution in one global analysis. Obesity carries an odds ratio of roughly 1.5 to 2, and obese asthma responds less well to inhaled corticosteroids. Occupational asthma is roughly 10 to 15 per cent of adult-onset asthma, from isocyanates, flour, latex, enzymes, wood dust, persulfates and laboratory animals, and that subgroup is curable by removal from exposure if caught early.

One protective finding is unusually reproducible. Growing up on a traditional farm with livestock and unpasteurised milk roughly halves asthma and allergy risk, from PARSIFAL, GABRIELA and the Amish against Hutterite comparisons. Aspirin- and NSAID-exacerbated respiratory disease accounts for roughly 7 per cent of adult asthma. Paracetamol, antibiotics in infancy and caesarean delivery have reported associations that are all CONTESTED and plausibly confounded.

The hygiene and microbial-exposure hypothesis explains the farm effect and the epidemic rise in high-income countries plausibly and has not produced a preventive intervention that works: no primary prevention of asthma has ever been demonstrated in a randomised trial. Why the prevalence rose so steeply and then plateaued is unexplained. Asthma is not one disease: the type-2-high eosinophilic steroid-responsive and type-2-low neutrophilic or paucigranulocytic steroid-resistant phenotypes have different treatment responses, and the type-2-low group has almost no effective therapy. Why some children remit at puberty and others do not is not predictable.

Cure status. CONTROLLABLE. Occupational asthma, workers removed from exposure early: CURABLE in roughly a third (complete recovery). Childhood asthma remitting at adolescence: stays CONTROLLABLE, since relapse in adulthood is common.

Inhaled corticosteroids suppress airway inflammation and control symptoms, and airway inflammation and hyperresponsiveness return within weeks of stopping, so the state is held rather than removed. Two trials make the point clearly. START, with 7,241 patients on three years of early budesonide, improved control and reduced severe exacerbations and did not alter the natural history: post-treatment lung function and remission rates converged with placebo. CAMP, with 1,041 children on four to six years of budesonide, found no effect on lung-function growth or on asthma persistence after treatment stopped.

Occupational asthma is CURABLE by removal from exposure if done early: complete recovery occurs in roughly a third of workers removed early, and the probability falls sharply with duration of continued exposure after symptom onset. Early diagnosis and removal is therefore genuinely curative and delay forecloses it.

Natural remission occurs in roughly 30 to 60 per cent of children with asthma, who become symptom-free in adolescence; relapse in adulthood is common and airway hyperresponsiveness often persists subclinically. That is remission.

Prevention.

No primary prevention of asthma has been demonstrated. Allergen avoidance in infancy, maternal diet modification, probiotics and early allergen introduction — which prevents food allergy, as LEAP showed — have not prevented asthma in randomised trials.

Inhaled corticosteroids to prevent exacerbations and death — STRONG, and the central fact of asthma care. A case-control study found each additional canister of inhaled corticosteroid per year was associated with a 21 per cent lower rate of asthma death. Inhaled corticosteroids reduce severe exacerbations by roughly 40 to 55 per cent against placebo across trials.

Avoiding short-acting beta-agonist monotherapy — STRONG. Reliever-only treatment is associated with increased mortality; the New Zealand fenoterol epidemic of the 1970s and 1980s and the SMART trial, with 26,355 patients on salmeterol without an inhaled corticosteroid and excess respiratory deaths, established this. GINA no longer recommends reliever-only treatment at any severity.

Tobacco control, including smoke-free homes and smoke-free pregnancy — STRONG for reducing incidence and severity.

Occupational exposure control — STRONG, and it is the only clearly preventable subtype: eliminating or enclosing isocyanates, flour dust and latex reduces incidence markedly in industry cohorts.

Air pollution reduction — MODERATE. Roughly 13 per cent of childhood asthma incidence is attributed to traffic pollution, and natural experiments including the Atlanta Olympics road closures and the Utah Valley mill closure showed measured falls in asthma attacks and admissions.

Influenza vaccination — MODERATE for reducing exacerbations. *Weight loss in obese asthma — MODERATE*. *Breastfeeding — WEAK and CONTESTED* for asthma specifically.

House dust mite avoidance measures — CONTESTED to negative. Cochrane found no clear benefit of physical or chemical mite-control measures for asthma outcomes. That contradicts very widely given advice and is printed.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Inhaled corticosteroid, beclometasone or budesonide	The foundation. Severe exacerbations reduced roughly 40 to 55 per cent; each extra canister a year associated with 21 per cent lower asthma mortality	yes, both	yes	€10–60 at international generic prices; €100–400 in high-income retail, year not stated in the source for either price
Inhaled corticosteroid with formoterol as both maintenance and reliever, or as-needed in mild asthma	SYGMA 1 and 2 and Novel START: as-needed budesonide with formoterol reduced severe exacerbations by roughly 60 per cent against a reliever alone and was comparable to maintenance corticosteroid at a much lower steroid dose. This is now the preferred GINA approach at all severities	Both components yes	yes	tens to hundreds of euro
Short-acting beta-agonist, salbutamol	Rescue only; must not be used as monotherapy	yes	yes	a few to tens of euro
Long-acting beta-agonist added to an inhaled corticosteroid	Exacerbations reduced and control improved against the corticosteroid alone; never to be used without one	yes, formoterol	yes	tens to hundreds of euro
Long-acting muscarinic antagonist, tiotropium, as add-on	Modest FEV1 and exacerbation benefit in uncontrolled asthma	yes	yes	hundreds of euro
Leukotriene receptor antagonist, montelukast	Less effective than an inhaled corticosteroid; neuropsychiatric adverse effects led to a United States boxed warning in 2020	no	yes	€20–150
Oral prednisolone for an exacerbation	Shortens the exacerbation and prevents relapse	yes	yes	a few euro a course
Intravenous magnesium sulfate in severe acute asthma	Hospital admission reduced in severe exacerbations, per Cochrane	yes, with the Model List restriction to eclampsia and severe pre-eclampsia	yes	a few euro a dose
Oxygen with spacer- or nebuliser-delivered salbutamol and ipratropium, acute care	Standard acute care; a spacer is as effective as a nebuliser for acute asthma in children and most adults, per Cochrane	yes	yes	Spacer a few to tens of euro
Omalizumab, anti-IgE	Exacerbations reduced roughly 25 to 40 per cent in allergic asthma	**NOT on the 24th Model List in any form**	Biosimilars emerging	tens of thousands of euro
Mepolizumab,	MENSA, mepolizumab:	no	no	tens of thousands of euro

Intervention	Effect size	EML	Off-patent	Cost per patient-year
benralizumab, reslizumab, anti-interleukin-5	exacerbations reduced 47 to 53 per cent; oral steroid sparing in SIRIUS			
Dupilumab, anti-interleukin-4 receptor alpha	QUEST, 1,902 patients: severe exacerbations reduced about 48 per cent, rate 0.46 against 0.87; FEV1 improved, with a larger effect at high eosinophil counts	no	no	tens of thousands of euro
Tezepelumab, anti-thymic stromal lymphopoietin	NAVIGATOR, 1,061 patients: exacerbations reduced 56 per cent, and effective irrespective of eosinophil count — the first biologic with benefit in type-2-low asthma	no	no	tens of thousands of euro
Allergen immunotherapy, subcutaneous or sublingual	Symptoms and medication use reduced in allergic asthma; Cochrane supports modest benefit, and a house dust mite sublingual tablet reduced exacerbations	no	partly	hundreds to thousands of euro
Bronchial thermoplasty	Modest symptom benefit; declining use	n/a	n/a	tens of thousands of euro

The price asymmetry is the single most important economic fact in this chapter. An inhaled corticosteroid costing €10 to €60 a patient-year (international generic prices, year not stated in the source) prevents the great majority of asthma deaths and is absent from more than half of public primary care facilities in low- and low-middle-income countries. The biologics cost tens of thousands of euro a patient-year and address the small severe-asthma minority. Essentially all of the 442,000 annual asthma deaths are preventable with the cheap drug rather than the expensive ones.

Simple means. A spacer device is the clearest example in the chapter of an effective device that can be made from waste material. A plastic spacer, or a homemade spacer from a 500 mL plastic bottle, makes a metered-dose inhaler far more effective, and WHO’s own asthma fact sheet names the homemade 500 mL bottle spacer. Randomised trials in children with acute asthma, by Zar and colleagues in South Africa and by Duarte and colleagues in Brazil, found a homemade bottle spacer as effective as a conventional commercial spacer for salbutamol delivery. A spacer is as effective as a nebuliser for acute asthma, per Cochrane, and a nebuliser needs electricity while a spacer does not.

An inhaled corticosteroid costs €10 to €60 a patient-year at international generic prices (year not stated in the source), is listed and off-patent, and is associated with 21 per cent lower asthma mortality per extra canister a year. It requires a pharmaceutical chain, a very cheap one, and the barrier is procurement and policy rather than cost.

Written asthma action plans with self-management education are paper and teaching time. Cochrane finds self-management education with a written action plan reduces hospitalisations by roughly 36 to 40 per cent and emergency visits substantially.

Breathing retraining needs printing precisely. Cochrane’s review of breathing exercises for asthma finds improved quality of life and reduced symptoms, with effects on quality-of-life scores exceeding the minimal important difference in several trials, and no consistent effect on lung function or exacerbations, at low to moderate certainty. Buteyko and Papworth methods reduce reliever use and improve symptom scores in small trials without changing underlying inflammation. Breathing retraining improves symptoms and reduces reliever use; it does not replace inhaled corticosteroids and does not prevent exacerbations.

Smoking cessation and smoke-free homes reduce severity and improve steroid responsiveness, since smokers respond less well to inhaled corticosteroids. Weight loss in obese asthma improves control and

lung function. Removal from occupational exposure is curative in roughly a third if done early; it costs nothing medically, and it costs a job, which is the real barrier. Prednisolone and magnesium in acute attacks cost a few euro a course each, both listed and off-patent. Sitting upright, calm reassurance and pursed-lip exhalation during an attack are free and reduce the work of breathing. Avoiding known triggers — smoke, cold-air exertion without warm-up, NSAIDs in aspirin-exacerbated disease, beta blockers — is free, and the NSAID and beta-blocker avoidance is potentially life-saving in those subgroups.

What does not work: Cochrane found no clear benefit from house dust mite control measures, despite that advice being almost universally given. It is printed.

Gaps. The WHO fact sheet gives no figure for children affected despite calling asthma the commonest chronic childhood disease. Prevalence estimates depend heavily on definition — questionnaire-reported wheeze, doctor diagnosis and bronchodilator reversibility give substantially different numbers — and the 363 million figure is model-based. No primary prevention of asthma has ever been demonstrated; the hygiene hypothesis explains the epidemiology and has yielded no working intervention. Why prevalence rose and then plateaued is unexplained. START and CAMP showed early inhaled corticosteroid treatment does not alter natural history, and that is widely misunderstood. House dust mite avoidance: Cochrane null against universal advice. Type-2-low asthma has almost no effective therapy except possibly tezepelumab, and it is a large minority of severe asthma. Mortality data are weakest where mortality is highest: asthma death certification is unreliable, and the 442,000 figure rests on modelling in countries with poor vital registration. Montelukast's neuropsychiatric risk was recognised late and the magnitude remains debated. Biologic trials use exacerbation rates over one year, and long-term disease-modification data do not exist for any biologic. The inverse relation between prevalence and mortality across countries is a treatment-access signal and its magnitude is not precisely quantified. Omalizumab is not on the 24th Model List in any form, and any claim otherwise is wrong.

> **Depth.** Starts in: an allergen protein. Size: 5 nm†; depth −2.01. First complaint: about 5 years († onset about age 5); time depth 50.34. One untreated course: no number ([B] comes and goes).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Infection and scarring of the lung

Pneumonia (ICD-11 CA40)

Pneumonia is coded in ICD-11 chapter 12 as CA40, and the organism-specific infections also appear in chapter 01. This entry treats it as a respiratory condition and complements the infectious-disease chapter.

What it is. Infection fills the air sacs of the lung with fluid and pus. Fever, cough and fast breathing follow, and the person cannot get enough oxygen. It is the largest infectious killer of children and of older adults.

Measured. Deaths from lower respiratory infections in 2023: 2,501,300 (95 per cent uncertainty interval 2,241,000 to 2,812,200), from GBD 2023; 2.7 million, about 4.4 per cent of all deaths and rank 4 of all causes, on WHO's top-ten page. GBD and WHO differ by about 200,000 and both are printed. GBD 2021 gave 2,180,000 (1,980,000–2,360,000), rank 7, with an age-standardised rate of 28.7 per 100,000. DALYs in 2023: 98.7 million (87.7–112), rank 4 of all causes globally. No single global incidence figure was located in the retrieved sources; estimates of roughly 120 to 150 million episodes of childhood pneumonia a year, and roughly 1,500 adult hospitalisations per 100,000 a year over age 65, exist in the literature.

Pneumonia is the single largest infectious cause of death in children under five: roughly 700,000 to 740,000 child deaths a year, about 14 per cent of all under-five deaths, from the WHO and UNICEF estimates. The WHO fact sheet on pneumonia in children, printed in November 2022 and reporting 2019 data, gives 740,180 deaths of children under five, which is 14 per cent of under-five deaths, with 22 per cent of deaths in children aged one to five. It states that only one third of children with pneumonia receive the antibiotics they need. That page is the oldest in the WHO set consulted for this book. For scale, there were 4.9 million under-five deaths in 2024.

Household air pollution causes 44 per cent of child pneumonia deaths and 22 per cent of adult pneumonia deaths, and lower respiratory infection is 21 per cent of the 2.9 million deaths attributed to household air pollution; almost half of under-five lower respiratory infection deaths are caused by particulate matter from household air pollution. A 44 per cent attributable fraction for child pneumonia deaths is the largest single environmental attribution in either chapter. Ambient air pollution: acute lower respiratory infections are 14 per cent of its 4.2 million premature deaths.

The age pattern is U-shaped, with the highest mortality in infants and in those over 70. The great majority of child pneumonia deaths occur in sub-Saharan Africa and south Asia. Child pneumonia deaths have fallen by roughly half since 2000, attributed to vaccination against Haemophilus influenzae type b and pneumococcus, improved case management and reduced undernutrition.

Where it starts. The organisms. Streptococcus pneumoniae is the commonest bacterial cause at all ages, followed by Haemophilus influenzae type b, now largely vaccine-preventable, and Staphylococcus aureus. Mycoplasma pneumoniae and Legionella appear in adults. Respiratory syncytial virus is the commonest viral cause in infants, with influenza, SARS-CoV-2, human metapneumovirus and parainfluenza also contributing. Pneumocystis jirovecii occurs in HIV, and Klebsiella and other Gram-negatives in hospital-acquired disease.

Undernutrition is the single largest child risk factor, and stunting and wasting multiply pneumonia mortality several-fold; about 150 million children under five were stunted in 2024, 43 million wasted. Household air pollution carries 44 per cent of child pneumonia deaths. Lack of exclusive breastfeeding in the first six months roughly doubles risk, and exclusive breastfeeding at 0 to 6 months stood at about 47 per cent globally in 2018 to 2025. Low birthweight and prematurity, crowding, second-hand tobacco smoke, incomplete vaccination, vitamin A and zinc deficiency, HIV and measles all contribute. In adults: age, chronic lung disease, heart failure, diabetes, immunosuppression, smoking, alcohol, aspiration risk from stroke, dementia or reduced consciousness, and inhaled corticosteroid use, where TORCH gave pneumonia at 19.6 against 12.3 per cent. Influenza infection predisposes to secondary bacterial pneumonia.

The causative organism is never identified in roughly 40 to 60 per cent of community-acquired pneumonia† even with modern molecular testing, so most treatment is empirical. Whether a given radiographic consolidation is bacterial or viral cannot be reliably determined at the bedside or on the film, which drives large amounts of unnecessary antibiotic use. Why one colonised child develops invasive pneumococcal pneumonia and another does not is not explained. The contribution of viral-bacterial co-infection to mortality is not well quantified.

Cure status. Bacterial pneumonia: CURABLE. Viral pneumonia in the immunocompetent: SELF-LIMITING with supportive care. Pneumocystis pneumonia: CURABLE with co-trimoxazole.

This is one of the clearest cures in medicine when the antibiotic reaches the patient in time. Appropriate antibiotics cure bacterial pneumonia in the large majority: untreated lobar pneumococcal pneumonia had a case fatality of roughly 30 per cent in the pre-antibiotic era, falling to roughly 5 per cent or less with penicillin, in the original comparisons of the 1930s and 1940s. Community case management with oral antibiotics by community health workers reduces child pneumonia mortality by roughly 35 to 42 per cent — a cure delivered by a trained non-clinician with a course of tablets costing cents.

Viral pneumonia is largely SELF-LIMITING in the immunocompetent and becomes lethal through hypoxaemia and secondary bacterial infection, both treatable. Oseltamivir for influenza shortens illness by roughly a day and, in observational data, reduces mortality in hospitalised patients; the trial evidence for mortality is weak and contested. Mortality remains high in the very old and in severe disease: 30-day mortality in hospitalised community-acquired pneumonia is roughly 10 to 15 per cent, and 25 to 50 per cent in those requiring intensive care.

Another chapter of this book declares the same disease CURABLE for bacterial and SELF-LIMITING for viral pneumonia, splitting by cause, which is the same split used here.

Prevention.

Pneumococcal conjugate vaccine — STRONG, with large measured effects. The vaccine reduces vaccine-type invasive pneumococcal disease by roughly 80 to 90 per cent in vaccinated children and produces

substantial herd protection in unvaccinated adults. Radiologically confirmed pneumonia in children was reduced by 37 per cent (95 per cent CI 27–45) per protocol and 36 per cent by intention to treat in the Gambian trial. A figure of 25 per cent as the low end of a range† appears without a traceable source and is not carried here as a measured value. Pneumococcal last-dose coverage was 71 per cent in 2025, and the vaccine is on the Essential Medicines List† and in routine immunisation in most countries.

Haemophilus influenzae type b vaccine — STRONG. Near-elimination of invasive disease where coverage is high; coverage was 78 per cent in 2025.

Measles vaccination — STRONG. Measles deaths fell from 762,800 in 2000 to 143,600 in 2023, a decline of 81.2 per cent, on GBD 2023; WHO's measles fact sheet gives 95,000 deaths in 2024 against 780,000 in 2000, with nearly 59 million deaths averted by vaccination between 2000 and 2024. Most measles deaths are from pneumonia, so measles vaccination is substantially a pneumonia prevention measure. First-dose coverage was 84 per cent in 2025 and two-dose coverage 77 per cent, with roughly 21 million children missing the routine first dose.

Exclusive breastfeeding for six months — STRONG. It roughly halves pneumonia incidence and reduces pneumonia mortality substantially, and it costs nothing. WHO estimates nearly 400,000 under-five deaths a year could be prevented by exclusive breastfeeding for six months and continued breastfeeding to two years or beyond.

Handwashing with soap — STRONG. Cluster-randomised trials in Karachi found handwashing promotion reduced pneumonia incidence in children under five by roughly 50 per cent. Soap and water.

Influenza vaccination — MODERATE in older adults and chronic disease.

Respiratory syncytial virus prevention — STRONG and newly available. Nirsevimab, a long-acting monoclonal antibody, reduced medically attended lower respiratory infection by roughly 75 to 80 per cent in infants, in HARMONIE and MELODY. The maternal RSVpreF vaccine reduced severe infant disease by roughly 70 to 80 per cent in the first 90 days, in MATISSE. Nirsevimab costs hundreds of euro per infant, a price that limits global reach.

Clean cooking fuel — STRONG on attributable burden, WEAK on randomised evidence, and the single most important unresolved disagreement in this entry. Household air pollution carries 44 per cent of child pneumonia deaths. RESPIRE, with chimney stoves in Guatemala, missed its primary pneumonia endpoint, though severe pneumonia was reduced in per-protocol analysis. CAPS, with cookstoves across 10,750 children in Malawi, found no reduction in pneumonia. HAPIN, with liquefied petroleum gas stoves, verified a 66 per cent reduction in fine particulate exposure and missed its primary birth-weight endpoint. Both the 44 per cent attribution and the three trial failures are printed, and neither side has conceded; the exposure-response threshold explanation is plausible and unproven.

Co-trimoxazole prophylaxis in HIV — STRONG. *Oral care in nursing homes and after stroke — MODERATE* for aspiration pneumonia. *Reducing crowding and second-hand smoke — MODERATE*.

Zinc supplementation — CONTESTED. It reduces pneumonia incidence by roughly 15 to 20 per cent in some trials and meta-analyses and not in others, and Cochrane rates it as uncertain for treatment. *Vitamin A supplementation — MODERATE* for child mortality generally, not specifically for pneumonia.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Oral amoxicillin for non-severe childhood pneumonia	Community case management with oral antibiotics reduces child pneumonia mortality roughly 35 to 42 per cent; oral amoxicillin is as effective as injectable penicillin for severe pneumonia, from the APPIS and NO-SHOTS trials	yes, section 6.2.1 Access group, listed first-choice for community-acquired pneumonia	yes	€0.20–1.00 a child course. UNICEF indicative price October 2026: US$0.54 for ten 250 mg dispersible tablets, about US$0.054 a tablet; US$0.41 for a 100 mL

Intervention	Effect size	EML	Off-patent	Cost
				bottle of 125 mg/5 mL suspension
Amoxicillin or amoxicillin-clavulanate with or without a macrolide, adult community-acquired pneumonia	Standard; mortality reduced against no treatment dramatically	yes	yes	a few to tens of euro a course
Benzylpenicillin or ampicillin with gentamicin, severe child pneumonia	The WHO standard for severe disease	yes	yes	a few to tens of euro a course
Ceftriaxone, severe disease or resistance		yes	yes	a few to tens of euro a course
Co-trimoxazole, Pneumocystis pneumonia and HIV prophylaxis	Curative for Pneumocystis pneumonia	yes	yes	a few to tens of euro a course
Oxygen	The single most important supportive treatment. Hypoxaemia is the main proximate cause of death in child pneumonia, and oxygen systems in Papua New Guinea district hospitals reduced child pneumonia mortality by 35 per cent	yes	yes	Concentrator hundreds to thousands of euro one-off; see the COPD entry for the comparison
Pulse oximetry	Identifies hypoxaemia that is invisible clinically; integrating it into case management changes treatment in a substantial minority of children	n/a	n/a	tens to hundreds of euro a device
Corticosteroids in severe community-acquired pneumonia	CAPE COD, 800 patients with severe pneumonia: 28-day mortality 6.2 against 11.9 per cent, hazard ratio 0.46, absolute risk difference 5.7 percentage points, recomputed number needed to treat 17.5. Earlier trials were mixed and ESCAPe was null. For COVID-19 pneumonia, RECOVERY, 6,425 patients: dexamethasone reduced 28-day mortality 22.9 against 25.7 per cent overall, absolute risk difference 2.8 points, number needed to treat 36, and in ventilated patients 29.3 against 41.4 per cent, absolute risk difference 12.1 points, recomputed number needed to treat 8.3, with a drug costing under €5	yes, dexamethasone and prednisolone	yes	€1–5 a course. UNICEF indicative price October 2026 for dexamethasone 4 mg: US$24.00 for 100 tablets, about US$0.24 a tablet
Oseltamivir, influenza	Symptoms shortened by about a day; the mortality benefit in hospitalised patients is observational and contested	yes	yes	a few to tens of euro a course

Intervention	Effect size	EML	Off-patent	Cost
Non-invasive ventilation or high-flow nasal oxygen	Intubation reduced in hypoxaemic respiratory failure; FLORALI found high-flow oxygen reduced 90-day mortality in non-hypercapnic hypoxaemic failure	n/a	n/a	thousands of euro a machine
Mechanical ventilation	Life-saving in respiratory failure	n/a	n/a	tens of thousands of euro a machine plus intensive care
Zinc as a treatment adjunct	Cochrane: uncertain benefit for treating child pneumonia	yes	yes	a few to a few euro a course

Oral amoxicillin at US$0.054 a tablet, the UNICEF indicative price in October 2026, delivered by a community health worker, reduces child pneumonia mortality by roughly 35 to 42 per cent. Against roughly 700,000 annual child pneumonia deaths, that is plausibly the largest measured mortality benefit per euro of any intervention in either chapter. Dexamethasone at a few euro a course with a number needed to treat of about 8 in ventilated COVID-19 pneumonia is the other extreme example.

Simple means. Counting respiratory rate is the diagnostic basis of community case management worldwide and needs no equipment. WHO's integrated management of childhood illness diagnoses pneumonia by counting breaths a minute — fast breathing thresholds of 60 or more under two months, 50 or more at two to eleven months, 40 or more at one to five years — and by looking for chest indrawing. A watch or a simple timer and sixty seconds.

Oral amoxicillin given by a community health worker costs cents a course and reduces child pneumonia mortality by 35 to 42 per cent. Oral is as effective as injectable even for severe pneumonia, per APPIS and NO-SHOTS, which removes the need for syringes, sterile technique and referral in a large share of cases.

Pulse oximetry costs tens to hundreds of euro is battery-powered, needs no consumables, and detects the hypoxaemia that kills. Oxygen is the single highest-yield piece of hospital equipment for pneumonia, and a concentrator with a reliable power supply is the cheap way to provide it: a concentrator costs hundreds to thousands of euro once plus hundreds of euro a year for electricity, while cylinders cost thousands of euro a year in delivery logistics. Oxygen systems in district hospitals reduced child pneumonia mortality by 35 per cent in Papua New Guinea. Solar-powered concentrator installations are in use and outcome data are limited.

Handwashing with soap reduced childhood pneumonia incidence by roughly 50 per cent in the Karachi cluster-randomised trial. Exclusive breastfeeding roughly halves pneumonia incidence, is free, and requires support rather than supply. Dexamethasone costs a few euro a course with a number needed to treat of about 8 for mortality in ventilated COVID-19 pneumonia and about 18 in severe bacterial pneumonia; it is a cheap tablet or ampoule, listed and off-patent. Upright positioning, continued feeding and fluids during illness are nursing care rather than technology. Reducing smoke exposure — moving the cooking fire outside, ventilation, lids on pots, dry fuel — addresses an attributable burden of 44 per cent of child pneumonia deaths, and the randomised stove trials failed to demonstrate benefit; both must be said.

The hard limit. Severe pneumonia with respiratory failure needs oxygen at minimum and sometimes ventilation. Oxygen is the binding constraint in most of the world: the drugs are cheap and available, and the oxygen often is not.

Gaps. GBD gives 2,501,300 deaths and WHO gives 2.7 million for 2023, and GBD 2021 gives 2,180,000; all are printed. No single global incidence figure was located. The organism is unidentified in 40 to 60 per cent of cases, so nearly all treatment is empirical and resistance surveillance is weak. The clean-cooking disagreement is the largest in this entry: a 44 per cent attributable fraction for child pneumonia deaths against three failed randomised stove trials. Neither side has conceded and the exposure-response threshold explanation is plausible and unproven. Zinc is contested: Cochrane uncertain, other meta-analyses positive. Corticosteroids in severe community-acquired pneumonia: CAPE COD strongly positive at hazard ratio

0.46, ESCAPe null, earlier trials mixed; the guidelines are changing and the question is not settled. Oseltamivir's mortality benefit rests on observational data, and the randomised evidence is weak and the subject of a long-running public dispute over trial data access. Child pneumonia mortality estimates come from verbal autopsy and modelling in the countries that carry most of the burden, and the roughly 700,000 figure is a model output. Distinguishing bacterial from viral pneumonia is not possible at the bedside, which drives antibiotic overuse of a scale that is not well measured. Oxygen availability in low-income hospitals is poorly documented; surveys suggest a majority of district hospitals in sub-Saharan Africa lack reliable oxygen, and systematic data are thin. One pneumococcal vaccine figure that circulates — a 25 per cent low end for radiologically confirmed pneumonia reduction — appears in no retrievable primary source and is not carried as a measured value. The WHO fact sheet on childhood pneumonia is dated November 2022 and reports 2019 data, the oldest vintage in the WHO set consulted for this book.

> **Depth.** Starts in: Streptococcus pneumoniae. Size: 1 µm†; depth +2.81. First complaint: about 42 hours ([L] 1–3 days); time depth 44.00. One untreated course: about 14 days († about 2 weeks); depth 45.90.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Bronchiectasis (ICD-11 CA24)

What it is. The airways are permanently widened and scarred, so mucus pools in them and becomes infected again and again. The person coughs up large amounts of sputum daily and loses lung function in steps. It is usually the end result of earlier severe infection.

Measured. No global prevalence, death or DALY figure for bronchiectasis was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all, and for a condition with prevalence over 1 per cent in the elderly it is a substantial hole.

Prevalence in high-income countries runs from roughly 67 to 566 per 100,000 adults depending on country and ascertainment method, from UK, United States, German and Spanish administrative studies; the eightfold range between studies is itself the finding. UK incidence rose from roughly 21 to 35 per 100,000 a year in women and 18 to 27 in men between 2004 and 2013. Prevalence rises steeply with age, exceeding 1 per cent above 70 in some series. Mortality is roughly 1.5 to 2 times that of the age-matched general population, with median survival after diagnosis of roughly 13 to 17 years in European cohorts. In low- and middle-income countries post-tuberculous bronchiectasis is probably the commonest form and is almost entirely unmeasured; studies in India, China and South Africa report tuberculosis as the cause in 25 to 50 per cent of cases. There is a female predominance in most high-income cohorts, roughly 60 to 65 per cent. Reported prevalence and incidence are rising in high-income countries, attributed largely to increased computed tomographic scanning and recognition rather than to a true increase.

Where it starts. Post-infective causes are the largest identified group: childhood pneumonia, pertussis, measles, tuberculosis — dominant in high-burden countries — non-tuberculous mycobacteria and adenovirus. No cause is found in roughly 25 to 45 per cent of cases in high-income cohorts. Bronchiectasis is found on computed tomography in roughly 30 to 50 per cent of moderate to severe chronic obstructive pulmonary disease. Cystic fibrosis is treated as a separate entry below. Primary ciliary dyskinesia affects roughly 1 in 10,000 to 20,000 and accounts for roughly 2 to 3 per cent of bronchiectasis. Immunodeficiency — common variable immunodeficiency, specific antibody deficiency, HIV — accounts for roughly 5 to 10 per cent of cases, and that group matters because immunoglobulin replacement changes the course. Allergic bronchopulmonary aspergillosis accounts for roughly 5 to 10 per cent in some series. Alpha-1 antitrypsin deficiency, rheumatoid arthritis at roughly 3 to 5 per cent of cases, inflammatory bowel disease and Sjögren syndrome all contribute. Aspiration and gastro-oesophageal reflux contribute, and a foreign body or tumour causing localised obstruction gives the one form with a potential surgical cure. Yellow nail syndrome, Mounier-Kuhn syndrome and Williams-Campbell syndrome are rare structural causes.

In 25 to 45 per cent of cases no cause is found at all despite systematic investigation. The vicious vortex model — impaired mucociliary clearance, infection, inflammation and structural damage reinforcing one another — is widely accepted and does not identify which link to break in a given patient. Why some

patients are chronically infected with Pseudomonas aeruginosa, a marker of much worse prognosis, and others never are is not predictable. Whether bronchiectasis found incidentally on computed tomography in chronic obstructive pulmonary disease patients is the same disease as primary bronchiectasis is unresolved and has direct treatment consequences.

Cure status. Established bronchiectasis: CONTROLLABLE. Localised disease confined to one lobe or segment with an identified local cause: CURABLE by surgical resection.

The airway dilatation is permanent and irreversible, and no treatment reverses it; the structural damage on computed tomography does not resolve. Airway clearance, antibiotics and treatment of the underlying cause slow progression and reduce exacerbations.

Localised bronchiectasis confined to one lobe or segment with an identified local cause — a foreign body, a tumour, prior focal infection — can be cured by surgical resection. Symptom resolution follows in roughly 70 to 90 per cent of selected patients in surgical series, with operative mortality under 2 per cent in modern practice. That is a genuine cure, available only to a small minority with focal disease and good lung function.

Treating the underlying cause changes the trajectory without reversing the damage: immunoglobulin replacement in antibody deficiency sharply reduces infections, steroids and antifungals treat allergic bronchopulmonary aspergillosis, antituberculous therapy treats active tuberculosis, and removal of a foreign body removes the obstruction. Lung transplantation is available for end-stage disease.

Prevention.

Tuberculosis control and complete treatment — STRONG, and quantitatively the most important measure globally, given that post-tuberculous bronchiectasis dominates in high-burden countries. Tuberculosis caused 1.23 million deaths in 2024 with 10.7 million new cases, and 83 million lives have been saved since 2000.

Childhood vaccination against measles, pertussis, Haemophilus influenzae type b and pneumococcus — STRONG. The historical decline of bronchiectasis in high-income countries followed vaccination and antibiotic availability; measles deaths fell 81.2 per cent from 2000 to 2023, and measles pneumonia was a major cause of post-infective bronchiectasis.

Prompt and adequate treatment of childhood pneumonia — STRONG by the same logic; community case management with oral amoxicillin reduces child pneumonia mortality 35 to 42 per cent.

Early diagnosis of immunodeficiency — MODERATE: immunoglobulin replacement prevents the progressive damage, and diagnostic delay in common variable immunodeficiency averages four to nine years, during which bronchiectasis develops.

Newborn screening for cystic fibrosis — STRONG; see that entry.

Removal of inhaled foreign bodies promptly — STRONG in the specific case. *Early diagnosis and treatment of allergic bronchopulmonary aspergillosis — MODERATE*. *Smoking cessation — MODERATE*. *Influenza and pneumococcal vaccination in established disease — MODERATE* for exacerbations.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Airway clearance physiotherapy	The foundation of treatment. Sputum clearance and quality of life improve; Cochrane finds improved quality of life and reduced symptoms at low to moderate certainty, with no mortality data	n/a	n/a	Training time; devices a few to tens of euro
Pulmonary rehabilitation	Exercise capacity and quality of life improve, comparable to the chronic obstructive pulmonary disease effects	n/a	n/a	hundreds to thousands of euro a programme

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Long-term macrolide, azithromycin or erythromycin	The best-evidenced drug therapy. BAT, azithromycin, 83 patients: exacerbations 0.59 against 1.57 per patient over a year. EMBRACE, 141 patients: exacerbation rate ratio 0.38. BLESS, erythromycin, 117 patients: exacerbations reduced. Roughly a halving of exacerbations across the three trials. Risks: macrolide resistance, hearing loss, QT prolongation, and mycobacterial infection must be excluded first	yes, both	yes	€30–150. UNICEF indicative price October 2026 for azithromycin 250 mg: US$0.56 for six tablets, about US$0.093 a tablet
Inhaled antibiotics, colistin, gentamicin, tobramycin, aztreonam	Bacterial load and exacerbations reduced in Pseudomonas-colonised patients; trial results are inconsistent, and the two phase 3 aztreonam trials AIR-BX1 and AIR-BX2 were negative for symptoms	yes, colistin, gentamicin and tobramycin	yes	hundreds to thousands of euro depending on agent
Brensocatib, dipeptidyl peptidase-1 inhibitor	ASPEN, 1,721 patients, 2025: exacerbation rate reduced roughly 20 to 21 per cent against placebo — the first drug developed specifically for bronchiectasis to succeed in phase 3	no	no	Price not established at compilation; expected high
Hypertonic saline, nebulised 6 to 7 per cent	Sputum clearance and quality of life improve; the evidence is weaker than in cystic fibrosis and the trials are small	no	yes	tens to hundreds of euro
Inhaled mannitol	Failed its primary endpoint of exacerbation rate in a large trial, though quality of life improved	no	no	thousands of euro
Bronchodilators	Symptomatic, used where airflow obstruction coexists; little bronchiectasis-specific evidence	yes	yes	tens of euro
Inhaled corticosteroids	Not recommended unless asthma or chronic obstructive pulmonary disease coexists; they increase pneumonia risk	yes	yes	tens of euro
Dornase alfa, recombinant human DNase	**Harmful in non-cystic-fibrosis bronchiectasis** — a randomised trial showed worse FEV1 and more exacerbations. A drug that works in cystic fibrosis is harmful here	no	no	tens of thousands of euro
Immunoglobulin replacement, antibody deficiency	Infections sharply reduced and progression slowed in that subgroup	yes, normal immunoglobulin	yes	tens of thousands of euro
Surgical resection, focal disease	Symptom resolution in 70 to 90 per cent of selected patients; operative mortality under 2 per cent	n/a	n/a	thousands to tens of thousands of euro
Antibiotics for exacerbations, fourteen days, guided by sputum culture	Standard care	yes, amoxicillin, doxycycline, co-amoxiclav, ciprofloxacin	yes	a few to tens of euro a course
Lung transplantation	End-stage disease	n/a	n/a	hundreds of thousands of euro in the first year

Simple means. This is a condition where physical technique carries most of the treatment.

Airway clearance by physical technique requires no equipment at all, only instruction. The active cycle of breathing technique, autogenic drainage and postural drainage are the foundation of bronchiectasis care worldwide and improve quality of life and sputum clearance. Twice-daily clearance for 15 to 30 minutes, taught once by a physiotherapist, is the core treatment of a lifelong disease.

Oscillating positive expiratory pressure devices — a flutter valve, an Acapella, an Aerobika — cost tens of euro are reusable for years, and need no power. Bubble positive expiratory pressure can be improvised from a plastic bottle and tubing: blowing through a tube into a bottle of water generates positive expiratory pressure and assists clearance, and it is used in low-resource settings, with small studies supporting an effect comparable to commercial devices.

Azithromycin is the single most cost-effective drug in the entry by a wide margin: tens to hundreds of euro a year, listed, off-patent, oral, and it roughly halves exacerbations across three randomised trials. The precondition is excluding mycobacterial infection, which requires sputum culture.

Exercise and pulmonary rehabilitation improve exercise capacity and quality of life; walking and sit-to-stand, no gymnasium. Hydration and steam or humidification before clearance to loosen secretions is standard practice with low-quality evidence. Hypertonic saline at 6 to 7 per cent can be made from salt and sterile water at trivial cost, though a nebuliser needs power, and the evidence is weaker than in cystic fibrosis. Vaccination against influenza and pneumococcus is listed, cheap and routine. Smoking cessation is free.

The hard limit. Diagnosis requires computed tomography of the chest: bronchiectasis is defined radiologically, no clinical feature or spirometric pattern establishes it, and chest radiography misses most cases. Sputum culture is needed to guide antibiotics and to exclude mycobacteria before macrolides. So the condition cannot be diagnosed or safely treated without computed tomography and a microbiology laboratory, even though its main treatment is a breathing technique and a tens of euro antibiotic.

Gaps. No GBD global burden figure for bronchiectasis was retrieved, and this entry is part of the seventeen-condition gap in this chapter’s introduction. Reported prevalence varies eightfold between high-income countries, 67 to 566 per 100,000, on methodology alone. Post-tuberculous bronchiectasis, probably the commonest form globally, is essentially unmeasured and almost absent from a trial evidence base that is European, North American and Australasian. No cause is found in 25 to 45 per cent of cases. The overlap with chronic obstructive pulmonary disease, found in 30 to 50 per cent of moderate to severe cases of that condition, is not resolved as to whether it is the same disease, and the treatment implications differ. Dornase alfa is beneficial in cystic fibrosis and harmful here — a clear demonstration that evidence does not transfer between the two, and a warning against extrapolation. Inhaled antibiotic trials are inconsistent, and AIR-BX1 and AIR-BX2 were negative for symptoms despite a microbiological effect. Airway clearance, the foundation of treatment, has only low to moderate certainty evidence and no mortality data, because trials of physiotherapy are hard to blind and have never been adequately powered for hard endpoints. Brensocatib, from ASPEN in 2025, is the first successful bronchiectasis-specific drug, and its price, durability and place in therapy are not yet established. Mortality and survival figures come from European specialist cohorts with referral bias.

> **Depth.** Starts in: a bronchus. Size: 5 mm†; depth +10.56. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number ([B] loss in steps).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. A widened airway does not return to its shape. Only a local part can be cut out. So it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Pulmonary fibrosis and interstitial lung disease (ICD-11 CB03, CB04)

What it is. The tissue between the air sacs thickens and scars, so oxygen cannot cross into the blood. The lungs shrink and stiffen. Breathlessness worsens steadily and in the commonest form, idiopathic pulmonary fibrosis, it is relentless.

Measured. No global prevalence, death or DALY figure for interstitial lung disease was retrieved from the GBD 2023 tables. GBD carries interstitial lung disease and pulmonary sarcoidosis as a cause and no figure was retrieved. GBD 2019 estimates gave roughly 4.7 million prevalent cases and roughly 180,000 deaths a year globally, from an earlier round.

Idiopathic pulmonary fibrosis incidence, from a systematic review in the European Respiratory Journal in 2015, read in a repository copy. In Europe and North America from 2000 onward under narrow criteria it runs at roughly 3 to 9 per 100,000 a year, with a results-section range of 2.8 to 9.3. The UK figures are 4.6 for 1991 to 2003, 7.44 for 2000 to 2008 and 8.65 for 2000 to 2012. Denmark gives 7.27 for 1995 to 2000 and 5.28 for 2001 to 2005, with a later local-records study giving 1.3 for 2003 to 2009. The United States gives 16.3 broad and 6.8 narrow in a 2006 claims analysis; Medicare over 65 for 2001 to 2011 gives 31.1 to 43.0 broad and 15.9 to 31.1 narrow, with an overall rate of 93.7; Minnesota over 50 gives 17.4 broad and 8.8 narrow. Italy, in Lazio, gives 7.5 by coding and 9.3 after case review. East Asia gives 1.2 to 4.16 across Taiwan, South Korea and Japan. South America gives 0.26 in Brazil in 1996 rising to 0.48 in 2010, with the discussion giving 0.4 to 1.2. Questionnaire-survey European estimates are Turkey 4.69, Spain 1.4 to 2.9, Greece 0.93 and Flanders 0.22.

Mortality per 100,000 a year, same review: a ten-country age-standardised comparison runs from 4.68 in Sweden to 13.36 in Northern Ireland on broad codes, and from 4.64 in Spain to 8.28 in England and Wales on specific codes. Multiple-cause mortality gives 12.98 for England and Wales in 2010 and 9.37 for the United States. The UK gives 2.54 overall for 1968 to 2008, rising from 0.92 in 1968 to 1972 to 5.10 in 2005 to 2008, roughly 5 per cent a year. The United States gives 3.65 in 1991, 5.08 for 1992 to 2003 and 7.57 for 1999 to 2003 on multiple-cause coding. Brazil rises from 0.65 in 1996 to 1.21 in 2010, and Japan gives 10.26 on broad coding.

The review excluded prevalence studies, so it reports no prevalence figures, and it does not report survival figures, noting only that a Taiwanese cohort had more severe disease and lower survival. Elsewhere, median survival in untreated idiopathic pulmonary fibrosis is roughly three to five years from diagnosis, which is worse than many cancers. The trend direction disagrees between datasets. Most studies show rising incidence, especially in UK datasets. Denmark fell from 2001 to 2005, with possible diagnostic transfer, and United States Minnesota fell in later years with low case numbers. A 2014 analysis found stable Medicare incidence from 2001 to 2011, and United States multiple-cause mortality plateaued from 2003. Mortality rose in most countries, with no change in Germany or New Zealand in one comparison. All of them are printed. Idiopathic pulmonary fibrosis is rare below 50 and rises steeply, with a median age at diagnosis of roughly 65 to 70 and a male predominance of roughly 1.5 to 2 to 1.

Where it starts. Idiopathic pulmonary fibrosis has no known cause by definition. Established associations follow.

Cigarette smoking: odds ratio roughly 1.6 to 2.9. Age is the strongest determinant.

Genetics. The MUC5B promoter variant rs35705950 is the strongest known risk factor. It is present in roughly 35 per cent of patients against 11 per cent of controls, with an odds ratio of roughly 4.5 heterozygous and 20 homozygous, and it is paradoxically associated with better survival. Telomerase mutations in TERT, TERC, RTEL1 and PARN appear in roughly 10 to 25 per cent of familial cases, and short telomeres predict worse outcome and worse response to immunosuppression.

Occupational and environmental dusts, including metal dust, wood dust, stone and silica, farming, livestock and birds: odds ratios of roughly 1.5 to 2.5 across case-control studies.

Gastro-oesophageal reflux and microaspiration are strongly associated and causality is contested. Viral infection with Epstein-Barr virus and other herpesviruses is associated without established causality.

Other interstitial lung diseases have known causes. Hypersensitivity pneumonitis from birds, mould, hot tubs or metalworking fluid, where antigen avoidance can halt or reverse it, making this the identifiable and partly curable group. Connective tissue disease interstitial lung disease: systemic sclerosis with lung involvement in roughly 50 to 80 per cent on computed tomography, rheumatoid arthritis, myositis with anti-MDA5 or anti-synthetase antibodies, Sjögren syndrome, lupus. Drug-induced disease from amiodarone, methotrexate, nitrofurantoin, bleomycin, immune checkpoint inhibitors and radiation. The

pneumoconioses, treated in the occupational entry below. Sarcoidosis, cause unknown, with roughly 10 to 30 per cent developing fibrosis. Smoking-related forms — respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, Langerhans cell histiocytosis — which improve or resolve with smoking cessation.

The cause of idiopathic pulmonary fibrosis is unknown. The MUC5B variant is common in the general population and most carriers never develop fibrosis, so it is a susceptibility marker rather than a cause. Why the fibrosis is progressive and self-sustaining once started is not explained. Whether reflux and microaspiration cause the disease or result from it has not been resolved, and the one randomised trial of anti-reflux surgery was inconclusive. Why antifibrotics slow decline by roughly half and never stop or reverse it is unexplained. The very wide between-country ranges in both incidence, 0.22 to 93.7 per 100,000 depending on criteria and population, and mortality, 4.64 to 13.36, reflect coding and case-definition differences more than true variation, and the true global burden is therefore not known.

Cure status. Idiopathic pulmonary fibrosis: RELIEF ONLY. Hypersensitivity pneumonitis in the acute and subacute stages: CURABLE by antigen avoidance. Smoking-related interstitial disease: CURABLE by cessation. Drug-induced disease: CURABLE by stopping the drug. Sarcoidosis: SELF-LIMITING in roughly 60 to 70 per cent. Connective tissue disease interstitial lung disease: CONTROLLABLE.

No treatment reverses established pulmonary fibrosis. Antifibrotics slow the rate of forced vital capacity decline by roughly 50 per cent and do not restore lost function.

Immunosuppression is actively harmful in idiopathic pulmonary fibrosis. The PANTHER-IPF trial, of prednisone with azathioprine and N-acetylcysteine, was stopped early for increased death and hospitalisation, with mortality of 8 against 1 per cent. That is one of the most important negative results in respiratory medicine: the standard treatment for decades made the disease worse.

Hypersensitivity pneumonitis is reversible or curable by antigen avoidance in the acute and subacute stages, and once fibrotic it behaves like idiopathic pulmonary fibrosis. Smoking-related interstitial disease improves or resolves with cessation. Drug-induced disease is often reversible on stopping the drug. Sarcoidosis remits spontaneously in roughly 60 to 70 per cent within two to three years, and corticosteroids control symptoms and have not been shown to alter long-term outcome. Connective tissue disease interstitial lung disease is CONTROLLABLE: immunosuppression with mycophenolate, cyclophosphamide, rituximab or tocilizumab in scleroderma stabilises or improves lung function in a substantial proportion, unlike in idiopathic disease. Lung transplantation is the only intervention that removes the disease, with median survival after transplantation for idiopathic pulmonary fibrosis of roughly five to six years against three to five years untreated.

Prevention.

Antigen avoidance in hypersensitivity pneumonitis — STRONG, and genuinely curative if early. Removing birds, remediating mould, changing metalworking fluid practice.

Avoiding and monitoring fibrogenic drugs — STRONG: amiodarone, methotrexate, nitrofurantoin, bleomycin, checkpoint inhibitors.

Smoking cessation — MODERATE for idiopathic pulmonary fibrosis, odds ratio 1.6 to 2.9, and *STRONG* for smoking-related interstitial disease, which improves or resolves on quitting.

Occupational dust control — MODERATE. Metal, wood, stone and silica dust carry odds ratios of roughly 1.5 to 2.5; see the pneumoconiosis entry for the control measures.

Screening in systemic sclerosis — MODERATE, since early treatment of scleroderma lung disease is more effective than late.

Family screening and genetic counselling in familial pulmonary fibrosis — WEAK: informative, with no preventive intervention available.

Nothing prevents idiopathic pulmonary fibrosis.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Pirfenidone	ASCEND, 555 patients: the proportion with a 10 per cent or greater decline in forced vital capacity or death reduced 47.9 per cent. CAPACITY pooled: decline slowed roughly 50 per cent. Pooled analyses show reduced mortality, hazard ratio about 0.52 at one year	no	**yes — generics available**	Branded tens of thousands of euro; generic thousands of euro in some markets
Nintedanib	INPULSIS 1 and 2, 1,066 patients: annual forced vital capacity decline −114.7 against −239.9 mL and −113.6 against −207.3 mL, roughly a 50 per cent reduction in decline; also effective in progressive fibrosing interstitial lung disease in INBUILD and in scleroderma lung disease in SENSCIS	no	no	tens of thousands of euro
Lung transplantation	Median survival five to six years post-transplant	n/a	n/a	hundreds of thousands of euro in the first year
Long-term oxygen therapy	Relieves exertional hypoxaemia and improves exercise capacity; a survival benefit has never been demonstrated in fibrosis, unlike in chronic obstructive pulmonary disease	yes, oxygen	yes	Concentrator hundreds to thousands of euro; see the COPD entry
Pulmonary rehabilitation	Six-minute walk distance improves by roughly 35 to 50 m and quality of life improves; the benefit wanes within six months without maintenance	n/a	n/a	hundreds to thousands of euro a programme
Mycophenolate, cyclophosphamide, rituximab or tocilizumab, connective tissue disease interstitial lung disease	Scleroderma Lung Study II: mycophenolate equivalent to cyclophosphamide with less toxicity; tocilizumab in focuSSced preserved forced vital capacity	Mycophenolate no; cyclophosphamide yes; rituximab is a listed medicine in sections 5.1.2 and 8.2.2	yes, both	Mycophenolate hundreds to thousands of euro; cyclophosphamide hundreds of euro
Corticosteroids, in sarcoidosis, hypersensitivity pneumonitis, acute exacerbations and drug-induced disease	Symptoms controlled; in sarcoidosis no effect on long-term outcome has been demonstrated	yes	yes	a few to tens of euro
Corticosteroids or immunosuppression in idiopathic pulmonary fibrosis	**HARMFUL.** PANTHER-IPF stopped early: mortality 8 against 1 per cent	—	—	—
N-acetylcysteine	No benefit in idiopathic pulmonary fibrosis overall; possible benefit in TOLLIP genotype subgroups, unconfirmed	yes	yes	tens to hundreds of euro
Sildenafil, for associated	STEP-IPF null on its	**NOT on the 24th**	yes	tens to hundreds of euro

Intervention	Effect size	EML	Off-patent	Cost per patient-year
pulmonary hypertension	primary endpoint; INSTAGE null	**Model List in any form**		
Anti-reflux therapy or surgery	Observational associations with slower decline; the WRAP-IPF randomised trial was inconclusive	Proton pump inhibitor yes	yes	tens to hundreds of euro
Opioids for refractory breathlessness, palliative	Low-dose morphine reduces breathlessness and is the best-evidenced symptom treatment in advanced fibrosis	yes, oral morphine, section 2.2	yes	tens to hundreds of euro

Generic pirfenidone is the key economic point. It is now off-patent with generics available at thousands of euro a patient-year against tens of thousands of euro for the brand, and it slows forced vital capacity decline by roughly 50 per cent with a pooled one-year mortality signal, hazard ratio about 0.52. Nintedanib remains on patent at tens of thousands of euro.

Simple means. Antigen avoidance is the only cure in this entry and costs nothing medically: removing the birds, remediating the damp, changing the job. In acute and subacute hypersensitivity pneumonitis it is curative. Stopping the offending drug in drug-induced disease is free and often reversible. Smoking cessation resolves or improves smoking-related interstitial disease and reduces idiopathic pulmonary fibrosis risk, and it is free.

Avoiding immunosuppression in idiopathic pulmonary fibrosis is a free decision that avoids the harm demonstrated in PANTHER-IPF, mortality 8 against 1 per cent. Not doing something is the intervention.

Pulmonary rehabilitation and walking give plus 35 to 50 m on the six-minute walk and improved quality of life; home-based programmes with a chair and a measured corridor achieve much of the benefit. The benefit wanes within six months without maintenance, so it must be continued.

Breathing retraining and pacing — pursed-lip breathing, paced activity, forward-lean positioning — and a hand-held fan to the face are free or nearly so. A fan directed at the face measurably reduces the sensation of breathlessness in randomised crossover trials, and it is one of the cheapest symptom interventions in medicine. Low-dose oral morphine for refractory breathlessness costs €10 to €100 a year, is listed and off-patent, and is the best-evidenced treatment for the symptom that dominates the illness; the UNICEF indicative price in October 2026 for morphine sulfate injection 10 mg/mL was US$5.71 for a box of ten ampoules, about US$0.57 an ampoule.

Oxygen relieves exertional hypoxaemia and improves exercise capacity, and no survival benefit has been shown in fibrosis. Concentrator against cylinder as in the chronic obstructive pulmonary disease entry: hundreds to thousands of euro once plus hundreds of euro a year for power, against thousands of euro a year for cylinders. Ambulatory oxygen matters more here than in chronic obstructive pulmonary disease because the desaturation is exertional. Vaccination against influenza, pneumococcus and COVID-19 is cheap, and acute infection precipitates fatal exacerbations.

The hard limit, stated plainly, and this is the clearest case in either chapter where diagnosis rather than treatment is the binding constraint. Interstitial lung disease cannot be diagnosed without high-resolution computed tomography, and distinguishing idiopathic pulmonary fibrosis from hypersensitivity pneumonitis and from connective tissue disease interstitial lung disease determines whether immunosuppression will help or kill: the same drug is beneficial in one and lethal in the other. That distinction requires high-resolution computed tomography, autoantibody testing and often multidisciplinary review or biopsy. Without it, treatment is a coin toss with a demonstrated mortality cost. There is no simple-means substitute.

Gaps. No GBD 2023 figure for interstitial lung disease was retrieved, and the roughly 180,000 deaths and 4.7 million prevalent cases come from an earlier round; this entry is part of the seventeen-condition gap in this chapter’s introduction. The incidence range in the primary systematic review spans 0.22 to 93.7 per 100,000 depending on country, criteria and population — a 400-fold range that is mostly methodological

— and no reliable global incidence figure exists. The review excluded prevalence studies entirely and reports no prevalence and no survival figures. Mortality coding is the central problem: broad against specific ICD codes give rates differing roughly twofold within the same country, and the ten-country comparison ranges from 4.64 to 13.36. The trend direction disagrees between datasets — rising in the UK, falling in Denmark and Minnesota, stable in United States Medicare from 2001 to 2011, plateauing in United States multiple-cause mortality from 2003, no change in Germany and New Zealand — and all of them are printed. The cause of idiopathic pulmonary fibrosis is unknown. Antifibrotics slow decline by about 50 per cent and do not stop it, and whether they extend survival rests on pooled and post-hoc analyses rather than a mortality-powered trial. Reflux is an observational association with an inconclusive trial. Sarcoidosis: corticosteroids control symptoms with no demonstrated effect on long-term outcome, and are widely used long-term. Oxygen has no demonstrated survival benefit in fibrosis, unlike in chronic obstructive pulmonary disease, and this is often assumed rather than known. Almost all evidence comes from Europe, North America and east Asia; incidence in Africa, south Asia and Latin America is essentially unmeasured, and the Brazilian figures of 0.26 to 0.48 are implausibly low and almost certainly ascertainment. Sildenafil is not on the 24th Model List in any form.

> **Depth.** Starts in: an air sac of the lung. Size: 200 µm†; depth +7.63. First complaint: about 65 years († onset about age 65); time depth 52.67. One untreated course: about 3.9 years († survival 3–5 years); depth 50.10.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Occupational lung diseases: silicosis, asbestosis and coal workers' pneumoconiosis (ICD-11 CA60–CA6Z)

What it is. Dust breathed in at work lodges permanently in the lungs and scars them. Stone and sand dust cause silicosis, asbestos fibres cause asbestosis, coal dust causes black lung. All three are entirely caused by the work and all three are irreversible.

Measured. All the pneumoconiosis figures below are aggregate across types, because the primary GBD 2021 analysis does not report silicosis, asbestosis and coal workers' pneumoconiosis separately. Everything in this table was read off its source.

Measure	1990	2021	Trend
Incident cases	42,188 (35,786–48,913)	62,866 (54,617–71,103)	Counts rose; age-standardised incidence roughly flat, estimated annual percentage change −0.02 (95 per cent CI −0.09 to 0.06)
Deaths	17,471 (15,589–19,436)	18,323 (16,041–20,916)	Counts rose slightly; age-standardised death rate fell from 0.46 to 0.22 per 100,000, estimated annual percentage change −1.21
DALYs	—	507,425, a 2017 figure cited from the paper's introduction	Only age-standardised DALY rates by region are reported for 2021
Prevalence	Not reported as a global total	About 527,500 for 2021, cited in the introduction from a separate source rather than from GBD 2021	Regional rates only; East Asia has the highest male rate at 19.00 per 100,000

Projections: roughly 62,061 incident cases in 2030 and 62,434 in 2035; roughly 15,246 deaths in 2030 and 13,863 in 2035.

Type-specific fragments exist, and none of them are GBD 2021 figures. For silicosis, China's National Occupational Disease Monitoring System reported an annual decline in incidence since 2010, average annual percentage change −4.7, and a separate 1990 to 2019 study reported a global decline in silica-attributed mortality, with an age-standardised mortality rate estimated annual percentage change of −1.22. For coal workers' pneumoconiosis, a GBD 2017 study reported declines in middle and low sociodemographic index regions without numbers, and incidence remains disproportionately high in low-

and middle-income countries, again without figures. Asbestosis is reported as rising in high-sociodemographic-index countries, without figures.

Asbestos-related disease beyond asbestosis is roughly an order of magnitude larger. WHO estimates roughly 200,000 or more deaths a year from all occupational asbestos exposure, including mesothelioma at roughly 30,000 to 38,000 deaths a year and asbestos-attributed lung cancer. The asbestosis figure alone therefore understates asbestos mortality by roughly a factor of ten.

Silicosis is re-emerging in high-income countries through engineered stone benchtop fabrication. Australian and United States case series report rapid, severe, progressive silicosis in young workers, with roughly 20 to 40 per cent of screened engineered-stone workers affected in some Australian cohorts. Australia banned engineered stone from July 2024, the first national ban.

Disease appears after ten to thirty years of exposure, so incidence peaks in middle and older age, and accelerated and acute silicosis can appear within months to five years at very high exposures. East Asia has the highest male rate at 19.00 per 100,000, and the burden is concentrated in mining, construction, stone-working and shipbreaking economies.

Where it starts. The cause is known completely and precisely in all three, and that is the distinguishing feature of this entry: there is no uncertainty about aetiology at all.

Silicosis comes from inhaled respirable crystalline silica, in mining, quarrying, tunnelling, sandblasting, foundry work, ceramics, glass, stone cutting, engineered stone fabrication and gemstone polishing, with an established dose-response where risk rises with cumulative exposure and with concentration. Asbestosis comes from inhaled asbestos fibres, with the amphiboles crocidolite and amosite more potent than chrysotile for mesothelioma and both fibrogenic, in mining, insulation, shipbuilding, construction, brake linings and shipbreaking, and in secondary household exposure from workers' clothing. Coal workers' pneumoconiosis comes from inhaled coal mine dust, and the respirable silica content of the dust is a major determinant of severity, which is why modern United States cases in thin-seam Appalachian mining have been unusually severe and rapidly progressive.

Co-factors multiply risk. Smoking multiplies asbestos-related lung cancer risk roughly fiftyfold over non-smoking non-exposed people and roughly fivefold over non-smoking asbestos-exposed people — a multiplicative interaction, and one of the best-documented in occupational medicine. Silica exposure roughly triples tuberculosis risk and silicosis raises it further, and silicotuberculosis is a major problem in southern African mining. Silica is an IARC Group 1 lung carcinogen, and asbestos is Group 1 for lung cancer, mesothelioma, laryngeal and ovarian cancer. Silica exposure is associated with rheumatoid arthritis, systemic sclerosis, lupus, ANCA-associated vasculitis and chronic kidney disease.

Why, at the same cumulative exposure, some workers develop progressive massive fibrosis and others only simple pneumoconiosis is not explained; host factors are suspected and not identified. There is no established safe exposure threshold for asbestos, and whether one exists for silica is disputed — the United States permissible limit of 50 µg/m³ is associated with measurable residual risk in modelling. The determinants of latency variation, from months to decades, are not understood. The reason modern Appalachian coal workers' pneumoconiosis is more severe than historical disease is attributed to silica content and not definitively established. Most importantly: in low- and middle-income countries, where most exposure occurs, there is essentially no surveillance, so the true incidence is unknown and the GBD figures almost certainly understate it substantially.

Cure status. RELIEF ONLY. This is the clearest RELIEF ONLY classification in either chapter.

No treatment removes or reverses pneumoconiosis. The dust is permanently retained, the fibrosis is established, and the disease progresses even after exposure ends; progression after cessation of exposure is documented in all three diseases. No drug has been shown to alter the course of any of them: corticosteroids, tetrandrine, whole-lung lavage and antifibrotics have been tried and none has established disease-modifying benefit in adequate trials. Whole-lung lavage removes some dust burden and is used in acute silicoproteinosis without altering long-term outcome. Lung transplantation is the only intervention that removes the diseased organ, and outcomes in silicosis are comparable to other fibrotic indications. Antifibrotics, nintedanib in particular, are indicated for progressive fibrosing interstitial lung disease,

which can include pneumoconiosis, on the basis of INBUILD, and pneumoconiosis-specific trial evidence is thin.

Treating the complications is effective, and that matters: tuberculosis is curable, which is important in silicotuberculosis, and pneumothorax, cor pulmonale, infections and hypoxaemia are all treatable.

So the disease cannot be cured, cannot be stopped, and is entirely preventable. That combination is the whole point of this entry.

Prevention. Prevention is complete and the evidence is unambiguous: eliminating exposure eliminates the disease. Every grade here is STRONG.

Banning asbestos — STRONG, and demonstrated at national scale. Roughly 70 countries have banned all forms of asbestos. In the countries that banned it early — Scandinavia, the Netherlands, the UK in 1999, Australia in 2003 — mesothelioma incidence has peaked and begun to fall in the cohorts born after the ban, with a thirty- to forty-year lag. Chrysotile asbestos is still mined and used in Russia, Kazakhstan, China, India and elsewhere, and WHO, the International Labour Organization and every major scientific body call for a global ban. This is the single clearest preventable occupational disease burden in the world, and the obstacle is commercial rather than scientific.

Substitution and process change — STRONG. Replacing silica sand in abrasive blasting, replacing engineered stone, wet cutting instead of dry. Australia's engineered stone ban of July 2024 is the first national prohibition of a silica product.

Engineering controls — STRONG: wet methods, local exhaust ventilation, enclosure, on-tool dust extraction. Wet cutting reduces respirable silica generation by roughly 80 to 95 per cent in workplace measurements.

Exposure limits and enforcement — STRONG where enforced. The United States respirable crystalline silica standard of 50 µg/m³ from 2016 and comparable European limits reduce measured exposures; the evidence that enforcement reduces disease is historical and ecological, and residual risk remains at the current limits.

Tuberculosis screening and preventive therapy in silica-exposed workers — STRONG: silica exposure roughly triples tuberculosis risk, and isoniazid preventive therapy reduced tuberculosis incidence in South African gold miners.

Smoking cessation — STRONG, because of the multiplicative interaction with asbestos for lung cancer, roughly fiftyfold combined.

Medical surveillance by chest radiography or computed tomography and spirometry — MODERATE for detection and for removing workers from further exposure, which slows but does not stop progression.

Respiratory protection — MODERATE. Effective when correctly fitted and worn, and it is the last line of the hierarchy of controls rather than the first; real-world protection factors fall well below laboratory ratings.

Compensation and surveillance systems — MODERATE, indirectly: recognised compensable disease creates economic pressure for control.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Removal from further exposure	Slows but does not stop progression; it is the first action in every case	n/a	n/a	Nothing medically; the cost is the job
Tuberculosis treatment and preventive therapy	Curative for tuberculosis; isoniazid preventive therapy reduced tuberculosis incidence in silica-exposed miners	yes, all first-line agents	yes	tens of euro a full curative course; isoniazid prophylaxis a few to tens of euro
Pulmonary rehabilitation	Exercise capacity and quality of life improve, as in other fibrotic disease,	n/a	n/a	hundreds to thousands of euro

Intervention	Effect size	EML	Off-patent	Cost
	plus 35 to 50 m on the six-minute walk			
Long-term oxygen therapy	For chronic hypoxaemia; the chronic obstructive pulmonary disease survival evidence, three-year mortality 45.2 against 66.7 per cent, has not been replicated in pneumoconiosis	yes	yes	Concentrator hundreds to thousands of euro
Bronchodilators	Symptomatic where airflow obstruction coexists, which is common in coal workers	yes	yes	tens of euro a year
Influenza and pneumococcal vaccination	Infective exacerbations reduced	yes	yes	a few to tens of euro
Whole-lung lavage	Removes dust burden in acute silicoproteinosis; no effect on long-term outcome demonstrated	n/a	n/a	thousands to tens of thousands of euro
Corticosteroids	No established disease-modifying benefit	yes	yes	a few to tens of euro
Nintedanib, progressive fibrosing phenotype	INBUILD supports use in progressive fibrosing interstitial lung disease generally; pneumoconiosis-specific evidence is thin	no	no	tens of thousands of euro
Tetrandrine, used in China for silicosis	A claimed antifibrotic effect; the evidence is low quality and not accepted internationally	no	yes	hundreds of euro
Lung transplantation	The only intervention that removes the diseased organ	n/a	n/a	hundreds of thousands of euro in the first year
Compensation and income support	Not a medical treatment, and it is the principal intervention available to an affected worker	n/a	n/a	Varies by jurisdiction

Simple means. Wet cutting is the single highest-impact simple means in either chapter, because it prevents an incurable disease with water. Water applied at the cutting point reduces respirable silica generation by roughly 80 to 95 per cent. A hose, a water-bottle attachment or a water-fed tool.

Working outdoors or in ventilated space, positioning upwind, enclosing the dusty process, wetting down before sweeping, and never dry-sweeping settled dust are all free or nearly free and all reduce exposure substantially. Not using the material at all — substituting non-silica abrasives, not using asbestos, not using engineered stone — is achievable at national scale, as Australia's engineered stone ban shows.

Changing and washing work clothes before going home prevents a disease in someone who never entered the workplace: household asbestosis and mesothelioma in workers' spouses and children from contaminated clothing is documented, and washing clothes at work is free.

Respirators cost a few to tens of euro for disposable FFP2 or FFP3 masks and tens of euro for reusable half-masks with P3 filters. They are effective when fitted and worn, and they are the last line of defence; fit-testing matters, and beard growth, poor fit and discomfort reduce real-world protection substantially.

Smoking cessation is the largest single mortality intervention available to an asbestos-exposed worker: the multiplicative interaction means cessation removes most of the lung-cancer excess, from roughly fiftyfold combined down toward the fivefold exposure-only level. It is free.

Tuberculosis treatment and isoniazid preventive therapy cost tens of euro for a full curative course, with all drugs listed and off-patent. In silica-exposed populations that is the treatable, curable part of the disease burden, and it is cheap. Pulmonary rehabilitation and walking give plus 35 to 50 m on the six-minute walk. Breathing retraining, pacing, forward-lean positioning and a fan to the face relieve breathlessness as in the fibrosis entry. Low-dose morphine for refractory breathlessness costs tens to hundreds of euro a year, listed and off-patent.

The honest summary, stated plainly. There is no treatment for these diseases and there never has been. Everything in the treatment table above is supportive or treats a complication. The entire effective intervention is prevention, and the core of prevention — water on the blade, not using asbestos, washing the clothes, not smoking — requires no industrial supply chain at all. The chain that is required is regulatory and organisational: exposure limits, inspection, enforcement and compensation. The binding constraint is not technology or money; it is whether the controls are applied.

Gaps. GBD 2021 does not report silicosis, asbestosis and coal workers' pneumoconiosis separately. For three diseases with entirely different causes, prevention and politics, only the aggregate exists in the primary global dataset, and that is a serious structural gap. No global prevalence total is reported in GBD 2021; the figure of about 527,500 comes from a separate source cited in the paper's introduction rather than from GBD 2021. No 2021 global DALY total is given, only the 2017 figure of 507,425, and the source round for that DALY figure is not clearly named in the paper. Surveillance is weakest where exposure is heaviest: mining, stone-working and shipbreaking in low- and middle-income countries have little or no occupational disease registration, so the 62,866 incident cases and 18,323 deaths are near-certainly substantial underestimates. Age-standardised rates are flat or falling while absolute counts rise — the disease is being described as improving while more people get it. The asbestosis figure captures only a small part of asbestos mortality; mesothelioma and asbestos-attributed lung cancer are counted elsewhere, and WHO's roughly 200,000 or more annual asbestos deaths is about an order of magnitude above the pneumoconiosis total. Engineered-stone silicosis is a new epidemic with no global figures at all, only national case series. Whether a safe exposure threshold exists for silica is disputed, and for asbestos none is established. No safe or effective treatment exists, and tetrandrine is used in China on evidence not accepted elsewhere — a genuine international disagreement about a drug given to patients. Asbestos is still mined and traded while every scientific body calls for a ban; that is a gap between evidence and policy rather than a gap in evidence.

> **Depth.** Starts in: a dust particle (silica or asbestos). Size: 5 µm†; depth +4.28. First complaint: about 14 years († latency 10–20 years); time depth 51.28. One untreated course: no number († permanent).
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The bound applies. The dust stays in the lung. It cannot be taken out. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

The upper airway, the sleeping airway, and the pleural space

Sleep-disordered breathing — obstructive sleep apnoea (ICD-11 7A41, chapter 07)

A note on placement. In ICD-11 the sleep-related breathing disorders were moved into a new standalone chapter 07, sleep-wake disorders, having been dispersed across the nervous system, mental and behavioural, and respiratory chapters in ICD-10. Obstructive sleep apnoea is therefore coded in chapter 07 rather than chapter 12. It is placed here because it is managed as a respiratory condition and because the respiratory chapter is where a reference work's reader will look for it. No condition in ICD-11 chapter 07 is a GBD level-3 cause, so no GBD burden figures exist for it, and its burden is distributed in GBD across cardiovascular, mental and respiratory causes.

What it is. The throat collapses repeatedly during sleep, so breathing stops for seconds at a time, dozens or hundreds of times a night. The person snores, wakes unrefreshed and is sleepy all day. It is very common and mostly undiagnosed.

Measured. Global prevalence among **adults aged 30 to 69**, using the 2012 American Academy of Sleep Medicine criteria. Mild to severe obstructive sleep apnoea, apnoea-hypopnoea index 5 events an hour or above: 936 million (95 per cent CI 903 to 970 million). Moderate to severe disease, index 15 or above: 425 million (399 to 450 million). The age band is part of the figure and must travel with it: both numbers are for adults aged 30 to 69 only, not all adults, and a book that prints 936 million people worldwide without the age band overstates the claim's scope. **The study's funding statement is the single word ResMed**, which

manufactures continuous positive airway pressure devices, and that is printed wherever either figure is used.

No GBD death or DALY figure exists, for the reason given in the placement note. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Prevalence estimates are highly sensitive to the diagnostic threshold and the scoring rules: the 2012 criteria give roughly double the prevalence of the older 1999 criteria, because hypopnoeas with 3 rather than 4 per cent desaturation are counted. Population studies find moderate to severe disease in roughly 10 to 17 per cent of men and 3 to 9 per cent of women in middle age, in the Wisconsin Sleep Cohort and HypnoLaus. Roughly 80 to 90 per cent of those affected are undiagnosed. Prevalence rises with age to a plateau around 60 to 70, with a male predominance of roughly 2 or 3 to 1 narrowing after menopause. Central sleep apnoea and obesity hypoventilation syndrome are separate entities; obesity hypoventilation affects roughly 0.15 to 0.3 per cent of adults and 8 to 20 per cent of patients referred for sleep apnoea with a body mass index above 30.

Where it starts. Obesity is the dominant modifiable factor: a 10 per cent weight gain predicts roughly a 32 per cent increase in the apnoea-hypopnoea index and a sixfold increase in the odds of developing moderate to severe disease, from the Wisconsin Sleep Cohort. For scale, 940 million adults, about 16 per cent, were living with obesity in 2024, and adult obesity has more than doubled since 1990. Craniofacial anatomy matters: retrognathia, maxillary narrowing, a long soft palate, a large tongue. East Asian populations have comparable prevalence to western populations at substantially lower body mass index because of craniofacial structure, which is an important and well-documented finding. Male sex, age and menopause contribute. Tonsillar and adenoidal hypertrophy is the dominant cause in children, and the reason adenotonsillectomy is curative in childhood disease. Alcohol and sedatives before sleep reduce upper airway tone. Smoking, nasal obstruction and supine sleep position contribute, as do hypothyroidism, acromegaly, Down syndrome and neuromuscular disease. Rostral fluid redistribution overnight contributes in heart failure and kidney failure.

The apnoea-hypopnoea index correlates poorly with symptoms and with outcomes: many people with a high index are not sleepy, and sleepiness does not track the index closely. That is the central problem of the field — the defining measurement may not be the clinically relevant one — and alternative metrics such as hypoxic burden and arousal intensity are proposed and not standardised. Which patients will derive cardiovascular benefit from treatment is not known, and the randomised trials have been null. Whether treating asymptomatic disease found on screening helps at all is unknown, and no trial supports it.

Cure status. Adults: CONTROLLABLE. Children with tonsillar and adenoidal hypertrophy: CURABLE by adenotonsillectomy. Selected adults with skeletal retrusion: CURABLE in roughly 40 to 45 per cent by maxillomandibular advancement, an index below 5, in meta-analysis. Disease caused by hypothyroidism or acromegaly: CURABLE by correcting the cause.

Continuous positive airway pressure abolishes the obstruction while it is worn and the apnoea returns the night it is stopped. That is the clearest “holds the state” treatment in either chapter.

Weight loss is genuinely disease-modifying. Bariatric surgery and large dietary weight loss produce remission in roughly 40 to 60 per cent of patients, and the Sleep AHEAD trial showed the index fell 5.2 events an hour more with intensive lifestyle intervention than control, with remission in roughly three times as many participants.

Adenotonsillectomy in children is curative in roughly 70 to 80 per cent of otherwise healthy children with the condition. The CHAT trial, with 464 children, showed improved behaviour, quality of life and polysomnographic normalisation against watchful waiting, 79 against 46 per cent. That is a genuine cure of a common childhood condition by one operation. Maxillomandibular advancement surgery in selected adults with skeletal retrusion gives surgical success in roughly 85 to 90 per cent and cure, an index below 5, in roughly 40 to 45 per cent in meta-analysis — the most effective surgical option in adults. Correcting hypothyroidism or acromegaly resolves the apnoea they caused. Hypoglossal nerve stimulation reduced the index by 68 per cent at twelve months in the STAR trial in selected patients and is not a cure.

Prevention.

Weight management — STRONG, and the only intervention with a demonstrated effect on incidence. A 10 per cent weight gain predicts roughly a 32 per cent increase in the index and sixfold higher odds of developing moderate to severe disease.

Avoiding alcohol and sedatives before sleep — MODERATE. *Smoking cessation — WEAK*. *Treating nasal obstruction and allergic rhinitis — WEAK* for severity.

Early treatment of childhood tonsillar hypertrophy — MODERATE, and it may prevent persistence into adulthood, though that is not established by trial. *Orthodontic maxillary expansion in children — MODERATE* in selected cases.

Screening asymptomatic adults — NOT RECOMMENDED, and CONTESTED. The United States Preventive Services Task Force concluded in 2017 and again in 2022 that the evidence is insufficient to assess the balance of benefits and harms of screening asymptomatic adults. Given the null cardiovascular trials, population screening has no demonstrated benefit.

Nothing prevents the craniofacial contribution, which is the dominant factor in much of Asia.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Continuous positive airway pressure	Sleepiness, quality of life and blood pressure improve; cardiovascular events do not. The SAVE trial, 2,717 randomised, 1,346 to treatment and 1,341 to usual care, mean 3.7 years follow-up: primary composite of serious cardiovascular events 17 against 15.4 per cent, hazard ratio 1.1 (95 per cent CI 0.91–1.32, p=0.34) — **no benefit**. Mean use 3.3 hours a night, with only about 42 per cent using it four hours or more. It did improve daytime sleepiness, health-related quality of life, mood and work attendance. RICCADSA and ISAACC were also null for cardiovascular events. Blood pressure falls by roughly 2 to 3 mmHg systolic on meta-analysis, more in resistant hypertension	no	n/a, a device	Machine hundreds to thousands of euro lasting five to ten years; masks and filters hundreds of euro a year. Another chapter of this book gives the device as hundreds of US dollars one-off and consumables as hundreds of US dollars a year, with no service life stated; both stand
Mandibular advancement, an oral appliance	The index reduced by roughly 50 per cent, less than continuous positive airway pressure, with better adherence, so health outcomes are often equivalent in randomised comparisons	no	n/a	hundreds to thousands of euro custom; tens to hundreds of euro thermoplastic
Weight loss by lifestyle intervention	Sleep AHEAD: the index 5.2 events an hour lower than control, with roughly threefold higher remission	n/a	n/a	Nothing
Bariatric surgery	Remission in roughly 40 to 60 per cent	n/a	n/a	thousands to tens of thousands of euro
Tirzepatide	SURMOUNT-OSA, 469 patients, 2024: the index reduced by 25 to 29 events an hour against 5 to 6 with placebo — the first drug with a large effect on severity	no	no	tens of thousands of euro a year
Adenotonsillectomy in children	CHAT: polysomnographic normalisation 79 against 46 per cent with watchful waiting; behaviour and quality of life improved	n/a	n/a	thousands of euro

Intervention	Effect size	EML	Off-patent	Cost
Maxillomandibular advancement in adults	Surgical success 85 to 90 per cent; cure, index below 5, in 40 to 45 per cent	n/a	n/a	tens of thousands of euro
Positional therapy	Effective in the roughly 25 to 30 per cent with supine-predominant disease	n/a	n/a	tens to hundreds of euro or free with improvised methods
Hypoglossal nerve stimulation	STAR: the index reduced 68 per cent at twelve months in selected patients	no	no	tens of thousands of euro
Non-invasive ventilation in obesity hypoventilation	**Reduces mortality** in obesity hypoventilation syndrome, unlike continuous positive airway pressure in sleep apnoea; the Pickwick trial	n/a	n/a	thousands of euro
Modafinil or solriamfetol, residual sleepiness on treatment	Wakefulness improved; symptomatic	no	Modafinil yes	Modafinil hundreds of euro; solriamfetol thousands to tens of thousands of euro
Supplemental oxygen alone	Oxygenation improves; sleepiness and the index do not, and it may prolong apnoeas. **Not a treatment for this condition**	yes, oxygen	yes	—

Simple means. Weight loss is the only intervention that modifies the disease itself: the index 5.2 events an hour lower than control in Sleep AHEAD with roughly threefold higher remission, and a 10 per cent weight gain raises the index roughly 32 per cent. It costs nothing and is hard.

Positional therapy can be improvised at no cost. In the 25 to 30 per cent with supine-predominant disease, keeping off the back abolishes much of the problem. A tennis ball sewn into the back of a shirt, a backpack or a pillow wedge — tested against commercial devices with comparable short-term effect, and adherence to improvised methods is poor over months.

Avoiding alcohol and sedatives in the evening is free and the effect on upper airway tone is immediate. Raising the head of the bed by 30 to 45 degrees reduces the index measurably in small studies: bricks under the bed legs. Nasal saline and treating nasal obstruction is cheap and improves treatment tolerance and reduces mouth breathing.

Myofunctional therapy — tongue and soft-palate exercises, and didgeridoo or wind-instrument playing — reduces the index by roughly 50 per cent and reduces snoring in small randomised trials. No equipment, ten to twenty minutes daily. The evidence is from small trials and effect sizes vary widely.

Thermoplastic boil-and-bite mandibular advancement devices cost tens to hundreds of euro against hundreds to thousands of euro for custom ones; they are less effective and less well tolerated and are far cheaper.

The honest comparison between a thermoplastic device or a tennis ball and a hundreds to thousands of euro machine: continuous positive airway pressure controls the apnoea best and is used only 3.3 hours a night on average, while the cheap measures have smaller effects and comparable real-world adherence problems. Because the randomised cardiovascular trials were null, the realistic goal of all of them is symptom relief, and for symptom relief the cheap options are a reasonable first step where the machine is unavailable.

Recognising the condition takes eight questions on paper and no equipment. Witnessed apnoeas, loud snoring, daytime sleepiness and the STOP-BANG questionnaire identify high-risk individuals with a sensitivity of around 84 to 93 per cent for moderate to severe disease, with low specificity. Confirmation needs at minimum overnight oximetry, a tens to hundreds of euro device, and preferably polysomnography or home sleep testing.

The hard limit. Diagnosis requires overnight measurement — oximetry at minimum, ideally a home sleep apnoea test. Continuous positive airway pressure requires a machine and mains power. Where neither exists, weight loss, position, alcohol avoidance and oropharyngeal exercises are the whole of what can be offered, and they address symptoms rather than any demonstrated cardiovascular risk.

Gaps. ICD-11 places sleep-disordered breathing in chapter 07, and no condition in chapter 07 is a GBD level-3 cause, so no GBD burden figures exist. A reference work must treat that chapter as a structural addition with no corresponding burden series. For a condition affecting 936 million people aged 30 to 69 there is no global mortality or DALY figure at all, and this entry is part of the seventeen-condition gap in this chapter's introduction. The 936 million and 425 million figures are from a single literature-based analysis funded by ResMed rather than from a population measurement programme, and both are for adults aged 30 to 69 only. Prevalence doubles or halves with the scoring criteria used, 2012 against 1999, so the headline figure is definition-dependent to an unusual degree.

Continuous positive airway pressure does not reduce cardiovascular events: SAVE gave a hazard ratio of 1.1 at p=0.34, and RICCADSA and ISAACC were also null. That contradicts a very large observational literature and a great deal of clinical and commercial messaging. The standard defence is that adherence was too low, at 3.3 hours with 42 per cent using four hours or more, and that sleepy patients were excluded — both are true and neither has been tested in a trial that resolves the question. The null results and the adherence figures are printed together.

The apnoea-hypopnoea index correlates poorly with symptoms and outcomes, and no replacement metric is standardised: the disease is defined by a number that may not be the right number. Screening asymptomatic adults has no demonstrated benefit, and screening is widely promoted. Between 80 and 90 per cent is undiagnosed, so all clinical-cohort data are heavily selected. Oral appliances are less effective than the machine on the index and often equivalent on outcomes because of adherence, and the field has no agreed way to handle that trade-off. Tirzepatide's large effect on the index has no outcome data and costs tens of thousands of euro a year. The craniofacial contribution means body-mass-index-based risk models developed in western populations underestimate risk in east Asian populations. Device and consumable prices differ between chapters of this book, in currency and in range, and both stand.

> **Depth.** Starts in: the throat. Size: 1 cm†; depth +11.19. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Chronic rhinosinusitis (ICD-11 CA0A)

What it is. The lining of the nose and the sinuses stays inflamed for months. The nose is blocked, discharge runs, the face feels full and smell fades. Some people grow polyps in the sinuses.

Measured. No global prevalence, death or DALY figure for chronic rhinosinusitis was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all, and for a condition affecting roughly 10 per cent of adults with quality-of-life impairment comparable to angina and chronic obstructive pulmonary disease, it is one of the largest unmeasured burdens in either chapter.

Prevalence by symptom-based criteria is roughly 10.9 per cent of adults in Europe, from the GA²LEN multicentre survey across twelve countries, 11.9 per cent in the United States, and roughly 8 per cent in China. Prevalence falls to roughly 3 to 6 per cent when endoscopic or computed tomographic confirmation is required rather than symptoms alone — a two- to threefold difference driven entirely by the definition. Chronic rhinosinusitis with nasal polyps affects roughly 2 to 4 per cent of adults, and the form without polyps is the larger group. Mortality is essentially zero and the burden is entirely morbidity. Quality-of-life impairment is comparable to angina, chronic obstructive pulmonary disease and chronic back pain on generic instruments in several studies, which is one of the better-documented findings in the field. Direct and indirect costs are high: roughly US$10 to 13 billion a year in the United States, much of it productivity loss, and roughly €1,500 to €2,000 a patient-year in European estimates. Prevalence peaks in middle age, roughly 40 to 60. Reported prevalence is broadly similar across high-income countries, and data from low-income countries are very thin.

Where it starts. Allergic rhinitis coexists in roughly 40 to 80 per cent of cases, though causality is contested. Asthma coexists in roughly 20 to 60 per cent, and the association is strongest with polyps and

with eosinophilic disease — the united airway pattern. Aspirin-exacerbated respiratory disease, combining asthma, polyps and NSAID sensitivity, affects roughly 9 to 16 per cent of patients with polyps, and that subgroup has the most severe and recurrent disease. Smoking and second-hand smoke carry an odds ratio of roughly 1.5 to 2. Anatomical factors — septal deviation, concha bullosa — carry a weaker association than is widely assumed, and surgical correction of anatomy alone often does not resolve the disease. Impaired mucociliary clearance from primary ciliary dyskinesia or cystic fibrosis, where chronic rhinosinusitis affects the great majority, contributes. Immunodeficiency — common variable immunodeficiency, specific antibody deficiency — accounts for roughly 10 to 20 per cent of refractory cases in referral series. Biofilm formation and Staphylococcus aureus superantigen are proposed mechanisms in polyposis and neither is established as causal. Allergic fungal rhinosinusitis occurs in a minority, and invasive fungal sinusitis in immunocompromised patients is a separate, rapidly fatal disease. Occupational irritant exposure, air pollution and gastro-oesophageal reflux contribute, the last contested. Granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis present with destructive sinus disease — rare, and the one group where missing the diagnosis is dangerous.

The cause is not established. The condition is defined by symptoms and duration rather than by a mechanism, and it is almost certainly several diseases. The division into type-2 eosinophilic, polyp-associated, biologic-responsive inflammation and non-type-2 inflammation is the most useful current framework and is not a complete account. Whether bacteria cause the chronic phase or colonise an already inflamed mucosa is unresolved, which is why the antibiotic evidence is so weak. Why polyps recur after apparently complete surgery in roughly 40 per cent of cases is not explained.

Cure status. Most cases: CONTROLLABLE. Odontogenic sinusitis, roughly 10 to 30 per cent of unilateral maxillary sinusitis: CURABLE by treating the dental source. A fungal ball, an obstructing tumour or a foreign body: CURABLE by removal. Acute rhinosinusitis: SELF-LIMITING.

Neither medical nor surgical treatment removes the disease in the common forms. Intranasal corticosteroids control symptoms while used, and symptoms return on stopping. Endoscopic sinus surgery improves symptoms substantially and is not curative: polyps recur in roughly 40 per cent within five years, and revision surgery rates are roughly 15 to 20 per cent. Biologics shrink polyps and improve symptoms dramatically and the effect reverses on withdrawal, which is the clearest demonstration that this is control rather than cure. Immunoglobulin replacement in antibody deficiency changes the course.

Acute rhinosinusitis is SELF-LIMITING, and that matters because acute sinusitis is one of the largest single reasons for inappropriate antibiotic prescribing worldwide. Roughly 70 to 80 per cent resolve within two weeks without antibiotics. Cochrane finds antibiotics give a small benefit, with a number needed to treat of roughly 11 to 15 for cure at seven to fourteen days, against substantial adverse-effect rates.

Prevention.

Avoiding unnecessary antibiotics in acute rhinosinusitis — STRONG as a stewardship measure, since 70 to 80 per cent resolve spontaneously and the number needed to treat is 11 to 15.

Avoiding NSAIDs in aspirin-exacerbated respiratory disease — STRONG for preventing acute deterioration in that subgroup. *Treating dental disease — STRONG* for odontogenic sinusitis specifically.

Smoking cessation and avoiding second-hand smoke — MODERATE, odds ratio 1.5 to 2. *Occupational irritant control — MODERATE*.

Aspirin desensitisation in aspirin-exacerbated respiratory disease — MODERATE: polyp recurrence and revision surgery are reduced in that subgroup.

Early diagnosis of immunodeficiency and vasculitis — MODERATE in the refractory minority.

Treating allergic rhinitis — WEAK: the association is strong and the preventive effect of treating it is not established. *Nasal saline irrigation — WEAK* for preventing recurrence.

Nothing prevents the common forms.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Intranasal corticosteroid, beclometasone, budesonide, fluticasone, mometasone	First-line. Cochrane: symptoms improved and polyp size reduced against placebo, at moderate to high certainty	yes, beclometasone	yes	tens of euro
Nasal saline irrigation, high volume	Cochrane: symptoms improved as an adjunct, at low to moderate certainty; large-volume low-pressure irrigation is better than a spray	n/a	n/a	a few to tens of euro or near zero home-made
Short course of oral corticosteroid	Substantial short-term polyp and symptom reduction; the effect wanes within three to six months and repeated courses carry cumulative harm	yes	yes	a few euro a course
Long-term macrolide, azithromycin or clarithromycin	Benefit in non-type-2 disease with normal IgE; the trials are inconsistent and the evidence is weak	yes	yes	tens to hundreds of euro
Antibiotics for acute exacerbations	Modest; acute rhinosinusitis number needed to treat 11 to 15, with 70 to 80 per cent resolving spontaneously	yes, amoxicillin, co-amoxiclav, doxycycline; amoxicillin is listed first-choice for sinusitis	yes	a few to tens of euro a course
Endoscopic sinus surgery	Substantial symptom improvement; polyp recurrence about 40 per cent at five years, revision 15 to 20 per cent	n/a	n/a	thousands of euro
Dupilumab, anti-interleukin-4 receptor alpha	SINUS-24 and SINUS-52, 724 patients: nasal polyp score −1.80 against +0.17, nasal congestion −1.25 against −0.38, smell markedly improved, and the need for surgery reduced by roughly 75 per cent	no	no	tens of thousands of euro
Omalizumab, anti-IgE	POLYP 1 and 2: polyp score and symptoms improved	**NOT on the 24th Model List in any form**	Biosimilars emerging	tens of thousands of euro
Mepolizumab, anti-interleukin-5	SYNAPSE: polyp score and need for surgery reduced	no	no	tens of thousands of euro
Aspirin desensitisation, aspirin-exacerbated respiratory disease	Polyp recurrence and revision surgery reduced in that subgroup	yes, aspirin	yes	a few to tens of euro
Antifungals, topical or systemic	**No benefit** in chronic rhinosinusitis, per Cochrane — a negative result against a once-popular hypothesis	Varies	Varies	—
Antihistamines, decongestants, montelukast	Little evidence in chronic rhinosinusitis itself	partly	yes	tens to hundreds of euro

The price asymmetry is extreme here too. An intranasal corticosteroid at tens of euro a patient-year is first-line and effective for most; the biologics cost tens of thousands of euro a patient-year for the severe polyp minority, in a condition with essentially zero mortality.

Simple means. Nasal saline irrigation costs essentially nothing beyond the vessel. Home-made isotonic or hypertonic saline from table or non-iodised salt, baking soda and boiled or distilled water, delivered by a neti pot, a squeeze bottle or a syringe. Cochrane supports symptom improvement as an adjunct, and large-volume low-pressure irrigation is better than a spray. One safety requirement must accompany the advice: the water must be boiled, distilled or appropriately filtered, because fatal Naegleria fowleri and Acanthamoeba infections have followed irrigation with untreated tap water.

Steam inhalation does not work, and that is worth printing because it is the commoner home remedy. Cochrane and the large UK primary-care trial found steam inhalation gave no benefit for chronic or recurrent sinus symptoms, while nasal irrigation did help.

An intranasal corticosteroid at tens of euro a patient-year is the single most effective medical treatment, with beclometasone on the Essential Medicines List and off-patent. It needs a pharmaceutical chain, a cheap one. Smoking cessation and smoke-free homes are free. Avoiding NSAIDs in aspirin-exacerbated disease is free and prevents severe reactions. Dental care cures odontogenic sinusitis, which is 10 to 30 per cent of unilateral maxillary disease. Not taking antibiotics for acute sinusitis is a free decision that avoids harm and resistance: 70 to 80 per cent resolve spontaneously and the number needed to treat is 11 to 15. Sleeping with the head elevated, humidifying dry indoor air and avoiding known irritants are low-cost symptomatic measures with little trial evidence.

The hard limit. Distinguishing chronic rhinosinusitis from a tumour, from invasive fungal disease in the immunocompromised and from vasculitis requires endoscopy and computed tomography. Those three are rare and dangerous, and missing them is the main risk of managing the condition on symptoms alone. The common disease itself can be treated substantially with saline and a cheap corticosteroid spray.

Gaps. No GBD global burden figure for chronic rhinosinusitis was retrieved for a condition affecting roughly 10 per cent of adults with quality-of-life impairment comparable to angina and chronic obstructive pulmonary disease, and this entry is part of the seventeen-condition gap in this chapter’s introduction. Prevalence varies two- to threefold with the definition — symptoms alone at 10.9 to 11.9 per cent against endoscopic or computed tomographic confirmation at 3 to 6 per cent — and there is no agreed diagnostic standard for epidemiology. The cause is unknown and the condition is almost certainly several diseases pooled by symptom definition. Why polyps recur in about 40 per cent after complete surgery is unexplained. Antifungals: Cochrane null, against a once-dominant hypothesis. Steam inhalation: null, against near-universal popular use. Long-term macrolides: inconsistent trials, and the phenotype that benefits is not reliably identifiable in practice. Biologic against surgery has barely been compared head-to-head, and the cost difference is roughly five- to fifteenfold. Almost all epidemiology and all trial evidence comes from high-income countries, and data from low-income settings are very thin. Repeated oral corticosteroid courses are widely used with cumulative harm that is acknowledged and not well quantified in this population. Omalizumab is not on the 24th Model List in any form.

> **Depth.** Starts in: the sinus lining. Size: 1 mm†; depth +9.10. First complaint: about 40 years († onset about age 40; [B] months); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Allergic rhinitis (ICD-11 CA08)

What it is. Pollen, dust mite or animal protein triggers an allergic reaction in the lining of the nose. It runs, blocks, itches and sets off sneezing, often with itchy eyes. It is not dangerous and it is very common, and it wrecks sleep and concentration. Mould is also a trigger. Symptoms come seasonally or year-round.

Measured. No global prevalence, death or DALY figure for allergic rhinitis was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Prevalence is roughly 10 to 30 per cent of adults and up to 40 per cent of children in high-income countries. The ISAAC and Global Asthma Network studies found rhinoconjunctivitis symptoms in roughly 8.5 per cent of six- and seven-year-olds and 14.6 per cent of thirteen- and fourteen-year-olds across 98 countries, with a twentyfold range between centres. The estimated global total is roughly 400 million people, and that is a modelled figure rather than a measurement. Mortality is essentially zero. The condition coexists with asthma in roughly 15 to 38 per cent of patients, and roughly 80 per cent of asthmatics have rhinitis — the one airway relation.

A second source line gives a global range of 10 to 40 per cent, depending on definition and region, and says about 20 per cent is commonly quoted for high-income countries†. The International Study of Asthma and Allergies in Childhood covered about 1.2 million children in 98 countries in its third phase†. It found current rhinoconjunctivitis symptoms in roughly 8 to 9 per cent of children aged 6 to 7 and roughly 14 to 15 per cent of adolescents aged 13 to 14†. Between-centre variation was more than ten-fold, from under 1 per cent to over 45 per cent†. The two source lines disagree on that range: more than ten-fold here, twentyfold in the paragraph above. Both are printed. The ten-fold figure carries a dagger; the twentyfold figure names its source, which was not opened again.

There is one well-measured functional effect. A UK study found students with symptoms on the day of an examination were roughly 40 per cent more likely to drop a grade than predicted, and sedating antihistamine use increased that further. Onset is usually in childhood or adolescence, prevalence peaks in the twenties and thirties, and it declines in later life. Prevalence rose substantially in high-income countries through the late twentieth century and has plateaued in many, and it is still rising in many low- and middle-income countries as they urbanise.

One source line gives onset in childhood or early adult life. The paragraph above gives childhood or adolescence. The two lines agree on the peak and on the decline in later life.

One source line states that GBD counts allergic rhinitis among conditions with high prevalence and low disability weight, so that its years lived with disability are substantial while its mortality is zero. The paragraph above records that no GBD 2023 figure for allergic rhinitis was retrieved. The two source lines disagree. One asserts a substantial GBD total without a figure. The other found no figure to read.

The third phase of the childhood survey, set against the first, showed increases in most low- and middle-income centres and a plateau or decline in several high-prevalence high-income centres. The trend above names its source, which was not opened again; here it carries a dagger.

One source line reports the same examination finding without a figure: United Kingdom adolescents with symptomatic seasonal rhinitis sitting summer examinations did measurably worse. It carries a dagger, where the finding above names its source, which was not opened again.

Where it starts. IgE sensitisation to inhaled allergens: house dust mite, grass, tree and weed pollens, cat, dog, horse, cockroach, Alternaria and other moulds. Atopic predisposition, with a heritability of roughly 33 to 91 per cent across twin studies, strong familial clustering and shared genome-wide loci with asthma and eczema. The atopic march — eczema and food allergy in infancy, then asthma and allergic rhinitis — is a consistent temporal sequence whose mechanism is incompletely understood. Urban living and the loss of early microbial exposure: growing up on a traditional farm roughly halves allergic rhinitis and sensitisation risk, from PARSIFAL, GABRIELA and the Amish against Hutterite comparison, which is the most reproducible protective finding in the field. Air pollution, particularly traffic-related and diesel exhaust, is associated with sensitisation and symptom severity, and diesel particles act as an adjuvant to pollen allergen in experimental studies. Climate change has changed the exposure itself: pollen seasons in the northern hemisphere have lengthened by roughly 20 days and pollen concentrations have risen by roughly 20 per cent since 1990 in North American monitoring data. Second-hand tobacco smoke in childhood contributes, and caesarean delivery and early antibiotic use are both CONTESTED and confounded. Occupational rhinitis from flour, latex, laboratory animals, enzymes and wood dust usually precedes occupational asthma and is a warning sign.

On re-exposure, mast cells degranulate and release histamine, leukotrienes and prostaglandins, and a late-phase infiltrate of eosinophils follows. This sequence is established.

A second source line puts twin-study heritability at roughly 0.33 to 0.75, commonly around 0.6†. The paragraph above gives roughly 33 to 91 per cent. The two source lines disagree on the upper bound. The first figure carries a dagger; the second names its source, which was not opened again. Genome-wide association studies have identified over 40 loci, each with a small effect. Parental atopy roughly doubles to triples a child's risk, and two atopic parents raise it more.

The same line states the farm effect as roughly 50 per cent lower risk of allergic rhinitis and atopic sensitisation in children who grow up on a traditional farm with livestock and drink unprocessed farm milk, in PARSIFAL, GABRIELA and related European studies. The association is strong, dose-related with the diversity of microbial exposure, replicated and observational. The paragraph above gives the same finding with a named source that was not opened again; here it carries a dagger.

The same line lists as established risk factors higher socioeconomic status in low- and middle-income settings, small family size, and indoor dampness and mould. It also lists caesarean delivery (modest) and early-life antibiotic exposure (modest and confounded) as established, and traffic-related air pollution as modest and consistent. The paragraph above calls caesarean delivery and early antibiotic use CONTESTED and confounded. The two source lines disagree on whether these two are established.

The pollen figures come from Anderegg and colleagues, *PNAS*, 2021, for North America between 1990 and 2018. Season length and pollen intensity are increasing with rising temperatures and carbon dioxide.

Pet ownership in infancy, long assumed to raise risk, shows neutral-to-protective associations in cohort studies.

Why sensitisation produces symptoms in some people and silent sensitisation in others is not explained — roughly a third of sensitised individuals have no symptoms. The hygiene and microbial-diversity hypothesis explains the epidemiology well and has produced no preventive intervention that works. Why prevalence rose and then plateaued is unexplained. The mechanism of the atopic march is not established, and whether treating one stage prevents the next is the central unresolved question.

Attempts to reduce the farm effect to a single organism or endotoxin dose have not succeeded. A large share of people with specific IgE to an allergen have no symptoms on exposure. That makes allergy testing a poor population-screening tool.

Cure status. CONTROLLABLE, by both routes. Drugs and allergen immunotherapy control the disease. Avoidance where a single removable allergen is responsible also controls it.

Pharmacotherapy controls symptoms while taken and they return on stopping. Allergen immunotherapy is the only treatment in either chapter with demonstrated persistence of benefit after withdrawal. The Preventive Allergy Treatment study, with 205 children on three years of grass or birch subcutaneous immunotherapy, found asthma developed in significantly fewer treated children and the effect persisted seven and ten years after treatment ended, with an odds ratio of roughly 2.5 for asthma in the control group. The GAP trial, with 812 children on a three-year grass sublingual tablet and two years of follow-up, reduced asthma symptoms and medication use at two years post-treatment, and its primary endpoint of asthma onset was not met. GT-08, with a grass sublingual tablet, showed symptom benefit sustained for two years after three years of treatment. Whether to call it cure is contested; it is at minimum genuine disease modification and in many patients effectively a lasting remission.

A second source line gives the improvement in symptom and medication scores against placebo on meta-analysis as roughly 20 to 40 per cent†, a modest average that conceals large responders and non-responders. The treatment table below gives roughly 30 to 40 per cent. The two source lines disagree on the lower bound. The first figure carries a dagger; the second names its source, which was not opened again. The same line reports persistent benefit and reduced asthma development at 10 years in the Preventive Allergy Treatment study. It reports a sustained effect in the two years after a three-year course of a five-grass sublingual tablet in the GAP trial. It gives the asthma result as roughly 2.5-fold lower odds in treated children at long-term follow-up†, and calls this the strongest claim for disease modification in allergy. The paragraph above gives the same odds ratio, roughly 2.5, and names a source that was not opened again; here

it carries a dagger. Treatment takes three to five years, and the subcutaneous route carries a small risk of a systemic reaction.

Avoidance where a single removable allergen is responsible — rehoming a cat, changing an occupation — is CONTROLLABLE and not a cure. The sensitisation persists and the symptoms return on re-exposure, so staying away is a continuing measure. This book draws the same line elsewhere: coeliac disease on a strict lifelong gluten-free diet is CONTROLLABLE, because reintroducing gluten reinstates the disease. Natural remission occurs in a minority with age.

The two source lines weigh avoidance differently, and the weaker reading is the better supported. One holds it curative with a single removable allergen. The other finds the evidence for allergen avoidance individually weak, and grades pet removal once sensitised WEAK, saying the evidence does not support routine pet removal. There is no avoidance row in the treatment table and no outcome figure behind the curative claim.

Prevention.

No primary prevention of allergic rhinitis has been demonstrated. Allergen-avoidance regimens in infancy, maternal diet modification, hydrolysed formula and probiotics have not prevented it in randomised trials.

One distinction is routinely blurred and must be printed: early allergen introduction prevents food allergy, with LEAP giving an 81 per cent relative reduction in peanut allergy, and has not been shown to prevent allergic rhinitis.

Allergen immunotherapy to prevent asthma in children with allergic rhinitis — MODERATE. The Preventive Allergy Treatment study showed persisting asthma reduction at seven and ten years; GAP missed its primary endpoint and showed reduced asthma symptoms and medication. This is secondary prevention of the next stage of the atopic march, and it is the best evidence that the march can be interrupted.

Occupational allergen control — STRONG for occupational rhinitis. *Avoiding second-hand tobacco smoke — MODERATE*. *Air pollution reduction — MODERATE*.

House dust mite avoidance — CONTESTED to negative. Cochrane found no clear benefit of mite-avoidance measures for allergic rhinitis outcomes, as for asthma. The advice is near-universal and the evidence does not support it, and that is printed.

The farm effect is reproducible and has not been translatable into an intervention; trials of farm-dust-derived products are early.

A second source line adds the following items.

Allergen immunotherapy to prevent new sensitisations and asthma onset in children with established rhinitis — MODERATE, from the Preventive Allergy Treatment study and GAP. Open-label elements and heterogeneity are the weakness. This line reads GAP as supporting the prevention of asthma onset. The paragraph above records that GAP missed its primary endpoint of asthma onset. The two source lines disagree on what GAP shows, and both are printed. The prevention of new sensitisations appears in this line only.

Breastfeeding — CONTESTED for allergic rhinitis specifically. Meta-analyses find a small protective association for asthma and eczema in early childhood and little consistent effect on rhinitis.

Avoiding tobacco smoke in pregnancy and infancy — MODERATE.

House dust mite avoidance. This line finds the evidence weak and the sources in disagreement. Cochrane reviews of mite-impermeable bedding for rhinitis and asthma have generally found no clinically important benefit as single measures, while multi-component environmental interventions show some effect. The grade above is CONTESTED to negative. The two lines differ on the grade and agree on the Cochrane finding.

Early-life exposure to farm environments and unprocessed milk — MODERATE as an association, and not actionable as an intervention. Raw milk carries infection risk, and no trial has tested it.

Pet removal once sensitised — WEAK. The evidence does not support routine pet removal. This sits against the avoidance stratum in the cure status above.

There is no established primary prevention of atopy itself. The rise in allergic disease over the twentieth century has no demonstrated preventive counter-measure at population level.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Intranasal corticosteroid, beclometasone, budesonide, fluticasone, mometasone	The most effective single drug class. Superior to oral antihistamines for nasal congestion and overall symptoms in head-to-head trials and meta-analysis	yes, beclometasone	yes	tens of euro
Second-generation oral antihistamine, cetirizine, loratadine, fexofenadine	Effective for sneezing, itch and rhinorrhoea; less effective than an intranasal steroid for congestion; non-sedating	yes, loratadine and cetirizine	yes	a few to tens of euro
First-generation antihistamine, chlorphenamine, diphenhydramine	Effective and sedating, and associated with impaired examination performance and driving; should not be first-line	yes, chlorphenamine	yes	a few to tens of euro
Intranasal antihistamine, azelastine	Faster onset than oral; useful as add-on	no	yes	tens to hundreds of euro
Intranasal corticosteroid with azelastine	Superior to either alone	no	partly	hundreds of euro
Nasal saline irrigation	Symptoms improved as an adjunct, at low to moderate certainty	n/a	n/a	a few to tens of euro or near zero home-made
Leukotriene receptor antagonist, montelukast	Comparable to antihistamines and less effective than an intranasal steroid; neuropsychiatric boxed warning in the United States from 2020	no	yes	€20–150
Subcutaneous allergen immunotherapy	Symptom and medication scores reduced roughly 30 to 40 per cent on meta-analysis; benefit persists years after stopping, per the Preventive Allergy Treatment study and GT-08; small risk of a systemic reaction	no	partly	hundreds to thousands of euro across three to five years of treatment
Sublingual immunotherapy, tablets or drops	Comparable efficacy to subcutaneous for grass and mite, and much safer, with no anaphylaxis deaths reported with tablets; GAP and GT-08 show persisting benefit	no	partly	hundreds to thousands of euro
Intranasal ipratropium	For rhinorrhoea specifically	yes	yes	tens to hundreds of euro
Oral or intranasal decongestant	Short-term only; rhinitis medicamentosa with use beyond five to seven days	partly	yes	a few to tens of euro
Oral corticosteroid	A short rescue course only; depot injectable corticosteroid is not recommended	yes	yes	a few euro a course

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Omalizumab	Effective, and not licensed or cost-justified for allergic rhinitis alone	**NOT on the 24th Model List in any form**	Biosimilars emerging	tens of thousands of euro

A second source line gives drug prices in US dollars, on the basis of generic or lowest available acquisition cost, 2024. The table above gives prices in euro, with market and year not stated. Both are printed. The two source lines do not reconcile them, and they disagree on listing status where noted below.

Intranasal corticosteroids work on all nasal symptoms including blockage. They take several days to work and must be used continuously. Off-patent, at US$5 to US$40 a patient-year at generic or lowest available acquisition cost, 2024†. The table gives tens of euro. The table lists beclometasone as on the Model List. This line says the nasal-formulation listing of beclometasone and budesonide needs checking against the 24th List†.

Second-generation oral antihistamines include desloratadine and bilastine as well as loratadine, cetirizine and fexofenadine. Off-patent, at US$2 to US$20 a patient-year at generic or lowest available acquisition cost, 2024†. The table gives a few to tens of euro. This line says listing status needs checking against the 24th List†. The table lists loratadine and cetirizine as on it.

Intranasal azelastine has onset within about 15 minutes, which oral agents do not match. Off-patent, at US$30 to US$100 a patient-year at generic or lowest available acquisition cost, 2024†. The table gives tens to hundreds of euro. This line says EML status needs checking against the 24th List†. The table says no.

Allergen immunotherapy is given subcutaneously, with the largest evidence base, or as sublingual tablets for grass, ragweed, house dust mite and tree, over three to five years. It costs US$500 to US$3,000 a patient-year at lowest available acquisition cost, 2024†. The table gives hundreds to thousands of euro across the whole three to five years. One figure is a year and the other a course. These are biological extracts, and standardised tablets are patented. This line says EML status needs checking against the 24th List†. The table says no.

Montelukast, off-patent, costs US$10 to US$50 a patient-year at generic or lowest available acquisition cost, 2024†. The table gives €20–150. This line says EML status needs checking against the 24th List†. The table says no.

First-generation antihistamines are off-patent and cost cents a day. The table gives a few to tens of euro. This line says chlorphenamine's listing status needs checking against the 24th List†. The table lists chlorphenamine as on it.

Generic loratadine and generic nasal beclometasone both cost under US$40 a year at generic or lowest available acquisition cost†.

Simple means. This is a condition affecting roughly 400 million people that can be controlled for tens of euro a year per person with Essential Medicines List drugs. Loratadine and cetirizine cost a few to tens of euro a year, are listed and off-patent, and beclometasone nasal spray costs tens of euro a year, listed and off-patent.

Nasal saline irrigation is essentially free: home-made saline from salt, baking soda and boiled or distilled water, in a neti pot or squeeze bottle, improves symptoms and reduces medication need as an adjunct. The same safety warning applies as in chronic rhinosinusitis — the water must be boiled, distilled or filtered, because fatal amoebic infections have followed irrigation with untreated tap water.

One source line finds from Cochrane and later reviews that saline irrigation gives modest but consistent symptom improvement, reduced medication use and no meaningful harm, with an effect smaller than that of intranasal steroids. That line does not mention the water warning above.

Allergen avoidance works where the allergen is single and removable: rehoming a cat, removing a bird, changing bedding, keeping windows shut during peak pollen, showering and changing clothes after outdoor exposure, drying washing indoors in pollen season. House dust mite measures specifically are the exception: Cochrane found no clear benefit, despite being the most commonly advised.

The same line adds staying indoors during peak pollen hours, washing hair after outdoor exposure, a pet-free bedroom, lower indoor humidity and less visible mould, and removing carpets in mite-sensitised households. It calls the evidence for these individually weak, at zero cost. The paragraph above says avoidance works where the allergen is single and removable. The two source lines disagree on how strong the evidence for avoidance is.

Pollen timing costs nothing: counts peak in early morning and evening for grasses, and planning outdoor activity accordingly is free. Wrap-around sunglasses and a mask during high pollen exposure reduce conjunctival and nasal deposition, with small studies supporting benefit. Petroleum jelly or a nasal barrier balm around the nostrils traps pollen, cheaply and with limited evidence. Smoke-free homes are free.

Cold compresses ease eye symptoms. Starting an intranasal steroid before the pollen season, and not after symptoms begin, improves control measurably and costs nothing extra.

Avoiding sedating first-generation antihistamines is a free choice with a measured benefit, since sedating antihistamine use was associated with further impairment of examination performance in the UK study. Chlorphenamine is the cheapest and most widely available antihistamine in low-income settings, which makes this a real trade-off rather than a simple recommendation.

The hard limit. Identifying which allergen is responsible requires skin prick testing or specific IgE measurement, and allergen immunotherapy — the only disease-modifying treatment — requires a standardised allergen extract, a supply chain and supervised administration. Symptom control, however, needs only saline and two cheap generic drugs.

One source line finds that the main access problem is not price but the absence of basic diagnosis, and of over-the-counter availability in some health systems.

Gaps. No GBD global burden figure for allergic rhinitis was retrieved, for a condition affecting roughly 400 million people with measured effects on sleep, school performance and productivity, and this entry is part of the seventeen-condition gap in this chapter’s introduction; the 400 million figure is a modelled estimate. ISAAC found a twentyfold prevalence range between centres, and how much is genuine and how much is questionnaire interpretation across languages and cultures is unresolved. No primary prevention has been demonstrated, and the farm effect is robust and has produced no usable intervention. Early allergen introduction prevents food allergy and not allergic rhinitis, and the two are routinely conflated. House dust mite avoidance: Cochrane null against near-universal advice. Whether immunotherapy prevents asthma is not settled: the Preventive Allergy Treatment study was positive and persisting at ten years, and GAP missed its primary endpoint; both are printed. Immunotherapy’s optimal duration, and how long the benefit lasts, are not established — three to five years is convention rather than trial-derived. Montelukast’s neuropsychiatric risk magnitude remains debated. Pollen seasons have lengthened by about 20 days and concentrations risen by about 20 per cent since 1990 in North American data; the clinical consequence has not been quantified prospectively, and comparable monitoring does not exist for most of the world. Almost all trial evidence is from high-income countries with temperate pollen seasons, and tropical allergen profiles — mite, cockroach, fungal — are under-represented. Omalizumab is not on the 24th Model List in any form.

Prevalence figures span 10 to 40 per cent because definitions vary. Self-reported symptoms, physician diagnosis, and symptoms with confirmed sensitisation give very different numbers, and they are not interchangeable. Breastfeeding’s effect on allergic rhinitis specifically is contested. House dust mite avoidance: Cochrane reviews find no benefit for single measures, while allergy guidelines continue to recommend multi-component avoidance, and sources disagree openly. Immunotherapy’s average effect is modest, heterogeneity between trials is high, no biomarker predicts who will respond, and most trials are manufacturer-sponsored. The cause of the twentieth-century rise is unknown, so no evidence-based population prevention strategy exists. The two source lines for this condition also differ on the between-centre range of the childhood survey, twin heritability, the evidence for allergen avoidance, what GAP shows for asthma prevention, whether caesarean delivery and early antibiotics are established risk factors, and the drug prices and listing statuses. Each is printed where it arises.

> **Depth.** Starts in: a pollen or allergen protein. Size: 5 nm†; depth −2.01. First complaint: about 15 minutes († minutes after exposure); time depth 39.34. One untreated course: about 7.4 weeks († one season); depth 47.10.

> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Pleural effusion (ICD-11 CB27)

What it is. Fluid collects between the lung and the chest wall and presses the lung inward. Breathlessness builds and the chest feels heavy. It is always a consequence of something else, never a disease in itself.

Measured. No global prevalence, death or DALY figure for pleural effusion was retrieved from the GBD 2023 tables, and the structural reason is that it is a sign rather than a GBD cause. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Incidence in high-income countries is roughly 300 to 400 per 100,000 population a year, which is roughly 1.5 million cases a year in the United States, from long-standing United States estimates. The commonest causes in high-income series are heart failure, roughly 500,000 a year in United States estimates, pneumonia at about 300,000, malignancy at about 200,000, pulmonary embolism at about 150,000, and then cirrhosis, post-cardiac surgery and renal failure.

In high-tuberculosis-burden countries, tuberculous pleural effusion is the commonest cause of an exudative effusion in young adults, accounting for roughly 25 to 50 per cent of effusions in series from sub-Saharan Africa, India and China, against under 5 per cent in western Europe. That is as sharp a geographic divergence as in the pericarditis entry.

Malignant pleural effusion develops in roughly 15 per cent of all cancer patients, with median survival after diagnosis of roughly four to nine months, varying by tumour type — shorter for lung and ovarian, longer for breast and mesothelioma — from the LENT and PROMISE prognostic scores. Pleural infection, empyema and complicated parapneumonic effusion, is rising in incidence in both children and adults, with mortality of roughly 10 to 20 per cent in adults and higher in the elderly and in those with comorbidity. Heart failure and malignant effusions rise with age, and tuberculous effusion is a disease of young adults.

Where it starts. Mechanistically, either raised hydrostatic pressure or reduced oncotic pressure, which gives a transudate, or increased pleural permeability or impaired lymphatic drainage, which gives an exudate. Light's criteria separate the two with roughly 98 per cent sensitivity for exudates, at the cost of misclassifying roughly 25 per cent of transudates in diuretic-treated heart failure as exudates.

Transudates: heart failure, the commonest single cause overall; cirrhosis with ascites; nephrotic syndrome; peritoneal dialysis; hypoalbuminaemia; constrictive pericarditis. Exudates: parapneumonic effusion and empyema; malignancy of lung, breast, lymphoma, ovary or mesothelium; tuberculosis; pulmonary embolism; rheumatoid arthritis; lupus; pancreatitis; oesophageal rupture; post-cardiac-surgery states; drug-induced disease; asbestos-related benign effusion; chylothorax. The risk factors are those of the underlying diseases; there is no independent risk factor for pleural effusion as such.

Roughly 15 to 20 per cent of effusions remain undiagnosed after full investigation including pleural fluid analysis and often biopsy, and a substantial share of those turn out to be malignant or tuberculous on follow-up. Light's criteria misclassify a quarter of diuretic-treated heart failure effusions, and the proposed corrections — the serum-to-pleural albumin gradient, N-terminal pro-B-type natriuretic peptide — are not universally applied. Why some parapneumonic effusions loculate and become empyema while others resolve with antibiotics alone is not predictable at presentation. Whether drainage of a malignant effusion improves survival as well as symptoms is unknown, because no trial has been designed to answer it.

Cure status. Where the underlying cause is curable — parapneumonic effusion, empyema, tuberculous effusion, heart failure effusion: CURABLE. Malignant effusion: RELIEF ONLY.

Drainage relieves breathlessness immediately and definitively for that episode, and thoracocentesis is one of the most immediately effective procedures in medicine.

Parapneumonic effusion and empyema are CURABLE with antibiotics plus drainage. MIST2, with 210 patients, showed intrapleural tissue plasminogen activator plus DNase reduced pleural opacity and surgical referral, from 16 to 4 per cent, against placebo, and either agent alone was ineffective. Tuberculous pleural

effusion is CURABLE with standard antituberculous therapy; most resolve without drainage, and corticosteroids do not improve outcome and are not recommended. Heart failure effusion resolves with treatment of the heart failure — diuretics rather than drainage.

Malignant pleural effusion is RELIEF ONLY and recurs unless the pleural space is obliterated. Talc pleurodesis gives success in roughly 70 to 80 per cent at one month, and the TAPPS trial, with 330 patients, found talc poudrage at thoracoscopy no better than talc slurry via a chest tube, with pleurodesis failure of 22 against 24 per cent — so the cheaper bedside method is equivalent. An indwelling pleural catheter: TIME2, with 106 patients, gave equivalent breathlessness relief to talc pleurodesis with fewer hospital days, 1 against 4.5, and more adverse events, and AMPLE confirmed the reduction in hospital days. Neither cures; both manage the fluid. Chylothorax, oesophageal rupture and trapped lung need specific surgical management.

Prevention. Nothing prevents pleural effusion as such; prevention is entirely prevention of the underlying diseases.

Treating heart failure to target — STRONG, since heart failure is the commonest cause: per 10 mmHg systolic reduction, heart failure relative risk 0.72, and the four pillars reduce hospitalisation substantially.

Prompt and adequate antibiotic treatment of pneumonia — STRONG for preventing empyema. *Pneumococcal and influenza vaccination — MODERATE* for preventing the parapneumonic effusions and empyemas that follow pneumonia; the pneumococcal vaccine reduces invasive pneumococcal disease by 80 to 90 per cent in vaccinated children with herd protection.

Tuberculosis control and complete treatment — STRONG where tuberculous effusion dominates.

Asbestos elimination — STRONG for mesothelioma and benign asbestos effusion. *Thromboprophylaxis — STRONG* for the embolism-related effusions. *Smoking cessation — STRONG* for lung cancer and therefore for malignant effusion.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Diagnostic and therapeutic thoracocentesis	Immediate relief of breathlessness; the diagnostic yield of fluid analysis is roughly 75 per cent for the cause	n/a	n/a	A needle, a syringe, a three-way tap and a drainage bag: a few to tens of euro
Ultrasound guidance	Reduces pneumothorax risk from roughly 10 to 18 per cent down to 1 to 3 per cent and reduces iatrogenic complications substantially; it is now standard of care for all pleural procedures	n/a	n/a	Handheld thousands to tens of thousands of euro and falling
Treating the cause: diuretics, antibiotics, antituberculous therapy, anticoagulation	Curative where the cause is curable; a full tuberculosis cure costs tens of euro	yes, all	yes	a few to tens of euro
Chest tube drainage, empyema or a large effusion	Small-bore tubes of 10 to 14 French are as effective as large-bore and much less painful	n/a	n/a	tens to hundreds of euro
Intrapleural tissue plasminogen activator with DNase, empyema	MIST2: surgical referral reduced from 16 to 4 per cent; either agent alone ineffective	no	partly	thousands of euro a course
Talc pleurodesis, by slurry through a tube or by poudrage	Success 70 to 80 per cent at one month; TAPPS found slurry equivalent to poudrage, failure 24 against 22 per cent	no	yes, talc is cheap	Talc tens to hundreds of euro; the procedure thousands of euro
Indwelling pleural catheter	TIME2: equivalent breathlessness relief to pleurodesis, hospital days 1 against 4.5, more adverse events	no	n/a	hundreds to thousands of euro plus drainage supplies
Surgical decortication or	For failed drainage in empyema and	n/a	n/a	thousands to tens

Intervention	Effect size	EML	Off-patent	Cost
video-assisted thoracoscopic surgery	for trapped lung			of thousands of euro
Corticosteroids in tuberculous effusion	**No outcome benefit; not recommended**	yes	yes	—
Systemic anticancer therapy	Effective in chemosensitive tumours — lymphoma, small cell carcinoma, breast cancer — which can resolve the effusion	Varies	Varies	Varies widely

Simple means. This entry has an unusually favourable ratio of effect to equipment.

Thoracocentesis with a needle and a syringe is one of the highest immediate-benefit-per-euro interventions in all of medicine. A needle, a syringe, a three-way tap and a drainage bag — a few to tens of euro of consumables — relieve breathlessness within minutes, at the bedside. The one essential safety addition is ultrasound guidance, which reduces pneumothorax risk from roughly 10 to 18 per cent down to 1 to 3 per cent; handheld ultrasound now costs thousands to tens of thousands of euro and is falling. Without ultrasound the procedure is still done and still works, at higher complication risk, and clinical site selection by percussion and auscultation is the fallback.

Clinical examination detects a moderate or large effusion reliably with no equipment at all: stony dull percussion, absent breath sounds and reduced vocal resonance. Percussion and a stethoscope. Sensitivity for effusions over roughly 500 mL is good, and small effusions are missed. Positioning — sitting upright and leaning toward the affected side — improves ventilation of the unaffected lung, and is free.

Treating the cause with cheap drugs: furosemide for heart failure effusion at a few to tens of euro a year, amoxicillin for parapneumonic effusion at a few to tens of euro a course, and antituberculous therapy for tuberculous effusion at tens of euro for a full curative course — all listed and off-patent. In the setting where pleural effusion is most often tuberculous, the cure costs tens of euro and needs no drainage.

Talc costs tens to hundreds of euro and sterile graded talc is the pleurodesis agent of choice; talc slurry through a small chest tube is equivalent to thoracoscopic poudrage per TAPPS, so the cheap bedside route is not inferior. Small-bore chest tubes cost tens to hundreds of euro and are as effective as large-bore and much less painful. Low-dose morphine and a fan to the face relieve refractory breathlessness in malignant effusion where drainage is not appropriate: tens to hundreds of euro a year for morphine, listed and off-patent.

The hard limit. Determining the cause requires pleural fluid analysis — protein, lactate dehydrogenase, glucose, pH, cytology, culture, and adenosine deaminase or a nucleic acid test for tuberculosis. Light's criteria need a laboratory that can measure protein and lactate dehydrogenase in both serum and pleural fluid. Without that, management is empirical, and imaging, a chest radiograph at minimum, is needed to confirm. So the relief is nearly free and immediate, and the diagnosis requires a laboratory.

Gaps. Pleural effusion is not a GBD cause, so no global burden figure exists at all, and this entry is part of the seventeen-condition gap in this chapter's introduction; the figure of roughly 1.5 million United States cases a year is an old estimate repeated widely. Between 15 and 20 per cent remain undiagnosed after full investigation†, and a substantial share prove malignant or tuberculous later. Light's criteria misclassify roughly a quarter of diuretic-treated heart failure effusions as exudates, and the corrections are not consistently applied. Tuberculous effusion is the commonest exudative cause in young adults in high-burden countries and under 5 per cent of cases in western Europe, and the guidelines and the trial evidence are largely from low-burden settings. Whether drainage of a malignant effusion affects survival is unknown; no trial has been designed to test it. TAPPS showed the expensive thoracoscopic route is not better than bedside slurry, and practice has not fully followed. Which parapneumonic effusions will loculate is not predictable, so the timing of intrapleural fibrinolytics and of surgery rests on judgement. Empyema incidence is rising in both children and adults and the reason is not established. Malignant effusion survival estimates of four to nine months come from specialist referral cohorts.

> **Depth.** Always the result of something else [B]. No depth is given.

> **Model reading.** Way of ending: restore proportion. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Pneumothorax (ICD-11 CB21)

What it is. Air leaks into the space between the lung and the chest wall, and the lung collapses away from the wall. There is sudden one-sided chest pain and breathlessness. If the pressure builds, it pushes the heart aside and kills within minutes.

Measured. No global prevalence, death or DALY figure for pneumothorax was retrieved from the GBD 2023 tables. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Primary spontaneous pneumothorax has an incidence of roughly 7.4 to 18 per 100,000 a year in men and 1.2 to 6 per 100,000 a year in women, from UK, United States and Scandinavian population studies. Secondary spontaneous pneumothorax runs at roughly 6.3 per 100,000 a year in men and 2.0 in women. Primary spontaneous pneumothorax is rarely fatal; secondary spontaneous pneumothorax carries mortality of roughly 10 per cent, because the underlying lung disease, usually chronic obstructive pulmonary disease, leaves little reserve. Recurrence after a first primary spontaneous pneumothorax is roughly 30 per cent within one to five years, rising to roughly 60 per cent after a second. Tension pneumothorax is the immediately lethal form; its incidence is not separately measured anywhere, and it is commonest in trauma and in ventilated patients. Primary spontaneous pneumothorax is a disease of tall thin young men, typically aged 15 to 34, with a sex ratio of roughly 3 to 6 to 1 male; secondary spontaneous pneumothorax peaks over 55 with chronic obstructive pulmonary disease.

Where it starts. Smoking is the dominant modifiable risk factor for primary spontaneous pneumothorax, and the relative risk is among the largest for any disease: the lifetime risk is roughly 12 per cent in male smokers against 0.1 per cent in male non-smokers, an approximately hundredfold relative risk, and the risk is dose-dependent.

A tall, thin body habitus contributes, because the apical pleural pressure gradient is more negative in a tall chest. Subpleural blebs and emphysema-like changes are found at surgery or on computed tomography in roughly 80 to 90 per cent of patients, including in the contralateral lung. Male sex and family history, with roughly 10 per cent having an affected relative, contribute. Genetic causes: Birt-Hogg-Dubé syndrome from FLCN mutations, with pneumothorax in roughly 75 to 80 per cent of affected individuals alongside renal tumours and skin fibrofolliculomas; Marfan syndrome; Ehlers-Danlos syndrome; alpha-1 antitrypsin deficiency.

Secondary causes. Chronic obstructive pulmonary disease is the commonest. Tuberculosis and post-tuberculous cavitation dominate in high-burden countries. Cystic fibrosis carries a lifetime risk of roughly 3 to 4 per cent. Pneumocystis pneumonia in HIV, lung cancer and lymphangioleiomyomatosis — the last with pneumothorax in roughly 65 to 80 per cent, often as the presenting event in young women — all contribute, as do necrotising pneumonia, interstitial lung disease, and catamenial or thoracic endometriosis. Iatrogenic causes: central line insertion, pleural procedures — reduced from 10 to 18 per cent down to 1 to 3 per cent with ultrasound guidance — transbronchial and transthoracic biopsy, and mechanical ventilation with high pressures. Trauma, penetrating and blunt chest injury. Diving and altitude change, and cannabis and crack cocaine smoking.

Why the bleb ruptures at a given moment is not predictable, and most episodes occur at rest rather than during exertion. Whether the subpleural blebs seen in 80 to 90 per cent of patients are the actual site of air leak is disputed — leaks are often found elsewhere at surgery, and the term “emphysema-like changes” was introduced partly to reflect that uncertainty. Why recurrence is roughly 30 per cent and who will recur cannot be predicted from imaging. Whether conservative management is safe in a wider group than currently treated is only now being tested.

Cure status. The episode: CURABLE — it resolves completely and lung function returns to normal. The recurrence risk: CURABLE in 95 to 99 per cent by video-assisted thoracoscopic pleurectomy or mechanical pleurodesis, recurrence 1 to 5 per cent. Tension pneumothorax: CURABLE instantly by

decompression. Secondary spontaneous pneumothorax: the episode is CURABLE; the underlying lung disease remains and carries its own label.

A pneumothorax resolves completely. Air is reabsorbed at roughly 1.25 to 2.2 per cent of the hemithorax a day spontaneously and faster with supplemental oxygen; the lung re-expands and function normalises.

Conservative management is effective and often sufficient, and that is a major and recent reversal. The PSP trial, published in the New England Journal of Medicine in 2020, randomised 316 patients with moderate to large primary spontaneous pneumothorax to conservative or interventional management. Lung re-expansion at eight weeks was 94.4 per cent conservative against 98.5 per cent interventional, a risk difference of −4.1 percentage points, which met non-inferiority in the complete-case analysis. Serious adverse events and recurrences were fewer in the conservative arm. Watching is as good as draining for a substantial proportion.

Surgical pleurodesis or pleurectomy reduces recurrence from roughly 30 per cent to 1 to 5 per cent after video-assisted thoracoscopic surgery with pleurectomy or mechanical pleurodesis. That is a genuine and durable cure of the recurrence risk. Chemical pleurodesis with talc through a chest tube gives recurrence of roughly 8 to 15 per cent, less effective than surgery and far less invasive. Tension pneumothorax is cured instantly by decompression: a needle through the chest wall converts an immediately lethal condition into a survivable one in seconds.

Prevention.

Smoking cessation — STRONG, and quantitatively the most important. Lifetime risk roughly 12 per cent in male smokers against 0.1 per cent in non-smokers, and cessation reduces recurrence risk substantially. This is among the largest relative risk reductions available from quitting for any single disease.

Surgical pleurodesis or pleurectomy after recurrence — STRONG. Recurrence from 30 per cent down to 1 to 5 per cent.

Ultrasound guidance for all pleural procedures — STRONG for iatrogenic pneumothorax: 10 to 18 per cent down to 1 to 3 per cent.

Lung-protective, low tidal volume ventilation — STRONG for ventilator-associated pneumothorax.

Tuberculosis control and treatment — STRONG where post-tuberculous cavitation is a leading cause.

Avoiding diving after a pneumothorax — STRONG by consensus; diving is contraindicated permanently unless definitive surgical pleurodesis has been performed.

Cannabis and crack cessation — MODERATE. *Screening relatives in Birt-Hogg-Dubé syndrome — MODERATE*, chiefly for the renal tumour risk.

Avoiding air travel for a defined interval after resolution, commonly one to two weeks after radiographic resolution, is consensus with WEAK evidence.

Avoiding strenuous exertion — WEAK and CONTESTED: most episodes occur at rest, and routine activity restriction is not evidence-based.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Needle decompression for tension pneumothorax	**Immediately life-saving, in seconds.** A large-bore cannula in the second intercostal space or in the fourth or fifth space in the mid-axillary line	n/a	n/a	A cannula: a few to a few euro
Conservative observation, primary spontaneous pneumothorax	PSP trial: re-expansion 94.4 against 98.5 per cent interventional, with fewer serious adverse events and fewer recurrences	n/a	n/a	Nothing but observation
Supplemental high-	Increases the rate of air	yes	yes	Concentrator or

Intervention	Effect size	EML	Off-patent	Cost
concentration oxygen	reabsorption roughly three- to fourfold by nitrogen washout			cylinder; see the COPD entry
Needle aspiration, 14 to 16 gauge	Success roughly 60 to 70 per cent, and as effective as chest tube drainage for primary spontaneous pneumothorax with fewer hospital admissions, per Cochrane and British Thoracic Society guidance	n/a	n/a	A cannula and a syringe: a few to tens of euro
Small-bore chest drain, 8 to 14 French, with or without a one-way valve	Effective; ambulatory devices allow outpatient management, and the RAMPP trial showed a shorter hospital stay	n/a	n/a	Tube tens to hundreds of euro; Heimlich valve tens of euro
Large-bore chest drain	No more effective than small-bore and more painful	n/a	n/a	tens to hundreds of euro
Talc or doxycycline chemical pleurodesis	Recurrence roughly 8 to 15 per cent	yes, doxycycline	yes	Talc tens to hundreds of euro; doxycycline a few to tens of euro
Thoracoscopic pleurectomy or mechanical pleurodesis	Recurrence from 30 per cent down to 1 to 5 per cent	n/a	n/a	thousands to tens of thousands of euro
Open thoracotomy pleurectomy	The lowest recurrence, about 1 per cent, and the most invasive	n/a	n/a	thousands to tens of thousands of euro
Autologous blood patch pleurodesis	For a persistent air leak; the patient’s own blood instilled through the drain, with success of roughly 70 to 90 per cent in small series	n/a	n/a	Essentially free
Endobronchial valves	For a persistent air leak in patients not fit for surgery	no	no	thousands to tens of thousands of euro

Simple means. This entry contains the single most dramatic example of a no-equipment life-saving intervention in either chapter.

Needle decompression of a tension pneumothorax: a large-bore cannula costing well under five euro, pushed through the chest wall, converts an immediately fatal condition into a survivable one within seconds. The diagnosis is clinical — breathlessness, hypotension, distended neck veins, tracheal deviation away from the affected side, absent breath sounds and hyper-resonance on that side — and a chest radiograph should not be waited for. That is the clearest case in either chapter where a trained person with almost nothing saves a life.

Conservative observation costs nothing and is the treatment for a substantial share of primary spontaneous pneumothorax: the PSP trial gave 94.4 per cent re-expansion with conservative management against 98.5 per cent with intervention, with fewer serious adverse events and fewer recurrences.

Needle aspiration with a cannula and a syringe costs a few to tens of euro has a success rate of 60 to 70 per cent, and is as effective as a chest tube for primary spontaneous pneumothorax with fewer admissions. A Heimlich one-way valve costs tens of euro and allows ambulatory management, and an underwater seal can be improvised from a bottle of water and tubing — the classic low-resource chest drainage system, requiring no suction and no power. High-concentration oxygen increases the reabsorption rate roughly three- to fourfold.

Autologous blood patch pleurodesis is effectively free and uses nothing the patient did not already have: the patient’s own blood, drawn from a vein and instilled down the existing drain, achieves pleurodesis in roughly 70 to 90 per cent of persistent air leaks in small series.

Smoking cessation is the single largest preventive effect in the entry and it is free: lifetime risk 12 per cent in male smokers against 0.1 per cent in non-smokers. Clinical examination — hyper-resonant percussion, absent breath sounds and reduced chest expansion on one side — diagnoses a large pneumothorax with percussion and a stethoscope; ultrasound, showing absent lung sliding, is more sensitive, and a radiograph is confirmatory. Sitting upright reduces the work of breathing.

The hard limit, with one critical caveat. A small pneumothorax cannot be reliably distinguished from other causes of chest pain without imaging, a chest radiograph at minimum, and ultrasound is more sensitive than supine radiography. Recurrence prevention requires surgery. And the caveat: the clinical signs that justify blind needle decompression are those of tension pneumothorax, and decompressing a chest that has no pneumothorax causes one. The judgement, not the equipment, is the constraint.

Gaps. No GBD global burden figure for pneumothorax was retrieved, and this entry is part of the seventeen-condition gap in this chapter's introduction. Incidence estimates vary roughly 2.5-fold between countries, 7.4 to 18 per 100,000 in men, on ascertainment differences. Tension pneumothorax incidence is not separately measured anywhere, despite being the immediately lethal form. The PSP trial reversed standard practice, and its non-inferiority margin and handling of missing data have been debated; guidelines are changing unevenly and practice varies widely, so both the trial result and the fact that practice has not uniformly followed are printed. Whether subpleural blebs are the actual site of air leak is disputed, so the basic pathological account is uncertain. Who will recur cannot be predicted, so the indication for surgery after a first episode is a judgement rather than a measurement. Air travel and diving restrictions after a pneumothorax are consensus-based with essentially no trial evidence, and the recommended intervals differ between guidelines. Activity restriction is widely advised and not evidence-based, since most episodes occur at rest. Post-tuberculous and HIV-related pneumothorax dominate in high-burden settings and are almost absent from a guideline evidence base that is European, North American and Australasian. Secondary spontaneous pneumothorax mortality of about 10 per cent comes from small series.

> **Depth.** Starts in: a bleb on the lung surface. Size: 1 cm†; depth +11.19. First complaint: about 10 seconds ([B] sudden); time depth 35.25. One untreated course: about 20 days († 2–4 weeks); depth 46.23.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status, given by stratum: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

The failing lung and the inherited lung

Acute respiratory distress syndrome (ICD-11 CB00)

What it is. A severe insult — infection, injury, inhalation — makes the lungs leak fluid into the air sacs everywhere at once. Oxygen cannot cross and the person needs a ventilator within hours. Many die, and those who live often take a year to recover.

Measured. No global prevalence, death or DALY figure for acute respiratory distress syndrome was retrieved from the GBD 2023 tables, and the structural reason is that it is a syndrome rather than a GBD cause. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Incidence is roughly 10.1 to 86.2 per 100,000 person-years depending on the country and the definition used — a nearly ninefold range across United States, Scandinavian, Australian and European estimates. The highest figures come from United States cohorts and the lowest from Europe, and the difference is widely attributed to ascertainment and intensive care bed availability rather than to true variation.

The LUNG SAFE study covered 459 intensive care units in 50 countries in 2016. It found the syndrome present in 10.4 per cent of intensive care admissions and 23.4 per cent of mechanically ventilated patients. Hospital mortality was 34.9 per cent for mild, 40.3 per cent for moderate and 46.1 per cent for severe disease. The single most reproducible finding about practice is under-recognition: clinicians recognised the syndrome in only 60.2 per cent of cases and in only 51.3 per cent of mild cases.

COVID-19 produced the largest cohort in history. GBD 2023 records 797,600 COVID-19 deaths (722,900 to 857,000) in 2023 alone, ranked twentieth, down from 7.89 million in 2021 when it ranked second; a large share of those deaths were acute respiratory distress syndrome. Survivors have persistent exercise limitation, muscle wasting, cognitive impairment and psychiatric morbidity; the Toronto cohort found persistent functional limitation at five years, with median six-minute walk distance of roughly 76 per cent of predicted. Incidence rises with age and mortality rises steeply with age. Mortality has fallen modestly over three decades, attributed mainly to lung-protective ventilation and to general improvements in critical care rather than to any specific drug.

Where it starts. The syndrome is always secondary to a precipitant. Pneumonia is the commonest cause at roughly 35 to 60 per cent, and non-pulmonary sepsis follows at roughly 30 per cent. Aspiration of gastric contents, major trauma especially with pulmonary contusion, long-bone fracture or massive transfusion, and transfusion-related acute lung injury — reduced substantially by excluding multiparous female plasma donors — all contribute. So do pancreatitis, burns and smoke inhalation, drowning, drug overdose with opioids or salicylates, inhaled toxins including chlorine, phosgene and paraquat, fat embolism, and high altitude as a related but distinct syndrome.

Risk-modifying factors: chronic alcohol use roughly doubles risk after a given insult; obesity, hypoalbuminaemia, cigarette smoking and air pollution exposure raise risk; and diabetes appears protective, a reproducible and unexplained finding. Mechanical ventilation itself causes lung injury and can initiate or worsen the syndrome, which is why the single most effective treatment is ventilating less aggressively.

The syndrome is defined by a consensus definition rather than by a mechanism, and the definition has changed four times: the 1967 description, the 1994 American-European Consensus Conference, the 2012 Berlin definition and the 2023 global definition. Each change alters measured incidence and mortality, which is why the incidence range is ninefold. The hyperinflammatory and hypoinflammatory subphenotypes identified by latent class analysis have different mortality and opposite responses to positive-end-expiratory-pressure strategy and to fluid management in retrospective reanalyses, which is the leading explanation for why dozens of drug trials were null in unselected populations, and it has not yet been tested prospectively. Why some patients fibrose and others resolve completely is unexplained. Why diabetes is protective is unknown.

Cure status. The lung injury itself: RELIEF ONLY. The episode, in survivors: SELF-LIMITING — it resolves under supportive care.

No treatment reverses the lung injury, and every disease-modifying drug trial has been null: surfactant, inhaled nitric oxide, prostacyclin, ketoconazole, lisofylline, N-acetylcysteine, statins in unselected patients in SAILS and HARP-2, beta-agonists in BALTI-2 and ALTA, neutrophil elastase inhibitors and granulocyte-macrophage colony-stimulating factor.

The episode is SELF-LIMITING in those who survive it. The injury resolves on its own, and the interventions that work — low tidal volume ventilation, prone positioning, conservative fluid management, extracorporeal support in refractory cases — support the lung and avoid adding harm rather than treating the syndrome. Hospital mortality is 34.9 to 46.1 per cent by severity, so the self-limiting course is not a benign one.

Lung function in survivors largely recovers, with most having near-normal spirometry by six to twelve months, and functional limitation, muscle weakness, cognitive impairment and psychiatric morbidity persist for years, with six-minute walk distance at roughly 76 per cent of predicted at five years. Corticosteroids are the one drug exception and they are mixed: positive in COVID-19 disease in RECOVERY, positive in DEXA-ARDS, and negative or harmful in earlier and in late-phase non-COVID trials.

Prevention.

Lung-protective ventilation in patients at risk and during surgery — STRONG. Low tidal volume ventilation reduces the incidence of the syndrome in at-risk ventilated patients, and intraoperative lung-protective ventilation, in the IMPROVE trial, reduced post-operative pulmonary complications.

Treating pneumonia and sepsis promptly — STRONG, since those are 65 to 90 per cent of precipitants. Early appropriate antibiotics in sepsis.

Conservative transfusion thresholds and male-donor or screened plasma — STRONG for transfusion-related acute lung injury, which fell substantially after donor screening was introduced.

Vaccination against influenza, pneumococcus and COVID-19 — STRONG for preventing the commonest precipitants.

Conservative fluid management in at-risk patients — MODERATE. *Aspiration precautions — head elevation, swallow assessment after stroke, avoiding over-sedation — MODERATE*. *Alcohol reduction — MODERATE*: chronic alcohol use roughly doubles risk after a given insult. *Smoking cessation — MODERATE*.

Aspirin and statins for prevention — CONTESTED to negative. LIPS-A, with aspirin, was null for preventing the syndrome in at-risk patients.

No drug prevents acute respiratory distress syndrome.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Low tidal volume ventilation, 6 mL/kg predicted body weight, plateau pressure 30 cmH_2O or below	ARMA, the ARDSNet trial, 861 patients: **mortality 31.0 against 39.8 per cent, number needed to treat 11 to prevent one death.** This is the single most important treatment and it consists of setting the ventilator differently	n/a	n/a	**Nothing — it is a setting**
Prone positioning, 16 hours a day or more in severe disease	PROSEVA, 466 patients with an arterial oxygen tension to inspired oxygen fraction ratio below 150: **28-day mortality 16.0 against 32.8 per cent, hazard ratio 0.39; 90-day mortality 23.6 against 41.0 per cent — number needed to treat 6 to prevent one death.** One of the lowest numbers needed to treat in all of critical care	n/a	n/a	**Nothing but staff time — it requires four or five people and no equipment**
Conservative fluid management	FACTT, 1,000 patients: more ventilator-free days, 14.6 against 12.1, and more intensive-care-free days; no mortality difference	n/a	n/a	**Nothing — it is a strategy**
Neuromuscular blockade with cisatracurium in severe disease	ACURASYS, 340 patients: adjusted 90-day mortality hazard ratio 0.68 favouring blockade; ROSE, 1,006 patients, was null with a lighter-sedation control arm. Unresolved, and both are printed	yes, atracurium	yes	tens to hundreds of euro a course
Corticosteroids	DEXA-ARDS, 277 patients on dexamethasone: ventilator-free days 12.3 against 7.5, 60-day mortality 21 against 36 per cent. RECOVERY, in COVID-19, 6,425 patients: 28-day mortality 22.9 against 25.7 per cent overall, and 29.3 against 41.4 per cent in	yes, dexamethasone	yes	a few euro a course

Intervention	Effect size	EML	Off-patent	Cost
	ventilated patients — number needed to treat about 8 in that group, with a drug costing a few euro. Earlier and late-phase non-COVID steroid trials were negative or harmful			
Higher positive-end-expiratory-pressure strategy	Meta-analysis: benefit confined to moderate to severe disease, with ALVEOLI, LOVS and EXPRESS individually null. ART, 1,010 patients, with recruitment manoeuvres plus pressure titration, found **increased mortality**, hazard ratio 1.20	n/a	n/a	**Nothing — a setting**
Venovenous extracorporeal membrane oxygenation	EOLIA, 249 patients: 60-day mortality 35 against 46 per cent, p=0.09 — did not reach significance, with 28 per cent crossover from control to treatment; post-hoc Bayesian and meta-analytic reanalyses favour it	n/a	n/a	tens of thousands to hundreds of thousands of euro
Inhaled nitric oxide	Oxygenation improves transiently; no mortality benefit, and increased renal dysfunction on meta-analysis	no	no	thousands to tens of thousands of euro a course
Surfactant, beta-agonists, statins, N-acetylcysteine, colony-stimulating factor, elastase inhibitors	All null for mortality in unselected disease	Varies	Varies	—
Early antibiotics and source control for the precipitant	The mortality benefit in sepsis is well established, and each hour of delay in septic shock is associated with increased mortality	yes	yes	a few to tens of euro a course
Nutritional support, thromboprophylaxis, head-of-bed elevation, sedation minimisation, early mobilisation	Bundled supportive care; each component has modest independent evidence	yes, enoxaparin	yes	tens to hundreds of euro

The defining economic fact. The three interventions with the largest measured mortality benefits — low tidal volume ventilation at a number needed to treat of 11, prone positioning at 6, and dexamethasone in COVID-19 disease at about 8 in ventilated patients for a few euro a course — cost almost nothing. Every expensive drug has failed, and extracorporeal support at tens of thousands to hundreds of thousands of euro missed significance in its only randomised trial. A ventilator is required and costs tens of thousands of euro; how it is set is free and matters more than anything else.

Simple means. Setting the ventilator correctly is the most important treatment and it is free. Low tidal volume ventilation at 6 mL/kg of predicted body weight reduces mortality from 39.8 to 31.0 per cent, number needed to treat 11. It is a number entered on a machine already in use. Predicted body weight must be calculated from height rather than from actual weight, which is a calculation done with a tape measure.

Prone positioning requires four or five people, pillows and a protocol, and no equipment whatsoever. It gives 28-day mortality of 16.0 against 32.8 per cent and 90-day mortality of 23.6 against 41.0 per cent in severe disease, number needed to treat 6. It is among the most effective interventions in critical care and its only cost is staff time and training. Awake proning was used widely in COVID-19 and reduced intubation in a meta-analysis of randomised trials, though a mortality benefit was not established.

Dexamethasone costs a few euro a course, is listed and off-patent, and has a number needed to treat of about 8 for mortality in ventilated COVID-19 disease. A cheap old steroid is the only drug that has clearly reduced mortality in this syndrome in a large trial.

Conservative fluid management is a strategy rather than a product and gives more ventilator-free days, 14.6 against 12.1, free. Head-of-bed elevation to 30 to 45 degrees, oral care, sedation minimisation and early mobilisation are nursing practice, free, and reduce ventilator-associated complications. Early antibiotics for the precipitating infection cost a few to tens of euro a course, listed and off-patent. Pulse oximetry costs tens to hundreds of euro and identifies the hypoxaemia that defines the syndrome. Vaccination against the precipitants is cheap, listed and routine.

The hard limit, stated as plainly as possible. This syndrome cannot be survived without mechanical ventilation in the great majority of cases. The minimum chain is a ventilator at tens of thousands of euro reliable oxygen, continuous nursing at roughly one nurse per one or two patients, sedation, suction, and blood gas or at minimum pulse oximetry monitoring. No positioning, drug or technique substitutes for that. What the simple means achieve is that once a ventilator exists, nearly all of the additional mortality benefit available comes free — from how it is set, from turning the patient over, and from a a few euro steroid. The inequity in outcomes worldwide is almost entirely about whether a ventilator and a nurse exist, not about whether the effective treatments are affordable.

Gaps. No GBD burden figure for acute respiratory distress syndrome exists, because it is a syndrome rather than a GBD cause, and this entry is part of the seventeen-condition gap in this chapter's introduction. Incidence estimates range nearly ninefold, 10.1 to 86.2 per 100,000, driven by definition and intensive care availability rather than by disease frequency. The definition has changed four times — 1967, 1994, 2012 and 2023 — and each change alters measured incidence and mortality, so figures from different eras are not comparable. The syndrome is recognised by clinicians in only 60.2 per cent of cases and 51.3 per cent of mild cases, so the epidemiology is built on a syndrome that is half-missed in practice. Dozens of drug trials have been null, and the subphenotype hypothesis — hyperinflammatory against hypoinflammatory, with opposite responses to pressure and fluid strategy in retrospective reanalysis — is the leading explanation and has never been tested prospectively. Neuromuscular blockade is unresolved: ACURASYS positive, ROSE null. Corticosteroids are unresolved: RECOVERY and DEXA-ARDS positive, earlier and late-phase trials negative or harmful, and the patient group and timing that benefit are not settled. Higher positive end-expiratory pressure is unresolved and clinically consequential: meta-analysis suggests benefit in moderate to severe disease while ART found increased mortality with recruitment manoeuvres. EOLIA missed significance for extracorporeal support at p=0.09 with 28 per cent crossover, reanalyses favour it, and practice has expanded on contested evidence at tens of thousands to hundreds of thousands of euro a patient. Why diabetes is protective is unknown. Long-term outcome data come from a small number of high-income cohorts, and survivorship in low-resource settings is essentially unmeasured. Most of the world has no epidemiology for this syndrome at all, because it has no intensive care registries.

> **Depth.** Starts in: the alveolar-capillary membrane. Size: 1 μm†; depth +2.81. First complaint: about 36 hours († within 72 hours after the insult); time depth 43.87. One untreated course: about 3 weeks († weeks); depth 46.27.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Cystic fibrosis lung disease (ICD-11 CA25, respiratory manifestation of 5C57.0)

A note on placement. Cystic fibrosis is classified in ICD-11 under chapter 05, endocrine, nutritional and metabolic diseases, as 5C57.0, with the bronchiectasis of cystic fibrosis coded in chapter 12. It is included here for its respiratory manifestation, which is what kills.

What it is. A single inherited faulty protein makes mucus thick and sticky throughout the body. In the lungs the mucus cannot be cleared, so infection and scarring build from infancy. Until recently it killed in childhood or early adulthood.

Measured. No global figure for cystic fibrosis was retrieved from the GBD 2023 tables or the chapter map. This is one of the seventeen conditions in this chapter for which the global data carry nothing at all.

Birth incidence is roughly 1 in 2,500 to 3,500 live births in European-ancestry populations, far rarer in east Asian populations at roughly 1 in 30,000 to 100,000, and intermediate in Latin American, Middle Eastern and African-ancestry populations. Carrier frequency is roughly 1 in 25 to 30 in European-ancestry

populations. Roughly 105,000 people are diagnosed across 94 countries, from 2022 modelling, and modelling suggests the true number may be substantially higher, with large under-diagnosis in Asia, Africa and Latin America.

Median predicted survival has transformed: from under five years in the 1950s to the mid-thirties and now over fifty years in high-income countries with registry data, with the UK and United States registries reporting median predicted survival in the fifties for children born recently. Respiratory failure causes roughly 60 to 80 per cent of deaths. In low- and middle-income countries median survival remains far lower and many patients are never diagnosed; the registry data describing the transformation come almost entirely from North America, Europe and Australasia. The adult population now exceeds the paediatric population in high-income countries — a complete inversion within one generation.

Where it starts. Autosomal recessive mutations in CFTR, the cystic fibrosis transmembrane conductance regulator, a chloride and bicarbonate channel. Over 2,000 variants have been described and roughly 400 to 700 are established as disease-causing. F508del is the commonest variant, present on roughly 70 per cent of alleles in European-ancestry populations and in roughly 85 to 90 per cent of patients on at least one allele.

The genotype-phenotype correlation is strong for pancreatic status and weak for lung disease: lung disease severity varies widely between siblings with identical CFTR genotypes, which is the central unexplained observation. Modifier genes — TGFB1, SLC26A9, EHF, the HLA region — explain part of the variance and much remains unassigned. Environmental modifiers with measured effects: second-hand tobacco smoke, which worsens lung function; air pollution; socioeconomic status, with a large and reproducible effect on survival independent of healthcare system; nutritional status, where body mass index strongly predicts lung function and survival; and early acquisition of Pseudomonas aeruginosa, a major adverse prognostic event.

Why siblings with identical genotypes have very different lung disease is unexplained, and modifier genes account for only part of it. The mechanism connecting channel dysfunction to the specific pattern of airway infection is incompletely understood: whether the primary defect is airway surface dehydration, bicarbonate-dependent mucus abnormality or impaired innate immunity is still argued. Whether modulators started in infancy will prevent lung disease entirely is not yet known — the first cohorts treated from infancy are only now growing up, and that is the most important open question in the field. The long-term durability and off-target effects of modulators over decades are unknown.

Cure status. CONTROLLABLE. That distinction must be stated precisely because it is widely blurred.

CFTR modulators restore partial channel function and dramatically improve disease, and they do not remove the genetic defect; treatment is lifelong and the benefit is lost on stopping. The landmark is elexacaftor with tezacaftor and ivacaftor. In patients with at least one F508del allele, roughly 85 to 90 per cent of all patients, the phase 3 trials of 2019 gave FEV1 improvement of roughly 14 percentage points, a 63 per cent reduction in pulmonary exacerbations, large sweat chloride falls and weight gain. Registry data since show falling transplant rates and falling mortality.

Roughly 10 per cent of patients have genotypes not responsive to any current modulator — nonsense, frameshift and splice variants with no channel protein to modulate — and they have had no share in the transformation. That is the central equity problem within the disease.

Lung transplantation replaces the organ, with median survival after transplant of roughly eight to ten years in cystic fibrosis, better than for most other indications. Gene therapy and gene editing are in trials; no genetic cure exists, and the repeated failure of inhaled gene therapy over thirty years should temper claims. Newborn screening does not cure and changes the trajectory: screened children have better nutritional status and lung function than those diagnosed clinically.

Prevention.

Newborn screening, immunoreactive trypsinogen plus DNA analysis — STRONG. Randomised and cohort comparisons show better nutritional status, growth and lung function in screened children, and screening is now routine in most high-income countries. It costs a few to tens of euro per infant screened within an existing dried-blood-spot programme.

Infection prevention and segregation — STRONG. Cohort segregation and strict infection control reduced epidemic Pseudomonas and Burkholderia cepacia complex transmission substantially after the outbreaks of the 1990s, and patients are no longer allowed to meet each other in person at clinics — a measure with a measured effect and a real human cost.

Early eradication of a first Pseudomonas aeruginosa isolation — STRONG. The EPIC and ELITE trials: inhaled tobramycin eradicates early Pseudomonas in roughly 65 to 90 per cent of cases and delays chronic infection.

Nutritional optimisation — STRONG. Body mass index predicts lung function and survival; the measures are a high-calorie diet, pancreatic enzyme replacement and fat-soluble vitamins.

Avoiding second-hand tobacco smoke — STRONG for lung function in diagnosed patients.

Carrier screening and genetic counselling — MODERATE for reducing incidence where offered; Ashkenazi Jewish community screening programmes and population carrier screening have measurably reduced birth incidence. This is prevention of births, and a reference work should state it as such rather than as a purely technical measure.

Vaccination against influenza, pneumococcus and COVID-19 — MODERATE. *Air pollution reduction — MODERATE*.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost per patient-year
Airway clearance physiotherapy	The historical foundation and still daily practice. Sputum clearance improves; Cochrane finds short-term benefit with no evidence that any one technique is superior	n/a	n/a	Training; devices a few to tens of euro
Dornase alfa, recombinant human DNase	FEV1 improved by roughly 5 to 6 per cent and exacerbations reduced by roughly 30 per cent, from the 1994 New England Journal of Medicine trial — **effective in cystic fibrosis and harmful in non-cystic-fibrosis bronchiectasis**	no	no	tens of thousands of euro
Hypertonic saline, nebulised 7 per cent	FEV1 improved modestly, roughly 3 per cent, and exacerbations reduced, from the 2006 New England Journal of Medicine trial	no	yes	hundreds of euro
Inhaled tobramycin or colistin for chronic Pseudomonas	FEV1 improved and exacerbations and hospitalisation reduced, from the 1999 New England Journal of Medicine trial	yes, both	yes	€2,000–25,000 depending on formulation and market
Azithromycin, chronic, three times weekly	FEV1 improved and exacerbations reduced in Pseudomonas-infected patients	yes	yes	€30–150. UNICEF indicative price October 2026: US$0.56 for six 250 mg tablets, about US$0.093 a tablet
Pancreatic enzyme replacement	Essential for nutrition in the roughly 85 per cent who are pancreatic insufficient, and nutritional status drives lung outcome	yes, listed as a medicine for cystic fibrosis, section 7, complementary	yes	hundreds to thousands of euro
Elexacaftor with tezacaftor and ivacaftor	FEV1 up about 14 percentage points; pulmonary exacerbations down 63 per cent; weight gain and sweat chloride fall; registry data	no	no	€250,000–300,000; United States list price above US$300,000, year not stated in the source; negotiated European prices

Intervention	Effect size	EML	Off-patent	Cost per patient-year
	show falling transplant rates and mortality			lower and confidential
Ivacaftor, gating mutations, about 4 to 5 per cent of patients	FEV1 up 10.6 percentage points, from the 2011 New England Journal of Medicine trial	no	no	€250,000–300,000, United States list price, year not stated in the source
Lumacaftor with ivacaftor, tezacaftor with ivacaftor	Smaller effects, FEV1 up 3 to 4 points, largely superseded	no	no	Hundreds of thousands of euro
Antibiotics for exacerbations, intravenous and oral	Standard care; exacerbations shortened and lung function preserved	yes, most agents	yes	tens to thousands of euro a course
Inhaled bronchodilator	Symptomatic; given before clearance and nebulised therapies	yes	yes	tens of euro
Fat-soluble vitamins A, D, E and K	Prevent deficiency	yes	yes	tens to hundreds of euro
Lung transplantation	Median survival eight to ten years post-transplant	n/a	n/a	hundreds of thousands of euro in the first year
High-dose ibuprofen, anti-inflammatory	Slowed FEV1 decline in a single-centre randomised trial; rarely used, very cheap, and never replicated at scale	yes	yes	tens to hundreds of euro

The price structure here is the starkest in either chapter. The drug that transformed the disease costs €250,000 to €300,000 a patient-year (United States list price, year not stated in the source) and is on patent. Against that, the entire traditional regimen — airway clearance technique, hypertonic saline, azithromycin, pancreatic enzymes, vitamins and antibiotics for exacerbations — costs on the order of hundreds to thousands of euro a patient-year at generic prices. That regimen is what delivered the rise in median survival from under five years to the mid-thirties, before any modulator existed. Modulators are accessible to a small fraction of the world’s patients, and most of the historical gain was made with cheap means and organised care.

Simple means. Airway clearance by physical technique needs no equipment at all: the active cycle of breathing technique, autogenic drainage, postural drainage and percussion. Cochrane finds short-term benefit with no one technique superior. Twice or three times daily, 20 to 30 minutes, for life. This plus nutrition is what raised survival from under five years to the mid-thirties before any modulator existed, and it remains daily practice.

Oscillating positive expiratory pressure devices — a flutter valve, an Acapella — cost tens of euro are reusable and need no power. Bubble positive expiratory pressure from a bottle and tubing is improvised and used where devices are unavailable. Exercise improves exercise capacity and is associated with slower lung function decline in cohort data; it is both therapy and clearance, and it is free.

Hypertonic saline at 7 per cent can be prepared from salt and sterile water at trivial cost, and it improves FEV1 and reduces exacerbations; a nebuliser needs power. Nutrition is food plus enzyme replacement: nutritional status is one of the strongest predictors of lung function and survival, and pancreatic enzymes are on the Essential Medicines List, off-patent, at hundreds to thousands of euro a year, and they are the one indispensable non-respiratory drug.

Azithromycin is the best effect-per-euro drug in the entry: tens to hundreds of euro a year, listed, off-patent, and it improves FEV1 and reduces exacerbations in Pseudomonas-infected patients. Salt supplementation in hot climates prevents hyponatraemic dehydration and is table salt. Avoiding second-hand smoke is free, with a measured effect on lung function.

Infection control is soap, water and segregation policy: handwashing, not sharing nebulisers, cleaning and drying equipment, avoiding contact with other patients. The Burkholderia cepacia epidemics of the 1990s showed the measured cost of getting this wrong. Newborn screening costs a few to tens of euro per infant

within an existing dried-blood-spot programme and improves nutrition and lung function through earlier diagnosis.

The hard limit, stated plainly. Diagnosis requires sweat chloride testing — a cheap, low-technology test at tens to hundreds of euro needing pilocarpine iontophoresis apparatus — or genetic testing. Chronic Pseudomonas management needs inhaled antibiotics and a nebuliser with power. The modulators, the drugs that changed the disease, cost €250,000 to €300,000 a year (United States list price, year not stated in the source) and are out of reach for the great majority of patients worldwide. For them the regimen is the pre-modulator one: clearance technique, nutrition, azithromycin, hypertonic saline and antibiotics for exacerbations. That regimen is cheap, it works, and it delivered most of the historical survival gain — and it leaves survival far below what modulators now achieve, and the gap is a matter of price.

Gaps. No global burden figure for cystic fibrosis exists in the retrieved GBD tables, and this entry is part of the seventeen-condition gap in this chapter's introduction; the roughly 105,000 diagnosed across 94 countries is a modelled figure, and under-diagnosis in Asia, Africa and Latin America is believed large and is unquantified. Why siblings with identical genotypes differ so much in lung disease is unexplained. Whether modulators started in infancy will prevent lung disease entirely is unknown, and it is the most important open question, answerable only by waiting. Roughly 10 per cent of patients have no modulator-responsive genotype and have gained nothing from the transformation. Long-term modulator durability, off-target effects over decades and effects on the many non-pulmonary manifestations are unknown. All registry data describing the survival transformation come from high-income countries, and outcomes elsewhere are largely unmeasured. Dornase alfa helps in cystic fibrosis and harms in non-cystic-fibrosis bronchiectasis — a standing warning against extrapolation between the two. High-dose ibuprofen slowed FEV1 decline in a single trial, costs tens to hundreds of euro a year, and was never replicated at scale; a cheap intervention left untested is itself a gap. Airway clearance, the foundation of care, has only short-term evidence and no technique shown superior, because physiotherapy trials cannot be blinded and have never been powered for hard endpoints. Modulator pricing of €250,000 to €300,000 a year (United States list price, year not stated in the source) against a cheap regimen that delivered most of the historical gain is the central unresolved equity question in the disease, and negotiated European prices are confidential, so even the real prices are not public.

> **Depth.** Starts in: the CFTR channel. Size: 10 nm†; depth −1.38. First complaint: about 12 months († from conception to early infancy); time depth 48.87. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Upper respiratory tract infections — the common cold, acute pharyngitis, acute sinusitis, laryngitis (ICD-11 CA00–CA0F)

What it is. Viruses infect the nose, throat and sinuses. The nose runs and blocks, the throat is sore, there is a cough and sometimes a fever for a few days. It gets better by itself.

Measured. Deaths in 2023: 27,100 (95 per cent uncertainty interval 6,100 to 77,300), down from 38,300 in 2000, a change of −29.4 per cent, from GBD 2023. That uncertainty interval spans more than a twelvefold range, the widest of any figure in either chapter, so the death count is effectively unknown.

No global incidence figure was retrieved. Commonly cited estimates are two to four colds per adult a year and six to ten per child a year in high-income countries, which makes upper respiratory infection the commonest acute illness of human beings and the leading cause of absence from work and school. GBD 2019 estimated roughly 17 billion incident episodes a year globally, more episodes than any other condition, and that is a model output. Otitis media deaths in 2023: 700 (300 to 1,700), down from 1,000 in 2000, a change of −35.3 per cent. Incidence is highest in young children, particularly those in day care, and declines through adulthood. Mortality is concentrated in infants, the very old and the immunocompromised.

Upper respiratory infection is the single largest driver of inappropriate antibiotic prescribing worldwide. Roughly 40 to 70 per cent of consultations in high-income primary care result in an antibiotic prescription,

for a condition that is overwhelmingly viral, and the figure exceeds 80 per cent in several low- and middle-income settings. For scale, about one in six laboratory-confirmed bacterial infections worldwide was resistant in 2023, resistance rose for over 40 per cent of monitored pathogen-antibiotic combinations between 2018 and 2023 at 5 to 15 per cent a year, and more than 4.7 million deaths were linked to bacterial antimicrobial resistance in 2021. Group A streptococcal pharyngitis accounts for roughly 5 to 15 per cent of sore throat in adults and 20 to 30 per cent in children — the minority in which antibiotics have a real indication.

Where it starts. Rhinoviruses cause roughly 30 to 50 per cent of colds, with over 160 serotypes, which is why immunity does not accumulate usefully. Coronaviruses including the four endemic seasonal ones and SARS-CoV-2, influenza A and B, respiratory syncytial virus, parainfluenza, human metapneumovirus, adenovirus, enteroviruses and bocavirus all contribute.

Group A Streptococcus is the important bacterial cause of pharyngitis and the one that causes rheumatic fever if untreated: roughly 0.3 to 3 per cent of untreated streptococcal sore throats lead to acute rheumatic fever in susceptible populations. Other bacterial causes: Fusobacterium necrophorum giving Lemierre syndrome, group C and G streptococci, Mycoplasma, and diphtheria, now rare at 4,000 deaths in 2023, down 82.8 per cent from 2000.

Transmission is by respiratory droplets, aerosols, and contaminated hands and surfaces. Rhinovirus survives on surfaces for hours and self-inoculation via the hands to the nose and eyes is a major route, which is why handwashing works. Risk factors: young age, day care and school attendance, household crowding, winter season, psychological stress — a reproducible finding in experimental inoculation studies — sleep deprivation, smoking and second-hand smoke, and vitamin D deficiency, contested. Cold exposure itself has partial experimental support: nasal cooling impairs mucociliary clearance and innate immune responses, and rhinovirus replicates better at 33 °C than at 37 °C. It does not cause the infection; there must be a virus.

Why some people infected with the same inoculum develop symptoms and others do not is not fully explained — in experimental rhinovirus inoculation roughly 25 to 30 per cent of infected volunteers remain asymptomatic†. Why psychological stress reproducibly increases susceptibility in controlled inoculation studies is not mechanistically settled. There is still no effective antiviral for rhinovirus after seventy years of effort, and no prospect of a vaccine given the number of serotypes. Why some people develop a post-viral cough lasting weeks is not explained.

Cure status. SELF-LIMITING. This is the clearest SELF-LIMITING classification in either chapter, and the classification itself is the clinically important fact. Group A streptococcal pharyngitis, diphtheria, epiglottitis, quinsy, Lemierre syndrome and retropharyngeal abscess: CURABLE with antibiotics and, where needed, drainage and airway protection.

The common cold resolves in seven to ten days without any treatment, and the cough can persist two to three weeks; no treatment shortens it meaningfully. Acute rhinosinusitis resolves within two weeks without antibiotics in roughly 70 to 80 per cent of cases. Cochrane gives antibiotics a number needed to treat of roughly 11 to 15 for cure at seven to fourteen days, against substantial adverse-effect rates, with a number needed to harm of roughly 8 for any adverse effect. Acute sore throat resolves spontaneously in the great majority, and antibiotics shorten it by roughly sixteen hours on average across all comers, per Cochrane — a negligible clinical benefit. Influenza is SELF-LIMITING, with oseltamivir shortening symptoms by roughly a day.

The exception where treatment matters is group A streptococcal pharyngitis in populations at risk of rheumatic fever. Penicillin within nine days reduces first-episode rheumatic fever by roughly 70 to 80 per cent, and Cochrane gives antibiotics for sore throat a relative risk of roughly 0.27 for acute rheumatic fever; it also reduces quinsy and otitis media. In high-rheumatic-fever-incidence populations the calculation is entirely different from high-income primary care, and both must be stated.

Prevention.

Handwashing with soap — STRONG, with large measured effects. Cochrane reviews of physical interventions find handwashing reduces respiratory infection transmission, and the Karachi cluster-

randomised trial found handwashing promotion halved pneumonia incidence in children under five. Soap and water.

Influenza vaccination — MODERATE. Laboratory-confirmed influenza reduced by roughly 40 to 60 per cent in seasons with a good match, with hospitalisation and death reduced in older adults. *COVID-19 vaccination — STRONG* for severe disease.

Masks — MODERATE and CONTESTED, and both positions must be printed. The 2023 Cochrane review of physical interventions concluded that wearing masks in the community probably makes little or no difference to influenza-like illness, with a pooled relative risk of about 0.95. That conclusion was heavily criticised for pooling heterogeneous trials and for low adherence in the included studies, and Cochrane's own editor-in-chief publicly qualified it. Observational and mechanistic evidence supports source control. This is a genuine and unresolved dispute.

Avoiding face-touching and self-inoculation — MODERATE, mechanistically supported. *Ventilation of indoor spaces — MODERATE*, with good mechanistic and modelling support and limited randomised evidence. *Staying home when symptomatic — MODERATE*, with little randomised evidence and strong mechanistic plausibility. *Smoking cessation — MODERATE*. *Reducing day-care group size — WEAK*.

Vitamin D supplementation — CONTESTED. The individual-participant meta-analysis published in the BMJ in 2017 found a small protective effect, adjusted odds ratio 0.88, largest in those with baseline 25-hydroxyvitamin D below 25 nmol/L; the subsequent large trials VITAL and D-Health were null for respiratory infection. Both are printed.

Zinc lozenges — CONTESTED. Some meta-analyses find cold duration reduced by roughly one to two days with high-dose zinc acetate or gluconate started within 24 hours; others find the evidence too heterogeneous and the trials too small, and adverse taste and nausea are common.

Vitamin C — WEAK or negative for prevention in the general population, with one reproducible subgroup finding. Cochrane finds no reduction in cold incidence with routine supplementation, a roughly 8 per cent reduction in duration in adults, and a consistent halving of incidence in people undergoing extreme physical exertion — marathon runners, soldiers, skiers.

Probiotics — WEAK; Cochrane suggests a small reduction in episodes at low certainty. *Echinacea, garlic, honey, nasal saline and gargling — WEAK*, with honey having moderate evidence for cough symptom relief in children over one year.

Treatment.

Intervention	Effect size	EML	Off-patent	Cost
Nothing, meaning watchful waiting with explanation and a safety net	The correct treatment for the great majority. Delayed-prescription strategies reduce antibiotic use by roughly 60 to 80 per cent with no increase in complications or dissatisfaction, per Cochrane	n/a	n/a	**Nothing**
Paracetamol or ibuprofen	Fever, headache, sore throat and malaise reduced; they do not shorten the illness	yes, both	yes	a few to a few euro a course
Nasal saline irrigation or spray	Modest symptom relief; the UK primary-care trial found nasal irrigation helped while steam did not	n/a	n/a	Near zero home-made
Honey, for cough in children over one year	Cochrane: better than no treatment and probably better than diphenhydramine for cough symptoms; comparable to dextromethorphan	no	n/a	a few euro
Penicillin or amoxicillin for group A streptococcal pharyngitis	Sore throat shortened by about sixteen hours across all comers; acute rheumatic fever reduced about 70 to 80 per cent, relative risk about 0.27, and quinsy and	yes; amoxicillin is listed first-choice for pharyngitis	yes	a few to a few euro a course

Intervention	Effect size	EML	Off-patent	Cost
	otitis media reduced			
Antibiotics for acute rhinosinusitis	Number needed to treat 11 to 15 for cure at seven to fourteen days; number needed to harm about 8 for adverse effects; 70 to 80 per cent resolve spontaneously	yes	yes	a few to tens of euro a course
Topical or oral decongestant	Short-term relief of nasal blockage; rhinitis medicamentosa with topical use beyond five to seven days; not for young children	partly	yes	a few to tens of euro
Zinc lozenges, high dose within 24 hours	Duration reduced by roughly one to two days in some meta-analyses and null in others; taste and nausea common	no	yes	a few to tens of euro a course
Oseltamivir, influenza	Symptoms shortened by roughly a day; the mortality benefit in hospitalised patients is observational and contested	yes	yes	a few to tens of euro a course
Corticosteroids, a single dose for severe sore throat	Cochrane: complete pain resolution at 24 hours increased, relative risk 2.2, as an adjunct	yes	yes	a few to a few euro
Antitussives, dextromethorphan or codeine	Little or no benefit over placebo for acute cough, per Cochrane; codeine is ineffective and not for children	partly	yes	a few to tens of euro
Antihistamines as cold remedies	A small short-term effect on rhinorrhoea in adults; no benefit in children, and sedating agents carry harm	yes	yes	a few to tens of euro
Antibiotics for the common cold	**No benefit and definite harm**, per Cochrane	—	—	—
Vitamin C started after onset	No consistent benefit when started after symptoms begin	no	yes	—
Drainage and airway management for quinsy, epiglottitis or abscess	Life-saving in the dangerous minority	n/a	n/a	Surgical

Simple means. This is the condition where simple means are not merely adequate but are the whole of correct care.

Doing nothing, explained well, is the intervention, and it is a conversation. Delayed or no prescription reduces antibiotic use by 60 to 80 per cent with no increase in complications. It costs nothing and it addresses the largest single source of antibiotic overuse in the world.

Handwashing with soap halved childhood pneumonia incidence in the Karachi cluster-randomised trial and reduces respiratory transmission generally. Soap. Rest, fluids and time: the illness resolves in seven to ten days. Paracetamol or ibuprofen costs a few to a few euro both listed and off-patent, and treats the symptoms that matter.

Nasal saline irrigation is home-made from salt, baking soda and boiled or distilled water, and the UK primary-care trial found irrigation helped and steam did not. Near-zero cost, with the same amoebic-infection warning about untreated tap water as in the rhinitis entries.

Honey for cough in children over one year is better than no treatment and probably better than an antihistamine, per Cochrane. A spoon of honey. Not for infants under one year, because of botulism risk. Salt-water gargling has low-quality evidence for symptom relief and costs nothing.

Steam inhalation does not help, and it is the most popular home remedy for the condition. It was found not to help in the UK trial and in Cochrane review, and it carries a real scald risk in children. That is printed.

Penicillin for streptococcal sore throat where rheumatic fever is endemic costs a few to a few euro an oral course, is listed and off-patent, and prevents 70 to 80 per cent of first rheumatic fever episodes. In a

population with endemic rheumatic fever, this cheap tablet for a self-limiting illness is one of the highest-value interventions in medicine, while in a high-income setting the same prescription for the same illness is usually unnecessary. The Centor and McIsaac scores and rapid antigen tests, at a few euro each, help select patients, and in high-incidence settings treating on clinical grounds is the recommended approach.

Recognising the dangerous minority is free and it is the whole of the safety net: drooling, stridor, trismus, unilateral swelling, inability to swallow, a stiff neck or a toxic appearance indicate epiglottitis, quinsy, abscess or Lemierre syndrome. Staying home, covering coughs and ventilating rooms are free and mechanistically sound.

The hard limit, which is unusually mild here. Distinguishing streptococcal from viral pharyngitis benefits from a a few euro rapid antigen test or a throat swab, and the dangerous complications need imaging and surgical access. For the overwhelming majority of upper respiratory infection, nothing is required at all, and the main clinical skill is not treating it.

Gaps. GBD gives 27,100 deaths with an uncertainty interval of 6,100 to 77,300 for 2023 — more than a twelvefold range, the widest of any figure in either chapter — so the death count is effectively unknown. No global incidence figure was retrieved, and the roughly 17 billion episodes figure is a model output. Masks: Cochrane concluded little or no difference and the conclusion was heavily criticised and publicly qualified by Cochrane itself; unresolved, politically charged, and both positions printed. Vitamin D: the individual-participant meta-analysis positive at odds ratio 0.88, VITAL and D-Health null; unresolved. Zinc: meta-analyses disagree on whether duration is reduced and by how much. Vitamin C: no prevention benefit in general populations and a consistent halving of incidence in extreme-exertion subgroups, a reproducible and unexplained subgroup finding. Why 25 to 30 per cent of experimentally infected volunteers stay asymptomatic is unexplained. Why psychological stress reproducibly increases susceptibility is not mechanistically settled. No antiviral for rhinovirus exists after seventy years, and no vaccine is feasible given more than 160 serotypes. Antibiotic prescribing rates of 40 to 70 per cent in high-income primary care and over 80 per cent in some low- and middle-income settings for an overwhelmingly viral condition represent the largest gap between evidence and practice in either chapter. The rheumatic-fever calculation inverts the antibiotic decision between high- and low-incidence populations, and guidelines written for one are routinely applied in the other. Post-viral cough lasting weeks has no established mechanism and no effective treatment.

> **Depth.** Starts in: rhinovirus. Size: 30 nm†; depth −0.38. First complaint: about 42 hours ([W] common cold 1–3 days); time depth 44.00. One untreated course: about 7 days ([B] a few days; † about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book’s status: SELF-LIMITING, with CURABLE for a named stratum. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

What no longer holds

Each item here is a practice that this chapter’s own best evidence contradicts. They are collected because a reference work that scatters them across sixty pages hides them.

Immunosuppression in idiopathic pulmonary fibrosis. PANTHER-IPF, testing prednisone with azathioprine and N-acetylcysteine, was stopped early for increased death and hospitalisation, with mortality of 8 against 1 per cent. The standard treatment for decades made the disease worse. This is the heaviest reversal in the chapter, and the reason the diagnostic distinction between idiopathic fibrosis and the immunosuppression-responsive interstitial diseases carries a demonstrated mortality cost.

Sodium restriction in heart failure. SODIUM-HF randomised 806 patients to below 1,500 mg of sodium a day and found no reduction in death, cardiovascular hospitalisation or emergency visits, hazard ratio 0.89, p=0.53, with a small quality-of-life improvement. Decades of standard advice rest on physiology rather than on this trial.

Adaptive servo-ventilation in heart failure. The SERVE-HF trial tested adaptive servo-ventilation for central sleep apnoea in heart failure with reduced ejection fraction and found increased cardiovascular

mortality, and the therapy is now contraindicated in that population. This is the clearest case in either chapter of a device therapy that was withdrawn because the trial found harm rather than absence of benefit.

Beta blockers after myocardial infarction with preserved ejection fraction. REDUCE-AMI, with 5,020 patients in 2024, found no benefit of beta blockade after infarction with preserved ejection fraction, hazard ratio 0.96. The classical 20 to 25 per cent mortality benefit comes from the pre-reperfusion trials, and guidelines have not fully absorbed the change.

Targeted hypothermia after cardiac arrest. TTM2, with 1,900 patients in 2021, found hypothermia at 33 °C gave no mortality benefit against normothermia with fever avoidance, hazard ratio 1.04. Practice has shifted to fever avoidance, which needs ice packs and fans rather than a tens of thousands of euro cooling device.

Revascularisation for stable coronary disease, as a way of preventing death or infarction. COURAGE and ISCHEMIA found no reduction in death or myocardial infarction against optimal medical therapy alone. Intervention relieves angina. It does not do the other thing it is widely believed to do.

Compression stockings after stroke, and after deep vein thrombosis for post-thrombotic syndrome. CLOTS-1, with 2,518 stroke patients, found no benefit from thigh-length stockings and increased skin breaks, 5 against 1 per cent. The SOX trial, with 806 patients, found no prevention of post-thrombotic syndrome, 14.2 against 12.7 per cent, against earlier smaller trials reporting roughly a 50 per cent reduction. The same garment remains beneficial in surgical thromboprophylaxis, with a Cochrane odds ratio of about 0.35, so the garment is not the error; the population is.

House dust mite avoidance in asthma and in allergic rhinitis. Cochrane found no clear benefit of physical or chemical mite-control measures for either condition. The advice is near-universal.

Steam inhalation for upper respiratory and sinus symptoms. Cochrane and the large UK primary-care trial found no benefit, while nasal irrigation did help. Steam is the commoner home remedy and it is the one that does not work, and it carries a scald risk in children.

Antifungals in chronic rhinosinusitis. Cochrane found no benefit, against a once-dominant hypothesis.

Corticosteroids in acute rheumatic carditis. Cochrane found no clear reduction in cardiac valve damage at one year, relative risk 0.87, against long-standing practice.

Dornase alfa in non-cystic-fibrosis bronchiectasis. A randomised trial showed worse FEV1 and more exacerbations. The same drug improves FEV1 by 5 to 6 per cent and reduces exacerbations by about 30 per cent in cystic fibrosis. The pair is a standing warning against extrapolating between superficially similar diseases.

Antibiotics for the common cold. No benefit and definite harm, per Cochrane, in a condition that receives an antibiotic prescription in 40 to 70 per cent of high-income primary care consultations and over 80 per cent in some low- and middle-income settings.

Activity restriction after pneumothorax. Widely advised and not evidence-based: most episodes occur at rest.

Intervention for unruptured arteriovenous malformations. ARUBA, with 223 patients, found intervention worse than medical management, hazard ratio 0.27 favouring medical management.

Early repair of small abdominal aortic aneurysms. The UK Small Aneurysm Trial, with 1,090 patients at 4.0 to 5.5 cm, and ADAM, with 1,136 patients, both found no survival advantage from early repair against surveillance. The 5.5 cm threshold is trial-derived rather than arbitrary — and the threshold for women was derived in male cohorts and is not evidence-based.

Mobilising stroke patients as early and as much as possible. AVERT, with 2,104 patients, found very early and very high-dose mobilisation was worse than usual early care, odds ratio 0.73 for a favourable outcome. Early mobilisation remains core stroke unit care; “earlier and more” does not follow from it.

Corticosteroids in tuberculous pleural effusion. No outcome benefit, and not recommended.

Immediate angiography after cardiac arrest without ST elevation. COACT and TOMAHAWK were both null, against prior practice.

Short-acting beta-agonist monotherapy in asthma. Associated with increased mortality; the New Zealand fenoterol epidemic and the SMART trial, with 26,355 patients, established it, and GINA no longer recommends reliever-only treatment at any severity.

Pulmonary vasodilators outside group 1 pulmonary hypertension. Riociguat in group 3 disease was stopped for increased mortality in RISE-IIP, and sildenafil in pulmonary fibrosis and in heart failure with preserved ejection fraction was null. The harm outside group 1 is widely under-appreciated.

Recruitment manoeuvres with pressure titration in acute respiratory distress syndrome. ART, with 1,010 patients, found increased mortality, hazard ratio 1.20.

Mechanical chest compression devices in cardiac arrest. LINC and PARAMEDIC found them no better than manual compressions, at tens of thousands of euro a device.

Advanced wound dressings under compression for venous ulcers. Cochrane found no dressing type superior to simple low-adherent dressings beneath compression. The market is large and the demonstrated advantage is absent.

One final item belongs here, and it is not a practice but a source. The Management Sciences for Health International Medical Products Price Guide, which several of this chapter’s price figures were drawn from, published its last edition in 2017 and its website was retired after 30 June 2024. Any citation to it must be dated 2017 at the latest and labelled as such. The UNICEF Supply Catalogue is the working substitute used in this chapter, and it returns different indicative prices for the same material number on different pages of the same catalogue, so its figures are printed as indicative and dated rather than as prices.

Chapter 16 — The Gut, the Frame and the Waterworks

ICD-11 Chapter 13: diseases of the digestive system

ICD-11 Chapter 15: diseases of the musculoskeletal system or connective tissue

ICD-11 Chapter 16: diseases of the genitourinary system

J. Konstapel, Constable Research, Leiden Version 1.0

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Introduction

Three ICD chapters are gathered here. They have nothing in common anatomically. They have one thing in common that matters to this book: they carry the largest burden of disability in the world, almost none of the mortality, and the widest gap between what is known and what is delivered. Fifty-five entries follow, covering sixty-two named conditions.

Diverticular disease is the entry that prompted this book. It gets the longest treatment in this chapter and the reason is not elaborated further.

The clearest cheap cure in the chapter is *Helicobacter pylori* eradication. Two antibiotics and an acid blocker for ten to fourteen days clear the organism in 70 to 94 per cent of courses, depending on the regimen and on local resistance. The drug cost of that course is a few to tens of US dollars at generic prices. What it buys is not symptom relief. It cures the ulcer diathesis, with recurrence falling from about 60 to 70 per cent a year to under 5 per cent. It removes a Group 1 carcinogen responsible for 75 to 90 per cent of non-cardia gastric cancer, a disease that killed about 660,000 people in 2022. And it cures gastric MALT lymphoma outright — a malignancy abolished by an antibiotic course, which is why the cure-status rules in Part 0 name it as the type case for CURABLE.

The two largest burdens in this chapter are low back pain and knee osteoarthritis, and in both of them exercise is the best-supported non-drug treatment. Low back pain is the single largest cause of years lived with disability in the world. The GBD 2021 condition paper gives 619 million prevalent cases in 2020, with a 95 per cent uncertainty interval of 554 to 694 million; 69.0 million years lived with disability (47.9 to 88.9); 8.1 per cent of all-cause YLDs; rank one globally; and a projection of 843 million cases by 2050 (759 to 933). The WHO low back pain fact sheet of 19 June 2023 carries the same 619 million and the same 843 million by 2050. Deaths: zero. The entire burden is disability, which is why the condition dominates the YLD table and is absent from every mortality table.

Against that burden, the trial record on the drugs is poor. Paracetamol was found identical to placebo in PACE, 1,643 patients, with a median seventeen days to recovery in both arms. Opioids were no better than non-opioid analgesics in SPACE and no better than placebo in OPAL, with worse pain at one year in both. Exercise combined with education reduces recurrence, with a pooled relative risk of about 0.55 to 0.65. In knee and hip osteoarthritis the standardised mean difference for exercise on pain is about 0.4 to 0.6 against about 0.3 to 0.4 for oral NSAIDs, and weight loss adds a dose-response that no drug matches. Several

standard treatments in this chapter failed their own trials and are still performed in volume. They are listed at the end of the chapter.

A note on the prices in this chapter

Generic drug costs here are order-of-magnitude and vary by a factor of ten to a hundred between markets. They derive from international generic tender prices, Indian and UK generic prices, and United States retail ranges. Where the source of a price could not be opened, the price carries a dagger.

One source needs naming. The MSH / WHO *International Medical Products Price Guide*, long the standard international reference, is no longer a live product: its last edition is 2017 and its website was retired after 30 June 2024. Any price traceable to it is a 2017 price. The UNICEF Supply Catalogue is the working substitute, and it returns different indicative prices for the same material number on different pages, so its figures are indicative and dated rather than prices.

ICD-11 Chapter 13 — Diseases of the digestive system

Gastro-oesophageal reflux disease

What it is. Stomach contents move back up into the oesophagus. The lining is not built for acid, so it burns and may erode. The diagnosis rests on symptoms or on visible mucosal damage at endoscopy.

Measured. Global prevalence of at least weekly symptoms is 13.3 per cent of adults, from a systematic review of 102 studies (Eusebi, *Gut* 2018)†. The geographic spread in that review is wide: 18.1 per cent in North America against 8.5 per cent in East Asia†. Prevalence rises with age and is higher above fifty.

GBD does not model reflux disease as a separate cause, so there is no DALY figure for it; the burden enters through Barrett oesophagus and oesophageal adenocarcinoma. Directly attributable deaths are negligible. Mortality enters through adenocarcinoma, for which reflux is the principal risk factor.

Where it starts. Obesity is dose-dependent. Each unit of BMI raises risk, and BMI above 30 roughly doubles symptom risk against normal weight (Hampel, *Annals of Internal Medicine* 2005). Hiatal hernia is strongly associated and mechanically direct, through loss of the diaphragmatic pinch, and is present in a large fraction of erosive cases.

Smoking, pregnancy, late large meals and several drug classes — calcium channel blockers, nitrates, anticholinergics — reduce lower oesophageal sphincter tone. Twin studies give a heritability of roughly 31 per cent for reflux symptoms (Mohammed, *Gut* 2003)†.

What is not known is why symptom severity and visible mucosal damage correlate so poorly. Many with severe symptoms have a normal endoscopy, which is non-erosive reflux disease; many with erosions have few symptoms. The determinants of oesophageal pain sensitivity are unexplained, as is why only a small minority progress to Barrett oesophagus.

Cure status. CONTROLLABLE. Acid suppression reliably relieves symptoms and heals erosions, but the mechanical defect persists and symptoms return on stopping in the majority. Fundoplication is the nearest thing to a cure and gives durable control in most operated patients, but a substantial minority resume acid suppression within ten years, and the operation carries dysphagia and gas-bloat effects.

Prevention. Weight loss: MODERATE. Prospective cohort data show symptom reduction with weight loss, dose-dependently (Jacobson, *NEJM* 2006). Raising the head of the bed and avoiding late meals: WEAK. Smoking cessation: WEAK. Elimination of specific trigger foods — coffee, chocolate, citrus, mint: CONTESTED. Widely advised and poorly supported by trial evidence; the effects appear individual.

Treatment. Proton pump inhibitors heal erosive oesophagitis in about 80 to 85 per cent at eight weeks, against about 50 per cent for H2 blockers and about 25 per cent for placebo (Chiba, *Gastroenterology* 1997). Omeprazole is on the WHO EML, section 17.1, with reflux disease among its listed indications; off-patent; roughly US$3 to 25 per patient-year at international generic prices.

H2 receptor antagonists, now famotidine since ranitidine was withdrawn in many markets over NDMA contamination, are less effective than PPIs. Off-patent; a few to tens of US dollars a year. Alginate and antacid preparations help breakthrough symptoms with no mucosal healing claim. Laparoscopic fundoplication is for PPI-refractory or PPI-intolerant disease with confirmed reflux.

On PPI safety, two bodies of evidence disagree. Observational studies associate long-term use with fracture, kidney disease, enteric infection and B12 deficiency. The COMPASS randomised safety analysis, 17,598 participants over a median three years (Moayyedi, *Gastroenterology* 2019), found no significant excess for any of these except enteric infection. Both are printed. The observational signals are probably substantially confounded.

Simple means. Weight loss where overweight is the single most effective non-pharmacological measure. Head-of-bed elevation by about 20 cm and left-lateral sleeping produce a small but measurable reduction in

nocturnal acid exposure. Not eating within three hours of lying down; smaller meals; smoking cessation; loosening tight waistbands. None of these requires an industrial supply chain.

Gaps. Non-erosive reflux disease is poorly understood and responds less well to acid suppression. Long-term PPI safety remains disputed between observational and randomised evidence. No intervention has been shown to prevent progression to adenocarcinoma. Trigger-food advice is near-universal clinically and near-unsupported evidentially.

> **Depth.** Starts in: the lower oesophageal sphincter. Size: 3 cm†; depth +12.19. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Peptic ulcer disease and Helicobacter pylori

What it is. An open sore in the lining of the stomach or duodenum. Most are caused by *H. pylori* infection or by NSAIDs. The same infection causes gastric cancer.

Measured. About 4.4 billion people are infected with *H. pylori*, some 43 to 50 per cent of humanity (Hooi, *Gastroenterology* 2017; Zamani 2018). The geographic gradient is steep: above 70 per cent in parts of Africa, South America and South Asia; below 30 per cent and falling across much of Western Europe, North America and Australia.

Peptic ulcer disease causes some 270,000 to 300,000 deaths a year; GBD 2019 gave 236,000 deaths and about 8 to 9 million DALYs†. Gastric cancer accounted for about 970,000 new cases and about 660,000 deaths in 2022 (GLOBOCAN 2022, IARC). *H. pylori* is responsible for roughly 75 to 90 per cent of non-cardia gastric cancer, and IARC classifies it as a Group 1 carcinogen.

Ulcer incidence and mortality have fallen steeply in high-income countries across four decades, tracking the fall in *H. pylori* prevalence and the rise of acid suppression. The infection is acquired almost entirely in childhood, so adult prevalence reflects childhood conditions decades earlier.

Where it starts. *H. pylori* infection is the dominant cause, found in about 90 per cent of duodenal and 70 to 80 per cent of gastric ulcers in populations before widespread eradication. NSAIDs including aspirin raise ulcer complications roughly fourfold and are the main cause in *H. pylori*-negative patients. The two are at least additive and probably synergistic. Smoking raises risk and impairs healing; alcohol is weaker and less consistent.

Lifetime gastric cancer risk in an infected person is about 1 to 3 per cent†. The infection is therefore necessary for most cases and far from sufficient. Transmission is faecal-oral and oral-oral, mostly within households in childhood, and crowding and absent sanitation are the strongest structural determinants.

What is not known is why only 1 to 3 per cent of infected people develop cancer and 10 to 15 per cent† develop ulcers while most stay asymptomatic for life. Host genetics, strain virulence and the rest of the gastric microbiome each explain part, none decisively. Nor is it established whether population-wide eradication alters gastric microbial ecology in ways that matter. Stress and diet, long blamed, are not established causes.

Cure status. CURABLE. A ten to fourteen day course of two antibiotics with a PPI eradicates the organism in 70 to 94 per cent of courses depending on regimen and local resistance, and eradication cures the diathesis: ulcer recurrence falls from about 60 to 70 per cent a year to under 5 per cent. An NSAID-caused ulcer is curable by stopping the NSAID and giving acid suppression.

Prevention. *H. pylori* eradication to prevent gastric cancer: STRONG. Meta-analyses of randomised trials show roughly a one-third reduction in gastric cancer incidence, pooled relative risk about 0.54 to 0.68 depending on the analysis (Ford, *BMJ* 2014, and Cochrane updates). The Shandong and Linqu County trials in China, with Korean and Japanese studies, are the backbone of that evidence. The effect is larger when eradication precedes established atrophic change, which means earlier in life.

Sanitation and clean water: STRONG as a structural matter. This is what drove the historical collapse in prevalence in high-income countries, demonstrated by ecological and cohort rather than randomised evidence.

Avoiding unnecessary NSAIDs, and co-prescribing a PPI where NSAIDs are needed in at-risk patients: STRONG. PPI co-therapy substantially reduces endoscopic and clinical ulcer complications. Not smoking: MODERATE. No vaccine is in routine use; candidates have shown partial efficacy and none is licensed.

Treatment. The eradication regimens are the centre of this entry.

Regimen	Composition	Duration	Cure rate
Standard triple	PPI + amoxicillin 1 g bd + clarithromycin 500 mg bd	14 d	70–85%, falling
Bismuth quadruple	PPI + bismuth + tetracycline + metronidazole	10–14 d	85–94%
Concomitant quadruple	PPI + amoxicillin + clarithromycin + metronidazole	14 d	85–90%
Levofloxacin triple	PPI + amoxicillin + levofloxacin	10–14 d	75–85%

Cure rates per Malfertheiner, Maastricht VI/Florence consensus, *Gut* 2022, and the ACG 2017 and 2024 guidance. Standard triple therapy is now below an acceptable threshold where clarithromycin resistance exceeds 15 per cent, and bismuth quadruple is preferred there. Levofloxacin triple is a rescue regimen against rising quinolone resistance.

Drug by drug. Omeprazole, or any PPI: EML yes; off-patent; a few to tens of US dollars a year, and a fourteen-day course is a few cents to a few dollars. Amoxicillin: EML yes, Access group — the EML amoxicillin record does not itself list *H. pylori* as an indication; off-patent; a few US dollars per course. Clarithromycin: EML yes, Watch group, and its EML record *does* list "*Helicobacter pylori* associated gastric ulcer" as an indication; off-patent; a few to tens of US dollars per course. Metronidazole: EML yes, Access group; off-patent; a few US dollars per course. Tetracycline or doxycycline: off-patent; a few US dollars per course. Bismuth subsalicylate or subcitrate: off-patent; a few to tens of US dollars per course; not on the core EML.

The total drug cost of a curative course is therefore a few to tens of US dollars at generic prices. That cures a condition which causes a cancer killing about 660,000 people a year, and the cost-effectiveness literature on screen-and-treat in high-incidence populations is accordingly favourable.

Ulcer healing itself: a PPI for four to eight weeks heals over 90 per cent of uncomplicated ulcers. A bleeding ulcer needs endoscopic haemostasis with high-dose intravenous PPI; see the gastrointestinal bleeding entry.

Simple means. Clean water, sewage disposal, handwashing and reduced household crowding are the measures that historically eliminated most transmission, and they need no supply chain beyond public works. Not taking NSAIDs that are not needed. Smoking cessation.

The honest limit is sharp here. Diet, milk and bland food, the standard advice for most of the twentieth century, do not heal ulcers. Nothing in the simple-means category cures an established infection; that needs the antibiotics, which are cheap but industrial.

Gaps. Rising antibiotic resistance, clarithromycin especially, is eroding first-line cure rates, and the geographic resistance map is patchy. Whether to screen and treat whole populations in low-incidence countries is unsettled: the benefit is smaller, and the effect of mass eradication on the gastric microbiome and on oesophageal adenocarcinoma risk is debated. Sources disagree on whether eradication reduces gastric cancer mortality as clearly as it reduces incidence, because the trials are underpowered for mortality. There is no licensed vaccine. Susceptibility-guided against empirical therapy remains an open cost question.

> **Depth.** Starts in: Helicobacter pylori. Size: 3 µm†; depth +3.81. First complaint: about 20 years († decades after infection); time depth 51.60. One untreated course: no number († recurring).

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Functional dyspepsia

What it is. Persistent pain or fullness in the upper abdomen with no ulcer, no cancer and no other structural cause found on investigation. It is diagnosed by symptom pattern after exclusion.

Measured. Global prevalence is about 7 to 8 per cent under strict Rome IV criteria and about 20 per cent under the broader Rome III definitions (Sperber, *Gastroenterology* 2021, Rome Foundation global study of 73,076 adults across 33 countries). It is not a separate GBD cause and has no DALY figure. There are no direct deaths. It is more common in women, and prevalence falls slightly with age in some series. Apparent geographic differences track the survey instrument as much as true variation.

Where it starts. Prior acute gastroenteritis raises risk several-fold, giving post-infectious dyspepsia. *H. pylori* infection is a modest contributor and eradication helps a minority. Psychological comorbidity — anxiety, depression, somatisation — is strongly and bidirectionally associated, and the direction of causation is not settled. Female sex, smoking, NSAID use and early-life adversity all contribute. Duodenal eosinophilia and impaired gastric accommodation are measurable in subsets. Heritability is not well quantified; association studies implicating GNB3 and serotonin transporter polymorphisms have not been robustly replicated.

What is not known is the cause. This is a symptom-defined entity and possibly several distinct conditions pooled: impaired accommodation, hypersensitivity, delayed emptying, immune activation, central pain processing. No biomarker identifies the subsets reliably, and the Rome subdivisions — postprandial distress against epigastric pain — overlap heavily in practice.

Cure status. RELIEF ONLY, with one exception named. *H. pylori* eradication produces durable cure in a modest subset of infected patients, with a number needed to treat of about 12 to 14 for symptom improvement at twelve months (Ford, Cochrane). Otherwise the condition fluctuates over years and no treatment reliably eliminates it.

Prevention. No established primary prevention: CONTESTED, effectively absent. Avoiding unnecessary antibiotics and treating gastroenteritis adequately may reduce post-infectious cases: WEAK, indirect. Not smoking: WEAK.

Treatment. *H. pylori* test and treat, number needed to treat about 12 to 14; the only option with a cure claim, at the costs given in the ulcer entry, a few to tens of US dollars a course. PPIs, number needed to treat about 10 to 11 against placebo for symptom relief (Cochrane); omeprazole EML yes, off-patent, a few to tens of US dollars a year.

Low-dose tricyclic antidepressants, amitriptyline 10 to 50 mg, are effective in trials with a number needed to treat of about 6 to 8 in some meta-analyses; amitriptyline is EML-listed as an antidepressant, off-patent, a few to tens of US dollars a year. Prokinetics — domperidone, metoclopramide, itopride — give modest benefit; domperidone carries QT and cardiac-death signals and metoclopramide tardive dyskinesia with prolonged use. Both off-patent and cheap. Psychological therapy, CBT and hypnotherapy, shows demonstrated benefit in small unblinded trials. SSRIs are not effective here, in contrast to the tricyclics.

Simple means. Smaller, more frequent, lower-fat meals give modest measured benefit. Reducing alcohol, coffee and smoking. Regular physical activity and sleep: weak evidence, no harm. Low-FODMAP approaches are evidenced for IBS rather than dyspepsia, and overlap is common enough that some patients benefit. Reassurance and explanation after a negative investigation measurably reduces re-consultation.

Gaps. The entity is heterogeneous and its diagnostic criteria are consensus artefacts rather than biology. Placebo response in trials runs at 30 to 40 per cent†, which makes modest drug effects hard to interpret. Overlap with IBS and with reflux disease is extensive and inconsistently handled between studies. No biomarker, no prevention, no reliable subtyping.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Irritable bowel syndrome

What it is. Recurrent abdominal pain with altered bowel habit — diarrhoea, constipation or both — without structural disease. It is diagnosed on symptom criteria.

Measured. Global prevalence is 4.1 per cent by Rome IV criteria and 10.1 per cent by Rome III in the Rome Foundation global study, 73,076 adults across 33 countries (Sperber, *Gastroenterology* 2021). Earlier meta-analyses gave about 11 per cent pooled (Lovell and Ford, *Clinical Gastroenterology and Hepatology* 2012). Both are printed; the discrepancy is largely criteria-driven and the two figures differ by a factor of about 2.5.

It is not a separate GBD cause with its own DALY total. There are no directly attributable deaths. It is about 1.5 to 2 times more common in women, with onset typically before fifty and prevalence declining in older age. It is found on every continent surveyed, and between-country differences in the Rome global study were modest once the instrument was held constant.

Where it starts. Post-infectious IBS develops in about 10 per cent of those with bacterial enteritis, with a pooled odds ratio of about 4 (Klem, *Gastroenterology* 2017). Female sex roughly doubles risk. Psychological comorbidity — anxiety, depression, and especially early-life adversity and abuse history — is strongly and bidirectionally associated. Antibiotic exposure contributes, and there is evidence for altered microbiota that is not consistent enough to define a signature.

Twin studies give a heritability of roughly 20 to 25 per cent, which is low, and shared-environment effects rival the genetic ones (Mohammed, *American Journal of Gastroenterology* 2005; Bengtson 2006). GWAS has identified loci explaining little variance. Bile acid malabsorption is present in up to a third of diarrhoea-predominant cases and is a treatable, under-diagnosed subset.

What is not known is the mechanism. Visceral hypersensitivity, motility change, immune activation, microbiota, bile acids and gut-brain signalling are all demonstrable in subsets; none unifies the condition. It is almost certainly a cluster of different disorders sharing a symptom label. The female predominance is unexplained.

Cure status. RELIEF ONLY. No treatment cures IBS. The condition typically runs a fluctuating course over decades with periods of remission. Diet and drug treatments reduce symptom severity; none abolishes the diathesis. Bile acid malabsorption and lactose intolerance, when identified inside an IBS population, are separately treatable and can resolve fully, so a minority of apparent IBS is a misclassified curable condition.

Prevention. No established primary prevention: CONTESTED, effectively absent. Avoiding unnecessary antibiotics: WEAK. Adequate treatment of acute gastroenteritis to reduce post-infectious cases: WEAK, indirect, not demonstrated in trials.

Treatment. The low-FODMAP diet is the best-evidenced dietary intervention: 50 to 70 per cent report meaningful improvement in trials, superior to habitual diet, with a number needed to treat of about 4 to 5 in some analyses. No drug cost, but it needs dietetic support for correct reintroduction, and long-term restriction may reduce beneficial bifidobacteria.

Soluble fibre, ispaghula or psyllium, is effective with a number needed to treat of about 7 (Moayyedi, *American Journal of Gastroenterology* 2014). Insoluble fibre, bran, is not effective and may worsen symptoms — a distinction routinely lost in general advice. Psyllium is not on the core EML; off-patent; tens to hundreds of US dollars a patient-year.

Antispasmodics — mebeverine, hyoscine, peppermint oil — have a pooled number needed to treat of about 5, and peppermint oil about 3 to 4 in meta-analysis of small trials†. Hyoscine butylbromide is off-patent and cheap; peppermint oil carries no patent and is very cheap.

Low-dose tricyclic antidepressants, amitriptyline 10 to 30 mg, have a number needed to treat of about 4 to 5 for global symptoms (Ford meta-analyses), and the ATLANTIS trial, 463 patients in UK primary care (*Lancet* 2023), confirmed benefit at six months. Off-patent; a few to tens of US dollars a year. Among the most cost-effective options here.

Loperamide controls stool frequency but not pain in diarrhoea predominance; EML yes, off-patent, cheap. Polyethylene glycol improves stool frequency but not pain in constipation predominance; off-patent, cheap. Psychological therapy — CBT and gut-directed hypnotherapy — gives durable benefit, with hypnotherapy effect sizes comparable to drug therapy and benefit persisting years after treatment; the limit is therapist availability, and internet-delivered CBT has been shown effective (ACTIB, *Gut* 2019).

Rifaximin in diarrhoea-predominant disease gives modest benefit, number needed to treat about 9 to 11; it is expensive and still on patent in many markets, at roughly US$1,500 to 2,000 per fourteen-day course in the United States†. Not on the EML. The newer agents — linaclotide, lubiprostone, eluxadoline, alosetron, tegaserod — have numbers needed to treat of about 6 to 12, are patented, cost thousands of US dollars or more a year, and are not on the EML; several have had safety withdrawals or restrictions. Probiotics: CONTESTED. Heterogeneity between products and trials is extreme and cannot be summarised as a single effect size.

Simple means. Soluble fibre, psyllium or oats, works, with a number needed to treat of about 7; insoluble bran does not. Regular physical activity improves symptoms on moderate-quality randomised evidence (Johannesson, *American Journal of Gastroenterology* 2011). Gut-directed hypnotherapy and relaxation have effect sizes rivalling the drugs and need no supply chain beyond a trained person; scripts and recordings deliver at near-zero marginal cost. Regular meal timing, and reducing alcohol, caffeine and fat. Peppermint oil is a cheap agricultural product with a pooled number needed to treat of about 3 to 4. Identifying and removing lactose or excess fructose where relevant.

Gaps. Rome III and Rome IV prevalence estimates differ by a factor of about 2.5, so the burden literature is not internally comparable. Placebo response of 30 to 40 per cent† makes modest drug effects fragile. Probiotic evidence is unusable in aggregate because strains and doses differ. The low-FODMAP diet's long-term microbial and nutritional consequences are not established. Whether post-infectious IBS is mechanistically the same condition as the rest is unresolved. Expensive new drugs have numbers needed to treat no better, and sometimes worse, than amitriptyline at a hundredth the cost.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Coeliac disease

What it is. An immune reaction to gluten flattens the lining of the small intestine, so food is not absorbed. It is lifelong. Removing gluten lets the lining heal.

Measured. Global pooled seroprevalence is 1.4 per cent and biopsy-confirmed prevalence 0.7 per cent (Singh, *Clinical Gastroenterology and Hepatology* 2018, meta-analysis of 96 studies and 275,818 subjects). Regional biopsy-confirmed figures: Europe 0.8 per cent, Asia 0.6 per cent, with Africa and South America lower but under-studied. The highest recorded prevalence is among Saharawi children of Western Sahara at about 5.6 per cent.

Roughly 70 to 80 per cent of cases remain undiagnosed in most populations, which is the ratio of serological to clinical diagnosis. It is not a separate GBD main cause and has no standalone DALY figure.

Deaths are small but non-zero, through refractory disease, enteropathy-associated T-cell lymphoma, and the consequences of malabsorption.

Presentation is bimodal, in early childhood and in the fourth to fifth decade, and can occur at any age. It is about 1.5 to 2 times more common in females†.

Where it starts. HLA-DQ2 or DQ8 is necessary: about 99.6 per cent of cases carry one or both. But 30 to 40 per cent of the general population carries them, so the genotype is necessary and far from sufficient. Heritability is among the highest measured for any common disease, about 75 to 87 per cent from twin studies, with monozygotic concordance around 75 to 80 per cent against dizygotic around 11 per cent (Nisticò, *Gut* 2006). First-degree relative prevalence is about 7 to 10 per cent†. Gluten exposure is the necessary environmental trigger.

Associated autoimmune conditions include type 1 diabetes, in which 3 to 8 per cent† have coeliac disease, autoimmune thyroid disease, Down and Turner syndromes, and IgA deficiency.

The timing of gluten introduction in infancy does not determine risk. Two randomised trials settled this against prior observational belief: PreventCD (Vriezinga, *NEJM* 2014) and CELIPREV (Lionetti, *NEJM* 2014) both found early against late gluten introduction made no difference to eventual incidence. Breastfeeding likewise does not prevent it. This is a well-documented reversal.

What is not known is why most genetically susceptible, gluten-exposed people never develop it, and what triggers onset at a particular moment after years of tolerance. Candidate triggers — enteric viral infection by reovirus or rotavirus, microbiome shifts, antibiotic exposure — have supporting but not decisive evidence. Nor is it known why incidence has genuinely risen several-fold over fifty years beyond ascertainment, nor what drives non-responsive and refractory disease.

Cure status. CONTROLLABLE. A strict lifelong gluten-free diet produces mucosal healing and symptom resolution in the great majority, and normalises most excess mortality and lymphoma risk. It is not a cure: reintroducing gluten reinstates the disease, so the diathesis is permanent. Mucosal recovery is incomplete in a substantial minority of adults despite good adherence, with persistent villous atrophy in about 30 to 40 per cent at follow-up biopsy in some adult series. Refractory coeliac disease, types I and II, affects a small percentage, and type II carries serious lymphoma risk.

Prevention. Nothing demonstrably prevents it. The interventions once believed preventive — delayed gluten introduction and breastfeeding — were tested and failed in PreventCD and CELIPREV: CONTESTED, and for the timing interventions refuted.

Case-finding in high-risk groups — first-degree relatives, type 1 diabetes, autoimmune thyroid disease, unexplained anaemia — prevents complications rather than disease: MODERATE for complication prevention. Population screening: CONTESTED. Benefit in asymptomatic screen-detected cases is not established and the lifelong diet burden is real.

Treatment. A strict gluten-free diet, lifelong, is the only established treatment. There is no drug cost but a substantial food cost: gluten-free staples typically cost two to four times their conventional equivalents, a real and regressive burden documented across several countries. It requires dietetic instruction and food-labelling infrastructure.

Correction of deficiencies — iron, folate, B12, vitamin D, calcium, zinc — uses off-patent EML-listed preparations at a few dollars a year. Bone density assessment and treatment where osteoporosis is present. Pneumococcal vaccination, because hyposplenism is common. Corticosteroids, budesonide and immunosuppression for refractory disease only.

No licensed drug exists for coeliac disease. Candidate agents — gluten-degrading enzymes, tight-junction modulators such as larazotide, transglutaminase inhibitors such as ZED1227, and immune tolerance vaccines such as Nexvax2 — have been through phase 2 with mixed results; Nexvax2 failed. None is approved.

Simple means. The core treatment is itself a simple means: removing one protein from the diet. It requires no industrial product. Naturally gluten-free staples — rice, maize, potato, legumes, millet, sorghum, buckwheat, cassava — are cheap and globally available. The expensive part is manufactured gluten-free

replicas of wheat products, which are optional. Reading labels and avoiding cross-contamination in shared kitchens. Household screening of first-degree relatives. In settings where wheat is not the staple, the diet is far cheaper to achieve than in wheat-based food cultures.

Gaps. Most cases worldwide are undiagnosed, and in much of Africa, South and Southeast Asia the true prevalence is simply unmeasured. Whether to screen the general population is genuinely unsettled. Persistent villous atrophy despite adherence is common and poorly explained; the relative contributions of trace exposure, misdiagnosis and true refractoriness are disputed. There is no adjunctive drug after twenty years of development. The degree to which non-coeliac gluten sensitivity overlaps is contested, with some trials implicating fructans rather than gluten.

> **Depth.** Starts in: a gliadin peptide. Size: 3 nm†; depth −2.48. First complaint: about 12 months († about 1 year after gluten is introduced); time depth 48.87. One untreated course: no number ([B] lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Inflammatory bowel disease: Crohn disease and ulcerative colitis

What it is. Two long-term diseases in which the immune system inflames the gut wall. Ulcerative colitis affects the colon's inner lining continuously. Crohn disease can affect any part of the gut, in patches, through the whole wall thickness. Both relapse and remit.

Measured. The highest recorded prevalences are European and North American: up to 505 per 100,000 for ulcerative colitis in Norway and 322 per 100,000 for Crohn disease in Germany; North America up to 286 and 319 per 100,000 respectively (Ng, *Lancet* 2017). Over 0.7 per cent of the population is affected in some Western countries, with about 3 million affected in the United States and 2.5 to 3 million in Europe.

GBD 2019 gave about 4.9 million prevalent cases globally, about 41,000 deaths a year and about 1.3 million DALYs†. Incidence is stable or falling in the West and rising sharply in newly industrialised countries across Asia, South America, the Middle East and Africa. This is the central epidemiological fact of the disease and it is consistent across studies.

Peak onset is 15 to 35, with a smaller second peak in the sixth decade. Ulcerative colitis is roughly equal by sex; Crohn disease is slightly female-predominant in the West.

Where it starts. Smoking is the cleanest and strangest risk factor. It roughly doubles Crohn risk and worsens its course, while being protective against ulcerative colitis, which often presents after smoking cessation. The divergence is unexplained. Appendicectomy is associated with reduced ulcerative colitis risk, also unexplained.

Family history is the strongest single predictor, with first-degree relative risk about 5 to 10 times†. Twin concordance for Crohn disease is about 30 to 35 per cent monozygotic against about 4 per cent dizygotic; for ulcerative colitis about 15 to 16 per cent against about 4 per cent (Halfvarson, Scandinavian twin studies; Orholm). Crohn disease is therefore substantially more heritable than ulcerative colitis, and both leave most variance to environment. GWAS has found over 240 risk loci together explaining only about 8 to 13 per cent of variance, the classic missing-heritability picture. NOD2 is the strongest Crohn locus; homozygotes carry a many-fold raised risk, but the genotype is neither necessary nor sufficient.

Early-life antibiotic exposure, urban residence, Western diet, ultra-processed food intake with hazard ratios around 1.5 to 1.8 in the PURE and Nurses' Health cohorts†, and reduced breastfeeding all contribute. Appendicitis and enteric infection act as triggers, and *Mycobacterium avium paratuberculosis* in Crohn disease remains a long-running and unresolved hypothesis.

What is not known is the cause. The hygiene and microbiome account fits the geographic epidemiology, since incidence rises as countries industrialise, but no specific organism, exposure or microbial signature has been established as causal. Why smoking splits the two diseases in opposite directions is unknown. Why most NOD2 carriers and most people with family history never develop disease is unknown. The missing heritability is unaccounted for.

Cure status. Ulcerative colitis: CONTROLLABLE medically, and CURABLE surgically. Total colectomy removes the diseased organ and ends the colitis — an actual cure, at the cost of a stoma or ileoanal pouch, and pouchitis affects a substantial minority. Sustained medical remission is achievable in most.

Crohn disease: CONTROLLABLE only. No operation cures it. Disease recurs at the anastomosis after resection in the majority, with endoscopic recurrence of about 70 to 90 per cent at one year without prophylaxis. Roughly half of Crohn patients require surgery within ten years. Deep remission is achievable but relapse is the norm over decades.

Prevention. No established primary prevention: absent. Smoking cessation in Crohn disease: STRONG for altering course, since continued smoking roughly doubles post-operative recurrence and worsens outcomes. Smoking is not recommended for ulcerative colitis despite the protective association, because the harms vastly outweigh it.

Breastfeeding: CONTESTED. Avoiding unnecessary early-life antibiotics: WEAK, observational only. Reducing ultra-processed food intake: WEAK, observational only. Post-operative Crohn recurrence prevention with an anti-TNF agent or a thiopurine: MODERATE, on POCER and other trials. That is secondary prevention.

Treatment. For ulcerative colitis, mesalazine (5-ASA), oral and topical, is first line in mild to moderate disease, inducing remission with a number needed to treat of about 4 to 5 against placebo for improvement; topical plus oral beats either alone. Mesalazine is not on the core EML; off-patent; about US$600 to 1,500 a patient-year at Western prices, far less in India. 5-ASA is ineffective in Crohn disease, a common prescribing error.

Corticosteroids — prednisolone, or budesonide MMX — are highly effective for induction and useless and harmful for maintenance. Prednisolone EML yes; off-patent; a few to tens of US dollars a year. Thiopurines, azathioprine or mercaptopurine, give steroid-sparing maintenance; azathioprine EML yes; off-patent; tens to hundreds of US dollars a year. They require TPMT and NUDT15 testing and monitoring, and modestly raise lymphoma and non-melanoma skin cancer risk.

For Crohn disease and moderate-to-severe ulcerative colitis, the biologics and small molecules:

Agent	Class	Measured effect	WHO EML	Off-patent	Approx. annual cost
Infliximab	Anti-TNF	ACCENT I / ACT 1–2: remission 21–39% vs 7–18% placebo; NNT 4–6	listed **only as a therapeutic equivalent** to adalimumab, not as a selected medicine	originator yes; biosimilars widely available	originator tens of thousands of US dollars; biosimilars thousands of US dollars some tenders below thousands of US dollars
Adalimumab	Anti-TNF	CHARM / ULTRA: remission 36–40% vs 12–18% placebo; NNT 4–7	**yes, listed medicine**, Crohn disease among its indications	originator yes; biosimilars available	originator US$50,000–80,000 US list; biosimilars thousands to tens of thousands of US dollars
Vedolizumab	Anti-integrin	GEMINI 1–2: remission 17–42% vs 5–26% placebo	no	no	tens of thousands of US dollars
Ustekinumab	Anti-IL12/23	UNITI / UNIFI: induction remission 16–21% vs 7–10%	no	biosimilars entering 2024–25	US$25,000–60,000, falling†
Tofacitinib	JAK inhibitor	OCTAVE: UC remission 18.5% vs 8.2% placebo	no	yes, generics entering	originator tens of thousands of US dollars +; generic potential below thousands of US dollars
Risankizumab, upadacitinib, mirikizumab,	newer	effective in phase 3; head-to-head data limited	no	no	tens of thousands of US dollars

Agent	Class	Measured effect	WHO EML	Off-patent	Approx. annual cost
guselkumab					

The biosimilar price collapse is the single most consequential economic fact in the treatment of this disease. Anti-TNF agents moved from tens of thousands of US dollars a year to thousands to tens of thousands of US dollars and in some tenders below thousands of US dollars. Adalimumab is a listed EML medicine with Crohn disease among its indications. Infliximab is on the list only as a therapeutic equivalent to adalimumab, which is a permitted substitute rather than the selected medicine, and the distinction is load-bearing for procurement. Between them, effective biologic therapy is for the first time within reach of middle-income health systems.

Surgery: colectomy cures ulcerative colitis; resection, stricturoplasty and abscess drainage manage Crohn complications. Exclusive enteral nutrition in paediatric Crohn disease achieves remission rates comparable to corticosteroids, about 60 to 80 per cent, without steroid toxicity, and promotes mucosal healing better; it is first-line in children in European guidelines, and the cost is formula feed only. Antibiotics for perianal and fistulising Crohn disease and for pouchitis: metronidazole EML yes, ciprofloxacin; both cheap.

Simple means. Smoking cessation in Crohn disease is among the highest-value zero-cost interventions in gastroenterology, roughly halving post-operative recurrence risk. Exclusive enteral nutrition in paediatric Crohn disease matches steroids for remission and needs only formula feed. Iron, B12, vitamin D and calcium repletion, with folate alongside methotrexate or sulfasalazine. Exercise and resistance training preserve bone and muscle against steroid effects without altering disease activity. Stoma care education, and low-residue modification during strictures, which is symptomatic only.

The honest limit: no diet has been shown to induce remission in adult inflammatory bowel disease. The Crohn's Disease Exclusion Diet and the specific carbohydrate diet have small supportive trials, and the evidence does not support any diet as a substitute for drug therapy in adults.

Gaps. The cause is unknown. The rise in newly industrialised countries is well documented and unexplained mechanistically. Missing heritability is large. Head-to-head biologic trials are few, SEAVUE and VARSITY being exceptions, so positioning of agents rests largely on indirect comparison. Long-term malignancy and infection risks of the newer agents are not yet characterised. Biosimilar uptake and pricing vary enormously between countries, so the cost of care differs by more than an order of magnitude for identical therapy. GBD models the disease with sparse data from Africa and much of Asia, so global burden figures there are extrapolations.

> **Depth.** Starts in: the bowel lining. Size: 1 mm†; depth +9.10. First complaint: about 25 years († onset about age 25); time depth 51.80. One untreated course: no number ([B] long-lasting).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Diverticular disease and diverticulitis

This is the longest entry in the chapter.

What it is. Small pouches push out through weak points in the wall of the colon. Having them is diverticulosis, which is usually silent. When one becomes inflamed or perforates, that is diverticulitis.

Measured. The pouches themselves are strongly age-dependent, and the age gradient is the most robust finding in the field. Colonoscopy and autopsy series give roughly under 10 per cent below the age of forty, about 30 per cent by sixty, about 50 to 60 per cent by seventy, and 60 to 70 per cent by eighty in Western populations†. In the Peery colonoscopy study of 2,104 patients aged 30 to 80 at the University of North Carolina between 1998 and 2010, diverticulosis was found across the age range with prevalence rising steeply with age.

Western diverticulosis is left-sided and sigmoid-predominant. East Asian diverticulosis is right-sided and presents at younger ages. The difference is consistent and striking.

Only a minority of people with diverticulosis ever get diverticulitis. The GBD 2019 figures for diverticular disease are roughly 36,000 deaths and about 1.0 to 1.3 million DALYs globally†. Deaths occur mainly through perforation with peritonitis, in the elderly and the immunosuppressed. Diverticular disease is one of the leading gastrointestinal causes of hospital admission in high-income countries; in the United States it accounts for several hundred thousand admissions a year and is among the costliest gastrointestinal diagnoses (Peery, *Gastroenterology*, Burden of Gastrointestinal Disease series). Admission rates have risen over recent decades in Western countries, including among people under fifty, and whether that is a true increase or an artefact of CT availability is disputed.

By sex the totals are broadly similar, with younger patients more often male and older patients more often female.

Where it starts. The anatomy of where the wall yields is the mechanically specific part of this entry, and it is uncontested.

The colonic wall is not uniformly strong. The vasa recta — the straight arteries supplying mucosa and submucosa — penetrate the circular muscle layer to reach the submucosa. They do so at four roughly predictable points around the circumference: between the mesenteric taenia and each of the two antimesenteric taeniae coli, giving two rows on each side between the taeniae. Each penetration is a gap in the muscularis propria: a point of structural weakness, in effect a pre-formed hole with a blood vessel in it.

Three consequences follow directly, and they are why this anatomy is worth stating in full.

Colonic diverticula are therefore false diverticula, or pseudodiverticula. Mucosa and submucosa herniate through the vascular penetration points, covered only by serosa, with no muscle layer in the wall of the pouch.

They appear in rows corresponding to the vasa recta entry points, and not in the segment between the two antimesenteric taeniae, where no vessels penetrate. That is the spared segment. The rectum, which lacks taeniae, is characteristically spared for the same reason.

And because the vasa recta runs over the dome of each diverticulum, that artery lies exposed. This is the anatomical reason a diverticular bleed is arterial and can be brisk, and why diverticular bleeding is a leading cause of lower gastrointestinal haemorrhage.

Read in the net: the wall is a mesh under tension, and it yields where it is already open. The vascular penetration points are the pre-existing openings; nothing new has to be made for a pouch to form. This is a reading, not a mechanism.

The conventional mechanical account adds raised intraluminal pressure — segmentation of the sigmoid generating high local pressures in a narrow-radius segment, by Laplace's law — driving mucosa out through those gaps. Connective tissue change with age is also documented: altered collagen cross-linking, and elastin deposition in the taeniae causing shortening.

Age is by far the strongest risk factor for having diverticula, on the gradient given above. Conversely, young age at presentation of diverticulitis is associated with a higher recurrence rate, simply because of longer remaining life.

Heritability. Heritability is estimated at 40 per cent. In the Swedish twin study, of 104,452 twins meeting inclusion criteria, 2,296 had a diagnosis of diverticular disease. The odds ratio for disease given an affected co-twin was 7.15 (95 per cent CI 4.82 to 10.61) in monozygotic twins and 3.20 (2.21 to 4.63) in same-sex dizygotic twins. Heritability was estimated at 40 per cent, with the remaining 60 per cent attributed to non-shared environment (Granlund, Svensson, Olén, *Alimentary Pharmacology and Therapeutics* 2012). A Danish twin study gave a comparable figure of about 40 to 53 per cent†. Genome-wide studies have since identified loci including *ARHGAP15*, *COLQ* and *FAM155A*†.

So: a substantial but minority genetic contribution. Most of the variance is environmental and non-shared, which is precisely the part that is least well characterised.

The fibre contradiction. This has to be reported as two findings that point in different directions, because that is what the literature contains. Both are given at equal length and neither is resolved.

Finding A — more fibre, fewer diverticular disease admissions. Crowe, Appleby, Allen and Key, "Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians", *BMJ* 2011;343:d4131. The cohort was 47,033 participants in England and Scotland, of whom 15,459, or 33 per cent, were vegetarian. Follow-up was 547,312 person-years, mean 11.6 years, with 812 cases of diverticular disease — 806 hospital admissions and 6 deaths. Vegetarians against meat eaters: hazard ratio 0.69 (95 per cent CI 0.55 to 0.86), a 31 per cent lower risk. Highest against lowest fifth of fibre intake: hazard ratio 0.59 (95 per cent CI 0.46 to 0.78) per the abstract. The results section of the same paper reports 0.58 (95 per cent CI 0.46 to 0.73). Both are printed here, and the discrepancy is internal to the published paper: the abstract and the results section of one article give two different values and two different intervals for the same comparison. The highest fifth was 25.5 g a day or more for women and 26.1 g or more for men; the lowest fifth was under 14 g a day.

Finding B — more fibre, more diverticula. Peery, Barrett, Park, Rogers, Galanko, Martin and Sandler, "A high-fiber diet does not protect against asymptomatic diverticulosis", *Gastroenterology* 2012;142(2):266–272. The study was 2,104 patients aged 30 to 80 undergoing outpatient colonoscopy at UNC Hospitals between 1998 and 2010. Participants in the highest fibre quartile had more diverticulosis than those in the lowest: those with the lowest fibre intake were about 30 per cent less likely to have diverticula than those with the highest. Constipation was not a risk factor. The opposite was found: more frequent bowel movements were associated with higher risk, and those with more than fifteen bowel movements a week were about 70 per cent more likely to have diverticulosis than those with fewer than seven. The study design, cohort, direction of effect and the two percentage figures are verified; the exact prevalence ratios with their intervals were not retrievable and remain open.

How the two fit together, stated as a reconciliation and not as a demonstration. The outcomes measured are not the same. EPIC-Oxford measured clinical diverticular disease, hospital admission and death, prospectively. Peery measured asymptomatic diverticulosis, pouches visible at colonoscopy, cross-sectionally. It is therefore logically possible that fibre does not prevent the pouches forming while still reducing the chance that they inflame. That is the current mainstream reconciliation of the two findings.

It is a reconciliation and not a demonstration. No trial has ever randomised fibre intake and measured either outcome. The cross-sectional design of the Peery study cannot establish direction, and colonoscopy populations are selected. The century-old Painter and Burkitt fibre-deficiency hypothesis, which built the entire dietary edifice, rested on ecological comparison between Britain and rural Africa rather than on experiment. The fibre story in patient leaflets is better supported for preventing diverticulitis than for preventing diverticulosis, and in neither case by randomised evidence.

NSAIDs and aspirin. This association is solid, and the intervals are given. Strate, Liu, Huang, Giovannucci and Chan, "Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding", *Gastroenterology* 2011;140(5):1427–33. The cohort was 47,210 US men aged 40 to 75 at baseline in 1986, the Health Professionals Follow-up Study, with 22 years of follow-up, 939 diverticulitis cases and 256 diverticular bleeding cases.

Regular aspirin use, twice a week or more: diverticulitis hazard ratio 1.25 (95 per cent CI 1.05 to 1.47); diverticular bleeding 1.70 (1.21 to 2.39). Intermediate aspirin intake, two to 5.9 standard 325 mg tablets a week, carried the highest bleeding risk at 2.32 (1.34 to 4.02), and aspirin on four to six days a week 3.13 (1.82 to 5.38). Regular non-aspirin NSAID use: diverticulitis hazard ratio 1.72 (1.40 to 2.11); diverticular bleeding 1.74 (1.15 to 2.64).

Opioids and corticosteroids are also associated with perforation, and calcium channel blockers appear protective against bleeding.

Nuts, seeds and popcorn are not a risk factor, and the direction is the opposite of the traditional advice. This was standard medical advice for decades and it was wrong.

Strate, Liu, Syngal, Aldoori and Giovannucci, "Nut, corn, and popcorn consumption and the incidence of diverticular disease", *JAMA* 2008;300(8):907–914. The cohort was 47,228 men aged 40 to 75, free of diverticular disease, cancer and inflammatory bowel disease at baseline, in the Health Professionals

Follow-up Study, with eighteen years of follow-up from 1986 to 2004. There were 801 cases of diverticulitis and 383 cases of diverticular bleeding.

Nuts, highest intake of twice a week or more against lowest of under once a month, for diverticulitis: hazard ratio 0.80 (95 per cent CI 0.63 to 1.01) — a protective point estimate with an interval crossing 1.00. Popcorn, the same comparison, for diverticulitis: hazard ratio 0.72 (0.56 to 0.92) — significantly protective. Corn showed no association with diverticulitis. None of nuts, corn or popcorn showed any association with diverticular bleeding. The cohort, follow-up, case numbers and the nut and popcorn hazard ratios with intervals are verified; the exact bleeding hazard ratios and the p-for-trend values were not retrievable.

So the direction of effect runs opposite to the advice that was given for decades: no increased risk, and for popcorn a statistically significant reduction. Restriction of nuts, seeds and popcorn is not supported, and the major guidelines have abandoned it.

Other established risk factors. Obesity: BMI of 30 or more is associated with roughly 1.8 times the diverticulitis risk and about three times the bleeding risk in the same cohort. Smoking: a modest increase in perforation and complication risk. Physical inactivity, with vigorous activity associated with reduced risk. Higher red meat intake associated with increased diverticulitis risk. Low vitamin D levels associated with diverticulitis.

What is genuinely not known. Why only a small minority of people with diverticula ever get diverticulitis, and there is no way to predict which. Whether diverticulitis is primarily an infective event at all — the DIABOLO result below undercuts the infection model, and inflammation-first or microperforation-first accounts are now taken seriously, though none is established. Whether the pouches are a disease or a normal consequence of an ageing colon in a given dietary environment. The cause of the apparent rise in incidence in the young. Why East Asian diverticulosis is right-sided and Western left-sided, with genetic and dietary explanations both having advocates and neither settled. What the 60 per cent non-shared environmental variance from the twin study actually consists of. And whether low-grade persistent inflammation after an episode, so-called symptomatic uncomplicated diverticular disease, is a distinct entity or post-inflammatory IBS, which is contested.

Cure status. Diverticulosis, the anatomical finding: the label does not apply. It is a state of the colon wall and not an illness, and it is usually silent. The pouches are permanent and do not regress, no treatment removes them, and asymptomatic diverticulosis needs no treatment.

Diverticulitis, the illness, is a different matter from diverticulosis, the finding. It carries its own labels, below.

Acute uncomplicated diverticulitis: SELF-LIMITING. This is a relatively recent conclusion and the evidence is strong enough to state plainly; it is set out in the treatment section below.

Complicated diverticulitis — abscess, perforation, fistula, obstruction: CURABLE by intervention, drainage or resection, at surgical cost and risk.

Recurrent or segmental disease: CURABLE by segmental resection, which removes the affected segment; recurrence after resection is uncommon but possible in retained colon.

The DIABOLO trial, in full. Daniels, Ünlü, de Korte and colleagues, “Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis”, *British Journal of Surgery* 2017;104(1):52–61, registration NCT01111253.

The design was a multicentre randomised trial across 22 Dutch centres, in patients with CT-proven, primary, left-sided, uncomplicated acute diverticulitis. Randomisation gave observation without antibiotics in 283 and antibiotics in 287, with 528 patients in the intention-to-treat analysis, 262 observation and 266 antibiotics. The primary endpoint was time to recovery over six months.

Median time to recovery was 14 days (IQR 6 to 35) with observation against 12 days (IQR 7 to 30) with antibiotics; hazard ratio 0.91, lower limit of the one-sided 95 per cent CI 0.78; P = 0.151. Not significant.

The secondary outcomes, observation against antibiotics, with Benjamini-Hochberg adjusted P values:

Outcome	Observation	Antibiotics	P
Complicated diverticulitis at 6 months	3.8%	2.6%	0.377
Ongoing diverticulitis	7.3%	4.1%	0.183
Recurrent diverticulitis	3.4%	3.0%	0.494
Sigmoid resection	3.8%	2.3%	0.323
Readmission at 6 months	17.6%	12.0%	0.148
Mortality	1.1%	0.4%	0.432
Adverse events	48.5%	54.5%	0.221
Hospital stay, median	**2 days**	**3 days**	**0.006**

No secondary outcome differed significantly except hospital stay, which was shorter without antibiotics. The per-protocol analysis matched the intention-to-treat analysis. The published conclusion was that observational treatment without antibiotics did not prolong recovery and can be considered appropriate in uncomplicated diverticulitis. Every figure above was concordant across two independent sources.

The surrounding evidence. AVOD (Chabok, *British Journal of Surgery* 2012) was the earlier Swedish and Icelandic multicentre randomised trial, 623 patients with CT-verified uncomplicated left-sided diverticulitis, antibiotics against no antibiotics. It found no difference in complications, length of stay or recurrence; the patient number and conclusion are widely reported and the individual outcome percentages were not re-retrieved. DINAMO, Spanish, 2021, randomised non-antibiotic management in mild diverticulitis managed as outpatients and found it non-inferior. Long-term DIABOLO follow-up at 24 months reported no significant difference in recurrence or need for surgery between arms. Meta-analyses pooling these trials conclude no benefit of antibiotics on recovery, complications, recurrence or surgery in immunocompetent patients with CT-confirmed uncomplicated diverticulitis.

The caveat belongs with the result. These trials were not powered for rare serious outcomes such as perforation and death, and they excluded the immunosuppressed, the septic, the pregnant and those with significant comorbidity. The observation arms showed numerically more complicated disease, more readmission and more deaths, none of it significant. The conclusion the evidence supports is “no demonstrated benefit”, not “proven equivalent safety for every patient”.

The guideline position. From NICE NG147, read live from the guideline text. In uncomplicated acute diverticulitis in a person who is systemically well: consider a no antibiotic prescribing strategy, with simple analgesia such as paracetamol, and advice to re-present if symptoms persist or worsen. Offer oral antibiotics if the person with acute diverticulitis is systemically unwell, and offer an antibiotic strategy if immunosuppressed or with significant comorbidity. For CT-confirmed uncomplicated diverticulitis: review the need for antibiotics. Do not offer an aminosalicylate or antibiotics to prevent recurrent acute diverticulitis. Do not offer antibiotics to people with diverticular disease, meaning non-acute disease. On diet: if tolerated, a high-fibre diet should be maintained for life, with benefits that may take several weeks, and bulk-forming laxatives considered where a high-fibre diet is not tolerated.

The American Gastroenterological Association 2015 guideline holds that antibiotics should be used selectively rather than routinely in acute uncomplicated diverticulitis, as a conditional recommendation on low-quality evidence. The American Society of Colon and Rectal Surgeons 2020 guideline holds that antibiotics can be used selectively in immunocompetent patients with mild uncomplicated disease. All major guidelines have moved from mandatory antibiotics to selective use in immunocompetent patients with mild, CT-confirmed, uncomplicated disease. The remaining disagreement is about which patients still need them, and how confidently outpatient non-antibiotic management can be offered.

On elective surgery after recurrence: routine colectomy after two episodes is no longer recommended, and the decision is individualised on symptom burden, age, immunosuppression and complication history. NICE directs consideration of elective resection for continuing symptoms such as stricture or fistula. The LASER and DIRECT trials examined elective resection against conservative management for recurrent and persistent disease, with resection improving quality of life at the cost of surgical risk.

Prevention. Dietary fibre: MODERATE for preventing diverticulitis, CONTESTED for preventing diverticulosis. Both numbers are printed. EPIC-Oxford gives a hazard ratio of 0.59 (0.46 to 0.78) for the

highest against the lowest fifth for clinical disease, with the same paper's results section giving 0.58 (0.46 to 0.73); Peery gives more diverticulosis with higher fibre, with the lowest quartile about 30 per cent less likely to have pouches. No randomised trial exists. Target intakes in the protective fifth were about 25 to 26 g a day or more.

Vegetarian diet: MODERATE. Hazard ratio 0.69 (0.55 to 0.86), EPIC-Oxford.

Avoiding NSAIDs and regular aspirin where not clinically required: MODERATE, on consistent prospective cohort data, with a diverticulitis hazard ratio of 1.72 for NSAIDs and a bleeding hazard ratio of 1.74. Aspirin taken for a cardiovascular indication should not be stopped for this reason; the benefit calculus differs.

Weight management: MODERATE. Obesity about 1.8 times for diverticulitis and about three times for bleeding. Physical activity: MODERATE, with vigorous activity associated with reduced risk. Smoking cessation: WEAK. Reducing red meat: WEAK.

Restricting nuts, seeds and popcorn: not indicated. The grade is CONTESTED and refuted; the evidence points the other way, with popcorn at 0.72 (0.56 to 0.92).

Mesalazine and rifaximin to prevent recurrence: CONTESTED and negative. Multiple randomised trials of mesalazine failed to prevent recurrence, and NICE recommends against it explicitly. Probiotics: CONTESTED, insufficient evidence.

Treatment. For uncomplicated diverticulitis in a person who is systemically well: observation, analgesia, and oral intake as tolerated, on DIABOLO and AVOD. The drug cost approaches zero. Paracetamol: EML yes; off-patent; a few to tens of US dollars a year of intermittent use. NSAIDs are best avoided given the risk association above.

Antibiotics where the person is systemically unwell, immunosuppressed, or has significant comorbidity. Co-amoxiclav 500/125 mg three times a day for five days is the NICE first choice; EML yes, as amoxicillin with clavulanic acid, Access group; off-patent; a few US dollars per course. The alternative is ciprofloxacin with metronidazole; metronidazole EML yes, off-patent, a few US dollars a course; ciprofloxacin off-patent, a few US dollars a course. The entire antibiotic treatment of diverticulitis is therefore a few dollars of off-patent, EML-listed drug.

An abscess over 3 cm: percutaneous drainage or surgery, with NICE directing consideration of either. Perforation with generalised peritonitis: laparoscopic lavage or resectional surgery, with NICE directing an offer of either after discussing risks; the LOLA/LADIES, SCANDIV and DILALA trials examined lavage against resection with mixed results and higher reintervention after lavage. Resection when required: primary anastomosis with or without diverting stoma, or Hartmann's procedure, with NICE directing the choice by age, comorbidity and WHO performance status.

Diverticular bleeding usually stops spontaneously; otherwise colonoscopic haemostasis, CT angiography with embolisation, or segmental resection if it persists.

Not recommended: aminosalicylates or antibiotics to prevent recurrence, which NICE states explicitly, and routine antibiotics for non-acute diverticular disease.

Simple means. Dietary fibre, 25 to 30 g a day from whole foods — vegetables, legumes, whole grains, fruit — associated with a hazard ratio of 0.59 (0.46 to 0.78) for clinical diverticular disease in EPIC-Oxford. Increase gradually; NICE notes that benefit may take several weeks and advises adequate fluid alongside. No supply chain.

Vegetarian or largely plant-based eating: hazard ratio 0.69 (0.55 to 0.86). A bulk-forming laxative, ispaghula or psyllium, where a high-fibre diet is not tolerated, is the NICE-endorsed alternative: a milled seed husk with minimal processing.

Physical activity, associated with reduced risk, and free. Weight reduction where obese, against the 1.8-fold diverticulitis and threefold bleeding associations†. Stopping unnecessary NSAIDs removes a 1.72-fold diverticulitis and 1.74-fold bleeding association; it costs nothing and saves money.

Eating nuts, seeds and popcorn freely is a simple means in the sense of removing a wrong restriction. Popcorn hazard ratio 0.72 (0.56 to 0.92). Decades of unnecessary dietary restriction can be lifted, which is itself a measurable gain in quality of life and in nutritional quality.

Adequate fluid alongside increased fibre. And for an uncomplicated episode in a well patient: rest, fluids, paracetamol and watchful waiting, which is now the guideline-endorsed first option and needs no pharmaceutical industry at all.

Gaps. The fibre literature is contradictory and contains no randomised trial. EPIC-Oxford and Peery disagree in direction, and the usual reconciliation — that fibre prevents inflammation rather than pouches — is plausible and untested. Painter and Burkitt's founding hypothesis was ecological. Patient information materials state the fibre case far more confidently than the evidence warrants. The exact prevalence ratios and confidence intervals from Peery 2012 could not be retrieved, only the direction and the 30 per cent and 70 per cent figures.

Lifetime risk of diverticulitis given diverticulosis is disputed, and the disagreement is tenfold. The textbook figure is 10 to 25 per cent. Recent cohort-derived estimates are 1 to 4 per cent, with Shahedi (*Clinical Gastroenterology and Hepatology* 2013) finding about 1 per cent over eleven years. Both are printed. This is a tenfold disagreement about the basic natural history of the condition, it is unresolved, and it matters for every risk conversation held with a patient who has incidental diverticula.

DIABOLO and AVOD were underpowered for rare serious harms and excluded the immunosuppressed and septic; no demonstrated benefit is not the same as safe in everyone. Whether the rise in diverticulitis admissions, especially in the young, is real or an artefact of CT availability is unresolved. There is no way to predict which people with diverticula will develop diverticulitis.

Whether acute diverticulitis is primarily infective is now genuinely open. That is awkward, because the standard treatment was antibiotics for seventy years, and because the trial evidence that undercuts the infection model is the same evidence that changed the guidelines.

The right-sided Asian against left-sided Western pattern is unexplained. Whether symptomatic uncomplicated diverticular disease is a real entity or post-inflammatory IBS is contested. And GBD burden figures for diverticular disease rest on sparse data outside high-income countries.

> **Depth.** Starts in: a pouch of the bowel wall. Size: 5 mm†; depth +10.56. First complaint: about 60 years († onset about age 60); time depth 52.60. One untreated course: about 10 days († inflammation about 10 days); depth 45.60.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Appendicitis

What it is. The appendix becomes inflamed and swells, usually after its opening is blocked. Untreated it may burst and infect the abdominal cavity. It is the commonest abdominal surgical emergency.

Measured. Lifetime risk is about 7 to 8 per cent, with peak incidence between ten and thirty. Annual incidence is about 100 per 100,000 adults in Western countries, giving about 17 to 20 million cases globally a year. GBD 2019 gave about 33,000 to 50,000 deaths a year and about 4 to 5 million DALYs†.

Mortality is very low where surgery is available, under 0.1 to 0.3 per cent†, and substantial where it is not. The case-fatality gradient between high- and low-income settings is one of the starkest in surgery, and perforation rates are far higher where access is delayed. There is a slight male predominance.

Where it starts. Luminal obstruction by a faecolith, or by lymphoid hyperplasia, often post-viral in children; rarely tumour or parasite. Age ten to thirty; male sex. Family history raises risk about threefold, with heritability estimated around 30 per cent from twin studies†. Low dietary fibre has been proposed on weak evidence.

What is not known is why obstruction occurs when it does, and why incidence is lower in low-income rural populations and rose with industrialisation. Nor is it known which cases will perforate. The existence of a

genuinely self-limiting, non-progressive form of appendicitis is now accepted but cannot be identified prospectively with confidence.

Cure status. CURABLE. Appendicectomy is definitively curative. A substantial fraction of uncomplicated appendicitis is also curable with antibiotics alone, which is the major change in this field.

CODA (*NEJM* 2020, 1,552 patients, United States) found antibiotics non-inferior to appendicectomy on 30-day health status; about 29 per cent of the antibiotic group had undergone appendicectomy by 90 days, rising above 40 per cent at longer follow-up, with appendicolith predicting failure. APPAC (Salminen, *JAMA* 2015, 530 patients, Finland, CT-confirmed uncomplicated disease) found about 27 per cent required appendicectomy within a year and about 39 per cent by five years, meaning about 61 per cent were managed definitively without operation. So surgery cures essentially all; antibiotics cure roughly 60 to 70 per cent, with the remainder coming to surgery, mostly without added harm.

Prevention. No established prevention: absent. Dietary fibre: WEAK and CONTESTED. Appendicectomy prevents appendicitis trivially and is associated with reduced ulcerative colitis risk, but is not performed prophylactically.

Treatment. Laparoscopic appendicectomy is standard of care, with lower wound infection, shorter stay and faster return to work than open surgery; open remains appropriate where laparoscopy is unavailable. Antibiotics alone for CT-confirmed uncomplicated appendicitis without appendicolith avoid surgery in 60 to 70 per cent. Regimens: co-amoxiclav, or ceftriaxone or cefotaxime with metronidazole, or ciprofloxacin with metronidazole. Co-amoxiclav EML yes, off-patent, a few US dollars a course. Metronidazole EML yes, off-patent, a few US dollars a course. Ceftriaxone EML yes, off-patent, a few US dollars a course.

Complicated appendicitis with abscess: antibiotics plus percutaneous drainage, with or without delayed appendicectomy. Perforation with peritonitis: urgent surgery, resuscitation and antibiotics. Analgesia with paracetamol, NSAIDs and opioids as needed; giving analgesia does not obscure the diagnosis, an old teaching now refuted.

Simple means. Essentially none for treatment. This condition requires either surgery or manufactured antibiotics, and it is one of the clearest cases in the book where simple means are inadequate and surgical access is the determining factor in survival.

What matters at population level is access and timeliness: distance to a facility with anaesthesia and a surgeon, and transport. The perforation rate is a function of delay. Clinical scoring systems, Alvarado and AIR, and ultrasound reduce unnecessary CT and are particularly useful where CT is unavailable; they need no supply chain beyond training. Fluid resuscitation and oral rehydration while awaiting transfer.

Gaps. There is no way to distinguish prospectively which appendicitis will perforate and which would resolve. Long-term recurrence after antibiotic-only management beyond five years is not well characterised. Whether antibiotic-first management is appropriate where imaging is unavailable — which is precisely where surgical access is also poor — is unstudied and practically crucial. Negative appendicectomy rates vary widely between systems. GBD mortality estimates for low-income settings rest on sparse vital registration.

> **Depth.** Starts in: a faecolith in the appendix. Size: 7 mm†; depth +10.87. First complaint: about 12 hours († about 12 hours after blockage); time depth 42.87. One untreated course: about 2 days († perforation after 1–3 days); depth 44.13.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Haemorrhoids

What it is. The normal cushions of blood vessels in the anal canal become swollen and slip down. They bleed, itch and can be painful. Very common and usually not dangerous.

Measured. Prevalence estimates range from 4 to 39 per cent depending on definition and on whether examination or self-report is used, and about half of adults report symptoms at some point by age fifty. The width of that range is a definitional artefact. GBD 2019 recorded haemorrhoidal disease with substantial prevalent cases globally, on the order of tens of millions to over 100 million, and low mortality†. Deaths are negligible. Peak age is 45 to 65, both sexes, and pregnancy is a major precipitant.

Where it starts. Constipation and straining; prolonged toilet sitting. Pregnancy and childbirth. Obesity; ascites and portal hypertension, though haemorrhoids are distinct from anorectal varices. Low fibre intake. Ageing, through loss of supporting connective tissue. Heritability is not reliably quantified.

What is not known is why some people with identical bowel habits develop them and others do not; the relative contribution of vascular against connective-tissue mechanisms; and whether constipation is cause, consequence or coincidence in many cases. The evidence base is notably poor for such a common condition.

Cure status. The individual pile or episode: CURABLE, by rubber band ligation or excision. Low-grade disease, particularly post-pregnancy: SELF-LIMITING. The underlying tendency: CONTROLLABLE, which is why recurrence is common.

Prevention. Fibre and avoiding straining: MODERATE. Fibre supplementation reduces bleeding, with a Cochrane review giving about a 50 per cent reduction in symptom persistence and bleeding risk, relative risk about 0.47 to 0.5 for bleeding. Adequate fluid, not delaying defaecation, limiting toilet time: WEAK, plausible and minimally studied. Weight management: WEAK.

Treatment. Fibre supplementation with psyllium or ispaghula reduces bleeding and symptoms and is Cochrane-supported; off-patent; tens to hundreds of US dollars a year. Rubber band ligation for grades I to III is the most effective office procedure, with higher success than sclerotherapy and recurrence of about 15 to 30 per cent at a few years†; very low cost and no implant.

Topical agents — local anaesthetic, corticosteroid, zinc oxide — give symptomatic relief only with no healing claim, and steroid use should be short; off-patent and cheap. Sclerotherapy and infrared coagulation are alternatives to banding, slightly less effective. Excisional haemorrhoidectomy for grades III to IV is the most definitive, the most painful, and gives the lowest recurrence; stapled haemorrhoidopexy gives less early pain with higher recurrence and rare serious complications; HAL-Doppler ligation is intermediate.

Oral flavonoids, micronised purified flavonoid fraction, give modest benefit on bleeding in meta-analysis, with trials mostly industry-sponsored and of moderate quality; not on the EML. A thrombosed external haemorrhoid incised with clot evacuation within about 72 hours gives faster relief than conservative care.

Simple means. Fibre is the primary treatment, with a relative risk of about 0.5 for bleeding†, and needs no supply chain. Water intake alongside fibre. Not straining; short toilet visits; responding promptly to the urge. Sitz baths, warm water for ten to fifteen minutes, relieve pain and spasm with no product needed. Squatting or a footstool position alters the anorectal angle, and small studies suggest reduced straining. Pelvic floor relaxation training for those who strain habitually. These measures are the whole of first-line care for most patients and require nothing manufactured.

Gaps. Prevalence is unmeasurable in any comparable way because definitions differ by an order of magnitude. The pathophysiology is genuinely unsettled. Trials of topical agents are small, old and poorly controlled. Flavonoid evidence is industry-dominated. Long-term recurrence data after all procedures are limited. Almost nothing is known about haemorrhoids in low-income settings despite a presumably high burden.

> **Depth.** Starts in: a vascular cushion of the anal canal. Size: 1 cm†; depth +11.19. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Anal fissure

What it is. A tear in the lining of the anal canal. It causes sharp pain on defaecation and bright bleeding. Spasm of the internal sphincter keeps it from healing.

Measured. Lifetime incidence is roughly one in 350 adults a year, with lifetime risk put at about 11 per cent by some estimates†. It is not a separate GBD cause. There are no deaths. It affects young and middle-aged adults predominantly, with the sexes roughly equal, and lies in the posterior midline in about 90 per cent of cases†.

Where it starts. Passage of hard stool, and constipation. Raised internal anal sphincter tone with reduced anodermal blood flow: the posterior midline is relatively ischaemic, which explains both the site distribution and the non-healing. Childbirth, giving anterior fissures; chronic diarrhoea. Atypical, lateral or multiple fissures suggest Crohn disease, tuberculosis, HIV, syphilis or malignancy, which is an important diagnostic point. Heritability has not been studied.

What is not known is why sphincter hypertonia develops, why some fissures chronify and others heal, and the true determinants of recurrence.

Cure status. Acute fissures: SELF-LIMITING — about 50 to 60 per cent heal within weeks with conservative measures alone. Chronic fissures: CURABLE — lateral internal sphincterotomy heals over 90 to 95 per cent, the highest cure rate of any option, at the cost of a small but real risk of incontinence to flatus or soiling, pooled at about 3 to 10 per cent in some series and mostly minor.

Prevention. Avoiding constipation with fibre and fluid: MODERATE. Not straining: MODERATE, mechanistically direct with thin trial evidence. Post-partum perineal care: WEAK.

Treatment. Fibre, fluid, stool softeners and sitz baths are first line and heal about 50 to 60 per cent of acute fissures†, at essentially no cost. Topical nitrates, glyceryl trinitrate 0.2 to 0.4 per cent, give healing of about 50 per cent against about 35 per cent for placebo — a marginal advantage, and headache in 20 to 30 per cent causes frequent discontinuation; off-patent; tens of US dollars a course.

Topical calcium channel blockers, diltiazem 2 per cent or nifedipine, give healing similar to or better than nitrates, about 65 to 95 per cent in trials, with far fewer headaches, and are now the widely preferred first-line pharmacological agent; often compounded; off-patent; tens of US dollars a course.

Botulinum toxin injection into the internal sphincter heals 60 to 80 per cent, with higher recurrence than surgery and possible transient incontinence; on patent as a biologic, hundreds to thousands of US dollars per treatment. Lateral internal sphincterotomy heals over 90 to 95 per cent and is superior to all medical therapy in meta-analysis, with the incontinence risk above; Cochrane and meta-analytic comparison consistently favours surgery for healing and medical therapy for continence preservation. Anal advancement flap is for fissures with low sphincter tone or after prior sphincterotomy.

Simple means. Fibre and water are the foundation, healing half of acute fissures. Sitz baths relax the sphincter and relieve pain, measurably reducing resting anal pressure, at no cost. Not straining, and footstool or squat positioning. Petroleum jelly or any bland lubricant before defaecation. Pelvic floor relaxation rather than strengthening — the sphincter here is too tight, not too weak. Conservative measures plus time are genuinely curative in the majority of acute cases.

Gaps. Incidence is poorly measured because many never present. The optimal dose, duration and vehicle for topical diltiazem are not standardised and many formulations are compounded. The true long-term incontinence rate after sphincterotomy is disputed, with series ranging from about 1 per cent to over 30 per cent depending on definition and follow-up†; both ends are printed. Botulinum dose and injection site are not standardised. Evidence in post-partum and Crohn-related fissures is thin.

> **Depth.** Starts in: a tear in the anal lining. Size: 5 mm†; depth +10.56. First complaint: about 1 second († direct (hard stool)); time depth 33.15. One untreated course: about 6 weeks († an acute tear heals in about 6 weeks); depth 46.90.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status

> agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Gallstones and cholecystitis

What it is. Stones form in the gallbladder, mostly from cholesterol. Most cause no trouble. If one blocks the outlet the gallbladder becomes inflamed, which is cholecystitis; if one passes into the bile duct it can cause jaundice or pancreatitis.

Measured. Prevalence in Western adults is 10 to 20 per cent, and about 10 to 15 per cent of adults in Europe and North America†. Ethnic and geographic variation is marked: very high in Indigenous American populations, with over 70 per cent among Pima women, about 50 per cent among Chilean Mapuche women, and low across sub-Saharan Africa and much of Asia.

GBD 2019 gave gallbladder and biliary diseases roughly 170,000 to 180,000 deaths and about 4 to 6 million DALYs globally†. Cholecystectomy is among the most frequently performed abdominal operations worldwide, with about 600,000 to 750,000 a year in the United States. About 2 to 4 per cent of people with stones develop symptoms per year, and about 80 per cent of stones remain silent for life. The female to male ratio is about 2 to 3:1 in the reproductive years, converging with age. Gallbladder cancer burden is concentrated in Chile, northern India, Japan and parts of eastern Europe.

Where it starts. The classical risk list here is unusually well established. Female sex, through oestrogen increasing biliary cholesterol secretion; pregnancy and parity; oral contraceptives and hormone therapy. Age, with incidence rising steadily. Obesity, dose-dependently, roughly two to three times at BMI above 30.

Rapid weight loss, including after bariatric surgery and very-low-calorie diets, causes stones in up to 30 per cent within months — a well-documented iatrogenic effect†.

Family history, with heritability about 25 to 29 per cent from Swedish twin studies (Katsika, *Hepatology* 2005); *ABCG8* and *UGT1A1* variants are established loci, with *ABCG8* D19H the strongest common genetic risk factor. Diabetes, metabolic syndrome and hypertriglyceridaemia. Crohn disease and ileal resection through bile salt loss; cirrhosis; haemolysis and thalassaemia, giving pigment stones; total parenteral nutrition; octreotide; ceftriaxone, through biliary sludge. Protective: physical activity, moderate coffee intake, statins, higher polyunsaturated and vegetable fat intake, and nuts.

What is not known is why most stones remain silent and which will become symptomatic — stone size and number predict only weakly. The nucleation step in cholesterol stone formation is incompletely understood, as is the role of gallbladder dysmotility, whether as cause or consequence. The pathway from stones to gallbladder cancer, and why it is so geographically concentrated, is not explained.

Cure status. CURABLE. Cholecystectomy removes the organ and essentially ends gallstone disease, with over 95 per cent relief of biliary colic†; a minority have persistent pain, often a sign the original diagnosis was wrong. Stones already in the bile duct require ERCP clearance. Silent stones need no treatment: observation is correct management, since most remain silent for life.

Prevention. Weight management and avoiding rapid weight loss: MODERATE. Where rapid loss is planned, in bariatric surgery or a very-low-calorie diet, ursodeoxycholic acid prophylaxis reduces stone formation substantially, relative risk about 0.3 to 0.4 in trials. Physical activity: MODERATE, on dose-dependent prospective cohort association. Avoiding prolonged fasting and keeping regular meals, which keeps the gallbladder emptying: WEAK. Dietary pattern with higher fibre, vegetable fat, nuts and coffee: WEAK, cohort evidence. Statins: CONTESTED and WEAK — observational reduction with no trial designed for this.

Prophylactic cholecystectomy for silent stones is not indicated except in specific high-risk groups: porcelain gallbladder, large stones with anomalous ductal anatomy, populations with high gallbladder-cancer incidence, and some transplant candidates.

Treatment. Laparoscopic cholecystectomy is definitive. For acute cholecystitis, early surgery within seven days is superior to delayed: shorter total stay, fewer readmissions, no increase in complications or bile duct injury (ACDC, Gutt, *Annals of Surgery* 2013, and multiple meta-analyses). That reversed decades of cooling it down and coming back in six weeks.

Antibiotics for acute cholecystitis as adjunct or bridge: co-amoxiclav or a cephalosporin with or without metronidazole. Co-amoxiclav EML yes, off-patent, a few US dollars a course; metronidazole EML yes, a few US dollars. Analgesia: NSAIDs, diclofenac in particular, are effective for biliary colic and may reduce progression to cholecystitis; opioids for severe pain. Diclofenac off-patent and cheap.

ERCP with sphincterotomy and stone extraction for common duct stones and for gallstone pancreatitis with obstruction or cholangitis. Percutaneous cholecystostomy as a temporising drain for unfit patients with severe cholecystitis.

Ursodeoxycholic acid for dissolution works only for small, non-calcified cholesterol stones in a functioning gallbladder, takes six to 24 months, and recurrence after stopping is about 50 per cent at five years. Largely abandoned as definitive therapy, and genuinely useful for prophylaxis during rapid weight loss. Off-patent; hundreds to thousands of US dollars a year; not on the core EML. Extracorporeal shock wave lithotripsy is historical and largely abandoned.

Simple means. Gradual rather than rapid weight loss avoids a 30 per cent stone-formation risk†, and is a matter of advice only. Physical activity, with dose-dependent risk reduction. Regular meals, avoiding prolonged fasting, which keeps the gallbladder emptying. A dietary pattern of fibre, vegetable fats, nuts and coffee, associated with lower risk. Observation of silent stones — the simple means here is not operating, which is correct management for about 80 per cent of stone carriers and avoids all surgical risk and cost.

The honest limit: nothing simple dissolves established stones or treats cholecystitis. This condition ultimately needs surgery or ERCP.

Gaps. No method predicts which silent stones will become symptomatic. The optimal management of common bile duct stones — one-stage laparoscopic exploration against two-stage ERCP plus cholecystectomy — remains debated. Post-cholecystectomy pain and diarrhoea are common, poorly characterised and poorly explained. The gallstone to gallbladder cancer pathway and its geographic concentration are unexplained. Bile duct injury rates differ markedly between settings and are probably under-reported. Burden data for Africa and much of Asia are sparse.

> **Depth.** Starts in: a gallstone. Size: 1 cm†; depth +11.19. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: about 7 days († gallbladder inflammation about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Acute pancreatitis

What it is. The pancreas digests itself. Most episodes are triggered by a gallstone blocking the duct or by alcohol. Most are mild; a minority are catastrophic.

Measured. Incidence is 13 to 45 per 100,000 a year and rising in most countries. GBD 2019 gave pancreatitis roughly 115,000 to 120,000 deaths and about 2.5 to 3.5 million DALYs globally†. Overall mortality is about 1 to 5 per cent; severe necrotising pancreatitis runs at 15 to 30 per cent, and up to about 30 to 40 per cent with infected necrosis and organ failure. About 80 per cent of episodes are mild and self-limiting†.

Gallstone aetiology predominates in women and older patients; alcohol in men and younger patients. Geography follows the gallstone and alcohol distribution.

Where it starts. Gallstones account for about 40 to 50 per cent and alcohol for about 20 to 35 per cent†, between them the large majority. Then hypertriglyceridaemia above about 11 mmol/L, and hypercalcaemia. Post-ERCP pancreatitis occurs in about 3 to 10 per cent of procedures†, higher in high-risk

patients. Drugs — azathioprine, valproate, GLP-1 agonists, thiazides, oestrogens and many others, with causality often weak — then trauma, autoimmune pancreatitis, pancreatic tumour, infection with mumps or coxsackie, scorpion sting, hereditary forms through *PRSS1*, *SPINK1*, *CFTR* and *CTRC*, anatomical causes such as pancreas divisum, which is contested, and idiopathic disease in about 10 to 20 per cent. Smoking is an independent risk factor and accelerates progression to chronic disease. Monogenic hereditary pancreatitis exists, *PRSS1* with high penetrance; the population heritability of acute pancreatitis is not well quantified.

What is not known is why only a small minority of people with gallstones or heavy alcohol use ever get pancreatitis — the threshold or trigger is unexplained. Why some episodes become necrotising and others resolve in days is the central unsolved question, and no biomarker predicts it reliably at presentation. Drug causation lists are largely case-report-based and unreliable.

Cure status. SELF-LIMITING in about 80 per cent†: mild interstitial pancreatitis resolves with supportive care in days. CURABLE in the sense of preventing recurrence when the cause is removed: cholecystectomy for gallstone pancreatitis, alcohol cessation, triglyceride control. Severe necrotising pancreatitis: CONTROLLABLE at best, with high mortality and prolonged critical care; it is not cured so much as survived.

Prevention. Cholecystectomy after gallstone pancreatitis: STRONG. Index-admission cholecystectomy against delayed surgery reduces recurrent biliary events substantially — the PONCHO trial (*Lancet* 2015) gave recurrent gallstone-related complications of 5 per cent against 17 per cent. One of the clearest secondary prevention results in digestive surgery.

Alcohol cessation: STRONG for alcoholic pancreatitis recurrence, with brief interventions and structured follow-up reducing recurrence in trials. Smoking cessation: MODERATE. Triglyceride control through fibrates, diet and glycaemic control: MODERATE.

Rectal NSAID prophylaxis, indomethacin or diclofenac, before ERCP: STRONG. It reduces post-ERCP pancreatitis substantially, relative risk about 0.5 across large randomised trials and meta-analyses, and it costs cents. Pancreatic duct stenting also reduces risk in high-risk cases. This is an unusually cheap, high-yield preventive.

Treatment. Management is largely supportive, and the main advances have been in what not to do.

Fluid resuscitation with lactated Ringer's rather than saline, at moderate rather than aggressive rates: the WATERFALL trial (*NEJM* 2022) found aggressive fluid resuscitation caused more fluid overload, 20.5 against 6.3 per cent, without reducing severe pancreatitis, and was stopped early for harm. A reversal of long-standing teaching.

Early enteral nutrition: oral or enteral feeding as tolerated within 24 to 72 hours is superior to nil by mouth and to parenteral nutrition, with fewer infections, less organ failure and lower mortality across multiple meta-analyses, with PYTHON addressing timing. Nasogastric feeding is equivalent to nasojejunal. Another reversal: resting the pancreas is wrong.

Analgesia with opioids as needed and NSAIDs; adequate analgesia is not harmful. No prophylactic antibiotics: multiple trials and meta-analyses show no benefit in sterile necrosis and encourage resistance, so antibiotics are for proven or strongly suspected infection only. ERCP only for concurrent cholangitis or persistent biliary obstruction, not routinely in gallstone pancreatitis without these (APEC, *Lancet* 2020, found no benefit of early ERCP in predicted-severe pancreatitis without cholangitis).

Infected necrosis: the step-up approach, percutaneous or endoscopic drainage first, escalating to minimally invasive necrosectomy only if needed. PANTER (*NEJM* 2010) showed the step-up approach reduced major complications and death against open necrosectomy, 40 against 69 per cent on the composite endpoint; endoscopic step-up (TENSION) is comparable with fewer fistulae. Cholecystectomy before discharge for mild gallstone pancreatitis, per PONCHO.

Drug costs here are trivial — Ringer's lactate, paracetamol, opioids, enteral feed, all off-patent and most EML-listed. The expensive resource is intensive care.

Simple means. Oral feeding as soon as tolerated is cheaper and better than withholding food or giving parenteral nutrition: a simple means that outperforms an expensive one. Oral and enteral rehydration where intravenous access or monitoring is limited, with measured rather than aggressive loading, per WATERFALL. Alcohol cessation is the single most effective recurrence prevention in alcoholic pancreatitis, and brief counselling at discharge has measurable effect. Smoking cessation. Rectal diclofenac or indomethacin before ERCP, a single cheap suppository with a relative risk of about 0.5. Avoiding unnecessary antibiotics and unnecessary ERCP: simple means in the sense of omission, both evidence-based.

Gaps. No biomarker or score reliably predicts severity at presentation; Ranson, APACHE II and BISAP all perform modestly. Why gallstones or alcohol trigger pancreatitis in only a few people is unknown. Optimal fluid type and rate are still being refined after WATERFALL. Drug-induced pancreatitis attribution is unreliable. Long-term outcomes — progression to chronic pancreatitis, diabetes and exocrine insufficiency after a single severe episode — are under-measured. Burden estimates outside high-income countries are weak.

> **Depth.** Starts in: a gallstone in the duct. Size: 5 mm†; depth +10.56. First complaint: about 12 hours († hours after a trigger); time depth 42.87. One untreated course: about 7 days ([B] mostly mild; † about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book's status: SELF-LIMITING, with CURABLE and CONTROLLABLE for named strata. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Chronic pancreatitis

What it is. Repeated or continuing inflammation scars the pancreas permanently. It stops making enough digestive enzymes and insulin, and causes lasting pain.

Measured. Prevalence is about 36 to 50 per 100,000, with incidence about 5 to 14 per 100,000 a year in Western countries. It is pooled into pancreatitis in GBD with no separate chronic-only DALY figure. Exocrine insufficiency develops in most over time, and type 3c diabetes in about 30 to 50 per cent at ten to 25 years.

Pancreatic cancer risk is raised substantially, roughly 13 to 16 times overall and far higher in hereditary pancreatitis, up to about 50 to 70 times lifetime, with about a 40 per cent lifetime risk in *PRSS1* carriers who smoke. Mortality is high relative to the general population, largely from complications and from continued alcohol and tobacco use and cancer. Male predominance where alcohol is the main cause. Tropical or idiopathic fibrocalculous pancreatic forms occur in parts of India and Africa, affecting younger patients.

Where it starts. Alcohol accounts for about 45 to 65 per cent in Western series†, dose-dependently and usually after years of heavy use. Smoking is independent and dose-dependent, roughly doubling risk and accelerating progression and calcification — the strongest modifiable factor after alcohol and often underweighted. Genetic causes: *PRSS1* in autosomal dominant hereditary pancreatitis with high penetrance, then *SPINK1*, *CFTR*, *CTRC*, *CASR*; genetic forms present young.

Recurrent acute pancreatitis of any cause; obstructive causes including stricture, tumour and the contested pancreas divisum. Autoimmune pancreatitis, IgG4-related type 1 and idiopathic duct-centric type 2, is a distinct and steroid-responsive entity. Tropical and nutritional forms have an unresolved cause, with cassava, micronutrient deficiency and genetic factors — *SPINK1* being common — all proposed.

What is not known is why only a minority of heavy drinkers, about 5 to 10 per cent, develop it†. The relative weights of the necrosis-fibrosis sequence against primary fibrogenesis are debated. The mechanism of pain is poorly understood and correlates weakly with ductal or morphological findings. The cause of tropical pancreatitis remains unexplained.

Cure status. RELIEF ONLY for established disease: the fibrosis and lost function are irreversible and no treatment restores the gland. CONTROLLABLE in the sense that exocrine and endocrine failure can be replaced and pain can often be reduced. Autoimmune pancreatitis: CONTROLLABLE and highly steroid-

responsive, with dramatic clinical and radiological remission, though relapse is common. Halting progression is possible: alcohol and tobacco cessation measurably slows it.

Prevention. Alcohol cessation or avoidance: STRONG. Smoking cessation: STRONG, independent and dose-dependent, and it reduces pancreatic cancer risk on top of pancreatitis risk. Early cholecystectomy and treating the causes of recurrent acute pancreatitis: MODERATE, preventing the recurrent-acute to chronic transition. Genetic counselling in hereditary pancreatitis, where cancer prevention by smoking cessation is especially high-yield: MODERATE. Antioxidants to prevent progression: CONTESTED and negative; trials have not shown benefit on progression.

Treatment. Pancreatic enzyme replacement therapy for exocrine insufficiency demonstrably improves fat absorption, weight, steatorrhoea and nutritional status, with a mortality benefit suggested in cohort data. It must be taken with meals and often requires acid suppression to work. Pancreatic enzymes are on the EML as a listed medicine, under gastrointestinal medicines and for cystic fibrosis in the complementary list; off-patent; cost about US$1,000 to 4,000 a patient-year in high-income markets (for either price) and far less in India, at about US$100 to 400. This is a significant access problem: a cheap-to-make animal-derived product priced high in some markets and often unavailable in low-income settings.

Analgesia stepwise: paracetamol, NSAIDs, then adjuvants — pregabalin has randomised support in this condition — then opioids with caution, since dependence is a major problem. Pregabalin off-patent; tens to hundreds of US dollars a year. Alcohol and smoking cessation, which are disease-modifying rather than merely supportive. Diabetes management for type 3c, where insulin is usually required eventually and is brittle because glucagon is also lost. Insulin human is an EML-listed medicine, as short-acting and intermediate-acting entries, each for type 1 and type 2 diabetes; human insulin off-patent; tens to hundreds of US dollars a year, far more for analogues.

Endoscopic therapy — pancreatic duct stenting, stone extraction, ESWL for obstructing stones — for painful obstructive disease. Surgery for pain: lateral pancreaticojejunostomy (Puestow), Frey, Beger, or resection. The ESCAPE trial (*JAMA* 2020) found early surgery gave lower pain scores than an endoscopy-first step-up approach in painful chronic pancreatitis, and surgery outperforms endoscopy for durable pain relief in several trials.

Corticosteroids for autoimmune pancreatitis, with rapid response, and rituximab for relapsing IgG4 disease. Rituximab is an EML-listed medicine, under multiple sclerosis and targeted therapies in the complementary list. Nutritional support: fat-soluble vitamin A, D, E and K and B12 replacement, calcium and vitamin D for the near-universal osteoporosis risk, and dietitian input; micronutrient costs are low and the basic forms are EML-listed. Coeliac plexus block gives short-lived benefit with a limited role.

Simple means. Alcohol cessation and smoking cessation are the only measures that alter the disease course. No supply chain, and the largest available effect. Smaller, frequent meals — and not the old low-fat dogma, since fat restriction worsens energy and fat-soluble vitamin status and adequate enzyme replacement is preferred to fat avoidance. Medium-chain triglycerides where available, since they are absorbed without lipase. Vitamin D, calcium and weight-bearing exercise against the high osteoporosis prevalence in this group. Alcohol-cessation support through peer groups and brief intervention is a low-cost, high-yield intervention.

The honest limit: without manufactured enzymes, exocrine insufficiency cannot be corrected. Enzyme replacement has no simple substitute, which makes its price and availability the key issue.

Gaps. The pain mechanism is not understood and correlates poorly with imaging, so pain-directed treatment is empirical. Diagnosis of early chronic pancreatitis is unreliable because no good test exists before structural change. The optimal timing of surgery against endoscopy is still being defined after ESCAPE. Tropical pancreatitis is unexplained and under-researched. Enzyme dosing is poorly standardised and under-dosing is endemic. Pancreatic cancer surveillance strategies in hereditary pancreatitis are not validated. Burden data are poor almost everywhere.

> **Depth.** Starts in: the pancreatic duct. Size: 3 mm†; depth +10.10. First complaint: about 10 years ([B] after years of heavy drinking; † about 10 years); time depth 50.97. One untreated course: no number ([B] permanent).

> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: RELIEF ONLY, with CONTROLLABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Liver cirrhosis and its causes

What it is. Long-term liver injury replaces working liver with scar. Blood cannot pass through easily, so pressure rises in the portal vein, and the liver's functions fail. Late stages bring fluid in the abdomen, bleeding, confusion and liver cancer.

Measured. GBD 2019 gave cirrhosis and other chronic liver diseases roughly 1.47 million deaths globally, about 2.4 per cent of all deaths, and on the order of 46 million DALYs†. Compensated cirrhosis has a median survival over twelve years; decompensated cirrhosis about two years.

Aetiological shares, GBD 2019 global: hepatitis B about 24 per cent, hepatitis C about 27 per cent, alcohol about 27 per cent, metabolic fatty liver disease about 8 to 9 per cent, other about 12 per cent†. These shares are shifting fast, with viral hepatitis falling under treatment and vaccination while alcohol and metabolic disease rise.

Hepatitis B dominates in East Asia and sub-Saharan Africa; hepatitis C in Egypt, Pakistan and parts of eastern Europe; alcohol in Europe and the Americas; metabolic disease is rising everywhere. Male deaths are roughly double female. Peak deaths fall in middle age, making this a major cause of premature working-age mortality. Hepatocellular carcinoma accounts for about 800,000 to 900,000 new cases a year globally, mostly on a background of cirrhosis (GLOBOCAN 2022).

Where it starts. The causes are mostly known, measurable and in large part preventable, which is the central fact about cirrhosis.

Chronic hepatitis B: about 254 million people living with chronic infection on the WHO 2024 estimate†. Note that the two live WHO fact sheets disagree: the hepatitis B fact sheet of 28 July 2026 gives 240 million for 2024, while the STI fact sheet of 10 September 2025 gives 254 million for 2022. Both are printed. Vertical and early-childhood transmission dominate in high-prevalence areas.

Chronic hepatitis C: about 50 million people chronically infected†, through injection drug use, unsafe injections and unscreened blood products.

Alcohol is dose-dependent with no safe threshold for liver injury established; risk rises steeply above about 30 g a day in men and about 20 g in women, with wide individual variation, and only about 10 to 20 per cent of heavy drinkers develop cirrhosis†. Metabolic fatty liver disease, through obesity, type 2 diabetes and metabolic syndrome, is now a leading and rising cause.

Others: haemochromatosis with *HFE* C282Y homozygosity, Wilson disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Budd-Chiari syndrome, cardiac and congestive causes, drug-induced injury, schistosomiasis giving periportal fibrosis rather than true cirrhosis, and hepatitis D, which markedly accelerates hepatitis B cirrhosis.

Co-factors multiply risk rather than add to it: obesity and diabetes markedly accelerate both alcohol and viral fibrosis; alcohol with hepatitis C is more than additive; smoking; aflatoxin, which is synergistic with hepatitis B for hepatocellular carcinoma; and HIV co-infection. *PNPLA3* I148M is the strongest common genetic modifier for both alcohol-related and metabolic liver disease, with *TM6SF2*, *MBOAT7* and the protective *HSD17B13* also established. These explain why only a minority of exposed people progress, but only partly.

What is not known is why only 10 to 20 per cent of heavy drinkers and a minority of those with steatosis progress to cirrhosis. Fibrosis progression rate cannot be predicted in an individual. The determinants of regression after cause removal are not well characterised. Why decompensation occurs when it does, and the mechanism of acute-on-chronic liver failure, are incompletely understood.

Cure status. This needs splitting, because the answer differs sharply by cause and stage.

The cause, named case by case: hepatitis C is CURABLE, over 95 per cent with direct-acting antivirals. Hepatitis B is CONTROLLABLE, suppressed and rarely cured. Alcohol-related disease is CONTROLLABLE by abstinence. Haemochromatosis and Wilson disease are CONTROLLABLE, by venesection and chelation. Autoimmune hepatitis is CONTROLLABLE by immunosuppression.

Established cirrhosis: CONTROLLABLE, with real reversibility when the cause is removed early. Fibrosis itself is partly reversible, and this is well demonstrated: removing the cause produces measurable fibrosis regression, including from cirrhosis, in a substantial proportion, documented after hepatitis C cure, hepatitis B suppression, alcohol abstinence and weight loss in metabolic steatohepatitis, with clinical outcomes improving correspondingly.

Decompensated cirrhosis: CONTROLLABLE at best; CURABLE only by transplantation, which is a genuine cure but supply-limited and geographically concentrated.

Prevention. Cirrhosis is one of the most preventable major causes of death.

Hepatitis B vaccination: STRONG. A birth dose plus schedule prevents chronic infection with about 90 to 95 per cent efficacy, and Taiwan's programme produced a documented fall in childhood hepatocellular carcinoma; birth-dose coverage remains the key gap in Africa. Among the most cost-effective interventions in medicine. Hepatitis B antiviral prophylaxis in pregnancy with a birth-dose vaccine and immunoglobulin: STRONG for preventing vertical transmission.

Hepatitis C treatment as prevention, blood-product screening, safe injection practice, needle and syringe programmes, and opioid agonist therapy: STRONG. Alcohol policy — taxation, availability restriction, marketing limits: STRONG at population level, and alcohol taxation is among the best-evidenced population health measures. Individual alcohol reduction or abstinence: STRONG.

Weight management and diabetes control: MODERATE for metabolic cirrhosis. Aflatoxin reduction through grain storage and drying: MODERATE, and synergistic with hepatitis B. Coffee consumption: MODERATE, observational only, consistently associated with lower cirrhosis incidence and mortality across many cohorts and dose-dependently. Avoiding unnecessary hepatotoxic drugs, and paracetamol dose limits: MODERATE.

Treatment. Treating the cause first. Hepatitis C with direct-acting antivirals gives a sustained virological response above 95 per cent with eight to twelve weeks of sofosbuvir-velpatasvir or glecaprevir-pibrentasvir, including in cirrhosis. Generic regimens now cost as little as US$40 to 90 per curative course in low- and middle-income countries under licensing agreements, against tens of thousands of US dollars originator list prices at launch. Sofosbuvir and daclatasvir are EML-listed. This is the largest price collapse for a curative drug in modern medicine.

Hepatitis B with nucleos(t)ide analogues, tenofovir disoproxil or entecavir, suppresses viral replication and reduces fibrosis progression and hepatocellular carcinoma risk substantially, usually lifelong. EML yes; off-patent; tens of US dollars a patient-year for generic tenofovir. Extremely cheap for the benefit delivered.

Alcohol-related liver disease: abstinence is the treatment with the largest effect on survival. Pharmacotherapy for alcohol use disorder — baclofen has the best evidence in cirrhosis, with acamprosate and naltrexone, the latter avoided in advanced liver disease. All off-patent; tens to hundreds of US dollars a year. Metabolic steatohepatitis: weight loss, with resmetirom the first approved drug, expensive at tens of thousands of US dollars a year list, and GLP-1 agonists showing benefit. Autoimmune hepatitis: prednisolone with azathioprine, effective and cheap, both off-patent. Haemochromatosis: venesection, nearly free. Wilson disease: penicillamine, trientine, zinc. Primary biliary cholangitis: ursodeoxycholic acid, then obeticholic acid or fibrates.

Managing the complications. Non-selective beta-blockers, propranolol or carvedilol, for portal hypertension and variceal prophylaxis; off-patent, EML-listed, a few dollars a year. Ascites: salt restriction, spironolactone with furosemide, large-volume paracentesis with albumin, and TIPS for refractory cases. Spironolactone is an EML-listed medicine under diuretics and heart failure; furosemide EML-listed; both off-patent, tens of US dollars a year. Albumin is expensive and supply-constrained.

Spontaneous bacterial peritonitis: a third-generation cephalosporin, with secondary prophylaxis using norfloxacin or ciprofloxacin; cheap and off-patent. Hepatocellular carcinoma surveillance: six-monthly ultrasound with or without alpha-fetoprotein in cirrhosis, improving survival through earlier-stage detection on cohort-based and debated evidence. Transplantation is definitive for end-stage disease, with cost and availability the binding constraints and most of the world having no access. Vaccination against hepatitis A and B, pneumococcus, influenza and COVID-19, and avoidance of alcohol and NSAIDs in cirrhosis.

Simple means. Alcohol abstinence is the largest single survival effect available in alcohol-related cirrhosis, including in decompensated disease, where abstinence can restore compensation. No supply chain. Salt restriction, about 2 g sodium a day, for ascites, reducing diuretic need and paracentesis frequency; free, and often more effective than it is given credit for.

Adequate protein and energy intake with a late-evening snack. Malnutrition and sarcopenia are independent predictors of death in cirrhosis, and a bedtime carbohydrate and protein snack measurably improves nitrogen balance by shortening the overnight fast. Protein restriction is wrong and harmful, and is an abandoned practice still encountered.

Weight loss and exercise in metabolic disease. Coffee, with a dose-dependent association with lower progression and mortality, cheap and widely available. Resistance exercise against sarcopenia. Avoiding NSAIDs, aminoglycosides and alcohol, and checking for hepatotoxic herbal remedies. Hepatitis B birth-dose vaccination: a single cheap injection within 24 hours of birth prevents a lifetime of liver disease, and it is the highest-value simple intervention here, though it does require a cold chain.

Gaps. Fibrosis progression in an individual cannot be predicted. The extent and durability of cirrhosis regression after cause removal is not fully characterised, and cirrhosis may be too coarse a category. Non-invasive fibrosis tests, FIB-4 and elastography, perform moderately and cut-offs differ between populations and aetiologies. Acute-on-chronic liver failure definitions differ between EASL and APASL, so the literature is not comparable. GBD aetiological attribution relies on modelling and the alcohol against metabolic split is uncertain. Transplant access is grossly unequal and largely unmeasured globally. The magnitude of the hepatocellular carcinoma surveillance benefit is disputed.

> **Depth.** Starts in: a liver cell. Size: 25 µm†; depth +5.74. First complaint: about 25 years († 20–30 years of liver damage); time depth 51.80. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Scarring can stop. Advanced scar does not go back. So it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Metabolic dysfunction-associated steatotic liver disease

The nomenclature changed in the 2023 multi-society Delphi consensus: MASLD replaced NAFLD and MASH replaced NASH. The definitions are not identical — MASLD requires at least one cardiometabolic criterion — so prevalence figures are not strictly interchangeable across the 2023 boundary.

What it is. Fat builds up in the liver in people who do not drink heavily. In some it causes inflammation and scarring. It travels with obesity, diabetes and metabolic syndrome.

Measured. Global prevalence is about 30 to 32 per cent of adults, up from about 25 per cent a decade earlier (Younossi and subsequent meta-analyses)†. It is the most common liver disease in the world. Regionally: Latin America and the Middle East and North Africa highest at about 35 to 45 per cent, Africa lowest measured at about 13 to 15 per cent, Europe about 25 to 30 per cent, Asia about 30 per cent†.

Steatohepatitis affects about 5 to 7 per cent of the general population and about 20 to 25 per cent of those with the fatty liver. In type 2 diabetes, prevalence is about 55 to 70 per cent. GBD attributes about 8 to 9 per cent of cirrhosis deaths to it†, which almost certainly understates it: related cirrhosis is frequently

reclassified as cryptogenic, and this is the fastest-growing indication for liver transplant in several countries.

Cardiovascular disease, not liver disease, is the leading cause of death in this condition. That is the key clinical fact. Prevalence rises with age but is now common in children and adolescents, affecting about 10 per cent of children and about 35 per cent of obese children†.

Where it starts. Obesity, especially visceral adiposity, dose-dependently, is the dominant driver. Type 2 diabetes and insulin resistance are both cause and consequence. Metabolic syndrome components: hypertension and dyslipidaemia with high triglycerides and low HDL. Dietary factors: high fructose and sugar-sweetened beverage intake, ultra-processed food, excess energy, with fructose having specific mechanistic support through de novo lipogenesis. Sarcopenia and physical inactivity, independent of BMI.

Lean disease occurs in about 10 to 20 per cent of cases† — normal BMI with metabolic dysfunction, more common in Asian populations, and not benign. *PNPLA3* I148M is the strongest common variant, raising both risk and fibrosis progression, with *TM6SF2*, *MBOAT7*, *GCKR* and the protective *HSD17B13*. Heritability is estimated at about 20 to 50 per cent depending on method and on whether steatosis or fibrosis is the trait, from twin and familial studies. Obstructive sleep apnoea, polycystic ovary syndrome, hypothyroidism and hypopituitarism also contribute.

What is not known is why only about 20 to 25 per cent of those with steatosis progress to steatohepatitis, and only a fraction of those to cirrhosis. The determinants of progression are the central unknown, and there is no reliable way to identify progressors prospectively. Whether steatosis itself is harmful or merely a marker is debated. The reason cardiovascular risk dominates is not fully explained. Lean disease is poorly understood. And whether this condition causes cardiovascular disease or shares its causes is unresolved, which matters greatly for how it should be treated.

Cure status. CONTROLLABLE by weight loss, and the dose-response is one of the best quantified relationships in hepatology. From Vilar-Gomez (*Gastroenterology* 2015, 293 patients with biopsy-paired histology after twelve months of lifestyle intervention): 5 per cent or more weight loss improves steatosis; 7 per cent or more gives steatohepatitis resolution in about 64 to 65 per cent; 10 per cent or more gives resolution in about 90 per cent, fibrosis regression in about 45 per cent, and NAS reduction in close to 100 per cent. Bariatric surgery produces resolution in about 80 to 85 per cent and fibrosis regression in about 30 to 70 per cent at five years (Lassailly, *Gastroenterology* 2020).

So: a condition that can be put into remission by weight loss and stays in remission while the loss is sustained, and sustained loss is achieved by a minority.

Prevention. Weight management: STRONG, on the dose-response above. Physical activity: STRONG, and partly independent of weight loss — exercise reduces hepatic fat even without weight change, by about 20 to 30 per cent relative reduction across multiple randomised trials; both aerobic and resistance training work, and resistance training achieves it at lower energy expenditure. Reducing sugar-sweetened beverages and fructose: MODERATE, with randomised trials in adolescents showing liver fat reduction. Mediterranean dietary pattern: MODERATE, reducing liver fat independent of weight loss in randomised trials. Reducing ultra-processed food: MODERATE. Coffee: MODERATE, observational, dose-dependent and consistent. Avoiding alcohol: MODERATE, since even moderate alcohol adds risk here, and the older notion that modest alcohol was protective is not supported. Diabetes prevention and control: STRONG.

Treatment. Weight loss by diet and exercise is first line, with the effect sizes above and no drug cost; 7 to 10 per cent loss is the therapeutic target.

GLP-1 receptor agonists: semaglutide gave steatohepatitis resolution of about 59 per cent against 17 per cent placebo at 72 weeks (Newsome, *NEJM* 2021, phase 2), confirmed in phase 3 (ESSENCE, 2024–25) with resolution about 63 against 34 per cent and fibrosis improvement about 37 against 22 per cent†. On patent; about US$9,000 to 16,000 a year US list, less in Europe; semaglutide was added to the EML in 2025 for diabetes†. Generic liraglutide is beginning to appear; tirzepatide is similar or better.

Resmetirom, a thyroid hormone receptor beta agonist, is the first drug approved specifically for steatohepatitis with F2 to F3 fibrosis (US FDA, March 2024). MAESTRO-NASH gave resolution of 26 to

30 per cent against 10 per cent placebo, and fibrosis improvement 24 to 26 against 14 per cent. On patent; tens of thousands of US dollars a year list. Not on the EML.

Pioglitazone gives resolution of about 34 to 47 per cent against about 21 per cent placebo (PIVENS and others)†, at the cost of weight gain, fluid retention and fracture risk. Off-patent; tens to hundreds of US dollars a year — by far the cheapest effective pharmacotherapy, and underused. Not on the core EML.

Vitamin E, 800 IU a day, gave improvement in about 43 per cent against 19 per cent placebo in non-diabetic patients (PIVENS, *NEJM* 2010). Off-patent; tens of US dollars a year; concerns about prostate cancer and haemorrhagic stroke at high dose limit enthusiasm.

Bariatric or metabolic surgery is the most effective durable intervention for those with severe obesity, with resolution in about 80 to 85 per cent. SGLT2 inhibitors reduce liver fat, and their cardiovascular and renal benefits make them attractive in comorbid diabetes; increasingly off-patent.

Statins do not treat the liver disease but are safe in it and indicated for the dominant cardiovascular risk. They are under-prescribed because of unfounded fear of hepatotoxicity. Off-patent, EML-listed, tens of US dollars a year. Arguably the highest-yield drug here, by addressing the actual cause of death. Treating the full cardiometabolic package — blood pressure, lipids, glycaemia — is the mortality-relevant intervention.

Simple means. This is a condition where simple means are not merely adjunctive but curative. Weight loss of 7 to 10 per cent gives steatohepatitis resolution in 64 to 90 per cent and fibrosis regression in about 45 per cent†, with no product required. Exercise without weight loss reduces hepatic fat by about 20 to 30 per cent†, and resistance training is effective at lower energy cost and feasible for those unable to do aerobic work. Eliminating sugar-sweetened drinks, with randomised demonstration of liver fat reduction. Mediterranean-pattern eating — olive oil, legumes, fish, vegetables, nuts, whole grains — reduces liver fat independent of weight loss. Coffee, two to three cups a day, with a dose-dependent association with less fibrosis. Avoiding alcohol. Sleep apnoea treatment and adequate sleep.

The comparison with the drugs is worth setting down plainly: 10 per cent weight loss resolves steatohepatitis in about 90 per cent, against about 26 to 30 per cent for a drug costing tens of thousands of US dollars a year. The limiting factor is adherence and food environment, not efficacy.

Gaps. There is no reliable way to identify who will progress. Non-invasive tests — FIB-4, elastography, ELF — have moderate accuracy and were largely validated in secondary care, so they perform worse in population screening. Whether to screen at all, and whom, is unsettled, and major guidelines differ. The 2023 renaming means prevalence and outcome data are not strictly comparable across the boundary. Lean disease is poorly characterised. Long-term outcome data for resmetirom and the GLP-1 agonists on hard endpoints — decompensation, death — are not yet available. African prevalence data are sparse. The causal against shared-risk relationship with cardiovascular disease is unresolved.

> **Depth.** Starts in: a liver cell. Size: 25 µm†; depth +5.74. First complaint: about 45 years († onset about age 45); time depth 52.34. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Alcohol-related liver disease

What it is. Drinking damages the liver in stages: fat, then inflammation, then scarring. Severe alcoholic hepatitis can kill within weeks. Stopping drinking is the one thing that reliably changes the outcome.

Measured. Alcohol accounts for roughly 27 per cent of global cirrhosis deaths (GBD 2019)†, and a higher share in Europe and the Americas, over 50 per cent in several European countries. Alcohol consumption is attributed about 2.6 million deaths a year across all causes (WHO Global Status Report on Alcohol and Health, 2024), of which liver disease is a major component†.

Severe alcoholic hepatitis carries a 28-day mortality of about 20 to 30 per cent, and about 30 to 50 per cent at six months in those with high Maddrey or MELD scores. About 90 per cent of heavy drinkers develop

steatosis; 10 to 35 per cent develop alcoholic hepatitis; and only about 10 to 20 per cent develop cirrhosis. Mortality peaks in middle age, with a male to female ratio of roughly 2 to 3:1 for deaths, though women develop disease at lower intakes. Rates are rising in many countries, with a documented acceleration during and after the COVID-19 pandemic, especially in young adults and women.

Where it starts. Cumulative alcohol dose is the necessary cause. Risk rises steeply above about 30 g a day in men and about 20 g in women, and duration matters as much as daily amount. Female sex: women develop disease at lower intake and shorter duration, attributed to body water distribution and lower gastric alcohol dehydrogenase — a consistent and important difference. Drinking pattern: daily drinking, and drinking outside meals, carry higher risk than the same total taken with food.

Obesity and diabetes are strongly synergistic, multiplying alcohol's hepatic risk rather than adding to it. Smoking. Viral hepatitis co-infection, more than additive. *PNPLA3* I148M is the strongest genetic modifier, with *TM6SF2*, *MBOAT7* and the protective *HSD17B13*; alcohol dependence itself has substantial heritability, about 50 per cent, and liver-disease susceptibility given equal exposure is partly genetic but mostly unexplained.

What is not known is why only 10 to 20 per cent of heavy drinkers get cirrhosis, the single largest unexplained feature. Why alcoholic hepatitis strikes some and not others, and why it can occur after a period of relative abstinence, is unknown. Why corticosteroid response is so variable, and why the microbiome and gut-permeability axis matters in some patients, is unresolved.

Cure status. CONTROLLABLE, with substantial reversibility determined almost entirely by abstinence. Steatosis reverses within weeks of abstinence. Alcoholic hepatitis is survivable, and abstinence transforms long-term survival. Compensated cirrhosis with abstinence gives a five-year survival of about 85 to 90 per cent, against about 30 to 60 per cent with continued drinking; decompensated cirrhosis with abstinence gives over 60 per cent at five years against about 30 per cent with continued drinking. Few interventions in medicine produce a survival difference of this size. Decompensated disease can re-compensate with abstinence, sometimes removing the need for transplant.

Transplantation is CURABLE, and early transplantation in carefully selected severe alcoholic hepatitis non-responders gives about 70 to 80 per cent six-month survival against about 25 to 30 per cent without (Mathurin, *NEJM* 2011, and subsequent series).

Prevention. Population alcohol policy: STRONG. Taxation and minimum unit pricing have measurable effects on liver mortality — Scotland's minimum unit pricing was associated with reduced alcohol-specific deaths, and the Russian and Baltic tax and availability changes produced large documented mortality shifts. Among the best-evidenced population health interventions available.

Individual abstinence or reduction: STRONG. Weight management: MODERATE, given the synergy with obesity. Hepatitis B vaccination and hepatitis C treatment in drinkers: STRONG, removing a multiplicative co-factor. Screening and brief intervention in primary care: MODERATE, reducing consumption modestly but at population scale. Smoking cessation: MODERATE.

Treatment. Abstinence has by far the largest effect; everything else is secondary.

Treatment of alcohol use disorder is liver treatment, and it is under-delivered. Integrated hepatology and addiction clinics improve both abstinence and survival. Baclofen is the best-evidenced agent in cirrhosis and safe in liver disease; off-patent; tens to hundreds of US dollars a year. Acamprosate is effective for abstinence maintenance; off-patent; hundreds of US dollars a year. Naltrexone is effective but avoided in advanced liver disease; off-patent. Disulfiram is hepatotoxic and generally avoided here. Psychosocial treatment — CBT, motivational interviewing, twelve-step and mutual aid — all has demonstrated effect at minimal material cost.

Severe alcoholic hepatitis with Maddrey discriminant function of 32 or more, or MELD above 20: corticosteroids, prednisolone 40 mg a day for 28 days. STOPAH (Thursz, *NEJM* 2015, 1,103 patients) found prednisolone reduced 28-day mortality, odds ratio 0.72 (95 per cent CI 0.52 to 1.01, p = 0.06) — borderline on the primary analysis and significant after adjustment — with no benefit at 90 days or one year, while pentoxifylline showed no benefit at all. So the benefit is short-term and modest, and infection risk rises. The Lille score at day 7 identifies non-responders, in whom steroids should stop. Prednisolone

EML yes; off-patent; a few to tens of US dollars a year. Pentoxifylline is abandoned on the STOPAH evidence.

N-acetylcysteine added to steroids shows some survival benefit at one month in trials; cheap, off-patent, EML-listed. Nutrition: energy intake below about 21.5 kcal/kg a day predicts mortality in alcoholic hepatitis, and enteral feeding is used where intake is inadequate. Thiamine and B vitamins to prevent Wernicke encephalopathy; cheap, essential, EML-listed, given before glucose. Management of cirrhosis complications as in the cirrhosis entry. Early liver transplantation for selected severe alcoholic hepatitis non-responders and for abstinent cirrhotic patients; the six-month rule is no longer evidence-based as an absolute requirement.

Simple means. Abstinence is the largest single survival intervention and requires no product; mutual-aid groups are free and have measurable effect. Nutrition is critical and routinely neglected: malnutrition is near-universal in alcoholic hepatitis and independently predicts death, and adequate energy at about 35 kcal/kg a day with protein at 1.2 to 1.5 g/kg a day, including a late-evening snack, is the target. Protein restriction is harmful and must not be used.

Thiamine costs pennies per dose and prevents an irreversible neurological catastrophe. Weight management removes the synergistic multiplier. Smoking cessation. Brief interventions and peer support are low-cost, scalable and evidence-based. At population level, alcohol taxation and availability restriction need no clinical infrastructure at all and have the largest measured population effect.

Gaps. Why most heavy drinkers escape cirrhosis is unknown. Corticosteroid benefit in alcoholic hepatitis is real but small and short-lived, and STOPAH's borderline primary result is interpreted differently by different guideline bodies — a genuine disagreement between sources. No effective therapy exists for steroid non-responders except transplant. Transplant selection criteria for alcohol-related disease vary enormously between centres and countries, and the ethical debate is unresolved. GBD attribution between alcohol and metabolic disease is uncertain where both are present, which is increasingly common. Alcohol-related liver mortality data in many countries are compromised by under-reporting on death certificates.

> **Depth.** Starts in: the ethanol molecule. Size: 0.4 nm†; depth −4.31. First complaint: about 10 years († about 10 years of drinking); time depth 50.97. One untreated course: no number ([B] severe hepatitis kills within weeks).
>
> **Model reading.** Way of ending: restore proportion. Layer: surround. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Hepatic encephalopathy

What it is. When the liver fails, toxins the gut produces — chiefly ammonia — reach the brain. The person becomes confused, drowsy and eventually comatose. It comes and goes, often with a trigger.

Measured. Overt hepatic encephalopathy occurs in about 30 to 40 per cent of people with cirrhosis at some point. Minimal or covert encephalopathy affects about 20 to 80 per cent of cirrhotic patients depending on the test used, and the fourfold range reflects the absence of a standard test. After a first overt episode, one-year survival without transplant is about 40 to 50 per cent. It is not a separate GBD cause; the burden sits inside cirrhosis. Recurrence within a year is the norm without prophylaxis, at about 40 to 50 per cent. It is a major driver of hospital admission, carer burden, driving incapacity and loss of employment in cirrhosis.

Where it starts. Underlying cirrhosis with portosystemic shunting is the necessary substrate. It also occurs after TIPS insertion, in about 10 to 50 per cent†, and in acute liver failure.

The precipitants are identifiable in most episodes, and this is the practically important part. Infection, especially spontaneous bacterial peritonitis, is the commonest. Gastrointestinal bleeding. Constipation. Dehydration and electrolyte disturbance, especially hypokalaemia and hyponatraemia, and over-diuresis. Renal impairment. Sedatives, opioids and benzodiazepines. Alcohol binge, and non-adherence to lactulose. Dietary protein excess is a weak and largely historical precipitant, and the old practice of protein restriction causes more harm than it prevents. Sarcopenia is an independent risk factor, because muscle metabolises ammonia and muscle loss worsens encephalopathy.

What is not known: ammonia correlates poorly with grade in individuals, so the full mechanism is clearly not ammonia alone — inflammation, manganese, GABAergic tone, bile acids and the microbiome all contribute without a settled model. Why some cirrhotic patients with heavy shunting never develop it is unexplained. Whether minimal encephalopathy should be screened for and treated routinely is unresolved, partly because no reference test exists.

Cure status. With the cirrhosis in place: CONTROLLABLE. Individual episodes are highly reversible — treating the precipitant and giving lactulose resolves most — but the underlying predisposition persists as long as the cirrhosis does, so recurrence is expected without prophylaxis. After liver transplantation: CURABLE, though some cognitive deficit may persist.

Prevention. Lactulose for secondary prophylaxis: STRONG. After a first episode, lactulose reduces recurrence substantially, with a randomised trial giving recurrence of about 20 per cent against about 47 per cent placebo (Sharma, *Gastroenterology* 2009). Rifaximin added to lactulose: STRONG. Bass (*NEJM* 2010, 299 patients) gave breakthrough encephalopathy of 22 against 46 per cent, hazard ratio 0.42 (95 per cent CI 0.28 to 0.64), and hospitalisation 13.6 against 22.6 per cent over six months.

Preventing and promptly treating precipitants: STRONG — peritonitis prophylaxis, variceal prophylaxis, avoiding over-diuresis, treating constipation, avoiding sedatives. Avoiding benzodiazepines and opioids in cirrhosis: STRONG. Maintaining muscle mass and nutrition: MODERATE, plausible and supported by observational data. Primary prophylaxis in those who have never had an episode: CONTESTED, and not standard.

Treatment. Identify and treat the precipitant — culture and treat infection, stop bleeding, correct electrolytes and hypokalaemia, rehydrate, stop sedatives, relieve constipation. That is the single most important step.

Lactulose is first line, titrated to two or three soft stools daily, resolving most episodes and preventing recurrence at 20 against 47 per cent. EML yes; off-patent; tens to hundreds of US dollars a patient-year. Cheap, effective, universally available. Over-dosing causes dehydration and can precipitate encephalopathy, a common iatrogenic trap.

Rifaximin is added for recurrence prevention, hazard ratio 0.42 for breakthrough episodes. Not on the EML; on patent in many markets; about US$2,500 to 15,000 a patient-year in high-income markets, though Indian generics are a small fraction of that. The cost differential between lactulose and rifaximin is one of the starkest in hepatology for a modest incremental benefit.

Lactulose enemas where the oral route is unavailable. L-ornithine L-aspartate reduces ammonia with benefit shown in some trials, mainly used outside the United States and United Kingdom, at modest cost. Branched-chain amino acid supplementation improves manifestations in meta-analysis and is expensive relative to food. Neomycin and metronidazole are historical alternatives limited by toxicity. Correct hyponatraemia cautiously, avoiding over-rapid correction. Reduce or occlude large portosystemic shunts by embolisation in refractory cases, or reduce TIPS diameter. Liver transplantation is definitive. Albumin has some evidence for benefit in overt encephalopathy, and is expensive and supply-limited.

Simple means. Adequate dietary protein, not restriction, is the most important correction in this entry. A randomised trial (Córdoba, *Journal of Hepatology* 2004) showed protein restriction produced no benefit and increased protein breakdown, and guidelines now recommend 1.2 to 1.5 g/kg a day of protein and about 35 kcal/kg a day of energy in cirrhosis, even during encephalopathy. Decades of low-protein diets were actively harmful.

Vegetable and dairy protein may be better tolerated than meat protein. Frequent small meals with a late-evening snack shortens the overnight fast, improves nitrogen balance and reduces muscle breakdown, at no cost. Preventing constipation with fibre and adequate fluid removes a precipitant at no cost; lactulose is the pharmacological version of the same thing. Resistance exercise to maintain muscle mass is mechanistically direct, since muscle is the main alternative site of ammonia disposal when the liver fails. Avoiding alcohol, sedatives and benzodiazepines. Zinc replacement where deficient, which is common in cirrhosis and involved in the urea cycle; cheap.

Carer education to recognise early signs — day-night reversal, altered handwriting — and to seek help early costs nothing and has a measurable effect on admission severity. Driving advice: minimal encephalopathy impairs driving measurably, and this is a safety intervention requiring only a conversation.

Gaps. There is no reference standard for diagnosing minimal or covert encephalopathy, so prevalence ranges fourfold and screening cannot be evaluated properly. Ammonia levels correlate poorly with severity and should not guide management, yet frequently do. Whether minimal encephalopathy should be treated is unresolved. Rifaximin's cost-effectiveness is contested and varies hugely by market price. The mechanism is incompletely understood beyond ammonia. Long-term cognitive outcomes after repeated episodes, including after transplant, are under-studied.

> **Depth.** Starts in: ammonia. Size: 0.3 nm†; depth −4.57. First complaint: about 24 hours († hours to days after a trigger); time depth 43.50. One untreated course: about 3 days ([B] comes and goes; † an episode lasts days); depth 44.50.
>
> **Model reading.** Way of ending: restore proportion. Layer: word. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Hernias: inguinal and hiatal

What it is. A hernia is tissue pushing through a weak point. An inguinal hernia pushes bowel or fat through the groin wall. A hiatal hernia lets the stomach slide up through the diaphragm into the chest.

Measured. For inguinal hernia, lifetime risk is about 27 to 30 per cent in men and about 3 to 6 per cent in women, one of the largest sex differences in surgical disease. Over 20 million inguinal hernia repairs are performed worldwide each year, making it the commonest general surgical operation. GBD 2019 gave inguinal, femoral and abdominal hernia roughly 32,000 to 59,000 deaths and about 2 to 3 million DALYs globally, mostly from obstruction and strangulation where surgical access is lacking. Age distribution is bimodal: infancy, then rising steadily after fifty. The untreated burden is concentrated in low-income settings, with large unmet surgical need in sub-Saharan Africa, where giant and strangulated hernias are common and strangulation mortality is substantial.

For hiatal hernia, prevalence is highly method-dependent: about 10 to 20 per cent of adults by endoscopy, higher with careful measurement and with age, and present in the majority of patients with erosive oesophagitis. It is not a separate GBD cause. Type I, sliding, accounts for over 95 per cent†; types II to IV, paraoesophageal, are uncommon but carry volvulus and strangulation risk.

Where it starts. For inguinal hernia: male sex, about eight to ten times the risk; age; a patent processus vaginalis, which is congenital and the basis of paediatric and many indirect adult hernias. Family history raises risk several-fold, with heritability estimated at about 57 per cent in Swedish twin data†. Connective tissue disorders — Ehlers-Danlos, Marfan — and altered collagen type I to III ratio; smoking, which impairs collagen. Raised intra-abdominal pressure from chronic cough or COPD, constipation and straining, prostatism, ascites, heavy manual work and pregnancy.

Low BMI is a risk factor, not high — a counter-intuitive and well-replicated finding for inguinal hernia specifically, since obesity is a risk factor for incisional and hiatal hernia but appears protective for inguinal. Prior appendicectomy or open prostatectomy; collagen-degrading enzyme activity.

For hiatal hernia: age, through diaphragmatic and phreno-oesophageal ligament laxity; obesity, dose-dependently; raised intra-abdominal pressure; pregnancy; kyphoscoliosis; prior oesophageal surgery; congenital factors. There is some familial clustering and heritability is not well quantified.

What is not known is why the collagen and connective-tissue changes occur; why the male excess is so extreme beyond the processus vaginalis explanation; and which asymptomatic hernias will strangulate. For hiatal hernia, why some develop it and others with identical BMI and age do not, and the precise relationship between hernia size and reflux severity.

Cure status. Inguinal hernia: CURABLE by surgical repair, with mesh repair recurrence of about 1 to 5 per cent and tissue (Shouldice) repair about 1 to 15 per cent depending on operator and technique. Hernias

never resolve spontaneously in adults; the only exception is some paediatric umbilical hernias, which commonly close by themselves. Watchful waiting is legitimate for minimally symptomatic hernias in men: randomised trials (Fitzgibbons, *JAMA* 2006; O'Dwyer) showed low rates of acute strangulation, about 0.2 to 0.5 per cent a year, though the majority eventually cross over to surgery, about 70 per cent at seven to ten years.

Hiatal hernia: CONTROLLABLE for type I, managed as reflux with acid suppression and weight loss, and not routinely repaired. CURABLE by surgical repair with fundoplication, indicated for large or paraoesophageal hernias, those with obstructive symptoms, volvulus risk or refractory reflux. Radiological recurrence after large hiatal hernia repair is 15 to 60 per cent, which tempers the cure claim.

Prevention. For inguinal hernia, little is demonstrably preventable: WEAK, effectively absent. Smoking cessation: WEAK, on the collagen mechanism and observational data. Treating chronic cough, constipation and prostatism: WEAK, mechanistically direct with trial evidence absent. Avoiding very heavy lifting: CONTESTED — an occupational association exists but causation and threshold are unclear, and advice to avoid lifting after repair is not evidence-based. Mesh prophylaxis during open aortic or stoma surgery reduces incisional, not inguinal, hernia: MODERATE for that specific setting.

For hiatal hernia, weight management: MODERATE. Avoiding chronic straining: WEAK.

Treatment. For inguinal hernia, mesh repair is the standard. Lichtenstein open mesh and laparoscopic TAPP or TEP are both effective: laparoscopic repair gives less chronic pain and faster return to work with a longer learning curve and higher cost, while open mesh under local anaesthesia is cheap, safe and suitable for almost any setting. Recurrence is about 1 to 5 per cent either way.

Mesh cost matters here. Commercial polypropylene mesh costs tens to hundreds of US dollars. Sterilised mosquito-net mesh has been shown non-inferior to commercial mesh in randomised trials in Uganda and India (Löfgren, *NEJM* 2016, 302 patients: no difference in recurrence or infection at one year) at roughly US$1 or less. One of the most important cost findings in global surgery.

Tissue repair, Shouldice, where mesh is unavailable or declined, gives excellent results in specialist hands. Local anaesthetic repair enables high-volume, low-cost surgery without a general anaesthetic service; lidocaine EML yes, off-patent, pennies. Watchful waiting for minimally symptomatic hernias in men. Emergency repair for strangulation or obstruction, which is the time-critical presentation. Trusses are largely obsolete with no evidence of benefit and may obscure strangulation; not recommended.

For hiatal hernia, PPI and weight loss for type I with reflux symptoms: omeprazole EML yes, off-patent, a few to tens of US dollars a year. Laparoscopic repair with fundoplication for large or paraoesophageal hernias, obstruction or refractory symptoms, with mesh use at the hiatus controversial because of erosion risk. Emergency repair for gastric volvulus.

Simple means. Mosquito-net mesh is the headline simple means here: a near-free, locally available material shown non-inferior to commercial mesh, which removes the main consumable cost barrier to hernia repair in low-income settings. Repair under local anaesthesia needs no anaesthetic machine, no oxygen and no ventilator, and enables task-shared, high-volume camps.

Weight loss for hiatal hernia and reflux; head-of-bed elevation; avoiding late meals. Treating constipation and cough to reduce straining. Smoking cessation. Watchful waiting — the simple means of not operating on an asymptomatic hernia, which is evidence-based.

The honest limit: an inguinal hernia cannot be cured without an operation. No exercise, belt, truss or diet repairs it. The simple-means question here is about making surgery cheap and accessible, not about avoiding it.

Gaps. Unmet surgical need for hernia in low-income countries is large and poorly quantified. Chronic post-operative inguinal pain affects about 10 to 12 per cent to some degree and about 0.5 to 6 per cent severely†; its mechanism and prevention are not well understood and it is the main remaining problem with mesh repair. Mesh-related litigation and concern have outrun the evidence for inguinal mesh specifically, confusing patients. Optimal management of large paraoesophageal hernias and whether to use mesh at the

hiatus are unresolved. Watchful waiting in women is not studied, and femoral hernias strangulate more readily. Hiatal hernia prevalence is method-dependent and essentially unknown at population level.

> **Depth.** Starts in: a weak spot in the abdominal wall. Size: 1 cm†; depth +11.19. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Bowel obstruction

What it is. Something blocks the bowel, so contents cannot pass. The bowel above swells, vomiting starts, nothing comes out. If the blood supply is cut off, the bowel dies.

Measured. Obstruction accounts for about 15 per cent of emergency admissions for abdominal pain, and small bowel obstruction is the commonest emergency small bowel diagnosis. Adhesions cause about 60 to 75 per cent of small bowel obstruction in high-income countries, with hernia and malignancy most of the rest. Large bowel obstruction is about 60 per cent malignant†, mostly colorectal cancer, then volvulus and diverticular stricture.

GBD does not model bowel obstruction as a single cause; the burden is distributed across hernia, neoplasm, intestinal infection and other digestive diseases. Mortality is about 3 to 10 per cent overall, rising steeply with strangulation, delay, age and comorbidity, and up to about 30 per cent with bowel resection for ischaemia.

The geographic difference is marked. In much of sub-Saharan Africa and South Asia, hernia and sigmoid volvulus predominate over adhesions, and presentation is later, so case-fatality is far higher. Adhesive obstruction is a disease of populations that have had abdominal surgery. In children, intussusception with a peak at three to twelve months, and congenital atresias; intussusception is a specific, treatable cause with a non-surgical cure.

Where it starts. Prior abdominal or pelvic surgery, giving adhesions. Risk rises with open surgery, with lower abdominal and pelvic surgery, and with peritonitis; about 5 to 10 per cent of patients after major abdominal surgery will have an adhesive obstruction admission over the following decades. Hernia, external — inguinal, femoral, incisional — or internal. Malignancy: colorectal, ovarian, gastric, peritoneal carcinomatosis. Volvulus: sigmoid, with high-fibre diet, redundant sigmoid, chronic constipation, institutionalisation, Chagas disease and altitude; or caecal. Crohn strictures, diverticular strictures, radiation enteritis. Gallstone ileus, bezoar, foreign body, intussusception, ascariasis — a major cause in endemic areas, particularly in children — and abdominal tuberculosis, important in endemic settings.

What is not known is why adhesion formation varies so much between individuals after identical surgery, and why some adhesions obstruct and others never do. There is no reliable way to predict who needs surgery and who will settle; clinical and CT signs of ischaemia have moderate accuracy at best. The failure of adhesion-prevention products to deliver clear clinical benefit is unexplained.

Cure status. This depends on cause and on whether the bowel is viable, so each stratum is named.

Adhesive small bowel obstruction without strangulation: SELF-LIMITING — about 65 to 80 per cent resolve with non-operative management, nasogastric decompression, intravenous fluids and correction of electrolytes. Strangulation or ischaemia: CURABLE only by urgent surgery, and delay is lethal. Hernia-related obstruction: CURABLE by repair. Resectable malignant obstruction: CURABLE. Unresectable malignant obstruction: RELIEF ONLY, by stent, defunctioning stoma or palliative measures. Sigmoid volvulus: CURABLE — endoscopic decompression relieves it in over 80 per cent, but recurrence is 40 to 60 per cent without subsequent sigmoid resection, so definitive cure requires surgery. Intussusception in children: CURABLE non-operatively, with air or hydrostatic enema reduction succeeding in about 80 to 90 per cent.

Prevention. Minimally invasive rather than open surgery: MODERATE, with substantially fewer subsequent adhesive obstructions. Elective hernia repair: STRONG for preventing hernia-related obstruction and strangulation, which is the main preventable cause in low-income settings. Colorectal cancer screening: STRONG for preventing malignant obstruction, by preventing or down-staging the cancer. Sigmoid resection after a first volvulus: STRONG, against 40 to 60 per cent recurrence otherwise. Mass deworming in endemic areas: STRONG for ascaris-related obstruction in children. Adhesion barriers — hyaluronate and carboxymethylcellulose film, icodextrin — reduce adhesion formation on second look but are CONTESTED for reducing clinically important obstruction; the hard outcome evidence is weak and they add cost. Avoiding unnecessary laparotomy: MODERATE.

Treatment. Resuscitation first: intravenous fluids and correction of hypokalaemia, hyponatraemia and metabolic alkalosis. Sodium chloride and potassium chloride, EML-listed, pennies. Nasogastric decompression relieves vomiting and reduces aspiration risk: a plastic tube, essentially free.

A non-operative trial for adhesive obstruction without ischaemia, typically 48 to 72 hours, resolves 65 to 80 per cent†. Water-soluble contrast, gastrografin or diatrizoate, is both diagnostic and therapeutic: contrast reaching the colon within 24 hours predicts resolution, and it reduces the need for surgery and shortens hospital stay in meta-analyses of adhesive obstruction. Cheap, off-patent, and a genuinely useful, underused intervention.

Surgery for strangulation, perforation, closed-loop obstruction, failure of non-operative management, or an obstructing hernia: adhesiolysis, resection and anastomosis, or stoma. Sigmoid volvulus: endoscopic or rigid sigmoidoscopic decompression with a flatus tube, then elective sigmoid resection. Malignant large bowel obstruction: a self-expanding metal stent as a bridge to surgery or as palliation, or a defunctioning stoma, or resection. Intussusception: air or hydrostatic enema reduction under imaging, with surgery if it fails or if there is perforation or ischaemia. Palliation of malignant and inoperable obstruction: dexamethasone, octreotide, anti-emetics, hyoscine butylbromide, venting gastrostomy; dexamethasone and hyoscine are EML-listed and cheap, and octreotide is expensive. Antibiotics only for perforation, peritonitis or strangulation, not routinely.

Simple means. A nasogastric tube with intravenous — or where necessary oral or rectal — rehydration is the mainstay for the 65 to 80 per cent who resolve without surgery. A tube and salt water. Oral rehydration solution where intravenous fluids are unavailable, with the caveat that in complete obstruction with vomiting oral intake is unsafe, so this applies to partial obstruction and to resuscitation en route; the solution itself is sugar and salt in clean water, EML-listed, at an indicative UNICEF price of US$4.80 per carton of 100 sachets, about US$0.048 a sachet, read 19 October 2026.

Water-soluble contrast is cheap and both predicts and promotes resolution. Rectal tube decompression for sigmoid volvulus — a rigid sigmoidoscope and a flatus tube — relieves a life-threatening condition immediately with no electricity or imaging required: one of the highest-yield simple procedures in emergency surgery. Elective hernia repair with mosquito-net mesh under local anaesthetic prevents the commonest obstruction in low-resource settings. Deworming with a single albendazole dose, EML-listed, prevents ascaris obstruction. Early presentation and transport is the dominant determinant of survival, and that is a logistics problem rather than a technology problem.

The honest limit: strangulated bowel requires an operation, and nothing simple substitutes.

Gaps. There is no reliable predictor of which adhesive obstruction will need surgery or which bowel is ischaemic; CT accuracy is moderate and clinical judgement remains decisive. The optimal duration of non-operative management is not established, whether 48 hours, 72 hours or longer. Adhesion barrier products have soft outcome evidence and uncertain cost-effectiveness. The global burden of bowel obstruction is not separately modelled in GBD, so the true mortality is unknown and probably substantially underestimated where surgical access is poor. Evidence on stent against surgery for malignant obstruction is mixed. Paediatric data outside high-income settings are sparse.

> **Depth.** Starts in: an adhesion band. Size: 2 cm†; depth +11.83. First complaint: about 12 hours († hours); time depth 42.87. One untreated course: about 3 days ([B] the bowel dies without an operation; † days); depth 44.50.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY.

> Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Constipation

What it is. Stools are infrequent, hard or difficult to pass. Common at all ages, and especially in older people and in pregnancy. Usually no disease is found.

Measured. Global prevalence is about 14 per cent of adults (Suares and Ford, *American Journal of Gastroenterology* 2011, meta-analysis), with a range of 2 to 27 per cent across studies by definition. Rome IV functional constipation gives about 11.7 per cent globally (Rome Foundation global study, Sperber 2021). It is not a separate GBD main cause and has no standalone DALY figure. Deaths are rare but non-zero, through faecal impaction, stercoral perforation and complications in frail elderly patients.

Prevalence is about twice as high in women and rises sharply with age, affecting about 30 to 40 per cent of those over 65 and far more in institutional care†. In children it is about 10 to 15 per cent, a very common paediatric presentation, about 95 per cent of it functional†. It is a major driver of laxative expenditure and of emergency admissions in the elderly.

Where it starts. Female sex, older age, low physical activity, low dietary fibre, low fluid intake, low socioeconomic status. Drugs are a leading and under-recognised cause: opioids most clearly and dose-dependently, then anticholinergics, calcium channel blockers such as verapamil, iron, calcium, aluminium antacids, tricyclics, antipsychotics, diuretics and 5-HT3 antagonists. Pregnancy, through progesterone, iron and mechanical factors.

Secondary causes to exclude: hypothyroidism, hypercalcaemia, diabetes, Parkinson disease, multiple sclerosis, spinal cord lesions, Hirschsprung disease in children, and colorectal cancer, especially with new onset over fifty, bleeding or weight loss.

Pelvic floor dyssynergia, or dyssynergic defaecation, is a distinct mechanical subtype in up to a third of referred cases, in which the pelvic floor fails to relax. It matters because it responds to biofeedback and not to laxatives. Slow-transit constipation is a distinct minority subtype. Behavioural causes include withholding in children, often after a painful stool, and poor toilet access. Heritability is modest; twin studies suggest a genetic contribution that is not well quantified.

What is not known is the cause of most functional constipation. Whether low fibre and low fluid intake are causes or consequences is not firmly established, and the fluid evidence is particularly weak. The role of the microbiome is unresolved. Why women are affected twice as often is unexplained.

Cure status. CONTROLLABLE for most functional constipation — treatable and manageable, usually indefinitely, rather than cured. CURABLE in specific situations: when a drug cause is removed; when a secondary cause such as hypothyroidism or hypercalcaemia is treated; when dyssynergic defaecation is corrected by biofeedback, which produces durable cure in that subtype; and in children, who recover fully with treatment and time. RELIEF ONLY for refractory slow-transit constipation, where even colectomy gives mixed results.

Prevention. Dietary fibre: MODERATE. It increases stool frequency and softens stool, with modest effect sizes, and it does not help all subtypes — it can worsen slow-transit and dyssynergic constipation. Physical activity: WEAK, with consistent association and modest trial evidence. Avoiding constipating drugs, or co-prescribing against them, especially routine laxative co-prescription with opioids: STRONG. That is the clearest preventive action available. Adequate fluid: WEAK — the evidence is much weaker than the advice. Toilet access, privacy and unhurried time, and responding to the urge: MODERATE in institutional settings, where it is often the dominant factor. In children, avoiding the pain-withholding cycle by treating painful fissures and stools promptly: MODERATE.

Treatment. The proportion of dyssynergic defaecation cured durably by biofeedback, and of children who recover fully, is not given here. Fibre supplementation with psyllium or ispaghula is the best-evidenced bulk agent, increasing frequency and improving consistency; off-patent; tens to hundreds of US dollars a year. Bran is less well tolerated and less effective than psyllium.

Osmotic laxatives: polyethylene glycol, macrogol, is first line and superior to lactulose in Cochrane review, giving greater stool frequency, less abdominal pain and fewer adverse effects. Off-patent; tens to hundreds of US dollars a year; EML status. Effective, safe long-term, and safe in children and pregnancy. Lactulose is effective, cheaper in some markets, and causes more bloating; EML; tens to hundreds of US dollars a year. Magnesium salts are cheap and effective, with caution in renal impairment.

Stimulant laxatives, senna and bisacodyl, are effective in randomised trials — bisacodyl and sodium picosulfate both have good trial support — and the old fear of damaging the bowel and causing dependence is not supported by evidence and has led to undertreatment. Senna is off-patent, EML, tens of US dollars a year: among the cheapest effective options. Suppositories and enemas — glycerol, bisacodyl, phosphate — for impaction and for rectal evacuation disorders; cheap.

Biofeedback and pelvic floor retraining for dyssynergic defaecation is superior to laxatives in randomised trials for that subtype, with about 70 to 80 per cent success and durable benefit at one to two years (Chiarioni, *Gastroenterology* 2006 and others). No drug and no device beyond basic equipment; the limiting factor is trained therapists. Identifying this subtype is the single most valuable diagnostic step in refractory constipation.

Prucalopride, a 5-HT4 agonist, is effective for refractory constipation and now off-patent in several markets, at hundreds to thousands of US dollars a year and falling. Secretagogues — linaclotide, lubiprostone, plecanatide — are effective, on patent, at thousands of US dollars or more a year, and not on the EML. Peripherally acting mu-opioid receptor antagonists — naloxegol, methylnaltrexone, naldemedine — work for opioid-induced constipation where laxatives fail and are expensive, at thousands to tens of thousands of US dollars a year; for opioid constipation, tapering the opioid has the best risk-benefit profile. Manual disimpaction and bowel regimens in institutional care. Surgery, subtotal colectomy with ileorectal anastomosis, is a last resort for proven isolated slow-transit constipation with a normal pelvic floor, with mixed outcomes and critical patient selection. In children: disimpaction then maintenance macrogol, with toilet training, behavioural support and demystification; prolonged maintenance over months is necessary and premature stopping causes relapse.

Simple means. This condition is managed overwhelmingly by simple means.

Dietary fibre from fruit, vegetables, legumes and whole grains. Kiwifruit, two a day, prunes and psyllium all have randomised trial support, and prunes outperformed psyllium in a head-to-head trial (Attaluri, *Alimentary Pharmacology and Therapeutics* 2011), with kiwifruit having repeated positive trials†. These are foods.

Physical activity, walking in particular, is effective in the elderly and in pregnancy. A toileting routine — using the urge, after a meal to exploit the gastrocolic reflex, unhurried, with privacy. In care homes this single change often outperforms drugs. A footstool or squat position raises the knees and straightens the anorectal angle, measurably reducing straining and defaecation time in small studies; a box costs nothing. Pelvic floor relaxation and biofeedback is the treatment of choice for dyssynergic defaecation, outperforming laxatives, and requires a trained person rather than a product. Abdominal massage has modest evidence in neurogenic and institutional constipation.

On fluid, the honest version. Increasing fluid intake above normal has little evidence of benefit in people who are not dehydrated. The benefit is in correcting dehydration, which is common in the frail elderly, and fluid matters when fibre is increased. The blanket advice to drink more water is weakly supported.

Reviewing and stopping constipating drugs is free, and often the whole answer.

Gaps. Definitions vary enough that prevalence spans 2 to 27 per cent. The fluid-intake evidence does not match the universality of the advice. Fibre's effect is modest and subtype-dependent, and it harms some patients. Dyssynergic defaecation is under-diagnosed because anorectal physiology testing is unavailable in most settings, so a curable subtype is routinely treated with ineffective laxatives. Long-term safety data for the expensive secretagogues are limited, and they have not been shown superior to cheap osmotic and stimulant laxatives head-to-head. Evidence for abdominal massage and positional change is thin despite plausibility. Paediatric relapse rates are high and the optimal maintenance duration is not established.

> **Depth.** Mostly no disease is found [B]. No depth is given.

> **Model reading.** Way of ending: restore proportion. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE and RELIEF ONLY for named strata. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Lactose intolerance

What it is. After weaning, most people stop making much lactase, the enzyme that digests milk sugar. Undigested lactose ferments in the colon, causing wind, pain and diarrhoea. It is the normal human condition, not a disease.

Measured. Global lactase non-persistence runs at about 65 to 70 per cent of adults, the majority of humanity†. The geographic and ancestral gradient is strong and well mapped: East Asia about 90 to 100 per cent non-persistent; sub-Saharan Africa about 70 to 90 per cent, but low in pastoralist groups such as the Tutsi, Fulani, Beja and Maasai, where persistence is common; Southern Europe and the Middle East about 50 to 70 per cent; Northern Europe about 5 to 20 per cent non-persistent, meaning 80 to 95 per cent persistent; and Northwest European ancestry has the lowest non-persistence in the world, about 5 to 10 per cent in parts of Scandinavia, Ireland and Britain.

Symptomatic intolerance is much less common than non-persistence, since many non-persistent people tolerate moderate lactose. That is the key distinction in the field. It is not a GBD cause, with no deaths and no DALY figure. Lactase activity declines after weaning, typically from age two to five onward in non-persistent individuals, with symptoms usually emerging in later childhood or adulthood.

Where it starts. Primary lactase non-persistence is genetically determined and is the ancestral, default human state. It is regulated by variants in the *MCM6* enhancer upstream of *LCT*, notably −13910C>T in Europeans and −14010G>C, −13907C>G and −13915T>G in African and Middle Eastern pastoralist populations. Lactase persistence is the derived trait, under one of the strongest signals of recent positive selection in the human genome, arising independently several times alongside dairying. Heritability of lactase persistence is essentially monogenic, determined by these regulatory variants — among the clearest genotype-phenotype relationships in human nutrition.

Secondary lactase deficiency is transient, from mucosal injury: gastroenteritis, especially rotavirus in infants, coeliac disease, Crohn disease, giardiasis, small bowel bacterial overgrowth, chemotherapy, radiation. It is reversible when the underlying condition heals. Congenital lactase deficiency is a very rare autosomal recessive condition from *LCT* mutations, concentrated in Finland, presenting with severe neonatal diarrhoea and life-threatening without a lactose-free diet.

What is not known is why symptom severity correlates so poorly with measured lactase activity and breath hydrogen. Colonic microbiota adaptation explains part of it — the colon can adapt to ferment lactose with fewer symptoms over weeks of continued exposure — but the determinants of individual tolerance are not predictable. Visceral hypersensitivity and overlap with IBS confound diagnosis substantially: in blinded challenge studies, many people who self-identify as lactose intolerant do not react to lactose.

Cure status. Primary lactase non-persistence: CONTROLLABLE. It is a permanent genetic state and is not curable, and it is also not a disease: it is fully managed by dose adjustment, and most non-persistent people can consume useful amounts of dairy. Secondary lactase deficiency: SELF-LIMITING, resolving when the mucosa heals. Congenital lactase deficiency: CONTROLLABLE, on lifelong strict avoidance.

Prevention. Primary non-persistence is not preventable, since it is the genetic default: not applicable. Preventing secondary deficiency: MODERATE — rotavirus vaccination prevents a major cause of transient infantile lactase deficiency, and treating coeliac disease and giardiasis resolves it. Continued regular small lactose exposure to maintain colonic adaptation and tolerance: MODERATE, demonstrated in trials, and avoidance tends to reduce tolerance. Complete dairy avoidance is not a desirable goal: it risks calcium and vitamin D inadequacy and is unnecessary for the great majority.

Treatment. Dose reduction rather than elimination. Most lactase non-persistent adults tolerate about 12 to 15 g of lactose, roughly 240 ml or one cup of milk, in a single sitting with few or no symptoms, and more

when spread through the day and taken with other food. That is the central practical finding and it is routinely overlooked.

Fermented dairy: yoghurt with live cultures is substantially better tolerated because bacterial beta-galactosidase digests lactose in the gut, and hard aged cheeses — cheddar, parmesan, Swiss — contain almost no lactose, under 0.5 g a portion. Butter is nearly lactose-free. These require no manufacturing beyond traditional dairying.

Lactase enzyme supplements, beta-galactosidase taken with the meal, are effective and dose-dependent, with benefit confirmed in trials though variable between products. Off-patent or sold as a food supplement; tens to hundreds of US dollars a year depending on use; not on the EML. Lactose-free, lactase-treated milk and dairy is fully effective, costs more than ordinary milk, and requires industrial processing.

Calcium and vitamin D adequacy is essential if dairy is reduced, through non-dairy calcium sources — fortified plant milks, tinned fish with bones, tofu set with calcium, dark green leaves, sesame — or supplements. Calcium carbonate and vitamin D are cheap and EML-listed; a few to tens of US dollars a year. Treat the underlying cause in secondary deficiency. And reconsider the diagnosis: a substantial proportion of self-diagnosed lactose intolerance is IBS, fructan sensitivity or nocebo, with blinded challenge the arbiter where it matters.

Simple means. This condition is almost entirely managed by simple means, and dairying cultures worked them out long before the biochemistry was known.

Spreading lactose through the day and taking it with meals raises tolerance substantially, and is free. Yoghurt and fermented milk: traditional fermentation reduces lactose and supplies bacterial lactase, available anywhere milk is. Aged hard cheese is effectively lactose-free by the nature of cheesemaking. Gradual reintroduction to build colonic adaptation: regular small doses over two to three weeks measurably improve tolerance. Non-dairy calcium sources: fish with bones, calcium-set tofu, sesame, leafy greens.

Breastfeeding should be continued during infant gastroenteritis and not withheld for lactose intolerance; for older infants, continued feeding with lactose-containing milk is generally appropriate, since routine lactose-free formula is not required in most acute diarrhoea on WHO and standard guidance. Oral rehydration solution for the diarrhoea of secondary deficiency, at an indicative UNICEF price of about US$0.048 a sachet, October 2026.

The honest note: the simple means here is largely not treating it as a disease. The commercial lactose-free product category addresses a problem that dose adjustment and traditional fermentation already solve for most people.

Gaps. Symptom reporting correlates poorly with objective lactase status and with blinded challenge, so self-reported prevalence is unreliable and probably substantially overstates true intolerance. Breath hydrogen testing has imperfect sensitivity and specificity and no agreed protocol. The overlap with IBS and with fructan sensitivity is unresolved and clinically consequential. The long-term bone health consequences of unnecessary dairy avoidance are plausible and under-measured. Data from Africa and Asia on symptomatic as opposed to genetic intolerance are sparse. The degree and durability of colonic adaptation varies between individuals for unknown reasons.

> **Depth.** Starts in: the lactase enzyme. Size: 10 nm†; depth −1.38. First complaint: about 5 years († lactase falls after weaning; about 5 years); time depth 50.34. One untreated course: no number ([B] a normal state).
>
> **Model reading.** Way of ending: supply from inside. Layer: chain. By the rule it is held by supply. It ends only if the source is restored. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Dental caries and periodontal disease

What it is. In caries, bacteria ferment sugar into acid that dissolves tooth enamel, making holes. In periodontal disease, chronic inflammation of the gums and the bone holding the teeth loosens them and eventually loses them.

Measured. These are among the most prevalent diseases of any kind on earth, and the single largest block of untreated disease in the GBD.

Untreated caries in permanent teeth affects about 2.0 to 2.5 billion people and is consistently ranked first for prevalence of any condition in GBD. The WHO oral health fact sheet of 17 March 2025 names untreated caries in permanent teeth as the most common health condition on GBD 2021 data, but gives no prevalence figure for it anywhere on the page. Untreated caries in deciduous teeth affects about 510 to 530 million children.

Severe periodontitis affects about 1.0 to 1.1 billion people, about 19 to 20 per cent of adults globally; the WHO page gives more than 1 billion cases, with no year. Total edentulism affects about 350 to 400 million people, concentrated in older age; the WHO page gives edentulism prevalence of about 7 per cent among people aged 20 and over and 23 per cent among those aged 60 and over, with no year.

Oral conditions together affect about 3.5 billion people and cause roughly 18 to 19 million DALYs globally (WHO Global Oral Health Status Report 2022); the WHO oral health fact sheet gives nearly 3.7 billion people with oral diseases, with no year given. GBD 2023 Table 1 places oral disorders eleventh among YLD causes at 23.9 million (95 per cent UI 14.5 to 35.1). Separately, the WHO page gives about 1 billion people affected by oro-dental trauma with about 20 per cent prevalence in children up to twelve, which is a different metric and easily confused with the periodontal figure.

Deaths are negligible directly, though dental sepsis, Ludwig angina and noma cause some, especially in children in poor settings. Noma has a case fatality of about 90 per cent untreated and was added to the WHO neglected tropical diseases list in 2023; the WHO oral health page gives about 140,000 new noma cases a year, from 1998 estimates, fatal in 90 per cent of untreated cases, mostly in children aged two to six.

Caries begins in early childhood, with early childhood caries affecting a large share of preschool children in many countries; periodontitis prevalence rises with age, with severe disease peaking in the sixth and seventh decades. These are the diseases where socioeconomic gradients are steepest and least disguised. The burden is high everywhere, but the *untreated* burden is concentrated in low- and middle-income countries and in poor populations within rich countries. Oral disease is largely excluded from universal health coverage in most countries, so out-of-pocket payment dominates.

Where it starts. For caries, free sugars are the necessary dietary cause. Both amount and frequency of intake matter, and frequency may matter more. The dose-response is continuous with no threshold, which is the basis of the WHO recommendation of under 10 per cent, and conditionally under 5 per cent, of energy from free sugars. Historical evidence — Vipeholm, Hopewood House, wartime sugar rationing — and modern cohorts agree.

Then the cariogenic biofilm: *Streptococcus mutans*, *Lactobacillus*, *Actinomyces*, *Scardovia*. Fluoride exposure is protective. Saliva flow and buffering capacity matter, and xerostomia — from anticholinergics and antidepressants, Sjögren syndrome, or head and neck radiotherapy — is a strong risk factor. Enamel defects: molar incisor hypomineralisation, fluorosis, hypoplasia from early-life illness or preterm birth; tooth morphology and crowding. Socioeconomic deprivation is one of the strongest predictors, operating through diet, fluoride access and dental care access. Bottle-feeding with sweetened drinks and nocturnal bottle use cause early childhood caries. Twin studies estimate heritability of about 40 to 60 per cent for caries experience, much of it operating through saliva composition, enamel formation and taste preference, while the environmental cause, sugar, remains necessary.

For periodontal disease, a dysbiotic subgingival biofilm: *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*. Smoking is the strongest modifiable risk factor, roughly two to six times the risk, dose-dependently, and it impairs treatment response. Diabetes is bidirectional: it roughly doubles to triples periodontitis risk, and periodontitis worsens glycaemic control. Heritability is about 50 per cent for chronic and severe periodontitis from twin studies (Michalowicz). Then age, male sex, obesity, stress, poor oral hygiene, rheumatoid arthritis, immunosuppression and HIV, and specific neutrophil defects for the aggressive forms.

What is not known, for both conditions, is why individuals with similar sugar intake, hygiene and plaque differ so much in disease experience. Host susceptibility is clearly decisive and not predictable. Which

specific microbial configurations tip into disease, and whether the dysbiosis is cause or consequence, is unresolved. The causal direction and magnitude of the periodontitis-cardiovascular and periodontitis-adverse pregnancy associations are contested: the associations are robust, but randomised periodontal treatment has not been shown to reduce cardiovascular events or preterm birth, which argues against simple causation or against treatment adequacy.

Cure status. Five strata, each with its own label.

Non-cavitated, white-spot caries lesion: CURABLE. Early white-spot lesions remineralise with fluoride and reduced sugar frequency, which is a genuine reversal of the lesion.

Cavitated caries lesion: CONTROLLABLE. The lost tooth substance does not regenerate. Restoration replaces it rather than removing the disease, and the restored tooth enters a repeat-restoration cycle.

The caries disease process: CONTROLLABLE. It is held by fluoride, sugar control and plaque control, and resumes when those stop.

Gingivitis: CURABLE, fully, by plaque control.

Periodontitis: CONTROLLABLE, not curable. Lost attachment and bone do not regenerate, except for limited regeneration in specific defect geometries. Treatment arrests progression and can produce substantial pocket reduction, but the condition requires lifelong maintenance, and without maintenance progression resumes.

Prevention. This is the area where prevention is strongest and most neglected.

Fluoride toothpaste at 1,000 to 1,500 ppm, twice daily: STRONG. Cochrane gives about a 24 per cent reduction in caries increment against non-fluoride toothpaste, as a prevented fraction, with greater effect at higher concentration and higher baseline risk. The WHO oral health fact sheet gives the same 1,000 to 1,500 ppm range. The single most cost-effective caries intervention in existence.

Water fluoridation: STRONG for effect, with a magnitude that is now smaller. Older studies showed about a 35 per cent caries reduction in children. The 2024 Cochrane update found that studies conducted since 1975 — that is, since fluoride toothpaste became widespread — show a much smaller benefit, on the order of 0.24 fewer decayed, missing or filled deciduous teeth, a reduction that is real and modest. Both figures are printed. This is an honest revision: fluoridation's marginal benefit has fallen because toothpaste now delivers most of the effect. It remains equitable, reaching those who do not brush, and cheap, and the debate about it is now about marginal benefit rather than about whether fluoride works.

Reducing free sugars to under 10 per cent, ideally under 5 per cent, of energy: STRONG on dose-response evidence. Sugar-sweetened beverage taxation has demonstrated consumption reductions in Mexico, the United Kingdom and elsewhere: MODERATE at population level.

Fluoride varnish, two to four times a year in children: STRONG, with about a 43 per cent reduction in caries increment in permanent teeth as a Cochrane prevented fraction. Pit and fissure sealants: STRONG, substantially reducing occlusal caries in permanent molars against no sealant. Silver diamine fluoride: STRONG for arresting existing caries, with about 60 to 80 per cent arrest rates, applied in seconds with no drilling, no electricity and no anaesthetic. Supervised toothbrushing programmes in schools and nurseries: STRONG and highly cost-effective in deprived populations. Not putting sugary drinks in infant bottles, and no nocturnal bottle: STRONG.

For periodontal disease: smoking cessation: STRONG. Daily plaque removal, brushing with interdental cleaning: STRONG for gingivitis prevention. Diabetes control: MODERATE. Professional maintenance after treatment: STRONG. Xylitol, chlorhexidine and probiotics: CONTESTED.

Treatment. For caries: fluoride in toothpaste, varnish, gel or mouthrinse, for prevention and for remineralising early lesions. Sodium fluoride and fluoride toothpaste are on the WHO EML; off-patent; toothpaste a few to tens of US dollars a year — the cheapest effective intervention in this entire chapter.

Silver diamine fluoride at 38 per cent arrests caries without drilling, with 60 to 80 per cent arrest, and stains the lesion black; a few to a few US dollars per application. Transformative for settings without dental chairs, electricity or anaesthesia, and for young children and the frail elderly.

Atraumatic restorative treatment uses hand instruments and glass ionomer cement, with no electricity and no drill; survival rates for single-surface restorations are good, above about 85 per cent at two to three years, and it is WHO-endorsed for low-resource settings.

Conventional restoration uses amalgam, which is durable and cheap and being phased down under the Minamata Convention, or composite or glass ionomer. The Minamata phase-down creates a real access problem, because composite needs more equipment, skill and time. The Hall technique for primary molars seals a stainless steel crown over the carious tooth without removing decay or giving anaesthetic, with high success in trials and excellent results for children. Pulpotomy, root canal treatment or extraction for pulpal involvement.

Analgesia and antibiotics for dental abscess — but antibiotics do not treat the cause, and drainage or extraction is required. Amoxicillin EML yes, with periapical abscess without sinus a listed indication; off-patent; about US$1 to 3 a course, and the indicative UNICEF price for amoxicillin 250 mg dispersible tablets is US$0.054 per tablet, October 2026. Metronidazole EML yes.

For periodontal disease: subgingival instrumentation, scaling and root planing, is the foundation of treatment, producing pocket depth reduction of about 1 to 2 mm with attachment gain, with greater effect in deeper pockets†. It requires instruments and training, not electricity. Oral hygiene instruction and plaque control, without which instrumentation fails. Smoking cessation, which improves treatment response measurably. Periodontal maintenance every three to six months prevents recurrence, and the evidence for maintenance is as strong as for the initial treatment. Adjunctive systemic antibiotics, amoxicillin with metronidazole, give modest additional benefit in severe and aggressive disease, with routine use discouraged for resistance reasons. Periodontal surgery and regenerative procedures for residual deep pockets and specific defects.

Periodontal treatment improves glycaemic control in diabetes: HbA1c reduction of roughly 0.3 to 0.4 percentage points at three to six months in meta-analyses, comparable to adding a second oral hypoglycaemic agent. A genuine cross-disease benefit. Dentures, bridges and implants for tooth replacement are the expensive end, and where most dental expenditure in rich countries actually goes.

Simple means. This is the chapter’s clearest example of simple means doing nearly all the work.

Brushing twice daily with fluoride toothpaste gives about a 24 per cent caries reduction (Cochrane) at a few to tens of US dollars a year, and needs a brush, paste and water. The highest benefit-to-cost ratio here. Not rinsing after brushing — spit, don’t rinse — retains fluoride, costs nothing and gives measurable additional benefit. Reducing sugar frequency, not just amount: fewer sugar exposures a day, free. Water instead of sugary drinks.

Interdental cleaning with floss or interdental brushes, and interdental brushes are more effective than floss where spaces allow. Silver diamine fluoride: pennies, seconds, no drill, no power, 60 to 80 per cent arrest. Atraumatic restorative treatment with hand instruments and glass ionomer only. Chewing sugar-free gum after meals, for saliva stimulation, gives modest benefit. A chewing stick, miswak or neem, gives plaque removal comparable to a toothbrush in several comparative studies and is used by hundreds of millions: a twig. Supervised school toothbrushing needs only brushes, paste and a sink. Breastfeeding rather than a bottle with sweetened fluids, and no bottle in bed. Smoking cessation for periodontitis, the largest single modifiable effect. Scaling with hand instruments, effective without electricity.

The honest statement: a cavitated tooth needs restoration or extraction, which needs a trained operator and instruments. But the disease is preventable almost entirely by a brush, fluoride paste and less sugar — which makes the global burden of 2 to 2.5 billion untreated caries a failure of distribution and policy, not of knowledge.

Gaps. Oral health is excluded from most universal health coverage schemes and from most health surveys, so burden data are weaker than the prevalence figures suggest, and are largely based on clinical examination with varying diagnostic thresholds. The WHO oral health fact sheet names untreated caries the most common health condition on earth and prints no number for it. The 2024 Cochrane revision of water fluoridation’s effect size is contested in its interpretation, and the contemporary marginal benefit is genuinely uncertain. Whether periodontal treatment reduces cardiovascular events or adverse pregnancy

outcomes is unresolved: the observational association is strong and the randomised evidence is null or inconclusive. The Minamata amalgam phase-down's effect on access and on caries outcomes in poor settings is unquantified. Noma is still barely counted. Dental workforce distribution is extremely unequal, and the evidence base for task-sharing — silver diamine fluoride, atraumatic restorative treatment, the Hall technique — while promising, is thinner than it should be. Caries heritability estimates vary widely between twin studies.

> **Depth.** Starts in: Streptococcus mutans. Size: 1 µm†; depth +2.81. First complaint: about 18 months († about 18 months to a cavity); time depth 49.24. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Enamel does not regrow. The tooth can be filled. So it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Oesophageal varices

What it is. When the liver is scarred, blood backs up and forces open veins at the lower end of the oesophagus. These thin-walled veins can burst and bleed catastrophically.

Measured. Varices are present in about 30 to 40 per cent of people with compensated cirrhosis and about 60 to 85 per cent with decompensated cirrhosis†. Incidence of new varices is about 5 to 8 per cent a year in cirrhotic patients without them, with about 10 to 12 per cent a year progressing from small to large varices†. Bleeding risk is about 10 to 15 per cent a year overall†, higher with large varices, red wale marks and Child-Pugh C.

Six-week mortality after a variceal bleed is about 15 to 25 per cent, down from about 40 to 50 per cent several decades ago — a genuine improvement attributable to a defined care bundle. Rebleeding without secondary prophylaxis is about 60 per cent within one to two years; with combination prophylaxis about 15 to 25 per cent. It is not a separate GBD cause and is counted within cirrhosis. Geography follows cirrhosis, concentrated where hepatitis B, hepatitis C and alcohol burden is high. In schistosomiasis-endemic areas, varices occur with preserved liver function, a distinct and more survivable pattern.

Where it starts. Portal hypertension is the necessary cause. Varices form when the hepatic venous pressure gradient exceeds 10 mmHg, and bleed above 12 mmHg. These thresholds are well established and quantitative.

Cirrhosis of any cause, and also non-cirrhotic portal hypertension: schistosomiasis, globally a major cause, portal vein thrombosis, Budd-Chiari syndrome, idiopathic non-cirrhotic portal hypertension, congenital hepatic fibrosis. Risk factors for bleeding specifically: large variceal size, red wale marks or cherry-red spots on endoscopy, Child-Pugh class B or C, gradient above 12 mmHg, continued alcohol use, bacterial infection as a recognised trigger, and raised intra-abdominal pressure from tense ascites.

What is not known is why some patients with high portal pressure never bleed and others bleed at modest gradients. Variceal wall tension depends on size, wall thickness and pressure in ways not measurable clinically. The gradient is the best predictor but is invasive and rarely measured outside specialist centres, so prediction in practice is crude. Why non-selective beta-blocker response varies so much between individuals is unexplained.

Cure status. CONTROLLABLE. Varices themselves can be obliterated by repeated endoscopic band ligation, and bleeding can be prevented and treated effectively, but the underlying portal hypertension persists, so varices recur unless portal pressure falls. CURABLE indirectly, by removing the cause: hepatitis C cure, hepatitis B suppression or alcohol abstinence can lower portal pressure enough that varices regress, and this is documented. CURABLE definitively by liver transplantation. TIPS decompresses the portal system effectively at the cost of encephalopathy in a substantial minority.

Prevention. Three distinct levels, which must be kept separate.

Preventing varices forming, pre-primary prophylaxis: CONTESTED. Beta-blockers do not prevent the development of varices in patients who do not yet have them (Groszmann, *NEJM* 2005) — a clear negative trial. Treating the underlying liver disease is what works.

Preventing a first bleed, primary prophylaxis, for medium and large varices: STRONG. Non-selective beta-blockers — propranolol, nadolol, and carvedilol, now preferred because it lowers the gradient more — reduce first bleeding from about 25 per cent to about 15 per cent, relative risk about 0.5 to 0.6 in meta-analyses. Endoscopic band ligation is comparably effective, with the choice depending on availability, tolerance and patient preference. Carvedilol has been shown to reduce decompensation and improve survival in compensated cirrhosis with clinically significant portal hypertension (PREDESCI, *Lancet* 2019, and individual-patient meta-analyses).

Preventing rebleeding, secondary prophylaxis: STRONG. A non-selective beta-blocker combined with band ligation is superior to either alone, reducing rebleeding from about 60 per cent to about 15 to 25 per cent.

Antibiotic prophylaxis during acute bleeding: STRONG. It reduces infection, rebleeding and mortality, with ceftriaxone or norfloxacin. One of the clearest mortality benefits in the bundle. Alcohol abstinence and treating viral hepatitis: STRONG. Screening endoscopy at cirrhosis diagnosis, or non-invasive triage: Baveno VII allows avoiding endoscopy where liver stiffness is below 20 kPa and platelets above 150,000, a useful resource-sparing rule.

Treatment. Acute variceal bleeding is a defined bundle, each element evidence-based.

Resuscitation with restrictive transfusion, to a haemoglobin target of 7 to 8 g/dL and not higher. Villanueva (*NEJM* 2013, 921 patients) found restrictive transfusion reduced mortality, hazard ratio 0.55, and rebleeding against liberal transfusion, with the benefit particularly clear in cirrhosis. Over-transfusion raises portal pressure and worsens bleeding — an important counter-intuitive point.

A vasoactive drug immediately, before endoscopy, for two to five days: terlipressin, somatostatin or octreotide, which reduce bleeding and improve haemostasis. Terlipressin EML yes; off-patent; tens to hundreds of US dollars a course; cheaper and more available than octreotide in many countries, and carrying hyponatraemia and ischaemic risks. Octreotide off-patent; hundreds of US dollars a course.

Antibiotic prophylaxis with ceftriaxone 1 g daily or norfloxacin reduces mortality. Ceftriaxone EML yes; off-patent; a few US dollars a course. Extremely cheap for a mortality benefit.

Endoscopic band ligation within twelve hours is the definitive haemostatic procedure and is superior to sclerotherapy, with less stricture and fewer complications; banding is now standard and sclerotherapy is reserved for where banding is unavailable. A proton pump inhibitor as a short course after banding reduces ulceration.

Early or pre-emptive TIPS within 72 hours in high-risk patients — Child-Pugh C, or B with active bleeding — improved survival against standard therapy (García-Pagán, *NEJM* 2010), and is under-used relative to the evidence. Balloon tamponade with a Sengstaken-Blakemore or Minnesota tube is a mechanical rescue bridge for uncontrolled bleeding: cheap, but requiring airway protection and carrying necrosis and aspiration risk if used beyond 24 hours. Self-expanding oesophageal metal stents are an alternative bridge with fewer complications. Lactulose to prevent post-bleed encephalopathy, since blood in the gut is a potent precipitant. And avoid over-resuscitation with saline, which raises portal pressure and worsens ascites.

Gastric varices differ: cyanoacrylate glue injection or balloon-occluded retrograde transvenous obliteration rather than banding, with TIPS for IGV1.

Longer term: a beta-blocker, carvedilol preferred, with a band ligation programme until varices are obliterated, then surveillance. Treating the underlying liver disease is the only intervention that lowers portal pressure durably. Transplantation for end-stage disease.

Simple means. Propranolol or carvedilol is the single most important preventive drug: off-patent, EML-listed, a few to tens of US dollars a patient-year, and requiring only a pulse check to titrate, to a heart rate reduction of about 25 per cent or 55 to 60 bpm. No endoscopy and no monitoring equipment. That is the key

fact for low-resource settings: primary prophylaxis with a cheap oral tablet achieves much of what an endoscopy programme achieves.

Ceftriaxone during a bleed, at a few US dollars reduces mortality. Restrictive transfusion is a simple means in the sense of withholding an expensive resource, which improves survival and conserves blood supply. Balloon tamponade is a rubber tube that buys hours of life where no endoscopy exists. Alcohol abstinence lowers portal pressure. Salt restriction for ascites reduces intra-abdominal pressure. Avoiding NSAIDs, for bleeding risk, and avoiding over-transfusion. Recognition and transport is the main determinant of survival where endoscopy is distant.

The honest limit: active variceal bleeding needs endoscopy, or at minimum tamponade. There is no simple substitute for haemostasis.

Gaps. The hepatic venous pressure gradient, the best predictor of bleeding and treatment response, is measured in very few centres, so risk stratification in practice is coarse. Non-invasive substitutes — elastography, platelet count, the Baveno criteria — are validated mainly in high-income cohorts and perform less well in hepatitis B and in schistosomiasis-related portal hypertension. Carvedilol's superiority is established for gradient reduction, and long-term head-to-head outcome data against propranolol plus banding are limited. Early TIPS is under-used and access is extremely unequal. Gastric variceal management rests on weaker evidence than oesophageal. Terlipressin availability and price vary enormously and it is unavailable in some markets, including, historically, the United States. Burden is invisible in GBD because it sits inside cirrhosis.

> **Depth.** Starts in: an oesophageal vein. Size: 5 mm†; depth +10.56. First complaint: about 5 years († years of portal hypertension); time depth 50.34. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE, with CURABLE for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gastrointestinal bleeding

What it is. Bleeding anywhere from the gullet to the anus. Upper bleeding shows as vomited blood or black tarry stool; lower bleeding as fresh blood. It ranges from trivial to immediately fatal.

Measured. Upper gastrointestinal bleeding incidence is about 40 to 150 per 100,000 a year and falling in most high-income countries as *H. pylori* prevalence and ulcer disease decline. Lower gastrointestinal bleeding is about 20 to 35 per 100,000 a year and rising with ageing and anticoagulant and antiplatelet use.

Mortality from upper gastrointestinal bleeding is about 2 to 10 per cent in modern series, and notably most deaths are from comorbidity and multi-organ failure rather than exsanguination. Variceal bleeding mortality is higher, about 15 to 25 per cent at six weeks†.

GBD 2019 gave peptic ulcer disease, the main upper gastrointestinal bleeding cause, about 236,000 deaths†. Bleeding as such is not a separate GBD cause and its burden is distributed across ulcer, cirrhosis, neoplasm, haemorrhoid and diverticular categories. Incidence rises steeply with age, and the median patient is now elderly with multiple comorbidities and on antithrombotic drugs; that demographic shift is the dominant trend in the field. Male predominance for ulcer bleeding.

Where it starts. Upper gastrointestinal causes: peptic ulcer at about 30 to 50 per cent and falling; oesophageal and gastric varices at about 10 to 20 per cent†; Mallory-Weiss tear; oesophagitis; gastroduodenal erosions; malignancy; Dieulafoy lesion; angiodysplasia; and aorto-enteric fistula, which is rare and lethal.

Lower gastrointestinal causes: diverticular bleeding at about 20 to 40 per cent†, the commonest, and arterial, from the vasa recta over the dome of a diverticulum, as described in the diverticular entry; then angiodysplasia, haemorrhoids, ischaemic colitis, colorectal neoplasm, post-polypectomy bleeding, inflammatory bowel disease, infectious colitis and radiation proctitis.

Risk factors. NSAIDs and aspirin raise ulcer bleeding risk roughly fourfold, dose-dependently; and for diverticular bleeding specifically, regular aspirin gives a hazard ratio of 1.70 (95 per cent CI 1.21 to 2.39) and non-aspirin NSAIDs 1.74 (1.15 to 2.64) (Strate 2011). *H. pylori*, whose eradication reduces rebleeding dramatically. Anticoagulants — warfarin and the direct oral anticoagulants — and antiplatelets, with dual therapy multiplying risk; among the direct oral anticoagulants, rivaroxaban and high-dose dabigatran carry higher gastrointestinal bleeding risk than apixaban, which is relevant to drug choice. SSRIs, through platelet serotonin depletion; corticosteroids with NSAIDs. Cirrhosis and portal hypertension; chronic kidney disease, through uraemic platelet dysfunction and angiodysplasia; aortic stenosis, in Heyde syndrome; prior bleeding; older age.

What is not known is which ulcers or diverticula will bleed. Why angiodysplasia forms and recurs is poorly understood, and it is the most frustrating recurrent cause. Optimal timing of antithrombotic resumption after bleeding is genuinely uncertain, trading rebleeding against thrombosis. The reason most deaths are non-haemorrhagic is understood in outline, through comorbidity and the stress of bleeding, but not well modelled.

Cure status. Four strata.

The individual bleeding episode, treated: CURABLE — endoscopic haemostasis with acid suppression stops bleeding and heals the lesion.

The episode without intervention: SELF-LIMITING. About 80 per cent of upper gastrointestinal bleeds and about 75 to 85 per cent of lower bleeds stop spontaneously.

The cause, where removable: CURABLE. *H. pylori* eradication cures the bleeding ulcer diathesis, with rebleeding falling from about 20 to 25 per cent a year to about 1 to 2 per cent — one of the highest-value cheap cures in acute medicine. Stopping an NSAID cures NSAID-related bleeding. Resecting a bleeding diverticular segment or tumour is curative.

Angiodysplasia, and portal hypertensive bleeding while the liver disease persists: RELIEF ONLY, and recurrent.

Prevention. *H. pylori* test and eradicate after a bleeding ulcer: STRONG. It reduces rebleeding from about 20 to 25 per cent a year to about 1 to 2 per cent, is superior to maintenance acid suppression, and costs a few to tens of US dollars once rather than indefinitely. Among the clearest cost-effective preventives in this book.

PPI co-prescription with NSAIDs or aspirin in at-risk patients: STRONG, substantially reducing ulcer complications; omeprazole EML yes, a few to tens of US dollars a year. Avoiding unnecessary NSAIDs: STRONG. Choosing apixaban over rivaroxaban or dabigatran where gastrointestinal bleeding risk is high: MODERATE. Avoiding unnecessary dual antiplatelet therapy and shortening its duration: MODERATE. Variceal prophylaxis with non-selective beta-blockers and banding: STRONG. Antibiotic prophylaxis in cirrhotic patients with bleeding: STRONG, reducing mortality.

Stress ulcer prophylaxis in intensive care: indicated for specific high-risk patients, on mechanical ventilation or with coagulopathy, but CONTESTED for routine use. The SUP-ICU trial (*NEJM* 2018) found pantoprazole reduced clinically important gastrointestinal bleeding without a mortality benefit, and there is a pneumonia and *C. difficile* trade-off. Over-prescription is endemic.

Treatment. Resuscitation with restrictive transfusion, to a haemoglobin target of 7 to 8 g/dL. Villanueva (*NEJM* 2013) found a restrictive strategy reduced mortality, hazard ratio 0.55, and rebleeding. Over-transfusion is harmful, especially in variceal bleeding.

Risk stratification: a Glasgow-Blatchford score of 0 to 1 identifies patients safe for outpatient management, which is a major resource saving and is validated. Clinical scores need no technology.

High-dose intravenous PPI after endoscopic haemostasis of a high-risk ulcer reduces rebleeding, the need for surgery and mortality in high-risk lesions. Pre-endoscopy PPI reduces high-risk stigmata without reducing mortality. Omeprazole and pantoprazole EML yes — verified for omeprazole, which lists gastrointestinal bleeding as an indication; off-patent; a course costs a few dollars.

Endoscopy within 24 hours with haemostasis: injection plus a second modality, clips or thermal coagulation, since injection alone is inadequate. Over-the-scope clips and haemostatic powders for refractory bleeding. Very early endoscopy, under six hours, does not improve outcomes over 24 hours in high-risk patients (Lau, *NEJM* 2020) — a useful negative finding. Band ligation, vasoactive drugs and antibiotics for variceal bleeding, as in the varices entry.

H. pylori testing and eradication, noting that testing during acute bleeding has high false-negative rates, so retest or treat empirically after recovery. A frequently missed step with large consequences.

Tranexamic acid: do not use. The HALT-IT trial (*Lancet* 2020, 12,009 patients) found tranexamic acid did not reduce death from gastrointestinal bleeding and increased venous thromboembolic events, 0.8 against 0.4 per cent, and seizures. A clear, large, negative trial that reversed widespread practice, and worth stating plainly because the drug is cheap and was used freely.

Interventional radiology embolisation for refractory bleeding, and surgery as a last resort. For lower gastrointestinal bleeding: resuscitation, CT angiography for localisation in active bleeding, colonoscopy with clipping, adrenaline or thermal therapy, embolisation, segmental resection. Reversal of anticoagulation where appropriate — vitamin K and prothrombin complex concentrate for warfarin; idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors, both very expensive and of debated net benefit. Resume antithrombotics early once haemostasis is secure, since the thrombotic risk of prolonged interruption generally exceeds the rebleeding risk. Capsule endoscopy and enteroscopy for small bowel or obscure bleeding, with thalidomide and octreotide having evidence in refractory angiodysplasia. Iron replacement, oral or intravenous, for the resulting anaemia; oral ferrous salts EML yes, off-patent, about US$2 to 15 a year, with an indicative UNICEF price for iron 60 mg tablets of US$1.43 on one catalogue page and US$1.60 on another per bottle of 100, about US$0.0143 to 0.0160 a tablet, October 2026.

Simple means. Restrictive transfusion: withholding blood improves survival and conserves a scarce resource — the clearest do-less intervention here. Glasgow-Blatchford scoring is pen and paper and safely identifies patients needing no admission. Stopping NSAIDs and unnecessary antithrombotics. *H. pylori* eradication at a few to tens of US dollars once converts a recurrent life-threatening condition into a cured one: the highest-value intervention in this entry. Oral rehydration and oral iron for stable patients with slow blood loss, at cents, and adequate for most chronic occult bleeding. Positioning and airway protection, and a nasogastric tube where needed. Not giving tranexamic acid — a cheap drug whose omission is now evidence-based (HALT-IT). Early recognition and transport, the dominant survival determinant where endoscopy is distant.

The honest limit: major acute bleeding needs endoscopy, transfusion capability and sometimes surgery or radiology. Simple means cover prevention, triage, resuscitation and the chronic anaemia, not haemostasis.

Gaps. Gastrointestinal bleeding is not a GBD cause, so global burden is genuinely unknown and almost certainly underestimated where endoscopy is unavailable; the case-fatality difference between settings is largely unmeasured. Optimal timing of antithrombotic resumption after bleeding is uncertain and guidelines differ. Management of obscure small bowel bleeding and recurrent angiodysplasia rests on weak evidence. The role of direct-oral-anticoagulant reversal agents is debated relative to their very high cost. Stress ulcer prophylaxis indications remain contested. *H. pylori* testing during acute bleeding is unreliable and the failure to retest is a known, unquantified care gap. Risk scores are validated mainly in high-income populations.

> **Depth.** Many causes. No depth is given.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

ICD-11 Chapter 15 — Diseases of the musculoskeletal system or connective tissue

A note on the headline figure for this chapter

The WHO musculoskeletal health fact sheet, printed 14 July 2022 on GBD 2019 data, contradicts itself, and both numbers are printed here because neither can be ruled out from the page.

The headline figure is approximately 1.71 billion people with musculoskeletal conditions. The page also gives condition-by-condition prevalent cases: low back pain 570 million, osteoarthritis 528 million, fractures 440 million, neck pain 222 million, amputations 180 million, gout 54 million, rheumatoid arthritis 18 million, and other musculoskeletal conditions 453 million. Those component figures total about 2.5 billion.

The page never states that people can have more than one condition, so the headline of 1.71 billion and the component total of about 2.5 billion stand unreconciled on the same page. The gap is about 800 million people. If comorbidity is the explanation, the page does not say so. Both figures are printed, and the discrepancy is named.

The same page gives musculoskeletal YLDs of about 149 million, which it calls 17 per cent of all YLDs worldwide, and regional totals of 441 million for high-income countries, 427 million for the Western Pacific and 369 million for South-East Asia. It also notes that about two-thirds of adults needing rehabilitation have musculoskeletal conditions.

Note also that the fact sheet's low back pain prevalence of 570 million (GBD 2019) differs from the 619 million on the WHO low back pain fact sheet (2020 data) and in the GBD 2021 condition paper. Both are printed in their entries. They are different GBD cycles, which is the likely explanation, and no page states it.

Low back pain

The single largest cause of years lived with disability in the world. The figures are given in full.

What it is. Pain in the lower back, with or without pain running down the leg. In the great majority no specific structural cause is identifiable, and imaging findings correlate poorly with pain. It is usually episodic and recurrent.

Measured. Low back pain is the leading cause of years lived with disability globally and has been since GBD began measuring it. The authoritative condition-specific analysis is Ferreira, de Luca, Haile, Steinmetz, Culbreth and colleagues, "Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021", *Lancet Rheumatology* 2023;5(6):e316–e329.

Prevalent cases in 2020: 619 million (95 per cent UI 554 to 694) people globally.

Years lived with disability in 2020: 69.0 million (95 per cent UI 47.9 to 88.9), up from 43.4 million (30.5 to 57.9) in 1990.

Low back pain accounted for 8.1 per cent of all-cause YLDs in 2020, up from 7.7 per cent in 1990, and is ranked first among all causes of YLDs.

Age-standardised prevalence in 2020: 7,460 per 100,000 (6,690 to 8,370), a 10.4 per cent decrease (−10.9 to −10.0) from 8,330 per 100,000 in 1990. The age-standardised rate is falling while absolute numbers rise, and the increase is driven by population growth and ageing. Age-standardised YLD rate in 2020: 832 per 100,000 (578 to 1,070), down 10.5 per cent since 1990.

Projection to 2050: 843 million cases (759 to 933), a 36.4 per cent increase (29.9 to 43.2) over 2020.

Deaths: none. Low back pain causes no direct mortality, and its entire burden is disability. That is why it dominates YLD rankings while being absent from every death ranking.

Prevalence is higher in females at every age, with the gap widening after 75: age-standardised prevalence 9,330 per 100,000 (8,370 to 10,500) in females against 5,520 (4,930 to 6,190) in males. Prevalence and YLDs rise with age, peaking around 85, with the highest YLD rate in the 80 to 84 age group at 2,440 per 100,000 (1,470 to 3,490). The older belief that low back pain peaks in middle age and declines is not supported; burden continues rising into old age.

Attributable burden in 2020: 38.8 per cent (28.7 to 47.0) of low back pain YLDs were attributed to the three modelled risk factors — occupational ergonomic factors at 22.0 per cent, smoking at 12.5 per cent, and high BMI at 11.5 per cent. The remaining 61 per cent or so is not attributable to any modelled risk factor.

The WHO low back pain fact sheet, printed 19 June 2023, carries 619 million people affected in 2020, and 843 million cases by 2050; it names low back pain the single leading cause of disability worldwide, puts non-specific low back pain at about 90 per cent of cases, and defines episodes as acute under six weeks, sub-acute six to twelve weeks and chronic over twelve weeks. The page also contradicts itself on the age of greatest prevalence: its Key Facts say prevalence increases with age up to 80 years, while its body says prevalence and disability are greatest among people aged 80 to 85. Both are printed. The GBD 2021 condition paper's peak around 85, and highest YLD rate at 80 to 84, is consistent with the body rather than with the Key Facts.

Geography: highest age-standardised prevalence in Central and Eastern Europe and North Africa and the Middle East, lowest in parts of Asia and Africa, though measurement differences contribute; the largest absolute burden is in Asia by population. Low back pain is also the leading cause of work absence and early retirement in most countries studied, with direct and indirect economic cost estimated in the hundreds of billions of dollars a year in the United States alone.

GBD 2023 Table 1 confirms the rank and gives low back pain 70.4 million YLDs (95 per cent UI 49.7 to 95.1), rank one, and 70.4 million DALYs, rank nine. Both the GBD 2021 figure of 69.0 million and the GBD 2023 figure of 70.4 million are printed, with their cycles named.

Where it starts. Occupational ergonomic exposure accounts for 22.0 per cent of attributable YLDs: heavy lifting, awkward and sustained postures, whole-body vibration in drivers and operators. Smoking accounts for 12.5 per cent, dose-dependently. High BMI accounts for 11.5 per cent, dose-dependently. A previous episode of low back pain is the strongest single predictor of a future episode.

Psychosocial factors are powerful and consistently outperform structural findings in predicting chronicity and disability: depression, anxiety, fear-avoidance beliefs, pain catastrophising, job dissatisfaction, low social support, and low expectation of recovery. These predict who moves from acute to chronic disability far better than any imaging finding. That is the single most robust and most clinically ignored finding in the field.

Heritability is substantial. Twin studies estimate about 30 to 45 per cent for low back pain generally and about 65 to 75 per cent for lumbar disc degeneration on imaging (Sambrook, *Arthritis and Rheumatism* 1999; Battié). Genetic factors explain more of disc degeneration than occupational loading does — a reversal of the traditional wear-and-tear model. GWAS has found loci including *SOX5*, *CHST3* and *SPOCK2*.

Imaging findings are common in people without pain, and this is the crucial negative finding. In asymptomatic adults, disc degeneration is present in about 37 per cent at age 20 and about 96 per cent at 80; disc bulges in about 30 per cent at 20 and about 84 per cent at 80; disc protrusions in about 29 per cent at 20 and about 43 per cent at 80 (Brinjikji, *AJNR* 2015, systematic review of imaging in asymptomatic populations). Degenerative findings are therefore largely age-normal, and their presence does not establish them as the cause of pain. This underpins the recommendation against routine imaging.

Specific identifiable causes account for only about 5 to 10 per cent†: vertebral fracture, malignancy, infection, axial spondyloarthritis, cauda equina syndrome. Radicular pain or sciatica from disc herniation is a distinct, identifiable minority.

What is not known is the cause of pain in the 90 to 95 per cent labelled non-specific†. That is the central fact: the world's leading cause of disability has no established pathoanatomical explanation in most cases. Which structures generate the pain — disc, facet joint, muscle, nerve, central sensitisation — cannot be reliably determined in the individual. Why identical imaging produces pain in one person and not another is unexplained. Why age-standardised rates are falling is not explained. Whether the condition is primarily nociceptive, neuropathic or nociplastic in most chronic cases is unresolved.

Cure status. Acute episodes: SELF-LIMITING. Chronic low back pain, beyond twelve weeks: RELIEF ONLY. Both halves matter.

Acute low back pain largely resolves: substantial improvement in pain and disability occurs within about six weeks in most people, with the steepest improvement in the first two weeks. But recurrence is the rule and not the exception, with roughly 60 to 70 per cent having a recurrence within twelve months†. The older claim that 90 per cent recover within six weeks is misleading, because it conflates improvement with cure and ignores recurrence.

Chronic low back pain is RELIEF ONLY. No treatment reliably cures it. All established treatments — exercise, psychological therapy, manual therapy, drugs, surgery — produce small to moderate average effects on pain and function, typically 5 to 15 points on a 100-point scale against control, often not sustained beyond six to twelve months. That is the evidence base, and it is stated plainly rather than disguised.

Sciatica from disc herniation is largely SELF-LIMITING: most resolve over weeks to months as the herniation resorbs, and surgery accelerates relief while one- and two-year outcomes converge with conservative management (SPORT and others).

CURABLE only for the small specific fraction: infection, by antibiotics; tumour; fracture stabilisation; cauda equina decompression.

Prevention. One clear winner, and a number of popular measures that do not work.

Exercise: STRONG, and the only consistently effective prevention. Exercise alone, or exercise with education, reduces the risk of a low back pain episode by roughly 35 to 45 per cent, pooled relative risk about 0.55 to 0.65 for exercise plus education (Steffens, *JAMA Internal Medicine* 2016, systematic review and meta-analysis of 23 trials). The effect wanes when exercise stops, so it requires continuation. No particular exercise type is clearly superior.

Education alone: WEAK, effectively ineffective. Education without exercise does not prevent episodes. Back belts and lumbar supports: CONTESTED and ineffective for prevention, with no demonstrated benefit in trials. Shoe insoles: ineffective for prevention.

Ergonomic interventions and lifting training alone: WEAK and CONTESTED. "Lift with your knees" training in isolation has repeatedly failed to prevent back pain in trials, which is surprising given the occupational attributable fraction. Comprehensive workplace programmes that include exercise and organisational change do better.

Smoking cessation: MODERATE, on the 12.5 per cent attributable fraction. Weight management: MODERATE, on the 11.5 per cent attributable fraction. Reducing occupational heavy lifting, vibration and awkward posture exposure: MODERATE — the 22.0 per cent attributable fraction makes this important at population level, though individual-level trial evidence for specific interventions is weak. Avoiding bed rest and staying active during an episode: STRONG for preventing chronicity. Addressing fear-avoidance and catastrophising early: MODERATE for preventing progression to chronic disability. Mattress firmness: WEAK, with medium-firm performing slightly better than firm in limited trials.

Treatment. Ordered by evidence. The evidence favours non-drug treatment, and this has been the consistent direction of guidelines — NICE NG59, the American College of Physicians, the *Lancet* Low Back Pain series of 2018 — for a decade.

Non-pharmacological, first line. Exercise therapy is the best-supported treatment for chronic low back pain, with a moderate effect on pain and function against no treatment, and no single type — motor control, Pilates, yoga, aerobic, strengthening, McKenzie, aquatic — clearly superior, so patient preference and

adherence should drive the choice. Effect sizes are modest, roughly 10 to 15 points out of 100 for pain in the better trials. The cost is a therapist's time, or free if self-directed.

Education, reassurance and advice to remain active reduces disability and healthcare use; bed rest is harmful. Cognitive behavioural therapy, mindfulness-based stress reduction and cognitive functional therapy are effective for chronic low back pain, with effects comparable to or exceeding drug therapy and better maintained. The RESTORE trial (*Lancet* 2023, 492 patients) found cognitive functional therapy produced clinically meaningful improvements in activity limitation against usual care, sustained at 52 weeks — among the larger effects demonstrated for any intervention in chronic low back pain.

Multidisciplinary biopsychosocial rehabilitation, for chronic disabling pain, is better than usual care and than physical treatment alone on pain and disability (Cochrane), and is resource-intensive. Manual therapy and spinal manipulation give a small short-term benefit comparable to other active treatments, reasonable as an adjunct to exercise rather than a stand-alone long-term strategy. Massage, acupuncture and heat give small short-term benefits at low risk; acupuncture's effect over sham is small and contested.

Pharmacological, and the comparative evidence against the drugs is the important part.

NSAIDs are the first-line drug. The effect against placebo is small: roughly 6 to 10 points on a 100-point pain scale, with a number needed to treat of about 6 to 9 for meaningful relief, plus gastrointestinal, renal and cardiovascular risks. Off-patent, EML-listed, a few to tens of US dollars a patient-year.

Paracetamol is not effective for low back pain. The PACE trial (Williams, *Lancet* 2014, 1,643 patients with acute low back pain) found paracetamol no better than placebo for time to recovery, with a median of 17 days in both groups, and no better for pain, disability, function, sleep or quality of life. A clear, large, negative trial that changed guidelines, and paracetamol was subsequently removed as a recommended first-line agent for low back pain in NICE NG59. It is still widely prescribed.

Muscle relaxants, short-term for acute pain, give a small benefit with sedation; benzodiazepines are not recommended. Duloxetine gives modest benefit in chronic low back pain; off-patent, tens to hundreds of US dollars a year.

Opioids are not recommended. The SPACE trial (Krebs, *JAMA* 2018, 240 patients with chronic back, hip or knee pain) found opioids were not superior to non-opioid analgesics for pain-related function over twelve months, and pain intensity was significantly worse in the opioid group, with more adverse effects. The OPAL trial (*Lancet* 2023, 347 patients with acute low back or neck pain) found opioids no better than placebo at six weeks, with worse pain at one year and more opioid misuse risk. Two good trials, both negative. Opioids should not be used for low back pain.

Gabapentinoids are not effective for non-radicular low back pain, and the evidence for sciatica is also negative; they are widely misprescribed. Systemic corticosteroids are not effective for non-radicular low back pain. Antibiotics for Modic changes is a contested and currently unsupported approach.

Interventional and surgical. Epidural corticosteroid injection gives short-term relief of radicular pain only, with no benefit for non-specific low back pain and no effect on long-term outcome or surgery rates. Radiofrequency denervation of facet joints is contested; the large MINT trials (*JAMA* 2017) found no clinically important benefit added to exercise.

Discectomy for persistent sciatica with confirmed herniation accelerates relief, with outcomes converging with conservative care by one to two years; it is appropriate for severe or persistent radicular pain and urgent for cauda equina syndrome. Decompression for symptomatic lumbar spinal stenosis with neurogenic claudication is effective for leg symptoms.

Spinal fusion for non-specific low back pain is CONTESTED and of limited value. Trials comparing fusion with intensive rehabilitation (Fairbank, *BMJ* 2005; Brox) found little or no advantage over structured rehabilitation, at substantial surgical risk and cost. Fusion rates vary enormously between countries and regions for identical indications, which is strong evidence of supply-driven practice. Spinal cord stimulation is expensive, recent sham-controlled trials have been disappointing, and NICE recommends against it for non-specific low back pain.

Imaging: do not image routinely. Imaging without red flags does not improve outcomes, increases surgery and cost, and labels age-normal findings as disease, on the Brinjikji data above. This is one of the strongest do-less recommendations in medicine and one of the most widely violated.

Simple means. Low back pain is the condition where simple means most clearly match or beat the industrial alternatives.

Exercise, for prevention and treatment. It prevents about 35 to 45 per cent of episodes (Steffens 2016) and is first-line treatment for chronic pain. Walking, strengthening, yoga, Pilates, aquatic exercise: no type is superior, so the cheapest available option is as good as the most expensive, and a walking programme costs nothing. The WalkBack trial (*Lancet* 2024, 701 adults) found a progressive walking programme with education significantly prolonged time to recurrence against control — walking as effective prevention.

Staying active and avoiding bed rest is free, and bed rest is actively harmful. Education and reassurance — that the back is not damaged, that imaging findings are age-normal, that activity is safe — measurably reduces disability and healthcare use, and costs a conversation. Heat application gives modest short-term benefit for acute pain: a hot water bottle. Weight loss and smoking cessation address about 24 per cent of the attributable burden between them. Psychological self-management, pain education and mindfulness have effect sizes comparable to the drugs and are deliverable in groups, in print, or digitally at near-zero marginal cost.

Not imaging, not prescribing opioids, not prescribing paracetamol, and not fusing spines for non-specific pain: four evidence-based omissions, each of which saves money and avoids harm.

Exercise against the drugs, set side by side. Exercise produces moderate improvements in pain and function in chronic low back pain, and prevents recurrence with a relative risk of about 0.55 to 0.65; no drug has been shown to prevent recurrence at all. NSAIDs give about 6 to 10 points out of 100 on pain against placebo, with gastrointestinal, renal and cardiovascular risk. Paracetamol gives nothing, being identical to placebo in PACE. Opioids give nothing better than non-opioids and are worse on pain at one year, in SPACE and OPAL. What the evidence supports is that exercise and psychological therapy outperform the entire analgesic pharmacopoeia for chronic low back pain, and are the only interventions that prevent recurrence. The drugs offer small short-term symptom relief with real harms. Guidelines have reflected this since 2016 to 2018.

Gaps. The cause of pain in 90 to 95 per cent of cases is unknown — an extraordinary gap for the leading cause of global disability. All treatment effect sizes are small and short-lived, and the field has produced no breakthrough in decades. Subgrouping and precision approaches to match patients to treatments have repeatedly failed to outperform generic exercise. Why age-standardised prevalence is falling while absolute burden rises is unexplained. The occupational attributable fraction of 22 per cent sits awkwardly with the repeated failure of lifting-training interventions. Chronic pain mechanisms — central sensitisation, nociplastic pain — are increasingly invoked and not measurable clinically. Most trials are from high-income countries, short-term, and use heterogeneous outcome measures despite core-outcome-set initiatives. Enormous unexplained geographic variation in surgery and imaging rates indicates that much care is supply-driven rather than need-driven. GBD estimates for Africa and parts of Asia rest on sparse primary data.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: about 6 weeks ([B] in episodes; † about 6 weeks); depth 46.90.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Neck pain

What it is. Pain in the neck, often spreading to the shoulder or arm. As with the low back, most cases have no identifiable structural cause, and imaging changes are common in people without pain.

Measured. The GBD 2021 neck pain analysis (*Lancet Rheumatology* 2024) reported roughly 203 million prevalent cases globally in 2020 with about 23 million YLDs†. GBD 2023 Table 1 gives neck pain 20.7 million YLDs (95 per cent UI 13.8 to 30.1), rank fifteen. Both are printed; they are different cycles and different quantities, and the 2023 figure is the verified one.

The WHO musculoskeletal health fact sheet gives 222 million prevalent neck pain cases and 22 million YLDs on GBD 2019 data. Neck pain ranks among the top fifteen causes of YLDs globally and consistently in the leading group of musculoskeletal conditions after low back pain. Point prevalence is about 15 to 20 per cent of adults; one-year prevalence about 30 to 50 per cent; lifetime prevalence about 50 per cent.

Deaths: none. The entire burden is disability. There is a female predominance of about 1.3 to 1.7 times, as with most chronic musculoskeletal pain†. Prevalence peaks in middle age, 45 to 60, then plateaus or declines slightly — a different pattern from low back pain, which keeps rising into old age. Highest reported figures come from Norway and parts of Europe and the Middle East, with measurement differences contributing substantially. Office and computer workers, and those with sustained neck flexion, have higher prevalence, and the occupational burden is substantial.

Where it starts. Occupational: sustained neck flexion and awkward posture, prolonged computer and now mobile device use, repetitive work, low job control, with dose-dependent associations. Psychosocial factors, as with low back pain: depression, anxiety, somatisation, job dissatisfaction and low social support strongly predict chronicity, better than imaging findings do. A previous episode is the strongest predictor.

Whiplash injury is a distinct and important subgroup: about 50 per cent of whiplash patients report neck pain at one year, and expectation of recovery, compensation systems and early psychological response predict outcome more strongly than collision severity. Smoking, high BMI, low physical activity and sleep disturbance all contribute. Twin studies estimate heritability of about 35 to 45 per cent for neck pain, with cervical disc degeneration on imaging more heritable at above about 70 per cent.

Imaging findings are age-normal: cervical disc degeneration is present in the majority of asymptomatic adults over 40, approaching 90 per cent and above in the elderly, and its presence does not establish causation.

Specific causes are a minority: cervical radiculopathy from disc herniation or foraminal stenosis; cervical myelopathy, which is important because it is progressive and surgically treatable; inflammatory arthritis, including rheumatoid atlantoaxial involvement and axial spondyloarthritis; infection; tumour and metastasis; fracture; and vertebral artery dissection, a rare but critical diagnosis presenting with neck pain and headache.

What is not known is the pain source in most non-specific cases. Why whiplash becomes chronic in half of patients despite minor tissue injury is contested and has been politicised by its medicolegal context. Whether device use is genuinely driving incidence, or whether this is a reporting artefact, is unestablished.

Cure status. Acute episodes: SELF-LIMITING, with acute neck pain typically improving substantially within weeks. But recurrence and persistence are common, with about 50 to 75 per cent still reporting some pain at one to five years in cohort studies, and chronic neck pain following a fluctuating long-term course. Chronic neck pain: RELIEF ONLY, with treatment effects small as in low back pain.

CURABLE for the specific causes: cervical radiculopathy often resolves spontaneously and surgery is effective when it does not; cervical myelopathy requires surgery to halt progression, and recovery of lost function is incomplete, which makes early diagnosis important; infection and tumour are treated specifically.

Prevention. Exercise: MODERATE, the best-supported preventive measure, particularly neck and shoulder strengthening in office and manual workers, with workplace exercise programmes reducing incidence and severity in trials. Workstation ergonomics alone: WEAK and CONTESTED — adjusting screens and chairs without an exercise or organisational component has weak evidence, mirroring the low back pain finding. Breaks and movement variation during sustained computer work: MODERATE. Addressing psychosocial work factors, job control and workload: MODERATE. Smoking cessation and weight management: WEAK.

Early active management and reassurance after whiplash: MODERATE for preventing chronicity — in contrast to soft collars, which are harmful and prolong recovery. Act-as-usual advice beats immobilisation. Sleep and stress management: WEAK.

Treatment. Exercise therapy is first line for chronic neck pain. Neck-specific strengthening and endurance exercise, with or without scapulothoracic and general exercise, produces modest improvements in pain and function, and strengthening appears more effective than stretching or range-of-motion work alone. The cost is therapist time, or free.

Education, reassurance and advice to stay active, particularly after whiplash. Manual therapy or mobilisation combined with exercise is better than either alone, and the combination is the best-supported package; cervical manipulation carries a rare but serious risk of vertebral artery dissection and stroke, so mobilisation is often preferred and high-velocity cervical thrust should be used cautiously.

NSAIDs give a small short-term benefit; off-patent, EML-listed, a few to tens of US dollars a year. Paracetamol: weak evidence, as for low back pain. Muscle relaxants, short-term only. Tricyclic antidepressants, duloxetine and gabapentinoids have limited evidence for chronic neck pain specifically and are used by extrapolation from other chronic pain; the gabapentinoids are not well supported. Opioids are not recommended: the OPAL trial included neck pain and found opioids no better than placebo at six weeks, with worse pain at one year.

Acupuncture, massage, heat, TENS and laser give small short-term effects at low risk. Psychological therapy, CBT, is effective for chronic pain with significant disability or distress, as in low back pain. Multidisciplinary rehabilitation for chronic disabling neck pain. Soft collars are not recommended and prolong recovery after whiplash. Injections: cervical epidural and facet injections have weak evidence; medial branch radiofrequency ablation has some support for confirmed facet-mediated pain, and the evidence is contested.

Surgery: anterior cervical discectomy and fusion, or posterior foraminotomy, for radiculopathy with persistent severe symptoms or progressive deficit; decompression for cervical myelopathy, to prevent progression. Surgery for non-specific axial neck pain is not supported, mirroring lumbar fusion. Imaging is not indicated without red flags — trauma, neurological deficit, systemic features, suspected myelopathy or malignancy — since age-normal degenerative findings mislead.

Simple means. Neck and shoulder strengthening exercise is the primary treatment and the best prevention, and can be done without equipment or with a resistance band; workplace programmes work. Movement breaks and posture variation during sustained screen work, where the key is varying position rather than finding one correct posture; free. Staying active and continuing normal activities after whiplash, and not wearing a collar: an evidence-based omission that speeds recovery. Education and reassurance about age-normal imaging findings. Heat, self-massage and relaxation training. Adjusting screen height, phone use posture and pillow: low-cost with modest evidence. Smoking cessation, weight management and sleep. Psychological self-management and pain education, deliverable in groups or digitally. Not imaging and not prescribing opioids.

The honest limit: cervical myelopathy and progressive radiculopathy require surgery, and delay causes permanent deficit. Recognising myelopathy — gait disturbance, hand clumsiness, hyperreflexia — is the one place where simple means must give way to urgent referral.

Gaps. Neck pain is substantially less researched than low back pain despite a comparable disability rank. The source of pain is unknown in most cases. Whiplash chronicity is contested and entangled with compensation systems, which makes the literature hard to interpret. Treatment effects are uniformly small and short-term. Whether device use is driving incidence is unestablished. Radiofrequency denervation evidence is conflicting. Optimal exercise dose and type are unclear. GBD neck pain estimates rely on fewer primary studies than low back pain, so uncertainty is wider, and the GBD 2021 figures carried above could not be verified against the primary paper.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 35 years († onset about age 35); time depth 52.11. One untreated course: about 6 weeks († about 6 weeks); depth 46.90.

> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Osteoarthritis of the knee, hip and hand

What it is. The cartilage in a joint thins and the underlying bone changes, causing pain, stiffness and loss of movement. It is a disease of the whole joint, not simply wear and tear, and it is the commonest form of arthritis.

Measured. The GBD 2021 osteoarthritis analysis gave about 595 million people, 7.6 per cent of the global population, with osteoarthritis in 2020, a 132 per cent increase in cases since 1990 (*Lancet Rheumatology* 2023). The WHO osteoarthritis fact sheet, printed 14 July 2023, gives about 528 million people worldwide in 2019, a 113 per cent increase since 1990. Both are printed; they are different cycles. The WHO musculoskeletal health fact sheet gives the same 528 million on GBD 2019 data, which is consistent between the two WHO pages.

Osteoarthritis YLDs are about 21 to 22 million†; GBD 2023 Table 1 gives 22.4 million (95 per cent UI 10.7 to 48.2), rank fourteen among YLD causes. Osteoarthritis is the leading cause of disability in the elderly.

Knee osteoarthritis is the commonest site, at about 365 million cases, about 61 per cent of all osteoarthritis; the hand accounts for about 15 to 20 per cent and the hip for about 5 to 10 per cent of cases. The WHO osteoarthritis fact sheet gives a knee prevalence of 365 million and names the knee as most frequently affected, followed by hip and hand, while giving no hip or hand figures; the page also never explicitly says that the 365 million refers to knee osteoarthritis alone. It gives 344 million moderate or severe cases that could benefit from rehabilitation, and typical onset in the late forties to mid-fifties. Projections are expected to keep increasing, with no number given on the WHO page; the condition literature projects about 1 billion people by 2050.

The WHO osteoarthritis page contradicts itself on the age share: its Key Facts say about 73 per cent of people with osteoarthritis are older than 55, while its body Scope section says about 70 per cent. Both are printed. It gives the female share as 60 per cent in Key Facts and about 60 per cent in the body, which is consistent.

Deaths are minimal directly, though osteoarthritis contributes to mortality indirectly through physical inactivity and through NSAID-related gastrointestinal and cardiovascular events. Prevalence rises steeply after 45, and radiographic knee osteoarthritis affects over 30 per cent of those over 60†, though symptomatic disease is less common: radiographic and symptomatic disease correlate only moderately, which is a key point. Female predominance, especially for knee and hand osteoarthritis, increasing after menopause, at about 1.5 to 2 times†; the hip is closer to equal.

Highest age-standardised rates are reported in high-income North America and parts of Asia, and knee osteoarthritis burden is rising fastest in low- and middle-income countries with rising obesity and ageing. Hip osteoarthritis is notably less common in Chinese and African populations than in European ones, an unexplained difference. Total knee and hip replacement are among the highest-volume elective operations in high-income countries, and demand consistently exceeds supply.

Where it starts. Age is the strongest risk factor, though osteoarthritis is not an inevitable consequence of ageing.

Obesity is the dominant modifiable risk factor for knee osteoarthritis: each 5 kg/m² increase in BMI raises knee osteoarthritis risk by roughly 35 per cent, and obesity raises risk about 2.5 to 4.6 times. The effect is partly mechanical and partly metabolic and inflammatory — obesity also raises hand osteoarthritis risk, which cannot be explained by load.

Joint injury: anterior cruciate ligament and meniscal injury raise knee osteoarthritis risk several-fold, with post-traumatic osteoarthritis developing in about 50 per cent within ten to twenty years of significant knee injury†; hip dysplasia and femoroacetabular impingement for the hip. Occupational loading: kneeling, squatting, heavy lifting, prolonged standing for knee and hip, and repetitive hand use for the hand. Female

sex and the post-menopausal state. Malalignment, varus or valgus, and quadriceps weakness — and quadriceps weakness precedes and predicts knee osteoarthritis rather than merely following it.

Heritability is substantial and site-dependent: about 40 to 65 per cent overall, with the highest estimates for hand at about 40 to 65 per cent and hip at about 50 to 60 per cent, and somewhat lower for knee at about 40 per cent (Spector and MacGregor twin studies). GWAS has identified over 100 loci — *GDF5*, *ASTN2*, *COL11A1*, *ALDH1A2* — explaining a modest fraction.

Running and recreational exercise do not cause osteoarthritis. Recreational runners have equal or lower rates than non-runners, and only elite or high-volume loading with injury raises risk. An important correction to common belief and to the wear-and-tear model.

What is not known is what initiates the disease at the molecular level, and why it progresses in some joints and not others. Pain correlates poorly with radiographic severity: many with severe radiographic change have no pain and vice versa. Central sensitisation, synovitis, bone marrow lesions and psychological factors all contribute, and the pain mechanism is only partly explained. No disease-modifying drug exists after decades of attempts, and no validated biomarker predicts progression. Why hip osteoarthritis is rare in some populations is unexplained.

Cure status. Medical treatment: RELIEF ONLY. Total knee or hip replacement: CURABLE for the joint, effectively. Both parts matter.

No disease-modifying drug exists. Cartilage loss is not reversed by any available treatment, and this has been the field’s central failure, with numerous candidate disease-modifying drugs failing in trials. But symptoms and function are substantially modifiable, and weight loss with exercise can produce clinically large improvements.

Total knee and hip replacement are highly effective. Hip replacement in particular is among the most successful operations in medicine, with about 90 to 95 per cent implant survival at ten years and about 80 to 85 per cent at twenty to 25 years, and large improvements in pain and function†. That is a functional cure for the joint, though about 15 to 20 per cent of knee replacement patients report persistent pain or dissatisfaction — an important and under-disclosed figure.

Early post-traumatic and mild disease: CONTROLLABLE with load management, strength and weight.

Prevention. Weight management: STRONG for knee osteoarthritis, the largest modifiable effect. Each 5 kg/m² BMI reduction meaningfully reduces incidence, and the Framingham data suggested a two-unit BMI reduction could reduce knee osteoarthritis incidence by about 20 to 30 per cent.

Injury prevention: STRONG. Neuromuscular training programmes such as FIFA 11+ and PEP reduce anterior cruciate ligament injury by about 50 to 70 per cent in athletes, which prevents post-traumatic osteoarthritis. One of the clearest primary prevention opportunities, and it needs no equipment.

Muscle strengthening, quadriceps in particular: MODERATE, since weakness predicts incident knee osteoarthritis. Occupational load reduction — kneeling, squatting, heavy lifting: MODERATE. Treating hip dysplasia and femoroacetabular impingement: MODERATE for the hip. Physical activity: MODERATE and protective, not a risk factor, contrary to popular belief; moderate recreational exercise is protective of joint health. Glucosamine and chondroitin for prevention: CONTESTED and ineffective. No drug prevents osteoarthritis: absent.

Treatment. All major guidelines — OARSI, ACR 2019, NICE NG226, EULAR — agree on the ordering: core non-drug treatment first, for everyone.

Core treatments, first line for all patients. Therapeutic exercise: land-based strengthening, aerobic, and neuromuscular or functional exercise. The effect size on pain is roughly 0.4 to 0.6 standardised mean difference against control — comparable to NSAIDs — with improvement in function and no serious harms. Benefit requires continuation; supervised programmes outperform unsupervised, and more sessions give better results. The cost is therapist time, or free.

Weight loss where overweight, with a clear dose-response. At 5 per cent loss or more there is measurable symptom improvement. At about 10 per cent loss the benefit is substantially greater: in the IDEA trial

(Messier, *JAMA* 2013, 454 adults with knee osteoarthritis), diet plus exercise achieving about 11 per cent weight loss produced greater pain reduction than either alone, with reduced knee compressive force and reduced inflammatory markers. At 20 per cent loss or more there is further improvement, approaching the effect of joint replacement on symptoms in some analyses. Combining diet with exercise is superior to either alone — the central practical finding. Education and self-management support. Aquatic exercise where land-based exercise is too painful, with similar benefit.

Pharmacological, adjunctive rather than primary. Topical NSAIDs are recommended before oral NSAIDs for knee and hand osteoarthritis: similar efficacy to oral for the knee, with far fewer systemic adverse effects. Off-patent; tens to hundreds of US dollars a year. Under-used.

Oral NSAIDs are effective with an effect size of about 0.3 to 0.4 standardised mean difference on pain, which is modest, and carry gastrointestinal, renal and cardiovascular risks; use the lowest dose for the shortest period, with a PPI in those at gastrointestinal risk. Ibuprofen, naproxen and diclofenac: EML yes; off-patent; a few to tens of US dollars a patient-year.

Paracetamol gives minimal benefit: network meta-analyses show effects that are statistically detectable but below clinical significance, around 3 to 4 points out of 100, and NICE NG226 moved away from recommending it routinely. Cheap and low-risk, and it should not be relied upon.

Intra-articular corticosteroid injection gives short-term relief, about two to four weeks, with effects largely gone by three months. One trial (McAlindon, *JAMA* 2017) found repeated three-monthly injections over two years produced greater cartilage loss than saline with no pain benefit, which argues against repeated long-term use. Off-patent, cheap. Duloxetine gives modest benefit and is useful where central sensitisation features; off-patent.

Opioids are not recommended. The SPACE trial found them no better than non-opioid analgesics for function in chronic back, hip or knee pain, with worse pain intensity at twelve months.

Intra-articular hyaluronic acid: CONTESTED. Meta-analyses give small effects of uncertain clinical significance; NICE recommends against it and some other guidelines permit it. Expensive, hundreds to thousands of US dollars a course.

Glucosamine and chondroitin: CONTESTED and ineffective. The GAIT trial (*NEJM* 2006, 1,583 patients) found neither glucosamine nor chondroitin, alone or combined, superior to placebo for the overall cohort. Widely sold.

Platelet-rich plasma and stem cell injections are not supported. The RESTORE trial (*JAMA* 2021, 288 patients) found platelet-rich plasma no better than saline for knee pain or cartilage structure at twelve months. Heavily commercialised regardless. Colchicine, methotrexate, hydroxychloroquine and anti-TNF agents are not effective for osteoarthritis; hand osteoarthritis trials of hydroxychloroquine and anti-TNF were negative.

Surgical. Total knee or hip replacement for severe symptomatic disease refractory to non-surgical care is highly effective, with the outcome figures above; cost varies from about US$1,500 in the Indian public sector to about US$30,000 to 50,000 in the United States†.

Arthroscopic partial meniscectomy, and arthroscopic lavage or debridement for osteoarthritis, are not effective. Multiple randomised and sham-controlled trials — Moseley, *NEJM* 2002; Kirkley, *NEJM* 2008; FIDELITY, Sihvonen, *NEJM* 2013, sham-controlled in degenerative meniscal tear — found no benefit over placebo surgery or over exercise therapy. The METEOR trial found physical therapy non-inferior to meniscectomy. Despite this, the procedure continues in large numbers: one of the clearest examples of low-value care persisting against strong evidence.

Osteotomy for unicompartmental disease with malalignment in younger patients. For hand osteoarthritis: thumb base splinting, hand exercise, topical NSAIDs; trapeziectomy for refractory thumb base disease; joint fusion or replacement for selected finger joints.

Simple means. Osteoarthritis is, with low back pain, the clearest case where simple means are first-line therapy rather than adjuncts.

Exercise has an effect size on pain comparable to NSAIDs, standardised mean difference about 0.4 to 0.6, without the gastrointestinal, renal and cardiovascular risks†. Strengthening, walking, cycling, tai chi — which has good trial evidence for knee osteoarthritis — and aquatic exercise. No equipment needed.

Weight loss, dose-dependently: 5 per cent gives benefit, 10 per cent substantially more on the IDEA trial, 20 per cent more still. Diet plus exercise beats either alone.

Walking aids, a stick or cane, reduce joint load and pain measurably: a stick. Footwear: comfortable, cushioned, flat flexible shoes; lateral wedge insoles are not effective, with negative trials. Tai chi has randomised evidence of benefit for knee osteoarthritis comparable to physical therapy and needs only space and instruction. Heat and cold application for symptomatic relief, free. Thumb splints for hand osteoarthritis: simple, cheap and effective for pain. Quadriceps strengthening at home with body weight or a resistance band. Injury prevention programmes of neuromuscular training reduce anterior cruciate ligament injury 50 to 70 per cent, preventing post-traumatic osteoarthritis: free, and done as a warm-up.

Not having arthroscopic meniscectomy; not using glucosamine, platelet-rich plasma or hyaluronic acid; not taking opioids: four evidence-based omissions saving substantial money.

Exercise against the drugs, set side by side. Exercise gives a standardised mean difference of about 0.4 to 0.6 for pain in knee and hip osteoarthritis, plus function gains, no serious adverse effects, and benefits to cardiovascular and metabolic health. Oral NSAIDs give a standardised mean difference of about 0.3 to 0.4 for pain, with gastrointestinal bleeding, renal and cardiovascular risks — a real harm profile, particularly in the elderly who are the main patient group. Paracetamol gives about 3 to 4 points out of 100, below clinical significance†. Opioids are no better than non-opioids and worse on pain at twelve months. Intra-articular steroid lasts two to four weeks, and repeated use may accelerate cartilage loss. What the evidence supports is that exercise matches or exceeds the analgesic drugs for pain, exceeds them clearly for function, and carries benefit rather than harm elsewhere in the body. Weight loss adds a dose-dependent effect no drug matches. The drugs are adjuncts for breakthrough symptoms, and the guidelines say so.

Gaps. No disease-modifying drug exists despite decades of effort, and no validated biomarker predicts progression. Pain correlates poorly with structural severity, so treatment targeting is imprecise and the pain mechanism is only partly understood. About 15 to 20 per cent of knee replacements leave persistent pain†, which is not well explained or well disclosed. Arthroscopic meniscectomy continues at scale despite sham-controlled negative trials — a practice-evidence gap rather than a knowledge gap. Why hip osteoarthritis is rare in some populations is unexplained. Optimal exercise type, dose and delivery are unsettled, and adherence declines markedly after supervised programmes end. Access to joint replacement is extremely unequal globally. GBD estimates rely on radiographic and self-report data that are not interchangeable, and primary data from Africa and much of Asia are sparse. The two WHO fact sheets that carry osteoarthritis figures disagree with the GBD 2021 condition paper on prevalence and with each other on the age share.

> **Depth.** Starts in: joint cartilage. Size: 2 mm†; depth +9.73. First complaint: about 55 years († onset about age 55); time depth 52.52. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Cartilage does not regrow. The joint can be replaced. So it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Rheumatoid arthritis

What it is. The immune system attacks the lining of joints, usually symmetrically in the hands, wrists and feet. Untreated it destroys joints and shortens life. Treated early, most people now do well.

Measured. Global prevalence is about 0.25 to 0.5 per cent, with GBD 2019 and 2021 estimating about 17.6 to 18 million people. The WHO musculoskeletal health fact sheet gives 18 million prevalent cases and 2.4 million YLDs on GBD 2019 data. GBD 2019 gave about 38,000 to 40,000 deaths a year and roughly 3 million DALYs†.

Female to male ratio is about 2.5 to 3:1†. Peak onset is 40 to 60, though it occurs at any age. Prevalence is highest in North America and northern Europe at about 0.5 to 1 per cent, lower in Southeast Asia and much of Africa at about 0.1 to 0.3 per cent, and very high in some Indigenous North American populations, with Pima and Chippewa figures up to 5 to 7 per cent†.

Life expectancy was historically reduced by about three to ten years, mainly from cardiovascular disease, and this gap has narrowed substantially with modern treat-to-target therapy, though not closed. Remission is now an achievable target in a substantial proportion, which is a transformation since the 1990s.

Where it starts. Smoking is the strongest established environmental risk factor, at roughly 1.5 to 2.5 times the risk overall, and the interaction with genetics is dramatic: in HLA-DRB1 shared epitope carriers who smoke, the risk of ACPA-positive disease rises many-fold, with odds ratios of about 20 to 40 for double-dose shared epitope plus smoking. This gene-environment interaction is one of the best-characterised in all of medicine.

HLA-DRB1 shared epitope alleles are the dominant genetic risk, with *PTPN22*, *STAT4*, *TRAF1/C5* and *PADI4*, the last prominent in Asian populations, and over 100 loci identified. Heritability is about 50 to 60 per cent from twin studies, with monozygotic concordance about 12 to 15 per cent and dizygotic about 3 to 5 per cent, and heritability is higher for ACPA-positive seropositive disease, about 50 to 65 per cent, than for seronegative.

Anti-citrullinated protein antibodies and rheumatoid factor appear years before symptoms, up to ten to fifteen years, defining a pre-clinical phase. That is the basis of current prevention trials.

Periodontal disease and *Porphyromonas gingivalis* are a leading hypothesis: the organism expresses a peptidylarginine deiminase that citrullinates proteins, potentially initiating the autoimmunity. The association is robust and the causation plausible and unproven; *Aggregatibacter actinomycetemcomitans* is also implicated. Lung exposures — silica, textile dust, air pollution — support the hypothesis that the disease may initiate at mucosal surfaces, lung, gum or gut, rather than in the joint.

Female sex, nulliparity and the post-partum period, which is a well-recognised onset window; breastfeeding is protective. Obesity, at about 1.2 to 1.3 times†, and worsening treatment response; low vitamin D, CONTESTED; high sodium intake interacting with smoking. Protective: moderate alcohol, a consistent association with unclear mechanism, oily fish and omega-3, higher socioeconomic status, and breastfeeding.

What is not known is the trigger that converts pre-clinical autoimmunity into arthritis. The second hit is unidentified, which is exactly what the prevention trials are trying to address. Why seronegative disease occurs at all and whether it is the same disease. Why the joints are targeted when the initiating event appears to be at mucosal sites. Why treatment response varies so much between individuals, and why there is still no biomarker to choose between biologics — treatment selection remains trial and error.

Cure status. CONTROLLABLE, and now very well controlled, though not cured. Remission is achievable in roughly 40 to 60 per cent with modern treat-to-target strategies, and low disease activity in considerably more — a transformation from the pre-methotrexate and pre-biologic era. Sustained drug-free remission occurs in a minority, about 10 to 20 per cent†, more often in those treated very early and in seronegative disease, and relapse on withdrawal is common, so the disease is suppressed rather than eliminated.

The window of opportunity is real: treatment within the first three to six months of symptom onset produces substantially better long-term outcomes and more remission, and delay causes irreversible joint damage. That makes early referral the single most important system factor. Established joint destruction is irreversible, though joint replacement restores function. Prevention of onset is now being tested and is partially supported, which is a genuinely new development.

Prevention. Smoking cessation: STRONG, and the only well-established modifiable preventive measure; risk declines after cessation, though slowly, over ten to twenty years. Oral and periodontal health: MODERATE — biologically plausible and epidemiologically supported, with periodontal treatment improving disease activity modestly in small trials, though prevention of onset is not demonstrated. Weight management: MODERATE. Breastfeeding: WEAK. Omega-3 and oily fish: WEAK.

Pharmacological prevention in the at-risk pre-clinical phase is emerging and partially supported. PRAIRI, a single rituximab dose, delayed onset. TREAT EARLIER, methotrexate in at-risk arthralgia, did not prevent arthritis but improved symptoms and MRI inflammation. APIPPRA, abatacept (*Lancet* 2024), significantly reduced progression to rheumatoid arthritis during treatment, with arthritis development of 6 against 29 per cent at twelve months, though the effect attenuated after stopping. So delay is demonstrated and durable prevention is not yet: MODERATE for delay, CONTESTED for prevention.

Vitamin D: CONTESTED — the VITAL trial secondary analysis suggested reduced autoimmune disease incidence with vitamin D plus omega-3, which is suggestive and not definitive. Cardiovascular risk management: STRONG for preventing the leading cause of death in rheumatoid arthritis — statins, blood pressure control, smoking cessation. That is prevention of the fatal complication rather than of the disease.

Treatment. The strategy, not any single drug, is what transformed outcomes: early diagnosis, treat-to-target with regular disease activity measurement, and escalation until remission or low disease activity.

Methotrexate is the anchor drug and the first-line conventional synthetic DMARD. Monotherapy achieves an ACR50 response in roughly 25 to 40 per cent†, and it potentiates every biologic. It is given weekly, orally or subcutaneously, with folic acid supplementation to reduce toxicity, and requires blood monitoring of liver and blood count. WHO EML: yes, listed under disease-modifying antirheumatic drugs with the indication rheumatoid arthritis, and separately for juvenile joint diseases. Off-patent. Cost tens to hundreds of US dollars a patient-year for the oral generic, often less; subcutaneous is more. This is the single highest-value drug in rheumatology: a few dollars a month delivering most of the achievable benefit for many patients.

Other conventional synthetic DMARDs: sulfasalazine at tens to hundreds of US dollars a year, hydroxychloroquine at tens to hundreds of US dollars leflunomide at hundreds of US dollars. All off-patent, with sulfasalazine and hydroxychloroquine EML-listed. Triple therapy — methotrexate with sulfasalazine and hydroxychloroquine — was non-inferior to methotrexate plus etanercept in the RACAT trial (*NEJM* 2013) and in TEAR. That is a critical finding for cost-constrained settings, since triple therapy costs a tiny fraction of a biologic.

Corticosteroids give rapid symptom control as a bridge while DMARDs take effect, and low-dose prednisolone has a disease-modifying effect; long-term use is limited by bone, glucose, infection and cataract toxicity. Prednisolone off-patent, EML-listed, a few to tens of US dollars a year.

Biologic DMARDs, for inadequate response to conventional DMARDs:

Agent	Class	Measured effect, with methotrexate	WHO EML	Off-patent / biosimilar	Approx. annual cost
Infliximab	Anti-TNF	ATTRACT / ASPIRE: ACR50 40–50% vs 20% MTX alone; major reduction in radiographic progression	listed **only as a therapeutic equivalent** to adalimumab, with rheumatoid arthritis among its indications, not as a selected medicine	originator off-patent; biosimilars widely available	originator tens of thousands of US dollars; biosimilars thousands of US dollars some tenders below thousands of US dollars
Adalimumab	Anti-TNF	PREMIER / ARMADA: ACR50 50–60% in combination vs 30% MTX alone	**yes, listed medicine**, rheumatoid arthritis among its indications	originator off-patent; biosimilars since 2018 in the EU, 2023 in the US	originator US$50,000–90,000 US list; biosimilars US$2,000–10,000
Etanercept	Anti-TNF	TEMPO: ACR50 60–70% combined	yes	biosimilars available	originator tens of thousands of US dollars +; biosimilars thousands to tens of thousands of

Agent	Class	Measured effect, with methotrexate	WHO EML	Off-patent / biosimilar	Approx. annual cost
					US dollars
Tocilizumab	Anti-IL6R	ACR50 40–55%; effective as monotherapy, unusual among biologics	yes	biosimilars entering	tens of thousands of US dollars falling
Rituximab	Anti-CD20	REFLEX: ACR50 27% vs 5% placebo in anti-TNF failures	**yes, listed medicine**, under multiple sclerosis and targeted therapies	biosimilars widely available	originator tens of thousands of US dollars a course; biosimilars thousands of US dollars
Abatacept	T-cell costimulation	ACR50 40–50%	no	no	tens of thousands of US dollars
Tofacitinib, baricitinib, upadacitinib	JAK inhibitors	ACR50 40–50%; upadacitinib superior to adalimumab in SELECT-COMPARE	no	tofacitinib generics entering	originator US$50,000–70,000 US list; generic tofacitinib potentially below thousands of US dollars

On JAK inhibitor safety: the ORAL Surveillance trial found tofacitinib did not meet non-inferiority against TNF inhibitors for major adverse cardiovascular events and malignancy in an enriched-risk population, which led to regulatory warnings and to restriction, in many jurisdictions, to patients who have failed a TNF inhibitor.

The biosimilar price collapse is the central economic fact. Anti-TNF agents fell from tens of thousands of US dollars a year to thousands to tens of thousands of US dollars and in some tenders below thousands of US dollars. Adalimumab is a listed EML medicine with rheumatoid arthritis among its indications; infliximab appears on the list only as a therapeutic equivalent to adalimumab, not as a selected medicine. Rituximab is a listed medicine, under multiple sclerosis and targeted therapies in the complementary list. Between them these make biologic therapy for rheumatoid arthritis feasible in middle-income health systems for the first time.

Treat-to-target monitoring with DAS28, CDAI or SDAI measured regularly, with escalation until target, produces better outcomes than any individual drug choice (TICORA, BeSt, CAMERA). It requires a measuring tape, a trained assessor and a CRP, not expensive technology.

Physiotherapy, occupational therapy and hand exercise maintain function, protect joints and provide aids and splints. Cardiovascular risk management, osteoporosis prevention, and vaccination — pneumococcal, influenza, hepatitis B, and zoster where appropriate before immunosuppression — with screening for latent tuberculosis and hepatitis before biologics. Surgery: joint replacement, tendon repair, cervical spine stabilisation; rates have fallen markedly with better drug control.

Simple means. Smoking cessation is the only established modifiable cause, and it also improves drug response and reduces cardiovascular death. Free.

Exercise, aerobic and resistance training, improves pain, function, fatigue and cardiovascular risk without worsening disease activity or joint damage — a long-held fear now refuted. That matters, because these patients have high cardiovascular mortality and become deconditioned.

Hand exercise programmes: the SARAH trial (*Lancet* 2015, 490 patients) found a tailored hand exercise programme improved hand function at twelve months at low cost, added to usual care. Taught exercises, no equipment.

Dental and periodontal hygiene has a plausible disease-modifying effect and gives a measurable improvement in disease activity in small trials: brushing and interdental cleaning. Weight management improves response to therapy. Joint protection and assistive devices, splints and adapted utensils are occupational therapy measures that preserve independence at minimal cost. Mediterranean diet and omega-3 give modest symptomatic benefit in trials: food, not a drug.

Methotrexate with folic acid at tens to hundreds of US dollars a year is manufactured but cheap, off-patent and EML-listed, and is the backbone of effective treatment worldwide. Triple conventional DMARD therapy at a few hundred dollars a year is non-inferior to methotrexate plus etanercept (RACAT) — the key affordability finding. Early referral: recognising persistent synovitis and referring within weeks rather than months is a knowledge and pathway intervention, not a technology, and it determines long-term outcome more than drug choice.

The honest limit: rheumatoid arthritis cannot be managed without DMARDs. Diet, exercise and hygiene are valuable adjuncts, not alternatives, and delay in starting a DMARD causes permanent damage.

Gaps. The initiating trigger is unknown, and the mucosal-origin hypothesis — gum, lung, gut — remains unproven. There is no biomarker to select between biologics, so treatment is sequential trial and error: a major and costly gap. Prevention trials show delay but not durable prevention, and whom to treat pre-clinically raises unresolved ethical questions. Whether seronegative disease is the same entity is unclear. Optimal tapering and withdrawal strategies after remission are not established. JAK inhibitor cardiovascular and malignancy risk is contested beyond the enriched-risk ORAL Surveillance population. Biosimilar availability and pricing vary by more than tenfold between countries, so the cost of treatment is not a single number. Access to any DMARD remains poor in much of Africa and South Asia, where the disease is under-diagnosed and GBD estimates rest on sparse data.

> **Depth.** Starts in: a citrullinated protein. Size: 10 nm†; depth −1.38. First complaint: about 5 years († ACPA antibodies about 5 years before onset); time depth 50.34. One untreated course: no number ([B] destructive if untreated).
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> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Ankylosing spondylitis and axial spondyloarthritis

What it is. Inflammation of the spine and of the joints where it meets the pelvis, causing back pain and stiffness that is worse with rest and better with movement. Over years the spine can fuse. It typically begins in young adulthood.

Measured. Prevalence of axial spondyloarthritis is about 0.3 to 1.4 per cent, with ankylosing spondylitis specifically about 0.1 to 0.5 per cent, closely tracking HLA-B27 prevalence in the population. GBD does not model axial spondyloarthritis as a separate top-level cause; it sits within other musculoskeletal disorders, which GBD 2023 Table 1 places eighth among YLD causes at 43.2 million (95 per cent UI 29.9 to 58.3). The burden of this condition is therefore substantially under-represented in global statistics relative to its disability impact in young working-age adults.

Onset is typically 20 to 30, and onset after 45 is rare, which is a useful diagnostic point. The male to female ratio is about 2 to 3:1 for radiographic ankylosing spondylitis but close to 1:1 for non-radiographic axial spondyloarthritis, and women are diagnosed later and more often missed, partly because of the historical male stereotype. Diagnostic delay averages five to ten years from symptom onset — comparable to endometriosis, and for similar reasons: young people with back pain are assumed to have mechanical pain.

Geography tracks HLA-B27: high in Northern European, Inuit, with up to 25 to 40 per cent B27 carriage†, and some Indigenous Siberian populations; low in sub-Saharan Africa and Japan; and the disease is correspondingly rare in populations with low B27 frequency.

Where it starts. HLA-B27 is present in about 85 to 95 per cent of people with ankylosing spondylitis against about 6 to 8 per cent of northern European populations, but only about 1 to 5 per cent of HLA-B27 carriers develop the disease, so the association is strong and far from sufficient.

Heritability is among the highest of any common disease, about 90 per cent, with HLA-B27 accounting for roughly 20 to 30 per cent of total genetic risk (Brown, twin and sibling studies). Other loci: *ERAP1*, which interacts with B27, *IL23R*, *IL12B*, *TNFSF15*. Sibling recurrence risk is about 5 to 10 times†. Family history is the strongest practical predictor.

Gut inflammation: subclinical gut inflammation is present in a substantial proportion, about 5 to 10 per cent develop overt inflammatory bowel disease†, and the gut-joint axis with microbial dysbiosis is a leading mechanistic hypothesis, supported by the shared response to IL-17 and IL-23 pathway drugs and by the association with *Klebsiella* and other organisms. It is not established as causal.

Associated conditions: acute anterior uveitis at about 25 to 40 per cent lifetime†, psoriasis, and inflammatory bowel disease — the spondyloarthritis family. Mechanical stress at entheses may localise inflammation, and smoking worsens progression and spinal damage.

What is not known is how HLA-B27 causes disease. The arthritogenic peptide, the misfolding and unfolded protein response, and the free heavy chain theories all have support and none is established, after fifty years. Why only a small minority of carriers are affected. Why men develop more radiographic fusion while women have similar symptom burden. Whether non-radiographic axial spondyloarthritis is early ankylosing spondylitis or a distinct entity that often does not progress, which is clinically important and genuinely unresolved. And whether any treatment prevents structural progression, which is contested.

Cure status. The disease: CONTROLLABLE, not curable. It is lifelong. Spinal deformity: CURABLE surgically by osteotomy, at high risk and as a last resort.

Symptom control is now good: NSAIDs help most, and biologics produce major improvement in a majority of NSAID-refractory patients, with ASAS40 response of about 40 to 60 per cent. Structural progression — syndesmophyte formation and fusion — is only partly modifiable: long-term observational data suggest TNF inhibitors slow radiographic progression after about four years of use, but the randomised evidence for prevention of structural damage is weaker than for symptoms, and this remains contested. Established fusion is irreversible: loss of spinal mobility, once fused, cannot be recovered, which is why early treatment and lifelong exercise matter.

Prevention. No primary prevention exists: absent. HLA-B27 screening is not recommended, since most carriers never develop disease.

Smoking cessation: MODERATE — smoking is associated with worse spinal damage, worse function and worse treatment response, and it is the clearest modifiable factor for preventing progression. Regular exercise throughout life: STRONG for preventing loss of mobility and deformity, as secondary prevention. Early diagnosis and treatment: MODERATE for preventing accumulated disability, and reducing the five to ten year diagnostic delay is the highest-value system intervention available.

Osteoporosis prevention: STRONG. Bone loss and vertebral fracture risk are increased in ankylosing spondylitis despite the paradoxical appearance of new bone formation, and this is often overlooked. Uveitis awareness: prompt treatment of a red painful eye prevents visual loss, and patient education costs nothing.

Treatment. Exercise and physiotherapy are the foundation, for everyone, lifelong. Supervised group exercise is superior to home exercise, which is superior to none; exercise maintains spinal mobility, posture and function and improves pain. This is genuinely first-line and is never superseded by drugs.

NSAIDs are first-line drug therapy and unusually effective here, more so than in mechanical back pain. Most patients respond well, and response to NSAIDs is itself a supportive diagnostic feature. Continuous rather than on-demand use may slow radiographic progression, which is contested. Ibuprofen, naproxen, diclofenac and indomethacin: EML yes; off-patent; a few to tens of US dollars a patient-year. Extremely cheap, and effective for most.

Biologics for persistent high disease activity despite NSAIDs. TNF inhibitors — adalimumab, etanercept, infliximab, certolizumab, golimumab — give an ASAS40 response of about 40 to 60 per cent against about 15 to 20 per cent placebo. Adalimumab is on the WHO EML as a listed medicine with axial spondyloarthritis as a listed indication. Infliximab is EML-listed only as a therapeutic equivalent to adalimumab, not as a selected medicine, and axial spondyloarthritis is among the indications of that therapeutic-equivalent listing; a bare “on the EML” overstates it. Biosimilars cost thousands to tens of thousands of US dollars a year against originator prices of tens of thousands of US dollars.

IL-17 inhibitors, secukinumab and ixekizumab, give similar efficacy and are an alternative after TNF failure; on patent, tens of thousands of US dollars. JAK inhibitors, tofacitinib and upadacitinib, are

effective with the same safety caveats as in rheumatoid arthritis. Note that IL-23 inhibitors, ustekinumab and risankizumab, failed in axial spondyloarthritis despite working in psoriasis and psoriatic arthritis — an instructive and unexplained dissociation.

Conventional synthetic DMARDs, methotrexate and sulfasalazine, do not work for axial disease, which is an important negative. Sulfasalazine has some effect on peripheral arthritis only, and prescribing methotrexate for axial spondyloarthritis is a common error. Local corticosteroid injection for sacroiliac joints or enthesitis; systemic steroids are not generally useful for axial disease, another contrast with rheumatoid arthritis.

Treat the extra-articular manifestations: topical steroids and mydriatics for uveitis, with urgent ophthalmology; inflammatory bowel disease treatment, choosing agents that treat both, noting that etanercept does not work for bowel disease so a monoclonal anti-TNF is preferred in that overlap. Osteoporosis assessment and treatment, often missed. Surgery: hip replacement, since hip involvement is common and disabling; spinal osteotomy for severe deformity; stabilisation for fracture. Smoking cessation.

Simple means. This condition has an unusually strong simple-means core, because exercise is genuinely disease-modifying for function.

Daily exercise is the single most important long-term intervention: spinal extension and mobility exercises, posture work, deep breathing and chest expansion, since chest wall involvement restricts breathing, and swimming, which is excellent because it loads the spine minimally while mobilising it. Group exercise and hydrotherapy outperform home exercise, and home exercise far outperforms nothing. No equipment required.

Postural awareness, and sleeping flat on a firm surface with a thin pillow, reduces flexion deformity over years. Smoking cessation is the clearest modifiable determinant of spinal damage. NSAIDs at a few to tens of US dollars a year are manufactured but extremely cheap, and more effective in this condition than in most back pain.

Patient education: recognising uveitis — a red painful eye with photophobia — and seeking same-day care prevents blindness; and recognising that rest worsens and movement improves the pain, which is counter-intuitive and often mismanaged. Weight-bearing exercise, calcium and vitamin D for the increased fracture risk. Early recognition and referral: the inflammatory back pain features — onset under 45, morning stiffness over 30 minutes, improvement with exercise, night pain, good NSAID response, alternating buttock pain — are a free diagnostic tool that could cut the five to ten year delay.

The honest limit: exercise does not control inflammation in active disease, and patients with high disease activity need NSAIDs and often biologics. Where biologics are unaffordable, NSAIDs plus intensive exercise is the realistic standard, and it is far from useless.

Gaps. How HLA-B27 causes disease is unknown after five decades. Whether any drug prevents structural progression is contested: the randomised evidence is weak and the observational evidence confounded. Whether non-radiographic axial spondyloarthritis is uniformly early ankylosing spondylitis is unresolved, which complicates treatment decisions and trial interpretation. The five to ten year diagnostic delay persists, and women are disproportionately affected by it. The failure of IL-23 inhibitors despite IL-17 success is unexplained and undermines the assumed pathway. MRI interpretation of sacroiliitis has significant inter-reader variability and false positives, in athletes and postpartum women, causing both over- and under-diagnosis. Axial spondyloarthritis is not separately modelled in GBD, so its global burden is effectively uncounted. There are almost no epidemiological data from Africa.

> **Depth.** Starts in: HLA-B27. Size: 10 nm†; depth −1.38. First complaint: about 26 years ([B] young adult; † about 26); time depth 51.84. One untreated course: no number ([B] the spine can fuse).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Psoriatic arthritis

What it is. An inflammatory arthritis that occurs in people with psoriasis. It affects joints, tendons, the spine and the fingers and toes, often asymmetrically, and can destroy joints.

Measured. It affects about 20 to 30 per cent of people with psoriasis, with a population prevalence of about 0.1 to 0.25 per cent, and up to 0.5 per cent in some studies. Psoriasis itself affects about 60 to 125 million people globally, about 2 to 3 per cent of adults, so the psoriatic arthritis pool is large. It is not modelled as a separate GBD cause and sits within other musculoskeletal disorders or within psoriasis, so its burden is under-represented.

Male to female ratio is approximately 1:1, unlike rheumatoid arthritis. Peak onset is 30 to 50. Skin disease usually precedes arthritis by about seven to ten years in about 70 to 80 per cent of cases†, which creates a window for early detection that is largely unused. Under-diagnosis is substantial: about 15 to 30 per cent of psoriasis clinic patients have undiagnosed psoriatic arthritis on screening. Geography follows psoriasis: higher in northern Europe and North America, lower in East Asia and much of Africa.

Where it starts. Psoriasis is the necessary precursor in nearly all cases. Risk is higher with severe psoriasis, and with scalp, nail and intergluteal or perianal involvement. Nail psoriasis is a particularly strong predictor: nail and enthesis share anatomical continuity with the distal interphalangeal joint, which may explain the distribution.

Genetics: HLA-B27 for axial disease; HLA-B*08, B*38, B*39 and C*06, with C*06 more associated with psoriasis than with arthritis; *IL23R*, *TNIP1*, *TRAF3IP2*. Heritability is high: the recurrence risk ratio in first-degree relatives is about 30 to 55 times, among the highest for any rheumatic disease, and twin data support a strong genetic component.

Obesity is a well-established, dose-dependent risk factor for developing psoriatic arthritis in people with psoriasis, and weight loss improves response to treatment. Physical trauma, the deep Koebner phenomenon, with joint or tendon trauma preceding onset, is an intriguing and repeatedly observed association. Infection — streptococcal, and HIV, where HIV-associated psoriatic arthritis can be severe. Smoking, which is paradoxically associated with psoriasis but inversely associated with psoriatic arthritis among psoriasis patients, an unexplained finding. Stress.

What is not known is why only 20 to 30 per cent of psoriasis patients develop arthritis, and no biomarker predicts who. The smoking paradox is unexplained. Why the disease pattern is so heterogeneous within one diagnosis — oligoarticular, polyarticular, axial, enthesitic, dactylitic, distal interphalangeal, arthritis mutilans — is unexplained, and these may be distinct entities. Whether treating psoriasis prevents arthritis is contested and confounded: observational data suggest biologics for the skin may reduce incidence.

Cure status. CONTROLLABLE, not curable. A lifelong disease with relapses. Remission or low disease activity is achievable in a substantial proportion with modern therapy, and the treat-to-target approach, as in TICOPA, improves outcomes. Structural joint damage is irreversible, and about 20 to 40 per cent develop erosive disease†; arthritis mutilans, the severe destructive form, affects a small percentage. Both skin and joints respond to several agents, which is a treatment advantage. Drug-free remission is uncommon.

Prevention. Weight management: MODERATE — obesity raises incidence dose-dependently in psoriasis patients, and weight loss improves both disease activity and treatment response. The clearest modifiable factor.

Screening psoriasis patients for arthritis: MODERATE for preventing accumulated damage. Simple questionnaires — PEST, PASE, EARP — are free and effective at case-finding, and dermatology-rheumatology collaboration is the practical mechanism. Given that skin disease precedes arthritis by years in most, this is an unusually tractable early-detection opportunity.

Treating psoriasis effectively to prevent arthritis: CONTESTED — observational evidence suggests biologic treatment of skin disease may reduce arthritis incidence, with no randomised evidence. Avoiding joint trauma: WEAK, based on the Koebner observation. There is no established primary prevention of psoriasis itself.

Treatment. Treatment is chosen by which domains are involved — peripheral arthritis, axial disease, enthesitis, dactylitis, skin, nails — which is why the GRAPPA and EULAR recommendations are domain-based.

NSAIDs for mild peripheral arthritis and enthesitis: off-patent, EML-listed, a few to tens of US dollars a year. Local corticosteroid injection for mono- or oligoarthritis, enthesitis and dactylitis; systemic steroids are used cautiously, because withdrawal can precipitate a severe pustular psoriasis flare.

Conventional synthetic DMARDs for peripheral arthritis. Methotrexate: the SEAM-PsA trial found methotrexate monotherapy produced meaningful responses, ACR20 about 51 per cent†, though etanercept was superior, and the earlier MIPA trial was equivocal. It treats both skin and joints and remains widely used first-line in most of the world on cost grounds. EML yes, listed for rheumatoid arthritis and for skin differentiation and proliferation disorders; off-patent; tens to hundreds of US dollars a year. Sulfasalazine and leflunomide give modest benefit for peripheral arthritis; off-patent and cheap. None of the conventional DMARDs work for axial disease or enthesitis. Hydroxychloroquine is generally avoided, since it may exacerbate psoriasis.

Biologics and targeted therapies, effective across more domains:

Agent	Class	Measured effect	WHO EML	Biosimilar / generic	Approx. annual cost
Adalimumab, etanercept, infliximab	Anti-TNF	ACR20 55–65% vs 15–25% placebo; effective for skin, joints, axial disease, enthesitis and dactylitis; inhibit radiographic progression	**adalimumab yes, listed medicine** with psoriasis among its indications; **infliximab only as a therapeutic equivalent** to adalimumab	biosimilars widely available	biosimilars thousands to tens of thousands of US dollars; originators tens of thousands of US dollars
Secukinumab, ixekizumab	Anti-IL17A	ACR20 50–60%; excellent skin response	no	no	tens of thousands of US dollars
Ustekinumab	Anti-IL12/23	ACR20 42–50%; good skin response	no	biosimilars entering 2024–25	US$25,000–60,000, falling†
Guselkumab, risankizumab	Anti-IL23	ACR20 52–64%; strong skin response, unlike in axial disease	no	no	tens of thousands of US dollars
Tofacitinib, upadacitinib	JAK inhibitors	ACR20 50–57%	no	tofacitinib generics entering	originator tens of thousands of US dollars; generic potentially below thousands of US dollars
Apremilast	PDE4 inhibitor	ACR20 32–40%, modest; oral, no monitoring required	no	generics entering	originator tens of thousands of US dollars; generics far lower

Treat-to-target: the TICOPA trial (*Lancet* 2015) showed tight control with protocolised escalation improved joint and skin outcomes against standard care. Physiotherapy and exercise for function, axial mobility and enthesitis. Skin and nail care, with dermatology collaboration. Cardiometabolic risk management, since psoriatic disease carries increased cardiovascular risk, metabolic syndrome, fatty liver and depression, which are often the bigger threat to life. Weight loss, which improves disease activity and treatment response measurably.

Simple means. Weight loss reduces incidence, improves disease activity and improves biologic response — among the few interventions affecting all three. Exercise maintains function and axial mobility and reduces cardiovascular risk, with no evidence of joint harm.

Methotrexate at tens to hundreds of US dollars a year is manufactured but cheap, off-patent and EML-listed, and treats skin and joints together; for most of the world this with NSAIDs is the realistic regimen.

NSAIDs at a few to tens of US dollars a year. Sunlight and natural ultraviolet exposure for psoriasis where appropriate is free phototherapy, with the obvious caution about burning and skin cancer risk. Emollients and simple topical treatments — coal tar, salicylic acid — are cheap and effective for mild skin disease. Smoking cessation and alcohol moderation, for cardiovascular risk and because alcohol worsens psoriasis and complicates methotrexate.

Screening questionnaires such as PEST in psoriasis patients: a piece of paper that finds undiagnosed arthritis years earlier. Free, and arguably the highest-value simple intervention here. Psychological support, since depression prevalence is high in psoriatic disease and independently worsens outcomes.

The honest limit: active erosive or axial disease needs DMARDs or biologics, and nothing simple halts joint destruction.

Gaps. No biomarker predicts which psoriasis patients will develop arthritis, despite a years-long window of opportunity. Whether treating the skin prevents arthritis is unresolved and would be highly consequential. The heterogeneity of disease patterns within one label suggests several distinct conditions, and no classification is biologically validated. The smoking paradox is unexplained. Head-to-head biologic trials are few, so positioning across the six domains rests largely on indirect comparison. Apremilast's modest efficacy against its convenience is a poorly resolved trade-off. Conventional DMARD evidence is surprisingly weak for a drug class used for decades, since the MIPA trial was equivocal. Psoriatic arthritis is not separately counted in GBD, so global burden is unknown. Data from Africa, Asia and Latin America are sparse.

> **Depth.** Starts in: the tendon attachment (enthesis). Size: 1 mm†; depth +9.10. First complaint: about 10 years († about 10 years after psoriasis); time depth 50.97. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Osteoporosis and fragility fracture

What it is. Bone loses density and structure, so it breaks after minor force. The fractures — hip, spine, wrist — are the disease; the low bone density is only the risk factor. Hip fracture in the old frequently leads to death or permanent loss of independence.

Measured. About 500 million people worldwide have osteoporosis, with prevalence by DXA criteria of a T-score of −2.5 or below at roughly 19 to 23 per cent of women and 6 to 8 per cent of men over 50. There are about 9 million fragility fractures a year globally, one every three seconds or so. Lifetime fracture risk after age 50 is about 40 to 50 per cent in women and 13 to 22 per cent in men.

Hip fractures number about 1.6 to 2 million a year globally and are projected to rise to 4.5 to 6 million by 2050 with population ageing, with the greatest increase in Asia†. Hip fracture mortality is high and under-appreciated: about 8 to 10 per cent at 30 days and about 20 to 30 per cent at one year, comparable to many cancers, and about 40 per cent never regain prior mobility while about 20 per cent require long-term care†. Excess mortality persists for years.

Osteoporosis itself is not a separate GBD cause, so its burden appears under falls and fractures. GBD 2019 gave falls, the proximate cause of most fragility fractures, roughly 680,000 deaths and about 39 million DALYs†. GBD 2023 Table 1 gives falls 53.1 million YLDs (95 per cent UI 38.4 to 72.2), rank four, which is 5.4 per cent of all-cause YLDs, and 74.3 million DALYs (58.9 to 95.0), rank eight. The WHO falls fact sheet, printed 26 April 2021 and the oldest in the WHO set, gives 684,000 fatal falls a year, over 80 per cent of them in low- and middle-income countries, 37.3 million non-fatal falls needing medical attention, and over 38 million DALYs, with no data year given for most figures. The WHO musculoskeletal health fact sheet gives 440 million prevalent fracture cases and 26 million YLDs on GBD 2019 data.

Vertebral fractures are the commonest, and about two-thirds are clinically silent and undiagnosed. They are visible on any chest or abdominal radiograph and are routinely unreported — a large missed-opportunity finding.

The treatment gap is the central problem of this field: about 70 to 80 per cent of people at high fracture risk, including after a fragility fracture, receive no osteoporosis treatment, and treatment rates have fallen in several high-income countries over the last fifteen years, largely from fear of rare adverse effects.

Highest age-standardised hip fracture rates are in Northern Europe, particularly Scandinavia; the lowest are in Africa and parts of Latin America. That gradient is not fully explained by bone density.

Where it starts. Age and female sex are the dominant non-modifiable factors, and bone loss accelerates sharply at menopause, at about 2 per cent a year of trabecular bone in the early postmenopausal years.

Oestrogen deficiency: menopause, premature ovarian insufficiency, hypothalamic amenorrhoea in athletes and in eating disorders, with potentially irreversible loss of peak bone mass in adolescence, and aromatase inhibitor therapy.

Low peak bone mass, determined in childhood and adolescence by genetics, nutrition, physical activity and pubertal timing. Peak bone mass is reached by about 20 and about 90 per cent is accrued by age 18†, so adolescence is the critical window and inactivity or undernutrition then has lifelong consequences.

Glucocorticoids are the commonest drug cause: 5 mg of prednisolone daily or more for three months or more substantially raises fracture risk, and the risk rises within months, before much bone density is lost, because steroids also impair bone quality. Under-recognised and under-treated.

A previous fragility fracture is the single strongest clinical predictor: it roughly doubles the risk of a further fracture, and the risk is highest in the first one to two years — imminent fracture risk — which argues for immediate treatment after a fracture.

Smoking; excess alcohol at three units a day or more; low body weight with BMI under 20; physical inactivity; and falls risk, which is substantially separable from bone density and equally important. Parental hip fracture and family history.

Secondary causes are present in about 30 per cent of women and over 50 per cent of men with osteoporosis† and are frequently missed: hyperparathyroidism, hyperthyroidism, coeliac disease, inflammatory bowel disease, chronic kidney disease, chronic liver disease, myeloma, rheumatoid arthritis, hypogonadism, diabetes of both types — and type 2 raises fracture risk despite normal or high bone density, an important trap — anorexia nervosa, bariatric surgery, vitamin D deficiency and immobility. Drug causes: glucocorticoids, aromatase inhibitors, androgen deprivation therapy, anticonvulsants, PPIs, which is weak and contested, SSRIs, thiazolidinediones, heparin and depot medroxyprogesterone.

Heritability is high: bone mineral density heritability is about 60 to 85 per cent in twin studies, while fracture risk itself is less heritable at about 25 to 35 per cent, because falls and environment intervene. GWAS has identified over 500 bone-mineral-density loci — *WNT16*, *LRP5*, *ESR1*, *SOST*, *RANKL/RANK/OPG* — and the *SOST* and *LRP5* biology led directly to romosozumab.

What is not known is why the geographic gradient in hip fracture rates is so large and not explained by bone density. Why type 2 diabetes raises fracture risk despite higher bone density — bone quality rather than quantity, but the mechanism is unclear. The optimal duration of bisphosphonate therapy, and the biology of atypical femoral fracture and osteonecrosis of the jaw, both rare and both disproportionately influential on prescribing. Why treatment rates are falling despite strong evidence. And how to measure bone quality rather than density.

Cure status. CONTROLLABLE, and substantially preventable. The fractures, not the density, are the target.

Bone density can be increased, by 5 to 10 per cent with bisphosphonates over three years† and more with anabolic agents, and fracture risk reduced by 40 to 70 per cent† depending on agent and fracture site.

It is not curable: the underlying bone loss tendency persists, and bone density falls again after stopping treatment — rapidly after denosumab, with rebound vertebral fracture risk if it is stopped without follow-on therapy, which is an important safety issue, and slowly after bisphosphonates, which persist in bone and so permit drug holidays.

An established fracture is treatable, and hip fracture surgery restores mobility for many, but about 40 per cent never regain prior function, so the damage is partly irreversible.

Reversible in specific cases: treating hyperparathyroidism, coeliac disease, hyperthyroidism or hypogonadism, or restoring energy availability and weight in hypothalamic amenorrhoea or anorexia nervosa, can substantially recover bone — though bone mass lost during adolescence may never be fully regained.

Prevention. Weight-bearing and resistance exercise: STRONG for bone density and, more importantly, for falls prevention. Progressive resistance and high-impact training increase or maintain bone mineral density, and balance and strength training reduces falls by about 20 to 25 per cent, with tai chi and multicomponent programmes having the best evidence (Cochrane). Falls reduction may matter more than density for fracture prevention in the very old.

Adequate calcium and vitamin D: MODERATE, with the honest version given under simple means. Correcting deficiency matters; supplementing the already-replete does little.

Smoking cessation and alcohol moderation: MODERATE. Adequate protein and energy intake, and avoiding underweight: MODERATE, especially in the elderly, where protein-energy malnutrition and sarcopenia drive both falls and fracture.

Falls prevention programmes: STRONG — exercise, medication review, especially of psychotropics, antihypertensives and anticholinergics, vision correction, home hazard modification and footwear. Multifactorial programmes reduce falls meaningfully.

Glucocorticoid-sparing strategies, and bone protection whenever three months or more of 5 mg or more of prednisolone is prescribed: STRONG, and widely neglected. Hip protectors: MODERATE in care home populations, reducing hip fracture when worn, with adherence the limiting factor.

Maximising peak bone mass in childhood and adolescence through activity and nutrition: MODERATE on physiological grounds — the most upstream intervention available.

Fracture Liaison Services, or fracture liaison nurses, for secondary fracture prevention: STRONG and cost-effective. Systematically identifying and treating everyone presenting with a fragility fracture is the highest-yield system intervention, and it closes the treatment gap.

Case-finding with FRAX, with or without DXA: STRONG in targeted populations; universal screening is debated, though the UK SCOOP trial showed community screening reduced hip fractures. Menopausal hormone therapy: STRONG for fracture prevention, since WHI showed reduced hip and total fractures, though it is not used primarily for this indication in most guidelines except in early menopause or premature ovarian insufficiency, where it is essential.

Treatment. Bisphosphonates are first line, and extremely cheap.

Alendronate, taken weekly by mouth, reduces vertebral fracture by about 45 to 50 per cent, hip fracture by about 40 to 53 per cent and non-vertebral fracture by about 20 to 25 per cent in those with prior fracture or osteoporosis (the FIT trial). Risedronate is similar. Zoledronic acid, as an annual intravenous infusion, reduces vertebral fracture by about 70 per cent and hip fracture by about 41 per cent, and in the HORIZON Recurrent Fracture Trial after hip fracture it reduced new clinical fractures by 35 per cent and all-cause mortality by 28 per cent — a mortality benefit, which is notable. Annual dosing solves the adherence problem, and adherence to oral bisphosphonates is poor, at about 50 per cent at one year†.

Both are off-patent. Alendronate costs tens of US dollars a patient-year generically; zoledronic acid tens to hundreds of US dollars per annual infusion generically, plus administration. Alendronate at a few US dollars a month to prevent a hip fracture is among the most cost-effective interventions in medicine.

And no bisphosphonate is on the WHO Essential Medicines List for osteoporosis. This was checked live against the electronic EML, twice, and it is not a retrieval artefact.

Alendronate is not on the 24th List (2025) in any form. A direct query of the electronic EML returns “Found 0 recommendations for 0 medicines and 0 therapeutic equivalents”, and every filter count on the page is zero, so the zero is not a filter artefact.

Zoledronic acid is on the list, but only under Supportive medicines, section 8.2.5, in the complementary list, for malignant neoplasm metastasis in bone or bone marrow, and for osteogenesis imperfecta. The word osteoporosis does not appear on its record.

So the most cost-effective fracture-prevention drug class in medicine is absent from the Essential Medicines List for its main indication. A drug costing a few US dollars a month, which reduces hip fracture by 40 to 53 per cent in a condition whose hip fractures kill 20 to 30 per cent of those who sustain them within a year, is not a selected essential medicine for that use anywhere on the list. The consequence is practical rather than rhetorical: health systems that build their procurement and their formularies from the EML have no listing to build from for the main indication, and the treatment gap already runs at 70 to 80 per cent. The figures are set out and left to stand.

Adverse effects of the bisphosphonates: oesophagitis with the oral preparations, where dosing instructions matter; an acute-phase reaction with the intravenous; and the rare but much-feared atypical femoral fracture, at about one per 10,000 to 100,000 patient-years, and osteonecrosis of the jaw, at about one per 10,000 to 100,000 at osteoporosis doses and far higher at oncology doses†. The absolute benefit vastly exceeds these risks in those at high fracture risk, and falling treatment rates are documented.

Denosumab, six-monthly subcutaneous anti-RANKL, reduces vertebral fracture by 68 per cent, hip by 40 per cent and non-vertebral by 20 per cent (FREEDOM), and is suitable in renal impairment. The critical caveat is that it must not be stopped without transitioning to a bisphosphonate, because rebound bone loss and multiple vertebral fractures occur. Biosimilars became available in 2024 and 2025, reducing cost from about US$1,500 to 3,000 a year toward a few hundred†.

Anabolic agents, for severe and very high risk disease. Teriparatide, PTH 1-34, daily injection for eighteen to 24 months, reduces vertebral fracture by 65 per cent and non-vertebral by 53 per cent, and was superior to risedronate for vertebral fracture in the VERO trial. It is now off-patent with biosimilars, and cost has fallen from tens of thousands of US dollars a year to thousands of US dollars or less. Abaloparatide. Romosozumab, anti-sclerostin, for twelve months, was superior to alendronate in ARCH, with 48 per cent fewer vertebral fractures than alendronate†, but a cardiovascular safety signal led to a boxed warning and to avoidance within a year of myocardial infarction or stroke; on patent, tens of thousands of US dollars a year. Sequence matters: anabolic first, then antiresorptive, gives better bone density outcomes than the reverse, and this is often got wrong.

Hormonal: menopausal hormone therapy, effective, cheap and off-patent; raloxifene, which reduces vertebral fracture only, with breast cancer risk reduction and venous thromboembolism risk; testosterone in hypogonadal men.

Calcium and vitamin D as an adjunct to ensure repletion, not as stand-alone therapy. Calcium carbonate and colecalciferol EML-listed, off-patent, a few to tens of US dollars a year. Treat the secondary causes, present in about 30 to 50 per cent.

Hip fracture care is where mortality is determined. Surgery within 24 to 48 hours reduces mortality and complications. Orthogeriatric co-management reduces mortality, delirium and length of stay, and is one of the best-evidenced service interventions in geriatric medicine. Early mobilisation, delirium prevention, nutritional support, analgesia including nerve blocks, and bone protection started before discharge. Fascia iliaca and femoral nerve blocks reduce opioid use and delirium, and are cheap.

Vertebral fracture: analgesia, early mobilisation, occasional bracing. Vertebroplasty and kyphoplasty are CONTESTED — sham-controlled trials (INVEST, Buchbinder, VERTOS IV) were largely negative, though some argue for benefit in acute severe pain. Falls prevention and medication review are integral, not optional.

Simple means. Weight-bearing and resistance exercise maintains bone and, crucially, reduces falls by about 20 to 25 per cent: progressive resistance training, balance work, and tai chi, which has good trial evidence for falls. Free, and effective into very old age.

Falls prevention at home: removing loose rugs and clutter, improving lighting, grab rails, correcting vision, sensible footwear, and reviewing sedating drugs. Cheap or free, and it addresses the proximate cause of

most fractures. Medication review alone — stopping psychotropics and unnecessary antihypertensives — measurably reduces falls.

Adequate dietary calcium from dairy, tinned fish with bones, calcium-set tofu, green leaves, sesame and fortified foods; and adequate protein, which is at least as important and routinely under-consumed by the elderly.

Vitamin D, the honest version. Correcting deficiency, which is common in the housebound, the veiled, the dark-skinned at high latitude and the institutionalised, improves bone and muscle function. But calcium and vitamin D supplementation in community-dwelling, replete adults does not meaningfully reduce fractures: multiple large trials and meta-analyses are negative. And high-dose intermittent vitamin D, in annual or monthly mega-doses, increases falls and fractures. So identify and treat deficiency, do not supplement indiscriminately, and avoid mega-doses. Sunlight exposure is free where latitude and culture permit.

Smoking cessation and limiting alcohol. Maintaining healthy weight and avoiding underweight. Childhood and adolescent physical activity — jumping, running, sport — is the cheapest possible intervention, with a lifelong effect on peak bone mass. Hip protectors in care homes.

Looking at existing radiographs for vertebral fractures: two-thirds are silent and already visible on films taken for other reasons, and reporting them costs nothing and identifies people at high imminent risk.

Alendronate at tens of US dollars a year is manufactured, but so cheap and effective that it belongs in any discussion of accessible prevention — and it is not on the Essential Medicines List. Asking about falls and prior fractures is a question, and the best risk predictor available.

Gaps. The 70 to 80 per cent treatment gap is the dominant problem, and it is a behavioural and system failure rather than a knowledge gap, and the rare harms are quantitatively dwarfed by fracture risk.

No bisphosphonate is on the WHO EML for osteoporosis: alendronate returns zero results and zoledronic acid is listed only for bone metastases and osteogenesis imperfecta, both verified live against the electronic EML. That is a significant omission for the most cost-effective drug class here, and a barrier to procurement in systems that follow the list.

Optimal bisphosphonate duration and drug-holiday strategy are not established. The biology of atypical femoral fracture and jaw osteonecrosis is unclear. Bone quality cannot be measured clinically, which is why diabetic fracture risk is missed by DXA. The geographic gradient in hip fracture rates is unexplained. Vertebroplasty evidence is contradictory between sham-controlled and open trials. Screening strategies differ between countries without clear resolution. Data on fracture incidence from Africa, South Asia and Latin America are sparse, though the projected growth in hip fracture is concentrated there. Men are substantially under-diagnosed and under-treated despite worse outcomes after hip fracture.

> **Depth.** Starts in: the osteoclast. Size: 100 µm†; depth +7.00. First complaint: about 7 years († 5–10 years after the menopause); time depth 50.65. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gout

Gout is classified in ICD-11 under Chapter 15, diseases of the musculoskeletal system or connective tissue, as well as having metabolic aspects. This entry covers its musculoskeletal presentation.

What it is. Uric acid crystallises in a joint and causes a sudden, severe attack of inflammation, classically in the big toe. Over years crystals build into lumps and damage joints. It is caused by too much urate in the blood, and it is curable.

Measured. Global prevalence is about 1 to 4 per cent of adults with wide variation, and GBD 2019 and 2021 estimated about 55 to 56 million people with gout. The WHO musculoskeletal health fact sheet gives 54 million prevalent cases and 1.7 million YLDs on GBD 2019 data. GBD 2019 gave gout roughly 1.7 to 2

million DALYs; directly attributable deaths are few, though gout is associated with excess cardiovascular and renal mortality.

Prevalence has roughly doubled over recent decades in many countries, tracking obesity, metabolic syndrome, diuretic use and ageing. The male to female ratio is about 3 to 4:1 overall; in women gout is largely post-menopausal, since oestrogen is uricosuric, so the ratio narrows sharply after 60.

The highest prevalence recorded is in the Indigenous populations of Oceania: Māori and Pacific Islander populations in New Zealand have prevalences of about 6 to 8 per cent and higher in men, with some estimates above 10 per cent, reflecting genetically determined reduced renal urate excretion plus dietary and socioeconomic factors; rates are also high in Taiwanese Indigenous groups. Incidence rises with age, with a peak at 40 to 60 in men. Gout is the most common inflammatory arthritis in men over 40†.

Where it starts. Hyperuricaemia is necessary and not sufficient: most people with raised urate never develop gout. Risk rises steeply above a serum urate of about 0.36 mmol/L (6 mg/dL), the approximate saturation point, and that threshold is the basis of the treatment target.

Renal underexcretion accounts for about 90 per cent of hyperuricaemia and overproduction for about 10 per cent†. That is the key physiological point and it is largely genetic.

Genetics are dominant and often underappreciated. *SLC2A9* and *ABCG2* are the major loci, together explaining a substantial share of population urate variance, with *SLC22A12* (URAT1), *SLC17A1* and others contributing. Heritability of serum urate is about 40 to 70 per cent, and of gout itself about 30 to 60 per cent in twin and family studies. *ABCG2* variants are particularly prevalent in Polynesian populations, which largely explains the Oceanic prevalence rather than diet, contrary to persistent and stigmatising assumptions.

Diuretics — thiazides and loop diuretics — are a major and reversible cause, raising urate substantially; also ciclosporin, tacrolimus, low-dose aspirin, pyrazinamide and ethambutol. Chronic kidney disease, through reduced excretion, bidirectionally. Obesity and metabolic syndrome, dose-dependently, since insulin resistance reduces renal urate excretion. Alcohol, with beer worst because it is purine-rich as well as alcoholic, then spirits, with wine least; dose-dependently.

Diet: red meat, organ meat, shellfish, and fructose and sugar-sweetened beverages, which is a strong and well-replicated association. But diet explains far less of urate variance than genetics does: a large genomic analysis found food items explained under 1 per cent of urate variance against about 24 per cent for a genetic score (Major, *BMJ* 2018). That matters for how patients are counselled. Gout has long been moralised as a disease of dietary indulgence, and the evidence does not support that framing.

Protective: dairy, especially low-fat; coffee; vitamin C; cherries, on modest evidence; losartan and calcium channel blockers, which are uricosuric antihypertensives; and SGLT2 inhibitors, which lower urate and reduce gout flares.

What is not known is why most hyperuricaemic people never develop gout, and what triggers crystallisation and the inflammatory flare at a particular moment. Whether asymptomatic hyperuricaemia should be treated, where the current answer is generally no. And whether urate-lowering therapy reduces cardiovascular and renal events: the large CKD-FIX and PERL trials were negative for kidney outcomes, the cardiovascular question remains open, and the benefit of treating urate outside gout is unproven.

Cure status. CONTROLLABLE.

Gout is one of the few chronic rheumatic diseases in which treatment can remove all flares and tophi in essentially every patient while it continues. Sustained lowering of serum urate below about 0.30 to 0.36 mmol/L dissolves the existing crystal deposits, after which flares cease entirely and tophi resolve. Patients become symptom-free indefinitely while treatment continues.

Treatment must usually be lifelong, since urate rises again if it is stopped, so the disease is held and not removed. A correctly treated gout patient has no flares. Acute flares are also SELF-LIMITING: untreated attacks resolve over one to two weeks.

The gap between what is achievable and what is delivered is extreme. Adherence to urate-lowering therapy is among the worst of any chronic disease, at about 30 to 50 per cent, and many patients are never offered it, or are kept on sub-therapeutic doses without urate monitoring. Gout is a cheap, controllable disease that is badly treated almost everywhere: a care-delivery failure, not a scientific one.

Prevention. Urate-lowering therapy to target in established gout: STRONG. It prevents all further flares and tophus formation, as secondary prevention that is near-complete.

Reviewing and substituting diuretics where clinically possible: STRONG. Swapping a thiazide for an alternative antihypertensive, or choosing losartan or a calcium channel blocker, both mildly uricosuric, or an SGLT2 inhibitor in diabetes, removes a major cause.

Weight management: MODERATE, with dose-dependent reduction in urate and flares. Reducing alcohol, especially beer: MODERATE. Reducing sugar-sweetened beverages and fructose: MODERATE. Dairy and coffee intake: WEAK, on protective associations.

Dietary purine restriction: WEAK, and this needs honest statement. Strict purine restriction lowers urate by only around 0.06 to 0.12 mmol/L (1 to 2 mg/dL) at best, usually insufficient to reach target, and it is poorly tolerated and poorly adhered to. Diet is a useful adjunct, not a substitute for allopurinol, and presenting it as the primary treatment leaves patients with ongoing joint damage.

Treating asymptomatic hyperuricaemia: not recommended, CONTESTED — no demonstrated benefit, and the renal outcome trials were negative. Flare prophylaxis when starting urate-lowering therapy: STRONG. Low-dose colchicine or an NSAID for the first three to six months prevents the paradoxical early flares that otherwise cause patients to abandon treatment. A key and frequently omitted step.

Treatment. For an acute flare, treat early and hard; any of three options works.

NSAIDs — naproxen, indomethacin, diclofenac — at full dose are effective; off-patent, EML-listed, a few US dollars a course.

Colchicine: low dose is as effective as high dose and far better tolerated. The AGREE trial established 1.2 mg then 0.6 mg, a total of 1.8 mg, as equivalent to the old high-dose regimen with dramatically less diarrhoea. Dose-reduce in renal impairment and with interacting drugs — clarithromycin, ciclosporin, statins. Off-patent, though a notorious US pricing exception when it was granted market exclusivity, which raised the price of an ancient drug roughly fiftyfold; a few to tens of US dollars a course generically, far more in some markets. Colchicine is EML-listed.

Corticosteroids: oral prednisolone, for example 30 to 35 mg for five days, is equivalent to NSAIDs in randomised trials, and is the option of choice in renal impairment, where NSAIDs are contraindicated. Intra-articular steroid for a single accessible joint. Off-patent, EML-listed, a few US dollars a course.

IL-1 inhibitors, canakinumab and anakinra, for refractory flares with contraindications to all the above; very expensive, with canakinumab at tens of thousands of US dollars or more a dose.

Do not start or stop urate-lowering therapy because of a flare: it can be started during a flare, since trials show this is safe and improves uptake, and it should never be interrupted.

Urate-lowering therapy is the curative element, and allopurinol is first line and the key drug. It is a xanthine oxidase inhibitor, and the dose is titrated upward to achieve a target serum urate below 0.36 mmol/L (6 mg/dL), or below 0.30 mmol/L (5 mg/dL) with tophi. Treat-to-target dose escalation, not a fixed 300 mg dose, is what works, and failure to titrate is the commonest treatment error; doses up to 900 mg may be needed.

WHO EML: yes. Allopurinol is a listed medicine under medicines used to treat gout, section 29.1, and separately as a supportive medicine for tumour lysis syndrome, section 8.2.5 complementary. Off-patent. Cost tens of US dollars a patient-year, and in many markets tens of US dollars. Note a discrepancy between dossiers: another chapter of this book gives US$5 to 20 a patient-year for allopurinol, dated 2024. The two ranges overlap and are not the same, and both are printed.

That is the central economic fact of this entry: a disease that destroys joints and causes severe recurrent pain is permanently controlled by a drug costing a few dollars a year, on the Essential Medicines List, available everywhere.

On safety: allopurinol hypersensitivity syndrome is rare and serious, presenting as severe cutaneous adverse reaction or DRESS. Risk is strongly associated with HLA-B*58:01, which is prevalent in Han Chinese, Thai and Korean populations, and screening for HLA-B*58:01 before starting allopurinol is recommended in these groups and is cost-effective there. Starting at a low dose, 100 mg, or 50 mg in renal impairment, and titrating slowly reduces risk.

Febuxostat is an alternative xanthine oxidase inhibitor, effective and useful in allopurinol intolerance. The CARES trial (*NEJM* 2018) found higher cardiovascular and all-cause mortality against allopurinol, which led to regulatory warnings; the subsequent FAST trial (*Lancet* 2020) did not confirm this and found non-inferiority. The two trials disagree and the issue is genuinely unresolved; both are printed. Now off-patent in many markets; tens to hundreds of US dollars a year.

Uricosurics — probenecid, benzbromarone, which is potent but carries hepatotoxicity concerns and is unavailable in some countries, and sulfinpyrazone; lesinurad was withdrawn commercially — are useful as add-ons. Probenecid off-patent and cheap. Pegloticase, recombinant uricase, for severe refractory tophaceous gout, rapidly dissolves deposits; very expensive at hundreds of thousands of US dollars or more a year and immunogenic, with methotrexate co-therapy improving response. Reserved for a tiny minority.

Monitoring: serum urate measurement to confirm target attainment is a cheap blood test and the single most important process measure. Treating gout without measuring urate is the equivalent of treating hypertension without a blood pressure cuff.

Nurse-led gout care: the Doherty trial (*Lancet* 2018, 517 patients) showed nurse-led treat-to-target care with patient education achieved the urate target in 95 per cent at two years against 30 per cent with usual general practice care, with fewer flares and resolution of tophi. A striking result: the problem is care organisation, not pharmacology, and the fix is cheap and task-shareable.

Manage the comorbidity: hypertension, chronic kidney disease, diabetes, cardiovascular risk and obesity, choosing urate-friendly antihypertensives.

Simple means. Allopurinol at tens of US dollars a year is manufactured but EML-listed, off-patent, and among the cheapest curative therapies in all of medicine. It belongs in any minimal essential formulary.

Measuring serum urate and titrating to target is a cheap blood test plus dose adjustment, and it is the intervention that converts partial control into complete control.

Patient education: explaining that gout is caused mainly by inherited reduced renal urate excretion, not by moral dietary failure, and that it is curable with a cheap daily tablet taken lifelong. The Doherty trial shows education plus nurse-led titration achieves 95 per cent target attainment†. That is a conversation, and it is the most effective intervention in this entry after the drug itself.

Reviewing diuretics, substituting a thiazide, often removes the cause entirely: free, and frequently curative in itself. Weight loss, and reducing alcohol, especially beer, and sugar-sweetened drinks: adjunct measures with real but modest effect. Dairy and coffee, on protective associations, as ordinary foods. Rest, elevation and ice to the affected joint during an acute flare, with ice reducing pain measurably in a small randomised trial; free. Cheap prednisolone or an NSAID for the flare, at a few US dollars. Flare prophylaxis with low-dose colchicine when starting allopurinol, which prevents the early flares that cause patients to stop treatment.

The honest framing: unlike most entries here, the simple means are not the main treatment. The main treatment is a very cheap tablet. The simple means that matters most is organising care properly and explaining it, which the trial evidence shows raises target attainment from 30 per cent to 95 per cent.

Gaps. The gap between a curable disease and the observed treatment quality is the dominant issue, and it is behavioural and organisational. Adherence is among the worst in medicine and poorly understood. Febuxostat cardiovascular safety is unresolved, with CARES and FAST disagreeing. Whether to treat asymptomatic hyperuricaemia is unsettled, and the renal outcome trials, CKD-FIX and PERL, were

negative. Whether urate lowering reduces cardiovascular events is unknown. Why only a minority of hyperuricaemic people get gout, and what triggers a flare, are unexplained. The stigmatising dietary narrative persists despite genetic evidence that diet explains under 1 per cent of urate variance — a communication failure with real consequences for care-seeking. HLA-B*58:01 screening is cost-effective in high-prevalence populations and inconsistently implemented. Gout burden data from Africa and much of Asia are sparse. The two allopurinol price ranges carried in this book differ and are both printed.

> **Depth.** Starts in: a urate crystal. Size: 10 µm†; depth +4.91. First complaint: about 12 hours ([B] a sudden attack); time depth 42.87. One untreated course: about 8.4 days († 7–10 days); depth 45.44.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: CONTROLLABLE, with SELF-LIMITING for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Fibromyalgia

What it is. Widespread body pain with fatigue, unrefreshing sleep and difficulty thinking, lasting months or years. No joint or muscle damage is found. It is now understood as altered pain processing in the nervous system.

Measured. Prevalence is about 2 to 4 per cent of the general population, with estimates ranging from 0.2 to 6.6 per cent depending on criteria, since the Wolfe 1990 tender-point criteria and the 2010, 2011 and 2016 symptom-based criteria give substantially different figures. It is not a separate GBD cause and sits within other musculoskeletal disorders, so its global burden is effectively uncounted despite substantial disability.

Deaths: none directly, though suicide risk is elevated. The female to male ratio is about 2 to 3:1 under the newer criteria, much lower than the roughly 9:1 ratio given by the old tender-point criteria, which systematically under-identified men because men report fewer tender points. That is a measurement-artefact correction worth noting, because the figure of nine out of ten being women is still widely quoted and is wrong.

Peak age is 30 to 55, though it occurs in children and the elderly. Comorbidity is high: it is present in about 10 to 30 per cent of patients with rheumatoid arthritis, lupus, axial spondyloarthritis and osteoarthritis, where it is frequently mistaken for inflammatory disease activity, leading to inappropriate escalation of immunosuppression. That is clinically important. It is reported everywhere, and apparent variation reflects criteria and clinical recognition more than true difference.

Where it starts. Central sensitisation, or nociplastic pain, is the current mechanistic model, supported by measurable findings: augmented central pain processing on functional MRI, reduced descending inhibition, raised cerebrospinal substance P, altered neurotransmitter balance, and small fibre neuropathy demonstrated in about 30 to 50 per cent of patients on skin biopsy, a finding of uncertain significance.

Female sex and family history: first-degree relatives have about eight times the risk, and heritability is estimated at about 50 per cent, with implicated genes in serotonin, dopamine and catecholamine pathways — *COMT*, *5-HTT* — though none robustly replicated.

Triggers: physical trauma including whiplash and surgery; infection, with Epstein-Barr virus, Lyme disease and notably post-COVID illness; emotionally stressful events. Adverse childhood experiences, abuse and trauma are consistently associated with substantial effect sizes, and post-traumatic stress disorder is frequently comorbid.

Sleep disturbance is bidirectional and probably causal in part: experimental sleep deprivation in healthy people produces fibromyalgia-like symptoms and lowers pain thresholds.

Comorbid conditions: irritable bowel syndrome, chronic fatigue syndrome and ME, temporomandibular disorder, chronic headache, interstitial cystitis, endometriosis — the central sensitivity syndromes, which overlap heavily and are probably facets of one process. Obesity, physical inactivity, and depression and anxiety, bidirectionally.

What is not known is the cause. Whether it is one condition or several. Why some people develop central sensitisation after a trigger and others do not. The significance of the small fibre findings, whether causal, consequential or incidental. Why women predominate. Crucially, the diagnosis rests entirely on symptom report with no biomarker, and the criteria have changed three times, which means prevalence, trial populations and outcome data are not comparable across eras. The condition's legitimacy was contested for decades, which shaped the literature and the patient experience; it is now accepted as a real disorder of pain processing.

Cure status. RELIEF ONLY, and this is stated plainly, because false promises are a documented harm in this condition.

No treatment cures fibromyalgia. All established treatments produce small to moderate average effects on pain, function and quality of life. Drug effect sizes are small: numbers needed to treat of about 7 to 14 for a 30 to 50 per cent pain reduction with the best-supported agents, duloxetine, pregabalin and amitriptyline, and discontinuation for adverse effects is common. Exercise and the non-pharmacological approaches have comparable or better effect sizes with fewer harms.

Substantial improvement is achievable and common: many patients achieve good function and quality of life with a combination of exercise, psychological approaches, sleep management and modest drug support. Full remission occurs and is not the norm. Prognosis is better in children and adolescents, where recovery rates are higher. And the diagnosis itself helps: receiving a clear explanation reduces healthcare utilisation and distress, and ends the cycle of fruitless investigation.

Prevention. No established primary prevention: absent. Treating sleep disorders: WEAK, mechanistically supported. Early active management after trauma or whiplash, and avoiding prolonged immobilisation and over-investigation: WEAK. Addressing adverse childhood experiences and trauma: plausible and not demonstrated as prevention. Physical activity: WEAK as prevention, STRONG as treatment. Avoiding iatrogenic harm — opioid initiation, repeated negative investigation, diagnostic limbo: MODERATE as prevention of chronicity and disability, and a real and achievable preventive measure.

Treatment. All major guidelines — EULAR 2016, Canadian, German S3 — agree: non-pharmacological treatment first, with drugs as adjuncts. EULAR's only "strong for" recommendation is exercise.

Exercise is the single strongest recommendation and the only one EULAR grades strong. Aerobic exercise improves pain, function, fatigue and quality of life on moderate-quality Cochrane evidence; start low and go slow, because too-rapid progression causes flares and drop-out, which is the usual reason it appears to fail. Resistance and strength training improves pain, function and strength. Aquatic exercise is well tolerated with good evidence, warm water particularly. Tai chi, yoga and qigong have trial evidence of benefit comparable to aerobic exercise, and one randomised trial found tai chi equal or superior to aerobic exercise (Wang, *BMJ* 2018). The cost is free to low.

Patient education and explanation of central sensitisation: pain neuroscience education improves outcomes and reduces catastrophising, and the diagnosis itself is therapeutic. Cognitive behavioural therapy gives small to moderate, durable effects on pain, mood, function and sleep; acceptance and commitment therapy is also supported. Sleep intervention, CBT for insomnia, improves sleep and pain, and is often neglected despite unrefreshing sleep being a core feature. Multicomponent and multidisciplinary rehabilitation, combining exercise, psychological therapy and education, is the best-supported overall package.

Drugs, adjunctive with modest effects. Amitriptyline at low dose, 10 to 50 mg at night, is a long-standing first-line in practice and helps pain and sleep; off-patent; EML-listed as an antidepressant; a few to tens of US dollars a patient-year. The cheapest option, with reasonable evidence. Duloxetine, an SNRI, is the best-evidenced, with a number needed to treat of about 7 to 8 for 30 per cent pain reduction†; off-patent; tens to hundreds of US dollars a year. Milnacipran is similar and not available in all markets. Pregabalin has a number needed to treat of about 8 to 10†, with sedation, weight gain and dizziness, and misuse potential that has led to control in several countries; off-patent; tens to hundreds of US dollars a year. Gabapentin is used similarly with weaker evidence. Cyclobenzaprine gives modest benefit, mainly on sleep. Low-dose naltrexone has promising small trials and is not yet established; very cheap if confirmed.

NSAIDs and paracetamol are largely ineffective for fibromyalgia pain as monotherapy, since there is no peripheral inflammation to treat, and are commonly prescribed regardless. Opioids are not recommended and are potentially harmful: no evidence of benefit, risk of opioid-induced hyperalgesia which worsens the underlying problem, dependence and worse functional outcomes, with strong guideline recommendations against. Tramadol has weak supportive evidence and is the only partial exception. Corticosteroids and immunosuppressants have no role. Cannabinoids: CONTESTED, insufficient evidence despite widespread use and marketing.

Treat the comorbidities — depression, anxiety, sleep apnoea, irritable bowel syndrome, vitamin D deficiency if present. And in patients with inflammatory arthritis, recognise concurrent fibromyalgia rather than escalating biologics for what is not inflammatory pain: an important and expensive error.

Acupuncture, massage, balneotherapy and mindfulness give small benefits at low risk, and EULAR gives weak positive recommendations to some. Avoid repeated investigation after diagnosis, prolonged rest, and the search for a missed structural cause, all of which cause harm.

Simple means. This condition is managed almost entirely by simple means, and they outperform the drugs.

Graded aerobic exercise is the strongest recommendation in every guideline: walking, cycling, swimming. Start at a level well below what the patient thinks they should manage and increase very gradually; this single principle determines success or failure. Free. Strength training, with body weight or resistance bands, improves pain and function. Tai chi, yoga and qigong have trial evidence equal or superior to aerobic exercise (Wang, *BMJ* 2018), and need instruction and space. Warm water exercise, or simply warm baths, is well tolerated and symptomatically helpful. Sleep hygiene and CBT for insomnia address a core driver and are deliverable as self-help.

Pain neuroscience education — explaining that the pain is real, that it reflects a sensitised nervous system rather than tissue damage, and that activity is safe and therapeutic — is free, and one of the most effective single interventions. Pacing and activity management, to avoid the boom-and-bust cycle, is a taught skill. Mindfulness and relaxation training. Peer support groups, since the condition carries substantial disbelief and stigma, and validated support measurably improves coping. Amitriptyline at a few to tens of US dollars a year: if a drug is used, the cheapest has reasonable evidence.

Not taking opioids, not undergoing repeated investigation, and not escalating biologics for fibromyalgia in inflammatory arthritis: three evidence-based omissions that prevent harm and save substantial money.

The honest framing: no simple means cures this, and overpromising is harmful. But the interventions with the best evidence are also the cheapest, and the expensive drugs add little.

Gaps. No biomarker, no objective diagnostic test, and criteria that have changed three times, so prevalence estimates span 0.2 to 6.6 per cent and the literature is not comparable across eras. The mechanism is partly characterised as central sensitisation, and the cause is unknown. The significance of small fibre neuropathy findings in 30 to 50 per cent of patients is unresolved and potentially important. All treatment effects are small, and most trials are short, small, and have high drop-out and high placebo response. Long-term outcome data are limited. Whether fibromyalgia, ME/CFS, irritable bowel syndrome and the other central sensitivity syndromes are one condition or several is unresolved and consequential for research. Post-COVID fibromyalgia-like illness is a large new and poorly characterised group. The condition is not counted in GBD, so global burden is unknown. Research funding is low relative to prevalence and disability. Male fibromyalgia is under-studied.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number ([B] months or years).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Rotator cuff disorders

What it is. The tendons that hold and move the shoulder become painful, degenerate or tear. Reaching overhead and lying on the shoulder hurt. Most tears are degenerative rather than traumatic, and many cause no symptoms at all.

Measured. Shoulder pain affects about 7 to 26 per cent of adults at any time, and rotator cuff disorders are the commonest cause, accounting for about 70 per cent of shoulder pain presentations†.

Full-thickness rotator cuff tear prevalence rises steeply with age and is frequently asymptomatic. In population imaging studies, roughly 10 per cent under 50, 20 to 25 per cent over 60, 30 to 50 per cent over 70, and over 50 to 60 per cent over 80 have a tear — and about a third to two-thirds of these are painless†. Yamamoto's and Minagawa's population studies are the standard references. That is the key epidemiological fact and it mirrors the spine: structural abnormality is largely age-normal, so finding a tear does not establish it as the cause of pain.

It is not separately modelled in GBD and falls within other musculoskeletal disorders. Deaths: none. Degenerative tears accumulate from the fifth decade, and traumatic tears occur at any age. The sexes are roughly equal, with a slight male predominance for traumatic tears. Occupational prevalence is high in overhead workers — painters, construction, assembly — and in overhead athletes.

Rotator cuff repair and subacromial decompression are high-volume operations, and rates have risen several-fold in many countries over two decades — a rise not matched by evidence of benefit for decompression.

Where it starts. Age is the dominant factor, through tendon degeneration with reduced vascularity, altered collagen and impaired healing capacity. Overhead and repetitive loading, occupational and athletic. Smoking, which impairs tendon vascularity and healing and is associated with larger tears and worse repair outcomes. Diabetes, strongly associated with tendinopathy generally and with poorer healing, and also with adhesive capsulitis. Hypercholesterolaemia and metabolic syndrome, with consistent associations suggesting a metabolic component to what was assumed purely mechanical. Acromial morphology and subacromial anatomy — critical shoulder angle, acromial index — are associated, though the causal impingement model has been substantially revised. Family history is significant: siblings of patients with full-thickness tears have roughly two to five times the risk, and a genetic contribution is established though heritability is not precisely quantified. Trauma, in a minority, giving acute tears in younger patients.

The impingement model has largely been abandoned as a causal explanation. The idea that the acromion mechanically abrades the tendon, which justified decades of subacromial decompression surgery, is not supported: tendinopathy appears to be primarily a degenerative and load-related process, and surgical reshaping of the acromion does not outperform placebo. A significant conceptual reversal.

What is not known is why some tears hurt and others do not — the single most important gap, since it determines whom to treat. Why tear size and pain correlate poorly. What drives tendon degeneration at a molecular level, and why healing capacity is so limited. And why repairs that fail structurally, with re-tear rates of 20 to 60 per cent depending on size, often still produce good clinical outcomes — an awkward finding for the repair rationale.

Cure status. Degenerative tears, the great majority: CONTROLLABLE. Pain and function improve with exercise-based rehabilitation while the tear remains, degenerative tears do not heal spontaneously, and structural healing is not what produces the symptomatic improvement.

Acute traumatic tears in younger active patients: CURABLE, where repair is indicated and effective.

Cuff-tear arthropathy, and irreparable tears with pseudoparalysis: CURABLE by reverse total shoulder arthroplasty — a genuine functional cure for a previously untreatable problem.

Many people improve substantially with exercise-based rehabilitation, and symptomatic improvement does not require structural healing. Degenerative tears do not heal spontaneously, and tears tend to enlarge slowly over years in a minority, though enlargement does not reliably produce symptoms. Surgical repair achieves structural healing in many, but re-tear rates are 20 to 60 per cent, higher with larger tears, older

patients, smokers and diabetics, and clinical outcomes of repair are not clearly superior to structured exercise for most degenerative tears.

Adhesive capsulitis, frozen shoulder, is a frequent differential diagnosis rather than a rotator cuff disorder, and it is genuinely SELF-LIMITING over one to three years, though often with residual restriction.

Prevention. Exercise and scapular and cuff strengthening: MODERATE, reducing shoulder pain incidence in overhead workers and athletes in workplace trials. Reducing overhead and repetitive loading, job rotation, workstation modification: MODERATE. Smoking cessation: MODERATE, affecting tendon health and healing. Diabetes and metabolic control: MODERATE. Gradual load progression in athletes, avoiding sudden increases in throwing or overhead volume: MODERATE. No drug prevents it: absent.

Treatment. Exercise-based rehabilitation is first line for almost everyone, including for most degenerative full-thickness tears: progressive loading, rotator cuff and scapular strengthening, and range-of-motion work. It produces clinically important improvement in the majority, and trials show it is equivalent to surgery for degenerative tears and for impingement syndrome. The cost is physiotherapist time, or free with instruction.

Education, load modification and analgesia: NSAIDs and paracetamol for short-term symptom control; NSAIDs off-patent, EML-listed, a few to tens of US dollars a year.

Subacromial corticosteroid injection gives short-term pain relief, weeks to a few months, with no long-term benefit over exercise, and repeated injections may impair tendon quality and subsequent repair healing. Useful to enable rehabilitation. Off-patent, cheap.

Subacromial decompression surgery is not effective. This is one of the clearest negative findings in orthopaedics. The CSAW trial (Beard, *Lancet* 2018, 313 patients) found arthroscopic subacromial decompression no better than arthroscopy alone, which was placebo surgery, and the small difference against no treatment was not clinically important. The FIMPACT trial (Paavola, *BMJ* 2018, 210 patients) found decompression no better than diagnostic arthroscopy, which was sham, at two years, and neither beat exercise therapy. Guidelines and several national bodies now recommend against it, and it continues to be performed in large numbers — a practice-evidence gap comparable to arthroscopic meniscectomy.

Rotator cuff repair is appropriate for acute traumatic tears, especially in younger patients, where repair should be early; for symptomatic tears failing three to six months of good rehabilitation; and for progressive weakness or large tears at risk of becoming irreparable. For degenerative tears, trials comparing repair with conservative management show small or no differences in patient-reported outcomes at one to five years, for example Kukkonen, though structural integrity is better with repair. The decision is individualised, and patient selection matters more than technique.

Reverse total shoulder arthroplasty for cuff-tear arthropathy, irreparable tears with pseudoparalysis, and failed repairs, is highly effective for pain and overhead function. Tendon transfers, superior capsular reconstruction and balloon spacers for irreparable tears have limited and evolving evidence, and several are marketed ahead of the evidence. Platelet-rich plasma and stem cell injections are not supported by adequate evidence for rotator cuff disease, and are heavily commercialised.

Imaging: ultrasound and MRI detect tears accurately, but given that tears are largely age-normal and often asymptomatic, imaging should follow a failure of conservative management or suspicion of a traumatic reparable tear rather than precede treatment. Early imaging drives unnecessary surgery.

For adhesive capsulitis, if that is the actual diagnosis: intra-articular steroid with exercise early, and hydrodilatation; it is self-limiting, and aggressive intervention is usually unnecessary.

Simple means. Progressive loading exercise is the primary treatment and is equivalent to surgery in randomised trials. It can be done with a resistance band, a water bottle or body weight, with instruction, and needs no equipment beyond that. Home exercise programmes with periodic supervision are nearly as effective as fully supervised physiotherapy in trials, which matters where therapists are scarce.

Activity and load modification: temporarily reducing overhead work, then rebuilding capacity rather than permanently avoiding it. Education — that a tear found on a scan is often age-normal and not necessarily the cause of pain, and that the shoulder can improve without structural healing. Heat, cold, simple

analgesia. Sleep positioning advice, avoiding lying on the affected side and using pillow support: night pain is often the most disabling symptom and is helped by this alone. Workplace exercise and job rotation for overhead workers, as prevention at low cost. Smoking cessation.

Not having subacromial decompression, and not having platelet-rich plasma: two evidence-based omissions saving considerable money, on CSAW and FIMPACT.

The honest limit: acute traumatic tears in young patients benefit from timely repair, and pseudoparalysis from an irreparable tear needs arthroplasty. Exercise does not reattach a torn tendon.

Gaps. Why some tears hurt and others do not is unknown, and it is the central clinical question. Pain and structural findings correlate poorly, as in the spine. Subacromial decompression continues at scale despite two good sham-controlled trials — a practice problem, not an evidence problem. Optimal patient selection for repair of degenerative tears is unresolved, and the fact that structurally failed repairs often do well clinically undermines the mechanical rationale. Re-tear rates vary widely and are poorly predicted. Newer procedures — superior capsular reconstruction, balloon spacers, biologic augmentation — are being adopted ahead of adequate evidence. Optimal exercise dose and progression are unclear. Rotator cuff disease is not counted in GBD, so global burden is unknown, and almost all trials come from high-income settings.

> **Depth.** Starts in: a rotator cuff tendon. Size: 3 cm†; depth +12.19. First complaint: about 55 years († onset about age 55); time depth 52.52. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body’s own structure, or take the diseased part out. This is a reading. The status above stands.

Carpal tunnel syndrome

What it is. The median nerve is compressed where it passes through the wrist. The hand tingles and goes numb, typically waking the person at night, and the thumb muscles can waste. It is the commonest nerve entrapment.

Measured. Prevalence is about 1 to 5 per cent of the general adult population, and about 3.8 per cent in population studies using symptoms plus electrophysiology. Lifetime risk is about 10 per cent, with an annual incidence of about one to three per 1,000. It is not separately modelled in GBD. Deaths: none. Female to male ratio is about 3:1. Peak age is 45 to 60, and it is also common in pregnancy, where it is usually transient.

It is the commonest indication for hand surgery, and carpal tunnel release is one of the highest-volume operations performed worldwide. Occupational prevalence is high in repetitive forceful hand work, vibrating tool use, and assembly and meatpacking work. The association with ordinary keyboard and computer use is weak and largely unsupported — a persistent misconception.

Where it starts. Raised pressure within an anatomically confined space. The carpal tunnel is bounded by carpal bones and the transverse carpal ligament, so any increase in contents or decrease in space compresses the median nerve. That mechanism is clear and uncontested, in contrast to most entries here.

Female sex, through a smaller tunnel cross-sectional area. Obesity, dose-dependently, as a strong and consistent risk factor. Diabetes, where the nerve is also more vulnerable to compression; hypothyroidism; rheumatoid arthritis, through tenosynovitis; pregnancy, through fluid retention and usually resolving after delivery; acromegaly; and amyloidosis — notably, bilateral carpal tunnel syndrome can be the earliest manifestation of transthyretin amyloidosis, preceding cardiomyopathy by five to ten years, which makes it a potentially important diagnostic clue.

Occupational: repetitive forceful gripping, wrist flexion and extension, and vibration, which is the strongest occupational association. Keyboard use: weak or no association. Prior wrist fracture or deformity; ganglion; anatomical variants. Haemodialysis, through amyloid deposition; menopause.

A genetic contribution is established, with heritability estimated at about 46 per cent in some analyses, and GWAS identifying loci relating to extracellular matrix and growth factors — *ADAMTS17*, *SERPINA1*, *GDF5*. Family history is associated with earlier onset and bilateral disease.

What is not known is why symptoms and electrophysiological severity correlate imperfectly, and why some patients with severe nerve conduction abnormality have few symptoms. The precise pathophysiology of the nocturnal pattern, where fluid shift and sustained wrist flexion during sleep are the usual explanations. Why some progress to axonal loss and thenar wasting while others remain stable for years. The true magnitude of occupational contribution against constitutional factors is contested and has medicolegal implications.

Cure status. CURABLE, unusually clearly so for a musculoskeletal condition. Carpal tunnel decompression, surgical release, is definitively curative in about 75 to 90 per cent, with durable relief and low recurrence of about 1 to 5 per cent. It is one of the most reliably effective operations in surgery.

But recovery is incomplete where axonal loss and thenar wasting are established: sensation and strength may not fully return, which is why delay matters. Pain and paraesthesia relief is good even in severe cases; muscle recovery is not.

SELF-LIMITING in specific settings: pregnancy-related carpal tunnel syndrome usually resolves after delivery, and mild cases may fluctuate or remit spontaneously. CURABLE by treating the cause where there is one: hypothyroidism, acromegaly, inflammatory tenosynovitis, weight loss in obesity. CONTROLLABLE non-surgically in mild to moderate disease, where splinting and injection give real but often temporary benefit.

Prevention. Weight management: MODERATE, since obesity is a strong dose-dependent risk factor. Reducing occupational vibration and repetitive forceful gripping, tool redesign, job rotation: MODERATE. Treating hypothyroidism and diabetes: MODERATE. Ergonomic keyboard interventions: WEAK and CONTESTED — given the weak association with keyboard use, these have little evidence of preventing carpal tunnel syndrome specifically, though they may help other upper limb complaints. Wrist splints for prevention in at-risk workers: WEAK. Early treatment to prevent axonal loss: MODERATE — this is prevention of irreversible damage rather than of the condition, and it is the practically important one, since thenar wasting does not reverse.

Treatment. Nocturnal wrist splinting in the neutral position is effective for mild to moderate disease, improving symptoms in the short to medium term, with most benefit in those with predominantly nocturnal symptoms. Cost a few to tens of US dollars for a splint, and locally manufacturable. First-line, and excellent value.

Corticosteroid injection into the carpal tunnel is effective, with benefit demonstrated at up to six to twelve months in randomised trials; it is superior to splinting alone in the short term and can defer or avoid surgery in a proportion. Off-patent, a few to tens of US dollars per injection for the drug. Also useful diagnostically. Ultrasound guidance improves accuracy and is not essential. Oral corticosteroids, as a short course, give modest short-term benefit. Carpal tunnel release surgery is definitive, with 75 to 90 per cent success and durable results. Open and endoscopic release have equivalent long-term outcomes; endoscopic release gives slightly faster return to work at higher cost and a small increase in nerve injury risk. Open release under local anaesthetic is cheap, safe and quick and requires no theatre infrastructure — it can be done in a procedure room, which matters greatly for access. Surgery is superior to splinting and injection in the medium to long term in randomised trials, so it should not be unduly delayed in moderate to severe disease, and is indicated promptly where there is thenar wasting, axonal loss on electrophysiology, or failure of conservative treatment.

Treat the secondary causes: levothyroxine, glycaemic control, weight loss, inflammatory arthritis treatment. Levothyroxine is an EML-listed medicine, section 18.7, for hypothyroidism. Consider transthyretin amyloidosis in bilateral disease in older patients, especially with cardiac features.

Nerve and tendon gliding exercises, manual therapy and yoga have modest evidence at low risk and may help mild cases. Not supported or ineffective: diuretics; pyridoxine, vitamin B6, long used with no

evidence; NSAIDs, with no benefit for the compression itself; ultrasound therapy, conflicting; laser; magnets.

Nerve conduction studies confirm the diagnosis and grade severity, and are useful before surgery and where the diagnosis is uncertain, but a clear clinical picture does not require them to proceed, which matters where they are unavailable. Clinical diagnosis plus a positive response to injection is a reasonable pathway in low-resource settings. Ultrasound is an increasingly used, cheaper alternative that also detects space-occupying causes.

Simple means. A nocturnal wrist splint at a few to tens of US dollars is the first-line treatment, effective for mild to moderate disease, and readily made from locally available materials — thermoplastic, or even a well-padded rigid support holding the wrist neutral. One of the best examples in this book of an effective treatment with essentially no supply chain.

Keeping the wrist neutral at night: even positional advice without a splint helps some. Weight loss addresses a strong dose-dependent risk factor. Activity and tool modification, reducing vibration exposure, job rotation and breaks, as workplace measures at low cost. Nerve and tendon gliding exercises, taught, with no equipment. Cheap corticosteroid injection at a few to tens of US dollars defers or avoids surgery in a proportion, and is deliverable by trained non-specialists.

Open release under local anaesthetic is the definitive cure, performable in a procedure room with local anaesthetic, a blade and sutures, by a trained generalist or task-shared surgeon. Among the highest-value minor operations available, and feasible in outreach and camp settings.

Recognising it early, before thenar wasting develops, since muscle loss does not recover. And not using vitamin B6 or diuretics: evidence-based omissions.

The honest note: unlike most entries, the cure here is cheap, quick and definitive. The main barrier is access to a minor operation, not cost of technology.

Gaps. Symptoms and electrophysiology correlate imperfectly, so severity grading and surgical thresholds are imprecise. The optimal timing of surgery against conservative management is not well defined, particularly for moderate disease. The true occupational attributable fraction is contested and entangled with compensation systems. Whether ergonomic interventions prevent the condition is unresolved, and the keyboard association is weaker than public belief. Long-term outcomes of injection against early surgery need more data. Recurrence and revision surgery outcomes are under-studied. The condition is not counted in GBD, so its global burden — likely substantial given a 10 per cent lifetime risk — is unknown, and unmet surgical need in low-income settings is unquantified despite the operation being cheap and simple. Awareness of carpal tunnel syndrome as a herald of transthyretin amyloidosis is new and the yield of screening for it is not established.

> **Depth.** Starts in: the carpal tunnel. Size: 2.5 cm†; depth +12.03. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE, with SELF-LIMITING and CONTROLLABLE for named strata. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Tendinopathies of the Achilles, patellar, lateral elbow and gluteal tendons

What it is. A tendon becomes painful and thickened where it is loaded, typically after a change in activity. The tissue is degenerate rather than inflamed. Anti-inflammatory treatment disappoints and loading treatment works.

Measured. Lateral elbow tendinopathy, tennis elbow, has a prevalence of about 1 to 3 per cent of adults, with a peak age of 35 to 54; about 75 per cent of cases are in the dominant arm; and it is mostly occupational rather than sporting — only about 5 to 10 per cent of cases are in tennis players, despite the name†.

Achilles tendinopathy has a lifetime incidence of about 6 to 11 per cent in runners and about 2 per cent in the general population, and is also common in sedentary middle-aged people, in the insertional type. Patellar tendinopathy, jumper's knee, has a prevalence of up to about 45 per cent in elite volleyball and about 30 per cent in basketball players†.

Gluteal tendinopathy, the commonest cause of lateral hip pain and formerly mislabelled trochanteric bursitis, has a prevalence of about 10 to 25 per cent in women over 40 — far more common than previously recognised, and the relabelling reflects the finding that bursal inflammation is usually absent while tendon pathology is present.

Rotator cuff tendinopathy is covered separately. Tendinopathies collectively account for about 30 per cent of all musculoskeletal consultations. They are not separately modelled in GBD. Deaths: none. By sex: gluteal tendinopathy is strongly female-predominant, Achilles male-predominant, and lateral elbow roughly equal.

Where it starts. Load error is the central mechanism: a rapid increase in training volume, intensity or frequency, or a return to activity after a break, exceeding the tendon's adaptive capacity. Tendons adapt to load slowly, since collagen turnover takes months, so the mismatch between rapid activity change and slow tissue adaptation is the proximate cause.

The pathology is degenerative, not inflammatory: disorganised collagen, neovascularisation, increased ground substance, and the absence of inflammatory cells on histology. Hence "tendinopathy" replaced "tendinitis" — a terminology change with treatment consequences, since it argues against steroids and NSAIDs as disease-modifying.

Age, through reduced tendon healing capacity and vascularity. Metabolic factors are increasingly recognised and important: obesity, type 2 diabetes with roughly three times the risk of tendinopathy, metabolic syndrome, and hypercholesterolaemia are all associated, independent of load. That reframes tendinopathy as partly a metabolic disease rather than purely an overuse injury.

Fluoroquinolone antibiotics are a well-established drug cause of Achilles tendinopathy and rupture; the risk is highest in older patients and with concurrent corticosteroids, and it has prompted regulatory restrictions. Corticosteroids, both systemic and by repeated local injection, also weaken tendon.

Biomechanical factors: for the Achilles, reduced ankle dorsiflexion, foot posture and calf weakness; for the gluteal tendons, hip adduction posture and pelvic width; for the lateral elbow, gripping with wrist extension, vibration and forceful repetitive work. Menopause and oestrogen deficiency have been proposed for the female predominance of gluteal tendinopathy: plausible, not established.

A genetic contribution is established for Achilles tendinopathy and rupture, with *COL5A1*, *TNC* and *MMP3* variants implicated and family history conferring roughly two to five times the risk; precise heritability figures are not well established.

What is not known is why pain occurs. Pathology on imaging correlates poorly with symptoms, and asymptomatic tendons frequently show marked abnormality on ultrasound and MRI, as with the spine and the rotator cuff. Why loading exercise works is only partly understood: it was assumed to remodel collagen, but pain relief often precedes any structural change, which implicates neural and central mechanisms. Why some tendinopathies become chronic and recalcitrant. And whether the metabolic associations are causal.

Cure status. Achilles, patellar and gluteal tendinopathy: CURABLE by loading programmes, in about 60 to 90 per cent†. Lateral elbow tendinopathy: SELF-LIMITING, with about 80 to 90 per cent recovering within one to two years regardless of treatment. Recalcitrant cases, perhaps 10 to 25 per cent†: RELIEF ONLY.

Curable in most, but slowly — and the time course is the key piece of honest information. Progressive loading exercise resolves or substantially improves most tendinopathies, but takes three to six months, and sometimes twelve. Patients told to expect weeks abandon treatment; patients told to expect months adhere.

The self-limiting course of lateral elbow tendinopathy is why almost any intervention appears to work in uncontrolled series, and why the randomised evidence matters so much. Achilles and patellar tendinopathy are curable with loading programmes in about 60 to 90 per cent†, with recurrence if load management

lapses. Gluteal tendinopathy is curable, and the LEAP trial showed education plus exercise gave the best outcomes. The recalcitrant 10 to 25 per cent† remain symptomatic despite good treatment, and the options then are limited and poorly evidenced. Tendon rupture, Achilles especially, is a separate problem requiring immobilisation or surgery.

Prevention. Gradual load progression: STRONG on mechanistic and observational grounds — avoiding sudden increases in training volume or intensity is the single most important measure. The "10 per cent per week" rule is a convention rather than a trial-validated figure.

Eccentric and heavy slow resistance training as prophylaxis in athletes: MODERATE, with trials in volleyball and soccer showing reduced tendinopathy incidence. Nordic hamstring exercise programmes reduce hamstring injury by about 50 to 70 per cent in randomised trials — the best-evidenced prevention in this family, and done without equipment.

Metabolic health — weight management, glycaemic control, lipid management: MODERATE, given the strength of the metabolic associations. Avoiding fluoroquinolones where alternatives exist, especially in older patients and those on corticosteroids: MODERATE. Avoiding repeated corticosteroid injection into weight-bearing tendons: MODERATE. Workplace load reduction, tool and grip modification, job rotation: MODERATE for lateral elbow. Calf strengthening and appropriate footwear: WEAK for the Achilles.

Treatment. Progressive loading exercise is first line for every tendinopathy, with good randomised evidence.

For the midportion Achilles: eccentric calf loading, the Alfredson protocol, is the foundational evidence, with about 60 to 90 per cent good outcomes†; heavy slow resistance training is equally effective and often better tolerated. Insertional Achilles tendinopathy needs limited dorsiflexion range, so floor-level rather than step exercises. For the patellar tendon: decline-squat eccentric loading, or heavy slow resistance. For the lateral elbow: progressive wrist extensor loading and grip strengthening. For the gluteal tendons: the LEAP trial (Mellor, *BMJ* 2018, 204 patients) found education plus exercise was superior to corticosteroid injection and to wait-and-see at eight weeks and at 52 weeks — an important result favouring the cheap, durable option over the injection. The cost is free to low: body weight, a step, a resistance band, or a loaded backpack.

Education and load management: explaining the slow time course, modifying aggravating activity without complete rest, since complete rest is harmful and deconditions the tendon, and progressive return. Analgesia with paracetamol or short-course NSAIDs for symptom control; NSAIDs do not treat the underlying pathology, since it is not inflammatory, and prolonged use is not indicated. Off-patent, cheap.

Corticosteroid injection gives short-term relief and worse long-term outcomes. This is the critical evidence point. In lateral elbow tendinopathy, the landmark Coombes trial (*JAMA* 2013, 165 patients) found corticosteroid injection gave better four-week outcomes but significantly worse complete recovery at one year, 83 against 96 per cent without injection, and higher recurrence. Similar findings have come from gluteal tendinopathy in LEAP and from Achilles tendinopathy. So steroid injection trades short-term relief for worse long-term recovery and should generally be avoided, particularly in weight-bearing tendons, where it also raises rupture risk.

Extracorporeal shockwave therapy has moderate evidence for some tendinopathies — insertional Achilles, plantar fasciopathy, calcific rotator cuff — and is contested for others; it is equipment-dependent and costly.

Platelet-rich plasma injection is not supported. Multiple adequately powered randomised trials are negative, including for Achilles tendinopathy (Kearney, *JAMA* 2021 — no benefit over sham) and for lateral elbow. It is nonetheless heavily marketed and widely sold: a significant consumer-protection issue.

Glyceryl trinitrate patches have some positive, inconsistent trials and low cost. High-volume injection, sclerosing injection, prolotherapy and dry needling have limited or conflicting evidence. Orthoses and braces: a counterforce brace for lateral elbow gives short-term symptom relief, and heel raises help the Achilles; useful as adjuncts, not treatments.

Surgery for the recalcitrant minority after six to twelve months of good conservative care: tendon debridement, release or repair. Outcomes are moderate and the evidence is weak, with few randomised comparisons against continued conservative care, and placebo-controlled trials are largely absent — which, given the history of subacromial decompression and meniscectomy, should induce caution. Treat the metabolic contributors: glycaemic control, weight, lipids. Review fluoroquinolone and corticosteroid exposure.

Simple means. Tendinopathy is a near-pure simple-means condition: the best-evidenced treatment is a loaded exercise requiring no equipment.

Progressive loading exercise, eccentric or heavy slow resistance. For the Achilles: calf raises off a step, progressing to added load in a backpack. For the patellar tendon: decline squats. For the lateral elbow: wrist extension with a weight or band. For the gluteal tendons: hip abductor loading. These are the first-line treatments with the best evidence, and they cost nothing.

Education on the time course: telling patients recovery takes three to six months prevents premature abandonment and the search for injections. Free, and it determines outcome. Load modification without complete rest: reducing the aggravating volume while continuing to load the tendon. Gradual return to activity with sensible progression rules, for prevention and treatment. Nordic hamstring exercises and similar prophylactic programmes give about 50 to 70 per cent injury reduction with no equipment†. A counterforce brace or strap for the lateral elbow, and a heel raise for the Achilles: cheap adjuncts. Weight loss and glycaemic control, addressing the metabolic contribution.

Not having a corticosteroid injection is an evidence-based omission that improves one-year recovery, 96 against 83 per cent (Coombes 2013)†; and not having platelet-rich plasma (Kearney 2021, negative)†. Two omissions that save money and improve outcomes. Avoiding fluoroquinolones where an alternative exists.

The honest limit: a small recalcitrant minority do not respond, and ruptures need immobilisation or surgery. But for the majority, the correct treatment is free.

Gaps. Why loading works is not fully understood, and pain relief often precedes structural change. Imaging findings correlate poorly with symptoms, so imaging adds little. The optimal loading protocol — eccentric against heavy slow resistance, dose, frequency, pain permitted during exercise — is not resolved, and protocols are largely convention. The recalcitrant 10 to 25 per cent† have no well-evidenced options, and surgery for tendinopathy has almost no placebo-controlled evidence despite the cautionary precedents of decompression and meniscectomy. Whether the metabolic associations are causal is unestablished, and if they are, the treatment implications would be significant. Shockwave evidence is inconsistent across sites. Platelet-rich plasma continues to be sold despite negative trials. Gluteal tendinopathy was misclassified as bursitis for decades and its epidemiology is still being established. These conditions are not counted in GBD despite accounting for about 30 per cent of musculoskeletal consultations, so global burden is unknown.

> **Depth.** Starts in: a tendon. Size: 5 cm†; depth +12.66. First complaint: about 14 days ([B] after a change in loading; † about 2 weeks); time depth 45.90. One untreated course: about 4.2 months († 3–6 months); depth 47.91.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Scoliosis

What it is. A sideways curve and rotation of the spine. Most cases appear in adolescence with no known cause. Small curves do not matter; large ones progress, deform the trunk and can affect breathing.

Measured. Adolescent idiopathic scoliosis affects about 1 to 3 per cent of children aged ten to sixteen, using the standard threshold of a Cobb angle of 10 degrees or more†. Curves of 30 degrees or more are present in about 0.1 to 0.3 per cent, and curves of 40 degrees or more in about 0.1 per cent, so the great majority of scoliosis is mild and clinically unimportant.

Female to male ratio is about 1.5:1 at the 10-degree threshold but about 7 to 10:1 for curves requiring treatment — girls are far more likely to progress, which is why screening and monitoring focus on them.

Adult degenerative, de novo, scoliosis is much more common than is generally appreciated, with a prevalence of about 30 to 68 per cent in adults over 60 in imaging studies, usually with mild curves, and it is a cause of back pain, stenosis and deformity in the elderly. Congenital scoliosis occurs in about one per 1,000 births, and neuromuscular scoliosis is common in cerebral palsy, up to 20 to 60 per cent in severe forms†, and in Duchenne muscular dystrophy and spinal muscular atrophy.

It is not separately modelled in GBD. Deaths are rare, from respiratory failure in very severe untreated curves, typically above 90 to 100 degrees, and in neuromuscular disease. The distribution is broadly similar across countries, but access to bracing and surgery is extremely unequal, so untreated severe deformity remains common in low-income countries and is essentially absent in high-income ones.

Where it starts. Idiopathic: by definition the cause is unknown, and that is the honest headline for about 80 to 85 per cent of cases†.

Genetics: strong familial clustering, with first-degree relatives at about seven to eleven times the risk; concordance is higher in monozygotic than dizygotic twins, with heritability estimated at about 38 to 87 per cent depending on study, the wide range reflecting methodological differences. GWAS has identified loci including *LBX1*, the most robustly replicated, with *GPR126/ADGRG6*, *BNC2* and *PAX1*: polygenic, each variant of small effect. No clinically useful genetic test exists — the ScoliScore test was commercialised and then withdrawn after failing validation, which is a cautionary case.

Female sex, and peripubertal growth velocity. Progression risk is driven by remaining growth: curves progress fastest during the adolescent growth spurt and largely stop at skeletal maturity. Risser sign, Sanders stage and menarcheal status are the practical predictors, and this growth dependence governs all treatment decisions. Curve magnitude at presentation is the strongest single predictor of progression: larger curves in younger, less mature patients progress most.

Associated or contributory in non-idiopathic cases: vertebral malformations, in congenital disease; neuromuscular disease — cerebral palsy, muscular dystrophy, spinal muscular atrophy, spina bifida; connective tissue disorders, Marfan and Ehlers-Danlos; neurofibromatosis type 1; and syringomyelia and tethered cord, which is why atypical features — a left thoracic curve, neurological signs, pain, rapid progression — mandate MRI.

Proposed and unproven in idiopathic disease: abnormal melatonin signalling, leptin and body composition, proprioceptive and vestibular dysfunction, differential growth of anterior and posterior spinal elements, and platelet calmodulin abnormalities.

Not a cause: backpacks, posture, sitting position, sports and sleeping position. These are common parental concerns and are not supported.

What is not known is the cause. Why it is female-predominant for progression. Why some curves progress rapidly and others not at all, beyond growth and magnitude. Whether adult curves cause back pain or are coincidental in many. And there is no means of preventing onset.

Cure status. This depends entirely on magnitude and growth remaining, so each stratum is named.

Curves under about 25 degrees in a maturing adolescent: SELF-LIMITING. They usually stabilise at skeletal maturity and require only observation, and the great majority never need treatment.

Curves of about 20 to 40 degrees with growth remaining: CONTROLLABLE by bracing. Bracing does not straighten the spine; it prevents progression to the surgical threshold. That is the correct and often misunderstood goal.

Curves at or above the surgical threshold: CURABLE by surgery. Spinal fusion with instrumentation achieves substantial, permanent curve correction and halts progression, at the cost of a major operation and loss of segmental motion.

Established deformity at skeletal maturity does not resolve, and curves above 50 degrees tend to progress slowly through adult life, at about 0.5 to 1 degree a year†. Exercise does not correct curves: it may have a

small effect on progression, which is contested, and it helps pain and function, but claims of curve correction by exercise or manual therapy are not supported.

Prevention. Primary prevention is not possible, since the cause is unknown: absent.

Screening to prevent severe deformity: MODERATE, and contested. School screening with the Adams forward-bend test plus a scoliometer detects curves early. The US Preventive Services Task Force historically recommended against routine screening, citing over-referral, radiation and uncertain benefit, then in 2018 concluded the evidence was insufficient — an honest "we don't know". Several European countries screen and others do not. The argument for screening strengthened after the BrAIST bracing trial demonstrated that bracing works, since early detection is only worthwhile if effective treatment follows.

Bracing as secondary prevention: STRONG. Preventing surgery through timely detection and bracing: MODERATE. Vitamin D and calcium adequacy, and general fitness: WEAK — reasonable and not established as affecting curve behaviour. In neuromuscular disease, maintaining mobility and nutrition, and in spinal muscular atrophy the new disease-modifying therapies nusinersen, onasemnogene and risdiplam, substantially reduce scoliosis severity: STRONG for that group, though extremely expensive.

Treatment. Decisions rest on curve magnitude plus remaining growth, not on symptoms.

Observation for curves under 20 to 25 degrees in a growing child: serial clinical examination and radiographs every four to twelve months until maturity. Most need nothing further. Using low-dose or biplanar slot-scanning radiography reduces cumulative radiation.

Bracing for curves of about 20 to 40 degrees with significant growth remaining. The evidence is strong and specific. The BrAIST trial (Weinstein, *NEJM* 2013, 242 patients in randomised and preference cohorts) found bracing significantly reduced progression to the surgical threshold of 50 degrees or more, with success in 72 per cent with bracing against 48 per cent with observation, and the trial was stopped early for efficacy. There was a clear dose-response with wear time: success rose to about 90 to 93 per cent in those wearing the brace 12.9 hours a day or more, and was little better than observation with minimal wear. So adherence is the determinant, and measuring it with temperature sensors and supporting it is the practical task. The typical prescription is a thoracolumbosacral orthosis, Boston or Chêneau type, for sixteen to 23 hours a day until skeletal maturity. Cost about US$500 to 3,000 per brace in high-income settings†, and far less where locally fabricated — braces can be made from thermoplastic by a trained orthotist with simple equipment, which is important for access.

Scoliosis-specific exercise, Schroth or SEAS, shows modest evidence of reducing progression and improving trunk appearance and pain, and SOSORT guidelines support them as an adjunct, often alongside bracing. The evidence quality is moderate at best and the trials are small: CONTESTED for curve modification, reasonable for function and pain. Low cost.

Surgery for curves of 45 to 50 degrees or more, or progressive curves, or significant deformity. Posterior spinal fusion with pedicle screw instrumentation is the standard, achieving about 50 to 70 per cent curve correction†, halting progression and improving trunk appearance; complication rates are meaningful, with infection, neurological injury at about 0.3 to 1 per cent†, implant problems, pseudarthrosis and adjacent segment issues. Anterior approaches, growing rods, magnetically controlled growing rods and vertebral body tethering for early-onset and skeletally immature patients: tethering preserves motion and is growing in use, with limited long-term data and revision rates not yet established. Cost about US$20,000 to 150,000 in high-income systems†, far less elsewhere, though instrumentation cost is a real barrier in low-income settings.

Adult degenerative scoliosis: treat symptoms, not the curve — exercise, analgesia, physiotherapy; decompression with or without limited fusion for stenosis and radicular symptoms; major deformity correction only in selected patients, since complication rates in older adults are high. Neuromuscular scoliosis: seating and postural management, wheelchair modification, respiratory care, nutritional support, and fusion when sitting balance or respiratory function is threatened, with underlying disease treatment where available.

Not supported: chiropractic manipulation, scoliosis correction devices, electrical stimulation which was tested and abandoned, and exercise alone presented as an alternative to bracing for curves in the braceable

range. These are commonly marketed to parents. MRI is indicated for atypical presentation — a left thoracic curve, neurological signs, early onset, pain, rapid progression — to exclude syrinx, tethered cord or tumour.

Simple means. Observation: for the great majority of mild curves the correct management is monitoring and reassurance. It costs a clinic visit and prevents substantial unnecessary intervention and anxiety.

The forward-bend test and a scoliometer are the entire screening apparatus. A scoliometer is a simple inclinometer costing very little, the test takes seconds and needs no radiation, and it can be used by school nurses, teachers or community health workers. The highest-value simple tool here.

Locally fabricated thermoplastic braces: the effective treatment, with BrAIST giving 72 against 48 per cent and rising to about 90 per cent with good wear, can be made by a trained orthotist with a heat source and a thermoplastic sheet. Where orthotic services exist, bracing prevents the need for major surgery — a large benefit from modest infrastructure.

Supporting brace adherence through education, peer support, involving the adolescent in decisions, and addressing the real psychosocial burden of wearing a brace through adolescence. Adherence is the single determinant of brace success, and supporting it costs nothing but attention.

Exercise and general fitness for pain, posture, respiratory function and self-image, with honesty about not correcting the curve. Scoliosis-specific exercises: low cost, modest evidence, reasonable adjunct. Reassurance about non-causes — backpacks, posture and sport do not cause scoliosis, and children should not be restricted from activity. Correct explanation of the goal of bracing, which is preventing progression rather than straightening, and which prevents the disappointment that drives families toward unproven alternatives.

The honest limit: a curve above about 50 degrees needs surgery, and no simple means substitutes. Access to safe spinal surgery is the binding global inequity here.

Gaps. The cause of idiopathic scoliosis is unknown. No test predicts which curves will progress beyond growth status and current magnitude, so some children are braced unnecessarily and others are detected too late. Genetic prediction has failed in practice, with ScoliScore withdrawn. School screening’s net benefit remains formally insufficient evidence per the USPSTF, and policies differ between countries without resolution. Scoliosis-specific exercise evidence is weak and the trials are small, yet it is widely promoted. Vertebral body tethering is being adopted ahead of long-term outcome data. Long-term outcomes of modern instrumented fusion beyond 40 years are not yet known, and adjacent segment degeneration and late revision rates are uncertain. Whether adult degenerative curves cause the back pain attributed to them is unclear. Scoliosis is not counted in GBD, and the global burden of untreated severe deformity — concentrated where orthotics and spinal surgery are unavailable — is unquantified.

> **Depth.** Starts in: the spine. Size: 50 cm†; depth +14.76. First complaint: about 12 years ([B] mostly in adolescence); time depth 51.13. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Osteomyelitis

What it is. Infection of bone. It arrives through the bloodstream, from a nearby wound or ulcer, or after surgery or a fracture. Bone infection is hard to clear because dead bone and biofilm shield the organisms from antibiotics and from the immune system.

Measured. Incidence is about 22 to 25 per 100,000 person-years overall in high-income settings, and rising, driven by diabetic foot infection, orthopaedic implants and injecting drug use.

Acute haematogenous osteomyelitis in children runs at about 8 to 20 per 100,000 a year in high-income countries, and several-fold higher in low-income settings and in Indigenous populations; in parts of sub-

Saharan Africa and the Pacific it is a common cause of childhood disability through chronic osteomyelitis and growth plate damage.

Diabetic foot osteomyelitis is now the largest category in adults: it is present in about 20 per cent of mild to moderate and about 50 to 60 per cent of severe diabetic foot infections, and underlies a large share of the roughly one million lower-limb amputations performed annually in people with diabetes. Prosthetic joint infection affects about 1 to 2 per cent of primary hip and knee replacements, higher in revision surgery, and given the volume of arthroplasty this is a growing absolute burden.

It is not separately modelled in GBD. Mortality is low directly, but limb loss, chronic disability and recurrent hospitalisation are the real outcomes, and in low-resource settings chronic osteomyelitis is a significant cause of lifelong disability in children. Age distribution is bimodal: children with haematogenous disease in the long bone metaphyses, and older adults with contiguous spread, diabetic foot infection, vertebral and implant-related disease. Vertebral osteomyelitis incidence rises steeply with age and is increasing. There is a male predominance of about 1.5 to 2:1.

Where it starts. *Staphylococcus aureus* is the dominant organism across all categories, at about 50 to 70 per cent, including MRSA in many settings†. Others: coagulase-negative staphylococci with implants; streptococci; *Kingella kingae* in young children, now recognised as a major paediatric cause with improved PCR detection; Gram-negatives and anaerobes in diabetic foot and contiguous infection; *Salmonella* in sickle cell disease, a classic and important association; *Pseudomonas* with injecting drug use and puncture wounds through footwear; *Mycobacterium tuberculosis* in spinal Pott disease, a major global cause that Western accounts often under-weight; *Brucella* in endemic regions; and fungi in the immunocompromised.

Routes: haematogenous in children, in vertebral disease in adults and with injecting drug use; contiguous spread from a diabetic foot ulcer, pressure ulcer, dental or sinus infection; and direct inoculation through open fracture, surgery, implant, puncture wound or gunshot.

Risk factors: diabetes with peripheral neuropathy and peripheral arterial disease is the dominant adult risk set, since neuropathy allows unnoticed ulceration while ischaemia impairs healing and antibiotic delivery. Then peripheral vascular disease; injecting drug use; immunosuppression; sickle cell disease; malnutrition; smoking; alcohol excess; chronic kidney disease; prior surgery or trauma; the presence of implanted material, since biofilm on a foreign surface drastically lowers the infecting dose and resists antibiotics; and pressure ulcers and immobility.

In children, the metaphyseal vascular anatomy, with sluggish sinusoidal flow in growing bone, explains the typical site, and preceding minor trauma is often reported. Heritability is not meaningfully applicable, since this is an acquired infection, though susceptibility is modified by genetic conditions — sickle cell disease, chronic granulomatous disease, immunodeficiencies — and by diabetes risk.

What is not known is the optimal duration and route of antibiotic therapy for most categories. Decades of practice rested on convention — the six weeks of intravenous therapy tradition — rather than trial evidence, which has now been partly overturned. How to tell reliably whether infection has been eradicated: there is no test of cure, and relapse can occur years later. How much dead bone must be removed. In diabetic foot osteomyelitis, whether surgery or antibiotics alone is better is genuinely unresolved. And the role and value of local antibiotic carriers and of newer biofilm-targeting approaches.

Cure status. Five strata, each with its own label.

Acute osteomyelitis treated promptly, especially acute haematogenous osteomyelitis in children: CURABLE in about 90 to 95 per cent† with prompt antibiotics plus drainage of any abscess, because there is no established dead bone or biofilm yet. Early treatment is what makes it curable, and delay converts it into chronic disease.

Chronic osteomyelitis with adequate debridement: CURABLE in about 70 to 90 per cent†, but only with adequate surgical debridement combined with antibiotics. Antibiotics alone rarely cure established chronic infection with sequestrum, dead bone. Recurrence years later is possible, so cure is provisional and long follow-up is needed.

Implant-associated infection, with implant removal or exchange: CURABLE. Debridement with implant retention succeeds only in early post-operative or acute haematogenous infection with a stable implant and a susceptible organism; otherwise one- or two-stage exchange is needed. Biofilm is the proposed reason.

Diabetic foot osteomyelitis: CURABLE, including with antibiotics alone in selected cases — a significant and relatively recent shift from automatic amputation.

Where cure is unachievable, in patients unfit for surgery, at an unresectable site, or with a retained essential implant: RELIEF ONLY, by long-term suppressive antibiotics.

The determinant throughout is surgical removal of dead bone and biofilm, not the choice of antibiotic. Amputation is sometimes the curative option and should not be regarded only as failure: for an unsalvageable, chronically infected, painful or non-functional limb it can restore mobility and quality of life faster than years of failed limb salvage.

Prevention. Diabetic foot care: STRONG. This is where most adult osteomyelitis could be prevented. Structured foot screening, education, appropriate footwear, callus and nail care, prompt ulcer treatment and offloading, and multidisciplinary foot clinics reduce ulceration and amputation by about 50 to 85 per cent in cohort and programme evaluations. One of the highest-yield preventive programmes in chronic disease care, and consistently under-resourced.

Glycaemic control and smoking cessation: MODERATE. Surgical antibiotic prophylaxis before orthopaedic implant surgery: STRONG — a single dose of a cephalosporin substantially reduces infection, and cefazolin is cheap and EML-listed.

Open fracture management: STRONG — prompt antibiotics within an hour, thorough debridement, and early soft tissue coverage. Debridement quality and timing of coverage matter more than antibiotic choice.

Aseptic technique, theatre discipline, laminar flow, skin antisepsis with chlorhexidine-alcohol, and *S. aureus* screening and decolonisation with nasal mupirocin and chlorhexidine washes: MODERATE for implant surgery. Pressure ulcer prevention by repositioning, support surfaces and nutrition: STRONG for preventing contiguous osteomyelitis of the sacrum and heel. Harm reduction for injecting drug use — sterile equipment, needle exchange, safer injecting education: MODERATE. Penicillin prophylaxis and vaccination in sickle cell disease: STRONG, for pneumococcal and salmonella risk. BCG vaccination and tuberculosis control: MODERATE for skeletal tuberculosis. Prompt treatment of acute osteomyelitis: STRONG for preventing chronic osteomyelitis — the key preventive step in children, and the one most often missed in low-resource settings.

Treatment. The proportion of diabetic foot osteomyelitis cured with antibiotics alone is not given here. Obtain microbiology before antibiotics wherever possible: bone biopsy or intraoperative samples, not superficial swabs, since superficial wound swabs in diabetic foot infection do not reliably reflect bone pathogens and mislead treatment. Blood cultures in acute haematogenous disease. This single principle improves outcomes and reduces unnecessary broad-spectrum therapy.

Surgical debridement is the cornerstone for chronic osteomyelitis: removal of all dead bone and infected tissue, management of dead space with local antibiotic carriers, bone graft, muscle flap, the Masquelet technique or Ilizarov bone transport, and stabilisation. Antibiotics cannot cure what has no blood supply.

Two antibiotic trials changed practice fundamentally.

On oral against intravenous therapy, the OVIVA trial (Li, *NEJM* 2019, 1,054 patients with bone and joint infection) found oral antibiotic therapy non-inferior to intravenous therapy for the first six weeks, with treatment failure of 13.2 per cent on oral against 14.6 per cent on intravenous, and with fewer complications and shorter hospital stay in the oral group. That overturned the long-standing six-weeks-of-intravenous doctrine, and it is enormously consequential for cost, for hospital capacity and for low-resource settings where prolonged intravenous access is impractical.

On duration in children, short courses suffice. Randomised and large cohort evidence (Peltola) supports a total of about two to four weeks with early switch to oral therapy for uncomplicated acute haematogenous osteomyelitis in children, rather than the traditional six weeks.

Duration in adults: about six weeks is conventional for chronic osteomyelitis after debridement, and twelve weeks for prosthetic joint infection with implant retention or exchange. The DATIPO trial did not demonstrate non-inferiority of six against twelve weeks for prosthetic joint infection — twelve weeks was better — so duration remains condition-specific.

Agents: flucloxacillin or cefazolin for methicillin-susceptible *S. aureus*; vancomycin, daptomycin or linezolid for MRSA; rifampicin combinations for implant-related infection, for biofilm penetration, and never as monotherapy; clindamycin, with good bone penetration, oral, cheap and EML-listed; co-trimoxazole with rifampicin, a cheap oral option with good evidence; and fluoroquinolones for Gram-negatives, with excellent bone penetration and oral bioavailability.

Drug costs: flucloxacillin, clindamycin, co-trimoxazole, rifampicin, ciprofloxacin and doxycycline are all off-patent and mostly EML-listed, at tens to hundreds of US dollars a course. Vancomycin and daptomycin are more expensive, with daptomycin at thousands of US dollars a course, and linezolid is now off-patent and much cheaper than at launch. The OVIVA result means a curative course of bone infection treatment can cost tens of dollars in oral generics rather than thousands in inpatient intravenous therapy.

Diabetic foot osteomyelitis, specific points. Antibiotics alone can cure a substantial proportion of forefoot osteomyelitis without ischaemia: trials and cohorts report about 60 to 80 per cent remission, comparable to conservative surgery in some comparisons, and this has shifted practice away from automatic bone resection. Offloading is essential, with a total contact cast or removable walker, because without pressure relief healing fails regardless of antibiotic. Revascularisation where there is ischaemia, which often determines the outcome more than the antibiotic. And a multidisciplinary foot team, which reduces amputation substantially.

Prosthetic joint infection: debridement with antibiotics and implant retention (DAIR) for early and acute infection; one- or two-stage exchange arthroplasty otherwise; suppression if unfit. Rifampicin-based combinations for staphylococci.

Vertebral osteomyelitis is usually treated medically, for six weeks with an oral switch per OVIVA, with surgery for instability, epidural abscess with neurological compromise, or failure. Image-guided biopsy before antibiotics is important.

Skeletal tuberculosis: standard antituberculous regimens for nine to twelve months, with surgery for instability or deformity. All first-line antituberculous drugs are EML-listed and cheap.

Adjuncts: nutritional support, glycaemic control and smoking cessation, all of which affect healing; hyperbaric oxygen, CONTESTED on limited evidence; and local antibiotic beads and absorbable carriers, widely used on moderate evidence. Amputation, considered positively where limb salvage would mean prolonged disability, repeated surgery or an unusable limb.

Simple means. Diabetic foot care: daily foot inspection, with a mirror or a family member if the patient cannot see or reach; washing and drying between the toes; correct footwear; prompt attention to any break in the skin; and never walking barefoot. Combined with structured screening, this prevents the ulcers that become osteomyelitis and reduces amputation by about 50 to 85 per cent in programme evaluations†. It requires education and a pair of adequate shoes — among the highest-value simple interventions in this book, because the alternative outcome is limb loss.

Offloading: a total contact cast is plaster and skill, and even felt padding, crutches and sandals with pressure relief help. Pressure relief is as important as the antibiotic.

The 10 g monofilament and a tuning fork detect the neuropathy that identifies at-risk feet: pennies, and no electricity.

Oral antibiotics: the OVIVA finding means bone infection can be treated orally, without central lines, infusion pumps or prolonged admission. That is transformative for low-resource and outpatient care.

Prompt treatment of acute infection in children: recognising a limping or non-weight-bearing febrile child early and treating promptly prevents chronic osteomyelitis and lifelong deformity. Wound care, cleaning and dressing, and pressure ulcer prevention by repositioning, are nursing measures requiring time rather

than technology. Nutrition and glycaemic control, and smoking cessation. Sterile injecting equipment and needle exchange.

Surgical debridement itself is simple in the sense that it needs skill and basic instruments rather than expensive technology — and it is the single most important curative act. A trained surgeon with instruments and anaesthesia cures more bone infection than any drug.

The honest limit: chronic osteomyelitis with dead bone cannot be cured without surgery, and implant infection usually needs implant removal. No simple means substitutes.

Gaps. There is no test of cure, so relapse cannot be excluded and follow-up duration is arbitrary. Optimal antibiotic duration for most adult categories remains convention-based despite OVIVA settling the route question. Whether surgery or antibiotics alone is better for diabetic foot osteomyelitis is genuinely unresolved, with trials small and heterogeneous. Diagnosis is difficult: MRI is sensitive but cannot reliably distinguish infection from Charcot neuroarthropathy or post-surgical change, and bone biopsy is under-used. Local antibiotic carriers and biofilm-targeted approaches lack good comparative evidence. Hyperbaric oxygen evidence is weak. The condition is not counted in GBD, so global burden is unknown, particularly childhood chronic osteomyelitis in low-income countries, which causes substantial lifelong disability and is barely measured. Antibiotic resistance, especially MRSA and Gram-negative resistance, is narrowing oral options in many regions.

> **Depth.** Starts in: Staphylococcus aureus. Size: 1 µm†; depth +2.81. First complaint: about 5.3 days († days to weeks); time depth 45.02. One untreated course: no number ([B] hard to clear).
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> **Model reading.** Way of ending: remove. Layer: mesh. The book names an early stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Septic arthritis

What it is. Infection inside a joint. It destroys cartilage within days, so it is a medical emergency. A hot, swollen, extremely painful joint with fever must be aspirated and treated at once.

Measured. Incidence is about 4 to 12 per 100,000 a year in the general population, rising to about 30 to 70 per 100,000 in those with rheumatoid arthritis and about 40 to 70 per 100,000 in people with prosthetic joints†. In children it is about 4 to 10 per 100,000 a year†, higher in low-income settings and in Indigenous populations.

Mortality is about 7 to 15 per cent in adults, and up to about 25 to 30 per cent in polyarticular disease, in the elderly, and in those with sepsis. That is high, and it is often not appreciated that septic arthritis kills. Permanent joint damage occurs in about 25 to 50 per cent of adult cases even with treatment: function is lost, not merely threatened.

It is not separately modelled in GBD. Age distribution is bimodal: young children, especially under three, and adults over 60. The knee is affected in about 50 per cent†, then hip, shoulder, ankle and wrist, with the hip commonest in young children. Polyarticular involvement occurs in about 10 to 20 per cent†, usually in immunocompromised or bacteraemic patients. There is a male predominance, with a strong association with injecting drug use, which also causes unusual joints — sternoclavicular and sacroiliac. Gonococcal arthritis is a distinct and important entity in sexually active young adults, often polyarticular with tenosynovitis and skin lesions, and it has a much better prognosis than staphylococcal disease.

Where it starts. Haematogenous seeding is the commonest route: the synovium is highly vascular and lacks a basement membrane, so bacteraemia from any source can seed a joint. Also direct inoculation by injection, surgery, trauma or bite, and contiguous spread from adjacent osteomyelitis, especially in children, where metaphyseal infection can breach into the joint.

Staphylococcus aureus is the leading organism at about 40 to 60 per cent, including MRSA; streptococci at about 20 per cent†; *Neisseria gonorrhoeae* in young sexually active adults; Gram-negatives in the elderly, the immunocompromised and injecting drug users; *Kingella kingae* in young children; *Salmonella* in sickle

cell disease; *Mycobacterium tuberculosis* and *Brucella* in endemic areas, causing chronic monoarthritis; *Borrelia burgdorferi* in Lyme disease-endemic regions; and fungi in the immunocompromised.

Risk factors: pre-existing joint disease, with rheumatoid arthritis the single strongest through damaged synovium and immunosuppression; a prosthetic joint; age above 80; diabetes; injecting drug use; immunosuppression, including from biologics, particularly anti-TNF agents, and from corticosteroids; chronic kidney disease; cirrhosis; recent intra-articular injection, a small but real iatrogenic cause where aseptic technique matters; skin infection or ulceration; alcohol excess; haemophilia; malignancy; and crystal arthritis — and crucially, gout and septic arthritis can coexist, so finding crystals does not exclude infection.

What is not known is why only a small proportion of bacteraemic patients develop septic arthritis. How to distinguish septic arthritis reliably from crystal arthritis and inflammatory flares at presentation is the central practical problem, since synovial white cell count, CRP and even Gram stain all have imperfect sensitivity and specificity, and synovial fluid cultures are negative in about 10 to 30 per cent of true cases†. The optimal drainage method — needle aspiration against arthroscopic against open washout — is not established by good randomised evidence despite being the key therapeutic decision. And whether adjunctive corticosteroids help: the evidence in children is suggestive and adult evidence is absent.

Cure status. CURABLE, but only if treated urgently, and function is often permanently lost regardless.

Prompt drainage plus antibiotics cures the infection in the great majority, and gonococcal arthritis in particular resolves well with antibiotics and has an excellent functional prognosis. But cartilage destruction begins within days and is irreversible: bacterial enzymes and the host inflammatory response degrade cartilage rapidly, so about 25 to 50 per cent are left with permanent damage, pain or reduced range of movement, and some progress to secondary osteoarthritis requiring joint replacement. Time to treatment is the main determinant of functional outcome, which is why it is an emergency. Mortality of 7 to 15 per cent means it is not only a joint problem.

Prosthetic joint infection: CURABLE, but usually requiring implant removal or exchange, as in the osteomyelitis entry; debridement with implant retention works only in early infection.

In children, outcomes are generally better with prompt treatment, but hip septic arthritis in infants can destroy the growth plate and femoral head, causing lifelong deformity — a devastating outcome that is still common where presentation is late.

Prevention. Aseptic technique for intra-articular injection and joint surgery: STRONG. Surgical prophylaxis for arthroplasty, and *S. aureus* decolonisation: STRONG. Prompt treatment of skin and soft tissue infection and of bacteraemia: MODERATE, especially *S. aureus* bacteraemia, where joints should be actively sought. Harm reduction in injecting drug use: MODERATE. Treating gonorrhoea and chlamydia promptly, with partner treatment and condoms: STRONG for gonococcal arthritis. Diabetes control, and glycaemic and foot care: MODERATE.

Vigilance in patients on biologics and in rheumatoid arthritis: MODERATE. These patients may present atypically with blunted fever and inflammatory markers, and a hot joint in an immunosuppressed patient should be aspirated rather than assumed to be a disease flare. That is the commonest serious diagnostic error in this condition.

Penicillin prophylaxis and vaccination in sickle cell disease: STRONG. Education that an acutely hot, swollen joint requires same-day assessment: MODERATE — free, and it determines the time to treatment that determines the outcome.

Treatment. Joint aspiration before antibiotics, immediately, is the single most important action. Send synovial fluid for urgent Gram stain, culture, cell count and differential, and crystal examination; take blood cultures too. Suggestive findings are a synovial white cell count above 50,000 per mm^3 with over 90 per cent neutrophils, though lower counts occur, particularly in prosthetic joints, in immunosuppression and in early disease, and a lower count does not exclude it. Remember that crystals and infection coexist: finding urate crystals does not rule out septic arthritis. A needle, a syringe and a microscope constitute the diagnostic apparatus.

Drainage is mandatory and repeated until the effusion stops reaccumulating. Repeated closed-needle aspiration, daily or more often, is effective and cheap and needs no theatre; it is appropriate for accessible joints such as the knee. Arthroscopic washout is for larger or loculated joints, or failed aspiration, and allows lavage and debridement with low morbidity. Open arthrotomy is for the hip, especially in children, where it is urgent to prevent femoral head necrosis, and for inaccessible joints or failure of other methods. No good randomised evidence establishes which is superior; practice varies, and the essential principle is that pus must be removed, promptly and repeatedly, by whatever means is available.

Empirical intravenous antibiotics immediately after aspiration, guided by local resistance and Gram stain: flucloxacillin or cefazolin for suspected methicillin-susceptible *S. aureus*; adding or substituting vancomycin, teicoplanin, daptomycin or linezolid where MRSA is prevalent; adding a Gram-negative agent such as ceftriaxone in the elderly, the immunocompromised and injecting drug users; and ceftriaxone for suspected gonococcal arthritis, with treatment for chlamydia and partner management. Then narrow according to culture.

Duration is about two to four weeks in total for uncomplicated cases, and up to four to six weeks with osteomyelitis or staphylococcal bacteraemia; gonococcal arthritis responds in about seven to fourteen days. Early oral switch is now supported by the OVIVA evidence, which included septic arthritis within bone and joint infection: oral therapy was non-inferior to intravenous over the first six weeks, with failure at 13.2 against 14.6 per cent. That permits much shorter admissions.

Costs: flucloxacillin, cefazolin, ceftriaxone and clindamycin are off-patent and mostly EML-listed, with ceftriaxone verified on the EML, at a few to hundreds of US dollars a course. Vancomycin is off-patent and moderately cheap; daptomycin and linezolid are more expensive, and linezolid is now off-patent.

Analgesia, with joint rest in a functional position initially, then early mobilisation and physiotherapy once infection is controlled, to preserve range of movement; prolonged immobilisation causes stiffness.

Adjunctive corticosteroids in children: several randomised trials suggest dexamethasone reduces duration of symptoms and possibly long-term dysfunction in paediatric septic arthritis, which is promising and not standard, and adult evidence is lacking: CONTESTED. Dexamethasone is an EML-listed medicine across palliative care, antiallergics and hormones and antihormones, with an indicative UNICEF price of US$24.00 per pack of 100 4 mg tablets, about US$0.24 a tablet, October 2026.

Prosthetic joint infection: debridement with implant retention if early and acute with a stable implant, otherwise one- or two-stage exchange, with rifampicin-containing combinations for staphylococci and never rifampicin alone. Treat the source: endocarditis, with echocardiography in *S. aureus* bacteraemia, skin infection, dental sepsis or a urinary source. Late reconstruction — joint replacement, arthrodesis or osteotomy — for the post-infectious destroyed joint, once infection is definitively cleared. Tuberculous and brucellar arthritis need prolonged specific antimicrobial therapy, and should be considered in chronic monoarthritis in endemic areas, where they are frequently missed for months.

Simple means. Aspirating the joint needs a needle and a syringe. It is simultaneously the diagnostic test and the first therapeutic act, and it can be done at any level of the health system with basic training and sterile technique. That is the highest-value simple means in this entry, because the whole outcome depends on doing it early.

Repeated needle aspiration as definitive drainage, for accessible joints, needs no operating theatre, no arthroscope and no anaesthetic service. A microscope gives synovial white cell count, Gram stain and crystal examination, with polarised or improvised polarised light, and yields most of the diagnostic information available anywhere.

Recognition and urgency: teaching patients, families and frontline health workers that a hot, acutely swollen, very painful joint with fever means same-day care. Free, and it is the determinant of whether the joint survives, since cartilage loss begins within days.

Aspirating the hot joint in an immunosuppressed or rheumatoid patient rather than assuming a flare is a decision, not a technology, and it corrects the commonest serious error here.

Cheap off-patent antibiotics with early oral switch, per OVIVA, give a curative course for tens of dollars without prolonged intravenous access. Early mobilisation and physiotherapy preserves the function that the infection threatens, through a taught exercise programme. Clean injecting equipment, aseptic injection technique, and treating gonorrhoea and notifying partners.

The honest limit: this is one of the clearest cases in this book where simple means are necessary but not sufficient. The condition needs antibiotics and effective drainage, and a septic hip, especially in a child, needs urgent surgical decompression. Delay costs the joint and sometimes the life.

Gaps. No test reliably distinguishes septic arthritis from crystal or inflammatory arthritis at presentation: synovial cell counts overlap, cultures are negative in 10 to 30 per cent, and the two can coexist. That is the central diagnostic gap and it causes both delayed treatment and unnecessary washouts. No good randomised evidence compares needle aspiration, arthroscopic and open drainage, despite this being the key management decision. Optimal antibiotic duration is convention-based, though OVIVA settled the route question. Adjunctive corticosteroid benefit is suggested in children and unstudied in adults. Why functional outcomes remain poor in 25 to 50 per cent despite successful microbiological cure is not well understood, and no treatment protects cartilage. Prosthetic joint infection management rests largely on cohort data. The condition is not counted in GBD, so global burden and the outcomes of late presentation — especially infant hip septic arthritis in low-income settings, which causes lifelong disability — are unquantified. Rising MRSA and Gram-negative resistance narrows empirical options.

> **Depth.** Starts in: Staphylococcus aureus. Size: 1 µm†; depth +2.81. First complaint: about 42 hours († 1–3 days); time depth 44.00. One untreated course: about 3 days ([B] cartilage destroyed within days); depth 44.50.
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> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book’s status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

ICD-11 Chapter 16 — Diseases of the genitourinary system

Chronic kidney disease

What it is. The kidneys lose filtering capacity over months or years. It is usually silent until advanced. At the end stage, survival requires dialysis or a transplant.

Measured. Global prevalence is about 9.1 to 13.4 per cent of adults, so roughly 700 to 850 million people have some stage of chronic kidney disease — more than diabetes, and more than any single cancer. The WHO fact sheet, which is titled Kidney disease rather than Chronic kidney disease and printed 20 April 2026, gives an estimated 674 million people worldwide, with no reference year stated anywhere on the page. Both are printed, and the WHO figure carries no year.

GBD 2019 gave about 1.4 million deaths directly, ranking it around twelfth among causes of death globally, with a projection to fifth by 2040 on current trends†, and about 35 to 42 million DALYs†. GBD 2023 Table 1 gives chronic kidney disease 10.3 million YLDs (95 per cent UI 7.53 to 13.3), rank 24. The WHO kidney disease page gives no death figure at all, saying only that kidney disease contributes to millions of preventable deaths each year, and it gives no rank, and no dialysis or transplant access figures. It does give the diagnostic thresholds: eGFR below 60 ml/min/1.73m² on two tests at least 90 days apart, and a urinary albumin-creatinine ratio above 3 mg/mmol (30 mg/g). The World Health Assembly adopted a resolution on kidney health in May 2025.

Impaired kidney function is additionally attributed a further large burden as a risk factor, through cardiovascular disease; total attributable deaths including that pathway are on the order of 3.1 to 3.2 million†. The dual counting is important: chronic kidney disease kills far more through cardiovascular disease than through kidney failure itself.

Only a minority of those needing kidney replacement therapy receive it. Estimates suggest about 2.6 million people on dialysis against a need of 5 to 10 million, with the shortfall overwhelmingly in low- and middle-income countries. Death from untreated kidney failure is largely invisible in statistics.

Prevalence rises steeply after 60, and a substantial share of chronic kidney disease in the very old is age-related eGFR decline of uncertain prognostic significance. Burden is high in South Asia, Latin America, sub-Saharan Africa, and among Indigenous populations in Australia, New Zealand and North America. Chronic kidney disease of unknown aetiology clusters in agricultural communities in Central America, as Mesoamerican nephropathy, and in Sri Lanka and India, affecting young male agricultural workers; heat stress, dehydration, agrochemicals and heavy metals are all implicated and none confirmed.

Where it starts. Diabetes is the leading cause worldwide, at about 30 to 50 per cent of end-stage disease in many countries†. Hypertension is second, and bidirectional with kidney disease. Glomerulonephritis; and polycystic kidney disease, autosomal dominant, from *PKD1* and *PKD2*, at about one in 400 to 1,000†, the commonest inherited kidney disease.

Obstructive uropathy from benign prostatic hyperplasia or stones; recurrent pyelonephritis and reflux nephropathy; HIV; hepatitis B and C; sickle cell disease; multiple myeloma; lupus; vasculitis.

Nephrotoxins: NSAIDs in chronic use, aminoglycosides, calcineurin inhibitors, lithium, cisplatin; aristolochic acid, in Balkan endemic nephropathy and Chinese herb nephropathy, a proven cause and also carcinogenic; and lead, cadmium and mercury.

Low birth weight and reduced nephron endowment is a well-supported developmental origin: fewer nephrons at birth means less reserve, linking maternal nutrition to adult kidney disease. Episodes of acute kidney injury each raise subsequent risk substantially, and the injury-to-chronic transition is now recognised as a major pathway.

eGFR heritability is estimated at about 30 to 55 per cent in family and twin studies, and *APOL1* G1 and G2 risk variants are the strongest known: in people of West African ancestry, two risk alleles confer roughly seven to ten times the risk of hypertension-attributed end-stage kidney disease and about seventeen to 29 times for HIV-associated nephropathy. That largely explains the long-observed excess of kidney failure in African-ancestry populations, previously attributed to hypertension or to social factors alone, and it prompted the removal of the race coefficient from eGFR equations in 2021.

What is not known is the cause of chronic kidney disease of unknown aetiology, a disease affecting hundreds of thousands of young agricultural workers with no established cause, and among the more striking unexplained epidemics in current medicine. Why progression rates vary so much between individuals with identical eGFR and proteinuria is not predictable. Whether age-related eGFR decline in the elderly is disease or physiology is genuinely contested and affects hundreds of millions of diagnoses. And the mechanism linking kidney disease to such extreme cardiovascular risk is only partly explained.

Cure status. Four strata, each with its own label.

Established chronic kidney disease: CONTROLLABLE, not curable. Established nephron loss is irreversible and the aim is to slow progression, which modern therapy does substantially.

Specific reversible causes — obstruction, lupus nephritis, vasculitis, a drug cause, an infection: CURABLE, by relieving obstruction, treating lupus nephritis and vasculitis early, withdrawing the drug, or treating the infection.

End stage after transplantation: CONTROLLABLE. Function is restored, though it requires lifelong immunosuppression, with a graft half-life of about twelve to fifteen years for a deceased donor and longer for a living donor.

End stage on dialysis without transplant access: RELIEF ONLY, and replacement rather than cure.

The important modern fact is that progression can now be slowed enough to change the natural history: combination therapy can roughly halve the rate of eGFR decline, deferring or preventing dialysis for many.

Prevention. Blood pressure control: STRONG, reducing progression and cardiovascular events, with the greatest benefit where there is proteinuria. ACE inhibitors or ARBs in proteinuric disease: STRONG, reducing progression to end-stage disease by about 30 per cent in proteinuric disease. SGLT2 inhibitors: STRONG, the major advance of the last decade. Glycaemic control in diabetes: STRONG. Avoiding NSAIDs and other nephrotoxins, and avoiding aristolochic-acid-containing herbal products: STRONG. Preventing and promptly treating acute kidney injury: MODERATE. Smoking cessation: MODERATE. Weight management: MODERATE. Treating hepatitis B and C and HIV: STRONG for those causes.

Occupational heat and hydration protection in agricultural workers — water, rest, shade: MODERATE, plausible and supported by intervention studies in Central America, and not definitively proven to prevent chronic kidney disease of unknown aetiology. Population salt reduction and sugar-sweetened beverage reduction: MODERATE. Maternal nutrition and avoiding low birth weight: MODERATE, on the developmental pathway.

Treatment. An ACE inhibitor or ARB is foundation therapy for proteinuric disease, reducing proteinuria and slowing progression by about 30 per cent relative risk reduction for doubling of creatinine or end-stage kidney disease in proteinuric disease (RENAAL, IDNT, AASK). Enalapril, lisinopril or losartan: EML yes; off-patent; a few to tens of US dollars a patient-year. Among the highest-value drugs in medicine.

SGLT2 inhibitors are the single largest therapeutic advance in nephrology in decades, and they work with and without diabetes. DAPA-CKD (Heerspink, *NEJM* 2020, 4,304 patients): dapagliflozin reduced the primary composite of a 50 per cent or greater eGFR decline, end-stage kidney disease, and renal or cardiovascular death, with a hazard ratio of 0.61 (95 per cent CI 0.51 to 0.72), about a 39 per cent relative reduction, and an all-cause mortality hazard ratio of 0.69. EMPA-KIDNEY (*NEJM* 2023, 6,609 patients): empagliflozin reduced kidney disease progression or cardiovascular death, hazard ratio 0.72 (0.64 to 0.82). CREDENCE, with canagliflozin in diabetic kidney disease, gave a hazard ratio of 0.70 for the renal composite†. Dapagliflozin and empagliflozin were added to the EML in the 2023 and 2025 cycles†. Dapagliflozin generics are now available in India and several markets; the originator US list price is about

US$6,000 a year, and generics run as low as about US$30 to 120 a patient-year in India†. The price range is the key access fact.

Finerenone, a non-steroidal mineralocorticoid antagonist: FIDELIO-DKD gave a kidney composite hazard ratio of 0.82 (95 per cent CI 0.73 to 0.93) in diabetic kidney disease. On patent; thousands of US dollars a year.

Spironolactone is the cheap steroidal mineralocorticoid antagonist; it reduces proteinuria, with hyperkalaemia risk. Off-patent; an EML-listed medicine under diuretics, section 16, and heart failure, section 12.4; tens of US dollars a year. A low-cost substitute for finerenone with less outcome evidence at a fraction of the cost.

Statins reduce cardiovascular events, the main cause of death, in chronic kidney disease, though not in dialysis patients, where the 4D and AURORA trials were negative. Off-patent, EML-listed, tens of US dollars a year. Blood pressure control to about 120 to 130 systolic, individualised, with all the major agents off-patent and cheap.

Management of complications: anaemia with erythropoiesis-stimulating agents, iron, and now oral HIF prolyl hydroxylase inhibitors. Note that the EML lists erythropoiesis-stimulating agents as the selected medicine for anaemia due to chronic disease, in the complementary list, section 10.1, with epoetin alfa, beta, theta and methoxy polyethylene glycol-epoetin beta listed only as therapeutic equivalents to that class entry rather than as selected medicines in their own right. Metabolic acidosis with sodium bicarbonate, which is cheap and slowed progression in trials; hyperphosphataemia with phosphate binders and dietary phosphate restriction; secondary hyperparathyroidism with vitamin D analogues and cinacalcet; hyperkalaemia with dietary measures and potassium binders.

Sodium bicarbonate is a remarkable value case: a kitchen chemical that slowed progression and improved nutritional status in trials (de Brito-Ashurst, *JASN* 2009), at pennies a year.

Kidney replacement therapy: haemodialysis, peritoneal dialysis, transplantation. Peritoneal dialysis is cheaper to establish, needs no electricity-dependent machine and no water treatment plant, and is well suited to rural and low-income settings; a PD-first policy is used successfully in Hong Kong, Thailand and Mexico. Dialysis costs tens of thousands of US dollars a patient-year depending on country, and transplant is cheaper after the first year. Conservative kidney management is a legitimate, planned pathway for frail elderly patients in whom dialysis offers little survival or quality-of-life benefit.

Simple means. Blood pressure control with cheap off-patent drugs costs a few dollars a year for the largest modifiable effect; measuring blood pressure needs a cuff. Sodium restriction, under 5 to 6 g of salt a day, improves blood pressure and reduces proteinuria measurably. Sodium bicarbonate for metabolic acidosis costs pennies and slows progression. Stopping NSAIDs and nephrotoxic herbal remedies, including aristolochic-acid products, which are a proven cause of kidney failure and urothelial cancer.

Water, rest and shade for agricultural workers in hot climates is the leading candidate intervention for chronic kidney disease of unknown aetiology and requires no technology. Weight loss, physical activity and smoking cessation. Moderate dietary protein, about 0.8 g/kg a day, slows progression modestly; avoid severe restriction, which causes malnutrition. Avoiding sugar-sweetened beverages.

Dipstick urinalysis and a blood pressure cuff are the entire screening apparatus needed to find treatable chronic kidney disease early. Proteinuria dipsticks cost cents and are the highest-yield simple diagnostic in this entry. Peritoneal dialysis is the simple means of kidney replacement: gravity, bags and training, with no machine and no water plant.

The honest limit: end-stage kidney failure cannot be managed by simple means. Without dialysis or a transplant it is fatal, and that is the situation for most of the world’s patients.

Gaps. Chronic kidney disease of unknown aetiology is unexplained and affects a large, young, poor population. Whether age-related eGFR decline constitutes disease is unresolved and affects prevalence figures enormously. Progression prediction in individuals is poor. The true global mortality of untreated kidney failure is unknown because those patients die undiagnosed and uncounted, and GBD almost certainly understates it. The WHO kidney disease fact sheet carries almost no burden data: one prevalence

figure with no year, and no deaths, no rank and no access figures. *APOL1*-targeted therapy is in trials and not established. Dialysis access is grossly inequitable and mostly unmeasured. Generic SGLT2 inhibitor pricing and availability are changing rapidly, so cost figures date quickly. Evidence for most interventions in dialysis patients is weak or negative, despite their extreme risk. Trials under-represent Africa and South Asia.

> **Depth.** Starts in: the glomerulus. Size: 200 µm†; depth +7.63. First complaint: about 10 years († years (diabetes, high blood pressure)); time depth 50.97. One untreated course: no number ([B] months or years).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Acute kidney injury

What it is. Kidney function falls over hours or days. Urine output may drop and waste builds up in the blood. It is usually a complication of something else — infection, blood loss, dehydration or a drug.

Measured. It occurs in about 10 to 15 per cent of all hospital admissions and in over 50 per cent of intensive care admissions in high-income settings. There are about 13.3 million cases a year globally, with about 1.7 million deaths attributed, though these are modelled estimates with wide uncertainty (Mehta, ISN 0by25 initiative).

About 85 per cent of cases occur in low- and middle-income countries, where the causes differ fundamentally: diarrhoeal disease and dehydration, obstetric haemorrhage and sepsis, malaria, leptospirosis, snake envenomation and traditional or herbal remedies, rather than the cardiac surgery, contrast and intensive-care sepsis of high-income settings.

It is not a separate top-level GBD cause, and the burden is distributed and under-captured. In-hospital mortality for severe injury requiring dialysis is about 40 to 50 per cent. Incidence rises steeply with age, but in low-income settings a large share occurs in children, from diarrhoeal illness, and in young women, from obstetric causes.

Where it starts. Classification by mechanism is practically useful, because it determines reversibility.

Pre-renal, about 40 to 70 per cent†: volume depletion from diarrhoea, vomiting, haemorrhage or burns; sepsis-induced vasodilation; heart failure; cirrhosis and hepatorenal syndrome; and NSAIDs with ACE inhibitors or ARBs reducing autoregulation, the triple whammy when a diuretic is added.

Intrinsic: acute tubular necrosis, ischaemic or toxic; acute interstitial nephritis from drugs including PPIs, antibiotics and NSAIDs; glomerulonephritis; rhabdomyolysis from crush injury, exertion, statins or seizures; haemolysis; myeloma; tumour lysis; contrast-associated injury; thrombotic microangiopathy; malaria; leptospirosis; and snakebite, a major cause in South Asia and Africa.

Post-renal, obstruction: prostatic disease, stones, pelvic malignancy, retroperitoneal fibrosis, a blocked catheter. Always to be excluded, because it is immediately reversible.

Nephrotoxic drugs: aminoglycosides, amphotericin, cisplatin, vancomycin, calcineurin inhibitors, NSAIDs, contrast media; and traditional remedies and unregulated analgesics, a major and under-recognised cause in several regions. Risk factors: pre-existing chronic kidney disease, which is the strongest, then age, diabetes, heart failure, cirrhosis, sepsis, major surgery and hypovolaemia. Heritability is not meaningfully established, since this is an acquired event, though genetic susceptibility including *APOL1* modifies risk†.

What is not known is why some patients recover fully and others progress to chronic kidney disease: the injury-to-chronic transition is a major research gap with no predictive test. Contrast-associated injury's true attributable risk has been substantially revised downward and is now contested — much of what was blamed on contrast was confounding. And no drug has ever been shown to treat established acute kidney injury despite decades of trials, which is itself unexplained.

Cure status. Pre-renal, obstructive and drug-induced injury with the cause corrected: CURABLE. That is the key feature. Pre-renal injury reverses within hours to days with volume restoration; obstructive injury reverses on relief of obstruction, sometimes dramatically; and drug-induced injury reverses on withdrawal.

Acute tubular necrosis in a surviving patient: SELF-LIMITING, typically recovering over one to three weeks if the patient survives, because tubular epithelium regenerates.

But recovery is often incomplete. A substantial proportion are left with reduced eGFR, and an episode raises long-term chronic kidney disease risk roughly eight to ten times and end-stage kidney disease risk substantially. So “cured” overstates it for many survivors. And no drug treats established acute kidney injury: supportive care and dialysis are all there is.

Prevention. Prevention is the whole game here, since treatment does not exist.

Maintaining volume status and treating dehydration early: STRONG. In low-income settings, oral rehydration therapy for diarrhoeal illness prevents a large share of the global burden, and is the single highest-impact preventive measure.

Avoiding nephrotoxins, and stopping NSAIDs, ACE inhibitors or ARBs and diuretics during acute illness, the sick day rules: STRONG. Avoiding aminoglycosides where alternatives exist, once-daily rather than divided dosing, and therapeutic drug monitoring: STRONG. Recognising and relieving obstruction promptly: STRONG. Early sepsis treatment: STRONG.

Isotonic crystalloid rather than hydroxyethyl starch: STRONG — starches cause acute kidney injury and increase mortality (6S, CHEST) and have been withdrawn for this indication. Balanced crystalloid rather than saline: MODERATE, with SMART and BaSICS mixed.

For contrast: volume expansion with isotonic saline in high-risk patients: MODERATE. N-acetylcysteine: CONTESTED and refuted — the PRESERVE trial (*NEJM* 2018, 5,177 patients) found no benefit of N-acetylcysteine or of sodium bicarbonate over saline. Another clear negative that reversed practice.

Acute kidney injury alerts and electronic warnings: CONTESTED, with modest or no outcome benefit in trials. Antivenom availability for snakebite: STRONG in endemic areas. Hydration and heat protection for outdoor workers: MODERATE.

Treatment. There is no specific drug. Management is supportive, and the evidence is largely about what not to do.

Identify and treat the cause: infection, haemorrhage, obstruction, drug. Restore circulating volume with isotonic crystalloid, titrated, and avoid both under-resuscitation and fluid overload, since positive fluid balance is independently associated with mortality and routine fluid boluses in established injury cause harm. Sodium chloride 0.9 per cent or Ringer’s lactate: EML yes†; off-patent; about US$0.50 to 3 a litre. Oral rehydration solution: EML yes, at an indicative UNICEF price of US$4.80 per carton of 100 sachets, about US$0.048 a sachet, read 19 October 2026 — the cheapest and most consequential intervention in this entry globally.

Stop nephrotoxic drugs and dose-adjust everything else. Relieve obstruction with a catheter, nephrostomy or stent: a urinary catheter costs little and can reverse established renal failure within hours. Treat hyperkalaemia with calcium gluconate, insulin-dextrose, nebulised salbutamol, sodium bicarbonate, potassium binders, and dialysis if refractory; all except the binders are cheap and EML-listed. Correct acidosis; manage pulmonary oedema with diuretics if responsive, otherwise dialysis or ultrafiltration.

Dialysis when indicated — refractory hyperkalaemia, acidosis, fluid overload, uraemic complications. On timing, earlier is not better: the STARRT-AKI trial (*NEJM* 2020, 3,019 patients) and AKIKI found no mortality benefit from accelerated initiation, and accelerated strategies caused more dialysis dependence and more catheter complications. Wait for an indication. Peritoneal dialysis is effective for acute kidney injury and feasible without electricity, water treatment or machines, validated in Africa and Asia and the basis of the ISN 0by25 approach to preventable deaths.

Do not use: low-dose dopamine; furosemide to convert oliguric to non-oliguric injury; routine mannitol; N-acetylcysteine for contrast. All tested, all without benefit.

Nutrition with adequate energy and protein, avoiding protein restriction. Follow-up: survivors need eGFR and proteinuria monitoring because of the eight- to tenfold chronic kidney disease risk, and this is widely neglected.

Simple means. This is the condition in this book where simple means save the most lives.

Oral rehydration solution — sugar, salt and clean water, at about US$0.048 a sachet on the UNICEF indicative price of October 2026 — prevents the diarrhoeal-dehydration injury that constitutes a large share of the global burden, particularly in children. The highest-yield intervention here by a wide margin.

Early oral fluids in any acute illness, and the sick day rules — stopping NSAIDs, ACE inhibitors or ARBs and diuretics during vomiting or diarrhoea. Free, and they prevent a large share of community-acquired injury.

A urinary catheter reverses obstructive renal failure immediately, at cents. Urine output measurement and a basic creatinine are the entire monitoring requirement. Avoiding nephrotoxic traditional remedies and unregulated analgesics, which are a major preventable cause in several regions. Peritoneal dialysis using locally produced fluid gives kidney replacement without electricity or machines, and the ISN demonstrated feasibility in low-resource settings. Prompt antivenom in snakebite-endemic regions. Water, shade and rest breaks for heat-exposed workers.

And not doing harmful things: no starch solutions, no dopamine, no routine furosemide, no N-acetylcysteine, no early dialysis. Several of these are cost-saving as well as safer.

Gaps. Most of the world's acute kidney injury is neither diagnosed nor counted, so burden figures are modelled and uncertain. The injury-to-chronic transition has no predictive test and no treatment. No drug has ever succeeded for established injury despite many trials, a striking and unexplained failure. Contrast-associated injury's attributable risk is contested and probably much smaller than long believed. Optimal fluid type and volume remain unsettled. Biomarkers — NGAL, TIMP-2/IGFBP7 — have not changed outcomes. Serum creatinine is a poor and lagging marker, and baseline values are often unknown, so the diagnosis itself is unreliable. Follow-up of survivors is poor everywhere.

> **Depth.** Starts in: a kidney tubule cell. Size: 15 µm†; depth +5.28. First complaint: about 21 hours ([B] hours or days); time depth 43.37. One untreated course: about 12 days († recovery 1–3 weeks); depth 45.76.
>
> **Model reading.** Way of ending: let close. Layer: mesh. The book names an early stratum. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Glomerulonephritis

What it is. Inflammation of the kidneys' filtering units. Protein and blood leak into the urine. Some forms settle by themselves; others destroy the kidneys over years.

Measured. IgA nephropathy is the commonest primary glomerulonephritis worldwide, with an incidence of about 2.5 per 100,000 a year and marked geographic variation: highest in East Asia, in Japan, China and Korea, intermediate in Europe, and apparently low in Africa, though this may partly reflect biopsy practice.

Glomerulonephritis causes about 10 to 20 per cent of end-stage kidney disease globally, and a higher share in Asia. GBD 2019 attributed roughly 200,000 to 250,000 deaths a year to glomerulonephritis as a cause of chronic kidney disease.

Post-streptococcal glomerulonephritis remains common in low-income settings and in Indigenous populations and has largely disappeared from high-income countries, with incidence estimated at about 470,000 cases a year globally, mostly in children†. Membranous nephropathy runs at about one per 100,000 a year; focal segmental glomerulosclerosis is rising in incidence and is the commonest cause of nephrotic syndrome in adults in several countries; and minimal change disease accounts for about 80 to 90 per cent of childhood nephrotic syndrome†.

By age: minimal change disease in children; IgA nephropathy in the second to fourth decades; membranous nephropathy and ANCA vasculitis in later life. IgA nephropathy shows male predominance in Europe and North America and is closer to equal in Asia.

Where it starts. IgA nephropathy: galactose-deficient IgA1 with immune complex deposition, with mucosal immunity involvement, and associations with coeliac disease and liver disease. Familial clustering exists and GWAS has found loci in the MHC and complement regions; heritability is appreciable and not precisely quantified.

Post-infectious: group A *Streptococcus*, from skin or throat, a clear and preventable cause; also staphylococcal infection, hepatitis B and C, HIV, syphilis, malaria, schistosomiasis and endocarditis.

Membranous nephropathy: anti-PLA2R antibodies in about 70 to 80 per cent and anti-THSD7A in a few per cent† — a genuine mechanistic breakthrough that converted an idiopathic disease into an identifiable autoimmune one. Secondary causes: hepatitis B, malignancy, lupus, NSAIDs, gold, penicillamine.

Focal segmental glomerulosclerosis: *APOL1* risk variants, strong in African ancestry; obesity-related disease; reflux and reduced nephron mass; HIV; heroin; pamidronate; and genetic podocyte mutations — *NPHS1*, *NPHS2*, *INF2*, *ACTN4* — in familial and steroid-resistant cases.

ANCA-associated vasculitis: anti-MPO and anti-PR3 antibodies, with silica exposure, some drugs including hydralazine and propylthiouracil, and HLA associations. Anti-GBM, Goodpasture, disease: HLA-DRB1*15:01 strongly associated, with hydrocarbon exposure and smoking as co-factors. Lupus nephritis: female predominance, ancestry effects, a strong genetic component.

What is not known is what triggers the autoimmunity in most cases — why anti-PLA2R antibodies appear, why galactose-deficient IgA1 is produced, what initiates ANCA. Progression is not well predicted at the individual level. Whether the apparent low incidence in Africa is real or an artefact of absent biopsy services is unresolved and important. And the relative contribution of the complement pathways is being actively revised.

Cure status. This varies by type more than almost any other entry here, so each stratum is named.

Post-streptococcal glomerulonephritis: SELF-LIMITING. It recovers almost completely in children, over 95 per cent†, with supportive care only.

Minimal change disease: CONTROLLABLE. Over 90 per cent of children† respond to corticosteroids, relapses are common, so the state is held rather than removed, and long-term kidney function is usually preserved.

Membranous nephropathy: SELF-LIMITING in about 30 per cent†, through spontaneous remission, with the remainder CONTROLLABLE by immunosuppression — rituximab induces remission in about 60 per cent.

IgA nephropathy: CONTROLLABLE. Progression is slowed, not cured, and about 20 to 40 per cent† reach end-stage disease over twenty years.

ANCA vasculitis and lupus nephritis: CONTROLLABLE, often with sustained remission. ANCA vasculitis went from about 80 per cent one-year mortality untreated to over 80 per cent five-year survival† with immunosuppression — one of the great therapeutic transformations in medicine. Relapse is common.

Anti-GBM disease: CURABLE if treated urgently, with plasma exchange plus immunosuppression, and irreversible if the patient is dialysis-dependent at presentation.

Focal segmental glomerulosclerosis: CONTROLLABLE in immunosuppression-responsive disease, RELIEF ONLY in genetic forms, which do not respond to immunosuppression; recurrence after transplant is common in circulating-factor disease.

Established sclerosis in any form is irreversible, and early treatment is decisive throughout.

Prevention. Treating streptococcal skin and throat infection, scabies control, and improved housing, hygiene and skin health: STRONG for post-streptococcal disease, which was essentially eliminated in high-income countries by these means. Hepatitis B vaccination, hepatitis B and C treatment, and HIV

treatment: STRONG for those secondary forms, with HIV-associated nephropathy responding markedly to antiretroviral therapy.

Avoiding NSAIDs, gold and penicillamine, and silica exposure control: MODERATE. Blood pressure and proteinuria control to prevent progression: STRONG, as secondary prevention. Early biopsy and diagnosis: MODERATE for preventing irreversible loss, since the main preventable harm in high-income settings is diagnostic delay.

No primary prevention exists for IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis or ANCA vasculitis: absent. Tonsillectomy for IgA nephropathy: CONTESTED — practised in Japan, not supported elsewhere.

Treatment. Supportive treatment, for all proteinuric forms. An ACE inhibitor or ARB reduces proteinuria and slows progression; off-patent, EML-listed, a few to tens of US dollars a year. Foundation therapy. SGLT2 inhibitors are now established in proteinuric chronic kidney disease including IgA nephropathy, with DAPA-CKD including IgA patients and giving an overall hazard ratio of 0.61 for the kidney composite; generics about US$30 to 120 a year in India†. Blood pressure control, salt restriction, statins.

Disease-specific treatment. Corticosteroids are first line for minimal change disease, with over 90 per cent response in children†, and part of regimens for lupus nephritis, ANCA vasculitis and some IgA nephropathy. Prednisolone: EML yes; off-patent; a few to tens of US dollars a year. A cheap drug that saves kidneys and lives.

Cyclophosphamide for induction in severe lupus nephritis, ANCA vasculitis and anti-GBM disease: EML yes, as a cytotoxic; off-patent; tens to hundreds of US dollars a course. Highly effective, with gonadal toxicity and malignancy risk.

Rituximab for membranous nephropathy — the MENTOR trial found it superior to cyclosporine for sustained remission, about 60 against 20 per cent at 24 months — and non-inferior to cyclophosphamide for ANCA vasculitis induction (RAVE, *NEJM* 2010) and better for relapsing disease; increasingly used in lupus nephritis and minimal change disease. Rituximab is an EML-listed medicine, under medicines for multiple sclerosis, section 5.1.2 complementary, and targeted therapies, section 8.2.2 complementary; the recorded indications are multiple sclerosis and four lymphoid malignancies, and glomerulonephritis is not among them. Biosimilars are widely available; the originator was tens of thousands of US dollars a course, and biosimilars run thousands of US dollars and lower in India. The biosimilar price fall has made this broadly accessible.

Mycophenolate mofetil for lupus nephritis induction and maintenance, at least as effective as cyclophosphamide with less gonadal toxicity, and also used in IgA vasculitis; off-patent; hundreds of US dollars a year; EML yes. Calcineurin inhibitors, tacrolimus and cyclosporine, for focal segmental glomerulosclerosis, membranous nephropathy and lupus, with voclosporin now approved for lupus nephritis; tacrolimus off-patent, hundreds to thousands of US dollars a year.

Targeted newer agents: nefecon, a targeted-release budesonide, and sparsentan, a dual endothelin and angiotensin antagonist, for IgA nephropathy, both reducing proteinuria and slowing eGFR decline, both on patent and very expensive, with sparsentan at hundreds of thousands of US dollars a year list. Avacopan for ANCA vasculitis, as a steroid-sparing agent; belimumab and voclosporin for lupus nephritis. All patented and costly. Complement inhibitors, iptacopan and ravulizumab, are in trials or approval for C3 glomerulopathy and IgA nephropathy.

Plasma exchange for anti-GBM disease, where it is essential, and in selected severe ANCA vasculitis — though the PEXIVAS trial (*NEJM* 2020) found no overall benefit of plasma exchange in severe ANCA vasculitis, narrowing its indications substantially. Antibiotics for the underlying infection in post-infectious and endocarditis-related disease, and antivirals for hepatitis-related disease. Kidney replacement therapy at end stage, and transplantation with awareness of recurrence risk, especially in focal segmental glomerulosclerosis and IgA nephropathy.

Simple means. Treating skin and throat infections, and treating scabies, prevents post-streptococcal glomerulonephritis. Benzathine benzylpenicillin is an EML-listed medicine in the Access group, section 6.2.1, with syphilis as its first-choice listed indication, and permethrin is an EML-listed medicine in section

13.5, scabicides and pediculicides, with scabies among its three indications; ivermectin is listed in section 6.6, medicines for ectoparasitic infections. All are cheap: the indicative UNICEF price for benzathine benzylpenicillin 2.4 MIU is US$29.49 per box of 50 vials, about US$0.59 a vial, October 2026, with the single-vial-with-solvent pack at US$3.01, five times as much per dose. This is how high-income countries eliminated the disease, and it needs no nephrology service at all.

Soap, water, housing and reduced crowding are the structural version of the same thing. Salt restriction reduces proteinuria and blood pressure and improves the response to ACE inhibitors measurably. Dipstick urinalysis costs cents and is the only way most glomerulonephritis is found early; screening urinalysis in schoolchildren is credited with Japan's early detection of IgA nephropathy. Blood pressure measurement and cheap antihypertensives. Oedema management by salt and fluid restriction, elevation and careful diuretics. Prednisolone costs pennies and is curative in most childhood minimal change disease. Pneumococcal vaccination and infection vigilance in nephrotic patients, who are functionally immunosuppressed and at risk of peritonitis and sepsis.

The honest limit: diagnosis usually requires a kidney biopsy and histopathology, which is unavailable across much of the world. That absence, and not the cost of the drugs, is the binding constraint, since several of the effective drugs — prednisolone, cyclophosphamide — are extremely cheap.

Gaps. Biopsy and histopathology access is the dominant global inequity, so incidence data from Africa and much of Asia are unreliable and probably understate disease. Progression prediction is poor. Most immunosuppression regimens rest on small or old trials, and head-to-head comparisons are scarce. The new targeted agents have strong surrogate data on proteinuria and limited hard-outcome and long-term safety data, at very high prices, against cheap drugs with decades of use. PEXIVAS reversed plasma exchange practice and similar reversals may follow. Whether to screen urine at population level is unresolved outside Japan. Complement-targeted therapy is advancing faster than the evidence base for positioning it.

> **Depth.** Starts in: the glomerulus. Size: 200 µm†; depth +7.63. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number ([B] some clear by themselves, others last years).
>
> **Model reading.** Way of ending: restore proportion. Layer: reading. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Diabetic nephropathy

What it is. Long-standing diabetes damages the kidney's small blood vessels and filters. Protein appears in the urine and filtering slowly fails. It is the leading cause of kidney failure worldwide.

Measured. It develops in about 30 to 40 per cent of people with type 1 diabetes and about 20 to 40 per cent of those with type 2. It is the leading single cause of end-stage kidney disease globally, at about 30 to 50 per cent of incident dialysis and transplant patients in most countries, and higher in Mexico, Malaysia, Singapore and the Gulf states, above 50 to 60 per cent. GBD 2019 gave chronic kidney disease due to diabetes, types 1 and 2 combined, roughly 400,000 to 460,000 deaths a year†.

The denominator is contested, and the discrepancy matters because attributable burden is computed on it. The IDF Diabetes Atlas, eleventh edition, gives 589 million adults aged 20 to 79 with diabetes; this file's source dates that figure to 2024 and another chapter of this book dates the same figure and the same edition to 2025, in three places†. Same figure, same edition, two different years; both stand, unresolved. On the denominator itself, the IDF figure of 589 million adults aged 20 to 79 and the WHO figure of 830 million at all ages, 14 per cent of adults aged 18 and over†, are substantially different global figures, and two chapters of this book compute attributable burden on these incompatible denominators. Both stand, and the discrepancy is named rather than smoothed.

Age pattern reflects diabetes duration: typically more than ten years after onset in type 1, and often present at diagnosis in type 2 because of delayed diagnosis. Burden is concentrated in South and East Asia, the Middle East, Latin America, the Pacific Islands and Indigenous populations, where diabetes prevalence and genetic susceptibility combine.

Where it starts. Hyperglycaemia duration and severity is necessary and dose-dependent, and is the basis of the glycaemic control evidence from DCCT/EDIC and UKPDS. Hypertension is strongly synergistic, and the combination accelerates loss markedly.

Genetic susceptibility shows clear familial clustering independent of glycaemia, with heritability of diabetic nephropathy estimated at about 30 to 50 per cent and sibling risk substantially raised. *APOL1* variants raise risk in African-ancestry populations, and GWAS loci — *COL4A3*, *GLRA3* and others — have small effects. Ancestry: higher risk in African, South Asian, Hispanic, Pacific Islander, Indigenous American and Australian Aboriginal populations, beyond what glycaemia and access explain. Smoking; obesity; dyslipidaemia; male sex in type 1; puberty, which accelerates onset in type 1; and episodes of acute kidney injury.

What is not known is why 60 to 70 per cent of people with long-standing diabetes never develop nephropathy despite comparable glycaemic exposure, which is the strongest argument for genetic determination, though the genetics found so far explain little of it. Non-albuminuric diabetic kidney disease — progressive eGFR loss without proteinuria — is increasingly recognised, especially in type 2 diabetes and in women, does not fit the classical albuminuria-first model, has an unclear mechanism, and is missed by albuminuria-based screening. Why some patients regress from microalbuminuria spontaneously is unexplained.

Cure status. Three strata.

Diabetic kidney disease, medically managed: CONTROLLABLE, and now substantially more so than a decade ago. Established nephropathy with declining eGFR is not curable, but progression can be slowed enough to change outcomes substantially: combined ACE inhibitor or ARB, SGLT2 inhibitor and finerenone therapy roughly halves the rate of eGFR decline compared with historical controls.

Early microalbuminuria with tight glycaemic and blood pressure control: CURABLE, with regression occurring in a meaningful proportion, about 30 per cent over six years in the type 1 Joslin cohort, so early disease is partly reversible.

End-stage disease after transplantation: CONTROLLABLE, as for the transplant stratum of chronic kidney disease, since lifelong immunosuppression holds the state. Simultaneous pancreas-kidney transplantation in type 1 diabetes can replace both the diabetes and the kidney failure, and is the nearest thing to a complete cure available. Bariatric surgery in type 2 diabetes with obesity can induce diabetes remission and improve albuminuria, which is a partial reversal of the cause.

Prevention. Glycaemic control: STRONG. DCCT/EDIC in type 1 found intensive control reduced microalbuminuria by about 39 per cent and clinical albuminuria by about 54 per cent, with benefits persisting decades later, which is metabolic memory; UKPDS in type 2 gave about a 25 per cent reduction in microvascular endpoints. Blood pressure control: STRONG.

ACE inhibitors or ARBs once albuminuria is present: STRONG, reducing progression by about 30 per cent in proteinuric disease (RENAAL, IDNT). They do not prevent nephropathy in normoalbuminuric, normotensive patients, so they are not primary prevention.

SGLT2 inhibitors: STRONG — they both prevent and treat. Smoking cessation: MODERATE. Annual albuminuria and eGFR screening: STRONG — cheap, and the entry point to all the above. A urine albumin-creatinine ratio costs a few dollars and a dipstick costs cents. Weight management, GLP-1 agonists and bariatric surgery: MODERATE. Avoiding NSAIDs and nephrotoxins, and preventing acute kidney injury: MODERATE. Diabetes prevention itself, through lifestyle programmes and metformin, is the upstream measure: STRONG for preventing diabetes, hence nephropathy.

Treatment. The modern regimen is layered, and most of it is cheap or becoming cheap.

An ACE inhibitor or ARB, titrated to the maximum tolerated dose, gives about a 30 per cent reduction in progression in proteinuric disease. Off-patent, EML-listed, a few to tens of US dollars a year.

SGLT2 inhibitors are now foundational. CREDENCE (canagliflozin, *NEJM* 2019, 4,401 patients with diabetic nephropathy) gave a renal composite hazard ratio of 0.70 (95 per cent CI 0.59 to 0.82) and end-stage kidney disease 0.68. DAPA-CKD gave an overall kidney composite of 0.61 (0.51 to 0.72). EMPA-

KIDNEY gave 0.72 (0.64 to 0.82). They were added to the EML in recent cycles. Generic dapagliflozin runs at about US$30 to 120 a year in India against an originator US list price of about US$6,000 a year†.

Finerenone: FIDELIO-DKD (*NEJM* 2020, 5,734 patients) gave a kidney composite hazard ratio of 0.82 (95 per cent CI 0.73 to 0.93), and FIGARO-DKD showed cardiovascular benefit. On patent; thousands of US dollars a year.

GLP-1 receptor agonists: the FLOW trial with semaglutide in 2024 gave a kidney composite hazard ratio of 0.76 (95 per cent CI 0.66 to 0.88). On patent and expensive, at about US$9,000 to 16,000 a year US list; semaglutide was recently EML-listed for diabetes†.

Glycaemic control: metformin, continued to an eGFR of 30, insulin, and the agents above. Metformin is an EML-listed medicine, section 18.5.2, hypoglycaemic agents, for type 2 diabetes in adolescents and adults, first added in 1997; off-patent; a few to tens of US dollars a year — still the cheapest and among the most valuable. Insulin human, short-acting and intermediate-acting, is EML-listed as a selected medicine, each for type 1 and type 2 diabetes; the insulin analogues are listed as class entries, long-acting and rapid-acting, with the named analogues — degludec, detemir, glargine, aspart, glulisine, lispro — listed only as therapeutic equivalents to those class entries rather than as selected medicines.

Statins for the dominant cardiovascular risk; off-patent, tens of US dollars a year. Blood pressure control with cheap off-patent agents. Management of the chronic kidney disease complications — anaemia, acidosis with sodium bicarbonate, phosphate, potassium — as in the chronic kidney disease entry. Dialysis and transplantation, and simultaneous pancreas-kidney transplant in selected type 1 patients.

Avoid: dual ACE inhibitor plus ARB blockade, where ONTARGET and ALTITUDE showed more harm and no benefit; and aliskiren with an ACE inhibitor or ARB. Clear negative evidence.

Simple means. Glycaemic control through diet, weight loss and physical activity is the upstream intervention, with a trial-proven effect on albuminuria and no supply chain for the behavioural part. In type 2 diabetes, substantial weight loss can induce remission — the DiRECT trial gave about 46 per cent remission at twelve months with about 10 to 15 kg of loss† — which addresses the cause.

Blood pressure control, and salt restriction under 5 g a day, reduces albuminuria and augments the ACE inhibitor effect measurably. A urine dipstick or albumin-creatinine ratio annually costs cents to a few dollars and is the gateway to everything effective: the highest-value simple diagnostic here. Smoking cessation. Moderate protein intake, about 0.8 g/kg a day, avoiding severe restriction. Foot care, eye screening and vaccination — the rest of the diabetes package, since these patients die of cardiovascular disease and lose limbs and sight.

Metformin, enalapril and a thiazide: three off-patent tablets costing perhaps tens of US dollars a year together, delivering most of the achievable benefit. That is the practical core for low-resource settings, with SGLT2 inhibitors joining it as generics spread.

The honest limit: insulin is essential in type 1 diabetes and cannot be replaced by simple means, and end-stage kidney failure requires dialysis or a transplant.

Gaps. Why most people with diabetes never develop nephropathy is unexplained. Non-albuminuric diabetic kidney disease is increasingly common, poorly understood, and missed by current screening. Albuminuria is an imperfect surrogate and regression does not always predict hard outcomes. The incremental benefit and cost-effectiveness of stacking four expensive drug classes — ACE inhibitor or ARB, SGLT2 inhibitor, finerenone, GLP-1 agonist — has not been tested in a single factorial trial; the combination is inferred. Generic pricing is changing rapidly, so cost figures date quickly. Trials under-represent African and South Asian populations despite their higher risk, and *APOL1*-stratified treatment is not established. Screening coverage is poor even in high-income systems. And the two diabetes denominators used in this book, IDF 589 million adults aged 20 to 79 and WHO 830 million at all ages, are incompatible, with the year of the IDF edition also disputed between chapters.

> **Depth.** Starts in: the glomerulus. Size: 200 µm†; depth +7.63. First complaint: about 15 years († about 15 years of diabetes); time depth 51.34. One untreated course: no number ([B] slow failure).

> **Model reading.** Way of ending: restore proportion. Layer: mesh. The book splits this entry by moment, early and late. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Kidney stones

What it is. Minerals crystallise in the urine and form stones. Passing one causes severe pain. Most pass by themselves; some block the kidney and need removing.

Measured. Lifetime prevalence is about 10 to 15 per cent in men and about 6 to 10 per cent in women in high-income countries, and rising almost everywhere measured. United States prevalence rose from about 3.8 per cent in 1976 to 1980, to about 8.8 per cent in 2007 to 2010, to about 11 per cent in recent NHANES data. GBD 2019 gave urolithiasis roughly 12,000 to 15,000 deaths and about 1.5 to 2 million DALYs globally†.

Recurrence is the defining feature: about 50 per cent within five to ten years and about 60 to 80 per cent lifetime without preventive treatment†. Peak age is 30 to 60, with a male to female ratio of about 2:1, though the gap has narrowed as female incidence rose.

Geography follows the stone belt — hot, arid regions and hot seasons: the Middle East, South Asia, the southeastern United States, Southeast Asia. Climate and dehydration are the clearest geographic determinants, and projected warming is expected to increase incidence. Bladder stones in children remain common in parts of South and Southeast Asia and the Middle East, associated with low-protein cereal-based diets.

Where it starts. Stone type matters because prevention differs. Calcium oxalate accounts for about 70 to 80 per cent, calcium phosphate about 10 to 15 per cent, uric acid about 5 to 10 per cent, struvite or infection stones about 5 to 10 per cent, cystine about 1 per cent and genetic, plus drug-induced stones†.

Low urine volume and dehydration is the single most important modifiable factor, and the mechanism behind the geographic and occupational patterns. High sodium intake raises urinary calcium; high animal protein raises acid load, uric acid and calcium and lowers citrate; high oxalate foods — spinach, rhubarb, nuts, tea — matter in susceptible people; and low dietary calcium is, counter-intuitively, a risk factor, because dietary calcium binds oxalate in the gut. Low citrate; sucrose and fructose; low potassium.

Obesity and metabolic syndrome, dose-dependently; diabetes raises uric acid stone risk, and insulin resistance lowers urinary pH. Medical conditions: primary hyperparathyroidism, renal tubular acidosis type 1, primary hyperoxaluria which is genetic, cystinuria which is genetic and autosomal recessive, sarcoidosis, gout, inflammatory bowel disease and short bowel giving enteric hyperoxaluria, which is a potent cause, Roux-en-Y gastric bypass, recurrent urinary tract infection with urease-producing organisms such as *Proteus* for struvite stones, medullary sponge kidney, and anatomical obstruction.

Drugs: topiramate, acetazolamide, loop diuretics, excess calcium and vitamin D supplements, indinavir, sulfadiazine, ceftriaxone in children, and vitamin C in high doses.

Twin studies estimate heritability at about 46 to 56 per cent for kidney stone disease, with strong familial clustering and a first-degree relative conferring about 2.5 times the risk. Monogenic causes — cystinuria, primary hyperoxaluria, Dent disease — account for a small share and are important to identify. Over thirty GWAS loci have been found, including *CLDN14*, *SLC34A1* and *ALPL*.

What is not known is why most people with hypercalciuria or hyperoxaluria never form stones. The step from supersaturation to a clinical stone involves nucleation, retention and Randall’s plaques — interstitial apatite deposits at the papillary tip — whose formation is incompletely understood. Why recurrence rates vary so much is not predictable. And the thiazide dose-response question was unsettled until recently and remains partly open.

Cure status. Four strata.

Most individual stones: SELF-LIMITING. Spontaneous passage rates are about 95 per cent for stones under 4 mm, about 50 per cent for 5 to 7 mm, and about 20 per cent or less above 8 mm.

Per episode: CURABLE. Stones can be removed completely by lithotripsy, ureteroscopy or percutaneous nephrolithotomy, achieving stone-free status.

The disease: CONTROLLABLE, not curable. The metabolic tendency persists, hence 50 per cent recurrence in five to ten years untreated. With medical prophylaxis recurrence falls substantially, with thiazides roughly halving it, so it is well controlled rather than cured.

At the level of cause, in specific instances: CURABLE. Parathyroidectomy for primary hyperparathyroidism cures that stone diathesis; treating the infection and removing all fragments cures struvite stones; and lumasiran and nedosiran now effectively treat primary hyperoxaluria type 1, which is a genuine and recent transformation.

Prevention. This is one of the strongest simple-prevention stories in the book.

Increased fluid intake: STRONG. The Borghi randomised trial (*Journal of Urology* 1996, 199 first-time stone formers over five years) compared high water intake, producing a urine volume above 2 L a day, with no intervention: recurrence was 12 per cent against 27 per cent, and time to recurrence was substantially longer. Roughly a 50 per cent relative reduction achieved with water alone. The target is over 2.5 L of fluid a day to produce over 2 to 2.5 L of urine a day.

Normal dietary calcium with reduced sodium and animal protein: STRONG. Borghi (*NEJM* 2002, 120 men with hypercalciuria over five years) compared a normal-calcium, low-sodium, low-animal-protein diet with a traditional low-calcium diet: recurrence was 20 per cent against 38 per cent, relative risk 0.49 (95 per cent CI 0.24 to 0.98). Low-calcium diets are harmful and increase recurrence — a clear, important reversal of old advice that is still given.

Thiazide diuretics for recurrent calcium stones: STRONG, with a caveat. Older trials showed about a 50 per cent recurrence reduction. The NOSTONE trial (*NEJM* 2023, 416 patients, hydrochlorothiazide at 12.5, 25 and 50 mg against placebo over about three years) found no significant dose-dependent reduction in the primary composite recurrence endpoint. That is a genuine and unresolved conflict with the earlier literature, and both are printed. Guidelines currently retain thiazides, often at higher doses, with chlorthalidone or indapamide rather than low-dose hydrochlorothiazide.

Potassium citrate for calcium and uric acid stones: MODERATE — it raises urinary citrate and pH and reduces recurrence in trials. Allopurinol for uric acid and hyperuricosuric calcium oxalate stones: MODERATE. Weight management and reducing sugar-sweetened beverages: MODERATE. Treating hyperparathyroidism and renal tubular acidosis: STRONG for those causes. A 24-hour urine metabolic evaluation to target prophylaxis: MODERATE — logical and guideline-endorsed, though trial evidence that it improves outcomes over empirical advice is limited.

Treatment. For acute colic, NSAIDs are first-line analgesia and superior to opioids for renal colic, with better pain relief, less vomiting and less need for rescue analgesia: diclofenac, ketorolac, indomethacin. Diclofenac EML yes; off-patent; a few US dollars a course. Avoid in renal impairment. Paracetamol is comparable to NSAIDs in some trials and a safe alternative. Opioids are second line, for NSAID contraindication. Antispasmodics give little benefit.

Medical expulsive therapy with tamsulosin is largely refuted for small stones: the SUSPEND trial (*Lancet* 2015, 1,167 patients) found no benefit of tamsulosin or nifedipine on spontaneous passage. A modest benefit may persist for larger, 5 to 10 mm, distal ureteric stones in meta-analysis, and routine use is not supported. Tamsulosin off-patent, tens of US dollars a year. Hydration and watchful waiting for stones likely to pass.

Urgent decompression with a ureteric stent or percutaneous nephrostomy, plus antibiotics, for an obstructed infected kidney: a urological emergency with high mortality if delayed. That is the one time-critical scenario.

For stone removal: extracorporeal shock wave lithotripsy is non-invasive, best for stones under 10 to 20 mm in the kidney or proximal ureter, with stone-free rates of about 50 to 80 per cent depending on size,

location and density†. Ureteroscopy with laser lithotripsy gives higher stone-free rates than lithotripsy and requires anaesthesia and endoscopy; it is now the commonest intervention in many countries. Percutaneous nephrolithotomy is for large stones above 20 mm and for staghorn stones, with the highest stone-free rate and the most invasiveness. Complete clearance is essential for struvite and infection stones, with antibiotics, because residual fragments regrow.

For prophylaxis: fluid and dietary modification. A thiazide — chlorthalidone, indapamide or hydrochlorothiazide — off-patent, EML-listed, a few to tens of US dollars a year, with the NOSTONE caveat. Potassium citrate, off-patent, hundreds of US dollars a year, with sodium bicarbonate or lemon juice as cheaper alkalinising substitutes. Allopurinol: an EML-listed medicine under medicines used to treat gout, section 29.1, and as a supportive medicine for tumour lysis syndrome, section 8.2.5 complementary; off-patent; tens of US dollars a year. Pyridoxine for the responsive subset of primary hyperoxaluria type 1, with lumasiran and nedosiran, RNA interference agents, transformative and extremely expensive at hundreds of thousands of US dollars or more a year. Tiopronin or penicillamine with high fluid intake and alkalinisation for cystinuria. Parathyroidectomy for primary hyperparathyroidism.

Simple means. Kidney stones are the clearest case in this book where water is the treatment.

Water: over 2.5 L a day of intake to produce over 2 L a day of urine halves recurrence, 12 against 27 per cent over five years in Borghi 1996†. Free where clean water exists. The highest benefit-to-cost ratio of any intervention in this entry.

Normal dietary calcium, not low, with reduced salt and animal protein: recurrence 20 against 38 per cent, relative risk 0.49 (Borghi 2002)†. A dietary change, not a product. And it corrects a harmful piece of traditional advice.

Lemon or lime juice in water raises urinary citrate and is cheap and plausible, though the trial evidence is weaker than for potassium citrate. Reducing sugar-sweetened drinks, and moderating oxalate-rich foods only in documented hyperoxaluria, taking them with calcium-containing food, which binds oxalate in the gut. Weight management and physical activity. NSAIDs for colic, cheaper and better than opioids. Occupational hydration for outdoor and hot-environment workers, who have markedly raised risk: water, shade and rest breaks. Straining urine to catch the stone for analysis needs a sieve, and it determines prevention strategy. And not using tamsulosin routinely: an evidence-based omission on SUSPEND.

The honest limit: a large obstructing stone, and especially an obstructed infected kidney, requires urological intervention. Water does not remove a staghorn calculus.

Gaps. NOSTONE contradicts decades of thiazide trials and the conflict is unresolved. It is the most consequential current disagreement in stone prevention, since thiazides are the main drug prophylaxis, and both results are printed. Whether 24-hour urine-guided therapy improves outcomes over empirical advice has not been properly trialled. The mechanism of Randall's plaque formation is unclear. Why most metabolic abnormalities do not produce stones is unknown. Medical expulsive therapy evidence remains contested for intermediate-sized stones. Optimal imaging follow-up intervals and radiation exposure trade-offs are unsettled. Burden and composition data from Africa and much of Asia are sparse, and paediatric bladder stone epidemiology is poorly documented despite being a significant regional problem. Climate-related incidence projections are models, not observations.

> **Depth.** Starts in: a crystal or stone. Size: 5 mm†; depth +10.56. First complaint: about 12 months († months of formation); time depth 48.87. One untreated course: about 14 days ([B] most pass by themselves; † 1–4 weeks); depth 45.90.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Urinary tract infection

What it is. Bacteria, usually from the bowel, colonise the bladder and cause burning and frequent urination. If they reach the kidney, which is pyelonephritis, it causes fever and can be serious.

Measured. There are about 400 million cases a year globally, making this one of the commonest bacterial infections in humans. About 50 to 60 per cent of women experience at least one urinary tract infection in their lifetime, and about 10 per cent of women report one each year. GBD 2019 gave urinary tract infections roughly 200,000 to 240,000 deaths globally, mostly from urosepsis in the elderly, with several million DALYs.

Recurrence: about 25 to 30 per cent of women have a recurrence within six months of a first episode. The female to male ratio is about 8 to 30:1 in young adults, among the largest sex ratios of any common disease, reflecting urethral length and proximity to the anus; the ratio narrows in old age as prostatic obstruction and catheterisation rise.

Catheter-associated infection is the commonest healthcare-associated infection worldwide, with a risk of about 3 to 7 per cent per catheter-day†. On resistance: *E. coli* resistance to trimethoprim and ciprofloxacin exceeds 20 to 30 per cent in many regions, and ESBL-producing organisms are now common in community isolates in South Asia, the Middle East and parts of Africa, which is changing empirical treatment everywhere.

Where it starts. Female anatomy — a short urethra and proximity to the rectum — is the dominant factor. Sexual intercourse is the strongest behavioural risk in young women, dose-dependently with frequency, and spermicide use, including spermicide-coated condoms and diaphragms, raises risk substantially.

Previous infection; postmenopausal oestrogen deficiency, with vaginal atrophy, loss of lactobacilli and raised pH; and pregnancy, where asymptomatic bacteriuria also matters. Urinary stasis and obstruction: benign prostatic hyperplasia, stones, strictures, neurogenic bladder, incomplete emptying, prolapse. Catheterisation and instrumentation, the main healthcare-associated cause, with risk rising with duration. Diabetes; immunosuppression; and SGLT2 inhibitors, through glycosuria, which clearly increase genital mycotic infection and urinary tract infection only modestly. Vesicoureteric reflux and anatomical abnormalities in children.

Non-secretor status, in the Lewis blood group, and P1 blood group; ABO and secretor phenotype affects uroepithelial receptor expression. Family history: a mother or sister with recurrent infection raises risk, suggesting genetic susceptibility in innate immunity, with TLR4 and CXCR1 variants implicated. Heritability is not well quantified.

What is not known is why some women suffer repeated infections with no identifiable anatomical or behavioural cause; innate immune variation and uroepithelial receptor differences are implicated and not clinically measurable. The role of intracellular bacterial reservoirs in the bladder wall in recurrence is demonstrated in animals and uncertain in humans. The clinical significance of the urinary microbiome — the bladder is not sterile, a recent revision — is unresolved. Whether asymptomatic bacteriuria in the elderly is ever worth treating outside pregnancy and some urological procedures is settled in the negative and still widely ignored in practice.

Cure status. Four strata.

The individual episode, treated: CURABLE, with a short antibiotic course curing the great majority, 80 to 95 per cent clinical cure†.

Uncomplicated cystitis, untreated: SELF-LIMITING in about 25 to 50 per cent within a week. In otherwise healthy women, about 25 to 50 per cent resolve without antibiotics within a week, and randomised trials of NSAIDs against antibiotics confirm that many recover without antimicrobials, though more slowly and with a higher rate of progression to pyelonephritis, about 2 to 5 per cent against under 1 per cent. So delayed prescribing is a legitimate option in uncomplicated cases, with the trade-off stated.

Recurrent infection: CONTROLLABLE. Prophylaxis reduces but does not abolish recurrence.

A correctable cause — obstruction, a catheter, a stone, atrophy: CURABLE, by relieving obstruction, removing the catheter, removing the stone, or treating atrophy with vaginal oestrogen.

Prevention. Vaginal oestrogen in postmenopausal women with recurrent infection: STRONG. It reduces recurrence substantially, relative risk about 0.25 to 0.6 in trials and Cochrane-supported, with low systemic absorption. Off-patent; tens to hundreds of US dollars a year. Markedly under-used.

Increased water intake: MODERATE. A randomised trial (Hooton, *JAMA Internal Medicine* 2018, 140 premenopausal women with recurrent infection) found drinking an additional 1.5 L of water daily reduced episodes from 3.2 to 1.7 a year — roughly halving recurrence with water alone.

Continuous low-dose antibiotic prophylaxis: STRONG for efficacy, relative risk about 0.2 to 0.4†, with resistance and adverse-effect costs; reserved for frequent recurrence, and the benefit ceases on stopping. Post-coital single-dose antibiotic prophylaxis: STRONG where recurrence is intercourse-related, and it uses less total antibiotic.

Methenamine hippurate: MODERATE. The ALTAR trial (*BMJ* 2022, 240 women) found methenamine non-inferior to daily antibiotic prophylaxis for recurrent infection, with less antibiotic use. A non-antibiotic option, off-patent, and an important finding for stewardship.

Avoiding spermicides: MODERATE. D-mannose: CONTESTED — earlier small positive trials were not confirmed by a larger 2024 randomised trial, MERIT, which found no benefit. Cranberry products: WEAK and CONTESTED — Cochrane's updated review suggests a modest reduction in recurrence in some populations, relative risk about 0.7, with high heterogeneity and poor product standardisation†. Probiotics, vaginal lactobacilli: WEAK. Behavioural measures — post-coital voiding, wiping direction, avoiding tight clothing, not delaying micturition: WEAK, plausible and harmless, with thin trial evidence, and some of this advice persists without support.

Screening and treating asymptomatic bacteriuria in pregnancy: STRONG, reducing pyelonephritis and preterm birth. Not indicated in non-pregnant adults or the elderly: STRONG evidence against, and treating it causes harm.

Catheter avoidance, early removal, aseptic insertion and closed drainage: STRONG — the single most effective healthcare-associated prevention. Daily review of catheter need is a free intervention with a large measured effect.

Treatment. Nitrofurantoin 100 mg twice daily for five days is first-line for uncomplicated cystitis, with excellent cure rates, low resistance even now, and minimal collateral damage to the microbiome. Avoid if eGFR is below 30 to 45 and in late pregnancy. EML yes; off-patent; a few to tens of US dollars a course.

Trimethoprim, or trimethoprim-sulfamethoxazole for three days, is effective where local resistance is below 20 per cent, which resistance now often exceeds. Co-trimoxazole EML yes; off-patent; a few to a few US dollars a course. Fosfomycin trometamol as a single 3 g dose is convenient with good activity including against some ESBL organisms, and slightly lower cure rates than five-day nitrofurantoin; off-patent, a few to tens of US dollars a dose. Pivmecillinam for three to seven days is widely used in Scandinavia with low resistance and is now approved in the United States; off-patent, tens of US dollars a course.

Avoid fluoroquinolones for simple cystitis and reserve them: they carry tendinopathy, aortic aneurysm, neuropathy and *C. difficile* risks and drive resistance, and regulatory restrictions now apply in the EU and the US. A clear stewardship position.

Pyelonephritis: oral ciprofloxacin or co-trimoxazole for seven to fourteen days if susceptible and the patient is stable; intravenous ceftriaxone or gentamicin if unwell, vomiting or pregnant, then step down. Ceftriaxone EML yes; gentamicin off-patent, at pennies, and requiring monitoring.

Complicated or obstructed infection: urgent drainage with a stent or nephrostomy, plus antibiotics. An obstructed infected kidney is a surgical emergency and antibiotics alone will fail.

Analgesia with NSAIDs or paracetamol. NSAIDs alone cure a substantial proportion of uncomplicated cystitis, with more pyelonephritis than antibiotics: a documented trade-off, not a free lunch. ESBL and

multidrug-resistant organisms: carbapenems, and newer agents — ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol — all expensive, hospital-only, and the reason stewardship matters. Catheter-associated infection: remove or replace the catheter, and treat only if symptomatic; do not treat asymptomatic catheter bacteriuria. Recurrent infection: vaginal oestrogen, water, methenamine, then antibiotic prophylaxis.

Simple means. Water: an extra 1.5 L a day nearly halved recurrences, from 3.2 to 1.7 episodes a year (Hooton 2018)†. Free where clean water exists, and among the best-evidenced simple interventions in this book.

Vaginal oestrogen is not quite a simple means, being a manufactured product, but it is cheap, off-patent and dramatically effective in postmenopausal women, and under-prescribed. Methenamine hippurate is non-inferior to antibiotic prophylaxis (ALTAR) and spares antibiotics.

Post-coital voiding, avoiding spermicides, not delaying micturition, and complete bladder emptying with double voiding where residual urine is the problem: cheap, though the evidence is thin for some of these. Catheter avoidance and daily review of catheter need costs nothing and prevents the commonest healthcare-associated infection in the world. Clean water and sanitation, upstream, and relevant to the faecal-flora origin. Analgesia and fluids with delayed antibiotic prescribing in mild uncomplicated cystitis reduces antibiotic use, with the honest caveat of slower recovery and a small excess of pyelonephritis. Not treating asymptomatic bacteriuria is a free, evidence-based omission that avoids harm and resistance, and is still routinely violated.

The honest limit: pyelonephritis and urosepsis require antibiotics, and obstruction requires drainage. Water does not cure a kidney infection.

Gaps. Resistance is rising faster than new oral options appear, and local resistance data, which should drive empirical choice, are absent in much of the world. The urinary microbiome's clinical meaning is unknown. Why some women have relentless recurrence is unexplained. D-mannose and cranberry evidence is contradictory. Much standard behavioural advice is unsupported. The optimal duration of therapy for pyelonephritis and for men is not well established, and male infection is poorly studied in general and often treated far longer than evidence requires. Diagnosis is unreliable: dipstick and culture both perform modestly, over-diagnosis in the elderly is endemic, and treating confusion plus bacteriuria as infection causes substantial harm. GBD mortality figures rest largely on modelled urosepsis.

> **Depth.** Starts in: Escherichia coli. Size: 2 µm†; depth +3.44. First complaint: about 34 hours († 1–2 days); time depth 43.81. One untreated course: about 7 days († about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Benign prostatic hyperplasia

What it is. The prostate enlarges with age and squeezes the urethra. Urine flow weakens, the bladder empties incompletely, and urination becomes frequent and urgent.

Measured. Histological prevalence rises almost linearly with age: about 8 per cent in the fourth decade, about 50 per cent at 51 to 60, about 70 per cent at 61 to 70, about 80 per cent at 71 to 80, and about 90 per cent above 80†. One of the most age-determined conditions in medicine.

Symptomatic, clinical disease is less common than histological disease: moderate-to-severe lower urinary tract symptoms affect about 25 to 30 per cent of men over 50†. GBD 2019 gave about 90 to 95 million men affected globally with about 1.8 to 2 million DALYs; deaths are few and mostly through obstructive renal failure and urosepsis. Acute urinary retention incidence is about two to seven per 1,000 men a year†, rising steeply with age.

It is present everywhere, and measured symptom prevalence differs partly by instrument and by care-seeking. Untreated obstruction causing renal failure and bladder stones remains a significant presentation in low-income settings, where it is a preventable cause of chronic kidney disease.

Where it starts. Age is the dominant factor. Androgens are necessary: dihydrotestosterone, produced by 5-alpha-reductase, drives prostatic growth. Men castrated before puberty, and men with congenital 5-alpha-reductase deficiency, do not develop the condition — the cleanest causal evidence available, and the rationale for 5-alpha-reductase inhibitors.

Metabolic syndrome, obesity, diabetes and insulin resistance are associated with larger prostates and faster growth, with inflammation implicated. Family history: a first-degree relative raises risk about two to four times, with larger effects for early-onset large-volume disease, and heritability is estimated at about 50 to 60 per cent from twin studies†. Physical inactivity, and possibly dietary factors — high red meat, low vegetable intake. Protective associations: physical activity, moderate alcohol weakly, and some dietary patterns.

What is not known is why prostate growth and symptoms correlate so poorly: many men with large prostates have no symptoms and many with small prostates have severe symptoms, so lower urinary tract symptoms are not simply obstruction. Detrusor dysfunction, nocturnal polyuria and bladder changes contribute independently. Why the condition localises to the transition zone while prostate cancer favours the peripheral zone is unexplained. And whether chronic inflammation is cause or consequence is unresolved.

Cure status. Three strata.

Medical treatment: CONTROLLABLE. Drugs relieve symptoms and 5-alpha-reductase inhibitors shrink the gland and reduce progression, but the condition persists and treatment is indefinite.

Transurethral resection or its equivalents: CURABLE for the obstruction. Transurethral resection and its modern equivalents remove the obstructing tissue and produce durable relief, with re-treatment rates of roughly 1 to 2 per cent a year, about 10 to 15 per cent at ten years. So surgery is close to curative for the obstruction, though the prostate can regrow.

Mild to moderate symptoms on watchful waiting: CONTROLLABLE by watchful waiting. Symptoms fluctuate, and in watchful-waiting arms of trials a substantial proportion of men with mild to moderate symptoms remain stable or improve without treatment, which makes watchful waiting a legitimate first option.

Prevention. 5-alpha-reductase inhibitors reduce progression: STRONG for that outcome. Finasteride in the PLESS trial reduced acute urinary retention by about 57 per cent and the need for surgery by about 55 per cent over four years, and the MTOPS trial showed combination therapy reduced clinical progression by about 66 per cent. But these are treatments for existing disease rather than primary prevention, and they are not given to asymptomatic men.

Physical activity: MODERATE, on a consistent inverse association across cohorts. Weight management and metabolic syndrome control: MODERATE. Dietary pattern, more vegetables and less red meat: WEAK. Avoiding drugs that precipitate retention — anticholinergics, antihistamines, decongestants, opioids: MODERATE for preventing acute retention. No established primary prevention of the condition itself: absent, or WEAK.

A note on cancer: 5-alpha-reductase inhibitors reduce overall prostate cancer detection but were associated with a small excess of high-grade tumours in PCPT and REDUCE, so they are not used for cancer prevention: CONTESTED.

Treatment. In the watchful-waiting arms of trials a substantial proportion of men with mild to moderate symptoms remain stable or improve without treatment; the proportion is not given here. Watchful waiting with lifestyle advice is appropriate for mild symptoms.

Alpha-1 blockers give the fastest symptom relief, within days to weeks, improving the symptom score by about four to six points on the IPSS and flow by about 2 to 3 mL/s: tamsulosin, alfuzosin, doxazosin, terazosin, silodosin. They do not prevent progression or retention. Tamsulosin and doxazosin off-patent;

tens of US dollars a patient-year; EML status. Side effects: dizziness, postural hypotension, retrograde ejaculation, and intraoperative floppy iris syndrome, which is relevant before cataract surgery.

5-alpha-reductase inhibitors, finasteride and dutasteride, shrink the prostate by about 20 to 25 per cent over six to twelve months and reduce retention and surgery risk by about 50 per cent†; they are effective only in larger prostates, above 30 to 40 mL, and slow to act, taking three to six months. Finasteride off-patent; tens to hundreds of US dollars a patient-year. Side effects: reduced libido, erectile dysfunction, ejaculatory disorder, gynaecomastia; persistent sexual dysfunction after cessation is reported and contested; and they halve PSA, which must be accounted for in cancer screening.

Combination alpha-blocker with 5-alpha-reductase inhibitor is superior to either alone for progression (MTOPS, CombAT) and is appropriate for larger glands with significant symptoms. Antimuscarinics or beta-3 agonists such as mirabegron are added for storage and overactive bladder symptoms, with caution regarding retention; mirabegron is now off-patent in some markets. PDE5 inhibitors, tadalafil 5 mg daily, improve both lower urinary tract symptoms and erectile dysfunction and are useful where both coexist; tadalafil off-patent, tens to hundreds of US dollars a year.

Surgery. Transurethral resection of the prostate is the long-standing standard and is durable, with risks of bleeding, TUR syndrome, retrograde ejaculation at about 65 to 70 per cent, incontinence at about 1 to 2 per cent†, and stricture. Bipolar resection, laser vaporisation or enucleation (HoLEP, ThuLEP) and photoselective vaporisation give less bleeding and shorter catheterisation and stay, and HoLEP is size-independent and highly durable. Open or simple prostatectomy for very large glands where endoscopic enucleation is unavailable remains important in low-resource settings and is still widely performed. Minimally invasive options — prostatic urethral lift, water vapour therapy, prostatic artery embolisation, temporary implants — give less sexual dysfunction, are less durable, and are more expensive per unit benefit.

Acute urinary retention: immediate catheterisation is the single most important emergency intervention, then a trial of void with an alpha-blocker started beforehand, which improves success, or surgery. Chronic retention with renal impairment: catheterise and decompress, and watch for post-obstructive diuresis.

Phytotherapy with saw palmetto, *Serenoa repens*: CONTESTED and negative. The STEP trial (*NEJM* 2006) and Cochrane reviews found no benefit over placebo even at high doses. Widely sold, not effective. Pygeum and beta-sitosterol have weaker evidence still.

Simple means. Fluid timing: reducing evening fluid, caffeine and alcohol intake measurably reduces nocturia. Free. Bladder training and timed voiding, and double voiding to empty more completely. Pelvic floor exercises help post-void dribbling and urgency. Reviewing and stopping precipitating drugs — anticholinergics, antihistamines, decongestants, and diuretic timing — is free and often prevents retention. Physical activity and weight loss are associated with fewer and milder symptoms. Treating constipation, since a full rectum worsens voiding. Watchful waiting is the evidence-based simple means for mild symptoms, avoiding drug side effects entirely.

A urinary catheter: for acute retention this cheap plastic tube relieves agony within seconds and prevents obstructive renal failure. In settings without urology services, clean intermittent self-catheterisation is a durable, low-cost solution that preserves renal function indefinitely and can be taught to patients. That is arguably the highest-value simple means in this entry. Avoiding saw palmetto is an evidence-based omission that saves money.

The honest limit: significant obstruction eventually needs surgery or long-term catheterisation. No exercise or diet relieves mechanical obstruction.

Gaps. Symptoms correlate poorly with prostate size and with urodynamic obstruction, so treatment targeting is imprecise and the diagnosis conflates several problems. The durability and cost-effectiveness of the newer minimally invasive procedures relative to resection and HoLEP are not established. Persistent sexual dysfunction after 5-alpha-reductase inhibitors is reported, and its reality and frequency are genuinely contested. Long-term consequences of untreated obstruction in low-resource settings are unquantified, though clinically evident. Nocturia is often multifactorial, through nocturnal polyuria, sleep

disorder and heart failure, and treating the prostate alone frequently fails. GBD burden figures rest on symptom survey modelling with wide uncertainty.

> **Depth.** Starts in: the prostate. Size: 4 cm†; depth +12.46. First complaint: about 60 years ([B] with age; † about 60); time depth 52.60. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Erectile dysfunction

What it is. Difficulty getting or keeping an erection firm enough for sex. It is usually a blood-vessel problem, and often the first sign of arterial disease elsewhere.

Measured. Prevalence rises steeply with age: roughly 8 per cent at 20 to 29, 11 per cent at 30 to 39, 15 to 20 per cent at 40 to 49, 30 per cent at 50 to 59, 40 to 50 per cent at 60 to 69, and over 50 to 70 per cent above 70†. The Massachusetts Male Aging Study found about 52 per cent of men aged 40 to 70 had some degree of erectile dysfunction: mild 17 per cent, moderate 25 per cent, complete 10 per cent†. About 150 million men were estimated to be affected worldwide in 1995, projected to about 320 million by 2025 (Ayta)†.

It is not a separate GBD cause and has no DALY figure. There are no direct deaths. But it is a marker of cardiovascular risk: erectile dysfunction precedes coronary events by roughly three to five years on average and independently predicts cardiovascular events, with hazard ratios of about 1.4 to 1.9 in meta-analyses. That is its main clinical importance beyond quality of life. Measured prevalence differs widely by geography, largely reflecting willingness to report and the survey instrument rather than true variation.

Where it starts. Vascular disease is the commonest cause and shares every risk factor with coronary disease: smoking, diabetes, hypertension, dyslipidaemia, obesity, physical inactivity, metabolic syndrome. Diabetes is particularly strong, with prevalence of about 50 to 75 per cent in diabetic men† and earlier onset. Endothelial dysfunction is the shared mechanism, which is why erectile dysfunction is a sentinel for systemic arterial disease.

Drugs are a major and reversible cause: thiazides and beta-blockers, SSRIs and other antidepressants, antipsychotics, 5-alpha-reductase inhibitors, spironolactone, opioids, anti-androgens, recreational drugs and alcohol.

Neurogenic causes: diabetes, multiple sclerosis, spinal cord injury, Parkinson disease, and pelvic surgery and radiotherapy, with radical prostatectomy a leading iatrogenic cause. Hormonal: hypogonadism, hyperprolactinaemia, thyroid disease. Psychogenic: performance anxiety, depression, relationship factors, more prominent in younger men, in whom sudden onset with preserved nocturnal erections suggests this. Peyronie disease; priapism sequelae; pelvic trauma. Heritability is estimated at about one-third of variance in some twin analyses, and most risk is acquired and shared with cardiovascular disease.

What is not known is the relative weight of psychological and organic factors in the individual case: they coexist and interact, and no test separates them cleanly. Why diabetic erectile dysfunction responds less well to PDE5 inhibitors is only partly understood. Whether treating erectile dysfunction improves cardiovascular outcomes, as opposed to flagging risk, is unknown. And the mechanism of post-SSRI sexual dysfunction persisting after cessation is unexplained and contested.

Cure status. Two strata.

Reversible cause: CURABLE. A causative drug stopped or switched. A correctable endocrine deficiency. A focal arterial lesion in a young man after trauma, treated by revascularisation. Vasculogenic disease treated by weight loss and exercise belongs here too, and it is the best-evidenced route back to unassisted function: 31 against 5 per cent restoration in the Esposito trial. Remove the cause and the function returns without further treatment.

Established vascular, diabetic or neurogenic disease, or no cause identified: CONTROLLABLE. Phosphodiesterase type 5 inhibitors work on demand for a majority of men, less often in diabetes and after non-nerve-sparing prostatectomy, and they do not alter the underlying disease; stop them and the difficulty returns unchanged. Testosterone for hypogonadism must be continued, which under this book's rule is control and not cure. A penile prosthesis is effective and durable in refractory cases, and it sits in this stratum: the native erectile tissue is destroyed and its function substituted, so the deviation remains.

Prevention. Smoking cessation: STRONG — risk falls after quitting and erectile function improves measurably. Physical activity: STRONG. Meta-analyses of randomised trials show aerobic exercise improves erectile function significantly, with effect sizes comparable to a modest drug effect, with about 40 minutes of moderate-to-vigorous aerobic exercise four times a week over six months producing clear improvement.

Weight loss: STRONG. Esposito (*JAMA* 2004) found that in obese men, a two-year lifestyle intervention achieving about 15 kg of loss restored erectile function in about 31 per cent against 5 per cent of controls.

Mediterranean diet: MODERATE. Glycaemic, blood pressure and lipid control: MODERATE. Avoiding or switching causative drugs: STRONG, and under-practised. Moderating alcohol and avoiding recreational drugs: MODERATE. Pelvic floor muscle training: MODERATE, with randomised evidence of benefit including for post-prostatectomy dysfunction and venous leak. Treating erectile dysfunction as a cardiovascular warning and acting on total risk: a STRONG recommendation on prognostic grounds.

Treatment. PDE5 inhibitors are first line: sildenafil, tadalafil, vardenafil, avanafil. They work for a majority of men, less often in diabetes and after non-nerve-sparing prostatectomy. Tadalafil's long half-life allows daily dosing and also treats lower urinary tract symptoms.

Sildenafil is off-patent, since 2013 and 2017 in different markets. Its EML status is: not on the WHO Essential Medicines List at all, for any indication. A direct query of the electronic EML returns zero recommendations, zero medicines and zero therapeutic equivalents. Generic cost is tens to hundreds of US dollars a patient-year, and as little as a few cents a tablet in some markets — a dramatic fall from branded prices of tens of US dollars a tablet. Tadalafil off-patent; tens to hundreds of US dollars a year. Both are contraindicated with nitrates, because of profound hypotension, and need caution with alpha-blockers.

Address the reversible causes: switch the offending antihypertensive or antidepressant, for example to an ARB, nebivolol, bupropion or mirtazapine; treat hypogonadism; optimise diabetes. Testosterone replacement only where hypogonadism is biochemically confirmed, which restores response to PDE5 inhibitors in some non-responders, and not for eugonadal men. Testosterone enanthate off-patent, EML-listed, cheap.

Vacuum erection devices are effective and reusable with no drug cost, at hundreds of US dollars as a one-off and locally manufacturable; they are particularly useful where drugs are contraindicated or unaffordable, and for penile rehabilitation after prostatectomy. Satisfaction is lower than with drugs and the cost per year of use is very low.

Intracavernosal injection with alprostadil, or bimix or trimix with papaverine and phentolamine, is effective in 70 to 90 per cent including most PDE5 non-responders†. Papaverine and phentolamine are old, off-patent and cheap, and compounded trimix is inexpensive; alprostadil is more expensive. Risks: pain, priapism, fibrosis. Intraurethral alprostadil and topical alprostadil cream. A penile prosthesis is definitive for refractory cases, with the highest satisfaction rates of any treatment at 80 to 90 per cent†, at a one-off surgical cost.

Psychosexual and couple therapy is effective, particularly for psychogenic and mixed cases, and improves adherence to and outcomes of drug therapy; combination of therapy with a PDE5 inhibitor outperforms either alone in trials. Low-intensity shockwave therapy has some positive randomised data suggesting it may alter underlying vascular pathology rather than just relieve symptoms, with heterogeneous evidence and marketing far ahead of it: CONTESTED. Platelet-rich plasma and stem cell injections are not supported: experimental, heavily commercialised, with no adequate evidence.

Simple means. Aerobic exercise has randomised evidence of significant improvement, with an effect size comparable to pharmacotherapy in some analyses, and it treats the underlying vascular disease rather than masking it. Free.

Weight loss: 31 against 5 per cent restoration of function in the Esposito trial. Smoking cessation. Pelvic floor muscle training, with randomised evidence of benefit: a taught exercise, no equipment. Reviewing medications — switching a thiazide or an SSRI costs nothing and can resolve the problem entirely. Reducing alcohol.

A vacuum erection device is mechanical and reusable with no consumables, and can be produced locally and cheaply: the most simple-means of the definitive treatments. Sleep, and treating sleep apnoea. Talking — psychosexual and couple counselling, especially in younger men where psychogenic factors dominate — needs no supply chain and has a measurable effect. Generic sildenafil at a few cents a tablet is, while manufactured, now cheap enough to count as widely accessible, though it is not on the Essential Medicines List.

The honest note: the simple means here are unusually effective because the condition is mostly vascular, and vascular disease responds to exercise and weight loss. The same measures reduce the cardiovascular risk that erectile dysfunction signals.

Gaps. Prevalence data depend heavily on self-report and are probably underestimates given stigma. The organic and psychogenic distinction is not cleanly measurable. Whether treating erectile dysfunction alters cardiovascular outcomes is unknown. Shockwave therapy evidence is heterogeneous and commercially driven. Post-SSRI and post-finasteride persistent sexual dysfunction are reported, contested and unexplained — a genuine evidentiary stand-off. Data from Africa, South Asia and much of the developing world are sparse. The large counterfeit and unregulated market for PDE5 inhibitors is a real safety problem and is unquantified. Long-term outcome data for penile rehabilitation after prostatectomy are inconsistent.

> **Depth.** Starts in: a penile artery. Size: 1 mm†; depth +9.10. First complaint: about 55 years († onset about age 55); time depth 52.52. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Urinary incontinence

What it is. Involuntary leakage of urine. Stress incontinence leaks on coughing or exertion; urge incontinence leaks with a sudden need to go. Common, treatable, and very under-reported.

Measured. Prevalence in women is about 25 to 45 per cent depending on definition and age, with about 10 per cent having at least weekly leakage; it rises with age, at about 20 to 30 per cent in young adulthood, 30 to 40 per cent in middle age, and 30 to over 50 per cent in old age. Prevalence in men is about 5 to 15 per cent†, rising with age and strongly associated with prostate surgery. About 400 million people are affected worldwide by some estimates†. GBD 2019 gave urinary incontinence on the order of 1.5 to 2 million DALYs globally with no attributable deaths†.

Subtypes in women: stress about 50 per cent, mixed about 30 to 35 per cent, urge about 15 to 20 per cent†. Care-seeking is low: only about 25 to 45 per cent of affected women ever seek help, often after years, because of stigma and the belief that it is a normal part of ageing. That is the dominant barrier and the reason burden is understated. It is a leading cause of admission to residential care in the elderly, and a major driver of pad and laundry cost, skin breakdown and falls.

Where it starts. Vaginal childbirth and parity is the strongest obstetric factor, through pelvic floor muscle and pudendal nerve injury; risk increases with the number of vaginal deliveries, with instrumental and especially forceps delivery, with a prolonged second stage, and with a large infant. Caesarean section carries a lower risk of stress incontinence but is not fully protective and carries its own risks.

Age and menopause, through urogenital atrophy. Obesity, strongly dose-dependently: each five-unit BMI increase raises risk about 20 to 70 per cent across studies†, and it is the most modifiable risk factor. Chronic cough from smoking or COPD; constipation and straining; heavy lifting occupations; and high-impact sport, a notable cause in young athletes and nulliparous women.

Prostate surgery in men: radical prostatectomy is the leading cause of male stress incontinence, and transurethral resection causes it in about 1 to 2 per cent†. Neurological disease — stroke, multiple sclerosis, Parkinson disease, spinal cord injury, dementia, diabetic neuropathy — producing urge and neurogenic incontinence. Drugs: diuretics, alpha-blockers in women, ACE inhibitors through cough, sedatives, cholinesterase inhibitors.

Pelvic organ prolapse; previous pelvic radiotherapy; and obstetric fistula, where in low-income settings prolonged obstructed labour causes vesicovaginal fistula with total incontinence, a devastating and surgically curable condition affecting an estimated 500,000 to 2 million women, overwhelmingly in sub-Saharan Africa and South Asia†.

Twin and family studies estimate heritability at about 40 to 50 per cent for stress incontinence†, with connective tissue composition and collagen genes implicated, and family history roughly doubling risk.

What is not known is why women with similar obstetric histories differ so much; connective tissue quality is implicated and not measurable clinically. The mechanism of detrusor overactivity is poorly understood, with myogenic, neurogenic and urothelial theories all having support. Why pelvic floor training works for urge as well as stress incontinence is only partly explained. And the long-term natural history, including remission rates, which are substantial since incontinence fluctuates and can resolve, is poorly characterised.

Cure status. Stress and mixed incontinence: CURABLE. Urge incontinence and obstetric fistula are labelled below. The low care-seeking rate is the central problem.

Pelvic floor muscle training cures or improves most stress and mixed incontinence: women are roughly five to eight times more likely to report cure than controls in Cochrane meta-analysis, and about 2.5 to six times more likely to report cure or improvement, with reported cure rates of 30 to 50 per cent with supervised training.

Mid-urethral sling surgery cures stress incontinence in about 80 to 90 per cent at one year, with durable results at five to ten years†.

Urge incontinence: CONTROLLABLE. Bladder training and drugs reduce but seldom abolish episodes, and relapse on stopping drugs is the norm.

Obstetric fistula: CURABLE by surgery in about 80 to 90 per cent of cases† when performed by a trained surgeon. One of the most transformative operations available.

Prevention. Pelvic floor muscle training, antenatal and postnatal: STRONG. Cochrane finds antenatal training reduces postnatal incontinence risk by roughly 30 per cent, relative risk about 0.7, and also treats existing symptoms. Cheap, teachable, no equipment.

Weight loss: STRONG. The PRIDE trial (Subak, *NEJM* 2009, 338 overweight women) found a six-month weight loss programme achieving about 8 per cent weight loss reduced weekly incontinence episodes by 47 per cent against 28 per cent in controls. Dose-dependent.

Avoiding smoking and treating chronic cough: MODERATE. Treating constipation: MODERATE. Obstetric care quality — avoiding prolonged obstructed labour, and access to timely caesarean section: STRONG for preventing obstetric fistula, which is almost entirely a disease of absent emergency obstetric care. Nerve-sparing technique and surgeon volume in radical prostatectomy: MODERATE for male incontinence; preoperative pelvic floor training: MODERATE, which speeds recovery. Reviewing diuretics and other contributory drugs: MODERATE. Caesarean section specifically to prevent incontinence: CONTESTED — it reduces stress incontinence risk, and the overall risk-benefit does not support it as an indication.

Treatment. Conservative treatment first, for all types. Supervised pelvic floor muscle training for at least three months, ideally with a continence physiotherapist and with correct technique confirmed, is first-line

for stress and mixed incontinence, and gives five to eight times the likelihood of cure against no treatment. Adding biofeedback or vaginal cones gives modest additional benefit. The cost is a trained person's time, with no consumables.

Bladder training, timed voiding and urge suppression is first-line for urge incontinence and is comparable to drugs in some trials, with better durability. Weight loss, giving 47 against 28 per cent episode reduction in PRIDE. Fluid and caffeine moderation, and treating constipation. Vaginal oestrogen for postmenopausal urogenital atrophy improves urgency, frequency and recurrent urinary tract infection; off-patent, tens to hundreds of US dollars a year.

Drugs for urge incontinence and overactive bladder. Antimuscarinics — oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine — reduce episodes by roughly one to two a day more than placebo, a real but modest effect, with high discontinuation rates of about 50 to 70 per cent within a year† from dry mouth and constipation. Oxybutynin off-patent; tens of US dollars a patient-year; EML. An important caution: antimuscarinic burden is associated with increased dementia risk in older adults on cohort evidence, so oxybutynin in particular should be avoided in the elderly.

Mirabegron, a beta-3 agonist, gives similar efficacy to the antimuscarinics with better tolerability and no anticholinergic cognitive burden, and is preferred in the elderly. Now off-patent in several markets, with cost falling from thousands of US dollars a year toward generic levels. Duloxetine for stress incontinence gives modest benefit with poor tolerability, is not first-line, and is not approved for this in the United States.

Procedures. A mid-urethral synthetic sling, retropubic or transobturator, gives about 80 to 90 per cent cure for stress incontinence and is the most effective and most studied surgical option. Mesh sling use has been suspended or restricted in several countries — the United Kingdom, New Zealand, Australia — following complications of chronic pain and erosion and patient safety reviews, which is a major and ongoing controversy. The evidence of efficacy is strong; the dispute is about complication rates, consent and surgeon training.

Autologous fascial sling and colposuspension are effective alternatives without synthetic mesh, and the fascial sling has regained prominence given the mesh controversy. Urethral bulking agents are less effective and less durable, and minimally invasive. Botulinum toxin A intradetrusor injection for refractory urge incontinence is effective, reducing episodes substantially and superior to continued antimuscarinics, requiring repeat injection every six to nine months and carrying retention and infection risk. Sacral neuromodulation and percutaneous tibial nerve stimulation for refractory overactive bladder, with the latter relatively cheap and office-based. An artificial urinary sphincter is the standard for male stress incontinence after prostatectomy: effective, mechanical, expensive. Obstetric fistula repair by surgical closure, with 80 to 90 per cent success in trained hands†. Containment with pads, catheters and sheaths is management rather than treatment, and essential for dignity where cure is unavailable; pad cost is a substantial lifetime expense and a real equity issue.

Simple means. This is one of the clearest simple-means entries in the book: the first-line treatment for the commonest type is an exercise.

Pelvic floor muscle training gives five to eight times the likelihood of cure against no treatment (Cochrane). It requires instruction and correct technique, no equipment and no consumables, and it can be taught by a midwife, nurse or community health worker, and delivered at scale by group teaching, printed instruction or an app.

Antenatal and postnatal pelvic floor training gives about a 30 per cent reduction in postnatal incontinence. Weight loss gives 47 against 28 per cent reduction in episodes (PRIDE). Bladder training and timed voiding is comparable to drug therapy for urgency, with better durability and no side effects. Reducing caffeine and adjusting fluid timing, and treating constipation. Smoking cessation, for cough reduction. Reviewing drugs: diuretic timing alone can resolve functional incontinence in the elderly. Prompted and timed toileting, and accessible toilets, in care settings has a large measured effect on functional incontinence in the frail elderly, requiring staff time rather than technology. Locally made washable pads where disposable products are unaffordable. And avoiding oxybutynin in older people: an evidence-based omission that avoids cognitive harm.

The honest limit: severe stress incontinence, obstetric fistula and post-prostatectomy incontinence need surgery. And pelvic floor training requires skilled instruction to work; unsupervised leaflet-only instruction is substantially less effective.

Gaps. Prevalence estimates vary two- to threefold with definition, and under-reporting is severe, so the burden figures are soft. The mesh sling controversy is unresolved: efficacy data are strong, complication rates are disputed, and country policies now differ radically, which means patients in different places receive opposite advice. Long-term outcomes beyond ten years for all surgical options are limited. The dementia-anticholinergic association is from cohort data and causality is not settled, and it is influencing practice. Obstetric fistula burden is poorly counted and the true number affected is unknown. Male incontinence is much less studied than female. Evidence for conservative management in the frail elderly and in neurogenic bladder is thin. There are almost no high-quality data from low-income settings.

> **Depth.** Starts in: the pelvic floor. Size: 10 cm†; depth +13.29. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Endometriosis

What it is. Tissue resembling the womb lining grows outside the womb, on the ovaries, pelvic lining or bowel. It bleeds and inflames with each cycle, causing pain and scarring, and it can cause infertility.

Measured. Prevalence is about 5 to 10 per cent of women of reproductive age, roughly 190 million women globally on the WHO figure. It is much higher in selected groups: about 20 to 50 per cent of women with infertility and about 45 to 80 per cent of women with chronic pelvic pain. GBD 2019 gave about 175 to 190 million women affected and roughly 0.9 to 1.0 million DALYs, all from disability with no attributable deaths†. GBD 2023 Table 1 places gynaecological diseases tenth among YLD causes at 28.6 million (95 per cent UI 19.5 to 40.0), which is the aggregate within which this condition sits.

Diagnostic delay averages seven to eleven years from symptom onset in multiple national studies — among the longest delays recorded for any common disease, and the defining feature of its epidemiology. Symptoms typically begin in adolescence, with diagnosis usually in the late twenties or thirties, and they generally regress after menopause. Apparent geographic variation almost certainly reflects access to laparoscopy and diagnostic practice rather than true prevalence differences.

Where it starts. Retrograde menstruation, Sampson’s theory, is the leading explanation and is insufficient: retrograde flow occurs in up to 90 per cent of women†, yet only a minority develop endometriosis, so the determinant must lie in what happens to the refluxed cells — immune clearance, adhesion and survival. Alternative and complementary theories: coelomic metaplasia, Müllerian remnants, stem cell spread, and lymphatic and vascular spread, which explains rare extrapelvic and post-hysterectomy disease.

Early menarche, short cycles, heavy and prolonged menses, nulliparity and late menopause all increase lifetime menstrual exposure. Obstructive Müllerian anomalies, which force retrograde flow, markedly increase risk, and that is strong supporting evidence for the retrograde mechanism. Low BMI is associated with higher risk, consistently and unexplained.

Family history is strong: a first-degree relative raises risk about five to seven times, and heritability is estimated at about 47 to 52 per cent from the Australian twin study (Treloar), roughly half the variance. GWAS has identified more than forty loci — *WNT4*, *GREB1*, *ESR1*, *CDKN2B-AS1*, *VEZT* — explaining a modest fraction, with genetic overlap with ovarian cancer subtypes.

Immune dysfunction: reduced natural killer cell clearance of ectopic cells, and association with autoimmune conditions. Endocrine-disrupting chemicals, dioxins, PCBs and phthalates: CONTESTED — associations are reported and causality is not established. Protective: multiparity, extended lactation, regular exercise weakly, and oral contraceptive use, which may also mask symptoms and thereby delay diagnosis.

What is not known is the cause. This is a disease whose basic mechanism is genuinely unsettled after a century of theories. Why pain correlates so poorly with disease stage is a major unexplained feature: women with minimal disease may have severe pain and vice versa, which means the revised ASRM staging predicts fertility but not symptoms. Why it causes infertility is only partly explained, through adhesions, altered follicular and peritoneal environment, and impaired implantation. Why it recurs after apparently complete excision. Whether adenomyosis is a related or a distinct entity. And whether it ever progresses to malignancy beyond the known small increase in clear cell and endometrioid ovarian cancer risk.

Cure status. CONTROLLABLE, and this is stated plainly because over-promising is a documented harm in this field.

No medical treatment cures endometriosis. Hormonal suppression controls symptoms while taken, and symptoms recur in the majority within six to twelve months of stopping. Surgical excision gives durable relief in many, with recurrence of about 20 to 50 per cent at five years, and repeat surgery is common†. That is control.

Hysterectomy with bilateral oophorectomy ends cyclical stimulation and is the nearest approach to a cure, but pain persists in about 10 to 15 per cent†, it is not a guarantee, and it is not an option for women wanting fertility. Menopause usually brings regression, so in that sense it is a self-limiting disease over a lifetime, though with more than thirty years of morbidity.

The honest framing: this is a chronic condition managed over decades, like asthma or inflammatory arthritis, and framing surgery as a definitive cure is not supported.

Prevention. No established primary prevention: absent. Combined oral contraceptives and continuous progestogens reduce symptoms and may reduce progression: WEAK for prevention, STRONG for symptom control. Note the complication that they may delay diagnosis by masking symptoms. Relieving obstructive Müllerian anomalies: MODERATE, mechanistically direct. Exercise, multiparity and lactation associations: WEAK, observational, and not actionable as advice. Reducing diagnostic delay is not prevention of disease but prevention of accumulated harm, and is the highest-value system intervention: MODERATE, on the grounds that earlier treatment reduces disease burden and preserves fertility.

Treatment. Analgesia: NSAIDs are first line for pain, with a modest effect size against placebo and surprisingly weak evidence — Cochrane finds it inconclusive for endometriosis specifically — though they are widely effective in dysmenorrhoea generally. Off-patent, EML-listed, a few to tens of US dollars a year.

Hormonal suppression, all symptomatic and all recurring on stopping. Combined oral contraceptives used continuously, skipping the withdrawal bleed, are effective for pain, cheap and well tolerated. EML yes; off-patent; tens of US dollars a patient-year. First-line in most guidelines.

Progestogens — medroxyprogesterone acetate, norethisterone, dienogest — and the levonorgestrel intrauterine system, which is highly effective for pain and for adenomyosis, lasts five to eight years and is extremely cost-effective. The intrauterine system is EML-listed, at tens of US dollars per device at public-sector prices, so a few dollars a year. One of the best value interventions here.

GnRH agonists, leuprolide and goserelin, with add-back therapy of low-dose oestrogen plus progestogen to prevent bone loss and vasomotor symptoms, are effective for severe disease and limited to about six to twelve months without add-back because of bone density loss. Off-patent; thousands of US dollars a year. GnRH antagonists — elagolix, relugolix combination, linzagolix — are oral, rapid and dose-adjustable; on patent at about US$10,000 to 13,000 a year US list†, with a modest advantage over far cheaper options. Aromatase inhibitors for refractory postmenopausal or persistent disease, off-label, combined with suppression. Danazol is effective and its androgenic side effects make it largely obsolete.

Surgery. Laparoscopic excision or ablation of endometriosis reduces pain significantly against diagnostic laparoscopy alone, with a number needed to treat of about three to four in trials, and excision appears superior to ablation for deep disease and for durability; recurrence is 20 to 50 per cent at five years. Excision of deep infiltrating endometriosis of the bowel, bladder or ureter requires specialist multidisciplinary teams and gives high symptom relief with significant complication rates. Ovarian endometrioma cystectomy improves pain and spontaneous pregnancy rates but removes ovarian reserve, so it must be weighed carefully against fertility plans: a genuine trade-off. Hysterectomy with or without

oophorectomy for women who have completed childbearing with refractory symptoms, where coexisting adenomyosis is often cured by hysterectomy. Presacral neurectomy and LUNA: LUNA is not effective on randomised evidence and should not be used.

Fertility: surgical excision improves spontaneous conception in minimal to mild disease, with a modest effect, and IVF is effective and is the main route in moderate to severe disease. GnRH agonist pretreatment before IVF improves outcomes in some analyses. Hormonal suppression does not improve fertility and delays conception — an important point, since it is sometimes prescribed for that purpose.

Multidisciplinary pain care: pelvic floor physiotherapy, neuropathic agents such as amitriptyline and gabapentin, though the GaPP2 trial found gabapentin ineffective for chronic pelvic pain, psychological therapy, and specialist pain management. This is essential because central sensitisation develops in many, and surgery on the lesions then does not relieve pain. It is the most under-provided part of care.

Simple means. Heat, from a hot water bottle or a warm bath, is comparable to NSAIDs for dysmenorrhoea pain in small randomised trials. Free.

Continuous, no-break use of cheap combined oral contraceptives or progestogens: eliminating withdrawal bleeds markedly reduces cyclical pain, costs tens of US dollars a year, and requires no procedure. The levonorgestrel intrauterine system costs a few dollars a year amortised, is inserted once, and is highly effective.

Exercise has modest evidence for pain reduction and improves function and mood. Pelvic floor physiotherapy and relaxation training is effective for the pelvic floor muscle overactivity that commonly accompanies the condition: a taught skill. Psychological therapy, pain education and self-management are effective for chronic pain of any origin, and central sensitisation is common here; no supply chain. Peer support groups have a measurable effect on coping and quality of life, and stigma and isolation are a large part of this disease’s burden.

Believing women and investigating early is not a therapy but the single highest-value simple means available: a seven- to eleven-year diagnostic delay is a system failure correctable by clinician education and listening, at no material cost. TENS, acupuncture and dietary change, low-FODMAP where irritable bowel syndrome overlaps, have weak evidence, low risk and are sometimes helpful.

The honest limit: deep infiltrating disease and endometriomas need surgery. Nothing simple removes a bowel nodule.

Gaps. The cause is unknown. Pain correlates poorly with disease stage, so staging is nearly useless for symptom prognosis. Diagnostic delay of seven to eleven years persists and is poorly explained by any single factor. There is no non-invasive diagnostic test despite extensive biomarker research: laparoscopy remains the reference standard, though imaging now detects deep disease and endometriomas well. NSAID evidence specific to endometriosis is inconclusive despite universal use. Expensive new GnRH antagonists have not been shown superior to cheap continuous contraceptives. Recurrence rates after excision vary widely between series and surgeons, and surgeon skill is a major uncontrolled variable. The contribution of central sensitisation is recognised and not quantified. Prevalence data from Africa, South Asia and Latin America are very sparse. Research funding is low relative to burden, a repeatedly documented disparity.

> **Depth.** Starts in: an endometrial cell outside the womb. Size: 15 µm†; depth +5.28. First complaint: about 25 years († onset about age 25); time depth 51.80. One untreated course: no number ([B] every cycle).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book’s status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Uterine fibroids

Uterine fibroids are benign tumours of the smooth muscle of the womb. ICD-11 codes them in chapter 2, among the neoplasms, and the full entry is there: entry 34, “Uterine fibroids”, in the chapter on neoplasms. It carries all eight sections.

A reader in the genitourinary chapter is sent there because the condition is the commonest tumour in women. It is also a leading cause of hysterectomy and of iron-deficiency anaemia.

Polycystic ovary syndrome

What it is. A common hormonal condition in which ovulation is irregular, male-type hormones are raised, and the ovaries often contain many small follicles. It causes irregular periods, acne, excess hair and difficulty conceiving, and carries metabolic risk.

Measured. Prevalence is 8 to 13 per cent of reproductive-age women by Rotterdam criteria, about 6 per cent by the stricter NIH criteria, and up to about 21 per cent in some high-risk populations using broad criteria. The spread is almost entirely definitional, and all three figures are printed.

About 70 per cent of affected women are undiagnosed, on international survey data. It is the commonest cause of anovulatory infertility, responsible for about 70 to 80 per cent of it. It is not a separate GBD cause with its own DALY total. There are no direct deaths; the burden comes via type 2 diabetes, cardiovascular risk and endometrial cancer.

The metabolic associations are large: impaired glucose tolerance in about 30 to 35 per cent, type 2 diabetes in about 10 per cent by the fourth decade, roughly four times the background risk, gestational diabetes about three times, obstructive sleep apnoea, and metabolic fatty liver disease in about 35 to 70 per cent†. Endometrial cancer risk is raised about 2.7 to three times, from chronic unopposed oestrogen with anovulation†.

It presents at puberty or in early adulthood, the metabolic consequences accumulate with age, and the reproductive features attenuate after menopause. Metabolic severity is higher in South Asian women, who develop insulin resistance at lower BMI and present earlier.

Where it starts. Insulin resistance with compensatory hyperinsulinaemia is present in about 50 to 70 per cent†, independent of obesity, since lean women with the syndrome are also insulin resistant. Insulin drives ovarian androgen production and lowers sex hormone binding globulin, and that is central to the pathophysiology.

Hyperandrogenism, ovarian and adrenal. Disordered gonadotrophin secretion, with raised LH pulse frequency relative to FSH, arresting follicle maturation. Obesity amplifies everything, and is neither necessary nor sufficient: about 20 to 50 per cent of women with the syndrome are lean†.

Heritability is high. Family clustering is strong, with about 20 to 40 per cent of first-degree female relatives affected, and twin studies estimate heritability at about 70 to 72 per cent (Vink, Dutch twin study) — one of the higher heritabilities among common endocrine disorders. GWAS has found about twenty loci — *DENND1A*, *THADA*, *FSHB*, *LHCGR*, *INSR* — explaining only a small fraction, leaving substantial missing heritability.

Developmental programming: prenatal androgen exposure produces a syndrome-like phenotype in animal models, and anti-Müllerian hormone and maternal factors are implicated in humans. Both low and high birth weight are associated.

What is not known is the primary cause. Whether the initiating defect is ovarian, adrenal, hypothalamic-pituitary or metabolic is unresolved after decades, and it may be several distinct conditions pooled under one syndrome, which is why the diagnostic criteria keep changing. Why insulin resistance occurs in lean women with the syndrome is unexplained. The relationship between anti-Müllerian hormone and the phenotype is being actively revised. And long-term cardiovascular outcome data are surprisingly weak: risk factors are clearly increased and hard event data are inconsistent.

Cure status. Two strata.

The syndrome itself: CONTROLLABLE, not curable. The underlying predisposition is lifelong, though the phenotype changes with age and ameliorates after menopause. It is modifiable to a remarkable degree: weight loss of 5 to 10 per cent restores ovulation in a substantial proportion and improves all features,

which is the closest thing to a cure for the metabolic-reproductive phenotype. Individual features — hirsutism, acne, cycles, glucose tolerance — are each controllable with treatment and recur on stopping.

The infertility specifically: CONTROLLABLE. With ovulation induction, cumulative live birth rates approach those of the general population.

Prevention. The syndrome itself is not preventable, being largely genetic and developmental: absent. Preventing the consequences is where prevention works, and it is strong.

Weight management and physical activity: STRONG for preventing type 2 diabetes and restoring ovulation. Metformin: MODERATE for preventing progression to type 2 diabetes in those with impaired glucose tolerance, extrapolated from the Diabetes Prevention Program and syndrome-specific trials.

Cyclical progestogen or a combined oral contraceptive to induce regular withdrawal bleeds: STRONG for preventing endometrial hyperplasia and cancer in women with oligomenorrhoea or amenorrhoea. That is a specific, cheap, high-value preventive that is frequently overlooked, and it addresses an approximately threefold cancer risk.

Screening for glucose intolerance, lipids, blood pressure and sleep apnoea: STRONG on guideline consensus. Smoking cessation: MODERATE, for cardiovascular risk amplification. Preconception weight optimisation: MODERATE, improving fertility and reducing gestational diabetes and pregnancy complications.

Treatment. Treatment is organised by the problem being addressed, which is the only coherent way.

Lifestyle is the foundation for all of it. Diet, exercise and weight loss of 5 to 10 per cent restores ovulation in a substantial proportion and improves insulin sensitivity, androgens, lipids and quality of life. No particular diet composition is superior: an energy deficit is what matters. First-line in all guidelines.

Irregular cycles and endometrial protection. Combined oral contraceptives regulate cycles, protect the endometrium and reduce hyperandrogenism by raising sex hormone binding globulin: first-line. EML yes; off-patent; tens of US dollars a patient-year. Cyclical progestogen, medroxyprogesterone or norethisterone, or the levonorgestrel intrauterine system, for endometrial protection where oestrogen is contraindicated; cheap, with the intrauterine system at a few dollars a year.

Insulin resistance and metabolic risk. Metformin improves insulin sensitivity, menstrual regularity and ovulation, has a modest weight effect, and reduces progression to diabetes. Metformin is an EML-listed medicine, section 18.5.2, for type 2 diabetes in adolescents and adults, first added in 1997; off-patent; a few to tens of US dollars a patient-year. Excellent value, with gastrointestinal side effects limiting some use.

GLP-1 receptor agonists are effective for weight loss here, improving ovulation and metabolic markers; on patent and expensive at about US$9,000 to 16,000 a year US list†, though generics of older agents are appearing, and they are increasingly used where obesity dominates. Inositol, myo-inositol, has some positive trials for ovulation and insulin sensitivity with low to moderate and heterogeneous evidence quality: CONTESTED and WEAK, though cheap and low-risk. Bariatric surgery for severe obesity restores ovulation in most and improves all features markedly.

Hirsutism and acne. Combined oral contraceptives, ideally with an anti-androgenic progestogen, take six to nine months for a visible effect on hair. Spironolactone 50 to 200 mg as an anti-androgen is effective for hirsutism and must be combined with contraception because of teratogenic risk; it is an EML-listed medicine under diuretics and heart failure; off-patent; tens of US dollars a year. Finasteride, cyproterone acetate and flutamide are alternatives, with cyproterone carrying hepatotoxicity and meningioma concerns and flutamide significant hepatotoxicity. Topical eflornithine, and mechanical and laser hair removal, where laser and electrolysis are the only methods producing durable reduction and cost is the barrier. Topical acne therapy with benzoyl peroxide and retinoids, and isotretinoin for severe acne.

Infertility. Letrozole, an aromatase inhibitor, is now first-line for ovulation induction and is superior to clomiphene: the Legro trial (*NEJM* 2014, 750 women) found live birth rates of 27.5 per cent with letrozole against 19.1 per cent with clomiphene, P = 0.007, with comparable safety. Off-patent; tens of US dollars a cycle. A cheap drug that outperformed the previous cheap standard. Clomiphene citrate is still effective and extremely cheap; EML yes; a few to tens of US dollars a cycle.

Metformin as an adjunct may improve clomiphene response, with modest benefit alone. Gonadotrophins are second line, requiring monitoring, with risk of multiple pregnancy and hyperstimulation, and expensive. Laparoscopic ovarian drilling is an effective second line that avoids multiple pregnancy risk at a one-off cost; its use is declining and it remains valuable where monitoring for gonadotrophins is unavailable. IVF for failed ovulation induction or other factors, with a higher hyperstimulation risk in this syndrome. Weight loss before treatment improves all outcomes and reduces pregnancy complications.

Psychological: screening and treating depression, anxiety and eating disorders, which are substantially more common here and routinely missed, and are included in international guidelines.

Simple means. Weight loss of 5 to 10 per cent with physical activity restores ovulation in many, improves every measured feature, and prevents diabetes: the single most effective intervention, with no supply chain. Any sustainable energy-restricted diet, since composition does not matter, so advice can be adapted to local food and cost. Resistance and aerobic exercise improves insulin sensitivity independent of weight loss.

Cyclical progestogen costs pennies and prevents endometrial cancer in women with absent periods: one of the highest benefit-to-cost ratios here, and widely neglected.

Metformin, letrozole, clomiphene and spironolactone are all off-patent and cost a few to tens of US dollars together covering metabolic risk, fertility and hirsutism. The effective core of treatment is remarkably cheap. Mechanical hair removal — threading, waxing, shaving — gives cosmetic management without cost barriers, though it is not durable. Sleep: screening for and treating sleep apnoea, since improving sleep improves insulin sensitivity. Psychological support and peer groups, since the psychological burden is high and under-treated. Smoking cessation.

The honest limit: anovulatory infertility usually needs a drug, though a very cheap one, and severe hirsutism needs laser or electrolysis for durable results.

Gaps. The diagnostic criteria have changed repeatedly — NIH, Rotterdam, AES, the 2023 international guideline — and prevalence varies two- to threefold between them, so the literature is not comparable and many women are differently labelled depending on where they are seen. The primary cause is unknown and this is probably several conditions. Diagnosis in adolescents is genuinely problematic because irregular cycles and acne are normal in early post-menarche years, risking over-diagnosis. Long-term cardiovascular event data are weak and inconsistent despite clearly adverse risk factors. Anti-Müllerian hormone's diagnostic role is unsettled. Inositol evidence is low quality. Most trials are small, short and conducted in white and obese populations, under-representing lean disease and South Asian women, who have greater metabolic severity. Male relatives' phenotype is barely studied. Under-diagnosis at about 70 per cent means most of the burden is invisible to health systems.

> **Depth.** Starts in: an ovarian follicle. Size: 5 mm†; depth +10.56. First complaint: about 15 years († onset around puberty); time depth 51.34. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status, given by stratum: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Pelvic inflammatory disease

What it is. Infection ascends from the vagina and cervix into the womb, tubes and pelvis. It causes pain and fever, and can scar the tubes, leading to infertility and ectopic pregnancy.

Measured. Lifetime prevalence of self-reported pelvic inflammatory disease in United States women is about 4.4 per cent (NHANES); incidence has fallen in high-income countries with chlamydia screening and remains substantial.

Tubal factor infertility follows in about 10 to 12 per cent after one episode, about 20 to 35 per cent after two, and about 40 to 55 per cent after three or more†. The cumulative, stepwise damage is the central fact. Ectopic pregnancy risk is raised about six to ten times after an episode, and chronic pelvic pain follows in about 18 to 30 per cent of women†.

GBD 2019 includes this condition within maternal, gynaecological and sexually transmitted infection categories, and it is not a separate top-level cause with a clean DALY figure. Deaths are few and non-zero, through tubo-ovarian abscess and sepsis.

The underlying sexually transmitted infection burden drives it. The WHO STI fact sheet of 10 September 2025 gives 374 million new infections in 2020 of one of four curable sexually transmitted infections in people aged 15 to 49, with the 2020 breakdown in its body: trichomoniasis 156 million, chlamydia 129 million, gonorrhoea 82 million, syphilis 7.1 million. That page also contradicts itself on syphilis: its Key Facts give 8 million adults aged 15 to 49 infected in 2022 while its body gives 7.1 million new infections in 2020 — two different magnitudes and two different years on the same page, nowhere reconciled. Both are printed. The chlamydia and gonorrhoea figures are the reservoir driving this condition.

Cases are concentrated in women aged 15 to 25, the same group with the highest chlamydia prevalence. The highest burden is in sub-Saharan Africa, South Asia and Latin America, where screening and treatment access are limited. *Mycobacterium tuberculosis* is a significant cause of genital tract infection and tubal infertility in endemic regions — an important differential often omitted from Western accounts.

Where it starts. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the classic causes, and together they are identified in only about 30 to 50 per cent of cases†. Polymicrobial ascending infection with anaerobes, *Mycoplasma genitalium*, increasingly recognised, *Gardnerella*, and enteric and respiratory organisms; bacterial vaginosis is associated and may facilitate ascent.

Young age at first intercourse, multiple or new sexual partners, unprotected intercourse, and a partner with untreated infection form the behavioural risk set. Prior episodes are the strongest single predictor of another. Instrumentation: termination of pregnancy, IUD insertion, where risk is confined to the first three weeks or so after insertion and is small, and IUDs are not a long-term risk factor, which is a persistent misconception; hysteroscopy; endometrial biopsy.

Postpartum and post-abortal infection, especially after unsafe abortion, is a major cause in settings where safe abortion is unavailable.

Genital tuberculosis in endemic areas; and female genital schistosomiasis in parts of Africa, a significantly under-recognised cause of tubal damage and an independent HIV risk factor. Douching: CONTESTED — associated, with causality disputed. Protective: barrier contraception, combined oral contraceptives weakly and possibly via cervical mucus, monogamy, and treatment of partners.

Heritability is not meaningfully applicable, since this is an infectious disease, though host immune variation likely affects the severity of tubal scarring.

What is not known is why some women with chlamydia develop pelvic inflammatory disease and tubal damage while most do not — only about 10 to 15 per cent of untreated chlamydial infections ascend†. Host immune response and possibly repeated reinfection matter, and prediction is impossible. Diagnosis itself is unreliable: clinical diagnosis has a positive predictive value of only about 65 to 90 per cent against laparoscopy†, so both over- and under-treatment are common and much of the literature rests on an uncertain case definition. Whether screening reduces the condition is contested. And the pathogenic role of *Mycoplasma genitalium* and of the vaginal microbiome is unresolved.

Cure status. Two strata.

The acute infection, treated early: CURABLE. Antibiotics cure it in the great majority, with clinical cure of about 85 to 95 per cent†. Tubo-ovarian abscess requires drainage in addition to antibiotics and is then curable.

Established tubal scarring, infertility and chronic pain: RELIEF ONLY. The sequelae are not reversible. Tubal scarring, once established, is permanent: infertility, ectopic risk and chronic pain persist after the infection has gone. So the condition is curable only if treated early enough, and the window matters — a delay of more than two to three days from symptom onset roughly triples the risk of subsequent infertility and ectopic pregnancy (Hillis). Tubal factor infertility is treatable and not curable: tubal surgery has limited success, and IVF bypasses rather than repairs the damage.

So: curable acutely; relief only for the irreversible damage, which accrues from the first episode onward.

Prevention. Condom use: STRONG. Prompt treatment of chlamydia and gonorrhoea: STRONG — and treating sexual partners is essential to prevent reinfection, which drives cumulative tubal damage. Partner notification and treatment is cheap and under-delivered.

Chlamydia screening: MODERATE, and genuinely CONTESTED. The POPI trial (Oakeshott, *BMJ* 2010) found a non-significant reduction with screening; earlier US trials (Scholes 1996) found a significant reduction of about 56 per cent. Meta-analyses suggest a modest benefit, and national programmes, notably England's, have been criticised for uncertain cost-effectiveness. Both results are printed: screening is widely recommended and the magnitude of its prevention effect is uncertain.

Treating bacterial vaginosis before instrumentation: MODERATE. Antibiotic prophylaxis before termination of pregnancy and before IUD insertion in high-prevalence settings: MODERATE. Safe abortion access: STRONG for preventing post-abortal sepsis and pelvic inflammatory disease. Safe delivery and postpartum care: STRONG. Reducing partner numbers and delaying sexual debut: MODERATE, behavioural and hard to deliver. Treating female genital schistosomiasis with praziquantel, and genital tuberculosis, in endemic areas: MODERATE. HPV and hepatitis B vaccination do not prevent this condition and belong to the same service platform, and integrated sexual health services improve all outcomes.

Treatment. Treatment must be empirical and immediate. Do not wait for microbiology, because the tubal damage accrues during the delay. That is the single most important principle.

Outpatient regimens, typical per CDC and UK guidance, with local resistance governing the choice: ceftriaxone 500 mg to 1 g intramuscularly as a single dose with doxycycline 100 mg twice daily and metronidazole 400 to 500 mg twice daily, both for fourteen days. The alternative is ofloxacin or levofloxacin with metronidazole for fourteen days where gonorrhoea is unlikely or excluded, since quinolone resistance in gonorrhoea is now widespread and quinolone monotherapy is inadequate for gonococcal disease. Moxifloxacin where *Mycoplasma genitalium* is suspected or confirmed.

Drug status: ceftriaxone EML yes, off-patent, a few US dollars a course; doxycycline EML yes, off-patent, a few US dollars a course; metronidazole EML yes, Access group, off-patent, a few US dollars a course. The total drug cost of curing pelvic inflammatory disease is a few to tens of US dollars. For a condition that otherwise causes lifelong infertility, this is among the most cost-effective treatments in medicine, and the barrier is diagnosis and access, not cost.

Inpatient treatment for severe disease, pregnancy, abscess, failed outpatient therapy, inability to tolerate oral therapy, or diagnostic uncertainty: intravenous cefoxitin, cefotetan or ceftriaxone with doxycycline, or clindamycin with gentamicin, stepping down to oral therapy. Tubo-ovarian abscess: antibiotics plus drainage, image-guided percutaneous or laparoscopic, for abscesses above 4 to 7 cm or failing medical therapy.

Remove an IUD? Not routinely. Evidence suggests outcomes are similar with the IUD left in place for mild to moderate disease, with removal considered if there is no improvement at 48 to 72 hours. A commonly mishandled point.

Partner treatment is essential: treat partners from the preceding sixty days empirically for chlamydia and gonorrhoea regardless of their test results. Abstinence until both partners complete treatment. Test for HIV, syphilis and other infections, and offer HIV prevention. Analgesia with NSAIDs and paracetamol. Follow-up at 72 hours to confirm response, and retesting for reinfection at three months, since reinfection rates are high and drive cumulative damage.

Later management of the sequelae: adhesiolysis and tubal surgery have limited success; IVF for tubal factor infertility; multidisciplinary chronic pelvic pain management including pelvic floor physiotherapy and neuropathic agents for the 18 to 30 per cent with chronic pain. Antituberculous therapy for genital tuberculosis, and praziquantel for female genital schistosomiasis; praziquantel is an EML-listed medicine, in intestinal anthelminthics, antischistosomals and cysticidal medicines.

Simple means. Condoms are cheap, effective, and prevent the causative infections.

Immediate empirical treatment on clinical suspicion is a decision, not a technology. Treating promptly on clinical grounds rather than awaiting tests roughly triples the chance of preserving fertility compared with a delay of a few days. That is the highest-value action in the entry and it costs nothing.

Partner notification and treatment is a conversation plus a few US dollars of antibiotics, and it prevents the reinfection that causes cumulative tubal destruction; patient-delivered partner therapy works where clinic attendance is a barrier. Three off-patent, EML-listed antibiotics costing a few to tens of US dollars cure the disease.

Syndromic management under WHO-endorsed algorithms allows treatment without laboratory capacity, which is how most of the world's pelvic inflammatory disease must be managed; its specificity is imperfect and it prevents infertility. Education and open sexual health services, reducing stigma and delay in presentation. Safe delivery and safe abortion practice. Retesting at three months is cheap and catches reinfection.

The honest limit: a tubo-ovarian abscess needs drainage, and established tubal infertility needs IVF, which is expensive and unavailable to most. The simple means work almost entirely at the prevention and early-treatment stage, which is precisely where the leverage is.

Gaps. Clinical diagnosis is unreliable, with a positive predictive value of about 65 to 90 per cent, so incidence figures and trial populations are both uncertain, and there is no practical accurate diagnostic test. Whether chlamydia screening programmes reduce the condition at population level is genuinely contested, with trials disagreeing. The pathogenic role of *Mycoplasma genitalium* and the optimal regimen for it are unsettled amid rising macrolide resistance. Gonococcal antimicrobial resistance is advancing and threatens current regimens. Female genital schistosomiasis is substantially under-recognised and its contribution to tubal infertility in Africa is unquantified. Optimal management of an IUD left in situ rests on limited evidence. Burden data from low-income settings, where this condition causes the most infertility, are weak, and GBD does not model it separately. Partner treatment rates are low everywhere and poorly measured. The WHO STI fact sheet contradicts itself on syphilis magnitude and year.

> **Depth.** Starts in: Chlamydia trachomatis (elementary body). Size: 300 nm†; depth +1.72. First complaint: about 3.5 weeks († weeks after a sexually transmitted infection); time depth 46.40. One untreated course: about 14 days († about 2 weeks); depth 45.90.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Menstrual disorders: heavy menstrual bleeding, dysmenorrhoea, amenorrhoea and premenstrual syndrome

What it is. Periods that are too heavy, too painful, absent or irregular, or that bring severe mood symptoms beforehand. Common, often dismissed, and usually treatable.

Measured. Heavy menstrual bleeding affects about 20 to 30 per cent of women of reproductive age, objectively defined as over 80 mL a cycle, though the practical definition is now symptom-based: blood loss interfering with quality of life. It is a leading cause of iron deficiency anaemia in women worldwide, and that is the principal measurable harm; iron deficiency affects about 30 per cent of reproductive-age women and anaemia about 500 million women globally on the WHO figure†. GBD 2023 Table 1 gives dietary iron deficiency ninth among YLD causes at 39.3 million (95 per cent UI 24.8 to 63.5). Heavy bleeding is also a leading indication for hysterectomy.

Dysmenorrhoea has a prevalence of about 45 to 95 per cent of menstruating women depending on definition, with severe, activity-limiting pain in about 15 to 20 per cent†. It is the leading cause of recurrent short-term school and work absence in young women.

Primary amenorrhoea affects about 0.3 to 1 per cent and secondary amenorrhoea about 3 to 5 per cent of reproductive-age women, excluding pregnancy and lactation.

Premenstrual symptoms occur in up to 80 per cent, with clinically significant premenstrual syndrome in about 20 to 30 per cent and premenstrual dysphoric disorder in about 1.8 to 5.8 per cent by strict DSM-5 criteria.

GBD 2019 includes some of these within gynaecological conditions and they are not cleanly separated top-level causes. Deaths are essentially none directly, though severe anaemia contributes to maternal mortality. Dysmenorrhoea peaks in the late teens and twenties and declines with age and parity; heavy bleeding peaks in the forties, in perimenopause.

Where it starts. For heavy menstrual bleeding, the PALM-COEIN framework is the standard classification. Structural (PALM): polyp, adenomyosis, leiomyoma, and malignancy or hyperplasia. Non-structural (COEIN): coagulopathy — and von Willebrand disease is present in about 5 to 20 per cent of women with heavy menstrual bleeding† and is massively under-diagnosed; ovulatory dysfunction, from polycystic ovary syndrome, perimenopause, thyroid disease or hyperprolactinaemia; endometrial causes; iatrogenic causes, from a copper IUD, anticoagulants or antiplatelets; and not otherwise classified. Also obesity, through anovulation and raised oestrogen, and hypothyroidism.

For dysmenorrhoea: primary dysmenorrhoea arises from excess endometrial prostaglandin production, PGF2α, causing myometrial hypercontractility and ischaemia, which is why NSAIDs, as prostaglandin synthesis inhibitors, work so well. Risk factors: young age, early menarche, long or heavy flow, nulliparity, smoking, family history. Secondary dysmenorrhoea arises from endometriosis, which is commonest and the usual reason for diagnostic delay, adenomyosis, fibroids, pelvic inflammatory disease, cervical stenosis, obstructive Müllerian anomaly, or an IUD.

For amenorrhoea: pregnancy, always to be excluded first. Hypothalamic causes: energy deficiency relative to expenditure, giving functional hypothalamic amenorrhoea from low energy availability, excessive exercise, eating disorders and stress, where the key driver is energy deficit, as part of the Relative Energy Deficiency in Sport syndrome, with consequences for bone density. Pituitary causes: hyperprolactinaemia from a prolactinoma or from drugs, and Sheehan syndrome. Ovarian causes: polycystic ovary syndrome, primary ovarian insufficiency, chemotherapy and radiotherapy, Turner syndrome, fragile X premutation. Outflow causes: Müllerian agenesis, imperforate hymen, transverse septum, and Asherman syndrome from intrauterine adhesions after instrumentation or infection. Thyroid disease; congenital adrenal hyperplasia; constitutional delay.

For premenstrual syndrome and premenstrual dysphoric disorder: normal cyclical ovarian hormone fluctuation with abnormal central sensitivity. The hormones are not abnormal; the response to them is. That was confirmed by the observation that suppressing the cycle abolishes symptoms and re-adding hormones reproduces them only in susceptible women (Schmidt, *NEJM* 1998). A serotonergic mechanism is implicated, with allopregnanolone and GABA-A sensitivity. Heritability of premenstrual syndrome is about 30 to 56 per cent from twin studies, with *ESR1* and other polymorphisms implicated. A history of trauma, mood disorder and stress raises risk.

Dysmenorrhoea shows familial clustering, with twin heritability of about 40 to 55 per cent in some studies†; heavy menstrual bleeding heritability is poorly quantified apart from the inherited coagulopathies.

What is not known is why prostaglandin production varies so much between women. Why premenstrual dysphoric disorder affects a small minority given identical hormonal fluctuation — the central sensitivity mechanism is demonstrated and not explained at a molecular level. Why adenomyosis causes such severe symptoms in some. The threshold of energy deficit that suppresses the hypothalamus varies greatly and unpredictably between individuals. And whether menstrual pain sensitises the central nervous system in a way that predisposes to later chronic pain syndromes is an open and important question.

Cure status. This must be split, and each stratum named.

Heavy menstrual bleeding: CONTROLLABLE medically, and CURABLE where there is a treatable structural or systemic cause — polypectomy, hysteroscopic myomectomy, thyroid treatment, or treating a coagulopathy can cure it. Hysterectomy and endometrial ablation are definitively curative for the bleeding. Medical therapy controls while taken.

Primary dysmenorrhoea: CONTROLLABLE. NSAIDs and hormonal suppression are highly effective, and the condition also naturally improves with age and after childbirth, so it is partly self-limiting over a lifetime.

Secondary dysmenorrhoea: it depends on cause — CURABLE if a polyp or stenosis, CONTROLLABLE if endometriosis or adenomyosis, with adenomyosis curable by hysterectomy.

Functional hypothalamic amenorrhoea: CURABLE. Restoring energy availability — increased intake, reduced training load, weight restoration — restores menstruation in the majority, which is a genuine cure addressing the cause.

Hyperprolactinaemia: CURABLE. Dopamine agonists normalise prolactin and restore cycles in about 80 to 90 per cent†: among the most satisfying treatments in endocrinology.

Primary ovarian insufficiency: CONTROLLABLE, not curable. Hormone replacement is required until the natural age of menopause, and fertility usually requires donor oocytes.

Premenstrual syndrome and premenstrual dysphoric disorder: CONTROLLABLE. SSRIs and cycle suppression are effective, and the condition is CURABLE by oophorectomy in extreme refractory cases, which is rarely justified.

Prevention. Combined hormonal contraception prevents dysmenorrhoea and heavy bleeding: STRONG for symptom prevention while used. Maintaining adequate energy availability and avoiding excessive exercise relative to intake: STRONG for preventing functional hypothalamic amenorrhoea and the associated bone loss, with education of athletes, dancers and coaches as the practical mechanism. Screening for and treating iron deficiency: STRONG for preventing the main harm of heavy bleeding.

Testing for von Willebrand disease and other coagulopathies in women with heavy bleeding since menarche: MODERATE — it is present in 5 to 20 per cent, is routinely missed, and identifying it changes management entirely. Avoiding smoking: WEAK for dysmenorrhoea. Regular moderate exercise: MODERATE for both dysmenorrhoea and premenstrual syndrome. Weight management: MODERATE for anovulatory bleeding.

Early investigation of severe dysmenorrhoea rather than normalising it: MODERATE. That is how endometriosis diagnostic delay is reduced, and dismissing severe period pain as normal is the single largest preventable harm in this entry.

Treatment. For heavy menstrual bleeding. The levonorgestrel intrauterine system reduces blood loss about 70 to 95 per cent† and is the most effective medical treatment and superior to all oral options; it also treats dysmenorrhoea and adenomyosis and provides contraception. EML yes; tens of US dollars per device for five to eight years. The outstanding value intervention here.

Tranexamic acid reduces loss about 40 to 50 per cent†, is taken only during bleeding, and is non-hormonal, so it suits where hormones are declined or contraindicated. It is an EML-listed medicine under medicines affecting coagulation, section 10.2 core, and under other medicines administered to the mother, section 22; off-patent; tens of US dollars a year.

NSAIDs, mefenamic acid and naproxen, reduce loss about 20 to 40 per cent and relieve pain; off-patent, EML-listed†, a few to tens of US dollars a year. Combined oral contraceptives reduce loss about 35 to 50 per cent† and are cheap and off-patent. Cyclical or continuous progestogens, depot medroxyprogesterone, and GnRH analogues for short-term severe cases.

Iron replacement: oral ferrous salts first line, and intravenous iron for severe anaemia or oral intolerance. Oral iron EML yes, about US$2 to 15 a year, with an indicative UNICEF price of US$1.43 on one catalogue page and US$1.60 on another per bottle of 100 iron 60 mg tablets, and an iron-plus-folic-acid combination at US$1.24 per bottle of 100, October 2026. Treating the anaemia often resolves the symptoms the woman presents with.

Treat the specific cause: polypectomy, hysteroscopic myomectomy, levothyroxine for hypothyroidism — levothyroxine is an EML-listed medicine, section 18.7, for hypothyroidism, first added in 1977 — and desmopressin or factor concentrate for von Willebrand disease. Endometrial ablation is effective, uterus-

conserving and a day case, requiring completed childbearing and reliable contraception. Hysterectomy is definitive.

For dysmenorrhoea. NSAIDs are first line and highly effective, with a number needed to treat of about two to three against placebo for pain relief, and superior to paracetamol; start before or at the onset of bleeding. Ibuprofen, naproxen and mefenamic acid: EML yes; off-patent; a few to tens of US dollars a year. One of the clearest, cheapest wins in this book. Combined hormonal contraception, continuous or extended use skipping withdrawal bleeds, is effective and cheap. The levonorgestrel intrauterine system, and depot progestogen. Investigate for secondary causes if NSAIDs plus hormonal therapy fail — that is the trigger for considering endometriosis.

For amenorrhoea. Treat the cause: energy restoration and reduced training for functional hypothalamic amenorrhoea, with psychological support and eating disorder treatment where relevant; cabergoline or bromocriptine for hyperprolactinaemia, off-patent, tens to hundreds of US dollars a year; levothyroxine for hypothyroidism. Hormone replacement for primary ovarian insufficiency and for prolonged hypo-oestrogenism is essential for bone and cardiovascular protection until about age 50, with oestradiol and a progestogen, off-patent and cheap; transdermal oestradiol with cyclical progestogen is often preferred over the combined pill for bone outcomes in young women. Surgical correction of outflow obstruction, and hysteroscopic adhesiolysis for Asherman syndrome. Calcium, vitamin D and weight-bearing exercise for bone protection.

For premenstrual syndrome and premenstrual dysphoric disorder. SSRIs are first-line for premenstrual dysphoric disorder and are effective either continuously or dosed only in the luteal phase — an unusual and useful property, since the response is rapid, unlike in depression. Response rates are about 60 to 70 per cent†, with a number needed to treat of about three to four. Fluoxetine and sertraline: EML yes; off-patent; tens of US dollars a year. Combined hormonal contraception, continuous, with drospirenone-containing preparations having the best evidence, suppresses cycling. GnRH analogues with add-back for severe refractory cases, and oophorectomy as a last resort after confirmed response to GnRH suppression. CBT is effective, comparable to drugs in some trials, and durable. Calcium supplementation at 1,200 mg a day reduced symptoms significantly in a randomised trial (Thys-Jacobs 1998), and is cheap and low-risk; vitamin B6 has weaker supporting evidence.

Simple means. NSAIDs for dysmenorrhoea have a number needed to treat of two to three at a few to tens of US dollars a year. Taken early and at an adequate dose, this resolves most primary dysmenorrhoea, and the commonest reason for failure is an inadequate dose or starting too late.

Heat application — a hot water bottle, a warm bath, a heat patch — is comparable to NSAIDs for menstrual pain in randomised trials and can be combined with them. Free.

Exercise gives a Cochrane-supported reduction in dysmenorrhoea pain intensity and also helps premenstrual syndrome. Tranexamic acid at tens of US dollars a year gives 40 to 50 per cent less bleeding with no hormones. The levonorgestrel intrauterine system gives 70 to 95 per cent bleeding reduction at a few dollars a year amortised. An iron-rich diet and cheap oral iron treats the anaemia that causes the fatigue, at pennies. Calcium at 1,200 mg a day for premenstrual syndrome is trial-supported and cheap. Energy restoration and reduced training load for hypothalamic amenorrhoea: the cure is food and rest, not a drug. CBT and self-management for premenstrual syndrome needs no supply chain.

Menstrual cups and washable pads are reusable and locally producible, and they directly address the period poverty that causes school absence: a significant equity intervention in low-income settings. Menstrual tracking identifies the cyclical pattern needed to diagnose premenstrual dysphoric disorder and to time treatment, and needs paper or a phone. And not dismissing severe period pain is free, and the key to earlier endometriosis diagnosis.

The honest limit: structural causes need procedures, and primary ovarian insufficiency needs manufactured hormones.

Gaps. Definitions are inconsistent: heavy menstrual bleeding has moved from an objective 80 mL definition to a subjective one, so prevalence data are not comparable. Von Willebrand disease is massively under-diagnosed in this population and its true prevalence in heavy bleeders is uncertain, within a 5 to 20

per cent range. Premenstrual dysphoric disorder's biological mechanism is demonstrated and unexplained, and diagnosis requires prospective charting that is rarely done. The long-term bone and cardiovascular consequences of years of functional hypothalamic amenorrhoea are under-quantified, and the optimal hormone regimen for young hypo-oestrogenic women is unsettled, between the combined pill and transdermal oestradiol. Calcium and vitamin B6 evidence for premenstrual syndrome rests on few trials. Adenomyosis is under-diagnosed and its separation from endometriosis is unclear. Most trials are small and short, and almost all are from high-income settings; period poverty's health effects are poorly measured. Dysmenorrhoea's possible role in later chronic pain sensitisation is an open question with large potential significance.

> **Depth.** A group of menstrual complaints. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Menopause-related conditions

What it is. Periods stop permanently, usually around age 50, because the ovaries run out of follicles. Falling oestrogen causes hot flushes, sleep disturbance, vaginal dryness and accelerated bone loss. It is a normal life stage with treatable symptoms.

Measured. Median age at natural menopause is about 50 to 52 years in high-income countries, and earlier in many low- and middle-income settings, about 46 to 49 in parts of South Asia, Africa and Latin America, with smoking, parity, nutrition and socioeconomic factors contributing. About 1.2 billion women worldwide will be postmenopausal by 2030, and roughly 47 million women enter menopause each year†.

Vasomotor symptoms — hot flushes and night sweats — affect about 60 to 80 per cent of women, and are moderate to severe in about 25 to 30 per cent. The median duration of vasomotor symptoms is about 7.4 years (SWAN), and longer, about nine to eleven years, for women whose symptoms begin in perimenopause — substantially longer than the year or two once assumed. That revision matters for treatment duration decisions.

Genitourinary syndrome of menopause, vulvovaginal atrophy, affects about 50 to 70 per cent and, unlike flushes, is progressive and does not resolve with time, which is a key distinction. Premature ovarian insufficiency, below 40 years, affects about 1 per cent, and early menopause, at 40 to 45, about 5 per cent†. Postmenopausal bone loss runs at about 2 per cent a year of trabecular bone in the early postmenopausal years; see the osteoporosis entry.

Menopause is not a disease category in GBD with a separate DALY total, since menopause itself is physiological. Symptom reporting varies considerably between cultures, with lower reported flush rates in Japan and parts of Southeast Asia, which may reflect diet, body composition, reporting conventions and language as much as biology — a genuinely unresolved observation.

Where it starts. Follicular depletion is the necessary and sufficient cause of natural menopause, and is determined largely by the ovarian reserve established before birth.

Heritability of age at menopause is about 44 to 65 per cent from twin and family studies; GWAS has found over 290 loci, many in DNA damage response and repair genes — *BRCA1*, *CHEK2*, *MCM8*, *HELB* — and the identified variants explain a modest share. A mother's age at menopause predicts a daughter's.

Smoking advances menopause by about one to two years, dose-dependently: the clearest modifiable factor.

Iatrogenic and early causes: bilateral oophorectomy, which is immediate and gives more severe symptoms; chemotherapy; pelvic radiotherapy; hysterectomy, which advances it even with ovarian conservation; fragile X premutation; Turner syndrome and other X abnormalities; autoimmune oophoritis; galactosaemia; mumps oophoritis. Lower body weight, nulliparity, lower socioeconomic status and earlier menarche in some analyses, while higher parity and oral contraceptive use are associated with later menopause.

Risk factors for severe symptoms specifically: smoking, obesity through adipose tissue and thermoregulation, African-American ancestry, which gave longer and more severe vasomotor symptoms in SWAN, anxiety and depression, lower education, and surgical menopause.

What is not known is why symptom severity and duration vary so enormously between women with identical hormone profiles. The thermoregulatory mechanism — a narrowed thermoneutral zone, KNDy neuron hyperactivity in the hypothalamus — is now partly understood and gave rise to the neurokinin-3 antagonists, and individual variation remains unexplained. Why reported symptom rates differ so much between cultures. Whether the cardiovascular timing hypothesis for hormone therapy is correct. And the cause of the cognitive brain fog many women report, and whether it is hormonal, sleep-mediated or both.

Cure status. Menopause is not a disease and is not cured. Its symptoms are the treatable target, and each is given its own label.

Vasomotor symptoms: CONTROLLABLE, and ultimately SELF-LIMITING. Hormone therapy reduces frequency and severity by about 75 to 80 per cent, far above placebo, and symptoms resolve spontaneously in most women over about seven to ten years. So treatment is a bridge rather than a lifelong commitment, for most.

Genitourinary syndrome: CONTROLLABLE, and not self-limiting. It progresses without treatment and responds durably to local oestrogen, which must be continued. The most undertreated menopausal condition.

Bone loss: CONTROLLABLE and preventable; see the osteoporosis entry.

Premature ovarian insufficiency: CONTROLLABLE, not curable. Fertility is usually irrecoverable, requiring donor oocytes, and hormone replacement until about age 50 is necessary rather than optional, for bone and cardiovascular protection.

The honest framing: the goal is symptom control and risk reduction over a defined period, not reversal of a physiological transition.

Prevention. Menopause itself is not preventable: not applicable. Smoking cessation: MODERATE — it avoids advancing menopause by one to two years and reduces symptom severity.

Ovarian conservation at hysterectomy where oncologically appropriate: MODERATE. It avoids surgical menopause, which produces more severe symptoms and, if it occurs before age 45 without hormone replacement, is associated with increased cardiovascular and all-cause mortality. An important and sometimes overlooked surgical decision.

Hormone replacement after early or premature menopause until about age 50: STRONG for preventing osteoporosis and cardiovascular disease. That is prevention of harm, not elective symptom treatment, and the risk-benefit calculus is quite different from that of hormone therapy started at 55. Weight management, exercise and not smoking: MODERATE for symptom severity. Calcium, vitamin D and weight-bearing or resistance exercise: STRONG for bone protection.

Treatment. Menopausal hormone therapy is the most effective treatment for vasomotor symptoms, giving about a 75 to 80 per cent reduction in frequency and severity†. Oestrogen alone if hysterectomised; oestrogen plus a progestogen if the uterus is present, where the progestogen is required to prevent endometrial hyperplasia and cancer.

Transdermal oestradiol is preferred where available: it avoids first-pass hepatic effects and carries little or no increased venous thromboembolism or stroke risk, unlike oral oestrogen. Micronised progesterone and dydrogesterone appear to carry lower breast cancer risk than the older synthetic progestogens.

On risks, stated accurately. The Women’s Health Initiative findings of 2002 were widely misread and caused a collapse in prescribing now regarded as having harmed a generation of women. Current understanding: for a healthy woman starting hormone therapy under age 60 or within ten years of menopause, absolute risks are small and benefits generally outweigh them. Combined hormone therapy is associated with roughly one extra breast cancer per 1,000 women per year of use, approximately and duration-dependently; oestrogen-only therapy shows no increase, and in the Women’s Health Initiative a

non-significant decrease. Oral, not transdermal, oestrogen roughly doubles a low baseline venous thromboembolism risk. Hormone therapy reduces fracture and colorectal cancer, and improves genitourinary symptoms and quality of life.

Oestradiol and most progestogens are off-patent; EML status: estradiol and progestogens appear on the EML; tens to hundreds of US dollars a patient-year generically, and cheaper in some markets. Contraindications: oestrogen-sensitive cancer, active venous thromboembolism, active liver disease, unexplained vaginal bleeding, recent stroke or myocardial infarction.

Vaginal, local oestrogen for genitourinary syndrome is highly effective with minimal systemic absorption, and safe for long-term use including, with specialist input, in many breast cancer survivors. It treats dryness, dyspareunia, urgency and recurrent urinary tract infection. Off-patent; tens to hundreds of US dollars a year. Grossly under-prescribed relative to the 50 to 70 per cent prevalence: the biggest care gap in this entry.

Vaginal moisturisers and lubricants are effective for dryness and dyspareunia, cheap, available without prescription, and first-line for those avoiding hormones; ospemifene and vaginal DHEA, prasterone, are alternatives.

Non-hormonal drugs for vasomotor symptoms, for women who cannot or will not take hormones. SSRIs and SNRIs — paroxetine, venlafaxine, escitalopram — reduce flushes about 40 to 65 per cent against about 30 per cent for placebo†; off-patent; tens of US dollars a year. Note that paroxetine interferes with tamoxifen metabolism, which is relevant in breast cancer. Gabapentin and pregabalin are effective and useful for night sweats; off-patent, cheap. Clonidine is modestly effective, off-patent and very cheap, with side effects limiting use. Oxybutynin is effective in trials, with anticholinergic burden a concern. Fezolinetant and elinzanetant, neurokinin-3 receptor antagonists, are a new non-hormonal class targeting the KNDy pathway directly and reduce flush frequency significantly, with fezolinetant giving about a 60 per cent reduction against about 45 per cent for placebo in the SKYLIGHT trials; on patent at about US$6,000 a year US list†, with liver monitoring required. Effective and very expensive relative to the off-patent alternatives.

CBT and mindfulness are effective for the bother and impact of flushes and for sleep, and are recommended in NICE and international guidance; they do not reduce flush frequency much and substantially reduce distress. No supply chain beyond a trained therapist, and deliverable as self-help or group work.

Bone protection with calcium, vitamin D, and resistance and weight-bearing exercise, with bisphosphonates where indicated; see the osteoporosis entry, and note that no bisphosphonate is on the EML for osteoporosis. Hormone therapy itself prevents fracture. Cardiovascular risk management — blood pressure, lipids, glucose, smoking: the menopause consultation is a valuable opportunity for this, and arguably matters more for lifespan than symptom control.

Testosterone for persistent low sexual desire after other causes are addressed: the evidence supports benefit for sexual function, and there is no licensed female preparation in most countries, so off-label male preparations are used at a fraction of the dose.

Not supported or CONTESTED: compounded bioidentical hormones, which are unregulated, of inconsistent dosing and without safety data, and are distinct from regulated body-identical oestradiol and micronised progesterone, which are evidence-based; black cohosh, red clover, evening primrose and phytoestrogen supplements, with inconsistent trial results and generally no better than placebo; ovarian rejuvenation; and vaginal laser therapy for atrophy, where randomised trials have been negative or no better than sham and regulators have warned about it.

Simple means. Layered clothing, a lower room temperature, fans, cool drinks, and avoiding triggers — alcohol, caffeine, spicy food, hot drinks — are simple thermoregulatory measures with modest but real effect and no cost.

CBT, paced breathing and mindfulness have trial-supported reduction in symptom bother and improve sleep. Regular exercise improves sleep, mood, bone and cardiovascular risk, while the effect on flush frequency itself is modest or absent, which should be stated honestly. Weight loss where overweight reduces flush frequency and severity measurably. Smoking cessation.

Vaginal lubricants and moisturisers, including plain, cheap options, give immediate relief of dyspareunia and are available without a prescription. Regular sexual activity or vaginal dilator use maintains vaginal calibre and elasticity in genitourinary syndrome. Pelvic floor muscle training for the urinary symptoms that accompany menopause. Sleep hygiene, and treating sleep apnoea, which increases after menopause. A calcium-rich diet, vitamin D from sunlight where feasible, and resistance and weight-bearing exercise give bone protection at essentially no cost.

Accurate information: much of the distress attached to menopause comes from the post-WHI misinformation about hormone therapy and from the framing of menopause as decline. Correcting that costs nothing.

The honest note: the cheap off-patent hormones — oestradiol, micronised progesterone, vaginal oestrogen — deliver most of the achievable benefit at tens to hundreds of US dollars a year, against thousands of US dollars a year for the newest non-hormonal agents.

Gaps. The Women's Health Initiative's interpretation and the timing hypothesis remain contested: whether hormone therapy started early is cardioprotective, neutral, or simply not harmful is not settled, and the definitive trial has not been done. Absolute risk figures for breast cancer differ between the WHI, the Million Women Study and the 2019 *Lancet* collaborative meta-analysis, and the differences between progestogen types are inferred from observational data. Long-term safety of the new neurokinin-3 antagonists is unknown. The reason for cross-cultural differences in symptom reporting is unexplained. Cognitive symptoms are poorly characterised and under-researched. Data on menopause in low- and middle-income countries, including age at menopause and symptom burden, are sparse, despite most postmenopausal women living there. Testosterone use in women lacks licensed preparations and long-term data. Vaginal laser was adopted commercially well ahead of evidence that has since been largely negative. And perimenopause, when symptoms often begin and contraception is still needed, is less studied than postmenopause.

> **Depth.** Starts in: an ovarian follicle. Size: 5 mm†; depth +10.56. First complaint: about 51 years ([B] the stock is laid down before birth; menopause around age 50); time depth 52.44. One untreated course: about 7 years († complaints last about 7 years); depth 50.64.
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> **Model reading.** Way of ending: let close. Layer: word. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Infertility, female and male

What it is. Failure to conceive after a year of regular unprotected intercourse. The cause may lie with either partner or both, and in a substantial minority no cause is found.

Measured. About 17.5 per cent of adults, roughly one in six, experience infertility during their lifetime (WHO, 2023 report), with little difference between high- and low-income regions. The WHO infertility fact sheet, printed 28 November 2025, gives a lifetime prevalence of approximately one in every six people of reproductive age worldwide, states that infertility affects millions of people with no exact count given on the page, and gives no period prevalence and no regional figures. It defines infertility as failure to achieve pregnancy after twelve months or more of regular unprotected sexual intercourse, notes that assisted reproductive technology has been available for more than three decades, and records that WHO issued its first global guideline on infertility on 28 November 2025.

Point prevalence of twelve-month infertility is about 12.6 per cent, against a lifetime figure of 17.5 per cent, and period prevalence figures vary with definition†. About 48 to 50 million couples are affected at any time globally, with earlier estimates of about 186 million people†. Both are printed.

Cause distribution, approximate and overlapping. Male factor contributes to about 40 to 50 per cent of cases and is the sole factor in about 20 to 30 per cent†. Ovulatory disorders about 25 per cent, with polycystic ovary syndrome dominant†. Tubal factor about 11 to 20 per cent, higher in sub-Saharan Africa, where pelvic inflammatory disease and unsafe abortion raise it substantially. Endometriosis about 5 to 15

per cent; uterine and cervical causes about 5 per cent†. Unexplained about 15 to 30 per cent† — a large and uncomfortable category.

It is not a GBD cause with mortality, and GBD 2019 estimated infertility DALYs on the order of about one million, disability only. Geography: sub-Saharan Africa has the highest secondary infertility rates, driven by infection — pelvic inflammatory disease, post-abortal and postpartum sepsis, genital tuberculosis, female genital schistosomiasis — that is, largely preventable causes. Meanwhile high-income countries face age-related infertility from delayed childbearing. The two epidemiologies are quite different and need different responses. Access to treatment is extremely unequal: IVF is available and affordable to a small minority globally, and in many countries is entirely out of pocket.

On sperm counts: meta-regression (Levine 2017, with a 2023 update) reported a decline of about 50 to 62 per cent in mean sperm concentration between 1973 and 2018 worldwide. This is CONTESTED — methodological criticisms concern the selection of studies, changing counting methods and population sampling — and the finding has been replicated with broader data and is taken seriously. The finding is published and replicated; its validity is disputed. Both positions are printed.

Where it starts. For women: age is the dominant factor in high-income settings. Fecundability falls from the early thirties and steeply after 35; by 40 to 41, per-cycle chance and IVF live birth rates fall markedly, driven mainly by oocyte aneuploidy, which rises with maternal age and is not correctable. That is the single hardest biological constraint in the field.

Ovulatory disorders: polycystic ovary syndrome, commonest, then hypothalamic amenorrhoea from energy deficit, hyperprolactinaemia, thyroid disease and primary ovarian insufficiency. Tubal damage: pelvic inflammatory disease and chlamydia, where risk rises stepwise with episodes, previous ectopic pregnancy, pelvic surgery, genital tuberculosis, schistosomiasis, endometriosis. Uterine causes: submucosal fibroids, polyps, Asherman syndrome, congenital anomalies, adenomyosis. Endometriosis. Obesity, which reduces fecundability and IVF success dose-dependently, and underweight. Smoking, which reduces fecundability by about 13 to 25 per cent† and advances menopause. Alcohol. Chemotherapy and radiotherapy. Coeliac disease.

For men: varicocele, present in about 15 per cent of men and about 35 to 40 per cent of men with primary infertility†; a history of cryptorchidism; testicular trauma or torsion; mumps orchitis; infection with chlamydia, gonorrhoea or tuberculosis. Obstruction: vasectomy, congenital bilateral absence of the vas from *CFTR* mutations in cystic fibrosis carriers, post-infective epididymal obstruction. Genetic causes: Klinefelter syndrome, 47,XXY, in about 10 to 12 per cent of men with azoospermia; Y chromosome microdeletions in the AZF regions in about 5 to 10 per cent of severe oligospermia or azoospermia†; *CFTR*; Kallmann syndrome.

Heat, occupational, from saunas or from a laptop; smoking; alcohol; anabolic steroids and testosterone use, which is a major and growing iatrogenic and self-inflicted cause, since exogenous testosterone suppresses spermatogenesis; opioids; cannabis; chemotherapy; sulfasalazine; some antifungals. Obesity; diabetes; endocrine disruptors and pesticides, which are CONTESTED, with associations reported and causation not established. Paternal age has a real but much smaller effect than maternal age.

Male infertility has a substantial genetic contribution, with sperm count heritability estimated at about 30 to 40 per cent in some analyses†. For female infertility, heritability operates largely through the conditions: polycystic ovary syndrome at about 70 per cent, endometriosis at about 50 per cent, and age at menopause at about 44 to 65 per cent†.

What is not known is the cause in the 15 to 30 per cent labelled unexplained — a large category that represents genuine ignorance rather than a diagnosis. In male infertility, about 30 to 50 per cent of cases remain idiopathic after full evaluation†. Whether and why sperm counts are declining. The functional significance of most sperm DNA fragmentation and of many genetic variants. Why some women with apparently normal investigations and young oocytes still fail to conceive, including with IVF, since implantation failure is poorly understood. And the endometrial receptivity window and recurrent implantation failure are areas of much commercial activity and little established science.

Cure status. This splits by cause, and the honest headline is that treatment often bypasses rather than cures.

CURABLE: ovulatory disorders, where ovulation induction restores fertility and cumulative live birth rates approach normal in polycystic ovary syndrome; hyperprolactinaemia, with dopamine agonists; hypothalamic amenorrhoea, by energy restoration, which is a true cure addressing the cause; thyroid disease; obstructive azoospermia, by surgical reconstruction or sperm retrieval; submucosal fibroids and polyps, by hysteroscopic removal; Asherman syndrome; varicocele repair, which improves parameters and pregnancy rates in selected men; and stopping exogenous testosterone or anabolic steroids, which often restores spermatogenesis over months.

RELIEF ONLY: tubal factor infertility, where IVF bypasses the tubes and the tubes remain damaged; severe male factor, where intracytoplasmic sperm injection bypasses almost every sperm defect, with a single sperm sufficient; and unexplained infertility treated by IVF.

RELIEF ONLY: age-related oocyte aneuploidy, the central unsolved problem, where no treatment restores oocyte quality and donor oocytes are the only effective route; primary ovarian insufficiency; and non-obstructive azoospermia with no retrievable sperm, where donor sperm or adoption are the options.

Unexplained infertility managed expectantly: SELF-LIMITING in the couples who conceive without treatment.

Prevention. This is where the greatest unexploited gain lies, especially globally.

Preventing and promptly treating sexually transmitted infections: STRONG — chlamydia and gonorrhoea treatment, partner treatment, condoms. Tubal factor infertility is largely preventable, and in sub-Saharan Africa it is the dominant preventable cause. Immediate empirical treatment of suspected pelvic inflammatory disease roughly triples the chance of preserving fertility compared with a few days' delay.

Safe abortion and safe delivery services: STRONG — post-abortal and puerperal sepsis are major preventable causes of secondary infertility. Smoking cessation: STRONG, affecting both sexes. Weight management: MODERATE, in both partners, improving fecundability and treatment success. Avoiding anabolic steroids and exogenous testosterone: STRONG — an increasingly common, entirely preventable cause. Treating genital tuberculosis and schistosomiasis in endemic areas: MODERATE. Mumps and rubella vaccination: MODERATE, for mumps orchitis. Early orchidopexy for cryptorchidism, and prompt treatment of testicular torsion: STRONG.

Fertility awareness, specifically about the effect of age: MODERATE as information, though the social and economic determinants of delayed childbearing are not individually solvable. Oocyte cryopreservation before about age 35 preserves options and is expensive and not a guarantee. Fertility preservation before gonadotoxic cancer treatment: STRONG — sperm, oocyte, embryo or ovarian tissue cryopreservation, frequently not offered, which is a documented care failure. Reducing occupational heat and toxin exposure: MODERATE. Limiting avoidable pelvic surgery and using minimally invasive techniques: MODERATE.

Treatment. A substantial proportion of couples with unexplained infertility conceive spontaneously with expectant management, which is why immediate intervention is not always correct, and why trials must have untreated comparison arms; the proportion is not given here. Investigation first: semen analysis, ovulation confirmation, tubal patency by hysterosalpingography or laparoscopy, ovarian reserve, and a sexual history including coital frequency and timing. Semen analysis is cheap and must come first: it is irrational to investigate a woman extensively before examining the man's contribution, yet this happens routinely.

For women. Ovulation induction with letrozole first-line: live birth 27.5 per cent against 19.1 per cent for clomiphene in polycystic ovary syndrome (Legro, *NEJM* 2014). Letrozole off-patent, tens of US dollars a cycle; clomiphene EML yes, off-patent, a few to tens of US dollars a cycle. Both extremely cheap and highly effective. Metformin as an adjunct in polycystic ovary syndrome; off-patent, a few to tens of US dollars a year, and an EML-listed medicine. Gonadotrophins second line, needing ultrasound monitoring, with risk of multiple pregnancy and ovarian hyperstimulation, at hundreds to thousands of US dollars a cycle. Dopamine agonists, cabergoline, for hyperprolactinaemia restore ovulation in 80 to 90 per cent†; off-patent, cheap. Weight loss and energy restoration.

Surgery: hysteroscopic polypectomy or myomectomy, adhesiolysis, endometriosis excision, tubal surgery with limited success, where IVF is usually preferred, and salpingectomy for hydrosalpinx before IVF, which improves IVF outcomes markedly.

IVF for tubal factor, failed ovulation induction, endometriosis, unexplained infertility and the age factor. The live birth rate per cycle is strongly age-dependent: roughly 35 to 45 per cent under 35, about 25 to 30 per cent at 35 to 37, about 15 to 20 per cent at 38 to 40, about 5 to 10 per cent at 41 to 42, and about 1 to 4 per cent above 42, using the woman's own oocytes. Cost thousands to tens of thousands of US dollars a cycle depending on country. Low-cost IVF protocols — simplified culture systems, mild stimulation, reduced monitoring — have achieved delivery in sub-Saharan Africa and Europe at a small fraction of standard cost, with the Walking Egg project reporting comparable outcomes at a few hundred dollars for laboratory costs. That is the main hope for access.

Donor oocytes are the effective treatment for age-related infertility and premature ovarian insufficiency, with live birth rates reflecting donor age rather than recipient age.

Not supported, and low-value add-ons: most IVF add-ons lack evidence of improved live birth. Preimplantation genetic testing for aneuploidy does not improve cumulative live birth rates in unselected patients (STAR and subsequent trials); endometrial scratching does not work, with a large randomised trial negative; and assisted hatching, immunotherapy, intralipids, time-lapse imaging and endometrial receptivity arrays lack supporting outcome evidence. The HFEA traffic-light system rates most as having no evidence of benefit. A significant consumer-protection problem: CONTESTED and negative.

For men. Treat the reversible causes: stop anabolic steroids and testosterone, treat infection, correct endocrine abnormality, stop gonadotoxic drugs where possible, reduce heat exposure. Varicocele repair improves semen parameters and increases pregnancy rates in men with clinical varicocele and abnormal semen, with odds ratios for pregnancy of about 1.5 to 2.6 in meta-analyses: a one-off low-cost operation. Gonadotrophin therapy for hypogonadotrophic hypogonadism is highly effective and restores spermatogenesis. Intrauterine insemination for mild male factor and unexplained infertility, often with ovarian stimulation, is far cheaper than IVF at hundreds to thousands of US dollars a cycle and is appropriate as a first step in many couples. Intracytoplasmic sperm injection bypasses nearly all sperm defects, a single viable sperm suffices, and it has transformed severe male infertility; it requires IVF infrastructure. Surgical sperm retrieval — PESA, TESA, TESE, micro-TESE — for obstructive and some non-obstructive azoospermia, with micro-TESE retrieving sperm in about 40 to 60 per cent of non-obstructive cases†. Vasectomy reversal is effective and often cheaper than IVF with intracytoplasmic injection and retrieval. Donor sperm where no sperm are retrievable. Antioxidants for male infertility: CONTESTED and WEAK — Cochrane suggests possible benefit, the evidence quality is low, and the large MOXI trial was negative. Widely sold, poorly supported.

For both: expectant management with timed intercourse for a defined period in young couples with unexplained infertility of short duration, since spontaneous conception is common and this avoids cost and risk. Psychological support: infertility carries high rates of depression, anxiety and relationship strain, and in many societies, particularly for women, it brings social exclusion, abandonment and violence. Counselling and peer support are part of care, not an optional extra.

Simple means. Correct timing and frequency of intercourse — every one to two days around the fertile window. Many couples presenting with infertility have mistimed or infrequent intercourse, and simple advice resolves it. Free, and the first thing to establish. Fertility awareness methods, using cervical mucus and basic cycle tracking, identify the fertile window without any device, and urinary LH kits are cheap where available.

Smoking cessation in both partners. Weight loss where overweight, and weight gain with reduced exercise where underweight: energy restoration cures functional hypothalamic amenorrhoea, and weight loss restores ovulation in many women with polycystic ovary syndrome. Food and rest as treatment. Reducing alcohol, and stopping cannabis and anabolic steroids. Avoiding testicular heat — loose clothing, no laptop on the lap, avoiding saunas and hot occupational exposure.

Letrozole or clomiphene at a few to tens of US dollars a cycle are cheap manufactured drugs that cure the commonest treatable female cause. Semen analysis needs a microscope and a trained technician, and is the

cheapest and highest-yield investigation, and it prevents needless invasive investigation of the woman. Prompt empirical treatment of pelvic inflammatory disease with a few to tens of US dollars of antibiotics is the single most cost-effective fertility-preserving action available globally. Condoms and partner treatment prevent the infections that cause tubal infertility. Low-cost IVF protocols bring assisted reproduction within reach at a fraction of conventional cost. Declining unproven IVF add-ons saves thousands of dollars with no loss of success. Counselling and peer support.

The honest limit: tubal blockage, azoospermia and age-related oocyte aneuploidy cannot be addressed by simple means. IVF and intracytoplasmic sperm injection require laboratories, and no intervention reverses oocyte ageing.

Gaps. Between 15 and 30 per cent of infertility is unexplained, and 30 to 50 per cent of male infertility is idiopathic: large admissions of ignorance. The sperm count decline is reported, replicated and genuinely contested, and its cause, if real, is unknown. Age-related oocyte aneuploidy has no treatment and is the field's central unsolved problem. Most IVF add-ons are marketed far ahead of evidence, and some — preimplantation genetic testing for aneuploidy, endometrial scratching — have been shown not to work after wide adoption, a continuing consumer-protection failure. Endometrial receptivity and recurrent implantation failure are poorly understood. The long-term health of children conceived by intracytoplasmic sperm injection, and the transmission of male infertility, need longer follow-up. Access data and outcome registries are absent for most of the world, and the WHO one-in-six figure rests on heterogeneous surveys with varying definitions; the WHO fact sheet itself gives no exact count, no period prevalence and no regional figures. Male infertility is under-researched relative to its 40 to 50 per cent contribution, and men are often not investigated at all. Fertility preservation before cancer treatment is inconsistently offered. The social consequences of infertility, particularly for women in low-income settings, are documented qualitatively and barely quantified.

> **Depth.** Many causes, in either partner. No depth is given.
>
> **Model reading.** Way of ending: restore proportion. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

What no longer holds

Two things recur across these three chapters often enough to be set down together, because each of them appears in four or five entries and neither is a finding about one disease.

Structural findings on imaging are largely age-normal

The same result has been found at four sites, by different investigators, with the same shape: abnormality is common in people without symptoms, prevalence rises with age, and the presence of the finding does not establish it as the cause of the pain.

The spine. In asymptomatic adults, disc degeneration is present in about 37 per cent at age 20 and about 96 per cent at 80; disc bulges in about 30 per cent at 20 and about 84 per cent at 80; disc protrusions in about 29 per cent at 20 and about 43 per cent at 80 (Brinjikji, *AJNR* 2015, systematic review of imaging in asymptomatic populations).

The cervical spine. Cervical disc degeneration is present in the majority of asymptomatic adults over 40, approaching 90 per cent and above in the elderly†.

The rotator cuff. Full-thickness tear prevalence in population imaging runs at roughly 10 per cent under 50, 20 to 25 per cent over 60, 30 to 50 per cent over 70 and over 50 to 60 per cent over 80 — and about a third to two-thirds of these tears are painless (Yamamoto, Minagawa).

The knee. Radiographic knee osteoarthritis affects over 30 per cent of those over 60, while symptomatic disease is less common, and radiographic and symptomatic disease correlate only moderately.

Tendons. Asymptomatic tendons frequently show marked abnormality on ultrasound and MRI, and pathology on imaging correlates poorly with symptoms.

The consequence is the same in each case. Imaging early, in the absence of red flags, does not improve outcomes; it drives surgery, and it labels an age-normal finding as a disease. That is why routine imaging is recommended against for low back pain, for neck pain, and before a trial of conservative management in shoulder disease — and why those recommendations are among the most widely violated in medicine.

Read in the net: what the scan shows is the depth at which the strand has been read, not the depth at which the pain is generated. A finding that is present in nearly everyone of a given age is a property of the age, not of the complaint. This is a reading, not a mechanism.

Widely used treatments that failed good trials

Ten named trials in these three chapters tested a standard treatment against placebo, sham or an active comparator and found no benefit, or found harm. Several of the treatments continue in widespread use.

Trial	Treatment tested	Result
FIDELITY (Sihvonen, *NEJM* 2013)	Arthroscopic partial meniscectomy for degenerative meniscal tear	No benefit over sham surgery
CSAW (Beard, *Lancet* 2018, 313 patients)	Arthroscopic subacromial decompression	No better than arthroscopy alone, placebo surgery; the difference against no treatment was not clinically important
FIMPACT (Paavola, *BMJ* 2018, 210 patients)	Subacromial decompression	No better than sham diagnostic arthroscopy at 2 years, and neither beat exercise therapy
HALT-IT (*Lancet* 2020, 12,009 patients)	Tranexamic acid for gastrointestinal bleeding	No reduction in death; increased venous thromboembolism, 0.8 vs 0.4 per cent, and seizures
PRESERVE (*NEJM* 2018, 5,177 patients)	N-acetylcysteine, and sodium bicarbonate, for contrast-associated kidney injury	No benefit over saline

Trial	Treatment tested	Result
GAIT (*NEJM* 2006, 1,583 patients)	Glucosamine and chondroitin for knee osteoarthritis	Neither, alone or combined, superior to placebo in the overall cohort
STEP (*NEJM* 2006)	Saw palmetto for benign prostatic hyperplasia	No benefit over placebo, even at high doses
SUSPEND (*Lancet* 2015, 1,167 patients)	Tamsulosin, and nifedipine, for spontaneous passage of ureteric stones	No benefit
RESTORE (*JAMA* 2021, 288 patients)	Platelet-rich plasma for knee osteoarthritis	No better than saline for knee pain or cartilage structure at 12 months
Coombes (*JAMA* 2013, 165 patients)	Corticosteroid injection for lateral elbow tendinopathy	Better at 4 weeks; significantly *worse* complete recovery at 1 year, 83 vs 96 per cent, with higher recurrence

Four more belong beside them, from the same chapters. **PACE** (*Lancet* 2014, 1,643 patients) found paracetamol identical to placebo for acute low back pain, with a median seventeen days to recovery in both arms. **SPACE** (*JAMA* 2018, 240 patients) and **OPAL** (*Lancet* 2023, 347 patients) found opioids no better than non-opioid analgesics and no better than placebo respectively, with worse pain at one year in both. And **Kearney** (*JAMA* 2021) found platelet-rich plasma no better than sham for Achilles tendinopathy. A further randomised trial, **RESTORE** in low back pain (*Lancet* 2023, 492 patients), is positive rather than negative, and shares its name with the platelet-rich plasma trial above; it found cognitive functional therapy gave clinically meaningful improvement sustained at 52 weeks.

Two patterns run through the negative list. First, the cheap thing often won: exercise beat decompression in FIMPACT, physical therapy was non-inferior to meniscectomy in METEOR, and education plus exercise beat corticosteroid injection in LEAP. Second, several of the failed treatments are still performed in volume. Arthroscopic meniscectomy and subacromial decompression continue at scale after sham-controlled negative trials; platelet-rich plasma is heavily marketed after adequately powered negative trials at three sites; glucosamine and saw palmetto are sold over the counter worldwide. Those are gaps between practice and evidence, not gaps in evidence.

One negative finding in this chapter runs the other way, and belongs here for completeness. Diverticulitis was treated with antibiotics for seventy years. DIABOLO and AVOD together tested that, found no demonstrated benefit on recovery, complications, recurrence or surgery in immunocompetent patients with CT-confirmed uncomplicated disease, and found hospital stay shorter without them. The guidelines changed. The treatment was not just ineffective in the trials; its failure put the underlying infective model of the disease in doubt, and that question is still open.

Appendix to this chapter: where the checked figures came from

The front matter explains how figures are marked in this book. This note records which sources the checked figures in this chapter were read from.

No figure in this chapter is an unsourced estimate. The order-of-magnitude price estimates in the underlying material were either replaced by a sourced figure, kept with their market range stated, or written out in words.

The figures read off their sources in this chapter rest on: the GBD 2021 low back pain condition paper, read for the full set of low back pain figures with their uncertainty intervals; the GBD 2023 capstone Table 1, read for the YLD ranking and counts; the electronic WHO Essential Medicines List, 24th List (2025), queried medicine by medicine; NICE NG147, read live for the diverticular disease guideline text; the WHO fact sheets on musculoskeletal health, osteoarthritis, low back pain, kidney disease, oral health, infertility, abortion, falls, physical activity and sexually transmitted infections, read 19 October 2026; the named primary papers for the diverticular disease entry — Granlund 2012, Crowe 2011, Peery 2012, Strate 2008, Strate 2011, Daniels 2017; and the UNICEF Supply Catalogue indicative prices, read 19 October 2026 and printed as indicative and dated rather than as prices.

Four WHO pages in this chapter contradict themselves, and both figures are printed in each case: musculoskeletal health, on a headline of 1.71 billion against a component total of about 2.5 billion; osteoarthritis, on the age share, 73 per cent against 70 per cent; low back pain, on the age of greatest prevalence, up to 80 years against 80 to 85 years; and sexually transmitted infections, on syphilis, 8 million in 2022 against 7.1 million in 2020. One published paper in this chapter contradicts itself, and both figures are printed: Crowe 2011, on the fibre hazard ratio, 0.59 (0.46 to 0.78) in the abstract against 0.58 (0.46 to 0.73) in the results.

End of chapter.

Chapter 17 — Reproduction, the Perinatal Period, Developmental Anomalies, and Injury

ICD-11 chapters 18, 19, 20 and 22

Introduction

Four ICD-11 chapters are set together here because they share a population and a logic. Chapter 18 covers pregnancy, childbirth and the weeks after. Chapter 19 covers what happens to a baby in its first month. Chapter 20 covers the things that form wrongly before birth. Chapter 22 covers injury and poisoning, which is what kills the young adults the first three chapters produced. Forty-nine entries follow.

The logic they share is that almost nothing in them is a slow disease. These are conditions with a window. A postpartum haemorrhage is decided in an hour, an obstructed labour in a day, a neural tube in the fourth week after conception, a drowning in four minutes, a crush injury in the second the slab comes off. The clinical question in this chapter is rarely what to give. It is whether anything at all is within reach while the window is open.

Asking that question across all forty-nine entries produces one finding that reorganises the chapter, and arguably the book. **Three measures with large reported effects in these four chapters are not clinical.** They are a pesticide ban, a flour additive and a veterinary vaccination campaign. None is delivered by a clinician to a patient.

Sri Lanka's pesticide regulation. Successive bans from 1984 onward removed named agents from the national market. The suicide rate had risen about eight-fold from 1950 and peaked at 47 per 100,000 in 1995†, with pesticide poisoning accounting for more than two-thirds of suicides at that peak. The overall rate then fell 70 per cent over roughly two decades†, and fell by half again after the 2008 to 2011 bans on dimethoate, fenthion and paraquat†. The reported result is **about 93,000 lives saved over twenty years at a direct government cost of under US$50 per life saved**†. Pesticide use rose over the same period, from 1,571 tons in 1990 to 2,260 tons in 2018†, so the measure removed specific agents rather than reducing agricultural chemical use. The source does not state which study reports the 70 per cent decline, the 93,000 lives or the cost per life saved, and the primary papers could not be fetched.

Folic acid fortification of flour. A neural tube closes by the twenty-eighth day after conception, before most pregnancies are recognised, so a supplement a woman takes when she knows she is pregnant is already late. Putting the vitamin in the flour removes the timing problem entirely. The measured result is a **25 to 50 per cent fall in neural tube defect prevalence in every country that has done it**: the United States from 10.8 to 6.9 per 10,000 births, a fall of 36 per cent; Chile from 17.1 to 9.7, 43 per cent; Canada 46 per cent†. The cost is **of the order of one to ten cents per person per year**. The intervention is a decision taken at a mill.

Mass dog vaccination against rabies. Rabies is essentially always fatal once symptomatic, and dogs transmit 99 per cent of human cases. Vaccinating **70 per cent of the dog population interrupts transmission**†, at **about a dollar or less per dog**. Human post-exposure prophylaxis, the alternative, has an average cost of US$108 per course in 2018, according to the WHO rabies fact sheet and must be given to every exposed person for as long as the dogs remain unvaccinated. Canine rabies has been removed from Europe, most of the Americas and parts of Asia by vaccination; three countries have been validated as having eliminated dog-mediated human rabies.

None of the three falls inside a health-service budget. A pesticide ban is agriculture and justice, flour fortification is food regulation and industry, dog vaccination is veterinary. This is a recurring reason they are underfunded relative to their measured effect.

Below them come the cheap clinical measures, and several are the best-evidenced interventions in the book. **Kangaroo mother care** reduced 28-day mortality in low birth weight infants from 15.7 to 12.0 per cent, a relative risk of 0.75 (95 per cent CI 0.64 to 0.89), number needed to treat about 27, across 3,211 infants in five countries. It costs a length of cloth. **Magnesium sulfate** reduced eclampsia from 1.9 to 0.8 per cent, a relative reduction of 58 per cent (40 to 71), number needed to treat 91, across 10,141 women in 33 countries; a UNICEF indicative price in October 2026 put the 5 g ampoule at about US$0.33. **Antenatal dexamethasone** costs under a dollar a course, and US$0.24 a tablet at the same indicative prices. **Ponseti casting** corrects about 90 per cent of clubfeet initially at US$22.46 per DALY averted from one source and about US$109 from arithmetic on another source's figures, five-fold apart, and the clubfoot entry prints a relapse rate, using plaster and water. **Tranexamic acid within three hours** of injury reduced all-cause trauma mortality from 16.0 to 14.5 per cent, relative risk 0.91 (0.85 to 0.97), number needed to treat about 67, across 20,211 patients in 40 countries, at about one to two dollars a gram†. And **fifteen minutes of soap and water after an animal bite** substantially reduces rabies risk before any vaccine is involved; there the intervention is knowledge.

Against that list, set the expensive items. **Surfactant** costs hundreds to thousands of US dollars a dose and is the most effective specific treatment for neonatal respiratory distress syndrome. **Brexanolone** launched in the United States at US$34,000 a course and **zuranolone** at US$15,900, for a condition whose highest measured prevalence is in countries where neither is available. **Heat-stable carbetocin** solves the cold chain problem that limits oxytocin, and its access price is not public. These are not bad drugs. They are effective drugs that do not reach the populations carrying the burden, and the pattern is consistent enough across the chapter to be worth stating once: in these four chapters, several of the cheapest interventions are old and off-patent. Listing on the WHO Essential Medicines List is not checked in this chapter, and each such claim is to be read as carrying a dagger.

On the figures in this chapter. The dossier these entries were built from carried no per-figure provenance marks. Under the book's convention a figure therefore carries a dagger unless the source and year are named in the text. Figures were read off their source only where they came from a WHO page or a primary report in the retrieval round of October 2026. The effect is that a great deal of this chapter either names a source that was not opened again or carries a dagger. That is the honest state of the material and not a defect in it.

ICD-11 Chapter 18 — Pregnancy, childbirth or the puerperium

Thirteen entries. The chapter-level denominators are these. Maternal deaths in 2023: **about 260,000** on the UN interagency estimate, a global maternal mortality ratio of **197 per 100,000 live births**, with low-income countries at 346 and high-income at 10. Sub-Saharan Africa carries about **182,000** of those deaths, roughly 70 per cent of the global total. Five complications account for about **75 per cent** of maternal deaths — severe bleeding, infection, hypertensive disorders, delivery complications and unsafe abortion — and WHO publishes no share for each one separately. Thirty-seven countries classed as conflict-affected or fragile carry **61 per cent** of maternal deaths on **25 per cent** of live births.

Sources disagree on the maternal death count. The UN Maternal Mortality Estimation Inter-Agency Group gives about 260,000 for 2023. GBD 2023 gives **239,900 (95 per cent uncertainty interval 207,800 to 280,300)** maternal-disorder deaths for the same year, down 39.5 per cent from 396,700 in 2000. The two rest on different models and different cause definitions: GBD's maternal disorders group counts late and indirect maternal deaths as separate sub-causes. Both are printed in every entry below. Neither is a count. GBD 2023 ranks maternal disorders 42nd among DALY causes at 15.6 million DALYs.

Postpartum haemorrhage

What it is. Heavy bleeding from the womb after a baby is born. Most often the womb fails to contract down after the placenta separates, so the vessels that supplied the placenta stay open. The standard definition is 500 mL or more of blood lost after vaginal birth, and 1,000 mL or more is severe.

Measured. Maternal haemorrhage deaths in 2023: **52,000 (35,800 to 70,000)**, down **61.2 per cent** since 2000. This is the largest single maternal cause in the GBD series and the largest decline in it. WHO names severe bleeding among the five complications accounting for about 75 per cent of maternal deaths, without a per-cause share.

No global incidence estimate for postpartum haemorrhage was found in a WHO or GBD source. The range of 5 to 15 per cent of births† that circulates rests on facility series of varying quality, not on a global estimation exercise, and is not asserted here.

The geography is simple. The deaths are where birth happens without a skilled attendant and without an intact uterotonic in the room. Sub-Saharan Africa carries about 70 per cent of all maternal deaths.

Where it starts. Uterine atony — the womb not contracting — is the mechanism in the large majority. The clinical four-cause scheme of tone, tissue, trauma and thrombin is a convention, not a measured partition.

Established risks: prolonged or obstructed labour, multiple pregnancy, high parity, a previous haemorrhage, a large baby, induced or augmented labour, retained placenta. Maternal anaemia does not cause the bleed. It converts a survivable bleed into a fatal one, because there is less reserve.

What is genuinely not known is why one woman's uterus contracts after delivery and another's does not. Most cases occur in women with no identified risk factor. That is why risk-factor screening fails as a triage tool and why prophylaxis is given to everyone. There is no validated predictive test.

Cure status. CURABLE. The bleed is an acute event with a defined endpoint: the uterus contracts, the bleeding stops, the woman recovers fully. One injection of a cheap off-patent drug at the moment of birth prevents most of it. A second cheap off-patent drug treats it. Where both fail, mechanical and surgical measures stop it. Nothing persists once the bleeding is stopped and the blood volume restored.

Prevention.

- **A uterotonic to every woman in the third stage of labour — STRONG.** Oxytocin 10 IU intramuscularly or intravenously is the WHO first choice. This is the intervention behind the measured 61.2 per cent fall in deaths.
- **Skilled birth attendance — STRONG.** Someone present who can give the uterotonic, massage the uterus and recognise the bleed. No single trial effect size exists; the evidence is the association across the interagency series and the fact that nothing below can be delivered without an attendant.
- **Antenatal correction of anaemia — MODERATE** for death, not for the bleed. It raises the volume a woman can lose before she decompensates.
- **Delayed cord clamping — does not prevent it,** and does not increase maternal bleeding either. It is safe alongside active third-stage management and benefits the baby.
- **Controlled cord traction — WEAK.** WHO lists it as optional where a skilled attendant is present. The uterotonic carries the effect.

Treatment. 1. Oxytocin, 10 IU intramuscularly or intravenously, for prevention and first-line treatment. On the WHO Essential Medicines List under Uterotonics, for postpartum haemorrhage, injection 10 IU/mL, first listed 1977. Off-patent. A UNICEF indicative price in October 2026 works out at **about US$0.24 per ampoule**. The decisive limit is the cold chain: oxytocin degrades at ambient tropical temperatures, so the drug that works is routinely the drug that has already spoiled by the time it reaches the birth.

2. Heat-stable carbetocin, the answer to that limitation. The CHAMPION trial randomised **29,645 women** at 23 sites in 10 countries after vaginal birth. For blood loss of 500 mL or more, or use of additional uterotonics: **14.5 per cent carbetocin against 14.4 per cent oxytocin, relative risk 1.01 (0.95 to 1.06)**, meeting the non-inferiority margin of 1.16. For blood loss of 1,000 mL or more: **1.51 against 1.45 per cent, relative risk 1.04 (0.87 to 1.25)**, which did not meet the 1.23 margin; the authors attributed that to low event rates and insufficient power rather than to observed inferiority. Carbetocin 100 µg/mL is EML-listed under Uterotonics. The heat-stable formulation is not off-patent. Ferring holds it and has committed to an access price in public-sector markets in low- and middle-income countries, so the price is a negotiated arrangement rather than a generic market, and it is not published.

3. Misoprostol, 600 µg oral for prevention and 800 µg sublingual for treatment. On the EML under Uterotonics and for medical abortion, oral solid 200 µg. Off-patent, cents a tablet. The decisive property is that it is a tablet: no cold chain, no needle, no skilled injector. It is less effective than intact oxytocin given by someone who can inject. At a home birth with no refrigerator the comparison is against nothing, and there it is the only uterotonic that can be present. It causes more shivering and fever than oxytocin.

4. Tranexamic acid, 1 g intravenously, repeated if bleeding continues. Treatment, not prevention. The WOMAN trial enrolled **20,060 women** at 193 hospitals in 23 countries. **Death due to bleeding: 155 of 10,036 (1.5 per cent) against 191 of 9,885 (1.9 per cent), relative risk 0.81 (0.65 to 1.00, p = 0.045)**, an absolute reduction of 0.4 percentage points and a number needed to treat of **267**; adjusted for baseline risk, 0.78 (0.62 to 0.98). The fragility index on that outcome is **0**: one event flips the significance, and that must be said plainly. Timing is the finding that matters: **within three hours, 1.2 against 1.7 per cent, relative risk 0.69 (0.52 to 0.91); after three hours, 2.6 against 2.5 per cent, relative risk 1.07 (0.76 to 1.51) — no benefit**. The composite primary endpoint of death from any cause or hysterectomy was null at 5.3 against 5.5 per cent, relative risk 0.97 (0.87 to 1.09). No excess of thrombotic events. On the EML, section 10.2 and under medicines administered to the mother, for haemorrhage and postpartum haemorrhage, injection 100 mg/mL. Off-patent, about one to two dollars a gram.

5. Mechanical and surgical measures, escalating. Uterine massage and bimanual compression, intrauterine balloon tamponade, uterine artery ligation, a B-Lynch or other compression suture, and hysterectomy as the last resort.

Simple means. This condition is unusually rich in them.

- **Uterine massage.** Rubbing up the fundus through the abdominal wall makes the uterus contract. Two hands and nothing else, and it is a standard part of active third-stage management.
- **Bimanual uterine compression.** One hand in the vagina, one on the abdomen, compressing the uterus between them. No equipment.
- **Aortic compression.** A fist above the umbilicus, as a holding measure during transfer.
- **The non-pneumatic anti-shock garment.** A neoprene and velcro compression suit applied from the ankles up, which shunts blood from the legs and pelvis to the vital organs and buys hours during transfer. Reusable for dozens of applications on manufacturer figures, with no power and no cold chain, and it is taught by demonstration. The evidence is positive and not definitive: observational and pre-post studies report reduced mortality and measured blood loss, while the cluster-randomised mortality evidence is weaker. Unit cost in the published literature is in the low hundreds of US dollars, amortised over many uses.
- **Condom-catheter balloon tamponade.** A condom tied over a urinary catheter and inflated with saline inside the uterus. Case series from Bangladesh and elsewhere report it effective, at the cost of a condom, a catheter and a bag of saline. The evidence is case series, and one cluster-randomised trial in Africa raised concern about harm where it displaces definitive care. It is a bridge to surgery.
- **Misoprostol tablets**, the only uterotonic that works as a simple means.
- **Early breastfeeding and skin-to-skin contact**, which release endogenous oxytocin. No trial has isolated an effect on haemorrhage, so this is listed as practice rather than as a measured intervention.

The minimum chain: nothing at all for massage, compression and positioning; a condom and a catheter for tamponade; one tablet for misoprostol.

Gaps. No global incidence estimate exists from WHO or GBD. The interagency and GBD maternal death totals disagree, at 260,000 against 239,900 for 2023, and so does their cause attribution. The WOMAN trial's fragility index is 0 on its one significant outcome and its composite primary endpoint was null; the honest statement is that early tranexamic acid reduces death from bleeding, the effect is real and modest at a number needed to treat of 267, and the headline significance is fragile. Carbetocin's access price is not public, so whether it displaces oxytocin at scale is a procurement question with no published data. The anti-shock garment's effect size is unsettled between study designs. Measured blood loss is itself unreliable: visual estimation underestimates, the 500 mL threshold is a convention, and trials using calibrated drapes and trials using estimation are not measuring the same thing.

> **Depth.** Starts in: the womb. Size: 20 cm†; depth +13.92. First complaint: about 10 minutes († minutes after birth); time depth 38.98. One untreated course: about 2 hours († hours); depth 41.24.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Pre-eclampsia and eclampsia

What it is. A disorder of pregnancy in which blood pressure rises and organs begin to fail, usually after 20 weeks. Pre-eclampsia is the state. Eclampsia is when it progresses to seizures. Delivery of the baby and the placenta ends it.

Measured. Maternal hypertensive disorder deaths in 2023: **48,200 (37,300 to 59,900)**, down **30.0 per cent** since 2000. Second-largest maternal cause in the GBD series, and a notably slower decline than haemorrhage at 61.2 per cent or sepsis at 38.7 per cent†. The 2015 round of the same series gave 46,900 deaths.

Pre-eclampsia affects approximately **2 to 8 per cent of pregnancies worldwide**†. That range is wide enough to be a statement about measurement rather than about disease.

Eclampsia incidence is 0.56 per 1,000 pregnant women in developed countries, and roughly 10 to 30 times that in low-income countries†. This gradient is the central measured fact about the condition. The disease occurs everywhere. The seizure and the death occur where magnesium sulfate and timely delivery are not.

Regionally, hypertensive disorders account for nearly a tenth of maternal deaths in Africa and Asia and about a quarter in Latin America. In high-income settings the incidence is rising, attributed to more chronic hypertension, diabetes and obesity.

Where it starts. Chronic pre-existing hypertension carries **7 to 8 times** the risk†. A first-degree relative with pre-eclampsia doubles it. A mother herself born small for gestational age has 50 per cent higher risk, and if both parents were born small, three times the risk. Obesity, diabetes, maternal age over 35, first pregnancy, twin pregnancy, kidney disease and antiphospholipid antibody syndrome are all established and none is quantified in the sources reached.

A history of pre-eclampsia **doubles later cardiovascular mortality risk**. That is a consequence, not a cause: the condition marks a vascular phenotype that outlasts the pregnancy.

The cause is not known. The leading account is abnormal placentation with incomplete remodelling of the spiral arteries, followed by release of anti-angiogenic factors into the maternal circulation. That describes a sequence. It does not identify a first cause, and it does not explain why the same placental findings appear without disease or why some cases present after delivery. There is no accepted aetiology, no preventive treatment that works for most women, and no treatment that resolves the condition short of ending the pregnancy. The screening algorithms predict. They do not explain.

Cure status. CURABLE — by delivery, and the cure is the end of the pregnancy. Delivery of baby and placenta is definitive and the disease resolves over days to weeks. Nothing else removes it. Antihypertensives control the pressure; magnesium sulfate prevents the seizure; neither touches the disorder. The qualification belongs in the label's reading rather than in the label: the only curative intervention is iatrogenic delivery, which before term transfers the whole burden of prematurity to the baby. That trade-off is the whole of clinical management.

Prevention.

- **Low-dose aspirin in high-risk women — STRONG.** The ASPRE trial gave aspirin 150 mg daily at bedtime from before 16 weeks to screened at-risk women and **reduced preterm pre-eclampsia before 37 weeks by 62 per cent and early pre-eclampsia before 32 weeks by 80 per cent, with no change in term pre-eclampsia**. Note the shape of that: it prevents the early, severe, dangerous form and does nothing for the mild term form. Combined screening on maternal history, mean arterial

pressure, uterine artery Doppler and placental growth factor identified over 75 per cent of the women who went on to develop the condition. Across unselected populations the figure is a much smaller 1 to 5 per cent absolute reduction†. Both are printed; they are not in conflict, they are different populations. Aspirin is EML-listed, off-patent and costs cents a course.

- **Calcium supplementation — CONTESTED.** WHO recommended at least 1 g daily in 2011, particularly where dietary calcium is low. Updated evidence indicates calcium may have little or no effect on preventing pre-eclampsia or its complications, with the observation that most trials began supplementation in the second trimester and may have started too late. Both positions printed.
- **Antioxidant vitamins C, D and E — no effect, and not recommended**. A settled negative.
- **Salt restriction, bed rest, exercise and diuretics — no proven preventive benefit**.
- **Antenatal care itself — STRONG**, for the outcome rather than the incidence. A blood pressure and a urine protein measured at a visit is how the condition is found before it seizes. The 10-to-30-fold eclampsia gradient is the measured consequence of its absence.

Treatment. 1. Magnesium sulfate, the anticonvulsant, and the clearest large-effect cheap-drug result in obstetrics. The Magpie trial randomised **10,141 women** — 5,071 to magnesium and 5,070 to placebo — at 175 hospitals in 33 countries, with 99.7 per cent analysed†. **Eclampsia: 0.8 per cent on magnesium against 1.9 per cent on placebo, a relative risk reduction of 58 per cent (40 to 71), number needed to treat 91 (63 to 143)**†. Maternal death was 0.2 against 0.4 per cent, a relative reduction of 45 per cent (−14 to 74) and **not statistically significant**†. Infant death among the 8,775 women randomised before delivery was 12.7 against 12.4 per cent, not significant†. Serious maternal morbidity was 3.9 against 3.6 per cent, not significant†. The published assessment of the trial doses was that their safety is beyond dispute.

Magnesium sulfate is also superior to diazepam and to phenytoin for treating established eclampsia, and WHO recommends it both to prevent and to treat. It is EML-listed under antiseizure medicines, with the restrictive note that it is for eclampsia and severe pre-eclampsia and not for other convulsant disorders; the listed forms are 500 mg/mL in a 2 mL ampoule intravenously and 500 mg/mL in a 10 mL ampoule intramuscularly. It is an inorganic salt and there is no patent to hold. A UNICEF indicative price in October 2026 works out at **about US$0.33 per 5 g ampoule**, so a full loading and maintenance course costs a few dollars.

This is the per-euro benchmark for the chapter: a 58 per cent reduction in eclampsia at a number needed to treat of 91, from a drug costing a few dollars, needing no cold chain, and administered intramuscularly where no intravenous line is possible.

2. Delivery, which is definitive. Timing follows severity and gestational age: expectant management, induction, or caesarean. Where preterm delivery is chosen, antenatal corticosteroids for fetal lung maturity and magnesium sulfate for fetal neuroprotection both apply.

3. Antihypertensives for severe hypertension, at a systolic of 160 mmHg or more or a diastolic of 110 or more. **Labetalol, hydralazine, nifedipine and methyldopa** are the standard agents and **no evidence favours one over another**; choice follows experience, cost and availability. A proposed target is 140 to 160 systolic and 90 to 105 diastolic. Hydralazine, methyldopa and nifedipine are EML-listed, all off-patent, cents to a few dollars a course. **ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy.**

Simple means.

- **A blood pressure cuff and a urine protein dipstick.** This is the detection technology for the entire condition. An aneroid or automated cuff needs manufacture but no supply chain beyond itself, and dipsticks are cheap consumables. Boiling urine to look for coagulated protein is the no-consumable fallback described in the older field literature.
- **Left lateral positioning, airway protection and padding during a seizure.** Standard first aid, no equipment, and it prevents aspiration and injury.
- **Intramuscular magnesium sulfate.** The regimen is designed to work without an infusion pump or reliable intravenous access: a loading dose into each buttock plus intravenous where possible, then

intramuscular maintenance. A syringe, a needle and ampoules of a salt. This is why magnesium reaches places where almost nothing else does.

- **Transfer with magnesium already given.** The point from Magpie is that the drug works where it is given, not where the woman arrives.

The minimum chain: a cuff, a syringe and ampoules of a salt. Nothing refrigerated, nothing powered.

Gaps. The aetiology is unknown, and that is an absent evidence base rather than a thin one. Magpie did not demonstrate a mortality benefit, at a relative reduction of 45 per cent with an interval from −14 to 74; sources reporting magnesium sulfate as proven to reduce maternal death overstate the trial. WHO 2011 and the updated reviews disagree on calcium, and both are printed. ASPRE's 62 and 80 per cent figures apply to a screened high-risk population, and the screening algorithm they depend on — placental growth factor and uterine Doppler — is unavailable in most settings carrying the mortality, so the intervention with the large effect and the population with the deaths are not currently the same population. Eclampsia incidence in low-income countries is given as a multiple, not as a rate, and no direct rate was located. Why the hypertensive-disorder death decline lags haemorrhage by half is not explained in any source reached.

> **Depth.** Starts in: a spiral artery of the placenta. Size: 300 µm†; depth +8.00. First complaint: about 8 months ([B] after 20 weeks; † about 34 weeks); time depth 48.48. One untreated course: about 14 days ([B] ends after delivery; † about 2 weeks); depth 45.90.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book's status: CURABLE. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Obstructed labour

What it is. The baby cannot pass through the pelvis, however hard the womb contracts. The labour stops progressing and stays stopped. Without intervention the uterus may rupture, the baby dies, and the pressure of the head against the pelvis destroys the tissue between bladder, vagina and rectum.

Measured. Obstructed labour and uterine rupture deaths in 2023: **12,200 (7,500 to 18,400)**, down 44.8 per cent since 2000†. About **6.5 million** cases of obstructed labour or uterine rupture were counted for 2015†.

The death figures disagree sharply across rounds of the same series, and not monotonically. GBD 2015 gives about **23,000** maternal deaths; GBD 2013 gives about **19,000** for 2013; GBD 2023 gives **12,200** for 2023. The cause definition has moved between rounds and ill-defined codes have been redistributed differently. All three are printed. None is a count, and the series cannot be read as a trend.

Obstructed labour accounts for about **8 per cent** of pregnancy-related maternal deaths† and affects roughly **2 to 5 per cent of deliveries** in Africa and Asia†. It is the leading cause of uterine rupture worldwide and one of the leading causes of stillbirth. Where caesarean section is available within hours it is an operative indication rather than a cause of death.

Where it starts. Fetal factors: a large baby, abnormal position or presentation, shoulder dystocia, and in humans broad fetal shoulders.

Maternal pelvic factors: a small pelvis shaped by malnutrition, vitamin D deficiency and calcium deficiency in the mother's own childhood. The pelvis that obstructs the labour was formed by the nutrition of the girl twenty years earlier. Young maternal age, where pelvic growth may be incomplete, carries the same mechanism, and child marriage and adolescent pregnancy are the upstream exposure. Birth canal obstruction can follow female genital mutilation or tumours. No effect sizes for any of these were located.

There is no validated way to predict cephalopelvic disproportion before labour. Pelvimetry, whether radiographic or clinical, has repeatedly failed as a screening test and is not recommended. Maternal height is a weak proxy. The diagnosis is made in labour, by the labour failing. That is why the intervention has to be available at the place of birth rather than arranged in advance.

Cure status. CURABLE. Caesarean section resolves it definitively and both mother and baby survive with normal subsequent life. Vacuum extraction resolves a subset. Symphysiotomy resolves it where no

operating theatre exists. There is no chronic phase once the obstruction is relieved. Its sequelae are separate conditions with their own status: prolonged obstruction before relief causes obstetric fistula, and may cause stillbirth or neonatal encephalopathy, and relieving the obstruction does not cure those.

Prevention.

- **Skilled birth attendance with access to operative delivery — STRONG**, and it is the only thing that is. A facility that can perform caesarean section is a facility where obstructed labour does not kill.
- **Improving female nutrition before and during pregnancy — MODERATE**, with an effect a generation long. No effect size located.
- **Preventing adolescent pregnancy and child marriage — MODERATE.** Mechanistically direct through incomplete pelvic growth, and unquantified.
- **Contraception and family planning — MODERATE.** Fewer pregnancies, fewer exposures.
- **Partograph use — CONTESTED.** The partograph is standard WHO practice for tracking labour progress and may identify obstruction, but **no outcome data showing that partograph use reduces mortality or complications** were found in the sources reached, and WHO's more recent labour-care guidance has moved away from the classical fixed progress lines. It is unproven for the outcome.
- **Ending female genital mutilation — STRONG** for the canal-obstruction subset, on mechanism; no effect size located.

Treatment. No drug treats obstructed labour. Augmenting contractions with oxytocin against a true obstruction causes uterine rupture, so this is the one place in obstetrics where the cheap effective uterotonic of the haemorrhage entry is contraindicated.

1. Caesarean section. Often the only option that saves both mother and infant. The inputs are an operating theatre, an anaesthesia provider, a surgeon or trained non-physician clinician, sterile instruments and blood. It is one of the three **Bellwether procedures** of the Lancet Commission on Global Surgery.

2. Vacuum extraction, where the obstruction is relative and the cervix fully dilated. A hand pump and a cup, reusable, no power.

3. Symphysiotomy — surgical division of the pubic symphysis to enlarge the pelvis. It is faster than caesarean, needs no anaesthesia beyond local, and leaves no uterine scar, which matters where a scarred uterus in a place without surgery jeopardises the next pregnancy. It has been largely abandoned in high-income practice and is historically associated with pain and gait disturbance. The published position is that it retains a place where caesarean is unavailable.

4. Supportive care: hydration, and antibiotics if membranes have been ruptured for more than 18 hours†.

5. Maternal position change, which can help labour progress before surgery is considered.

Simple means.

- **Changing the mother's position** — upright, all-fours, lateral, the Gaskin manoeuvre. Free, immediate, and it resolves a proportion of malpositions.
- **The shoulder dystocia manoeuvres** — McRoberts position, suprapubic pressure, delivery of the posterior arm, all-fours. Hands only, and they resolve the majority at the bedside.
- **Hydration and oral fluids** during prolonged labour.
- **Recognising it and moving.** The measured determinant of survival is the interval between obstruction and operative delivery, so a transport arrangement is a simple means.
- **Symphysiotomy** is the simple-means operative answer: a scalpel, local anaesthetic and someone trained. No theatre, no general anaesthesia, no blood bank.
- **A partograph** is a sheet of paper, with the outcome evidence noted above.

What cannot be improvised: for the irreducible cases, a caesarean section, which requires surgery, anaesthesia and blood. There is no simple means that substitutes. This is the condition where the Lancet Commission's finding bites hardest.

Gaps. The death figures disagree across GBD rounds, at about 23,000 for 2015, about 19,000 for 2013 and 12,200 for 2023, in a way that is not monotonic; the cause definition and the redistribution of ill-defined codes both moved. The partograph has no demonstrated mortality effect despite being near-universal practice, and that is a live gap rather than a settled negative. No effect sizes were located for any risk factor or any preventive measure. Symphysiotomy's evidence base is old and contested, with thin long-term maternal outcome data, and sources recommending it for low-resource settings and sources treating it as obsolete are both current. Cephalopelvic disproportion has no antenatal predictor, so no screening intervention is available even in principle.

> **Depth.** Starts in: the baby's head against the pelvis. Size: 10 cm†; depth +13.29. First complaint: about 12 hours († hours into labour); time depth 42.87. One untreated course: about 2 days ([B] days without an operation); depth 44.13.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Maternal sepsis

What it is. Infection of the womb and surrounding tissues during pregnancy, labour or after birth, spreading into the bloodstream. It usually enters during or after delivery. It begins with fever and abdominal pain and progresses to organ failure.

Measured. Maternal sepsis and other pregnancy-related infections, deaths in 2023: **26,700 (19,000 to 37,100)**, down **38.7 per cent** since 2000. The decline is slower than haemorrhage and faster than hypertensive disorders. WHO names infection among the five complications accounting for about 75 per cent of maternal deaths, describing infections as usually occurring after childbirth, without a per-cause share.

No global incidence estimate was located. The WHO Global Maternal Sepsis Study of 2017 was a facility-based prevalence study rather than a global incidence estimate. The deaths are concentrated where delivery is unclean, where caesarean section is performed without sterile technique or prophylactic antibiotics, and where postpartum follow-up does not exist.

Where it starts. Caesarean section is the dominant procedural risk factor for postpartum endometritis. Prolonged rupture of membranes, prolonged labour, multiple vaginal examinations in labour, retained placental tissue and obstructed labour all raise risk. Unclean delivery — unwashed hands, non-sterile instruments, contaminated surfaces — is the classical route, and unsafe abortion is a distinct one. Anaemia and undernutrition act as susceptibility factors. GBD counts maternal deaths aggravated by HIV separately at **1,700 (1,000 to 2,300)** in 2023, down 38.9 per cent. No effect sizes for these were located.

What is not known is which women with the same exposures progress to sepsis. There is no useful predictive test. The organisms are heterogeneous — group A and B streptococci, *E. coli*, anaerobes, *Staphylococcus aureus*, and in some settings *Clostridium* — so no pathogen-directed strategy covers the condition. Early recognition criteria are also poorly calibrated, because the physiological changes of pregnancy and the puerperium move pulse, temperature and white-cell count, and the standard sepsis scores perform worse here than in the general population.

Cure status. CURABLE. Antibiotics plus removal of the source — retained tissue, or drainage of an abscess — resolves it, and recovery is complete. The determinants of survival are the interval to antibiotics and whether a source needs surgical removal. Nothing persists after cure, except fertility consequences where the uterus or tubes are damaged or removed.

Prevention.

- **Clean delivery practice — STRONG.** Handwashing, sterile or clean instruments, a clean surface, clean cord cutting. This is the oldest measured result in the field: Semmelweis's handwashing intervention at the Vienna lying-in hospital in 1847 took maternal mortality on the affected ward from

the high teens in percentage terms to low single figures within a year. The modern effect size for the bundle in current practice was not retrievable.

- **Prophylactic antibiotics before caesarean section — STRONG.** A single pre-incision dose substantially reduces postpartum endometritis and wound infection, on Cochrane-level evidence. The pooled relative risk was not retrievable here. The drugs are cheap, off-patent and EML-listed.
- **Skilled birth attendance — STRONG**, as the delivery vehicle for everything above.
- **Avoiding unnecessary vaginal examinations and unnecessary caesarean — MODERATE.**
- **Active management of the third stage, and ensuring the placenta is complete — MODERATE**, retained tissue being a nidus.
- **Safe abortion access — STRONG** for the abortion-related subset.
- **A postpartum follow-up contact in the first week — MODERATE.** Most postpartum sepsis presents after discharge.

Treatment. 1. Broad-spectrum antibiotics, early. WHO's standard combination for severe puerperal sepsis is **ampicillin plus gentamicin plus metronidazole**, started on clinical suspicion without waiting for cultures. All three are EML-listed and off-patent, and a full parenteral course costs a few US dollars. No randomised comparison against no antibiotic exists or could ethically exist; the evidence is the historical case-fatality change and the dose-response with time to antibiotic observed in sepsis generally.

2. Source control. Manual or surgical removal of retained products, drainage of an abscess, and hysterectomy where the uterus itself is the source and cannot be salvaged.

3. Supportive care. Intravenous fluids, oxygen, and vasopressors where available. In settings without critical care, fluids and antibiotics are the whole of what can be given.

4. Tetanus prophylaxis where the entry route suggests it.

Simple means.

- **Handwashing with soap and clean water.** The single highest-yield act in the history of this condition, and it requires soap.
- **A clean delivery kit.** Soap, a clean plastic sheet, clean string, a sterile razor blade, clean gloves. Packaged and distributed at near-zero unit cost, and designed precisely to be a simple means.
- **Clean cord cutting and cord care**, which prevents neonatal tetanus and neonatal sepsis by the same act.
- **Boiling instruments.** Sterilisation without an autoclave.
- **Oral antibiotics where parenteral is impossible**, as a holding measure during transfer. Less effective, and better than the interval.
- **Recognition teaching for the family.** Fever, foul discharge or abdominal pain in the first week after birth means go now. It costs nothing and addresses the dominant delay.
- **Oral fluids** during transfer.

The minimum chain: soap for prevention, manufactured antibiotics for treatment. There is no simple-means substitute for the antibiotic. Prevention is nearly free and cure is not improvisable.

Gaps. No global incidence estimate was located: the deaths are estimated and the incidence is not published. No effect sizes were retrievable for prophylactic antibiotics at caesarean or for the clean-delivery bundle, both of which are standard of care on evidence that exists and was not reachable here. Sepsis definitions changed during the period the trend covers — Sepsis-3 in 2016 and WHO's maternal sepsis definition in 2017 — so part of the measured 38.7 per cent fall may be definitional. The organism mix is not globally characterised, because blood-culture capacity is absent in most settings carrying the mortality, so the pathogen distribution where women die is substantially unknown. Antimicrobial resistance in maternal sepsis is poorly quantified and is the clearest threat to the CURABLE classification; no figures were located.

> **Depth.** Starts in: a bacterium. Size: 1 μm†; depth +2.81. First complaint: about 42 hours († 1–3 days after delivery); time depth 44.00. One untreated course: about 3 days († days); depth 44.50.

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Unsafe abortion complications

What it is. Injury, bleeding and infection following an abortion performed by someone without the skills, or in an environment not meeting minimal medical standards, or both. The complications, not the procedure, are the condition coded here.

Measured. Maternal abortive outcome deaths in 2023: **19,600 (12,200 to 30,800)**, down 54.8 per cent since 2000†. That line also contains spontaneous abortion, so it cannot be read as deaths from unsafe abortion.

Induced abortions worldwide: **about 73 million a year**, which is 29 per cent of all pregnancies and 61 per cent of unintended pregnancies. **About 45 per cent of induced abortions** fell into the unsafe category on global estimates for 2010 to 2014, and one third of unsafe abortions were performed under the least safe conditions. A review covering 2009 to 2020 linked **8 per cent of maternal deaths** to abortion, and WHO notes these are often misclassified and underreported.

The central measured fact is a two-orders-of-magnitude gradient. Death rates are below 1 per 100,000 for safe abortion and above 200 per 100,000 abortions where unsafe abortion is common.

In 2012, **7 million women a year** in developing countries were treated in hospitals for complications of unsafe abortion. Cost estimates from 2006 put post-abortion treatment in developing countries at **US$553 million a year**, with households losing **US$922 million** in income to related long-term disability.

Over half of unsafe abortions occur in Asia, mostly in south and central Asia. In Latin America and Africa roughly **three in four** abortions were unsafe, and in Africa nearly half of all abortions occurred under the least safe conditions.

Where it starts. Legal restriction is the dominant determinant, and the finding is specific. WHO states that restricting access **does not reduce the number of abortions**, and that the share which are unsafe is significantly higher in countries with highly restrictive laws. The law determines the safety, not the frequency.

Beyond that: unmet need for contraception, absent trained providers, absent misoprostol and mifepristone, cost, stigma, distance, and conscientious objection without referral. Adolescence and poverty act as access barriers. No effect sizes beyond the legal association were located.

What is genuinely not known is the true numbers. WHO states plainly that abortion-related maternal deaths are often misclassified and underreported. Where the act is criminal it is not recorded, so incidence, complication rate and death rate in exactly the settings that matter most are the least reliably measured quantities in maternal health. The 45 per cent unsafe figure derives from a 2010 to 2014 estimation exercise and had not been updated on the fact sheet current in December 2025.

Cure status. CURABLE. The complications — incomplete abortion, haemorrhage, sepsis, uterine or bowel perforation — are each curable with standard treatment: uterine evacuation, antibiotics, transfusion, and surgery for perforation. Recovery is complete in the large majority treated in time. Infertility and chronic pelvic infection follow a minority. The classification is unambiguous. The problem is entirely one of reaching treatment, and of whether reaching it is legally safe for the woman.

Prevention.

- **Access to safe abortion — STRONG.** The measured effect is the gradient above: under 1 per 100,000 against over 200 per 100,000. This is the largest single preventive effect size in this chapter for any condition, and it is achieved by changing who performs the procedure and where, not by any new technology.
- **Contraception — STRONG.** It prevents the unintended pregnancy upstream. No single effect size located; the arithmetic link is that 61 per cent of unintended pregnancies end in abortion.

- **Misoprostol and mifepristone availability — STRONG.** WHO's consolidated guideline holds that first-trimester medical abortion can be self-managed with accurate information and quality medicines, with a trained health worker available if needed. That moves the procedure out of the unsafe category without requiring a facility.
- **Post-abortion care provided without legal jeopardy — STRONG** for death among those who already have the complication.
- **Comprehensive sexuality education — MODERATE.**
- **Legal restriction as prevention — contradicted.** WHO's position is explicit.

Treatment. 1. Uterine evacuation for incomplete abortion. Misoprostol 600 µg oral, with regimens varying — tablets, no cold chain, EML-listed for spontaneous abortion incomplete without complication, off-patent, cents a tablet. **Manual vacuum aspiration**, a hand-held syringe and cannula needing no electricity, reusable, and preferred over sharp curettage, which carries higher perforation and intrauterine adhesion risk. Electric vacuum aspiration where power and a facility exist.

2. Antibiotics for sepsis — ampicillin, gentamicin and metronidazole, all EML-listed, all off-patent, a few dollars a course.

3. Blood transfusion for haemorrhage. Tranexamic acid has not been trialled in this indication specifically, though the bleeding mechanism is the one the WOMAN trial addressed.

4. Laparotomy for perforation of uterus or bowel. A Bellwether requirement.

5. Anti-D immunoglobulin where indicated and available, and **contraception provided before discharge**, which is the measured intervention against the repeat event.

Simple means.

- **Manual vacuum aspiration.** A hand-powered syringe. No electricity, no theatre, reusable after cleaning, and usable under local anaesthesia and paracervical block by a trained mid-level provider. This is among the clearest cases in the chapter of a simple means that is also the standing best treatment.
- **Misoprostol tablets.** Shelf-stable, oral, cents each, effective for both evacuation and bleeding. Their existence is why medical abortion and post-abortion care can happen without a facility.
- **Oral rehydration and oral antibiotics** as holding measures during transfer.
- **Accurate information.** WHO's own position is that first-trimester medical abortion can be self-managed given accurate information and quality medicines. Information is the lowest-chain intervention there is.
- **Bimanual compression and uterine massage** for the bleeding.

The minimum chain: two tablets and a plastic syringe. This is one of the shortest supply chains of any curative intervention in this book.

Gaps. The numbers are the weakest in the chapter and WHO says so: criminalisation and misclassification make incidence, complication rate and death rate systematically under-measured where they are highest. The 45 per cent unsafe figure is from 2010 to 2014 and was not updated on the fact sheet current in December 2025. The cost figures are from 2006 and the 7-million-complications figure from 2012; none has been refreshed. GBD's maternal abortive outcome line is not coextensive with unsafe-abortion complications, since it includes spontaneous abortion, and ectopic pregnancy is counted separately, so the 19,600 figure cannot be read as deaths from unsafe abortion. Legal change as an intervention has not been and cannot be randomised; the evidence is the cross-national association WHO reports, which is strong, consistent and observational.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 24 hours († hours to days); time depth 43.50. One untreated course: no number.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Obstetric fistula

What it is. A hole between the vagina and the bladder or rectum, torn open by days of obstructed labour pressing the baby's head against the mother's pelvis until the tissue dies. Urine or faeces then leaks continuously and uncontrollably. The baby is almost always already dead.

Measured. Women and girls living with fistula: **about 500,000** across the Arab States, Asia, Latin America and the Caribbean, and sub-Saharan Africa. New cases are given only as thousands each year, with no number published. No annual incidence estimate was located from any source.

About 90 per cent of women who develop fistula deliver a stillborn baby. Repairs directly supported by UNFPA number more than **153,000**, and the Campaign to End Fistula is active in more than **55 countries**.

The condition is concentrated among the poorest and most marginalised women, especially far from medical services, and is **virtually eliminated in high-income countries**.

No GBD cause series exists for obstetric fistula as a separate entity. Its mortality is carried inside obstructed labour, and its years lived with disability are largely uncounted.

Where it starts. Prolonged obstructed labour without operative delivery is the cause. It is a single-cause condition and the cause is the absence of a caesarean section.

Upstream: child marriage, adolescent pregnancy with incomplete pelvic growth, malnutrition and stunting, poverty, distance from a facility, and female genital mutilation. Iatrogenic fistula from surgical injury at caesarean or hysterectomy is a separate and, in some series, increasing minority route. No effect sizes were located.

What is not known is how many women have it. The 500,000 figure is an estimate of unknown vintage repeated across agency documents, and no incidence estimate exists. Women with fistula are commonly divorced, expelled from their households and socially hidden, which is precisely why they are not counted. **The size of this condition is not known to within a factor of two.**

Cure status. Localized, with access to reconstructive surgery: CURABLE — closure in 80 to 90 per cent of first repairs of simple fistula†. Without access to surgery: RELIEF ONLY.

Reconstructive surgery closes the fistula and continence returns. Published surgical series report closure rates commonly in the 80 to 90 per cent range for first repairs of simple fistula, with lower rates for complex and repeat cases and residual stress incontinence in a minority after successful closure. UNFPA's own page gives no success rate and no cost figure, and an authoritative pooled figure was not retrievable. The condition does not heal spontaneously once established, which is why the second stratum is RELIEF ONLY rather than SELF-LIMITING.

Prevention.

- **Skilled birth attendance with timely access to caesarean section — STRONG.** This prevents essentially all obstetric fistula, and the measured evidence is the near-total absence of the condition in countries with universal access.
- **Preventing child marriage and adolescent pregnancy — MODERATE.** Mechanistically direct, unquantified.
- **Family planning to reduce early and closely spaced pregnancies — MODERATE**.
- **Addressing malnutrition and stunting in girls — MODERATE**, with a generation-long effect.
- **Partograph and labour monitoring — CONTESTED** on outcome evidence, as in obstructed labour.
- **Ending female genital mutilation — STRONG** for the subset it causes.

UNFPA names skilled birth attendance including midwives, timely emergency obstetric care, modern family planning, and addressing poverty, gender inequality, child marriage and adolescent pregnancy. None of these carries an effect size on that page.

Treatment. 1. Surgical repair, by the vaginal or abdominal route depending on site and complexity. No drug treats this. The inputs are a trained fistula surgeon, an operating theatre, anaesthesia, and post-

operative catheter care for one to several weeks. Surgical volume and surgeon experience are the strongest predictors of closure in published series, which is why the condition is managed in dedicated centres and campaigns rather than in general surgical services.

2. Continuous bladder catheterisation in the first weeks after a fresh fistula. A proportion of early small fistulae close spontaneously with catheter drainage alone. This is the cheapest curative intervention available for the condition, and it requires a catheter and a drainage bag.

3. Physiotherapy and pelvic floor rehabilitation for residual incontinence after closure.

4. Treatment of associated conditions — nerve injury causing foot drop, which is common after prolonged obstructed labour, amenorrhoea, secondary infertility, vaginal stenosis, and dermatitis from constant wetting.

5. Social reintegration support. Not medical, and UNFPA and the published programmes treat it as part of the intervention because the condition's burden is largely social.

Simple means.

- **Early continuous catheterisation.** A Foley catheter and a bag can close a fresh small fistula without any surgery. The limiting factor is that the woman must reach a health worker within days, which is the same failure that caused the fistula.
- **Barrier creams and skin care** for the excoriation caused by constant urine contact. This prevents the secondary dermatitis that makes the condition unbearable.
- **Perineal hygiene, frequent washing, absorbent cloth**, changed often. Relief rather than cure, and it is what most affected women have.
- **Case-finding by community health workers and by radio.** The main constraint on fistula campaigns is that affected women do not know repair exists. Announcing it is close to free and is the measured bottleneck in campaign throughput.
- **Transport support to a repair campaign.** The surgery is free at campaigns. The bus fare is often what prevents it.
- **Nutritional support before surgery.**

The minimum chain: a catheter for the earliest cases, and for the rest an operating theatre and a trained surgeon. There is no simple-means substitute for fistula repair.

Gaps. The prevalence figure of 500,000 has no stated date or method and is repeated across agency documents, and no incidence estimate exists at all; this is the least-measured condition in the chapter. No GBD cause series covers it, so its years lived with disability are absent from the global burden accounts. UNFPA publishes no success rate and no cost per repair, and published series range widely by fistula complexity and surgeon volume. The share that is iatrogenic rather than obstructed-labour in origin is not globally quantified and appears to be rising in some settings. Long-term outcomes after successful closure — continence at five years, subsequent fertility, subsequent delivery outcomes — are thinly reported.

> **Depth.** Starts in: the tissue between bladder and vagina. Size: 1 cm†; depth +11.19. First complaint: about 5.5 days († 3–10 days after tissue death); time depth 45.05. One untreated course: no number ([B] permanent leaking).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Gestational diabetes mellitus

What it is. Blood sugar that rises above normal during pregnancy in a woman who did not have diabetes before. The placenta's hormones make the mother's tissues resist insulin, and if her pancreas cannot compensate, glucose rises. It usually resolves after delivery.

Measured. There is **no global figure.** The WHO diabetes fact sheet publishes none for gestational diabetes. GBD does not report it as a separate cause: it has no deaths line and no DALY rank of its own.

Published prevalence estimates range from roughly **2 per cent to over 20 per cent** of pregnancies, and the range is driven mainly by which diagnostic criteria are used rather than by real population differences. Adopting the IADPSG and WHO 2013 thresholds roughly doubles the measured prevalence in the same population. No single global estimate is asserted here.

The trend is rising, tracked to rising maternal age and maternal obesity, and not quantified in a reachable source. The highest reported prevalences are in South Asia, the Middle East and North Africa, and that comparison is confounded by criteria.

Where it starts. Established: maternal overweight and obesity before pregnancy, and excessive gestational weight gain; maternal age; previous gestational diabetes or a previous macrosomic baby; family history of type 2 diabetes; South Asian, East Asian, Middle Eastern, Hispanic and Indigenous ancestry, which carry higher risk at lower body mass index than European ancestry; and polycystic ovary syndrome. No effect sizes were located from a reachable authoritative source.

Two things are genuinely unsettled. First, whether gestational diabetes is a distinct condition or simply the detection of pre-existing impaired glucose tolerance under the stress test of pregnancy: a substantial share of women diagnosed have abnormal glucose handling that persists or recurs, and the condition strongly predicts later type 2 diabetes. Second, where the threshold should be drawn. The glucose-to-outcome relationship is continuous with no inflection, so the diagnostic cut-off is a decision about how many women to treat rather than a discovery about a disease boundary. That is the main reason the prevalence figures cannot be compared.

Cure status. The hyperglycaemia of this pregnancy: SELF-LIMITING — the placenta is the cause and its delivery removes it. The consequences for this birth: CONTROLLABLE — treating the hyperglycaemia measurably reduces macrosomia, shoulder dystocia and pre-eclampsia, so intervention is not without value. The woman's elevated lifetime risk of type 2 diabetes: not removed by anything done in the pregnancy.

Prevention.

- **Pre-pregnancy weight management — MODERATE.** Mechanistically direct; trials of pre-conception weight loss are small.
- **Diet and physical activity in pregnancy — MODERATE.** Meta-analyses of exercise and dietary interventions report relative reductions in incidence of the order of 20 to 40 per cent, with substantial heterogeneity†. An exact pooled figure was not retrievable.
- **Metformin for prevention — CONTESTED.** Trials in obese pregnant women reduced gestational weight gain and did not consistently reduce incidence.
- **Myo-inositol, probiotics, vitamin D — WEAK.** Signals in small trials, not replicated at scale.
- **Screening is not prevention.** Universal against risk-factor-based screening changes who is diagnosed, not who develops the condition, and which approach improves outcomes is itself contested.

Treatment. 1. Diet and exercise. First line and sufficient in the majority, commonly reported as 70 to 85 per cent of cases controlled without drugs†. Not a drug, and no supply chain beyond advice and food.

2. Insulin. The standard pharmacological treatment and the one with the longest safety record in pregnancy. Human insulin, short-acting and intermediate-acting, is EML-listed for type 1 and type 2 diabetes; the analogue entries are listed as classes, and the named analogues — degludec, detemir, glargine, aspart, glulisine, lispro — are listed only as therapeutic equivalents to those class entries, not as selected medicines. Human insulin is off-patent and remains expensive relative to its production cost, and its price is a standing access problem; it is EML-listed partly for that reason. Insulin requires a cold chain, injection equipment and glucose self-monitoring: three supply chains at once.

3. Metformin. EML-listed for type 2 diabetes mellitus, oral solid 500 mg, first added 1997. Off-patent, cents a day, oral, no cold chain. It crosses the placenta and long-term offspring follow-up is reassuring to

date and not complete. It is increasingly used first-line where insulin's cold chain is unavailable, which is the relevant consideration for most of the world.

4. Glibenclamide. Oral, cheap, EML-listed, off-patent. Inferior to insulin and to metformin on neonatal outcomes in head-to-head trials, and a third-line option.

5. Delivery timing and mode. Induction at or near term where macrosomia is suspected; the trade-offs are not settled.

6. Postpartum glucose testing at 6 to 12 weeks and lifelong thereafter. The intervention with the largest long-term value, and the one most often omitted.

Simple means.

- **Dietary change.** Reducing refined carbohydrate and spacing intake across the day controls the majority of cases with no manufactured input whatever. This is the primary treatment and it is a simple means.
- **Walking after meals.** Measured postprandial glucose reductions from short post-meal walks are consistent across small trials. Free.
- **Fasting and post-prandial glucose measured with a strip meter.** A meter and strips are a manufactured consumable chain, and a small and cheap one, and they convert the condition into something manageable at home. Urine glucose dipsticks are the lower-chain fallback and are much less sensitive.
- **Breastfeeding after delivery**, associated with lower subsequent maternal type 2 diabetes incidence in cohort studies, and free.
- **Weighing the mother** and tracking gain.

The minimum chain: for most women, nothing manufactured. For the minority needing drugs, metformin tablets are the short chain and insulin is the long one.

Gaps. There is no global prevalence figure, and WHO says so; any number quoted is a modelled estimate over incommensurable diagnostic criteria. The diagnostic threshold is unsettled and the choice of criteria changes measured prevalence roughly two-fold, which is the single largest source of disagreement in the field. Whether screening and treating mild gestational diabetes improves outcomes enough to justify universal screening is contested, with professional bodies in different countries reaching different conclusions on the same evidence. No effect sizes for risk factors or for lifestyle prevention were retrievable from a primary source. GBD does not carry the condition as a cause, so it has no place in the global burden accounts despite affecting a large share of pregnancies. Long-term offspring outcomes after in-utero metformin exposure are not yet complete.

> **Depth.** Starts in: a placental hormone. Size: 5 nm†; depth −2.01. First complaint: about 6 months ([B] from the second trimester); time depth 48.23. One untreated course: about 12 weeks ([B] normal after delivery); depth 47.53.
>
> **Model reading.** Way of ending: let close. Layer: word. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Hyperemesis gravidarum

What it is. Vomiting in pregnancy severe enough to cause dehydration, weight loss and electrolyte disturbance. Far beyond ordinary morning sickness. It can prevent a woman eating or drinking at all for weeks.

Measured. Prevalence is given as **0.3 to 2.0 per cent** of pregnant women, with some sources as high as 3 per cent†. A second figure on the same page gives **0.3 to 1.5 per cent**†, and an infobox on it gives **about 1 per cent**†. All are printed; the sources disagree within a narrow band and none is a measurement, because ascertainment depends on whether admission is recorded.

It is the **second most common reason for hospital admission in the first half of pregnancy**, after preterm labour, with no hospitalisation rate given. United States hospitalisation costs have been estimated at **US$3 billion a year**†.

There is no deaths line in the GBD maternal series. It is not a notable cause of maternal death where intravenous fluids are available. Historically it was.

Onset is typically at 5 to 6 weeks gestation, β-hCG peaks around 8 to 12 weeks, and most women improve by the early second trimester; some continue throughout pregnancy and occasionally after birth.

Where it starts. The substantive finding is recent. A *Nature* paper of December 2023 linked hyperemesis gravidarum to **abnormally high levels of GDF15 and to increased maternal sensitivity to that hormone**. GDF15 is produced by the placenta and acts on the hindbrain, and maternal pre-pregnancy GDF15 exposure appears to determine sensitivity. No effect size is reported on the source consulted. This is the most substantive aetiological finding the condition has ever had.

Also established: first pregnancy, multiple pregnancy, obesity, and trophoblastic disorder. Family history is strong and long-observed — family members with hyperemesis make the diagnosis more likely. Associations with *H. pylori* infection, raised thyroid hormone production, low maternal age and low pre-pregnancy body mass index are reported. No effect sizes are given for any risk factor.

Until the GDF15 work nothing about the mechanism was established, and the condition was for decades attributed to maternal psychology — a misattribution that caused measurable harm through undertreatment. The GDF15 finding has not yet produced a treatment, the quantitative relationship between level, sensitivity and severity is uncharacterised, and why some women with high GDF15 are unaffected is not known.

Cure status. The emesis: SELF-LIMITING — it ends with the pregnancy and in most women well before it, typically early in the second trimester. No treatment removes it. The thiamine deficiency it produces: CURABLE, and it must be treated. Untreated, it causes Wernicke's encephalopathy, which is permanent brain injury. Vitamins A and B are depleted within about two weeks of poor intake.

So self-limiting must not be read as intervention adding nothing. Everything in the treatment section is symptom control and replacement of what has been lost, except the thiamine, which prevents a non-self-limiting disease.

Prevention.

- **Nothing prevents it.** No intervention has been shown to prevent hyperemesis gravidarum in a woman who is going to develop it. That belongs stated plainly rather than filled in.
- **Early treatment of nausea and vomiting of pregnancy — MODERATE** for preventing progression to the severe form. The observational basis is that early antiemetic treatment reduces hospitalisation; no trial has established that it prevents the severe syndrome.
- **Thiamine supplementation — STRONG** for preventing Wernicke's encephalopathy, which is the preventable catastrophe.
- **Prophylactic antiemetics in a woman with prior hyperemesis — WEAK.** Common practice, thin evidence.
- GDF15-directed prevention does not exist.

Treatment. 1. Rehydration and electrolyte replacement. Intravenous fluids with potassium as needed. This is the intervention that changed hyperemesis from a fatal to a survivable condition, and it is not a drug.

2. Thiamine, which is the non-negotiable item. Thiamine must be supplemented to reduce the risk of Wernicke's encephalopathy, and it must be given **before or with** any glucose-containing fluid, because glucose without thiamine precipitates the encephalopathy. EML-listed, off-patent, cents a dose; UNICEF indicative prices in October 2026 for thiamine were printed at US$1.29, US$1.42 and US$5.55 for the same material number on different pages, which is why these are indicative figures and not a price. **A few cents prevents permanent brain injury,** and it is routinely omitted.

3. Pyridoxine with doxylamine. Effective for nausea and vomiting of pregnancy, with some question over its effectiveness in hyperemesis specifically; a Cochrane review found limited evidence for vitamin B6 on outcomes. Pyridoxine is EML-listed, off-patent, cents.

4. Metoclopramide. Used and relatively well tolerated. EML-listed, off-patent, cents a course.

5. Ondansetron. May be beneficial, and the evidence is limited. Concerns exist about an association with **cleft palate**: the signal is observational, the absolute risk increase reported is small, and professional positions differ. EML-listed as an antiemetic for chemotherapy-induced emesis, off-patent, low cost now generic.

6. Corticosteroids. The evidence is weak. They may slightly raise the risk of cleft lip and palate and suppress fetal adrenal activity; hydrocortisone and prednisolone are inactivated by the placenta and may be used after 12 weeks†. A later-line option.

7. Enteral or parenteral nutrition in refractory cases.

Negatives, reported as such: acupuncture is ineffective. Ginger has limited and inconsistent evidence. Medicinal cannabis has been used and has no trial evidence.

Simple means.

- **Oral rehydration solution**, sipped in small volumes where it can be kept down. Sugar, salt and water, and the first-line simple means for the central problem. UNICEF indicative prices put low-osmolarity sachets at **US$0.048 each** in October 2026.
- **Dry, bland food, small and frequent.** Named as first line on the source consulted.
- **Thiamine tablets** where parenteral is unavailable — a tablet costing a fraction of a cent, preventing permanent neurological injury.
- **Cold foods**, since odour is a dominant trigger, with avoidance of cooking smells and ventilation.
- **Rest in a dark quiet room**, and removal of trigger exposures.
- **Pyridoxine tablets and ginger** — cheap, oral, weakly evidenced, harmless.
- **Being believed.** The condition's documented history of psychological misattribution is itself a source of undertreatment, and the measured consequence of undertreatment is in the gaps below.

The minimum chain: oral rehydration salts and thiamine tablets carry mild and moderate cases. Severe cases need intravenous fluids, and there is no simple-means substitute for an intravenous line and a bag of saline.

Gaps. The prevalence sources disagree at 0.3 to 2.0 per cent, 0.3 to 1.5 per cent and about 1 per cent, and none is a measurement. The GDF15 finding is recent and has produced no treatment and no quantified risk model. Ondansetron's cleft palate signal is unresolved: observational, small in absolute effect, inconsistent across studies, and professional bodies differ. Corticosteroid evidence is weak and the teratogenicity signal unquantified. On offspring outcomes, children of mothers with **undertreated** hyperemesis had about **four-fold higher neurobehavioural diagnoses** in one observational study; that single study has obvious confounding and is also the only quantified statement available on the consequences of undertreatment — it cannot bear weight and should not be discarded. Maternal outcomes include lower miscarriage risk and higher preterm birth risk, and severe cases with under 7 kg weight gain have been linked to lower birth weight and small-for-gestational-age infants; both observational. No cost-effectiveness analysis of any treatment was located.

> **Depth.** Starts in: GDF15. Size: 5 nm†; depth −2.01. First complaint: about 4.3 weeks († about 6 weeks of pregnancy); time depth 46.60. One untreated course: about 12 weeks († about 12 weeks); depth 47.53.
>
> **Model reading.** Way of ending: let close. Layer: word. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Preterm labour

What it is. Labour starting before 37 completed weeks of pregnancy. The womb begins contracting and the cervix opens while the baby is still immature. The labour itself is the condition coded here; the consequences for the baby belong to the perinatal chapter.

Measured. An estimated **13.4 million babies were born preterm in 2020, more than 1 in 10 of all babies**. The rate ranged from **4 to 16 per cent** of births by country.

WHO's own fact sheet gives two different global figures. The body text gives 13.4 million; the page metadata gives **15 million**. Both are printed, and the disagreement is internal to one page.

Deaths: about **900,000 children died in 2019** from preterm birth complications, and WHO states that **three-quarters of those deaths could be prevented with current, cost-effective interventions**. GBD 2023 gives **623,300 (509,700 to 735,000)** deaths from neonatal preterm birth complications in 2023, down 41.4 per cent since 2000. The two do not reconcile beyond the difference in year and model, and both are printed.

Prematurity is the leading cause of death in children under 5. WHO describes the number of preterm births as rising, gives no year-by-year figures, and notes that it publishes updated global preterm analyses only every three to five years.

Where it starts. Previous preterm birth is the strongest single predictor. Multiple pregnancy, a short cervix on ultrasound, cervical surgery and uterine anomaly all raise risk. So do infection — intrauterine infection, bacterial vaginosis, urinary tract infection, and periodontal disease, the last contested. Pre-eclampsia and other medical indications for **iatrogenic** preterm delivery are a large and growing share of the total in high-income countries and must be counted separately from spontaneous preterm labour. Short interpregnancy interval, maternal age at both extremes, low maternal body mass index, smoking, heavy physical work and psychosocial stress are established, as is assisted reproduction, largely through multiple pregnancy. No effect sizes were located.

The cause of spontaneous preterm labour is not known in most cases. It is a syndrome with several recognised pathways — infection and inflammation, uteroplacental ischaemia, cervical insufficiency, uterine overdistension, stress — and in the majority of individual cases no pathway is identified. There is no accurate predictive test: fetal fibronectin and cervical length have negative predictive value and poor positive predictive value. **Tocolytics delay delivery by days and do not improve neonatal outcomes**, which is itself the clearest evidence that the mechanism is not understood, because suppressing the contractions does not address whatever started them.

Cure status. RELIEF ONLY, for the labour itself. No treatment reliably stops preterm labour and returns the pregnancy to a normal course. Tocolysis buys 48 hours†. It does not cure. What those 48 hours buy† is the window for antenatal corticosteroids and for transfer to a facility, and those interventions do change the baby's survival substantially. So the condition is RELIEF ONLY and the intervention it permits is among the most effective in this book.

Prevention.

- **Vaginal progesterone in women with a short cervix or prior preterm birth — MODERATE.** It reduces preterm birth before 34 weeks and reduces neonatal morbidity in meta-analyses, with the magnitude differing between the short-cervix and prior-preterm-birth populations; the large OPPTIMUM trial was null. Both the positive meta-analyses and the null trial are reported.
- **Cervical cerclage in selected women — MODERATE.** The benefit is confined to specific indications, principally a short cervix with prior loss, and it is not beneficial unselected.
- **Smoking cessation — STRONG.** One of the few preventive measures with a consistent effect across settings.
- **Treating asymptomatic bacteriuria — STRONG**, for preterm birth and for pyelonephritis. A cheap antibiotic and a clear effect.
- **Treating bacterial vaginosis — CONTESTED.** It does not consistently reduce preterm birth despite the epidemiological association.

- **Avoiding non-medically-indicated early delivery, and reducing multiple embryo transfer in assisted reproduction — STRONG** for the iatrogenic share, which is the share most amenable to policy.
- **Adequate interpregnancy interval, nutrition, and reducing heavy physical work — WEAK.**
- **Antenatal care itself — STRONG**, as the delivery vehicle: it is where the short cervix is found, the bacteriuria treated, the corticosteroids given and the transfer arranged. WHO recommends a minimum of eight contacts, starting before 12 weeks.
- **Low-dose aspirin — MODERATE**, through its pre-eclampsia effect, which removes an indication for iatrogenic preterm delivery.

Treatment. The highest-evidence treatments here treat the baby, not the labour.

1. Antenatal corticosteroids, the single highest-value intervention in this entry. The ACTION-I trial enrolled **2,852 women and their 3,070 babies** at 29 secondary and tertiary hospitals in Bangladesh, India, Kenya, Nigeria and Pakistan. Dexamethasone produced a **significantly lower risk of neonatal death and of stillbirth**, with **no increase in possible maternal bacterial infections**. WHO's own page does not publish the relative risk or its interval, and the trial's reported relative risk for neonatal death of approximately 0.84 could not be verified against the primary paper, so no relative risk is asserted here.

The significance of ACTION-I is specific. Antenatal corticosteroids had been standard in high-income settings since 1972, but a prior WHO cluster trial in 2015 found **harm** at population level when they were given in low-resource settings without accurate gestational age assessment and adequate newborn care. ACTION-I established benefit in hospitals that had both, and that condition is attached to the recommendation.

Dexamethasone is EML-listed in several sections, off-patent, and costs **under US$1 for a full course**; UNICEF indicative prices in October 2026 work out at about US$0.24 a 4 mg tablet. Betamethasone is the alternative: equivalent in effect, more expensive, and supply-constrained.

2. Magnesium sulfate for fetal neuroprotection, given before anticipated preterm birth, which reduces cerebral palsy in the surviving child. The same salt, EML-listed, off-patent, a few dollars.

3. Tocolysis with nifedipine or atosiban. Nifedipine is cheap, oral, EML-listed and off-patent. It **delays delivery by up to 48 hours† and does not improve neonatal mortality or morbidity.** Its value is entirely instrumental: it buys the corticosteroid window and the transfer.

4. Antibiotics for preterm prelabour rupture of membranes, which reduces neonatal infection. Erythromycin, EML-listed, off-patent, cheap. **Co-amoxiclav is specifically avoided** in this indication because of the increased necrotising enterocolitis signal in the ORACLE trial.

5. Intrapartum antibiotic prophylaxis against group B streptococcus where screening or risk-based protocols apply. Penicillin, EML-listed, off-patent, cents.

6. In-utero transfer to a facility with newborn care. Not a drug, and measured as one of the strongest determinants of preterm survival.

7. Delayed cord clamping at the preterm birth.

Simple means.

- **Delayed cord clamping.** Waiting 60 seconds or more before cutting transfers placental blood to the preterm baby, reduces the need for transfusion, and reduces mortality in meta-analysis of preterm births. It costs nothing and requires only that the attendant wait.
- **Skin-to-skin contact and kangaroo mother care immediately after a preterm birth.** The largest simple-means effect in this book: 28-day mortality relative risk 0.75†.
- **Keeping the baby warm** — drying, a hat, a warm room, body contact. Neonatal hypothermia is a major preterm killer and the countermeasure is free.
- **Immediate breastfeeding support and expressed milk**, which prevent necrotising enterocolitis and sepsis. No supply chain.

- **Clean delivery practice.**
- **Not sending the mother home.** Recognising threatened preterm labour and keeping her where corticosteroids and newborn care are is a decision rather than a resource.
- **Accurate gestational age by last menstrual period or fundal height** where ultrasound is unavailable. This is the input the earlier cluster trial lacked and ACTION-I had, and it is the difference between the corticosteroid helping and harming.

The minimum chain: dexamethasone ampoules and a syringe for the corticosteroid. Everything else in the list requires nothing manufactured.

Gaps. WHO's own fact sheet gives two different global figures for preterm births, 13.4 million in the body text and 15 million in the metadata, and its 900,000 deaths for 2019 does not reconcile with GBD's 623,300 for 2023. All are printed. WHO publishes no numeric effect size for antenatal corticosteroids or for kangaroo mother care on that page, and the ACTION-I relative risk could not be verified against the primary paper. The earlier cluster trial and ACTION-I reached opposite conclusions on corticosteroids in low-resource settings; the reconciliation through gestational-age accuracy and level of newborn care is plausible and is WHO's position, and it is an interpretation of a discrepancy rather than a measured finding. Progesterone's positive meta-analyses and the null OPPTIMUM trial remain unresolved. The share of preterm birth that is iatrogenic rather than spontaneous is not globally reported, which makes the global rate hard to interpret and the trend harder. There is no accurate predictive test and no treatment that stops preterm labour, and both are absences rather than thin evidence. Global preterm estimates are updated only every three to five years, so the rising trend rests on few data points.

> **Depth.** Starts in: the cervix. Size: 3 cm†; depth +12.19. First complaint: about 7.4 months ([B] before 37 weeks; † about 34 weeks); time depth 48.43. One untreated course: about 12 hours († hours); depth 42.87.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Ectopic pregnancy

What it is. A pregnancy that implants outside the womb, almost always in a fallopian tube. The tube cannot accommodate it. It ruptures and bleeds into the abdomen, which kills quickly.

Measured. Ectopic pregnancy deaths in 2023: **12,700 (8,500 to 17,800)**, **up 28.6 per cent** since 2000†. **This is one of only three causes in the entire maternal series that increased** — the others being other direct maternal disorders at plus 1.2 per cent and late maternal deaths at plus 10.8 per cent — and it is the largest proportional increase of any maternal cause.

Incidence is given as less than **2 per cent of pregnancies** worldwide, and as about **11 to 20 per 1,000 live births** in developed countries†; an infobox on the same source gives about 1.5 per cent of pregnancies†. It rises to as high as **4 per cent** with assisted reproductive technology†.

The measured gradient is in case fatality. Developed world figures are **0.1 to 0.3 per cent**†; a United Kingdom series for 2003 to 2005 gives 10 deaths among 32,100 cases, about **0.03 per cent**†; a UK Confidential Enquiry for 2006 to 2008 gives 6 deaths in 2.3 million pregnancies, 0.26 per 100,000†. The developing world figure is **1 to 3 per cent**† — a ten-fold or greater difference.

Ectopic pregnancy accounts for about **6 per cent of first-trimester maternal deaths** on one estimate and **6 to 13 per cent** on another. Both printed. A GBD-based analysis gives **3,478 ectopic pregnancy deaths in low-income countries in 2019** (2,849 to 4,187), 0.68 per 100,000 population and 37.69 DALYs per 100,000.

Where it starts. One figure is quantified: **endometriosis carries about 270 per cent higher risk, roughly an odds ratio of 2.7**, in a 30-year study of over 14,000 women†. Prior ectopic pregnancy carries a recurrence risk of about **10 per cent**†.

Risk tiers are given without odds ratios. High: tubal sterilisation, an intrauterine device in situ, prior ectopic, pelvic inflammatory disease, endometriosis, salpingitis isthmica nodosa. Moderate: smoking, more than one recent sexual partner, infertility, chlamydia. Low: douching, age over 35 or under 25, gamete intrafallopian transfer.

The dominant upstream exposure is tubal damage from chlamydia and gonorrhoea, which is why ectopic incidence tracks sexually transmitted infection prevalence.

What is genuinely not known is why the deaths are rising while every other major maternal cause falls. Candidate explanations — rising assisted reproduction, rising chlamydia prevalence, better ascertainment of a previously misclassified cause, and improved detection moving cases into the counted category — were not separated by any analysis located. This is the most important open question in the maternal data and no source reached offers an answer.

Cure status. CURABLE. Methotrexate resolves a selected subset medically and surgery resolves the rest definitively. Both cure the episode, and subsequent fertility is substantially preserved: a randomised study in 2013 found two-year intrauterine pregnancy rates of about **64 per cent after radical surgery, 67 per cent after medication and 70 per cent after conservative surgery**. Recurrence is about 5 per cent after salpingectomy and 8 per cent after salpingostomy, with intrauterine pregnancy rates of 56 and 61 per cent respectively. The condition kills only when not diagnosed before rupture. The entire clinical problem is detection in time.

Prevention.

- **Preventing and treating chlamydia and gonorrhoea — STRONG** on mechanism, by preventing tubal damage. Chlamydia screening programmes have been associated with reduced pelvic inflammatory disease; the ectopic-specific effect size was not located.
- **Early pregnancy ultrasound and β-hCG access — STRONG for death, not for incidence.** This is the decisive intervention and it is detection: finding the ectopic before it ruptures is what separates 0.03 per cent case fatality from 3 per cent.
- **Not using an intrauterine device in a woman at high ectopic risk — MODERATE**, with the framing stated correctly: an intrauterine device **reduces** absolute ectopic risk by preventing pregnancy overall, and raises the proportion of pregnancies that are ectopic among its rare failures.
- **Reducing multiple embryo transfer and managing assisted reproduction — MODERATE**, for the 4 per cent figure above.
- **Smoking cessation — MODERATE.**
- There is **no primary prevention** for ectopic pregnancy in a woman with already-damaged tubes.

Treatment. 1. Methotrexate, for the selected subset: low β-hCG, a small mass, no rupture, haemodynamic stability and reliable follow-up. It works best when β-hCG is low and the mass small. Contraindications are a mass over 3.5 cm, a ruptured tube, and renal or hepatic dysfunction. **Regimens differ by country and so do their failure rates:** the United States uses up to four intramuscular doses, and France uses a single dose, which has a greater chance of failure. One source recommends giving methotrexate only when β-hCG rises by less than 35 per cent over 48 hours. **No success percentage is given on the sources consulted.** Published series commonly report 65 to 95 per cent† depending on selection and regimen, and no pooled figure is asserted here. Methotrexate is EML-listed as a cytotoxic medicine, off-patent, and costs a few US dollars a dose. The real supply-chain constraint is serial β-hCG measurement: the drug is cheap and the laboratory follow-up is unavailable in most places where women die of this.

2. Surgery — laparoscopy or laparotomy, with salpingostomy to open the tube and remove the pregnancy, or salpingectomy to remove the tube. It is recommended for rupture, a fetal heartbeat, or unstable vital signs. Surgery is needed for 0.5 to 11 per cent of pregnancies of unknown location. **Laparotomy requires no laparoscopic stack and is the operation that is actually available in low-resource settings.** It is one of the three Bellwether procedures, and this is exactly the indication for which it is included.

3. Expectant management for spontaneously resolving cases with falling β-hCG.

4. Resuscitation and transfusion for the ruptured, bleeding patient. This is the emergency, and blood availability is the determinant.

5. Anti-D immunoglobulin where indicated.

Simple means. The honest answer here is largely negative and that must be said plainly.

- **A urine pregnancy test.** A cheap shelf-stable strip. In a woman of reproductive age with abdominal pain and a positive urine pregnancy test, ectopic is the working diagnosis until excluded. This single consumable is the highest-yield item in the entry: it converts abdominal pain into a surgical emergency.
- **Clinical examination and the history** — amenorrhoea, abdominal pain, shoulder-tip pain, syncope, cervical excitation. No equipment.
- **Recognition teaching and transport.** The determinant of death is the interval from rupture to laparotomy.
- **Positioning and nothing by mouth during transfer**, with intravenous fluids where available.

A ruptured ectopic pregnancy requires a laparotomy and usually blood. **There is no simple means that substitutes for abdominal surgery.** Methotrexate requires a laboratory. The urine pregnancy test is the only genuine simple means in this entry, and its function is to send the woman to the surgery she needs. With obstructed labour, this is the clearest case in the chapter for the Lancet Commission's argument.

Gaps. The 28.6 per cent rise in deaths from 2000 to 2023 is unexplained in any source located, and whether it is a real increase, an ascertainment artefact, or a consequence of assisted reproduction and rising chlamydia is not established. Methotrexate success rates are not given on the sources reachable, and the United States four-dose and French single-dose regimens have acknowledged different failure rates with no head-to-head figure here. Risk factors are tiered and almost entirely unquantified: only endometriosis at an odds ratio of about 2.7 and prior ectopic at about 10 per cent recurrence carry numbers. Cost is not discussed in the sources consulted. Case-fatality sources give 0.1 to 0.3 per cent and 0.03 per cent for high-income settings, a ten-fold spread within one category, almost certainly from ascertainment of the denominator; both printed. GBD's low-income figure of 3,478 for 2019 and its global figure of 12,700 for 2023 come from different analyses and different years and cannot be compared.

> **Depth.** Starts in: the blastocyst. Size: 100 µm†; depth +7.00. First complaint: about 5 weeks († 6–8 weeks of pregnancy); time depth 46.72. One untreated course: about 6 hours ([B] ruptures and kills fast); depth 42.24.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Miscarriage

What it is. A pregnancy that ends by itself before the fetus can survive outside the womb. Most happen in the first twelve weeks, and most are caused by a chromosomal error in the embryo that was present from conception.

Measured. GBD counts miscarriage inside maternal abortive outcome, at **19,600 deaths (12,200 to 30,800)** in 2023, down 54.8 per cent since 2000. That line also contains induced and unsafe abortion, so **no separate death figure for miscarriage exists in the GBD series.**

No WHO or GBD global incidence estimate was located. The clinically standard figures — roughly 10 to 15 per cent of recognised pregnancies ending in miscarriage, and a substantially higher proportion of all conceptions including those lost before recognition — come from cohort studies rather than a global estimation exercise, and are not asserted here as global figures. Recurrent miscarriage, meaning three or more consecutive losses, affects approximately 1 per cent of couples attempting pregnancy in the published cohorts†.

Incidence is not strongly patterned by income. **Death from miscarriage is**, because it is death from the haemorrhage or sepsis of an incomplete miscarriage without access to evacuation.

Where it starts. Fetal chromosomal abnormality is the cause in roughly half of first-trimester miscarriages in karyotyped series — most commonly autosomal trisomy, and most commonly arising de novo at meiosis. This is the dominant cause and it is not preventable.

Maternal age is the strongest risk factor, acting through oocyte aneuploidy, with risk rising steeply after 35 and sharply after 40. Antiphospholipid syndrome, uncontrolled thyroid disease, uncontrolled diabetes, uterine anomaly or fibroids distorting the cavity, and cervical insufficiency in the second trimester are established. Smoking, heavy alcohol use, high caffeine intake, obesity and underweight are associated with modest effect sizes. Infections include listeriosis, syphilis, malaria in pregnancy, rubella, cytomegalovirus and Zika.

Not associated, despite persistent belief: moderate exercise, sexual intercourse, air travel, previous induced abortion, and most occupational exposures. Reporting these negatives matters, because the dominant maternal experience of miscarriage is misplaced self-blame. No effect sizes were retrievable.

The cause is unknown in roughly half of cases and in the great majority of recurrent miscarriage. After full investigation most couples with recurrent miscarriage receive no explanation. The proposed mechanisms — immunological, thrombophilic, endometrial receptivity — have generated many treatments and almost no trial-proven ones, which is the signature of an unidentified mechanism.

Cure status. The loss itself: SELF-LIMITING. The pregnancy loss completes, and in the large majority the uterus empties without intervention; expectant management succeeds in most complete and incomplete miscarriages given time. Nothing prevents or reverses the loss once it has begun. The complications — retained tissue causing haemorrhage or sepsis: CURABLE. The deaths recorded above are entirely from these.

Recurrent miscarriage is not self-limiting in the sense that matters to the couple, and no treatment has been shown to cure it either.

Prevention. This section is mostly negative and must be reported that way.

- **Nothing prevents chromosomally abnormal miscarriage**, which is the largest category. This is the central fact and the one most often obscured.
- **Progesterone — CONTESTED, with one qualified positive.** The PROMISE trial was null for recurrent miscarriage. The PRISM trial was null overall and found benefit in the subgroup with bleeding **and** three or more previous miscarriages, and United Kingdom guidance now offers progesterone to that specific subgroup. Both results printed; this is a subgroup finding and should be read as one.
- **Levothyroxine for overt hypothyroidism — STRONG.** For subclinical hypothyroidism or thyroid autoimmunity — **CONTESTED**, with the TABLET and T4LIFE trials null†.
- **Aspirin plus heparin in antiphospholipid syndrome — STRONG** for that specific diagnosis, with **no benefit in unexplained recurrent miscarriage**, where the ALIFE and SPIN trials were null.
- **Smoking and alcohol cessation, caffeine reduction, weight normalisation — MODERATE.**
- **Folic acid does not prevent miscarriage.** It prevents neural tube defects. The distinction matters.
- **Pre-pregnancy diabetes control — MODERATE.**
- **Malaria prevention in pregnancy — STRONG** in endemic areas, for the malaria-attributable share, by intermittent preventive treatment and insecticide-treated nets.
- **Cervical cerclage — MODERATE**, in selected second-trimester cases only.
- **Immunotherapy, intravenous immunoglobulin, paternal leucocyte immunisation — ineffective, and harmful in some trials.** A settled negative.
- **Bed rest — no evidence of benefit.** A settled negative that continues to be prescribed.

Treatment. For the miscarriage itself, treatment means completing the uterine evacuation, and all three options are acceptable with differing profiles.

1. Expectant management. Waiting. It succeeds in the majority, and requires only that bleeding and infection be watched for. Free.

2. Misoprostol, 600 to 800 µg, with the regimen varying by whether the sac is retained. EML-listed, off-patent, cents a tablet. The MifeMiso trial showed that adding mifepristone to misoprostol for missed miscarriage increased the rate of complete miscarriage without surgery. Mifepristone is EML-listed as a co-package with misoprostol for induced abortion and for fetal death; availability is restricted by regulation rather than by patent, and cost is low. Oral and vaginal tablets, no cold chain, no theatre.

3. Manual or electric vacuum aspiration. A hand-powered syringe, no electricity, local anaesthesia, reusable. Preferred over sharp curettage, which has higher perforation and intrauterine adhesion rates and should be regarded as superseded.

4. Antibiotics for septic miscarriage — ampicillin, gentamicin, metronidazole. EML-listed, off-patent, a few dollars.

5. Uterotonics and tranexamic acid for the haemorrhage.

6. Anti-D immunoglobulin where the mother is RhD-negative and the gestation is beyond the local threshold. EML-listed, off-patent as a plasma-derived product, with supply rather than patent the constraint. This prevents haemolytic disease in a **later** baby: the intervention and its beneficiary are a pregnancy apart.

7. Investigation after recurrent miscarriage — karyotype, antiphospholipid antibodies, thyroid function, uterine imaging. It finds a cause in a minority.

Simple means.

- **Expectant management.** Doing nothing, competently, with instructions on when to return. The majority of miscarriages need no intervention at all, and this is both the lowest-chain and an entirely evidence-based option.
- **Misoprostol tablets.** Cents, shelf-stable, oral.
- **Manual vacuum aspiration.** A plastic syringe.
- **Oral analgesia** — paracetamol, ibuprofen. The pain of miscarriage is routinely undertreated.
- **Oral rehydration**, and iron for the blood loss.
- **Clear information on what to expect and when to come back** — how much bleeding is too much, and what fever means. This is the intervention that converts a self-limiting event into a safe one, and it costs a conversation.
- **Being told it was not her fault.** The established epidemiology — a chromosomal error arising at meiosis, with no preventive action available — is the content of that statement, and stating it is free.

The minimum chain: nothing for the majority; one tablet or one plastic syringe for the rest; antibiotics if it becomes septic.

Gaps. GBD gives no separate figure for miscarriage, merging it with induced abortion inside maternal abortive outcome, so the miscarriage mortality burden is not separately published. No global incidence estimate exists from WHO or GBD: the familiar 10 to 15 per cent figure is from cohorts, and total conception loss including pre-recognition loss is not measurable at population scale. On progesterone, PROMISE was null and PRISM was null overall and positive in a subgroup, and guidelines differ internationally on the same data. Recurrent miscarriage has no established cause in most cases and almost no trial-proven treatment; the field has a long record of interventions adopted on mechanism and abandoned on trial. Effect sizes for risk factors were not retrievable. The psychological burden of miscarriage is substantial and almost entirely unmeasured in the global burden accounts, where it carries no disability weight.

> **Depth.** Starts in: the embryo (chromosome error). Size: 100 µm†; depth +7.00. First complaint: about 7 weeks ([B] mostly before 12 weeks; † about 9 weeks); time depth 47.04. One untreated course: about 2 days († days); depth 44.13.
>
> **Model reading.** Way of ending: let close. Layer: chain. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CURABLE. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Postpartum depression

What it is. Depression beginning in the weeks or months after giving birth. Low mood, inability to feel pleasure, exhaustion beyond that of a new baby, and often intrusive fears about the baby. It is distinct from the brief low mood of the first days.

Measured. Global prevalence is given as roughly **10 to 20 per cent** of postpartum women; an infobox on the source consulted gives about **15 per cent of births**; and a review gives a mean of **10 to 15 per cent**, noting that cultural factors and stigma may hinder accurate reporting. All printed.

United States: **11.5 per cent overall, varying by state from 8 to 20.1 per cent**†. **About 60 per cent of United States women are not diagnosed, and about half of those diagnosed are not treated**; a second source gives up to 50 per cent of cases undiagnosed†.

Middle East: pooled prevalence **27 per cent**, with a country range of 10 to 40 per cent — Iran 40.2, Bahrain 37.1, Saudi Arabia about 10 — and 31 per cent in the first three months against 19 per cent in months 4 to 12†. Africa: **15 to 25 per cent**, with national figures from about 7 per cent in Morocco to 43 per cent in Uganda†.

South America: Brazil 42 per cent, Guyana and Colombia 57 per cent, Venezuela 22 per cent†. **The source is internally inconsistent here**, citing around 60 per cent for several South American countries while giving lower country-specific values for the same countries. Cross-country comparisons from it are not reliable.

Paternal postpartum depression: **8 to 10 per cent of fathers**†; a Japanese study found 13.6 per cent within four months of birth†. Postpartum psychosis: about **1 to 2 per 1,000 women**†, a separate and far more dangerous condition.

No GBD cause line exists for postpartum depression. Its burden sits inside depressive disorders. No trend was quantified in any source reached.

Where it starts. The quantified risks are social.

- **Mother-in-law conflict: risk ratios of 1.8 and 2.7** across four studies†.
- **Family violence: about 2.5 times higher risk** in Middle Eastern samples†.
- **A female infant: 2 to 4 times higher risk** in Egyptian and Jordanian studies†. The risk factor is the social response to the baby's sex, not the baby.
- **Absence of spousal support: 42.9 per cent of women without spousal support had postpartum depression against 14.7 per cent of those with it**†.
- **A partner with postpartum depression:** fathers develop it about half the time when their partner has it.
- **Race in the United States: African American mothers at the highest estimated risk, about 25 per cent, and Asian mothers the lowest at 11.5 per cent**†.
- Lesbian and bisexual mothers had significantly higher screening scores than heterosexual mothers in one study.
- Prenatal depression, prior postpartum depression, low income and low social support are all established associations with no effect sizes given.

The biology is not known. The hormonal-withdrawal hypothesis — the abrupt fall in oestrogen and progesterone after delivery — motivated the allopregnanolone analogues, and those drugs work, which is suggestive. Why only a minority of women are susceptible to the same hormonal change is not known, and no biomarker predicts it. The measured risk factors are overwhelmingly social and the effective new drugs are neurosteroidal, and nothing in the reachable literature reconciles those two facts.

Cure status. The episode: CURABLE. Most episodes remit, with treatment faster and more reliably than without, and the woman returns to her previous state. The susceptibility: CONTROLLABLE. A prior episode is the strongest predictor of another.

Not CONTROLLABLE for the episode, because the episode genuinely resolves. Not SELF-LIMITING, because untreated episodes can persist for a year or longer and some do not remit. An untreated episode also has consequences for the child's development that treating a later episode does not undo.

Prevention.

- **Psychosocial and psychological interventions — MODERATE.** A 2013 Cochrane review found psychosocial interventions reduced the risk of postnatal depression — home visits, telephone peer support, and interpersonal psychotherapy — and no pooled effect size is given on the source consulted.
- **Telephone peer support for high-risk women — MODERATE**.
- **Counselling for women at high risk**, which the United States Preventive Services Task Force supports; that is the strongest formal endorsement available in this section.
- **Identifying and treating prenatal depression — MODERATE.** Prenatal depression is the strongest modifiable predictor.
- **Spousal and family support — MODERATE**, with the largest observational effect size in the entry at 42.9 against 14.7 per cent.
- **Addressing family violence — MODERATE** on mechanism, at a risk ratio of about 2.5.
- **Screening alone — WEAK.** Screening without a treatment pathway does not change outcomes. The United States figures — 60 per cent undiagnosed, half of the diagnosed untreated — are a statement about pathways, not about instruments.
- **Routine universal prophylactic antidepressants — not recommended, no evidence of benefit.**

Treatment. The proportion of episodes that remit with treatment, and without it, is not given here. **1. Psychological therapy** — cognitive behavioural therapy and interpersonal psychotherapy. Individual social and psychological interventions were found about equally effective. These are the first-line treatments with the best evidence and no pharmacological risk to a breastfed infant. **A 2021 meta-analysis found that non-specialist providers — lay counsellors and nurses — often deliver effective care**, which is the finding that makes treatment deliverable where there are no psychiatrists. Peer support is effective.

2. Selective serotonin reuptake inhibitors, sertraline first. Low-certainty evidence supports their effectiveness, which is a weaker statement than the prescribing volume implies and should be reported as it stands. Sertraline is first-line because little passes into breast milk. A recent study found **adding sertraline to psychotherapy gave no additional benefit**, and the source concludes it is unclear which antidepressants work best or for whom. Fluoxetine is the EML-listed SSRI and sertraline is also listed; both off-patent, cents a day, a month of generic treatment costing a few US dollars or less.

3. Brexanolone, an intravenous allopregnanolone analogue approved in the United States in 2019. Some trials showed effects within 48 hours. It requires a **60-hour infusion**, enrolment in a risk-management programme, and continuous monitoring; side effects include sedation and loss of consciousness. Not on the EML, not off-patent, and launched in the United States at approximately **US$34,000 per course** before administration costs. This is the price-per-effect outlier of the chapter and the opposite of the magnesium sulfate case.

4. Zuranolone, an oral allopregnanolone analogue approved in the United States in 2023, given as a 14-day course. Side effects are sedation, somnolence and dizziness, and long-term efficacy is uncertain. Not on the EML, not off-patent, launched at approximately **US$15,900 per 14-day course** in the United States.

5. Electroconvulsive therapy, effective for severe postpartum depression that fails medication, and the treatment of choice for postpartum psychosis with risk to life.

6. Repetitive transcranial magnetic stimulation. Tentative evidence.

7. Light aerobic exercise, useful for mild to moderate cases.

Reported as unclear: acupuncture, massage, bright light therapy, omega-3 supplementation†. Hormone therapy has some evidence and estradiol patches may help; oestrogen carries clot risk up to 12 weeks postpartum, and no studies included breastfeeding women†.

Simple means. This condition is unusually well served by them, which is the central practical finding.

- **Non-specialist delivered talking therapy.** Lay counsellors and nurses often deliver effective care. The Thinking Healthy Programme in Pakistan and the Friendship Bench model in Zimbabwe are the worked examples: supervised lay workers delivering a structured brief psychological intervention. No drug, no clinician, no supply chain. **This is the single most important item in this section.**
- **Telephone peer support** — a phone.
- **Home visiting**.
- **A ten-item self-report questionnaire on one sheet of paper.** The Edinburgh Postnatal Depression Scale. **A score of 13 or more suggests postpartum depression and warrants further assessment**. Free, translated into most languages, widely validated. Note an inconsistency in use: a neonatal intensive care protocol uses 12 as the threshold while the general cut-off is 13†, and a score above zero on the self-harm item triggers immediate referral.
- **Practical help with the baby, and sleep.** Sleep deprivation is both a symptom and a driver, and arranging that someone else takes a night is an intervention.
- **Breastfeeding support.** Difficulty with feeding is a common precipitant, and supporting it is free.
- **Exercise** — walking.
- **Asking the question at all.** With 50 to 60 per cent of cases undiagnosed, the single highest-yield act is a health worker asking two questions at a postnatal contact.

The minimum chain: a sheet of paper and a trained lay worker. Nothing manufactured.

Gaps. Prevalence estimates range from about 7 to 57 per cent† across countries, and the source consulted is internally inconsistent for South America; most estimates rely on Western-developed screening tools and self-report, which the source itself flags as a bias, so cross-country comparison is not currently reliable. No systematic comparison between low- and middle-income and high-income countries exists in the sources reached. SSRI evidence is low-certainty and adding sertraline to psychotherapy added nothing, so the prescribing base is wider than the evidence base. There is no GBD cause line, so the condition is absent from the global burden accounts despite affecting roughly one in seven births. Screening thresholds differ between protocols in use. The two new effective drugs cost tens of thousands of dollars a course and are unavailable in the settings with the highest measured prevalence; the treatment with the best evidence for scale and the treatment with the fastest effect sit at opposite ends of the cost range, and no located analysis compares them per outcome. Paternal postpartum depression is measured at 8 to 10 per cent and has essentially no intervention evidence base.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 4 weeks ([B] weeks to months after birth); time depth 46.53. One untreated course: about 6 months († about 6 months); depth 48.23.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Maternal anaemia

What it is. Too little haemoglobin in the blood during pregnancy. Most often from lack of iron, because the baby's demand exceeds the mother's supply. It leaves the mother tired and breathless, and leaves her with no reserve if she bleeds at delivery.

Measured. WHO's standing published estimate is that anaemia affects approximately **37 per cent of pregnant women worldwide**, on a 2019 base year, and the WHO diagnostic threshold in pregnancy is **haemoglobin below 110 g/L**†. Both are reported as the standing figures; neither was verified against a source fetched in the retrieval round.

GBD reports anaemia as an **impairment** rather than a cause, with large contributions to years lived with disability; dietary iron deficiency ranks 9th among causes of years lived with disability in 2023 at **39.3 million (24.8 to 63.5)**. Anaemia has no maternal deaths line. Its mortality contribution is indirect, counted within GBD's indirect maternal deaths — **23,000 (16,300 to 32,700)** in 2023, down 22.5 per cent — together with other conditions aggravated by pregnancy. It is the mechanism by which a survivable postpartum haemorrhage becomes a fatal one.

Prevalence is highest in South Asia and sub-Saharan Africa, where hookworm, malaria, schistosomiasis and dietary iron inadequacy act in combination.

The trend is the point. **Global anaemia prevalence in women of reproductive age has been close to flat for two decades**, against a maternal mortality ratio that fell about 40 per cent over the same period. It is one of the least-improved indicators in maternal health.

Where it starts. Iron deficiency is the dominant cause, from low dietary intake of bioavailable iron, from closely spaced pregnancies depleting stores, and from chronic blood loss.

Three infections make the regional pattern: **hookworm** through intestinal blood loss, **malaria in pregnancy** through haemolysis and placental sequestration, and **schistosomiasis**. Folate, vitamin B12 and vitamin A deficiency contribute. **Haemoglobinopathies** — sickle cell trait and disease, the thalassaemias — are a major non-nutritional contribution in high-prevalence populations, and iron will not correct them. Short interpregnancy interval, adolescent pregnancy, high parity, HIV and chronic inflammation all raise risk. No effect sizes were retrievable.

What is not known is how much of the flat global trend is dietary, how much infectious and how much haemoglobinopathy, because the population-level causal partition of anaemia is not established in most high-burden settings. Surveys measure haemoglobin, not its cause. Ferritin and inflammatory markers are rarely measured at scale. This matters directly: iron supplementation is the near-universal programmatic response and it will not correct the non-iron fraction, whose size is unknown. There is also an unresolved question about iron supplementation in malaria-endemic settings, where trials have raised safety concerns.

Cure status. Iron-deficiency anaemia, which is most cases: CURABLE. Iron replacement restores haemoglobin and the mother recovers completely. Thalassaemia and sickle cell disease: CONTROLLABLE. Other non-iron causes: CONTROLLABLE, by disorder.

Curing the episode without addressing the cause — hookworm, malaria, diet, closely spaced pregnancies — produces recurrence. Maternal anaemia as a measured prevalence figure is a mixture whose curable fraction is large and not total.

Prevention.

- **Daily oral iron and folic acid supplementation in pregnancy — STRONG**, and WHO-recommended as routine antenatal care at 30 to 60 mg elemental iron plus 400 µg folic acid daily. This also delivers the folic acid that prevents neural tube defects, so one tablet carries two effects.
- **Intermittent weekly iron and folic acid supplementation — MODERATE**, where daily is not tolerated or not feasible.
- **Food fortification of staples with iron — MODERATE.** The evidence base is weaker than for folic acid fortification, because iron fortificants have bioavailability and taste problems that folic acid does not.
- **Deworming with albendazole or mebendazole after the first trimester in hookworm-endemic areas — STRONG** for the hookworm fraction. A single tablet, cents, EML-listed.
- **Intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine, plus insecticide-treated nets — STRONG** in endemic areas, for both anaemia and low birth weight.
- **Delayed cord clamping — STRONG for the baby's iron stores**, reducing infant anaemia at six months. It does not treat the mother.
- **Birth spacing and contraception — MODERATE**, allowing iron stores to recover.
- **Antenatal care with haemoglobin measurement — STRONG**, as the delivery vehicle.

Treatment. 1. Oral iron salts — ferrous sulfate, fumarate or gluconate, with folic acid. The fixed combination of iron 60 mg plus folic acid 400 µg is EML-listed and off-patent, and a UNICEF indicative price in October 2026 put a bottle of 100 tablets at US$1.24, or **about US$0.012 a tablet**. A full pregnancy's supplementation therefore costs well under one US dollar. The limitation is gastrointestinal side effects causing substantial non-adherence, which is the main reason programmatic coverage does not translate into haemoglobin change. Alternate-day dosing improves absorption and tolerability.

2. Intravenous iron — ferric carboxymaltose or iron sucrose — for severe anaemia, late pregnancy, oral intolerance, or where time to delivery is short. Iron sucrose is EML-listed on the complementary list and off-patent; the newer high-dose formulations are not. Iron sucrose is moderately cheap and ferric carboxymaltose substantially more expensive, and the latter allows a single large dose, which matters when a woman presents once at 34 weeks and will not return. Both need an infusion facility and resuscitation capacity. Trials in Africa and India have shown intravenous iron corrects severe late-pregnancy anaemia faster than oral; whether that translates into fewer deaths is being tested and is not established.

3. Blood transfusion for severe symptomatic anaemia or acute blood loss. It requires a blood bank, which is one of the measured gaps behind the obstetric haemorrhage deaths.

4. Treating the cause — albendazole or mebendazole for hookworm, antimalarials, and vitamin B12 or folate replacement where deficient.

5. For haemoglobinopathy — transfusion programmes, hydroxyurea in sickle cell disease, and specialist management. Hydroxyurea is EML-listed for other specified sickle cell disorders and other haemoglobinopathies. Iron is **contraindicated** in iron-loaded thalassaemia, which is why diagnosing the cause matters.

Simple means.

- **Iron and folic acid tablets.** About a cent a tablet. The single highest-value-per-euro item in this entry and, alongside magnesium sulfate, in the chapter.
- **Dietary change** — pulses, dark green leaves, offal where culturally acceptable; vitamin C-containing food eaten with the iron source to raise absorption; avoiding tea and coffee with meals, which inhibit it. All free.
- **Cooking in iron pots.** Measured to raise dietary iron content and, in trials in some settings, haemoglobin. It requires an iron pot.
- **Handwashing, footwear and sanitation.** The hookworm transmission route runs through bare feet and open defaecation, so shoes are a haematological intervention in hookworm-endemic areas.
- **Insecticide-treated bed nets** for the malaria fraction.
- **Delayed cord clamping** at the birth, for the baby's stores. Free.
- **Clinical pallor assessment** of conjunctiva, palms and tongue where no haemoglobinometer exists. Insensitive for mild anaemia and usable for severe. A **haemoglobin colour scale** — a printed card compared against a blood drop — is the next step up and costs almost nothing.

The minimum chain: a tablet costing about a cent, taken daily. For the severe cases presenting late, intravenous iron or blood, and both need a facility.

Gaps. The 37 per cent prevalence figure could not be verified against a source fetched in the retrieval round and is reported as WHO's standing published estimate. The causal partition of anaemia is unknown in most high-burden settings: iron is given to everyone because the non-iron fraction cannot be identified without laboratory capacity that does not exist there, and the size of the fraction iron cannot fix is genuinely not known. Global anaemia prevalence has not fallen while maternal mortality fell about 40 per cent, and no located analysis explains the divergence. Iron supplementation safety in malaria-endemic settings is unresolved: trials in children raised concerns about increased malaria morbidity with iron in high-transmission areas, and whether that extends to pregnancy is contested. Whether intravenous iron reduces maternal deaths, as opposed to correcting haemoglobin, is under trial and not established. Adherence rather than supply is the binding constraint on oral iron programmes, and adherence is poorly measured. GBD treats anaemia as an impairment rather than a cause, so it has no deaths line and its contribution to the maternal deaths it enables is not separately quantified anywhere.

> **Depth.** Starts in: haemoglobin. Size: 6.5 nm†; depth −1.77. First complaint: about 5 months († second trimester); time depth 48.06. One untreated course: no number.
>
> **Model reading.** Way of ending: supply from outside. Layer: word. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

ICD-11 Chapter 19 — Certain conditions originating in the perinatal period

Eight entries. The chapter-level denominators are these. Neonatal deaths in 2022: **2.3 million**, in the first 28 days of life, about 6,500 a day, and **47 per cent of all under-5 deaths**. The figure was 5.0 million in 1990 and has fallen **44 per cent since 2000**, with the decline slowing since 2010. **Seventy-five per cent of neonatal deaths occur in the first week and about 1 million in the first 24 hours**.

The highest regional neonatal mortality rates are sub-Saharan Africa at **27 per 1,000 live births** and central and southern Asia at **21**, with national rates in 2022 ranging from **0.7 to 39.4 per 1,000**. Sixty-four countries are projected to miss the 2030 target.

GBD 2023 gives **neonatal disorders 1,628,000 deaths (1,506,000 to 1,748,000)** in 2023, down 37.6 per cent since 2000 — a lower figure than the 2.3 million above, because GBD's neonatal disorders is a cause group rather than all deaths occurring in the neonatal period. Both are printed. GBD 2023 ranks neonatal disorders **2nd among all DALY causes at 170 million DALYs (159 to 183)** and 13th among causes of years lived with disability at **23.6 million (18.0 to 29.8)**.

No global neonatal mortality rate is asserted here. The reachable WHO page reports 2022 and gives no global rate and no 2023 figure, and the interagency report carrying the 2024 rate was not reached. Deriving a rate by arithmetic from deaths and births would present an estimate as a measurement.

Preterm birth complications

What it is. The problems a baby has because it was born too early. The lungs, gut, brain, immune system and skin are all unfinished. The baby cannot keep itself warm, cannot feed reliably, and cannot fight infection.

Measured. Preterm birth complications: **623,300 deaths (509,700 to 735,000)** in 2023, down 41.4 per cent since 2000. **The single largest cause of neonatal death in the GBD series.** WHO gives about **900,000 children died in 2019** from preterm birth complications and states that three-quarters of those deaths could be prevented with current, cost-effective interventions. Both figures printed; different years, different models.

Prematurity is the leading cause of death in children under 5. Births: 13.4 million preterm in 2020, more than 1 in 10 babies, with the same page's metadata giving 15 million†; the country rate ranges from 4 to 16 per cent.

The survival gradient is the central measured fact. In low-income settings, **half of babies born at or below 32 weeks die**, often from lack of warmth, breastfeeding support, and treatment for infections and breathing difficulties — WHO's own list, and every item on it is a simple means. In high-income countries almost all of these babies survive. For extremely preterm babies under 28 weeks, **more than 90 per cent die within the first few days in low-income countries against under 10 per cent in high-income settings**.

Where it starts. The cause of the complications is immaturity of every organ system, with gestational age at birth the dominant determinant. The causes of the preterm birth itself belong to the preterm labour entry.

Gestational age is the strongest predictor of every outcome, with risk rising steeply below 32 weeks and sharply below 28. Birth weight contributes independently of gestation. **Male sex carries higher mortality and morbidity at every gestational age**, consistently and unexplained. Absence of antenatal

corticosteroids, absence of a skilled attendant, delivery outside a facility with newborn care, and multiple pregnancy all raise risk. No effect sizes beyond the survival gradients were located.

Two things are not known. Why the male disadvantage exists. And, more consequentially, the **viability threshold is not a biological constant but a function of available care** — the same 24-week baby survives in one country and does not in another, so statements about the limit of viability are statements about the health system. Which component of newborn care accounts for most of the gradient is not separated by any analysis located: WHO's list of warmth, feeding, infection treatment and breathing support is given without weights.

Cure status. CURABLE for the neonatal course: the condition is time-limited and the child recovers completely. Prematurity is not a disease that persists; it is a developmental deficit that closes. A baby that survives the neonatal period at an appropriate weight and without brain injury becomes a normal child. That is also why the intervention set is so cost-effective: the investment is weeks long and the benefit is lifelong.

Two qualifications. A share of survivors carry permanent sequelae — cerebral palsy, cognitive impairment, retinopathy of prematurity, chronic lung disease — and those are RELIEF ONLY or CONTROLLABLE in their own right. And the cure is delivered by supportive care over weeks, not by a treatment that removes anything.

Prevention. Prevention of the preterm birth belongs to the preterm labour entry. For the complications, given a preterm birth:

- **Antenatal corticosteroids — STRONG.**
- **Kangaroo mother care — STRONG**, and the largest simple-means effect in this book.
- **Delayed cord clamping — STRONG.** It reduces mortality in preterm infants in meta-analysis, reduces the need for transfusion, and improves iron stores.
- **Thermal care from the first minute — STRONG.** Drying, a hat, skin-to-skin, a warm room. Hypothermia is a leading preterm killer and a free intervention prevents it.
- **Exclusive breastfeeding or expressed breast milk — STRONG.** It reduces necrotising enterocolitis and late-onset sepsis, and the effect size for necrotising enterocolitis with human milk against formula is large in meta-analysis.
- **Clean delivery and hand hygiene in newborn care — STRONG.**
- **In-utero transfer to a facility with newborn care — STRONG.**
- **Caffeine citrate for apnoea of prematurity — STRONG.**
- **Magnesium sulfate antenatally for fetal neuroprotection — STRONG**, for cerebral palsy reduction.
- **Prophylactic probiotics for necrotising enterocolitis — MODERATE**, with the caveat that benefit was clearest in exclusively human-milk-fed very low birth weight infants.
- **Vitamin K at birth — STRONG**, for haemorrhagic disease of the newborn.
- **Avoiding unnecessary antibiotic exposure — MODERATE.**

Treatment. 1. Kangaroo mother care, the highest-evidence, lowest-cost treatment in this chapter. The iKMC trial randomised **2,944 mothers and 3,211 infants** at five tertiary hospitals in Ghana, India, Malawi, Nigeria and Tanzania, at birth weights of 1.0 to 1.799 kg.

28-day mortality: 12.0 per cent on immediate kangaroo mother care against 15.7 per cent on conventional care. Relative risk 0.75 (95 per cent CI 0.64 to 0.89), p = 0.001. An absolute reduction of 3.7 percentage points and a **number needed to treat of about 27**†. Mortality at 72 hours was 4.6 against 5.8 per cent, relative risk 0.77 (0.58 to 1.04), not statistically significant†. The trial was stopped early by its data monitoring committee for benefit.

A 25 per cent relative reduction in neonatal death, from holding the baby against the mother's skin. No drug, no device, no electricity, no supply chain. WHO's 2022 recommendations state that immediate kangaroo mother care after birth can substantially reduce mortality in preterm and low-birthweight babies, and WHO's preterm fact sheet gives no numeric effect size, so the figures above are the trial's.

The earlier evidence — the original Colombian work and the subsequent Cochrane reviews — established benefit for **stabilised** low-birth-weight infants. iKMC's contribution was to show benefit when started immediately, before stabilisation, which overturned the prior standard of stabilising in an incubator first.

2. Antenatal corticosteroids, given to the mother before the birth. The ACTION-I trial, 2,852 women and 3,070 babies at 29 hospitals in Bangladesh, India, Kenya, Nigeria and Pakistan, found a significantly lower risk of neonatal death and of stillbirth with no increase in possible maternal bacterial infections. WHO does not publish the relative risk and it could not be verified against the primary paper. Dexamethasone is EML-listed and off-patent at a few US dollars per full course. Conditional on accurate gestational age assessment and adequate newborn care.

3. Thermal care and feeding support. Not drugs. WHO names the absence of warmth and of breastfeeding support as direct causes of the deaths above.

4. Caffeine citrate for apnoea of prematurity. EML-listed under medicines administered to the neonate, for apnoea of the newborn. Off-patent, low cost. The CAP trial showed reduced bronchopulmonary dysplasia and improved neurodevelopmental outcome at 18 to 21 months†.

5. Surfactant for respiratory distress syndrome. Beractant is EML-listed under medicines administered to the neonate. Not off-patent for most products, and **of the order of several hundred US dollars a dose**. This is the expensive item in neonatal care and the one that does not reach low-resource settings.

6. Continuous positive airway pressure. Bubble CPAP is the low-cost form and belongs in simple means.

7. Antibiotics for suspected sepsis — ampicillin plus gentamicin.

8. Human milk, and donor human milk where the mother's is unavailable, which reduces necrotising enterocolitis.

9. Vitamin K at birth, and iron and vitamin supplementation from a few weeks.

Simple means. This entry is the richest in the book for simple means, and the evidence behind them is first-rate rather than second-best.

- **Kangaroo mother care. Relative risk 0.75 for 28-day mortality, over 3,211 infants in five countries**†. Continuous skin-to-skin contact between the carer's chest and the naked baby, with a cloth wrap to hold it, plus exclusive breastfeeding. **Cost: a length of cloth.** It delivers thermal care, feeding, infection protection through colonisation with maternal flora, cardiorespiratory stabilisation and bonding at once. No other intervention in this book has this effect size at this cost.
- **Skin-to-skin contact in the first minutes**, which is the mechanism of the above and standard immediately after any birth.
- **Delayed cord clamping.** Waiting at least 60 seconds. It reduces preterm mortality in meta-analysis, reduces transfusion need, and raises iron stores at six months. It costs nothing and requires the attendant to wait.
- **Early and exclusive breastfeeding, including expressed milk by cup or tube**, which prevents necrotising enterocolitis and sepsis. Cup feeding needs a cup.
- **The thermal care bundle**: immediate drying, removing the wet cloth, a hat, skin-to-skin, delayed bathing, a warm room, and keeping mother and baby together. Free.
- **Bubble CPAP.** Oxygen or air bubbled through a bottle of water to generate positive airway pressure, with nasal prongs. It needs a gas source, which is the limiting input, and no ventilator and no electricity for the pressure itself. Published series from low-resource units report substantial reductions in mortality from respiratory distress.
- **Clean hands.**
- **Chlorhexidine cord care** in high-mortality community settings.
- **A clock and a counting finger.** Respiratory rate counted for one minute is the diagnostic test for respiratory distress and for pneumonia.
- **Cup feeding and nasogastric tube feeding** by a trained family member.

The minimum chain: a cloth, a cup, clean hands and someone willing to hold the baby continuously. Everything that produces the iKMC effect size is in that list.

Gaps. WHO's 900,000 deaths for 2019 and GBD's 623,300 for 2023 do not reconcile beyond the year difference; both printed. WHO publishes no numeric effect size for kangaroo mother care or antenatal corticosteroids on its own fact sheet, and the ACTION-I relative risk could not be verified against the primary paper. The components of the survival gradient are not weighted: WHO lists warmth, feeding, infection treatment and breathing support without saying how much of the 90-against-10 per cent mortality difference under 28 weeks each accounts for, and that is the most consequential analytic gap in the chapter — the intervention set is known and the priority ordering within it is not. iKMC was conducted in tertiary hospitals, so its applicability to home and primary-level births, where most of the deaths are, is an extrapolation. Surfactant and mechanical ventilation are effective and unaffordable at scale where the mortality is, and no located analysis addresses what the optimal package is at a given budget. Global preterm estimates are updated only every three to five years. Long-term neurodevelopmental follow-up of survivors in low-income settings is almost absent, so the sequelae burden is unmeasured where it is largest.

> **Depth.** Starts in: immature organs. No size is given. First complaint: about 1 hour ([B] from birth); time depth 40.61. One untreated course: about 4.3 weeks († weeks); depth 46.60.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book's status: CURABLE, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Birth asphyxia and neonatal encephalopathy

What it is. The baby does not get enough oxygen around the time of birth. The brain is injured by the lack of oxygen and blood flow. The baby may not breathe at birth, may have seizures, and may be left with permanent brain damage.

Measured. Neonatal encephalopathy due to birth asphyxia and trauma: **562,100 deaths (471,400 to 678,700)** in 2023, down **31.9 per cent** since 2000†. The second-largest neonatal cause, and a notably slower decline than preterm birth complications at 41.4 per cent†.

WHO names birth complications among the leading causes of neonatal death; together with prematurity, infections and congenital anomalies these account for **almost 4 in 10 under-5 deaths**, a proportion that was the same in 2000 and in 2022.

No global incidence figure for neonatal encephalopathy was located from WHO or GBD. The commonly cited literature figure is of the order of 1 to 3 per 1,000 live births in high-income settings and several times that in low-income settings; it is not asserted here as a global estimate.

Neonatal encephalopathy is the leading cause of cerebral palsy attributable to perinatal events, and a leading cause of epilepsy and of cognitive impairment originating at birth. The surviving-disability burden is not separately quantified in the GBD cause structure reached. The deaths are concentrated where labour is not monitored and where no one at the birth can resuscitate a newborn.

Where it starts. Intrapartum events: obstructed labour, uterine rupture, cord prolapse, placental abruption, shoulder dystocia, and uterine hyperstimulation including from inappropriate oxytocin augmentation. Antepartum factors: pre-eclampsia, fetal growth restriction, maternal infection and chorioamnionitis, maternal diabetes, post-term pregnancy, multiple pregnancy. And the absence of a skilled attendant able to recognise fetal distress and to resuscitate. No effect sizes were located.

Two things are not known, and one of them is in the condition's name. **What share of neonatal encephalopathy is actually caused by intrapartum asphyxia is not established.** A significant proportion of cases have antenatal origins — infection, inflammation, thrombophilia, genetic and metabolic conditions, congenital brain malformation — and present as encephalopathy at birth without an intrapartum hypoxic event. The term birth asphyxia therefore attributes a cause that is not established in the individual case, and the GBD cause label embeds that attribution.

The second is the hypothermia contradiction, which has its own paragraph below.

Cure status. The established brain injury: RELIEF ONLY. Once hypoxic-ischaemic injury has occurred, nothing removes it. Therapeutic hypothermia reduces the extent of injury if started within six hours, in settings where it has been shown to work, and that is mitigation. Cerebral palsy, epilepsy and cognitive impairment resulting from it are permanent. The acute asphyxia, in the minute before: essentially preventable, and reversible. A baby that does not breathe at birth and is successfully resuscitated within the first minute has, in the large majority of cases, **no injury at all.**

Everything in prevention and simple means is about that minute.

Prevention.

- **Newborn resuscitation capability at every birth — STRONG.** This is the decisive intervention. Helping Babies Breathe and similar structured programmes teach bag-and-mask ventilation of the non-breathing newborn to birth attendants including non-clinicians. Published evaluations in Tanzania and elsewhere reported reductions in early neonatal mortality and in fresh stillbirth of the order of **25 to 50 per cent** after implementation†. **The implementation evidence is pre-post and programme evaluation rather than randomised**, and a large cluster-randomised trial of the package in India and other settings did not reproduce the effect. Both results belong in the record.
- **Skilled attendance and intrapartum fetal monitoring — STRONG** for the outcome, with the qualification that continuous electronic fetal monitoring against intermittent auscultation has not shown a mortality benefit in high-income trials and increases caesarean rates. **Intermittent auscultation with a Pinard stethoscope or a Doppler is the evidence-supported standard**, not continuous electronic monitoring.
- **Timely caesarean section for fetal distress and for obstructed labour — STRONG.**
- **Avoiding uterine hyperstimulation from oxytocin augmentation — STRONG** on mechanism. This is an iatrogenic cause and avoiding it is free.
- **Managing pre-eclampsia and growth restriction — MODERATE.**
- **Antenatal corticosteroids** where preterm delivery is anticipated, which reduces the overlapping preterm burden.
- **Delayed cord clamping and immediate thermal care** are supportive and do not prevent asphyxia.
- **Partograph — CONTESTED** on outcome evidence.

Treatment. 1. Newborn resuscitation with bag-and-mask ventilation, using air. This is the treatment, and it is delivered in the first minute by whoever is present. **Air, not 100 per cent oxygen**, for term newborn resuscitation: meta-analysis of trials found lower mortality with room air than with 100 per cent oxygen†. This is a rare instance where the correct treatment is the one requiring no supply at all. The sequence is dry, stimulate, clear the airway if needed, position, and ventilate at about 40 breaths a minute; chest compressions and adrenaline are needed in a very small minority. The equipment is a self-inflating bag, a mask and a suction device, reusable, no power, **tens of US dollars a set**.

2. Therapeutic hypothermia. Cooling to 33 to 34 °C for 72 hours, started within six hours. This is the clearest case in the book of a guideline that does not travel between contexts, and it needs its own statement.

In high-income settings, meta-analysis of the major trials — CoolCap, TOBY, NICHD, ICE and neo.nEURO — found reduced death or major disability, with a number needed to treat of approximately 7 for the composite outcome†. On that evidence cooling became standard care for moderate and severe neonatal encephalopathy across high-income neonatal units.

The HELIX trial, conducted in India, Sri Lanka and Bangladesh in 2021, found no reduction in death or disability and an increase in mortality with cooling. That is a direct contradiction of the high-income result, in a population carrying the same nominal diagnosis, from the same intervention delivered to protocol.

The contradiction is not resolved. The candidate explanations — different injury timing, antenatal rather than intrapartum origin, co-existing infection, the absence of intensive care to support a cooled baby — have not been separated by any analysis located. What follows for practice is unambiguous even though the mechanism is not: WHO does not recommend therapeutic hypothermia outside settings with intensive care

and the capacity to deliver it to protocol, and the low-cost adaptations — phase-change material, water bottles — are **unsupported rather than merely unproven**, because the trial conducted in the settings they were designed for found harm.

3. Anticonvulsants for neonatal seizures. Phenobarbital first line, EML-listed for epilepsy or seizures and for status epilepticus, off-patent; a UNICEF indicative price in October 2026 works out at about US$0.017 a 30 mg tablet. Levetiracetam is increasingly used, and trial evidence favours phenobarbital for initial seizure control.

4. Supportive intensive care — ventilation, blood pressure support, glucose and electrolyte management, treatment of coagulopathy and renal failure.

5. For survivors with impairment: physiotherapy, occupational therapy, feeding support, spasticity management, epilepsy treatment. All relief.

Simple means.

- **Bag-and-mask ventilation with room air.** A self-inflating bag and a mask, reusable, costing a few tens of dollars, used by a trained birth attendant who need not be a doctor. **This is the single highest-value simple means in this chapter alongside kangaroo mother care**, because the window is one minute and the alternative is death or permanent brain injury.
- **Drying and stimulation.** A substantial share of newborns who do not breathe immediately will breathe after being dried and rubbed. A cloth and two hands.
- **Clearing the airway** — positioning, and suction with a bulb or a mucus extractor.
- **Thermal care during and after resuscitation.** Hypothermia worsens the outcome and warming is free.
- **Delayed cord clamping in the baby who is breathing**, with immediate clamping only where resuscitation at the mother's side is impossible. Resuscitation with the cord intact is increasingly supported and requires only that the resuscitation happen beside the mother.
- **A Pinard stethoscope.** A wooden or plastic cone for intermittent auscultation of the fetal heart in labour. It costs almost nothing, is the evidence-supported monitoring standard, and needs no battery.
- **Counting the fetal heart rate for a full minute** after a contraction.
- **Not augmenting labour against an obstruction.** A decision, not a resource.
- **Structured training.** Helping Babies Breathe uses a doll, a bag and mask, and a laminated flipchart. The entire intervention is a teaching package.

The minimum chain: a bag, a mask and a trained pair of hands. There is **no simple means for the established brain injury**, and the HELIX result means the improvised cooling approaches are not supported.

Gaps. The causal attribution in the condition's name is not established: an unknown but substantial share of neonatal encephalopathy is not caused by intrapartum asphyxia, and GBD's cause label embeds the attribution. No global incidence estimate was located. HELIX contradicts the high-income hypothermia trials and the contradiction is unresolved; it is the most important open question in the entry. Helping Babies Breathe has positive pre-post evaluations and a null cluster-randomised trial, and the programme is widely implemented on the pre-post evidence; both printed. Continuous electronic fetal monitoring does not reduce mortality and raises caesarean rates, and it remains standard in high-income practice, so the sources and the practice disagree. The disability burden among survivors is not separately quantified in the global accounts, and long-term follow-up in low-income settings is almost absent. The 31.9 per cent decline is the slowest of the major neonatal causes and no analysis located explains why.

> **Depth.** Starts in: the brain (oxygen shortage). Size: 10 cm†; depth +13.29. First complaint: about 5 minutes ([B] around birth); time depth 38.34. One untreated course: no number ([B] can be permanent).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. Brain cells that died do not regrow. So it is held, not ended. The book's status, given by stratum: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Neonatal sepsis

What it is. Bacterial infection in the bloodstream of a newborn. It can be acquired from the mother during birth, which is early-onset, or from the environment afterwards, which is late-onset. Newborns have little immune defence, so it progresses within hours.

Measured. Neonatal sepsis and other neonatal infections: **223,200 deaths (155,600 to 315,200)** in 2023, down 31.3 per cent since 2000†. The third-largest neonatal cause. It is described in the clinical literature as the single most common cause of in-hospital and community neonatal death in developing countries, with no figure or year attached to that statement on the source consulted.

A unit error in the source must be carried as a correction. United States early-onset sepsis incidence is **about 0.77 to 1 per 1,000 live births**†. **The source as fetched renders this as "0.77 to 1 per 100,000", which is inconsistent by two orders of magnitude with the low-birth-weight figures printed beside it on the same page.** The figure is reported here as per 1,000, which is the standard unit in that literature, and the discrepancy is stated rather than silently corrected. The original sources could not be checked directly.

Low birth weight raises early-onset sepsis incidence to roughly **26 per 1,000 and 8 per 1,000 live births** in two cited groups, and the source does not specify which group corresponds to which figure. African American preterm infants in the United States: **5.14 per 1,000 live births with a 24.4 per cent case fatality ratio**†.

Culture yield is the central diagnostic problem: only 3 to 8 per cent of infants who receive a sepsis workup have positive cultures. So the measured incidence is partly a measure of clinical suspicion.

Early-onset sepsis declined after the 1990s with group B streptococcus screening, and intrapartum antibiotics reduced its incidence between 2000 and 2020. No global incidence estimate per 1,000 live births was located from WHO or GBD.

Where it starts. Early-onset: maternal group B streptococcus colonisation, prolonged rupture of membranes, chorioamnionitis, maternal fever in labour, preterm birth, unclean delivery. Late-onset: the hospital environment, intravascular catheters, mechanical ventilation, prolonged hospitalisation, formula rather than breast milk feeding, unclean cord care, unwashed hands.

Prematurity and low birth weight raise risk steeply — the low-birth-weight incidence figures above are an order of magnitude above the general population. Mothers with poor healthcare access, low socioeconomic status or substance use have higher rates, and African American preterm infants have the highest infection and mortality rates in the United States data.

Organisms: **group B Streptococcus, *E. coli* and *Listeria monocytogenes*** are the empirically targeted maternal-tract organisms, with *Streptococcus pneumoniae* and *Neisseria meningitidis* also causing meningitis and bacteraemia, and anaerobes suspected in necrotising enterocolitis or intestinal perforation. **In low- and middle-income settings the organism mix differs substantially — Klebsiella, Staphylococcus aureus and Acinetobacter are prominent — and the empirical regimens designed around group B Streptococcus and *E. coli* are not matched to it**.

Three things are not known. The organism distribution where the deaths occur: blood culture capacity is absent in most high-mortality settings, so the pathogen mix is substantially unknown exactly where it determines whether the recommended antibiotics work. Which antibiotics are superior: the source states this plainly, citing Cochrane reviews on early-onset and late-onset regimens that could not resolve it. And, with only 3 to 8 per cent of workups culture-positive, how much of the measured incidence is disease.

Cure status. CURABLE. Antibiotics given early cure neonatal sepsis and the baby recovers completely. The determinants of survival are the interval to the first dose and whether the organism is susceptible. Where antibiotics are given promptly and the organism is susceptible, case fatality is low; where either fails, it is very high — the 24.4 per cent figure above is from a high-risk group in a high-income country. Meningitic sepsis leaves sequelae — hearing loss, hydrocephalus, cognitive impairment — in a share of survivors, and those are separate and permanent.

Antimicrobial resistance is the live threat to this classification. Where the prevalent organisms are resistant to ampicillin and gentamicin, the condition is not reliably curable with the drugs that are available, and that situation already exists in parts of South Asia and sub-Saharan Africa.

Prevention.

- **Clean delivery and hand hygiene — STRONG.** The highest-yield preventive act, and nearly free.
- **Chlorhexidine 7.1 per cent cord cleansing in high-mortality community settings — STRONG.** Trials in Nepal, Bangladesh and Pakistan found reductions in neonatal mortality of the order of **20 to 38 per cent** and in omphalitis of the order of 50 to 75 per cent, in community settings where unclean substances were traditionally applied to the cord. **WHO recommends it specifically for home births where neonatal mortality exceeds 30 per 1,000, and specifically recommends dry cord care elsewhere** — a trial in a hospital setting in Africa showed no benefit. The effect is conditional on the baseline practice, and both results belong in the record. The pooled relative risk could not be verified.
- **Intrapartum antibiotic prophylaxis against group B streptococcus — STRONG** for early-onset group B disease. The measured consequence is the decline in early-onset sepsis after the 1990s. Penicillin is EML-listed, off-patent, cents.
- **Exclusive breastfeeding — STRONG**, reducing late-onset sepsis and necrotising enterocolitis.
- **Kangaroo mother care — STRONG**, partly through colonisation with maternal rather than hospital flora.
- **Probiotics — MODERATE, and conditional.** A 2017 meta-analysis of 37 studies found **reduced late-onset sepsis risk only in exclusively human-milk-fed very low birth weight infants**, with no safety problems reported. An Indian randomised trial of **4,556 neonates** using *Lactobacillus plantarum* reported reduced sepsis risk, cited via news coverage on the source consulted rather than the primary publication.
- **Maternal tetanus immunisation**, for the tetanus fraction.
- **Avoiding unnecessary antibiotic exposure — MODERATE.** Antibiotic overuse in infants is linked to microbiome changes associated with asthma, food allergies and childhood obesity, and promotes resistance.
- **Infection control in neonatal units — STRONG.** Hand hygiene, catheter care bundles, cohorting.

Treatment. 1. Empirical antibiotics, immediately on clinical suspicion. WHO's recommended first line is **ampicillin, or benzylpenicillin, plus gentamicin**. Amoxicillin is EML-listed as an Access group antibiotic with neonatal sepsis among its first-choice indications; a UNICEF indicative price in October 2026 puts 250 mg dispersible tablets at **about US$0.054 each**. A full parenteral course costs a few US dollars.

The common alternative regimen is a third-generation cephalosporin, usually cefotaxime. **Ceftriaxone is specifically avoided in neonates because of kernicterus risk** — it displaces bilirubin from albumin. The antibiotic choice is constrained by the jaundice entry.

Which antibiotics are superior is unknown. The regimens are standard on pharmacological reasoning and susceptibility patterns, not on comparative trial superiority. Clindamycin is often added where necrotising enterocolitis or intestinal perforation is suspected.

2. Source control — removal of an infected catheter, and surgery for necrotising enterocolitis with perforation.

3. Supportive care — fluids, oxygen, thermal control, glucose, and inotropes where available.

4. Adjuncts, with their results reported honestly.

- **GM-CSF: a 2009 randomised trial found it corrects neutropenia and does not reduce sepsis or improve survival**. A clear negative.
- **Intravenous immunoglobulin: the INIS trial found no benefit**. A clear negative.

- **Heart rate characteristics monitoring:** a randomised trial of **3,003 very low birth weight infants** found a **22 per cent reduction in all-cause mortality**, and a later report gave a **40 per cent reduction in mortality after infection**†. A positive result for a monitoring rather than a therapeutic intervention.
- **The Sepsis Risk Calculator:** an independent Greek cohort of **2,084 infants** found it would significantly reduce antibiotic use **and would have missed a significant portion of clinical early-onset sepsis cases**. A systematic review linked its use to reduced antibiotic therapy. The trade-off is explicit and unresolved.

Simple means.

- **Handwashing with soap.** The highest-yield act in the entry, for both prevention and interruption of unit outbreaks.
- **Chlorhexidine cord cleansing** in the specific setting where it works. A small bottle of antiseptic, with a 20 to 38 per cent mortality reduction in community settings that traditionally apply harmful substances to the cord.
- **Dry cord care** — nothing applied at all — in settings where that is already the practice. Here the simple means is the absence of an intervention.
- **A clean delivery kit** — soap, a clean sheet, a sterile blade, clean string.
- **Exclusive breastfeeding from the first hour.** Colostrum is an immune intervention. Free.
- **Kangaroo mother care**, which substitutes maternal skin flora for hospital flora.
- **Counting the respiratory rate and taking the temperature.** The clinical signs — poor feeding, lethargy, temperature instability, fast breathing — are detectable by a trained family member or community health worker with no equipment. **WHO's integrated management algorithms for possible serious bacterial infection are built to be used by non-clinicians precisely because the cure depends on the interval.**
- **Oral or intramuscular antibiotics at community level** where referral is impossible. WHO's simplified regimens for young infants with possible serious bacterial infection when referral is not feasible — oral amoxicillin plus injectable gentamicin, in reduced-duration schedules — were established by the AFRINEST and SATT trial programmes to be non-inferior to full hospital regimens for defined clinical syndromes. **This is the finding that puts cure within reach of a community health worker.**

The minimum chain: soap for prevention, manufactured antibiotics for cure. There is no simple-means substitute for the antibiotic. Prevention is nearly free and cure is not improvisable.

Gaps. The source as fetched reports United States early-onset sepsis incidence as 0.77 to 1 per 100,000 live births, which is inconsistent by two orders of magnitude with the low-birth-weight and African-American-preterm figures given beside it. It is reported here as per 1,000, the standard unit in that literature, and flagged; the original papers could not be checked directly. No global incidence estimate exists in the sources reached. The organism mix where the deaths occur is unknown for want of blood culture capacity. Which antibiotic regimen is best is unknown, and two Cochrane reviews could not settle it. Only 3 to 8 per cent of sepsis workups are culture-positive, so incidence figures largely measure clinical suspicion. No antimicrobial resistance statistics were available on the source consulted, and resistance is the principal threat to curability; this is the most serious data gap in the entry. Chlorhexidine cord care works in community settings and not in hospital settings, so the effect depends on what it replaces, and the pooled figure could not be verified. The Sepsis Risk Calculator reduces antibiotic use and misses cases, and that trade-off is unresolved. The low-birth-weight incidence figures of 26 and 8 per 1,000 are reported without which group each belongs to.

> **Depth.** Starts in: group B streptococcus. Size: 1 µm†; depth +2.81. First complaint: about 24 hours († within 72 hours); time depth 43.50. One untreated course: about 2 days ([B] runs fast); depth 44.13.
>
> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The book's status: CURABLE. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Neonatal jaundice and kernicterus

What it is. Yellow staining of a newborn's skin and eyes from bilirubin, the breakdown product of red blood cells. Most of it is normal and passes. If the level climbs high enough the bilirubin enters the brain and causes permanent injury, which is kernicterus.

Measured. Haemolytic disease and other neonatal jaundice: **30,300 deaths (16,700 to 47,800)** in 2023, down **69.4 per cent** since 2000†. **This is the largest proportional decline of any cause in this chapter** and one of the largest in the book.

The two best available death estimates differ threefold. GBD 2023 gives 30,300. A 2018 analysis based on the GBD 2016 study gives **over 100,000 late-preterm and term babies dying each year from jaundice, mostly in low- and middle-income countries**. The years and the methods differ. Neither source explains the gap, and both are printed; it is the largest unresolved quantitative disagreement in this chapter.

Jaundice itself affects about **60 per cent of term and 80 per cent of preterm newborns** in the first week of life†; an infobox on the same source gives a broader more than 50 per cent of babies†. Both printed.

Kernicterus incidence: no numeric global or regional figure was located. The source states that screening, phototherapy and exchange transfusion have dramatically reduced severe complications. Kernicterus is rare in term infants even at 25 mg/dL and substantially more likely in preterm infants†.

Deaths and kernicterus are overwhelmingly in low- and middle-income settings. In high-income countries kernicterus is a reportable near-elimination event. G6PD deficiency prevalence is high across sub-Saharan Africa, the Mediterranean, the Middle East and Southeast Asia, which patterns the severe cases.

Where it starts. Physiological immaturity of hepatic bilirubin conjugation in the first week is the cause of the normal 60 to 80 per cent. Haemolysis from rhesus or ABO blood group incompatibility, G6PD deficiency and hereditary spherocytosis produce the dangerous levels. Prematurity raises vulnerability at any given bilirubin level, through lower albumin binding and an immature blood-brain barrier. Sepsis, cephalohaematoma and bruising from instrumental delivery, and inadequate feeding and dehydration — which concentrate bilirubin and reduce its excretion — all contribute. **Ceftriaxone and certain other drugs displace bilirubin from albumin**, which is an iatrogenic route and the reason ceftriaxone is avoided in neonates. Breastfeeding jaundice from insufficient intake in the first days and breast milk jaundice, a later benign prolonged form, are distinct entities, and the first is a feeding problem rather than a reason to stop breastfeeding. No effect sizes were located.

What is not known is **the bilirubin level at which an individual baby will be injured.** The treatment thresholds are population conventions rather than individual tolerances. The source notes kernicterus is rare in term infants even at 25 mg/dL, which means many babies tolerate levels at which others are injured, and no test identifies which. Albumin binding capacity, the bilirubin-to-albumin ratio and individual blood-brain barrier variation have all been proposed and none is established as a clinical discriminator. Also unknown: how many kernicterus cases occur, because in the settings where they occur they are not registered.

Cure status. The jaundice, before the brain is stained: CURABLE. Blue light converts bilirubin in the skin to water-soluble isomers that the baby excretes. **Phototherapy removes the cause of injury using light.** Exchange transfusion removes it mechanically where light is insufficient. A baby treated in time has no sequelae whatever and needs no follow-up. Kernicterus, once established: RELIEF ONLY. It is permanent — choreoathetoid cerebral palsy, sensorineural hearing loss, upward gaze palsy, dental enamel dysplasia, cognitive impairment. Nothing reverses it.

The two strata are divided by a window of hours to days. The 69.4 per cent death decline is what happens when the light arrives in time, and the over-100,000 estimate is what happens when it does not.

Prevention.

- **Anti-D immunoglobulin to RhD-negative mothers — STRONG.** Prophylaxis in pregnancy and after delivery, and after any sensitising event including miscarriage, prevents rhesus haemolytic disease in subsequent babies. This came close to eliminating the single most dangerous cause of neonatal jaundice in countries that implemented it, and the 69.4 per cent death decline substantially

reflects it. EML-listed, off-patent as a plasma-derived product with supply rather than patent the constraint, moderate cost. **Its absence is why severe haemolytic disease persists where antenatal care does not include blood grouping.**

- **Early and effective feeding — STRONG.** Adequate milk intake drives bilirubin excretion. Free.
- **Universal pre-discharge bilirubin screening with a nomogram — MODERATE.** It reduces severe hyperbilirubinaemia and readmission, and has been adopted as standard in several high-income systems.
- **G6PD screening in high-prevalence populations — MODERATE.** It identifies the babies who need closer watching and whose families need to avoid known triggers.
- **A postnatal follow-up contact in the first three to five days — STRONG.** Bilirubin peaks after most babies have gone home, and the babies who develop kernicterus are very often babies who were discharged well.
- **Not using ceftriaxone in neonates — STRONG**, for the iatrogenic route.
- **Avoiding naphthalene mothballs, menthol-containing products and known oxidant triggers in G6PD-deficient infants — MODERATE.**
- **Parent education on recognising deepening jaundice** — including that jaundice progressing to the palms and soles, poor feeding or lethargy means return immediately. Free, and it addresses the dominant delay.

Treatment. 1. Phototherapy. Blue light at 460 to 490 nm, applied to the maximum skin area. The landmark randomised trial establishing it was published in 1968, and the original observation was made in 1958; the source gives no effect size from that trial. With intensive phototherapy, total serum bilirubin should fall by 1 to 2 mg/dL within 4 to 6 hours, and the source attaches no citation to that figure. The 2022 American Academy of Pediatrics threshold is that any newborn above **359 µmol/L, or 21 mg/dL**, should receive phototherapy, with lower thresholds for preterm babies and those with risk factors, on gestational-age and hour-specific nomograms.

Not a drug. The equipment is an LED or fluorescent blue light unit. **LED units cost of the order of hundreds of US dollars are low-power, long-lived, and can run from solar or battery supply**. This is the pivotal fact about the condition: the cure is a lamp.

2. Exchange transfusion, for bilirubin above the exchange threshold or for rapidly rising levels despite intensive phototherapy. The 2004 American Academy of Pediatrics guidance is that any newborn above **428 µmol/L, or 25 mg/dL**, should undergo exchange transfusion. It lowers bilirubin by roughly 50 per cent. It requires cross-matched blood, umbilical venous access and a trained operator, and it carries real procedural mortality and morbidity. **This is the procedure that phototherapy exists to avoid, and the procedure that is unavailable in most places where it is needed.**

3. Intravenous immunoglobulin in haemolytic disease, to reduce the need for exchange transfusion. The evidence is moderate and has weakened in later trials.

4. Adequate hydration and feeding support. Not fluids for their own sake — intravenous fluid supplementation does not reduce bilirubin in the well-hydrated — but effective feeding does.

5. Treating the underlying cause — sepsis, and for haemolytic disease the antenatal management of rhesus disease including intrauterine transfusion.

Phenobarbital, agar, charcoal and metalloporphyrins have all been proposed; none is standard, and tin-mesoporphyrin remains investigational.

Simple means. This is the entry where the simple-means question has the most interesting answer in the book.

- **Filtered sunlight phototherapy.** Sunlight contains the therapeutic wavelengths. The problem is that it also contains ultraviolet and infrared, which burn and overheat. Randomised trials in Nigeria used canopies of commercially available window-tinting film that filter out ultraviolet and most infrared while transmitting the blue therapeutic band. They were designed as **non-inferiority comparisons against conventional electric phototherapy**, with the primary outcome the proportion of treatment

days on which the method achieved an adequate rate of bilirubin decline, and they reported filtered sunlight **non-inferior**, with monitored safety outcomes — sunburn, hyperthermia, dehydration — remaining acceptable under supervision. The primary papers could not be retrieved, so the sample sizes, percentages and confidence intervals are not asserted. What can be stated without them: filtered sunlight phototherapy has been tested in randomised non-inferiority trials in a high-burden setting and found non-inferior, and it requires a canopy, tinting film and supervision.

- **Unfiltered sunlight exposure is not recommended.** The burn, hyperthermia and dehydration risks are real and WHO has not endorsed it. The distinction between filtered and unfiltered is the whole of the evidence, and conflating them is dangerous.
- **Solar-powered and battery LED phototherapy units.** Low-power LED arrays running from a small photovoltaic panel and battery. This is the engineering answer where mains electricity is absent, and it keeps the intervention inside the trialled modality rather than substituting an untested one.
- **Effective breastfeeding, frequently.** Bilirubin leaves in the stool and feeding drives it. Free, and it is the single most common deficiency in the babies who become severely jaundiced.
- **Looking at the baby in daylight, pressing the skin, and checking the palms and soles.** Clinical assessment by cephalocaudal progression is insensitive, free, and detects the severe cases. **An icterometer** — a strip of calibrated yellow glass or plastic pressed against the nose — costs almost nothing.
- **Postnatal home visits on days 2 to 4.** The intervention is a visit.
- **Anti-D immunoglobulin** is not a simple means, being plasma-derived and cold-chain dependent, and it is named here because its absence creates the cases.

The minimum chain: a lamp, or a canopy of tinting film and the sun. For the cases beyond light, cross-matched blood and an operator, and there is no simple-means substitute for exchange transfusion.

Gaps. The two best available death estimates differ threefold: 30,300 from GBD 2023 against over 100,000 from the 2018 analysis based on GBD 2016. Both printed; the discrepancy is not explained in either source. No kernicterus incidence figure exists at global or regional level: the condition that matters most is the one least counted, because it occurs where vital registration does not. The filtered sunlight trial figures could not be verified, so the non-inferiority conclusion is reported and the numbers are not. The injury threshold is a convention rather than a measurement, and no test identifies the individual baby's tolerance; the 2004 and 2022 guidance thresholds differ, and the 2022 revision raised phototherapy thresholds in some categories, so guidance has moved in both directions. The 1 to 2 mg/dL per 4 to 6 hours figure for intensive phototherapy carries no citation on the source consulted. The 1968 trial established phototherapy without a reported effect size in the source reached, and the modern evidence base is nomogram-driven observational practice rather than contemporary randomised comparison, because withholding phototherapy is no longer ethical. G6PD deficiency patterns the severe cases and G6PD screening coverage is not reported anywhere located.

> **Depth.** Starts in: bilirubin. Size: 1 nm†; depth −3.48. First complaint: about 2.5 days († day 2–3); time depth 44.33. One untreated course: about 10 days ([B] usually normal and it passes); depth 45.60.
>
> **Model reading.** Way of ending: let close. Layer: word. The book splits this entry by moment, early and late. By the rule it closes by itself. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Low birth weight and small for gestational age

What it is. A baby born weighing less than 2,500 grams. Either because it was born early, or because it grew poorly in the womb, or both. Small for gestational age means below the tenth weight centile for its gestation — a baby that did not grow as it should have.

Measured. WHO names low birth weight as a cause of hearing loss and other sequelae and publishes no global count on the fact sheets reachable.

GBD does not carry low birth weight as a **cause**. It is a **risk factor** in the GBD risk architecture, as low birthweight and short gestation, which ranks fifth among the top ten risks by health loss in 2023. That is why it has no deaths line of its own in this chapter. As a risk factor it attributes a very large share of neonatal death to itself, overlapping almost entirely with preterm birth complications, asphyxia and sepsis, and the figures cannot be added.

The standing published estimates, reported as such: approximately **14.7 per cent of live births, about 19.8 million babies, were low birth weight in 2020**, with the large majority in South Asia and sub-Saharan Africa and the global trend close to flat since 2000†. Neither was verified against a source fetched in the retrieval round.

Small for gestational age and preterm overlap partially, and the three groups — preterm appropriately grown, term small for gestational age, and preterm and small — carry different risks. **Term small-for-gestational-age babies are the largest group in South Asia, and preterm is the dominant route in sub-Saharan Africa**.

Like anaemia, low birth weight prevalence is among the least-improved maternal and newborn indicators.

Where it starts. Maternal undernutrition before and during pregnancy — short stature, low pre-pregnancy body mass index, inadequate gestational weight gain — is the dominant driver of term small-for-gestational-age in South Asia. Maternal anaemia contributes. **Malaria in pregnancy**, through placental sequestration, is a major driver in sub-Saharan Africa. Pre-eclampsia and placental insufficiency, smoking including second-hand smoke, and household air pollution from solid cooking fuels all restrict growth; smoking's effect on birth weight is one of the best-quantified exposures in perinatal epidemiology. Adolescent pregnancy, short interpregnancy interval, high parity, maternal infections including HIV and syphilis, multiple pregnancy, congenital anomalies and congenital infections all raise risk. Female sex carries a lower mean birth weight and is not pathological. **The mother's own birth weight** matters: the intergenerational transmission of growth restriction is established and is why the condition does not respond quickly to intervention. No effect sizes were retrievable.

Three things are not known. How to distinguish, at birth and without serial antenatal measurement, a baby that is **constitutionally small** from one that is **growth-restricted** — a crucial difference, because the first is well and the second is at risk; customised growth standards partly address this and are contested. How much of the flat global trend is nutritional, infectious or intergenerational, because the causal partition has not been established at population level. And whether antenatal detection of growth restriction improves outcomes, which is not settled, because detection leads to earlier delivery, which trades growth restriction for prematurity.

Cure status. The weight deficit itself: CURABLE. A low birth weight baby that survives and is fed catches up, and most reach a normal weight in infancy or childhood. The developmental-origins metabolic consequence, in a share: RELIEF ONLY. The established association with adult cardiovascular disease, type 2 diabetes and hypertension is strong and observational, and nothing reverses it.

The stunting that follows in a proportion of these children is only partly reversible and only if addressed early. Rapid catch-up growth itself carries metabolic risk, so the cure is not simply to feed more.

Prevention.

- **Balanced energy-protein supplementation for undernourished pregnant women — STRONG.** Meta-analyses show reduced small-for-gestational-age and low birth weight, with an effect modest in grams and meaningful at the threshold.
- **Multiple micronutrient supplementation in pregnancy rather than iron-folic acid alone — STRONG.** Meta-analysis shows reductions in low birth weight and small-for-gestational-age of the order of **10 to 15 per cent relative** for low birth weight†. WHO's recommendation has moved toward it in the context of rigorous research and implementation. Cost is a few US dollars per pregnancy for the UNIMMAP formulation — slightly more than iron-folic acid, which is the barrier.
- **Intermittent preventive treatment of malaria in pregnancy plus insecticide-treated nets — STRONG** in endemic areas, with measured increases in mean birth weight.

- **Smoking cessation in pregnancy — STRONG.** One of the largest single modifiable effects on birth weight.
- **Clean cooking fuel and reducing household air pollution — MODERATE.**
- **Treating maternal anaemia — MODERATE.**
- **Preventing adolescent pregnancy, and birth spacing — MODERATE.**
- **Syphilis screening and treatment in pregnancy — STRONG** for the syphilis-attributable fraction. A single dose of benzathine benzylpenicillin, EML-listed with syphilis as its first-choice indication; a UNICEF indicative price in October 2026 works out at **about US$0.59 a 2.4 MIU vial** in the fifty-vial pack, against US$3.01 for the single-vial pack with solvent.
- **Low-dose aspirin for women at risk of pre-eclampsia — MODERATE**, via the placental pathway.
- **Deworming in hookworm-endemic areas — MODERATE**, via anaemia.
- **Antenatal care with fundal height or ultrasound growth monitoring — MODERATE**, with the caveat that the benefit of detection is itself uncertain.
- **Improving girls' nutrition and preventing stunting — STRONG and generation-long.** The most important and the slowest.

Treatment. For the baby after birth. **1. Kangaroo mother care.** The iKMC trial population **was** low birth weight babies, at 1.0 to 1.799 kg: **28-day mortality 12.0 against 15.7 per cent, relative risk 0.75 (0.64 to 0.89), p = 0.001**, over 3,211 infants in five countries†. **This is the primary treatment for low birth weight and it is free.**

2. Exclusive breastfeeding, with expressed milk by cup or tube where suck is immature, and donor human milk where the mother's is unavailable. It reduces necrotising enterocolitis and sepsis.

3. Thermal care — drying, a hat, skin-to-skin, a warm room, delayed bathing.

4. Delayed cord clamping at birth. It raises haemoglobin and iron stores, reduces infant anaemia at six months, reduces transfusion need in preterm infants, and reduces mortality in preterm infants in meta-analysis. **Free.**

5. Vitamin K at birth, iron supplementation from two to six weeks, and vitamin D. All EML-listed, off-patent, cents.

6. Monitoring and treating hypoglycaemia. Low birth weight babies have minimal glycogen reserve. Early and frequent feeding is the prevention; measured glucose and oral or intravenous dextrose the treatment.

7. Treating infection promptly. These babies carry an order-of-magnitude higher sepsis incidence.

8. Growth monitoring and nutritional support through infancy, with attention to the catch-up growth trade-off above.

Simple means.

- **Kangaroo mother care.** A cloth. **Relative risk 0.75 for 28-day mortality**†.
- **Skin-to-skin contact from the first minute.**
- **Delayed cord clamping.** Waiting 60 seconds. Free, and one of the few interventions whose benefit extends to the infant's haemoglobin at six months.
- **Breastfeeding initiation within the first hour.** Free, and the strongest determinant of whether a low birth weight baby feeds successfully at all.
- **Cup feeding and expressed milk** — a cup and a clean container.
- **Weighing the baby.** A spring scale or a beam scale. **Knowing the birth weight is what triggers everything else in this list**, and an unweighed baby is an unidentified one. A colour-coded weighing sling costs a few dollars.
- **A hat.** The head is the largest surface area for heat loss in a small baby.
- **The thermal care bundle.**

- **Hand hygiene.**
- **Community-based follow-up with weighing.**

The minimum chain: a cloth, a cup, a scale and a hat. The entire effective treatment package for low birth weight in the setting where most of it occurs is in that list, and the iKMC effect size attaches to the first item.

Gaps. The prevalence figures could not be verified against a source fetched in the retrieval round and are reported as the standing interagency estimates. GBD treats low birth weight as a risk factor rather than a cause, so it has no deaths line and its burden overlaps irreducibly with preterm birth, asphyxia and sepsis; the figures cannot be summed with those entries. Constitutional smallness cannot be distinguished from growth restriction without serial measurement, and customised growth standards are contested. Whether antenatal detection of growth restriction improves outcomes is unsettled, because the response to detection is earlier delivery, which substitutes prematurity for restriction. The causal partition of low birth weight is not established at population level. Global prevalence has not fallen while neonatal mortality fell 44 per cent†, and no located analysis explains the divergence. The developmental-origins literature is observational, large, consistent, and unable to exclude confounding by the socioeconomic conditions that produce both the low birth weight and the adult disease. The catch-up growth trade-off is unresolved: the nutritional intervention that corrects the deficit may carry the metabolic risk, and no trial has settled the optimal trajectory.

> **Depth.** Starts in: the placenta. Size: 20 cm†; depth +13.92. First complaint: about 9 months († at birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Respiratory distress syndrome of the newborn

What it is. A preterm baby’s lungs lack surfactant, the substance that keeps the air sacs from collapsing at the end of each breath. The baby works harder and harder to reinflate collapsed lungs and tires. Also called hyaline membrane disease.

Measured. GBD **includes neonatal respiratory distress syndrome inside preterm birth complications** and does not report it as a separate cause, so **there is no separate deaths figure**.

Incidence is a steep function of gestational age: in the published literature it affects the large majority of babies born before 28 weeks, declining to a small minority at 34 to 36 weeks and rarely occurring at term†. No global incidence estimate was located.

The relevant measured quantity is the survival gradient. In low-income settings **half of babies born at or below 32 weeks die**, often from untreated breathing difficulties among other causes, and **more than 90 per cent of babies under 28 weeks die within the first few days in low-income countries against under 10 per cent in high-income settings**.

In high-income settings, mortality from respiratory distress syndrome fell steeply from the late 1980s with surfactant and from the 1970s with antenatal corticosteroids. In low-income settings the fall has been much smaller, because the two effective interventions have very different prices.

Where it starts. Gestational age is the dominant determinant: surfactant production rises sharply after about 34 weeks, so risk is essentially a function of how early the birth is. Absence of antenatal corticosteroids raises it, because the drug accelerates surfactant production. **Male sex** carries higher incidence and severity at the same gestation, consistently and unexplained. **Maternal diabetes** delays surfactant maturation independently of gestation, so a diabetic mother’s baby may have respiratory distress syndrome at a gestation where it would be unexpected. **Caesarean section without labour** raises risk, because labour itself promotes lung fluid clearance. Perinatal asphyxia, hypothermia, multiple pregnancy, being the second twin, and family history all contribute. No effect sizes were located.

Two things are not known. The male disadvantage. And, more practically, **how much of the respiratory mortality in low-resource settings is respiratory distress syndrome and how much is pneumonia,**

sepsis, transient tachypnoea or meconium aspiration, because the diagnosis requires chest radiography and blood gases that are not available. The conditions are treated as one clinical syndrome of respiratory distress, and the component proportions are unknown exactly where the deaths are.

Cure status. The syndrome itself: SELF-LIMITING. It is self-resolving within days to a week as the baby's own surfactant production begins, and the entire clinical task is to keep the baby alive and the lungs open until that happens. Surfactant replacement and positive airway pressure do that, and a baby that survives it has normal lungs. Nothing persists. Bronchopulmonary dysplasia in a share of survivors: CONTROLLABLE at best. It affects particularly the most immature and those ventilated longest, and carries years of increased respiratory morbidity. Aggressive mechanical ventilation is itself a cause of it, which is why the shift toward CPAP and less invasive surfactant administration has been the main advance of the last two decades.

Prevention.

- **Antenatal corticosteroids — STRONG, and this is the prevention. Dexamethasone, a few US dollars a course, EML-listed, off-patent**. The ACTION-I trial, 2,852 women and 3,070 babies in five countries, found significantly lower neonatal death and stillbirth in low-resource hospitals, and WHO publishes no relative risk on that page. The original high-income evidence is the Liggins and Howie trial of 1972 and the subsequent Cochrane review, which established reductions in respiratory distress syndrome, neonatal death and intraventricular haemorrhage.
- **Preventing preterm birth — STRONG** where possible.
- **Avoiding non-medically-indicated caesarean before 39 weeks — STRONG.** An iatrogenic cause, and avoiding it is free.
- **Maternal glycaemic control — MODERATE.**
- **Thermal care from the first minute — STRONG.** Hypothermia worsens surfactant function and increases oxygen consumption. Free.
- **Delayed cord clamping — MODERATE**, for reduced need for respiratory support in preterm infants.
- **Antenatal thyrotropin-releasing hormone — ineffective and harmful.** A settled negative, reported because it was once standard.

Treatment. 1. Antenatal corticosteroids, given before birth to the mother. **The highest effect-per-euro intervention in this entry by a wide margin.**

2. Continuous positive airway pressure, started early. Trials comparing early CPAP against routine intubation and ventilation — COIN, SUPPORT, CURPAP and the subsequent meta-analyses — found **CPAP non-inferior or superior for death or bronchopulmonary dysplasia**, with less intubation. Early CPAP is now the first-line respiratory support for spontaneously breathing preterm infants. **Bubble CPAP** is the low-cost implementation; published series from low-resource neonatal units report substantial mortality reductions after introduction, on pre-post rather than randomised evidence. The equipment is a gas source, tubing, nasal prongs and a water column, and **the gas source is the binding constraint** — oxygen concentrators running on mains or solar power have changed that in some settings.

3. Exogenous surfactant replacement. The single most effective specific treatment: the original randomised trials and meta-analyses established **reductions in mortality of the order of 30 to 40 per cent relative** and reductions in pneumothorax in treated preterm infants. Animal-derived preparations — poractant alfa, beractant, calfactant — outperform the early synthetic ones. Beractant is EML-listed under medicines administered to the neonate for respiratory distress syndrome of the newborn. Not off-patent for the current animal-derived products in most markets, and the manufacturing — porcine or bovine lung extraction and purification — is itself a barrier independent of patent. **Cost: hundreds to thousands of US dollars a dose**, with some babies needing more than one. **This is the most expensive single item in the chapter's treatment set and the clearest case in it of an effective treatment that does not reach the patients who need it.** Administration has moved from intubation-surfactant-extubation toward **less invasive surfactant administration** via a thin catheter in a baby on CPAP, which avoids intubation altogether.

4. Supplemental oxygen, with targeted saturation. Both too little and too much oxygen cause harm: too much causes retinopathy of prematurity and oxidative lung injury. The target saturation trials — SUPPORT, BOOST-II and COT — found **lower targets reduced retinopathy and increased mortality**, and the current consensus target of 90 to 95 per cent is a compromise with acknowledged uncertainty†. **A pulse oximeter is therefore essential equipment**, and it is cheap at tens of dollars and low-power.

5. Mechanical ventilation where CPAP fails. Effective and expensive, and itself a cause of bronchopulmonary dysplasia.

6. Caffeine citrate, which reduces apnoea, facilitates extubation and reduces bronchopulmonary dysplasia. EML-listed, off-patent, low cost.

7. Thermal care, fluid and glucose management, and treatment of concurrent sepsis.

Simple means.

- **Bubble CPAP.** Blended air or oxygen delivered through nasal prongs, with the expiratory limb submerged in a column of water to a depth of 5 to 8 cm, which sets the pressure. **Assemblable from tubing, a bottle, water and a measuring scale.** It needs a gas source and a flow meter, which are manufactured, and no ventilator, no electricity for the pressure generation, and no electronics. **The most important intermediate technology in neonatal care**, and the reason respiratory distress syndrome is survivable in units with no ventilator.
- **Oxygen from a concentrator** running on mains or solar, which removes the cylinder supply chain.
- **A pulse oximeter.** Tens of dollars, battery or solar powered, and it is what prevents both hypoxia and oxygen toxicity. Close to a simple means in cost and entirely essential.
- **Thermal care:** drying, a hat, skin-to-skin, a warm room, delayed bathing. Hypothermia directly worsens surfactant function. Free.
- **Kangaroo mother care** once the baby is stable enough — and iKMC established benefit when begun before stabilisation.
- **Positioning.** Prone positioning improves oxygenation in the preterm infant. Free.
- **Counting the respiratory rate and observing grunting, recession and nasal flaring.** The clinical diagnosis requires no equipment, and the Silverman-Andersen score is a laminated card.
- **Feeding by cup or tube** rather than withholding feeds unnecessarily.
- **Antenatal dexamethasone.** Not quite a simple means — ampoules and a syringe — and close to one, and its effect is the largest here.

The minimum chain: a gas source and a bottle of water. Below that, thermal care, positioning and kangaroo care remain. **There is no simple-means substitute for surfactant**, and that is the honest limit of this entry.

Gaps. There is no separate GBD cause line and no global incidence estimate; the condition sits inside preterm birth complications. The component diagnoses within neonatal respiratory distress are not separated in low-resource settings for want of radiography and blood gases, so what proportion of those deaths surfactant would prevent is unknown. Surfactant costs hundreds of dollars a dose and is EML-listed, and the gap between listing and availability is the central practical fact, which no located analysis quantifies. The ACTION-I relative risk could not be verified against the primary paper and WHO does not publish it. Bubble CPAP's mortality evidence in low-resource settings is pre-post rather than randomised. Optimal oxygen saturation targets are unresolved, with lower targets reducing retinopathy and increasing mortality across three trials, and the current compromise target acknowledged as such. The male disadvantage is unexplained. Long-term pulmonary outcomes of survivors in low-resource settings are essentially unmeasured.

> **Depth.** Starts in: an air sac of the newborn lung. Size: 100 µm†; depth +7.00. First complaint: about 1 hour († minutes to hours after birth); time depth 40.61. One untreated course: about 7 days († about 1 week); depth 45.27.
>
> **Model reading.** Way of ending: let close. Layer: mesh. By the rule it closes by itself. The book splits the status by stratum: SELF-LIMITING and CONTROLLABLE. Reading and status agree in part. Recovery route: do no more than is needed. The cause stops by itself. Guard until it does. This is a reading. The status above stands.

Neonatal hypothermia

What it is. A newborn's body temperature falling below normal. Babies are born wet, have a large surface area for their weight, little fat, and cannot shiver effectively. In a cool room a naked wet newborn loses heat fast enough to become hypothermic within minutes.

Measured. GBD does not carry neonatal hypothermia as a cause. **It has no deaths line.** Its mortality contribution is counted within preterm birth complications, sepsis and other neonatal disorders, because it kills by worsening those conditions rather than as a recorded cause of death.

WHO names the absence of **warmth** first in its list of what the babies in low-income settings die from: often from lack of basic care such as warmth, breastfeeding support, and treatment for infections and breathing difficulties.

WHO's classification thresholds: normal axillary temperature **36.5 to 37.5 °C**; **mild hypothermia, or cold stress, 36.0 to 36.4 °C; moderate 32.0 to 35.9 °C; severe below 32.0 °C**†.

Facility-based studies across South Asia and sub-Saharan Africa have repeatedly measured hypothermia in a large fraction — in many series a majority — of newborns in the first hours, including in warm climates and including inside hospitals. **No global estimate exists**, and the facility series are not comparable: different thresholds, different timing of measurement, different ambient conditions. No figure is asserted here.

It is not a cold-climate condition. It is measured in tropical settings, because the relevant comparison is the newborn's thermoneutral requirement — an ambient temperature of around 28 to 30 °C for a naked term baby, and higher for a preterm one — rather than the outdoor climate. The trend is unknown, because it is not tracked.

Where it starts. The mechanism is simple physics. **Evaporation** from wet skin is the largest early loss, which is why immediate drying matters most. Convection, conduction and radiation to cool air, cool surfaces and cool walls follow.

Low birth weight and prematurity raise risk steeply, through a higher surface-area-to-mass ratio, less subcutaneous fat, less brown adipose tissue and immature thermoregulation; risk rises steeply below 2,000 g. Delayed drying, early bathing, separation from the mother, cool delivery rooms, transport without thermal protection and resuscitation under a cool open warmer all contribute. Asphyxia impairs thermoregulation. **Sepsis can cause hypothermia rather than fever in a newborn, which makes hypothermia a sign as well as a cause.** No effect sizes were located.

What is not known is how much neonatal mortality is attributable to hypothermia, because it is not recorded as a cause and because it is almost always present alongside the condition that is recorded. Observational studies consistently find hypothermia at admission strongly associated with death, commonly with mortality odds rising substantially per degree below normal, and **the direction is not establishable from those data**: a sick, septic, asphyxiated or very preterm baby becomes cold *because* it is dying, as well as dying because it is cold. The attributable fraction is therefore genuinely unknown, and that is the single reason a condition prevented by a free intervention has no burden figure.

Cure status. CURABLE. Rewarming corrects hypothermia and the baby recovers completely, provided rewarming is achieved before the metabolic consequences — hypoglycaemia, acidosis, coagulopathy, pulmonary hypertension, increased oxygen consumption — have caused secondary injury. The intervention is heat. There is no residual condition.

The rate of rewarming matters and is debated. Rapid rewarming has been associated with apnoea and instability in very preterm infants, and slow rewarming prolongs the metabolic stress. Current guidance favours rewarming at approximately 0.5 °C an hour for severe hypothermia in a very preterm baby and more rapid rewarming in a term baby, with monitoring.

Prevention. This entry is almost entirely prevention, and the prevention is free.

- **The WHO warm chain — STRONG.** Ten steps, essentially all costless: a warm delivery room at at least 25 °C and ideally higher for preterm births; **immediate drying**; **immediate skin-to-skin**

contact; **breastfeeding within the first hour**; **delayed bathing and weighing**, with bathing postponed at least 24 hours and ideally longer for small babies; appropriate clothing and bedding including a hat; keeping mother and baby together; warm transport; warm resuscitation; and training and awareness.

- **Immediate drying and removal of the wet cloth — STRONG.** The single highest-yield act, because evaporation is the largest loss. It takes seconds and a dry cloth.
- **Skin-to-skin contact and kangaroo mother care — STRONG.** The mother's chest is a thermostatically regulated heat source, and the iKMC mortality effect of relative risk 0.75 operates partly through this mechanism.
- **A hat — STRONG.** The head is the largest exposed surface in a newborn.
- **Delayed bathing — STRONG.** Bathing a newborn in the first hours is a measurable cause of hypothermia and has no benefit. **Stopping doing something is the intervention.**
- **Plastic wrap or a food-grade polyethylene bag for very preterm babies immediately at birth — STRONG.** Randomised trials and the subsequent Cochrane review found occlusive plastic wrapping of preterm infants at birth significantly reduces hypothermia on admission. **Cost: a plastic bag.**
- **Raising the delivery room temperature — STRONG**, and free where climate permits, which is most of the high-burden world.
- **Warm transport — STRONG.**

Treatment. Every effective treatment here is also a simple means. No drug treats hypothermia.

1. Skin-to-skin rewarming on the mother's chest. First line for mild and moderate hypothermia. The physiological evidence is direct and the iKMC trial carries the mortality outcome. **Free.**

2. A radiant warmer or incubator for severe hypothermia or where the mother is unavailable. Effective, and it requires electricity.

3. A warm room, warm blankets, a hat, and a dry covered head.

4. Thermal mattresses and phase-change material warming mattresses. Chemically activated or warm-water-filled, used for transport and for delivery-room stabilisation. Low cost, no electricity, and trials in low-resource settings support their use for transport.

5. Treating the consequences: blood glucose measurement and correction — hypothermia and hypoglycaemia travel together, both are fatal and both are cheap to fix — oxygen for the increased consumption, and **treating sepsis**, because hypothermia may be its presenting sign.

6. Monitoring temperature. A low-reading thermometer is required: standard clinical thermometers do not read below 35 °C, so severe hypothermia is systematically missed by the wrong instrument. **A thermometer that reads to 25 °C costs a few dollars and is the single most-overlooked item in this entry.**

Simple means. This entry is **entirely** simple means. It is the clearest case in the book of a condition that kills at scale and is prevented by acts requiring nothing manufactured.

- **Drying the baby immediately with a cloth, and discarding the wet cloth.** Seconds. Largest single effect.
- **Skin-to-skin contact on the mother's chest, immediately and continuously.** Free, and it is simultaneously the prevention, the treatment, and the delivery mechanism for the iKMC mortality benefit at relative risk 0.75†.
- **Kangaroo mother care with a cloth wrap.** A length of cloth.
- **A hat.** A knitted or cloth cap.
- **Not bathing the baby.** Delaying the bath 24 hours or more. The intervention is omission.
- **Closing the windows and doors of the delivery room.** Free.
- **A plastic bag for the very preterm baby at birth.** Food-grade polyethylene, Cochrane-supported.

- **Warm transport:** the baby carried skin-to-skin against the carrier's chest under their clothing, with a hat and a blanket. This is both the warmest and the cheapest transport incubator available, and it works on a motorcycle.
- **A low-reading thermometer.** A few dollars. Without it, severe hypothermia is invisible.
- **Warm water bottles or warmed cloth**, with care against burns.
- **Teaching the family.** The warm chain is a list of behaviours, and the whole intervention is knowing it.

The minimum chain: a dry cloth, a hat, and the mother. Nothing else is strictly necessary for the majority of cases, and a low-reading thermometer and a plastic bag complete the set for a few dollars.

Gaps. There is no burden figure at all — no GBD cause line, no global prevalence estimate, no deaths attributed. A condition prevented by a dry cloth has no number against its name, and that absence is itself the finding. The attributable fraction of neonatal mortality is unknown because of the reverse-causation problem above: the observational associations are strong and uninterpretable as causal. Facility prevalence studies are not comparable, with different thresholds, timings and ambient conditions, and no pooled estimate exists. No effect sizes for the warm-chain components, individually or as a bundle, were retrievable; the bundle is recommended on physiological grounds and observational data rather than randomised evidence of mortality benefit, with two exceptions — plastic wrapping for preterm infants, which is randomised and Cochrane-supported, and kangaroo mother care, which is randomised. The optimal rewarming rate is debated and the guidance differs by maturity. Hypothermia is both a cause and a sign of sepsis, and no clinical rule distinguishes them at the bedside. It is not tracked as an indicator, so there is no trend.

> **Depth.** Starts in: the body of the newborn. Size: 50 cm†; depth +14.76. First complaint: about 15 minutes ([B] loses heat fast); time depth 39.34. One untreated course: about 6 hours († hours); depth 42.24.
>
> **Model reading.** Way of ending: supply from outside. Layer: surround. By the rule it ends when the shortage is supplied in time. The book's status: CURABLE. Reading and status agree. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Neonatal tetanus

What it is. Tetanus in a newborn, from spores entering through the cut umbilical cord. The toxin causes rigid spasms: the baby stops feeding, arches backward, and convulses at any touch or sound. It begins in the first days of life.

Measured. Neonatal tetanus deaths: **just over 7,700 in 2021**, from an estimated **46,898 in 2000** — a fall of **84 per cent**. WHO attributes the decline largely to scaled-up tetanus toxoid-containing vaccine immunisation, and the fact sheet gives only these two data points.

As of July 2026, 8 countries have yet to achieve maternal and neonatal tetanus elimination. Elimination is defined as **fewer than one neonatal tetanus case per 1,000 live births in every district** — a district-level rather than national threshold. WHO does not state how many countries have achieved it.

The global elimination goal was launched at the World Health Assembly in 1989, and the elimination initiative in 1999. In 2025, **85 per cent of infants worldwide received 3 doses of DTP-containing vaccine**.

Case fatality with and without treatment is not reported on the WHO fact sheet. The published clinical literature gives neonatal tetanus case fatality approaching 100 per cent without treatment and, with intensive care including ventilation, of the order of 10 to 30 per cent; without ventilation it remains very high†. Those are reported as the standing clinical literature position and were not verified.

The remaining cases are concentrated in the eight countries without elimination, and in conflict-affected and inaccessible districts within countries that have achieved it nationally.

Where it starts. This is a condition whose causation is fully understood. ***Clostridium tetani* spores**, ubiquitous in soil, dust and animal faeces, enter the umbilical stump. WHO names three risk practices: **non-sterile instruments for cutting the umbilical cord; contaminated cord coverings; and deliveries by**

people with unclean hands or on contaminated surfaces. Traditional cord applications — ash, dung, oil, mud, clarified butter — are the classic route. **Absence of maternal immunisation** removes the baby's only protection, because maternal antibody crosses the placenta. Home birth without a skilled attendant and without a clean delivery kit raises exposure. **WHO gives no figures** for the contribution of any of these practices.

Very little about the mechanism is unknown. This is the most completely understood condition in the chapter: a known organism, a known toxin, a known portal of entry, a vaccine with a known mechanism, and a prevention understood in full. **What is not known is where the remaining cases are.** In the districts that still have them, surveillance is weakest, so the 7,700 figure is a model output and the true distribution within the remaining eight countries is poorly characterised. Also not well characterised: how much of the residual is immunisation failure, how much unclean delivery, and how much both.

Cure status. RELIEF ONLY, and this must be stated plainly because it is the exception in this chapter.

Once the toxin has bound to nerve terminals, nothing removes it. Antitoxin neutralises only circulating toxin. Recovery depends on the regeneration of new nerve terminals over weeks, during which the baby must be kept alive through spasms that prevent breathing. With ventilation and intensive care a share survive; without ventilation most die. Treatment is entirely supportive: control the spasms, protect the airway, feed, and wait.

This is the striking asymmetry of the entry: the condition is almost perfectly preventable at a cost of cents, and almost untreatable at a cost of weeks of intensive care. A two-dose course of a vaccine costing a fraction of a dollar prevents what a fully equipped intensive care unit often cannot cure.

Prevention.

- **Maternal tetanus toxoid immunisation — STRONG, and it is effectively complete protection.** WHO recommends **6 doses over a lifetime**, three primary and three booster. Maternal immunisation with an adequate course confers passive protection on the newborn through transplacental antibody. **The measured consequence is the 84 per cent fall in deaths from 2000 to 2021**, which WHO attributes largely to immunisation scale-up. The vaccine is EML-listed, off-patent, and of the order of a few US cents to a few tens of cents a dose at supply-division prices. **No efficacy figure is given** on the WHO fact sheet: the 84 per cent decline is an attribution rather than a measurement of vaccine efficacy. The historical trial and field evidence for maternal immunisation is of the order of 80 to 100 per cent protection with two or more doses†.
- **Clean delivery and clean cord care — STRONG.** WHO lists it as prevention and gives no figures. The three named risk practices are the targets: a sterile blade, clean hands, a clean surface, and nothing applied to the cord.
- **Skilled birth attendance — STRONG**, as the delivery vehicle for both.
- **Chlorhexidine cord cleansing — MODERATE** for the omphalitis and sepsis route; its specific effect on tetanus is not separated in the trials.
- **The combination is what achieves elimination.** The elimination strategy is explicitly both: immunise women of reproductive age in high-risk districts, and promote clean delivery. Neither alone reaches the district threshold.

Treatment. All of it supportive. **1. Tetanus antitoxin** — human tetanus immunoglobulin, or equine antitoxin where the human product is unavailable. It neutralises circulating unbound toxin and does nothing for bound toxin, so it limits progression rather than reversing disease. Intrathecal administration has been studied with some benefit reported and is not universal practice. EML-listed under sera and immunoglobulins, off-patent as a plasma- or serum-derived product with supply the constraint. Cost is moderate and supply in high-burden settings is unreliable.

2. Spasm control — benzodiazepines, principally **diazepam**, in high and sustained doses, with **magnesium sulfate** as an adjunct. Trials in adults found magnesium reduced the requirement for other drugs without reducing the need for ventilation. Both are EML-listed and off-patent; diazepam costs cents and magnesium sulfate about US$0.33 an ampoule on October 2026 indicative prices. The limit is that the doses required to control spasms suppress breathing, which is why ventilation determines survival.

3. Airway protection and mechanical ventilation, with neuromuscular blockade where needed. This is the intervention that separates survival from death, and it is the one unavailable in the settings where the cases are.

4. Antibiotics — metronidazole, preferred over penicillin, which is a GABA antagonist and may worsen spasms — to eliminate the organism at the wound. EML-listed, off-patent, cents.

5. Wound and cord care — cleaning and debridement of the umbilical stump.

6. Nutrition by nasogastric tube; a dark, quiet environment to reduce spasm triggers; and management of autonomic instability.

7. Immunisation of the surviving baby and of the mother. Surviving the disease confers no immunity, because the toxin dose required to cause disease is below that required to immunise.

Simple means. For **prevention**, this entry is almost entirely simple means.

- **A sterile razor blade or a boiled instrument for cutting the cord.** One of the cheapest life-saving items that exists.
- **The clean delivery kit** — soap, a clean plastic sheet, clean string, a sterile blade, clean gloves. Designed to be distributable at near-zero unit cost.
- **Handwashing with soap.**
- **Dry cord care — applying nothing at all.** The intervention is the removal of a practice. Free, and it addresses one of WHO's three named risk factors directly.
- **Boiling instruments** where no sterile blade exists.
- **Teaching the traditional birth attendant and the family.** The entire preventive package is a set of behaviours plus one blade.

For **treatment**, the honest answer is largely negative and must be stated.

- **A dark, quiet room, and minimal handling.** This reduces spasm frequency, and it is real: spasms are triggered by light, sound and touch.
- **Nasogastric feeding** by a trained family member.
- **Positioning and airway suction.**
- **Diazepam**, a cheap manufactured drug that can be given rectally where no intravenous access exists.
- **Magnesium sulfate** intramuscularly.
- **What cannot be improvised is ventilation**, and ventilation is what determines whether the baby lives. Hand-bagging a baby for the two to three weeks the toxin takes to clear is not a sustainable intervention, and attempts at it are the historical practice this condition's mortality reflects.

The minimum chain: for prevention, a blade and a vaccine vial. For cure, an intensive care unit. The ratio between those two is the entire argument of this entry.

Gaps. WHO gives no case fatality figures, with or without treatment; the figures above are from the standing clinical literature and were not verified. WHO gives no vaccine efficacy figure, and the 84 per cent decline is an attribution across a period in which clean delivery also improved, so the immunisation and clean-delivery contributions are not separated. WHO does not state how many countries have achieved elimination, only that 8 have not as of July 2026. The latest death figure on the fact sheet is for 2021, no 2023 figure was available, and GBD does not report neonatal tetanus as a separate cause in the series consulted. The residual case distribution within the remaining countries is poorly characterised because surveillance is weakest where the cases are, so the 7,700 figure is a model output. No effect sizes are given for clean delivery practices, individually or as a bundle. Elimination is defined at district level and countries are validated nationally, so a validated country can retain districts above the threshold: the indicator and the achievement are not the same thing. Intrathecal antitoxin and magnesium sulfate as an adjunct both have supportive and not definitive trial evidence, largely from adult tetanus.

> **Depth.** Starts in: Clostridium tetani. Size: 4 µm†; depth +4.07. First complaint: about 7 days ([B] the first days of life; † about 7 days); time depth 45.27. One untreated course: about 3 weeks († weeks); depth 46.27.

> **Model reading.** Way of ending: remove. Layer: mesh. By the rule it ends when the foreign party is taken away in time. The bound applies. The toxin is fixed to the nerve. It cannot be taken off. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

ICD-11 Chapter 20 — Developmental anomalies

Eleven entries. The chapter-level denominators are these. Congenital anomalies accounted for **54.8 million DALYs** in 2023, the 13th leading DALY cause; GBD 2021 gave **52.3 million** for congenital birth defects, a different cause label between rounds, and both are printed.

About 240,000 newborns die within 28 days of birth each year from congenital disorders, and a further **about 170,000 children aged 1 month to 5 years**. The total number of babies born with a congenital disorder is not given anywhere on the WHO page.

WHO's own page contradicts itself on where they occur. Its key facts state that **nine of ten** children born with a serious congenital disorder live in low- and middle-income countries; its body text states that about **94 per cent** of severe congenital disorders occur there. Two different shares for the same statistic on one page, with no explanation. Both are printed.

The most common severe types are named as heart defects, neural tube defects and Down syndrome, with **no prevalence figures given for any of them**. Parents related by blood is described as **nearly doubling** the risk of neonatal and childhood death, intellectual disability and other anomalies, qualitatively and without a figure.

WHO lists the preventive measures — folic acid, avoiding alcohol and tobacco, rubella vaccination, iodine, diabetes control, reducing heavy-metal and pesticide exposure, justified medication and radiation use, screening for rubella, varicella and syphilis, and pre-conception care — **without quantifying any of them**. Where an effect size appears below it comes from elsewhere and is sourced there.

Neural tube defects

What it is. The tube that becomes the brain and spinal cord fails to close in the first four weeks after conception, before most women know they are pregnant. If the lower end stays open it is spina bifida: the spinal cord is exposed and the legs, bladder and bowel are affected. If the upper end stays open it is anencephaly: the brain does not form and the baby dies.

Measured. Over 300,000 births affected each year worldwide, and about **71,000 deaths in 2010**. Both figures are old and no current cause-specific GBD figure was retrievable.

Spina bifida in the United States: about **3.5 per 10,000 births, roughly 1,500 cases a year**, down from about **5 per 10,000** before folic acid fortification†. United States annual deaths from neural tube defects fell from about **1,200 to 840**†, with the year of the decline not given.

No anencephaly prevalence figure is given on the source consulted. Affected infants are usually stillborn or die within hours or days, and **no treatment exists**.

WHO names neural tube defects among the three most common severe congenital disorders, without a prevalence figure.

A measurement caveat that matters: birth-based prevalence undercounts neural tube defects, because prenatal diagnosis and termination remove affected pregnancies from the denominator. One study found the share of affected pregnancies ending in abortion **roughly doubled between 1986 and 1999**†. Comparisons of birth prevalence across countries and across time are therefore partly measuring termination rates rather than occurrence.

Where it starts. Maternal folate status at conception is the dominant modifiable cause. Folic acid supplementation reduces neural tube defect prevalence by about 70 per cent, on a randomised

controlled trial in women with a previous affected pregnancy published in 1991†. **The remaining roughly 30 per cent are not folate-dependent**†.

Also established: a previous affected pregnancy, with a substantially elevated recurrence risk, which is why the trial used that population; maternal diabetes; maternal obesity; maternal hyperthermia in early pregnancy. **Antiepileptic drugs, valproate in particular and also carbamazepine**, are a major iatrogenic cause and the reason valproate prescribing in women of childbearing potential is now restricted in many jurisdictions. Folate antagonists — methotrexate, trimethoprim, some antimalarials — contribute. Consanguinity raises risk, as it does for anomalies generally. Genetic factors are real and incompletely mapped, with MTHFR variants among others. Fumonisin exposure from mould-contaminated maize has been implicated in some high-prevalence populations. No effect sizes beyond the 70 per cent figure were located.

The mechanism by which folic acid prevents the defect is not known. The effect is one of the best-established in all of preventive medicine and the pathway is not identified. It is not simply correction of deficiency, because the effect occurs in women who are not folate-deficient, and the dose-response is not fully characterised. What causes the folate-unresponsive 30 per cent is also not known. The result is a measurement without a mechanism, and the residual is a cause without a name.

Cure status. Anencephaly: RELIEF ONLY. In practice no treatment exists. Infants are stillborn or die within hours or days, and nothing is attempted beyond comfort care. Spina bifida: CONTROLLABLE. Surgical closure of the defect prevents infection and further damage and does not restore the nerve function already lost. The paralysis, bladder and bowel denervation, and hydrocephalus requiring shunting are permanent and lifelong. Management — shunt revision, bladder catheterisation, bowel programmes, orthoses, pressure-area care, scoliosis surgery, latex avoidance — holds the state and does not remove it.

Prenatal in-utero repair changes this a little. The MOMS trial in 2011 found prenatal repair of myelomeningocele **reduced the need for shunting and improved motor outcomes at 30 months**, at the cost of increased preterm birth and uterine dehiscence. That is improved control, not cure.

Neither stratum is CURABLE, which is exactly why the prevention below carries the weight it does. This is the clearest case in the book where the intervention that matters is one taken before the woman knows she is pregnant.

Prevention. Folic acid — STRONG, and this is the single best-documented population prevention in the chapter.

The trial evidence: folic acid supplementation reduces neural tube defect prevalence by **about 70 per cent**†.

The country before-and-after data from mandatory flour fortification:

Country	Before	After	Change
United States	10.8 per 10,000, 1995–1996	6.9, end of 2006	**−36 per cent**†
United States, affected pregnancies	about 4,000, 1995–1996	about 3,000, 1999–2000	roughly 1,000 fewer a year†
Chile	17.1 per 10,000, 1999–2000	9.7, 2001–2002	**−43 per cent**†
Canada	—	—	**−46 per cent** in incidence after mandatory fortification†
Costa Rica, South Africa, Canada	—	—	**25 to 50 per cent** declines in affected pregnancies; no country-specific figures, years or counts are given for these three
United States spina bifida	about 5 per 10,000	3.5 per 10,000, 2017	—
United States deaths	about 1,200 a year	840 a year	**−30 per cent**†

The United States required folic acid in enriched grain products in 1996, with mandatory compliance from January 1998; Canada made grain fortification mandatory by 1998†.

A projection, reported as a projection and not a result: **150,000 to 210,000 neural tube defects preventable per year globally**†, derived from the 50 to 70 per cent preventable share rather than observed in any country.

The gap that defines the field: the source consulted does not state how many countries have mandatory fortification, and the standing reference dataset was not reachable. **The measured effect is 25 to 50 per cent in every country that has done it, and most countries have not.**

Other prevention:

- **Periconceptional folic acid supplementation — STRONG**, at 400 µg daily for all women who may become pregnant and 4 to 5 mg for women with a previous affected pregnancy. The limitation is timing: the neural tube closes by day 28, so supplementation must precede the recognised pregnancy. **This is why fortification outperforms supplementation as a population strategy** — it does not depend on the woman knowing she is pregnant or planning to be.
- **Avoiding valproate in women of childbearing potential — STRONG.** Iatrogenic prevention.
- **Pre-pregnancy diabetes control and weight management — MODERATE.**
- **Avoiding hyperthermia in early pregnancy — WEAK.**
- **Prenatal screening — this is detection, not prevention.** Maternal serum alpha-fetoprotein and second-trimester ultrasound reduce birth prevalence by enabling termination, which is why the measurement caveat above matters. It is not a reduction in occurrence.
- **Folic acid does not prevent miscarriage.** The distinction is often blurred.

Folic acid is EML-listed, off-patent, and costs **a fraction of a cent a tablet**: a UNICEF indicative price in October 2026 works out at about **US$0.0054 per 5 mg tablet**. Fortification of flour costs of the order of **US$0.01 to 0.10 per person per year**†. Published cost-effectiveness analyses of mandatory fortification repeatedly find it among the most cost-effective public health interventions available, with benefit-cost ratios reported in the tens. **This is the leading candidate for the highest life-saving effect per euro in this chapter.**

Treatment. For anencephaly: **none.** Comfort care only.

For spina bifida, no drug treats it. **1. Postnatal surgical closure of the defect**, within the first days. It prevents infection and further cord damage and does not restore lost function. It requires a paediatric neurosurgical service.

2. Ventriculoperitoneal shunting for the hydrocephalus that accompanies most myelomeningocele. Lifelong, with repeated revisions for blockage and infection. **Endoscopic third ventriculostomy with choroid plexus cauterisation** is the shunt-free alternative developed substantially in East Africa, and a significant advance for settings where shunt revision is not accessible.

3. Prenatal in-utero repair, with the MOMS results above. Available in very few centres.

4. Bladder management — clean intermittent catheterisation, anticholinergics, and surveillance for renal damage. **Renal failure, not the paralysis, is the historical cause of death in spina bifida**, and catheterisation is what prevents it.

5. Bowel management — programmes, laxatives, enemas.

6. Orthoses, wheelchairs, physiotherapy, and orthopaedic surgery for hip, knee and foot deformity and for scoliosis.

7. Pressure-area care. Insensate skin ulcerates; prevention is positioning and inspection.

8. Latex avoidance. Latex allergy prevalence is high in this population from repeated surgical and catheter exposure.

9. Treatment of tethered cord and syringomyelia as they present.

Simple means. For prevention, this is the entry where the simple means is also the best intervention available.

- **A folic acid tablet costing a fraction of a cent**, taken before conception. Nothing in this book has a better ratio of cost to prevented disability.
- **Fortified flour.** Once the mill adds it, the woman need do nothing and need know nothing. **Of the order of US$0.01 to 0.10 per person per year.** The intervention is a decision taken at a mill.
- **Dietary folate** — dark green leafy vegetables, pulses, liver. Free, and insufficient on its own to reach the protective intake in most diets, which is why fortification exists.

For care of the affected child:

- **Clean intermittent catheterisation taught to the parent and later the child.** Reusable catheters, clean water and soap. **This is the intervention that prevents renal failure**, and it is teachable to a family.
- **Pressure-area inspection and repositioning.** A mirror and a routine.
- **A bowel programme** — timing, diet and manual techniques.
- **Keeping the back lesion clean and covered before surgery** — a sterile or clean moist dressing, which prevents the meningitis that kills unoperated babies.
- **Positioning the newborn prone** to avoid pressure on the sac.
- **Physiotherapy and range-of-movement exercises** taught to the family.
- **Locally made orthoses and adapted seating.**
- **Parent-to-parent teaching.**

The minimum chain: for prevention, one tablet. For the affected child, neurosurgery, and there is no simple means that substitutes for closing the defect or draining the hydrocephalus. The asymmetry between a fraction of a cent and a neurosurgical service is the whole of the entry.

Gaps. The folic acid fortification systematic review could not be read, so the country table is built from the 2010 public health review and secondary sources and is less complete than that review would allow; Costa Rica and South Africa are reported only inside the 25 to 50 per cent band without country-specific figures. The number of countries with mandatory fortification is not stated in any source reached. Birth prevalence undercounts occurrence because of termination, and the termination share roughly doubled between 1986 and 1999, so cross-country and cross-time comparisons are partly comparisons of termination rates. The mechanism of the folic acid effect is unknown, and the cause of the folate-unresponsive 30 per cent is unknown. The global burden figures are old — 300,000 affected births from a 2012 report and 71,000 deaths from the 2010 burden study — and no current cause-specific figure was retrievable. The 150,000 to 210,000 preventable per year is a projection, not an observation. No anencephaly prevalence figure was located. The MOMS benefit is measured at 30 months, with limited longer-term outcomes and limited applicability outside specialist centres. Fortification's safety debate — the possibility of masking vitamin B12 deficiency, and a contested association with certain cancers — is live in the literature and no source reached resolves it.

> **Depth.** Starts in: the neural tube. Size: 2 mm†; depth +9.73. First complaint: about 9 months ([B] fails to close in the first 4 weeks; the sign shows at birth); time depth 48.61. One untreated course: no number († permanent).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The cord and the nerves that lay open do not regrow. So it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Congenital heart defects

What it is. The heart forms wrongly in the first weeks of pregnancy. A hole between chambers, a narrowed or missing valve, a great vessel in the wrong place, or a chamber that never developed. Some cause no symptoms; some kill within days unless operated on.

Measured. Birth prevalence is given as **about 4 to 75 per 1,000 live births**, depending on how it is diagnosed; **moderate-to-severe cases at 6 to 19 per 1,000**; and heart defects occurring in **about 1 per cent**

of live births, or 2 to 3 per cent including bicuspid aortic valve†. The nearly twenty-fold range is a statement about ascertainment, not about populations.

People living with it: **48.9 million in 2015** on one round of the burden study, **34.3 million in 2013** on another†. Both printed.

The death figures disagree substantially across rounds and all are printed. 2017: **261,247 (216,567 to 308,159)**, including 180,624 among infants under 1 year†. 2015: **303,300**†. 2010: **223,000**†. The derived trends disagree too: 366,000 in 1990 falling to 303,300 in 2015 on one round; 278,000 falling to 223,000 in 2010 on another; and a 34.5 per cent decline from 1990 to 2017 on a third†. The rounds are not consistent with each other and none is a count.

Congenital heart defects are the leading cause of birth-defect-related deaths, and WHO names heart defects first among the three most common severe congenital disorders.

Ventricular septal defects are collectively the most common type; about 30 per cent of adults have a probe-patent foramen ovale; and the source gives no shares for other types.

About **94 per cent of severe congenital disorders occur in low- and middle-income countries**, where paediatric cardiac surgery is largely unavailable. So the prevalence is roughly uniform and the mortality is not.

Where it starts. The identified genetic contributions, as attributable shares: **aneuploidies 5 to 8 per cent; copy number variants 10 to 12 per cent; inherited protein-coding variants 3 to 5 per cent; de novo protein-coding variants about 10 per cent**†. Together these account for under 40 per cent of cases.

Monochorionic twins carry about 9 times the risk of singletons, on a meta-analysis of four studies†. De novo defects carry a recurrence risk in offspring of **3 to 5 per cent**, higher for left ventricular outflow tract obstruction, heterotaxy and atrioventricular septal defects. **Down syndrome carries congenital heart disease in about 40 per cent of newborns**†.

Maternal obesity raises risk as obesity increases, with no effect size given. Maternal diabetes, phenylketonuria, lupus, rubella, consanguinity, and having a parent with congenital heart disease are all established without effect sizes. Drug exposures named are alcohol, hydantoin, lithium and thalidomide, and paternal alcohol use is listed as a risk factor.

The cause is unidentified in the majority. **Identified genetic mechanisms account for under 40 per cent of cases and the remainder have no identified cause.** The identified environmental exposures account for a small share of the total. Also not known: why measured birth prevalence ranges nearly twenty-fold across studies, which the source attributes to diagnostic method rather than real variation — meaning the true occurrence is not established even approximately.

Cure status. The split is by lesion, and the entry contains three. Small ventricular septal defects that close spontaneously in infancy: SELF-LIMITING. Anatomically correctable lesions: CURABLE. Secundum atrial septal defect, most ventricular septal defects, patent ductus arteriosus, coarctation, and simple pulmonary or aortic valve stenosis are corrected with a single operation after which the child is normal and needs no further treatment. **A substantial fraction of congenital heart disease is a one-operation cure in childhood followed by a normal life.** Complex lesions — single-ventricle physiology, transposition, tetralogy, hypoplastic left heart: CONTROLLABLE. These are palliated rather than cured. Staged operations and arterial switch produce survival into adulthood with a circulation that is not normal, requiring lifelong cardiology, anticoagulation, arrhythmia management, and in some cases transplantation. The deviation remains.

The source gives no numeric survival rates, which is a real gap for an entry whose cure status depends on them.

Prevention.

- **Rubella vaccination — STRONG** for the congenital rubella fraction. WHO names rubella vaccination for children and women, and screening for rubella, varicella and syphilis, without effect

sizes. Rubella-containing vaccine is EML-listed, off-patent and costs cents a dose. Congenital rubella syndrome is eliminable, and has been eliminated in the Americas.

- **Pre-pregnancy diabetes control — MODERATE.** WHO names controlling diabetes before and during pregnancy.
- **Avoiding alcohol in pregnancy — MODERATE.**
- **Avoiding valproate and hydantoin, lithium and thalidomide in pregnancy — STRONG** for those specific iatrogenic routes.
- **Maternal weight management — MODERATE.**
- **Maternal phenylketonuria control — STRONG** for that rare specific cause.
- **Folic acid — CONTESTED** for congenital heart defects specifically. The evidence is much weaker than for neural tube defects; some fortification studies report reductions and the finding is not secure.
- **Reducing the alternatives to single-embryo transfer in assisted reproduction — MODERATE**, via the nine-fold monochorionic twin risk.
- **There is no prevention for the majority of cases**, because the majority have no identified cause.

Detection, which is not prevention and determines survival:

- **Pulse oximetry screening of newborns — STRONG for mortality.** Performed at or after 24 hours of life, or earlier if the newborn is discharged or oxygen is stopped. **Pass: saturation of 95 per cent or more in the right hand and foot with a difference of 3 points or less. Fail: below 90 per cent in the right hand or foot**, which triggers further workup including echocardiography. Retest an hour later if 90 to 94 per cent or the difference exceeds 4 points. State-level implementation in the United States has been associated with fewer emergency hospitalisations for critical congenital heart disease, lower infant mortality and fewer early cardiac deaths, and was **not shown to significantly increase resource use or cost**. False positives occur, not all congenital heart disease is detected, and it should be used alongside prenatal ultrasound and physical examination. **A pulse oximeter costs tens of dollars, runs on batteries, and the test takes minutes.** This is one of the highest-value screening interventions in the chapter.
- **Prenatal ultrasound**, which detects a share of major defects and allows delivery at a centre with cardiac surgery.

Treatment. The source gives no numeric survival rates, so the ordering below is by established practice rather than by reported effect size.

1. Surgical repair. Open cardiac surgery with cardiopulmonary bypass for most significant lesions, and staged palliation for single-ventricle physiology. The inputs are a surgeon, a cardiac anaesthetist, a perfusionist, a bypass circuit, paediatric intensive care, blood products and echocardiography. **This is the most infrastructure-dependent treatment in the whole of this chapter** and it exists in a small minority of countries.

2. Catheter-based intervention — device closure of atrial septal defect and patent ductus arteriosus, balloon valvuloplasty, balloon atrial septostomy, stenting. It avoids bypass and requires a catheterisation laboratory and fluoroscopy.

3. Prostaglandin E1 infusion to keep the ductus arteriosus open in duct-dependent lesions. **This is the drug that keeps a newborn with critical congenital heart disease alive long enough to reach surgery.** Its EML status could not be confirmed against the sections reachable. Off-patent, moderate cost, and it requires refrigeration and a syringe pump.

4. Diuretics, ACE inhibitors, beta blockers and digoxin for heart failure from a shunt lesion pending repair. Spironolactone is EML-listed for heart failure; all of these are off-patent and cost cents a day.

5. Ibuprofen or paracetamol for closure of patent ductus arteriosus in preterm infants, as an oral or intravenous alternative to surgical ligation. Both EML-listed, off-patent and cheap; indomethacin is the traditional agent.

6. Oxygen, careful fluid management and nutritional support. Growth failure is a major problem in unrepaired shunt lesions, and feeding support is part of treatment.

7. Antibiotic prophylaxis against infective endocarditis in defined high-risk lesions; the indications have narrowed considerably.

8. Arrhythmia management, anticoagulation and transplantation for the palliated circulations.

Simple means. This entry has the least favourable simple-means profile in the chapter, and that should be stated first.

- **A pulse oximeter.** Tens of dollars, battery-powered, no consumables. It converts an undetected lethal lesion into a diagnosed one. **It is the single most valuable low-cost item in the entry**, and its value is entirely in triggering a referral that must then exist.
- **A stethoscope and clinical examination** — murmur, femoral pulses, cyanosis, hepatomegaly, respiratory rate, feeding history and growth. It detects a large share of significant lesions and costs nothing beyond the stethoscope.
- **Counting the respiratory rate and weighing the baby.** Failure to thrive and tachypnoea are the presentation of a large shunt, and both are measurable with a scale and a clock.
- **Nutritional support** — high-energy feeding, including fortified expressed breast milk, for the infant with a large shunt. Free or nearly so, and it determines operability.
- **Diuretics** — furosemide tablets, cents a day, which hold a child with heart failure for months.
- **Treating anaemia and intercurrent infection** promptly. Both decompensate an unrepaired lesion.
- **Keeping the child warm and avoiding dehydration.**
- **Teaching the family the warning signs** — poor feeding, sweating with feeds, blue spells, fast breathing.

What the chain minimally requires, stated plainly: cardiac surgery with cardiopulmonary bypass. There is no simple means, no improvisation and no drug that substitutes for it. For the lethal lesions this is the clearest example in the book of a condition that is curable in principle and untreated in practice.

Gaps. The rounds of the burden study disagree substantially on deaths — 223,000 for 2010, 303,300 for 2015, 261,247 for 2017 — and the trend statements derived from them differ; all printed, none a count. Birth prevalence ranges nearly twenty-fold by diagnostic method, so the true occurrence is not established. No numeric surgical survival rates are given on the source consulted, which is a substantial gap for an entry whose cure status depends on them. The cause is unidentified in the majority, with identified genetic mechanisms accounting for under 40 per cent. No current cause-specific figure was retrievable; GBD 2023 reports only the aggregate congenital anomalies DALY figure. Prostaglandin E1's EML status could not be confirmed. Folic acid's effect on congenital heart defects is contested, unlike its effect on neural tube defects. Pulse oximetry screening's evidence is state-level association rather than randomised, and "not shown to significantly increase cost" is a weaker statement than a cost-effectiveness figure. Coverage of paediatric cardiac surgery globally is not quantified in any source reached, so the size of the treatment gap is unknown.

> **Depth.** Starts in: the embryonic heart tube. Size: 1 mm†; depth +9.10. First complaint: about 9 months ([B] first weeks of pregnancy; the sign shows at birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Cleft lip and palate

What it is. The lip, the roof of the mouth, or both fail to fuse in early pregnancy, leaving a gap. The baby cannot generate suction to feed. Speech, hearing and teeth are affected later. Surgery closes it.

Measured. Prevalence: **about 1 in 1,000 to 1 in 1,500 births**. No global annual count, no deaths figure and no cleft-specific DALY figure was located; GBD reports only the aggregate congenital anomalies figure.

The burden is overwhelmingly morbidity rather than mortality. Feeding failure in infancy can be fatal in settings without feeding support, and the long-term burden is speech, hearing, dental, nutritional and social.

Occurrence is roughly uniform with some population variation, higher in parts of Asia and among Indigenous American populations and lower in populations of African descent. **The untreated prevalence is not uniform.** In high-income countries essentially every cleft is repaired in infancy, and in low-income settings a large number of adults live with unrepaired clefts, which is why surgical missions find them. No trend was quantified in any source reached.

Where it starts. Maternal smoking in pregnancy is one of the better-established environmental associations, with a modest relative risk. Maternal alcohol use contributes. Antiepileptic drugs, particularly valproate and topiramate, are established; corticosteroids carry a weak signal; and **ondansetron carries a contested cleft palate signal**. Folate status has a weaker and less consistent effect on clefts than on neural tube defects. Maternal diabetes and obesity raise risk. Genetic factors are real: cleft lip with or without cleft palate and isolated cleft palate have partly distinct genetics, multiple susceptibility loci including IRF6 are identified, and about 30 per cent of cases are syndromic†. Consanguinity and family history raise risk, with sibling recurrence elevated several-fold. No effect sizes were located. The cause is unknown in most non-syndromic cases. Cleft is the standard textbook example of a multifactorial threshold trait, and multifactorial is a description of ignorance about the specific combination. Whether cleft lip with cleft palate and isolated cleft palate are one condition or two remains partly unresolved. The ondansetron signal is unresolved.

Cure status. CURABLE, and this is one of the clearest surgical cures in the chapter. Primary closure of the lip at a few months and of the palate at around a year produces a child who eats, speaks and grows normally. The operation is anatomically definitive.

Two qualifications. The full course is not one operation: speech therapy, grommets for middle ear effusion, orthodontics, alveolar bone grafting, and in some cases revision surgery or pharyngoplasty for velopharyngeal insufficiency extend over years. And residual scarring, mild speech difference and dental problems persist in a share. The condition is nonetheless removed — a repaired cleft is not a lifelong disease — which places it in CURABLE rather than CONTROLLABLE.

The repair is among the cheapest high-impact operations in surgery. Published cost-effectiveness analyses in low-income settings report costs per DALY averted tens of US dollars, comparable to the clubfoot figures below. An exact figure could not be verified.

Prevention.

- **Maternal smoking cessation — MODERATE.** The best-established modifiable exposure.
- **Avoiding alcohol in pregnancy — MODERATE.**
- **Avoiding valproate and topiramate in women of childbearing potential — STRONG** for those routes.
- **Folic acid — CONTESTED** for clefts specifically. Weaker and less consistent than its neural tube defect effect, though some fortification studies report reductions.
- **Pre-pregnancy diabetes control and weight management — MODERATE.**
- **Genetic counselling** for families with an affected child, which informs and does not prevent.
- WHO lists the general congenital-disorder prevention measures without quantifying any of them.
- **There is no prevention for the majority of cases.**

Treatment. No drug treats cleft lip or palate. **1. Surgical repair.** Lip closure typically at **3 to 6 months**; palate closure typically at **9 to 18 months**, timed to precede speech development. The rule of tens — 10 weeks, 10 pounds, haemoglobin 10 — is the classic operability threshold. Millard rotation-advancement and its variants for the lip; various palatoplasty techniques. It requires a surgeon and paediatric anaesthesia, and **safe anaesthesia for an infant is the binding constraint in low-resource settings, not the surgical technique.**

2. Feeding support, immediately from birth. This comes before surgery in importance and is the difference between life and death in the first months. A baby with a cleft palate cannot generate negative

pressure and will not feed from breast or standard teat. Specialised cleft teats, squeezable bottles and the Haberman feeder solve it, and so do far cheaper means.

3. Speech and language therapy. Essential after palate repair, and the functional outcome depends on it at least as much as on the surgery.

4. Middle ear management. Otitis media with effusion is near-universal in cleft palate because of eustachian tube dysfunction. Grommets and hearing surveillance prevent the hearing loss and the consequent speech and educational delay.

5. Orthodontics and alveolar bone grafting in childhood and adolescence, and orthognathic surgery in a minority.

6. Secondary surgery for velopharyngeal insufficiency, fistula closure, and lip or nose revision.

7. Dental care. Caries risk is high.

8. Nutritional support and growth monitoring throughout infancy.

Simple means.

- **Feeding technique. This is the central simple means and it saves lives in the first months.** Upright positioning, a squeezed soft bottle, a cup and spoon, expressed breast milk delivered by cup or spoon, slower paced feeding with frequent burping, and a finger supporting the cleft to help a seal. **A modified ordinary teat with an enlarged or cross-cut hole** works where a cleft teat is unavailable. All of it is teachable to a mother in one session and costs nothing beyond a cup.
- **Expressed breast milk by cup**, which keeps the baby on breast milk when direct breastfeeding fails, preserving the immune and nutritional benefits.
- **Weighing the baby.** Growth faltering is the sign that feeding is failing, and the scale is what detects it.
- **Teaching the mother to support the lip cleft with a finger or thumb** to allow a seal. A proportion of isolated cleft lip babies breastfeed successfully this way.
- **Speech stimulation and play by the parent**, where no therapist exists. Structured parent-delivered speech programmes have been used in low-resource settings; the evidence base is thin and the alternative is nothing.
- **Hearing checks by observation** — response to sound, speech development milestones.
- **Dental hygiene** — a brush.
- **Nasoalveolar moulding with strapping and simple appliances** before surgery, in some protocols, to narrow the gap.
- **Case-finding.** As with fistula, families often do not know repair exists. Announcing a surgical mission is close to free and is the throughput constraint.

The minimum chain: a cup and a taught technique will keep the baby alive and growing. **The repair itself requires an operating theatre and safe infant anaesthesia, and there is no substitute for that.**

Gaps. No global count, no deaths figure and no cleft-specific DALY figure: WHO gives only a prevalence range and GBD reports only the aggregate congenital anomalies figure, which is thin accounting for a condition this common and this treatable. The untreated prevalence — how many people are living with unrepaired clefts — is not quantified anywhere located, and that is the number that would size the surgical need. No effect sizes for any risk factor or preventive measure were retrievable, and the cost per DALY averted could not be verified. Folic acid's effect on clefts is contested. The ondansetron cleft palate signal is unresolved and matters because ondansetron is widely used for nausea in early pregnancy. Long-term functional outcomes after repair in low-resource settings — speech, hearing, education, employment, psychosocial — are almost unmeasured, and the surgical mission model generates little follow-up data. Whether cleft lip with palate and isolated cleft palate are one condition is partly unresolved.

> **Depth.** Starts in: a facial process of the embryo. Size: 5 mm†; depth +10.56. First complaint: about 9 months ([B] early pregnancy; visible at birth); time depth 48.61. One untreated course: no number.

> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Down syndrome and other trisomies

What it is. An extra copy of a chromosome. In Down syndrome it is chromosome 21. The extra chromosome affects every tissue: intellectual development, the heart, the gut, hearing, vision and the immune system. It arises at conception and is present in every cell.

Measured. Global incidence: **about 1 per 1,000 births**†. United States: **about 1 in 700 births** and **1.4 per 1,000 live births** on two sources†; in the 1950s it was **2 per 1,000 live births**†, and the fall reflects prenatal screening and termination rather than a change in occurrence. Norway: **1.1 per 1,000**†. All printed.

People affected: **5.4 million globally in 2015**†. **Deaths: 27,000 in 2015, down from 43,000 in 1990, on one source; about 17,000 globally as of 2010 on another**†. Both printed; they do not reconcile.

Life expectancy, as a measured trend: **about 12 years in 1912; about 25 years in the 1980s; 50 to 60 years in the developed world in the 2000s; about 10 per cent reaching age 70 in the early 2000s**†. Infant mortality in the first year was 4 to 12 per cent in data from 1985 to 2003†. **A four- to five-fold increase in life expectancy within a century, achieved almost entirely by treating the heart defects and infections rather than by anything addressing the chromosome.**

WHO names Down syndrome among the three most common severe congenital disorders, without a prevalence figure.

Other trisomies: trisomy 18 and trisomy 13 occur at roughly 1 in 5,000 and 1 in 10,000 to 16,000 live births respectively in the published literature, with very high early mortality; no figure from a source fetched in the retrieval round is available and none is asserted. Sex chromosome aneuploidies are recorded with no global figure retrieved.

Where it starts. This is one of the best-quantified risk gradients in medicine. **Maternal age, risk of Down syndrome at delivery: age 20, 1 in 1,441; age 30, 1 in 959; age 40, 1 in 84; age 50, 1 in 44**†.

But mothers aged 35 and younger account for about 70 per cent of cases, because they have far more children overall†. This is the single most important and most misunderstood fact in the entry: the risk is concentrated in older mothers and the cases are concentrated in younger ones, which is why age-based screening offers alone miss most cases.

Advanced paternal age is a risk factor for women over 35, and about 10 per cent of cases are linked to it†. The mechanism is meiotic non-disjunction, overwhelmingly maternal in origin, arising in the oocyte. About 95 per cent of cases are full trisomy 21 from non-disjunction; the remainder are translocation forms, some inherited and therefore carrying a recurrence risk, and mosaic forms.

Why oocyte non-disjunction increases with maternal age is not known. The candidate mechanisms — cohesin degradation over decades of meiotic arrest, spindle checkpoint weakening, reduced recombination — are plausible and none is established as the determinant. **Nothing modifiable has been identified.** There is no exposure to avoid, no supplement to take, and no intervention that reduces the chance of the event. This is the clearest case in the chapter of a condition with a precisely measured risk and no preventable cause.

Cure status. CONTROLLABLE. Nothing removes the extra chromosome and nothing is in prospect that would. Every treatment addresses an associated condition, and the four- to five-fold life expectancy increase above was achieved entirely that way: cardiac surgery, antibiotics, thyroid replacement, leukaemia treatment, and the end of institutionalisation.

The state is held well and increasingly long. **Intellectual disability is present in nearly all cases** and is permanent, and Down syndrome accounts for about a third of all intellectual disability. The associated conditions are individually treatable, several of them curable, and the total burden is substantially a function of whether they are treated.

The associated conditions and their measured frequencies:

- **Congenital heart disease: about 40 per cent of newborns.**
- **Hearing problems: 50 to 90 per cent of children**; otitis media with effusion 50 to 70 per cent; chronic ear infections 40 to 60 per cent.
- **Vision problems: 38 to 80 per cent**; strabismus 20 to 50 per cent; **cataracts 15 per cent**; keratoconus 21 to 30 per cent.
- **Thyroid problems with hypothyroidism: 20 to 50 per cent; congenital hypothyroidism 1 per cent.**
- **Sleep apnoea: about half to 60 per cent.**
- **Constipation: nearly half**; Hirschsprung's disease 2 to 15 per cent.
- **Coeliac disease 7 to 20 per cent**; type 1 diabetes more common.
- **Epilepsy: 5 to 10 per cent of children and up to 50 per cent of adults.**
- **Alzheimer's disease: about 15 per cent of those living to 40 and over, and 50 to 70 per cent of those reaching 60.** This is the dominant determinant of late-life outcome and it is RELIEF ONLY.
- **Autism 5 to 10 per cent of children; mental illness in nearly 30 per cent of children.**
- **Atlantoaxial instability 1 to 2 per cent.**
- **Leukaemia: 10 to 15 times more common in children; acute lymphoblastic leukaemia 20 times; acute megakaryoblastic leukaemia 500 times. Transient myeloproliferative disease in 3 to 10 per cent of newborns, of whom about 10 per cent progress to acute megakaryoblastic leukaemia.** Solid cancers of lung, breast and cervix are less common; testicular germ cell cancer more common.

Prevention. There is no prevention. No exposure, supplement, behaviour or treatment reduces the chance of trisomy 21 occurring. The only modifiable factor is maternal age at childbearing, and the risk gradient above is not a basis for a preventive recommendation.

What exists is prenatal screening, which detects rather than prevents, and whose consequence is overwhelmingly termination. That must be reported as what it is.

Prenatal screening detection rates:

Screen	Timing	Detection rate	False positive rate
Combined test	10–13.5 weeks	**82–87 per cent**	5 per cent
Quad screen	15–20 weeks	**81 per cent**	5 per cent
Integrated test	15–20 weeks	**94–96 per cent**	5 per cent
Cell-free fetal DNA	from 10 weeks	**96–100 per cent**	**0.3 per cent**

Common screening overall gives 90 to 95 per cent detection with 2 to 5 per cent false positives; nuchal translucency alone 75 to 80 per cent with 6 per cent false positives; second-trimester blood markers about 60 to 70 per cent; and cell-free DNA first-trimester accuracy 98.6 per cent.

The outcome of diagnosis: about 92 per cent of diagnosed European pregnancies are terminated, and about 75 per cent in the United States, with a range of 61 to 93 per cent†. These are the measured consequences of the screening programme and the reason the United States birth prevalence fell from 2 per 1,000 in the 1950s to about 1.4 per 1,000.

Prevention of the associated conditions, where the real preventive gains are:

- **Newborn pulse oximetry and echocardiography — STRONG** for the 40 per cent with heart defects.
- **Newborn and annual thyroid screening — STRONG** for the 20 to 50 per cent with thyroid disease.
- **Hearing screening at birth and annually — STRONG** for the 50 to 90 per cent with hearing problems. Untreated hearing loss compounds the intellectual disability and is largely preventable.
- **Vision screening including for cataract — STRONG.**

- **Coeliac screening; a sleep study for apnoea; cervical spine assessment before anaesthesia or sport.**
- **Early intervention, education and inclusion — STRONG** for functional outcome. The life expectancy and functional gains of the last fifty years are substantially attributable to deinstitutionalisation and education rather than to medicine.

Treatment. There is no treatment for the trisomy. Treatment is of the associated conditions. **1. Cardiac surgery** for the 40 per cent with congenital heart disease. **This is the single largest contributor to the life expectancy increase above.** Atrioventricular septal defect, the characteristic lesion, requires bypass surgery in infancy.

2. Levothyroxine for hypothyroidism. EML-listed for hypothyroidism, oral solid 25, 50 and 100 µg, first added 1977; off-patent, **cents a day**. It treats a condition affecting up to half of this population, cheaply and completely.

3. Hearing management — grommets, hearing aids, and treatment of recurrent otitis media. The commonest treatable contributor to apparent cognitive limitation.

4. Vision management — spectacles, strabismus surgery, cataract surgery.

5. Leukaemia treatment. Children with Down syndrome and acute lymphoblastic or myeloid leukaemia have better response rates to standard chemotherapy for myeloid leukaemia and greater treatment toxicity, requiring dose modification. Transient myeloproliferative disease of the newborn usually resolves spontaneously and requires surveillance rather than treatment.

6. Surgical treatment of duodenal atresia and Hirschsprung's disease in the newborn period.

7. Treatment of sleep apnoea — adenotonsillectomy, and continuous positive airway pressure.

8. Early intervention, physiotherapy, speech and language therapy, occupational therapy, and educational support. The strongest determinants of functional outcome, and none is a drug.

9. Epilepsy treatment, for the 5 to 10 per cent of children and up to 50 per cent of adults.

10. Coeliac management — a gluten-free diet for the 7 to 20 per cent.

11. Dementia care from the fifth decade. RELIEF ONLY, and the dominant late-life issue.

Nothing targeting the trisomy itself exists. Trials of cholinesterase inhibitors, memantine, antioxidants and GABA-A antagonists for cognition in Down syndrome have been negative.

Simple means.

- **Breastfeeding support.** Hypotonia makes latching and sustained sucking difficult, and most babies with Down syndrome can breastfeed with positioning support, patience and expressed-milk supplementation. Free, and it matters because of the infection burden.
- **Feeding and growth monitoring** with a scale and the Down-syndrome-specific growth charts.
- **Physiotherapy and positioning taught to the parent.** Hypotonia responds to handling; the gross motor milestones come later and they come. Parent-delivered programmes are the standard where no therapist exists.
- **Speech and language stimulation by the family**, with sign and gesture as a bridge, because expressive speech lags comprehension substantially.
- **Looking in the eyes for a white pupil**, and **observing response to sound** — two examinations requiring nothing.
- **Checking for constipation and managing it** with diet and fluid. It affects nearly half.
- **Dental hygiene.** Periodontal disease is common.
- **Education and inclusion.** The largest measured functional gains of the past half-century came from schooling and from not institutionalising children, and neither is a medical technology.
- **Parent-to-parent support and accurate information at diagnosis.** What parents are told at birth shapes the child's life course, and in many settings it is still inaccurate and pessimistic.

- **A thyroid blood spot** — a heel prick and a card. Low chain, very high value here given the 20 to 50 per cent frequency.

The minimum chain: for the conditions that determine survival, cardiac surgery, with no substitute. For the conditions that determine function, levothyroxine tablets, grommets, spectacles and education. **Most of what improves life with Down syndrome is not pharmaceutical.**

Gaps. The death figures do not reconcile: 27,000 in 2015 against about 17,000 in 2010; both printed. Birth prevalence figures measure occurrence minus termination, and the United States fall from 2 per 1,000 in the 1950s to 1.4 per 1,000 is a screening effect rather than a biological one, so **any trend statement about Down syndrome prevalence is a statement about screening policy.** The 70 per cent figure — that mothers aged 35 and younger account for most cases — is routinely omitted from accounts of maternal-age risk, and it determines screening policy. No figure from a source fetched in the retrieval round is available for trisomy 18 or 13, or for Klinefelter and Turner syndromes. Life expectancy figures are all from high-income settings; life expectancy with Down syndrome in low-income countries, where the 40 per cent with heart defects are largely unoperated, is not reported anywhere located, and the gap is likely very large. Several associated-condition frequencies are given as very wide ranges reflecting differing ascertainment. No current cause-specific burden figure was retrievable. No cognition-targeted treatment works, and the trial record is uniformly negative. Termination rates are from 1999 and 2012 sources and will have moved with cell-free DNA screening; no current figure was located.

> **Depth.** Starts in: chromosome 21. Size: 1.5 μm†; depth +3.18. First complaint: about 9 months ([B] arises at conception); time depth 48.61. One untreated course: no number († lifelong).
>
> **Model reading.** Way of ending: restore proportion. Layer: chain. By the rule it is held, not ended. The book's status: CONTROLLABLE, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Clubfoot

What it is. The foot is turned inward and downward at birth, with the sole facing inward. The bones, ligaments and tendons are all shortened on the inner side. Untreated, the child walks on the outside or top of the foot, which ulcerates and disables.

Measured. Birth prevalence: **about 1 in 800 live births**†, and **0.5 to 2.0 per 1,000 live births in low- and middle-income countries**†. Annual burden: **150,000 to 200,000 children every year**†.

Treatment coverage is the central measured fact: less than 15 per cent of children born with clubfoot in low- and middle-income countries start treatment. A survey of 2015 data found **11 per cent coverage across all such countries and 14 per cent in respondent countries**, for children under age 1†.

Service availability: treatment is offered in **113 of 193 UN member states**, **80 countries showed no evidence of such activity**, and in most countries programmes do not cover all new patients.

No deaths figure and no clubfoot-specific DALY figure exists; the condition does not kill. Occurrence is roughly uniform, and **untreated prevalence is concentrated entirely in low- and middle-income countries**, because in high-income countries essentially every case is treated in infancy.

Where it starts. Male sex, at roughly twice the rate in boys. Strong familial clustering, with sibling recurrence elevated several-fold. Bilateral in about half of cases. Breech presentation, oligohydramnios and first pregnancy raise risk, as does maternal smoking in pregnancy, with a reported interaction with family history. It is associated with spina bifida, arthrogryposis and some syndromes, and **syndromic clubfoot is stiffer, more resistant to casting and has worse outcomes**, so distinguishing it from idiopathic clubfoot at presentation matters for the prognosis. No effect sizes were located.

The cause of idiopathic clubfoot, which is the large majority, is not known. A primary germ plasm defect in the talus, abnormal muscle fibre composition, a neurogenic abnormality, intrauterine constraint and a vascular abnormality have all been proposed, and none is established. The genetics are clearly contributory and incompletely mapped. **There is no preventive intervention because there is no identified modifiable cause.**

Cure status. CURABLE — and with the Ponseti method it is among the clearest curable-with-simple-means cases in all of surgery. A deformity that permanently disables is corrected with plaster casts applied weekly over about six weeks, by a trained non-surgeon, followed in most cases by a tendon release under local anaesthesia and a bracing period.

Success rates: **four of five systematic reviews reported initial correction rates around or above 90 per cent**†; one series reported **96.4 per cent, 661 of 686 feet**†; the method is described as effective in more than 90 per cent of patients, and the cost-effectiveness model assumes 90 per cent success†. A programme funder's own model assumes **80 per cent**, which it describes as a subjective guess lower than the published rates, and that is printed because it is the most conservative figure available and it comes with its reasoning.

The relapse qualification must be stated. A 2021 review found **47 per cent relapse across studies averaging 14.5 years of follow-up, and 79 per cent of relapsed patients needed further surgery**. The 2020 Cochrane review found only low-certainty evidence for some comparisons; it included 21 trials with 905 participants, the largest at 100. So initial correction is achieved in about 90 per cent and is well documented, long-term durability is substantially less certain, and relapse — usually managed by repeat casting rather than major surgery if caught early — is common. Bracing adherence is the main determinant and the main failure mode.

Cost figures disagree, and all are printed. **US$167 per patient** for average treatment on the abstract of one paper, against **US$140** in the results section of the same paper, which is internally inconsistent. **US$170 per patient in Pakistan**†. **About US$652 total per child — US$543 from non-governmental organisations at 2022 prices, plus US$109 from governments**†. An estimated average of **US$317 per child in 2017, falling to US$82 by 2030**†. Against those: over **US$30,000 for recurrent bilateral cases in the United States**†.

Cost-effectiveness: **US$22.46 per DALY averted, sensitivity range US$5.28 to 29.75**. **This is among the lowest cost-per-DALY figures for any surgical or orthopaedic intervention in the literature.** A funder's model estimates about 6 DALYs averted per child treated and publishes no cost per DALY; dividing its US$652 by 6 gives roughly **US$109 per DALY**, which that source notes is arithmetic rather than its own figure. **The two cost-per-DALY figures differ roughly five-fold, at about US$22 and about US$109**, and both are printed; the difference is driven by the cost per child and by the included cost perspective. The arithmetic is internally consistent: US$22.46 × 6 = US$134.76, which sits just below the US$140 to 167 range, and US$652 ÷ 6 = US$108.67, matching the printed figure.

Prevention.

- **There is no prevention.** No modifiable cause is identified.
- **Maternal smoking cessation — WEAK**, the only modifiable association, with a reported family-history interaction.
- **Folic acid — no established effect** on clubfoot.

What substitutes for prevention is early detection, because the method works best in the first weeks of life and becomes harder with age.

- **Newborn examination of the feet — STRONG.** It costs nothing and requires looking.
- **Prenatal ultrasound**, which detects a share from the second trimester and allows the family to be prepared and referred.
- **Community case-finding and referral — STRONG** for coverage, which is the binding constraint at 11 to 15 per cent.

Treatment. No drug treats clubfoot. **1. The Ponseti method.** First line, and it displaced primary surgery entirely.

- **Weekly manipulation and above-knee plaster casting**, typically **5 to 7 casts over about 6 weeks**, correcting the deformity components in a specific sequence: cavus, adductus, varus, then equinus.
- **Percutaneous Achilles tenotomy** under local anaesthesia in about 80 to 90 per cent of cases†, to correct the residual equinus. **A scalpel, local anaesthetic, and no operating theatre.**

- **Foot abduction bracing** — full-time for about 3 months, then at night and during naps until age 4 or 5. **Bracing adherence is the single determinant of relapse** and the main reason for the 47 per cent long-term figure.
- **Deliverable by trained non-physician health workers** — physiotherapists, orthopaedic officers, clinical officers. This is what makes it scalable.

2. Repeat Ponseti casting for relapse. First line for relapse detected early, and it avoids surgery.

3. **Tibialis anterior tendon transfer** for dynamic supination relapse in the walking child.
4. **Extensive soft-tissue release surgery**, now a salvage option rather than a primary treatment. It produces a stiff, painful, scarred foot in the long term, which is why Ponseti replaced it. Osteotomy and arthrodesis in the neglected adolescent or adult foot.

5. The French functional physiotherapy method — daily manipulation and taping, an alternative with comparable short-term results in trained hands and far more labour-intensive.

Simple means. This is one of the strongest entries in the book for simple means, because the standard best treatment **is** the simple means.

- **Plaster of Paris.** Rolls of plaster bandage and water. The correction of a permanently disabling deformity is achieved with plaster, hands and a weekly appointment. **The casting materials for a full course cost a few US dollars**.
- **Trained hands rather than a surgeon.** The method is explicitly designed to be taught to non-physicians, and the training package is a course plus supervision.
- **A scalpel and local anaesthetic** for the percutaneous tenotomy. No theatre, no general anaesthesia.
- **Locally manufactured foot abduction braces.** Steenbeek braces, made from leather, plywood and a steel bar by a local workshop, cost a few US dollars against hundreds for imported designs and are the standard in African clubfoot programmes. **This is the clearest example in this chapter of a device whose supply chain was deliberately shortened to the point of local manufacture.**
- **Parent-delivered bracing.** The parent applies the brace, checks the skin, and brings the child back. Adherence is the outcome determinant and the parent is the intervention.
- **Looking at the newborn's feet.** Free.
- **Community case-finding.** At 11 to 15 per cent coverage the overwhelming constraint is not the treatment but finding the children.
- **A follow-up card and a walk to a clinic.**

The minimum chain: plaster, water, a scalpel, local anaesthetic, a locally made brace and a trained non-surgeon. Everything needed to cure a disabling congenital deformity in about 90 per cent of cases is in that list, for a few dollars in materials and a cost in the low hundreds of dollars at most.

Gaps. The cost figures disagree by more than four-fold — US$140 to 167 per patient from a paper internally inconsistent between abstract and results, US$317 from a 2017 estimate, US$652 from a 2022 funder model — and the cost-per-DALY figures differ roughly five-fold in consequence; all printed. The 2020 Cochrane review found only low-certainty evidence for some comparisons, with 21 trials, 905 participants and the largest at 100, so the best-documented success rate in this entry rests on systematic reviews of small studies and on programme series rather than large trials. The 47 per cent relapse figure at 14.5 years' mean follow-up, with 79 per cent of relapsed patients needing further surgery, sits uneasily beside the 90 per cent initial correction rate; both are true of different time horizons and the long-term figure is less often quoted. Many cost and coverage sources are authored by people affiliated with clubfoot programmes, and the funder rates its own uncertainty as high, particularly on disability weights, relapse, economic effects and marginal impact; its shallow review did not assess the systematic reviews' quality in depth. Its 80 per cent assumed success rate is lower than every published rate and is described as a subjective guess. No deaths figure and no clubfoot-specific DALY figure exist, the burden is entirely disability, and the disability weight is contested. The number of untreated children alive today is not quantified: the 11 to 15 per cent coverage figure implies a very large accumulated untreated population and no source located sizes it. There are no effect sizes for risk factors and no identified preventable cause.

Syndromic and idiopathic clubfoot have different outcomes and are not separated in most of the coverage and success data.

> **Depth.** Starts in: the fetal foot. Size: 3 cm†; depth +12.19. First complaint: about 9 months ([B] at birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Developmental dysplasia of the hip

What it is. The ball of the hip joint does not sit properly in the socket. The socket may be too shallow, or the hip may slip in and out, or be dislocated outright. Caught in the first months it is corrected by a harness; caught late it needs surgery and often leaves a damaged joint.

Measured. Birth prevalence: **about 1 in 1,000 babies have hip dysplasia**†. **Meaningful hip instability: 1 to 2 per cent of term births**†. The two figures measure different things — frank dysplasia against detectable instability — and the ten-fold difference is the reason screening is contested.

Early newborn instability may affect as many as **1 in 60 newborns, falling to about 1 in 240 by one week**†, with no publication year given. Most neonatal instability resolves spontaneously within days.

Females are affected **about eight times more often than males**. Native Americans have the highest reported risk at **about 25 to 50 per 1,000**†, with no year given. The left hip is more often affected, and in most unilateral cases it is the left.

About **7.5 per cent of hip replacements address problems arising from hip dysplasia**. There is no deaths figure and no DALY figure.

Where it starts. Breech presentation is described as probably the most important single risk factor, whether delivered vaginally or by caesarean, with **no effect size given**; the mechanism is intrauterine hip position, not the delivery. **If one identical twin is affected, the other has about a 40 per cent risk**†. Female sex carries eight-fold risk, and the source states that female sex alone, without other known risk factors, accounts for **75 per cent of cases**, while **noting itself that this statement is ambiguous and should be read cautiously**.

Swaddling and restrictive carriers — tight swaddling and cradle boards that hold the hips adducted and extended — are linked to the condition, with no effect size given. **This is the one genuinely modifiable cause**, and the historical evidence is the high rates in populations using cradle boards and the fall following swaddling-education campaigns in Japan and elsewhere.

Firstborn status, a locus on chromosome 13, the hormone relaxin as a proposed contributor, and oligohydramnios are also named.

Almost all of the effect sizes are missing. The source gives numbers only for the twin concordance at 40 per cent and the sex ratio at eight-fold, and flags the 75 per cent figure as ambiguous. And one thing is genuinely unresolved: **whether dysplasia reliably causes early osteoarthritis.** It is often cited as doing so, **some studies contradict it**, and **no study has yet found a reliable method for predicting outcomes**. That matters, because the justification for universal screening rests on preventing a late consequence whose inevitability is contested.

Cure status. Mild neonatal instability, which is most of it: SELF-LIMITING. Many mild cases resolve without specific treatment, and most neonatal instability resolves within days. Caught early: CURABLE. The source states that the Pavlik harness or Frejka pillow usually gives normal results when used in the first year, and **gives no success rate and no source for that statement**. The published literature reports harness success in the region of 85 to 95 per cent for reducible hips treated in the first months†; no figure is asserted here, because the source consulted does not supply one. Caught late: CONTROLLABLE. Surgery and casting may be needed, and the result is a joint that has been reduced rather than a normal joint. Untreated cases can lead to arthritis, limping and low back pain.

Harness complications bear on the risk-benefit of screening and belong in the record: **femoral nerve palsy and avascular necrosis have been reported**, and **whether these result from improper application or from the disease itself is unresolved**.

Prevention.

- **Avoiding tight swaddling that holds the hips adducted and extended — MODERATE, and this is the only real prevention.** Hip-healthy swaddling allows the legs to flex and abduct. The evidence is the historical rates in cradle-board populations and the declines following education campaigns, and **no effect size was located.** Cost: zero. It is a change in technique, and the baby can still be swaddled.
- **Baby-carrying positions that abduct the hips**, with the legs astride the carrier's body, are protective; the historically low rates in populations carrying babies this way are the supporting observation.
- **There is no other prevention.** Breech position, sex and genetics are not modifiable.

Screening is detection rather than prevention, and it is genuinely contested.

- **Clinical examination of all newborns — recommended**. **A 2024 systematic review found clinical tests are not sufficiently reliable for diagnosis**.
- **Ultrasound**, generally preferred up to about 4 months, and **it should usually not be performed before 3 to 4 weeks of age** because of normal physiological laxity, which would otherwise generate large numbers of false positives.
- **Universal ultrasound screening against targeted screening produced an insignificant reduction in late diagnoses, and is therefore not recommended**. This is the key finding and it is a negative one.
- **Isolated hip clicks are no longer clinically significant** on 2021 guidance† — a sign that was screened on for decades and has been discarded.
- Newborn hip examinations may be painful; oral glucose has been suggested for pain relief and is not widely accepted.

Treatment. No drug treats hip dysplasia. **1. Observation** for mild instability in the first weeks, since most resolves.

2. The Pavlik harness, or Frejka pillow. Worn for weeks to months, holding the hips flexed and abducted so the femoral head seats in the socket and the socket deepens in response. First line under about 6 months. **A cloth-and-strap device.** The source states it usually gives normal results in the first year and supplies no success rate. Complications are femoral nerve palsy and avascular necrosis. It requires serial clinical and ultrasound monitoring, which is the real resource requirement.

3. Closed reduction under anaesthesia with hip spica casting, where the harness fails or the child presents after about 6 months, with an arthrogram to confirm reduction.

4. Open reduction, with or without femoral or pelvic osteotomy, for later presentation or failed closed reduction.

5. Pelvic and femoral osteotomy in the older child, and periacetabular osteotomy in the adolescent and young adult with residual dysplasia.

6. Total hip replacement in adulthood for the degenerate joint — about 7.5 per cent of hip replacements address dysplasia-related problems.

7. Abduction bracing and physiotherapy as adjuncts.

Simple means.

- **Hip-healthy swaddling and carrying. The prevention is a technique, taught in one demonstration, costing nothing.** Allow the hips to flex and spread; carry the baby with the legs astride. This is the only genuinely preventive simple means in the entry and it works on the only modifiable cause.
- **Clinical examination — the Ortolani and Barlow manoeuvres.** Two hands, no equipment, performed at every newborn check and at subsequent visits. Imperfect, as the 2024 review found, and free, and in settings with no ultrasound it is the entire screening programme.

- **Looking for asymmetry** — unequal thigh skin creases, limited abduction, apparent leg-length difference, and in the walking child a limp or waddling gait. Free, and limited abduction in the older infant is the most useful single sign.
- **The Pavlik harness is itself close to a simple means** — cloth straps and buckles. Locally manufactured harnesses are used in some programmes, as with the Steenbeek brace.
- **Parent-applied harness care and skin checks.**
- **A hip spica cast** is plaster, a materials cost of a few dollars, though it requires anaesthesia for the reduction.
- **Return appointments.** The outcome depends almost entirely on the age at detection, so a follow-up card is an intervention.

The minimum chain: two hands for the examination and a change in swaddling technique for the prevention. For the dysplastic hip that needs reduction, anaesthesia and plaster; for the late presentation, major orthopaedic surgery, with no substitute.

Gaps. The source gives no harness success rate despite describing its results as usually normal, which is a significant absence for the entry's central treatment, and the figure could not be verified elsewhere. Almost no effect sizes exist: only twin concordance at 40 per cent and the sex ratio at eight-fold are quantified, and breech presentation is called the most important single risk factor with no number attached. The "female sex accounts for 75 per cent of cases" statement is flagged as ambiguous by the source itself. **Both the recommended and the unrecommended screening strategies have negative evidence against them:** universal ultrasound screening produced an insignificant reduction in late diagnoses and is not recommended, and clinical examination, which is recommended, was found insufficiently reliable by a 2024 review. Whether dysplasia reliably causes early osteoarthritis is contested, and no reliable method for predicting outcomes exists, so the late consequence that justifies screening is not established as inevitable. Whether harness complications are iatrogenic or disease-related is unresolved, which prevents a clean risk-benefit calculation for early treatment. The early instability figures have no publication year. There is no deaths or DALY figure, no global incidence estimate, and no cost or cost-effectiveness figure. The high-prevalence population figures are reported without a year or a method.

> **Depth.** Starts in: the hip socket. Size: 2 cm†; depth +11.83. First complaint: about 9 months († at birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Congenital hypothyroidism

What it is. A baby is born without enough thyroid hormone, because the gland did not form properly or because the mother and baby lacked iodine. Thyroid hormone is required for brain development. Untreated, the child is permanently intellectually disabled; treated within the first weeks, the child develops normally.

Measured. Primary congenital hypothyroidism: **about 1 in 2,000 to 1 in 3,000 births worldwide**†. Central congenital hypothyroidism: **about 1 in 16,000 to 1 in 30,000 births**†. Severe deficiency: **about 1 in 4,000 newborns**, with more having mild or moderate deficiency†.

Global prevalence across 1969 to 2020: **4.23 to 4.28 per 10,000 newborns**, varying by region and income level, most prevalent in the Eastern Mediterranean and in upper-middle-income countries, and least prevalent in Europe and high-income countries.

The incidence has risen, mainly from wider newborn screening and lower TSH thresholds, with preterm survival, older maternal age and environmental toxin exposure named as possible contributors. The rise is substantially a detection effect.

Risk factors named are female sex and gestational age over 40 weeks†. In Down syndrome, congenital hypothyroidism affects about 1 per cent and thyroid problems with hypothyroidism 20 to 50 per cent†.

No deaths figure and no DALY figure specific to congenital hypothyroidism were located. **The burden is intellectual disability, and it is entirely preventable.** It is described as the most common preventable cause of intellectual disability.

Where it starts. Worldwide, iodine deficiency is the most common cause. In the developed world, developmental thyroid defects rather than iodine deficiency dominate, with the dysgenesis breakdown given as **agenesis 22 to 42 per cent, ectopy 35 to 42 per cent, and gland-in-place defects 24 to 36 per cent**; recent studies report more cases from in-place glands with hormone production defects.

Also established: genetic defects in thyroid development and in hormone synthesis; in-utero lithium exposure; **topical iodine in preterm neonates under 32 weeks**, which can cause transient dysfunction and is an iatrogenic route; maternal antibodies, which can cause temporary hypothyroidism; and organochlorine and dioxin-like chemicals, associated in one study. No effect sizes beyond the dysgenesis shares were located.

The cause of thyroid dysgenesis, which dominates where iodine is sufficient, is not known. Most cases are sporadic, the monogenic causes explain a minority, and why a gland fails to descend or to form is not established. The rising incidence is also not explained: lower thresholds and wider screening account for much of it, and whether any real increase is occurring, and whether the additional mild cases detected at lower thresholds actually benefit from treatment, is unresolved and consequential.

Cure status. CURABLE. A **heel-prick blood spot** costing a few cents detects it. A **levothyroxine tablet costing cents a day**, started in the first one to two weeks of life, prevents the intellectual disability entirely. The treatment is lifelong and it is replacement of a missing hormone rather than management of a disease process, and the child's development is normal.

The evidence: screening substantially reduces the risk of irreversible neurodevelopmental harm, and the goal is to start treatment within the first 1 to 2 weeks of life†. **Developmental outcomes at 24 months for treatment started within the first 3 weeks: developmental quotients of about 89 to 92 in severe cases, 96 to 98 in moderate and 99 to 100 in mild, across domains**† — essentially normal development in moderate and mild cases and near-normal in severe. Most promptly treated children grow and develop normally, including bone growth, puberty, fertility and cardiac health. Even treated infants with no thyroid gland at all may have normal cognition, though mild learning problems and lower academic performance are possible.

Against that, the cost of missing it: **severe untreated congenital hypothyroidism causes growth failure and permanent intellectual disability**, and **before screening, fewer than half of severe cases were recognised in the first month, and most untreated severe cases had an IQ below 80**†.

The ratio is a few cents of test and cents a day of tablet against permanent intellectual disability.

Prevention. Two distinct things, which must not be conflated.

Preventing the condition.

- **Iodine fortification or supplementation — STRONG** for the iodine-deficiency fraction, which is the most common cause worldwide. WHO lists iodine fortification or supplementation among its congenital-disorder prevention measures **without quantifying it**, and the source consulted for this entry reports no data on iodisation programmes. Universal salt iodisation is among the cheapest population interventions in existence, of the order of a few US cents per person per year, and the global decline in iodine deficiency disorders since the 1990s is attributed to it. **The exact effect on congenital hypothyroidism incidence could not be sourced**, and no figure is asserted.
- **Avoiding topical iodine in very preterm neonates — STRONG** for that iatrogenic route.
- **Avoiding in-utero lithium exposure where alternatives exist — MODERATE.**
- **There is no prevention for thyroid dysgenesis**, the dominant cause where iodine is sufficient.

Preventing the harm — newborn screening, which is where the measured benefit is.

- **Heel-prick dried blood spot TSH testing, ideally at least 48 hours after birth — STRONG**.
- **Adding free T4 improves detection of central congenital hypothyroidism**†.

- **Preterm or ill infants: a repeat test at 10 to 14 days is advised**, because delayed TSH rise causes false negatives.
- **Follow-up at 4 to 6 weeks**, because maternal antibodies can cause transient hypothyroidism.
- In central congenital hypothyroidism, screening may reveal combined pituitary hormone deficiencies, which changes long-term management.
- **Coverage is the gap.** Newborn screening is universal in high-income countries and absent or partial across much of South Asia and sub-Saharan Africa, which is where the higher prevalence is. **No coverage figure was located.**

Treatment. 1. Levothyroxine. One drug, and it is sufficient. Dose 10 to 15 µg/kg daily, typically 12.5 to 37.5 or 44 µg. **Start within the first 1 to 2 weeks of life**: the interval to the first dose is the determinant of the outcome. EML-listed for hypothyroidism, oral solid 25, 50 and 100 µg, first added 1977. Off-patent. **Cost: cents a day**, with a year of treatment for an infant costing a few US dollars; the source describes treatment as simple, effective and inexpensive and gives no cost figures. It is lifelong, with dose adjustment by weight and by TSH and free T4 monitoring. Practical caveats: the tablet must be crushed and given in water or milk; soy, iron and calcium interfere with absorption; and the preparation's potency must be reliable, which makes product quality a real issue in markets with poor regulation.

2. In central congenital hypothyroidism, hydrocortisone must be started before levothyroxine when ACTH deficiency is present, to avoid adrenal crisis. This is a safety rule with a fatal failure mode and it belongs in the treatment order.

3. Monitoring — TSH and free T4 at intervals through infancy and childhood, with dose adjustment. **This is the resource requirement that limits the intervention more than the drug does.**

4. Re-evaluation at age 2 to 3 to distinguish permanent from transient congenital hypothyroidism, so that children with transient disease can stop treatment.

5. Iodine supplementation where deficiency is the cause.

Simple means.

- **The heel-prick blood spot on a filter paper card.** A lancet, a card, and a postal route to a laboratory. **The consumable cost is a few cents.** This is the screening technology for the condition and it is among the shortest supply chains of any diagnostic in the book — the card can be posted.
- **Levothyroxine tablets, crushed in water.** Cents a day, no cold chain, oral, once daily.
- **Clinical examination for the untreated case**, where no screening exists: prolonged jaundice, a large fontanelle, umbilical hernia, macroglossia, hypotonia, hoarse cry, constipation, poor feeding, cold mottled skin, delayed milestones, and a goitre in dyshormonogenesis. **These signs appear after the window for preventing brain injury has largely closed**, which is exactly why screening exists — and in its absence they are what can be done.
- **Iodised salt.** A few cents per person per year, delivered through the existing salt trade, and requiring nothing of the individual.
- **Growth monitoring** — length and weight plotted. Growth failure is the visible sign.
- **Teaching the parent to give the tablet daily and consistently**, away from soy, iron and calcium. Adherence over years is the long-run determinant.
- **A treatment card** recording the dose and the next review.

The minimum chain: a lancet, a filter paper card, a laboratory and a tablet. The laboratory is the only part that is not improvisable, and a single central laboratory can serve a very large population by post.

Gaps. No cost figures appear in the source consulted, which calls treatment inexpensive without quantifying it; the figures given here are order-of-magnitude from the generic market. No data on iodisation programme effects on congenital hypothyroidism incidence appear in the source consulted, despite iodine deficiency being named the most common cause worldwide, and **this is the largest gap in the entry: the leading cause globally has the least-quantified prevention.** No newborn screening coverage figure was located, so the size of the preventable burden is unknown, and the prevalence is highest where screening is least available. There is no deaths or DALY figure. The rising incidence is largely a detection effect of

lower thresholds, and whether the additional mild cases detected benefit from treatment is unresolved — a live question about over-treatment that no source reached settles. Dysgenesis shares vary widely between studies and the more recent data shift toward gland-in-place defects, suggesting the classification itself is moving. Long-term academic outcomes in treated athyreosis rest on a 1994 source, with no modern cohort figure located. Levothyroxine product quality in poorly regulated markets is a real risk to the CURABLE classification and is unquantified.

> **Depth.** Starts in: the thyroid gland. Size: 1 cm†; depth +11.19. First complaint: about 9 months ([B] at birth); time depth 48.61. One untreated course: no number ([B] permanent if untreated).
>
> **Model reading.** Way of ending: supply from inside. Layer: word. By the rule it is held by supply. It ends only if the source is restored. The book's status: CURABLE. Reading and status do not agree; see Appendix E. Recovery route: supply for life what the body does not make, or restore the source. This is a reading. The status above stands.

Hypospadias

What it is. In a baby boy the opening of the urethra is not at the tip of the penis but somewhere along its underside. The penis may also curve downward. It affects urination standing and, in severe cases, later sexual function.

Measured. Birth prevalence: **about 1 in 250 males, roughly 4 per 1,000 male births**†. The same source also states it may affect as many as **1 per cent of males** at birth, which is 10 per 1,000†. Both printed. Including milder cases, prevalence reaches up to **4 per cent, or 40 per 1,000**, in one Danish cohort of 1,072 boys†. **A ten-fold range across definitions.**

Prevalence varies by country, and **the source states that national registries cannot reliably determine incidence or geographic variation because their reporting requirements differ**.

No trend is reported. The source cites a 1999 paper on international trends without stating its findings†. A widely discussed reported doubling in some registries in the late twentieth century is contested and partly ascertainment, and no trend is asserted here.

Severity distribution: about **90 per cent of male cases are distal**, and the rest proximal†. **No studies have estimated prevalence in newborn females**.

There is no deaths figure and no DALY figure. The condition does not kill; the burden is functional, surgical and psychological.

Where it starts. The quantified figures available: **chordee, or downward curvature, in about 10 per cent of distal and 50 per cent of proximal cases at surgery**†; **undescended testicle in about 3 per cent of distal and 10 per cent of proximal cases**†; and **disorders of sex development or syndromes in about 10 per cent of cases**†, with proximal hypospadias and undescended testes requiring investigation for a disorder of sex development.

Identical twins: when one is affected, the other is affected only 25 per cent of the time†. **This is the strongest single piece of evidence against a predominantly genetic cause** — a 25 per cent concordance in genetically identical individuals.

Genetic, environmental and prenatal hormonal factors have been studied and **the source gives no effect sizes for any of them**. The epigenetic model is **explicitly described as unproven**, and a 2023 study reported altered foreskin DNA methylation in patients. The standing hypotheses in the wider literature involve androgen action during the critical window of urethral closure — placental insufficiency, low birth weight, and endocrine-disrupting chemical exposure — and none is established.

The cause is not known in almost all cases. **This is one of the least-explained conditions in this chapter:** the twin concordance rules out simple genetics, the environmental hypotheses are unproven, the epigenetic model is described by its own proponents as unproven, and the registries cannot even establish geographic variation reliably. The reported secular trend, which drives much of the endocrine-disruptor hypothesis, is itself contested.

Cure status. Minor cases with a well-formed forward-directed opening: no intervention is required. Distal hypospadias, 90 per cent of cases: CURABLE. Tubularised incised plate repair is used for all distal cases, with **complications in under 10 per cent**. Proximal hypospadias, repair successful: CURABLE in 55 to 85 per cent depending on technique. Proximal, often needing more than one operation: CURABLE. Most are anatomically corrected in the end. The same repair for proximal cases with a straight or mildly curved penis gives **about 85 per cent success**; foreskin-based repair for proximal cases gives **55 to 75 per cent**.

Urethroplasty failure rates by graft type are given as **about 5 per cent for simple repairs, 15 to 20 per cent with buccal grafts, and nearly 50 per cent with grafts from other skin†**. **The source itself flags this figure as failing verification**, and it is printed with that caveat. Fistulas in severe cases are below 5 per cent for third-degree repairs at high-volume centres†. Common complications are fistula, glans dehiscence, meatal stenosis, stricture and diverticulum, and most appear within six months.

Functional and satisfaction outcomes qualify the surgical success figures. Erectile problems are more common with chordee, and ejaculation problems occur at similar rates whether or not the hypospadias was repaired. **Patients were less satisfied than surgeons**. That is a measured discrepancy and it belongs in the record.

Prevention.

- **There is no established prevention**, because there is no established cause. That must be stated plainly.
- **Avoiding endocrine-disrupting chemical exposure in pregnancy — CONTESTED.** Mechanistically plausible, epidemiologically inconsistent, and the reported secular trend that motivates it is itself contested.
- **Avoiding exogenous progestins and certain hormonal exposures in early pregnancy — WEAK.**
- **Folic acid — no established effect** on hypospadias.
- **Managing placental insufficiency and preventing fetal growth restriction — WEAK**, via the low-birth-weight association.
- WHO's general measures, including reducing exposure to hazardous substances such as heavy metals or pesticides, are listed **without quantification**.
- **What exists instead of prevention is examination of the newborn genitalia**, which is detection, and it matters because **circumcision must be avoided in a boy with hypospadias**: the foreskin is the graft material for the repair. **Not circumcising is a free and consequential intervention**, and failing to examine before a routine circumcision removes the repair material.

Treatment. No drug repairs hypospadias. **1. Surgical repair.** Single-stage tubularised incised plate repair is the standard for distal cases, with under 10 per cent complications†. Proximal cases use the same technique where the penis is straight or mildly curved, at about 85 per cent success; foreskin-based repairs at 55 to 75 per cent; or **staged repair** — severe cases with a scrotal opening and significant curvature are often corrected in two stages. It requires paediatric urological surgery, magnification, fine suture, paediatric anaesthesia, and a urinary stent or catheter postoperatively.

2. Timing. The WHO standard is to delay surgery until the child can consent, unless emergency repair is needed, and the source gives no specific age for this. That position sits against the long-standing paediatric urological convention of operating at 6 to 18 months. **Results are probably not affected by age at repair: adults and children had similar outcomes in a direct comparison**. That finding is what makes the deferred-consent position tenable, and it should be reported alongside it.

3. Pre-operative hormone treatment — testosterone or human chorionic gonadotropin to enlarge a small penis before surgery. **The evidence on whether this improves repair success is conflicting**. Testosterone is EML-listed, off-patent, low cost.

4. Repair of complications — fistula closure, meatotomy or dilation for stenosis, and urethroplasty for stricture, with the graft-type failure rates above.

5. Investigation for a disorder of sex development in proximal hypospadias with undescended testes, which is about 10 per cent of cases. Karyotype, hormonal profile, imaging.

6. No surgery, where the opening is well-formed and the stream is forward.

Simple means. This entry has a thin simple-means profile and that should be said first.

- **Examining the newborn's genitalia, and not circumcising a boy with hypospadias. This is the single most important low-cost act in the entry**: it costs nothing, takes seconds, and preserving the foreskin preserves the graft material on which the repair depends. Losing it converts a straightforward repair into a difficult one.
- **Reassurance and accurate information for minor cases.** A well-formed forward-directed opening needs no operation, and telling the family so prevents unnecessary surgery.
- **Sitting to urinate.** A behavioural adaptation that resolves the principal practical problem of an unrepaired distal hypospadias. Free, and for an adult who will never have access to surgery it is the whole of management.
- **Post-operative catheter and dressing care taught to the parent**, which is the main determinant of whether a repair in a low-resource setting succeeds or fistulates.
- **Hygiene, and recognising urinary retention or infection** after repair.
- **Referral before any circumcision decision.**

The minimum chain: paediatric urological surgery with magnification and fine suture. There is no simple means, no drug and no improvisation that repairs hypospadias. The honest position is that for an unrepaired distal case the adaptation above is adequate for life, and for a proximal case it is not.

Gaps. Prevalence spans ten-fold, from 4 to 40 per 1,000, depending on whether mild cases are included, and the source states registries cannot reliably establish incidence or geographic variation, so the occurrence is not known even approximately. No trend is reported, despite the secular-increase hypothesis being the main driver of the endocrine-disruptor literature. The cause is unknown, the epigenetic model is explicitly unproven, and the 25 per cent identical-twin concordance rules out simple genetics without identifying what replaces it. The urethroplasty graft failure figures are flagged by the source itself as failing verification, and are printed with that flag. Patients were less satisfied than surgeons, so the surgical success rates are surgeon-assessed and the patient-assessed outcome is worse, with no reconciled figure. Pre-operative hormone treatment evidence is conflicting. **The WHO position of deferring until the child can consent and standard paediatric urological practice of operating in infancy are in direct conflict**, and the evidence that outcomes do not depend on age at repair is a single comparison. No prevalence estimate exists for females. No deaths, DALY, cost or cost-effectiveness figures were located for any part of this entry.

> **Depth.** Starts in: the urethral fold. Size: 1 mm†; depth +9.10. First complaint: about 9 months († at birth); time depth 48.61. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status, given by stratum: CURABLE. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Limb reduction defects

What it is. Part or all of a limb fails to form in the womb. A missing hand, a shortened forearm, absent fingers, or a missing leg. The child is born with the limb already absent; nothing was lost.

Measured. No global figure was retrieved for congenital limb anomalies, in the current or the prior round. GBD reports only the aggregate congenital anomalies figure of 54.8 million DALYs for 2023.

The standing figures in the published registry literature — approximately **4 to 7 per 10,000 live births** for all limb reduction defects combined, with transverse defects more common than longitudinal — are reported as the registry literature position and were not verified.

Traumatic amputation, which is a different condition, is far more common: 180 million prevalent amputations and 5.5 million years lived with disability on the 2019 burden study. That figure is for acquired amputation and belongs with the injury chapter; it is printed here to mark the scale difference.

Prosthesis access determines the burden. Globally, **only 5 to 35 per cent of people who need wheelchairs have access** — the nearest available proxy, since no equivalent figure for prosthetic coverage was located. The standing position is that a large majority of people needing prostheses and orthoses worldwide do not receive them.

There is no deaths figure. The condition does not kill.

Where it starts. Amniotic band sequence — fibrous bands constricting a developing limb, producing a transverse amputation-like defect — is one of the better-understood mechanisms. Vascular disruption during limb development is another.

Thalidomide is the historical and definitive teratogenic cause, producing characteristic phocomelia; the episode from 1957 to 1962 established teratology as a field and remains the clearest demonstration that a limb reduction defect can have a single identifiable chemical cause. **Thalidomide is still in use for multiple myeloma and for leprosy reactions, and continues to produce cases where pregnancy prevention programmes fail**, notably in Brazil.

Misoprostol taken in early pregnancy in an unsuccessful abortion attempt is an established cause of limb defects and of Möbius sequence, documented particularly in Brazil. **This creates a direct link to the unsafe abortion entry: restricted abortion access produces a congenital anomaly.**

Also established: maternal diabetes, chorionic villus sampling before 10 weeks, maternal smoking, and some antiepileptics. Genetic syndromes — Holt-Oram, Fanconi anaemia, TAR syndrome, Roberts syndrome, the VACTERL association — account for a minority of cases and carry other anomalies that matter more. Consanguinity raises risk as it does generally. No effect sizes were located.

The cause is unknown in most cases. Limb development is well understood embryologically — the apical ectodermal ridge, the zone of polarising activity, the HOX gene expression pattern — and that understanding has not translated into identified causes for sporadic human cases. Most are isolated, sporadic and unexplained. The thalidomide and misoprostol examples show that chemical causes exist and are identifiable, which makes the absence of identified causes for the remainder a genuine gap rather than a theoretical one.

Cure status. RELIEF ONLY. The limb cannot be restored, and that must be stated without softening: no treatment makes the missing limb grow. Everything available is substitution with a prosthesis, adaptation by training the child to function with what is present, or surgical modification to make substitution or function better.

What that relief achieves is nonetheless very substantial, and the classification should not be read as a counsel of despair. Children with congenital limb difference, unlike adults with acquired amputation, have never had the limb and develop compensatory function from the start; functional outcomes are generally good, and many children with unilateral upper limb difference decline prosthetic use because they function better without it. **The measured burden is largely determined by access to prostheses, mobility aids, education and employment — social and logistical rather than medical.**

Where surgery helps: separating fused digits, lengthening a short segment, creating a functional pinch grip, revising a limb to accept a prosthesis, correcting associated deformity. These improve function and none cures.

Prevention.

- **Thalidomide pregnancy prevention programmes — STRONG, and proven by the failure cases.** Mandatory contraception, pregnancy testing and restricted distribution for women of childbearing potential taking thalidomide or lenalidomide. The Brazilian cases demonstrate what happens when the programme is not enforced. The drug is EML-listed for multiple myeloma with that restriction attached.
- **Reducing unsafe abortion by providing safe abortion access — STRONG** for the misoprostol-attributable fraction. This is a direct consequence of the unsafe abortion entry and is worth stating plainly: where abortion is restricted and misoprostol is used unsuccessfully, limb reduction defects and Möbius sequence result. **The preventive intervention is legal and logistical, not medical.**

- **Pre-pregnancy diabetes control — MODERATE.**
- **Avoiding chorionic villus sampling before 10 weeks — STRONG** for that iatrogenic route; a settled procedural rule.
- **Maternal smoking cessation — WEAK.**
- **Avoiding known teratogenic antiepileptics where alternatives exist — MODERATE.**
- **Genetic counselling** for families with a syndromic cause, which informs and does not prevent.
- **Folic acid — no established effect** on limb reduction defects.
- **There is no prevention for the sporadic majority.**
- **Prenatal ultrasound** detects many major limb defects from the second trimester; this is detection, and its consequences are preparation, referral, and in some cases termination.

Treatment. There is no drug. **1. Prosthetic fitting and rehabilitation.** Timing follows developmental milestones — a passive lower-limb prosthesis around the time of pulling to stand, with upper-limb fitting debated and often later. It requires repeated refitting through growth, which is the dominant cost and the dominant reason provision fails. **Note the measured preference: many children with unilateral upper-limb difference reject prostheses and function better without them.** Prescribing is therefore not automatic, and rejection is not failure.

2. Occupational and physiotherapy. Teaching function with the limb as it is. For unilateral upper-limb difference this is often more valuable than a prosthesis.

3. Orthoses and mobility aids, including wheelchairs, with the access figure above.

4. Reconstructive surgery — syndactyly release, digit transfer or pollicisation to create a thumb, limb lengthening by distraction osteogenesis, rotationplasty, and revision amputation to produce a prosthesis-tolerant residuum.

5. Investigation for associated anomalies and for a syndrome. Limb defects are a marker, and the cardiac, haematological and renal anomalies may matter more than the limb.

6. Pain management for the minority with pain. Phantom sensation is less common in congenital absence than in acquired amputation.

7. Education, inclusion and vocational support. The largest determinants of life outcome, and not medical.

Simple means.

- **Teaching function early, by the parent.** A child with a limb difference develops compensatory strategies spontaneously, and supporting rather than correcting this is the single most valuable intervention and it costs nothing. The main harm in low-resource settings is not absent prosthetics but exclusion from school and from play.
- **Locally made prostheses and orthoses.** The Jaipur Foot and comparable designs, made from rubber, wood, aluminium and locally available materials by trained technicians, cost of the order of tens of US dollars against thousands for imported components, are repairable locally, tolerate water and agricultural work, and are refittable as the child grows. **This is the limb-defect equivalent of the Steenbeek brace: a deliberate shortening of the supply chain to the point of local manufacture.**
- **Crutches, sticks and locally made walking aids** from wood.
- **Adapted tools and utensils** — a strap, a cuff, a modified handle. Occupational therapy in its cheapest form is a workshop and some imagination.
- **Residual limb hygiene and skin inspection**, to prevent the ulceration that causes prosthesis abandonment. A mirror and a routine.
- **Sock and liner management**, with improvised padding from cloth where liners are unavailable.
- **School inclusion.** A decision, not a resource, and the measured determinant of adult outcome.
- **Parent-to-parent contact and accurate information at birth.** As with Down syndrome, what the family is told at diagnosis shapes the child's life.

- **Examining the newborn for associated anomalies** — looking at the heart, the kidneys and the blood count where a syndrome is suspected.

The minimum chain: **nothing, for the functional training and inclusion that matter most.** For a prosthesis, a local workshop and locally available materials, which is a real and demonstrated short chain rather than an aspiration.

Gaps. No global figure of any kind was retrieved, in the current or the prior round, and the registry range is reported as the literature position and is unverified. **For a condition with a known chemical cause in living memory, the absence of a current global count is a notable gap.** No deaths, DALY, cost or cost-effectiveness figures specific to limb reduction defects were located. No prosthetic coverage figure was located, and the wheelchair figure is used as a proxy and is not the same measure. The cause is unknown in most cases despite limb development being embryologically well characterised. The misoprostol-attributable fraction is not quantified anywhere located, though the causal link is established, and given its policy implications that is a consequential absence. Ongoing thalidomide-attributable cases are not globally counted, and the Brazilian cases are documented largely in regional literature. Prosthesis rejection rates and functional outcomes with and without prostheses are poorly quantified, particularly for children, and the prescribing convention is not well supported by outcome data. Transverse and longitudinal defects, and isolated and syndromic cases, are not separated in most available data, and they have different causes and different outcomes.

> **Depth.** Starts in: the limb bud. Size: 1 mm†; depth +9.10. First complaint: about 9 months ([B] already absent at birth); time depth 48.61. One untreated course: no number ([B] nothing was lost).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The limb was never built. There is nothing to rebuild. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Congenital cataract

What it is. The lens of the eye is cloudy at birth or becomes cloudy in the first weeks. Light cannot reach the retina, so the visual part of the brain never learns to see. If the lens is not removed within weeks, the blindness becomes permanent even if the eye is later cleared.

Measured. Birth prevalence: **about 1 to 6 cases per 10,000 live births. The source gives no citation for this figure and tags it as needing one**, and it is printed with that flag. Share of childhood vision loss: **nearly 10 per cent worldwide**, also unsourced on that page and printed with the flag. The source does describe congenital cataract as a significant cause of childhood blindness.

No global count of affected children, no deaths figure and no DALY figure was located. In Down syndrome, cataracts affect 15 per cent — one of the few quantified subpopulation figures available.

In low-income countries where treatment is unavailable, the condition may go untreated and vision may be lost, with no figure given. The standing position in the childhood-blindness literature is that cataract is among the leading avoidable causes of childhood blindness and that the avoidable fraction is concentrated in low- and middle-income countries. No trend is reported anywhere located.

Where it starts. The overall split, unsourced on the page consulted and printed with that flag: **about one third are part of a broader syndrome or disease, one third are isolated inherited traits, and one third have undetermined causes**.

Approximately 50 per cent of cases may have a genetic cause, which is highly heterogeneous, with more than 25 loci and genes implicated†. Autosomal dominant inheritance is the commonest pattern in isolated familial cataract.

Congenital rubella is listed as an infectious cause and given as the source's example of a syndromic cataract, with **no percentage given**. It is the classic preventable cause and the one with a vaccine. Other congenital infections — toxoplasmosis, cytomegalovirus, herpes, varicella — contribute.

Metabolic diseases — galactosaemia, Lowe syndrome, peroxisomal disorders — are described as more commonly associated with bilateral cataracts, unsourced, with a recommendation for a basic laboratory workup for bilateral cases of unknown cause. Prematurity, maternal diabetes, corticosteroid exposure, radiation and trauma are also named, and consanguinity is relevant given the autosomal recessive forms. No effect sizes were located.

The cause is unknown in about a third, by the source's own split. The genetics are described as highly heterogeneous with more than 25 loci, which is a statement that no single mechanism accounts for the inherited cases. The practical unknown that matters more: **the share of the global burden that is rubella-attributable is not quantified**, and that share is vaccine-preventable at a cost of cents.

Cure status. CURABLE — but only inside a window of weeks, and this is the entry's defining fact.

The lens can be removed and the eye optically corrected. But the visual cortex requires patterned visual input in early infancy to develop, and if it does not receive it the blindness becomes permanent regardless of later surgery. **The cataract is curable; the deprivation amblyopia it causes is RELIEF ONLY.** The window separates the two.

The surgical timing thresholds are the operative numbers of the entry: **visually significant unilateral cataracts should be removed before 6 weeks of age, and visually significant bilateral cataracts before 10 weeks**†.

Treatment options for children under 2 with bilateral visually affecting cataracts include intraocular lens implantation or lensectomy, on a 2022 Cochrane review; **the source does not report that review's findings**.

The source says early detection gives the most favourable outcome and that prompt surgery can restore vision, and **its claim that many individuals achieve good visual outcomes is unsourced, and it gives no quantitative success rates**. That is a significant evidential gap for the entry's central claim and it is reported as such rather than filled in. What is not in doubt: a baby whose dense bilateral cataracts are removed in the first weeks and who is then optically corrected and patched develops useful vision; a baby operated at two years does not. The effect is binary in time and the surgery itself is straightforward.

Prevention.

- **Rubella vaccination — STRONG, and it is the clearest preventable cause.** WHO names rubella vaccination for children and women, and screening for rubella, varicella and syphilis, among its congenital-disorder prevention measures, **without quantifying them**. Rubella-containing vaccine is EML-listed, off-patent and costs cents a dose, and congenital rubella syndrome has been eliminated in the Americas, which is the demonstration. **The rubella-attributable share of congenital cataract is not quantified anywhere located**, so the size of this preventable fraction is unknown.
- **Avoiding corticosteroid and radiation exposure in pregnancy where avoidable — MODERATE.**
- **Pre-pregnancy diabetes control — MODERATE.**
- **Genetic counselling** for familial cases, which informs and does not prevent.
- **There is no prevention for the genetic and idiopathic majority**, about two-thirds by the source's split.

Detection, which here is almost equivalent to cure because of the window:

- **The newborn red reflex examination — STRONG, and it is the whole screening programme.** An ophthalmoscope or a direct light held at arm's length; a normal eye reflects red, and a cataractous eye shows a white or absent reflex. **Performed at the newborn check and at subsequent infant visits, it detects the cases inside the 6-to-10-week window.** It also detects retinoblastoma, which makes it doubly valuable.
- **Universal newborn eye examination — STRONG** as policy; coverage is the gap and no coverage figure was located.
- **Examining siblings and relatives** in familial cases.

Treatment. There is no drug. **1. Surgical removal of the lens, within the window** — before 6 weeks for unilateral and before 10 weeks for bilateral visually significant cataract†.

2. Optical correction immediately after surgery. An eye without a lens has no focusing power at all, so this is not optional and is part of the same intervention.

- **Aphakic spectacles** — thick, cheap, immediately available, adjustable as the eye grows. **The low-chain option.**
- **Contact lenses** — better optics, requiring handling, replacement and hygiene.
- **Intraocular lens implantation**, an option for children under 2 with bilateral cataracts alongside lensectomy†. In unilateral cases the Infant Aphakia Treatment Study found no visual acuity advantage of primary intraocular lens over contact lens at age 5, with substantially more adverse events and reoperations in the lens group, **so the simpler option is not inferior**. The source consulted does not report these findings, and they are reported here as the standing position in the paediatric ophthalmology literature.

3. Amblyopia treatment — occlusion of the better eye in unilateral cases. This is as important as the surgery and it is where most treatment failures occur, because it depends on months of daily parental adherence. A patch costs pennies.

4. Treatment of associated conditions — glaucoma, which is a common long-term complication after infant cataract surgery and requires lifelong surveillance; posterior capsule opacification; retinal detachment; strabismus surgery.

5. Investigation for a cause — the basic workup for bilateral cases of unknown cause, and galactosaemia screening, because treating it has systemic consequences beyond the eye.

6. Low vision rehabilitation and education for the children in whom the window was missed. **This is where the untreated global burden sits**, and it is RELIEF ONLY.

Simple means.

- **The red reflex test. A torch or an ophthalmoscope held at arm's length in a dim room.** This single examination, costing nothing and taking seconds, is what separates a curable condition from permanent blindness. **It is among the highest-value simple means in this chapter**, and it can be taught to any health worker or midwife.
- **Teaching the mother to look at her baby's eyes** for a white pupil, and to come at once. In settings with no newborn examination, the parent is the screening programme.
- **Aphakic spectacles.** Thick plus lenses in a cheap frame, adjusted as the child grows. Not elegant optics and entirely adequate, and the Infant Aphakia Treatment Study finding means the cheap option is not the inferior one.
- **An eye patch** — adhesive or cloth — for amblyopia treatment. Pennies, and months of daily use, and the outcome depends on it more than on the surgical technique.
- **Parent-delivered patching with a calendar and a reward chart.** Adherence is the intervention.
- **Case-finding in the community**, and referral to a surgical outreach.
- **Low vision aids** — magnifiers, large print, good lighting, preferential seating — for the children operated too late. Cheap and under-provided.
- **Braille and education** where vision is not recoverable.
- **Examining the newborn for the associated anomalies** that point to a syndrome or a metabolic cause.

The minimum chain: a torch for detection, and microsurgery with an operating microscope and paediatric anaesthesia for the cure. The detection is nearly free and the cure is not improvisable — and because the window is six to ten weeks, **a detection system without a surgical service within reach does not save the sight.** That asymmetry is the practical core of the entry.

Gaps. The two headline figures — 1 to 6 per 10,000 births, and nearly 10 per cent of childhood vision loss — are both tagged as needing a citation on the source consulted, are printed with that flag, and **should not be treated as sourced.** The one-third split of causes is also unsourced. No quantitative surgical success

rates are given, and the source's claim that many individuals achieve good outcomes is unsourced; **for an entry classified CURABLE, the absence of any success rate is the most serious gap.** The source does not report the findings of the 2022 Cochrane review it cites on intraocular lens against lensectomy, and the Infant Aphakia Treatment Study findings are not on it either and are reported as the standing literature position. The rubella-attributable share is not quantified, so the size of the vaccine-preventable fraction is unknown, and given that the vaccine costs cents that is a consequential absence. No global count of affected children, no DALY figure and no cost figure was located. No coverage figure for newborn red reflex screening was located, so the size of the detection gap is unknown. Long-term outcomes — glaucoma incidence after infant cataract surgery, final visual acuity, educational attainment — are thinly reported and almost absent for low-resource settings.

> **Depth.** Starts in: the lens of the infant eye. Size: 6 mm†; depth +10.73. First complaint: about 9 months ([B] at birth or in the first weeks); time depth 48.61. One untreated course: about 6 weeks ([B] permanent blindness unless removed within weeks); depth 46.90.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE, with RELIEF ONLY for a named stratum. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Fetal alcohol spectrum disorder

What it is. Alcohol crosses the placenta and damages the developing brain. The child is left with lifelong difficulties in learning, attention, memory, impulse control and judgement. In the full form there are also characteristic facial features and growth restriction.

Measured. The prevalence figures on the source consulted are internally inconsistent by a factor of six to ten, and all are printed.

Global prevalence of fetal alcohol spectrum disorder: **7.7 per 1,000 people**, with no year given†. The infobox on the same page gives **1 in 20, approximately 390 million, to 1 in 13, approximately 600 million, for all types, marked as unconfirmed**†. The body text gives a general population estimate of **about 1 in 20, with some estimates as high as 1 in 7**, with no year†, which conflicts with the infobox's own 1-in-13 upper bound. The source is internally inconsistent in at least three places, and none of the figures can be relied on.

Full fetal alcohol syndrome prevalence: **0.2 to 9 per 1,000**, with no source and no year given†.

The condition is described as highly misdiagnosed and underdiagnosed, with true rates likely underestimated, so every prevalence figure is a floor.

Alcohol use in pregnancy globally: **about 1 in 10 women drink during pregnancy, and 20 per cent of those binge drink**, with no year given†. The highest reported alcohol use during pregnancy, cited to 2017: **Ireland 60 per cent, Belarus 47, Denmark 46, the United Kingdom 41, the Russian Federation 37**†. **These are alcohol-use-in-pregnancy figures, not prevalence figures for the disorder**, and the two are frequently conflated.

Western Australia: a birth rate of 0.02 per 1,000 for non-Indigenous births and 2.76 per 1,000 for Indigenous births† — **a 138-fold difference within one jurisdiction**, and the starkest inequality figure in this chapter.

South Africa does not appear on the source consulted. The Western Cape wine-region cohorts, which report the highest fetal alcohol syndrome prevalences measured anywhere, are the standing reference in this field and could not be sourced.

There is no deaths figure and no DALY figure.

Where it starts. The cause is known and is a single exposure, which distinguishes this entry from the rest of the chapter. **Prenatal alcohol exposure. No safe level of fetal alcohol exposure has been established**.

Risk estimates cited to 2017†:

- **Any drinking during pregnancy: about 15 per cent risk of the spectrum disorder and about 1.5 per cent risk of the full syndrome.**
- **Two standard drinks a day, or six in one session: 4.3 per cent risk of the full syndrome, about 1 in 23.**
- **Alcohol-related congenital abnormalities: about 1 in 67 drinkers.**
- **Mothers with alcohol use disorder: about one third of their children have the full syndrome**.

Low-to-moderate drinking, under 12 g of ethanol a day: the evidence is inconsistent and contradictory.

Randomised trials on pregnant women are considered unethical, so all risk estimates come from observational data. This is the central methodological constraint of the field and it is why the dose-response at low intake cannot be settled.

Modifying factors in the wider literature — maternal nutrition, maternal and fetal alcohol dehydrogenase variants, binge pattern, timing in gestation, smoking, and socioeconomic deprivation — determine why the same exposure produces different outcomes, and none is quantified in the source consulted.

Two things are genuinely not known: **why only a minority of exposed children are affected**, and **whether there is a threshold below which no harm occurs.** The second cannot be answered by the available method, because observational data cannot distinguish a true threshold from confounding and a trial is not permissible. Abstinence is therefore recommended universally on precautionary grounds, which is a defensible policy and is not the same as a demonstrated dose-response. The source states the limitation directly: it presents recommendations and risk data and **does not include trial evidence showing that abstinence reduces incidence**.

Cure status. RELIEF ONLY. The brain injury is permanent and nothing reverses it. Prenatal alcohol exposure causes structural and functional brain damage established before birth. There is no treatment that removes it, no medication that targets it, and no developmental process that compensates for it. Every intervention is management of consequences — educational accommodation, behavioural support, treatment of co-occurring attention deficit hyperactivity disorder and mental illness, and structuring the environment so that impaired judgement and memory are less costly.

What relief achieves is nonetheless substantial and measurable in the literature on secondary disabilities: early diagnosis, a stable caring home, and absence of violence exposure are repeatedly associated with markedly lower rates of school exclusion, unemployment, mental illness, substance misuse and incarceration in affected individuals. **The primary disability is fixed; the secondary disabilities are largely preventable**, and that distinction is where all the clinical value lies.

Diagnostic criteria matter here because the classification depends on them. The full syndrome requires all of: height or weight at or below the tenth percentile; all three facial features — smooth philtrum, thin vermilion, short palpebral fissures; clinically significant central nervous system impairment; and confirmed or unknown prenatal alcohol exposure. Partial fetal alcohol syndrome requires two or three facial features, impairment in three or more brain domains, and confirmed exposure. Alcohol-related neurodevelopmental disorder requires minimal or no facial features, impairment in three or more domains, and confirmed exposure. **Four North American diagnostic systems exist, they agree on the full syndrome's criteria and differ on the other conditions, and the Canadian 2016 guidelines removed growth as a diagnostic criterion**†.

Prevention. This is the only entry in this chapter where the condition is 100 per cent preventable by a single avoidable exposure, and that should be stated first.

- **Abstinence from alcohol during pregnancy and while trying to conceive**, recommended by the United States Surgeon General, the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, WHO and NICE. **STRONG on mechanism and on the precautionary principle**, and the source notes explicitly that it does not include trial evidence showing that abstinence reduces incidence, because such a trial is not possible. The honest grading is STRONG for the recommendation and not formally demonstrated by trial for the effect size.

- **Alcohol warning labels — WEAK.** United States alcohol containers have carried warning labels since 1988, and their effect on drinking in pregnancy is small in the evaluation literature.
- **Screening and brief intervention in antenatal care — MODERATE.** Structured brief interventions reduce alcohol consumption in pregnancy in trials; the effect on incidence of the disorder has not been measured.
- **Treating maternal alcohol use disorder — MODERATE** for the highest-risk group: about one third of children of mothers with alcohol use disorder have the full syndrome, so this group carries a very large share of the severe cases and is the highest-yield target.
- **Contraception for women with alcohol use disorder who do not wish to conceive — MODERATE.** Much prenatal alcohol exposure occurs before pregnancy is recognised, so preventing unintended pregnancy in heavy drinkers prevents exposure that no antenatal intervention can reach. This is the same timing logic as folic acid.
- **Population alcohol policy — MODERATE at population level, CONTESTED in attribution.** Pricing, availability restriction and marketing restriction reduce population consumption, including among women of childbearing age. The disorder-specific effect has not been measured.
- **Addressing the structural determinants** behind the 138-fold Indigenous and non-Indigenous disparity in Western Australia — dispossession, poverty, trauma, and the absence of services. **The disparity figure is measured; the interventions that would close it are not.**

Treatment. There is no treatment for the brain injury. Treatment is management. **1. Early diagnosis.** The strongest single predictor of better long-term outcome in the secondary-disability literature. It requires a clinician who will ask about prenatal alcohol exposure and a system that will record the answer, and **the source states the condition is highly misdiagnosed and underdiagnosed**.

2. A stable, structured caring environment. Repeatedly the strongest protective factor against the secondary disabilities. Not a medical intervention.

3. Educational accommodation and individualised support. Externalising the executive functions the child lacks — routine, visual structure, repetition, concrete instruction, supervision — rather than expecting internal regulation that is not available.

4. Treatment of co-occurring conditions — attention deficit hyperactivity disorder, with a reported stimulant response less reliable than in the idiopathic form; anxiety; depression; sleep disorder; epilepsy. Methylphenidate is EML-listed, off-patent and low cost. These treatments work on the comorbidity, not on the disorder.

5. Speech and language therapy, occupational therapy and physiotherapy as indicated.

6. Treatment of associated physical anomalies — cardiac, renal, skeletal, vision and hearing.

7. Caregiver training and support. Parent- and carer-directed behavioural programmes adapted for the disorder have a small and real evidence base.

8. Transition and adult support — supported employment, supported decision-making, and intervention in the justice system, where affected adults are heavily over-represented.

No pharmacological treatment targets the disorder itself and no candidate is close.

Simple means.

- **Asking the question.** Prenatal alcohol exposure is ascertained by asking, and the diagnosis is impossible without it. Non-judgemental enquiry in antenatal care and in paediatric assessment costs nothing and is the gateway to everything else.
- **Telling women that no safe level has been established, before conception.** Information, delivered once, is the entire preventive technology for a 100-per-cent-preventable condition. The limitation is timing: the message must arrive before the pregnancy is recognised.
- **Contraception for heavy drinkers who do not wish to conceive.** Cheap, and it reaches the exposure window that antenatal care cannot.

- **A structured, predictable daily routine** at home and at school. The single most effective management intervention, and it requires nothing but consistency.
- **Visual schedules, written reminders, simplified instructions, consistent carers.** Externalising memory and executive function with paper and routine.
- **Supervision appropriate to functional rather than chronological age.** A decision, not a resource, and it prevents a large share of the secondary disabilities.
- **School inclusion with accommodation**, and avoiding exclusion, which is the proximate cause of much of the adult outcome.
- **Measuring and plotting growth, and examining the face.** The facial features and growth restriction are diagnosed by a ruler, a photograph and a trained eye: palpebral fissure length is measured with a plastic ruler, and philtrum and vermilion are graded against a printed lip-philtrum guide. **The diagnostic instrument for fetal alcohol syndrome is a printed card.**
- **Caregiver support groups and parent-to-parent contact.**
- **Avoiding punitive framing of the mother.** Practical rather than sentimental: maternal shame and fear of child removal are the main documented barriers to disclosure, and without disclosure there is no diagnosis.

The minimum chain: a conversation and a printed card. For a condition with no treatment, essentially all of the available value is in low-chain detection and environmental management.

Gaps. The prevalence figures on the source consulted are mutually inconsistent by a factor of six to ten — 7.7 per 1,000 globally; 1 in 20 to 1 in 13 in the infobox, marked unconfirmed; 1 in 20 with some estimates as high as 1 in 7 in the text. All are printed and none can be relied on; for a condition of this importance this is the worst quantitative evidence base in the chapter. The full syndrome prevalence figure has no source and no year, and several other figures carry no year at all. South Africa is absent from the source consulted, and the Western Cape cohorts report the highest measured prevalences in the world, so their absence materially understates the upper end of the global range. Alcohol-use-in-pregnancy figures are routinely misread as prevalence figures for the disorder; they are not, and the source lists them under a heading that invites the confusion. Four diagnostic systems disagree on everything except the full syndrome, and the Canadian 2016 guidelines removed growth as a criterion, so prevalence comparisons across jurisdictions are partly comparisons of diagnostic systems. No trial evidence that abstinence reduces incidence exists and cannot ethically be generated, and the dose-response at low intake is inconsistent and contradictory and will remain so. The 138-fold Western Australian disparity is measured and unexplained in the source, and no intervention evidence addresses it. There is no deaths figure, no DALY figure, no cost figure and no cost-effectiveness analysis of any intervention. Underdiagnosis is acknowledged by the source and unquantified, so every prevalence figure is a floor.

> **Depth.** Starts in: the ethanol molecule. Size: 0.4 nm†; depth −4.31. First complaint: about 6.8 years († from conception to diagnosis about 6 years); time depth 50.61. One untreated course: no number ([B] lifelong).
>
> **Model reading.** Way of ending: rebuild. Layer: surround. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The brain was built under alcohol. It cannot be rebuilt. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

ICD-11 Chapter 22 — Injury, poisoning or certain other consequences of external causes

Seventeen entries covering thirteen named conditions: poisoning is written as one general entry plus four agent-class sub-entries.

A structural note that governs every figure below. Chapter 22 codes the **nature of the lesion** — fracture, burn, laceration, poisoning effect. Chapter 23 codes the **external cause** — fall, road crash, animal contact, intent. **GBD reports injury burden by external cause, not by lesion type.** Every burden figure in these

entries therefore attaches to the paired external cause, and that is stated where it applies. There is no series for fracture of femur; there is one for falls.

The chapter-level denominators are these. Total injury deaths: **4.4 million a year**, nearly 8 per cent of all deaths, split into **3.16 million unintentional** and **1.25 million violence-related**; about **90 per cent of injury-related deaths are in low- and middle-income countries**, and injuries and violence cause an estimated **10 per cent of all years lived with disability**. Twice as many males as females are killed by injuries and violence each year.

Road injuries accounted for **75.3 million DALYs (59.8 to 89.2)** in 2023, the 6th leading DALY cause, with the age-standardised rate down 13.3 per cent (−25.5 to 2.9) since 2010, **not statistically significant**. Falls accounted for **74.3 million DALYs (58.9 to 95.0)**, the 8th leading cause, and **53.1 million years lived with disability (38.4 to 72.2)**, the 4th leading such cause. Unintentional injuries as a group accounted for **155.8 million DALYs**. Self-harm: **35.2 million DALYs** and about **746,000 deaths** in 2021. Interpersonal violence: **30.2 million DALYs**. Drowning: **17.0 million DALYs**.

As lesions rather than causes: **440 million prevalent fractures and 26 million years lived with disability**, and **180 million prevalent traumatic amputations with 5.5 million years lived with disability**, both on the 2019 burden study; and **about 1 billion people affected by oro-dental trauma**.

The governing finding for this chapter is the Lancet Commission on Global Surgery, 2015. Its figures were read off the report itself in the retrieval round of October 2026.

- **About 5 billion people lack access to safe, affordable surgical and anaesthesia care when needed**. The model's own bounds are 4.8 billion as a lower and 5.3 billion as an upper bound, and 5 billion is the rounded midpoint.
- **143 million additional surgical procedures are needed in low- and middle-income countries each year** to save lives and prevent disability — total estimated need minus surgery already delivered, and the report calls the figure likely conservative.
- **32.8 million people a year face catastrophic health expenditure from the out-of-pocket medical costs of surgical and anaesthesia care**, meaning out-of-pocket costs exceeding 40 per cent of household income. **Adding non-medical costs — transport, lodging, food — raises it to 81.2 million a year**. Printing 33 million without the 81.2 million prints the narrower of two figures the report gives together.
- **Projected cumulative losses to the global economy from surgical conditions, 2015 to 2030: US$20.7 trillion, equal to 1.3 per cent of projected output, of which US$12.3 trillion falls on low- and middle-income countries**.
- **The three Bellwether procedures: caesarean delivery, laparotomy and open fracture treatment.** The report's definition is that they serve as a proxy for surgical systems able to provide a broad range of procedures: a facility able to perform all three is functioning at a level complex enough for most other surgery.
- The core indicator on access targets **at least 80 per cent of the population able to reach a facility providing the Bellwether procedures within 2 hours, by 2030**, and the workforce indicator targets **20 specialist surgical, anaesthetic and obstetric physicians per 100,000 population in every country by 2030**.

Each Bellwether procedure is the irreducible requirement for a group of conditions in these four chapters. Caesarean section resolves obstructed labour and prevents obstetric fistula and a large share of neonatal encephalopathy. Laparotomy resolves ruptured ectopic pregnancy, perforation from unsafe abortion, and abdominal bleeding from road traffic injury. Open fracture care prevents limb loss and infected non-union, the commonest severe lesion of road traffic injury and of falls. Beyond Bellwether capacity sit cardiac surgery with bypass and paediatric neurosurgery, which are the clearest cases in this book of conditions curable in principle and untreated in practice.

For a large number of entries below, the honest cure status is CURABLE and the honest simple-means section ends with a sentence saying that nothing improvisable substitutes for an operation. The conditions

concerned are not uncertain, not poorly understood and not awaiting research. They are curable conditions whose cure is a first-level hospital, and about 5 billion people do not have access to one.

Road traffic injury

What it is. Injury from a crash on a road — a car, a motorcycle, a bicycle, a truck, or a pedestrian struck by one. The lesions are fractures, head injury, chest and abdominal injury, and open wounds. It is the leading cause of death for young people.

Measured. Annual deaths: **approximately 1.16 million**. **A second WHO page gives a different figure for the same quantity, and both are printed.** The cross-cutting injuries and violence sheet gives road traffic as about one in three of 4.4 million injury deaths, which is approximately **1.47 million**; the standalone road traffic sheet gives 1.16 million. The two pages use different, unstated data years. The Global Status Report on Road Safety 2023 gives a third figure, **1.19 million**, a 5 per cent drop since 2010, covering 2010 to 2021. All three stand, unresolved.

Non-fatal injuries: **20 to 50 million more each year**, many leaving a disability — a two-and-a-half-fold uncertainty on the morbidity burden.

DALYs: **75.3 million, the 6th leading DALY cause in 2023**, with the age-standardised rate down 13.3 per cent (−25.5 to 2.9) since 2010 — **not statistically significant, so the global rate cannot be said to have fallen**.

The leading cause of death for children and young adults aged 5 to 29. Two thirds of fatalities are among people aged 18 to 59, and the male fatality risk is about **3 times** the female.

92 per cent of road deaths occur in low- and middle-income countries, which have **about 60 per cent of the world's vehicles**. The body text of the same page gives more than 90 per cent, and both are printed. Road crashes cost most countries **3 per cent of GDP**.

Vulnerable road users account for **53 per cent of road traffic deaths — pedestrians 23 per cent, powered two- and three-wheeler riders 21, cyclists 6, micro-mobility users 3 — against 30 per cent for occupants of cars and other four-wheeled light vehicles**. Pedestrian deaths rose 3 per cent to **274,000** between 2010 and 2021, and cyclist deaths rose nearly 20 per cent to **71,000**. **Eighty per cent of the world's roads fail pedestrian safety standards and 0.2 per cent have cycle lanes**.

Regional shares of global road traffic deaths: South-East Asia 28 per cent, Western Pacific 25, Africa 19, the Americas 12, Eastern Mediterranean 11, Europe 5.

The target is at least a **50 per cent reduction** in deaths and injuries by 2030.

Where it starts. This is the best-quantified risk-factor set in the chapter.

- **Speed. Each 1 per cent increase in mean speed produces a 4 per cent increase in fatal crash risk and a 3 per cent increase in serious crash risk**. **Pedestrian death risk is 4.5 times higher at 65 km/h than at 50**. **Car-to-car side impact fatality risk is 85 per cent at 65 km/h**.
- **Drink-driving.** Crash risk rises at low blood alcohol levels and **increases significantly at a blood alcohol concentration of 0.04 g/dl or higher**. For drug-driving, **amphetamine users have about 5 times the fatal crash risk of non-users**.
- **Mobile phone use. Drivers using a phone are about 4 times more likely to be in a crash**.
- **Non-use of helmets, seat belts and child restraints**, with the effect sizes given under prevention.
- **Vehicle fleet and road design.** The mismatch between 92 per cent of the deaths and 60 per cent of the vehicles is the summary statistic: the deaths are where the roads, the vehicles and the trauma care are worst, not where the traffic is heaviest.
- Young age, male sex, pedestrian and motorcyclist exposure, night driving, and unsafe public transport.

Little about the mechanism is unknown; this is one of the most completely characterised causes in the book. What is genuinely unresolved is **why the global age-standardised rate has not fallen significantly**

despite half a century of known effective interventions and two decades of global target-setting. The interventions work where they are implemented. The measured global rate reflects that they are largely not.

That gap can now be sized, and the sizing is in the legislation data rather than on the fact sheet. The road traffic injuries fact sheet carries **no legislation data at all**. The Global Status Report on Road Safety 2023, dated 13 December 2023, carries it:

- **Six countries have laws meeting WHO best practice on all five risk factors** — speeding, drink-driving, motorcycle helmets, seat belts and child restraints.
- **140 countries, about two thirds of UN Member States, have laws meeting best practice for at least one of the five**.
- **Twenty-three countries changed their laws to meet best practice since the 2018 report**.
- **Thirty-five countries legislate on all key vehicle safety features**.
- **Fifty-one countries require safety inspections covering all road users**.

WHO's reachable pages give these counts **by the number of risk factors covered**, not as a separate country count for each of the five individually. The per-factor counts are in the full report, which did not render as text. So no claim of the form "N countries have best-practice speed laws" is made here: the sourceable structure is six and 140.

Cure status. The classification is by lesion, and the chapter's structure requires that it be stated that way. Most road traffic injury: CURABLE. Fractures unite, lacerations heal, spleens and livers are repaired or removed, and the patient returns to normal life. The determinant is whether surgery, blood and anaesthesia are available within hours. Traumatic brain injury, for the established injury: RELIEF ONLY. Spinal cord injury: RELIEF ONLY. Traumatic amputation: RELIEF ONLY — 180 million prevalent amputations and 5.5 million years lived with disability.

Stated as one line: a road traffic injury is curable in the majority and unpreventable in its consequences for the minority who sustain brain or cord injury. The whole of the public health value is in prevention.

Prevention. This is the richest prevention section in the book and every figure is measured.

Speed management — STRONG. The relationship is a dose-response — 1 per cent more mean speed for 4 per cent more fatal crash risk — so **the intervention is continuous: any reduction in mean speed reduces deaths proportionally**. Pedestrian death risk falls 4.5-fold going from 65 to 50 km/h. **Thirty km/h zones in residential and school areas are the WHO-recommended standard**, and the published evaluation literature consistently reports large reductions in pedestrian casualties following their introduction. The instruments are urban speed limits, enforcement including automated enforcement, traffic calming, and road design that enforces speed physically.

Helmets — STRONG. Correct helmet use reduces the risk of death in a crash by more than 6 times and the risk of brain injury by up to 74 per cent. **This is the largest single measured protective effect in this chapter.** The instruments are a mandatory helmet law, enforcement, and standards so that the helmets sold actually protect.

Seat belts — STRONG. Wearing a seat belt reduces the risk of death among vehicle occupants by up to 50 per cent. The instruments are a mandatory wearing law covering all seating positions, enforcement, and fitment requirements.

Child restraints — STRONG. Child restraints can reduce infant deaths by 71 per cent. The instruments are a mandatory law, availability and affordability of restraints, and vehicle anchorage requirements.

Drink-driving law — STRONG. Risk rises from low blood alcohol and increases significantly at 0.04 g/dl or higher. The WHO-recommended legal limit is **0.05 g/dl for the general population and 0.02 g/dl for young and novice drivers**. The instruments are blood alcohol limits, random breath testing, graduated licensing and alcohol-ignition interlocks. The published evaluation literature on random breath testing and on lowering limits reports substantial reductions in alcohol-related crash deaths, and **no effect size is given on the WHO fact sheet**.

Mobile phone restriction — MODERATE. A four-fold crash risk from the exposure, and a weaker legislative effect size, because enforcement is difficult.

Other established measures, MODERATE, with **no effect sizes on the WHO fact sheet**:

- **Safe road infrastructure** — separated footways and cycleways, safe crossings, roundabouts, median barriers, lighting. Eighty per cent of the world's roads fail pedestrian safety standards.
- **Vehicle safety standards** — electronic stability control, anti-lock brakes, airbags, pedestrian-protective front-end design, and the UN vehicle regulations. Thirty-five countries legislate on all key vehicle safety features.
- **Motorcycle-specific measures** — daytime running lights, antilock brakes, rider training.
- **Post-crash care**, which determines whether a survivable injury is survived.
- **The Safe System approach** — designing so that human error does not produce death, rather than relying on individual compliance.

Treatment. Treatment is trauma care, and the single largest drug finding is CRASH-2.

1. Tranexamic acid, given within 3 hours of injury. The best-evidenced drug in trauma. The CRASH-2 trial randomised **20,211 adult trauma patients** within 8 hours of injury at 274 hospitals in 40 countries; 10,096 were allocated to tranexamic acid and 10,115 to placebo, with 10,060 and 10,067 analysed.

- **All-cause mortality: 14.5 per cent, 1,463 patients, against 16.0 per cent, 1,613. Relative risk 0.91 (95 per cent CI 0.85 to 0.97), p = 0.0035.** An absolute reduction of 1.5 percentage points and a **number needed to treat of about 67**†.
- **Death due to bleeding: 4.9 per cent, 489 patients, against 5.7 per cent, 574. Relative risk 0.85 (0.76 to 0.96), p = 0.0077**†.
- Regimen: 1 g loading dose over 10 minutes, then 1 g by infusion over 8 hours†.
- **The timing finding, consistent with the WOMAN trial: benefit is confined to administration within 3 hours, and later administration showed no benefit and, in the bleeding-death analysis, possible harm**. The summary page consulted gives no subgroup results by time, and the finding is reported as the published position of the trial collaboration.

Tranexamic acid is EML-listed for haemorrhage not elsewhere classified, injection 100 mg/mL, off-patent, at **a few US dollars a gram**†. **A reduction in all-cause trauma mortality of 1.5 percentage points for a drug costing a couple of dollars, deliverable by intravenous injection anywhere, is among the highest effect-per-euro results in the whole of this book.** CRASH-2 did not demonstrate cost-effectiveness: the trial aimed to assess it and reports no result. Published analyses since have estimated costs per life-year in the low tens of dollars in low-income settings, and no figure is asserted here.

2. Haemorrhage control and resuscitation — direct pressure, tourniquets, pelvic binders, blood transfusion, damage-control surgery. **Blood availability is the determinant and it is the commonest absent input.**

3. Airway management and ventilation.

4. Surgery — laparotomy for abdominal bleeding, thoracotomy, external and definitive fixation of fractures, debridement of open wounds. **Two of the three Bellwether procedures, laparotomy and open fracture care, are road-trauma procedures**.

5. Antibiotics and tetanus prophylaxis for open wounds.

6. Tranexamic acid for head-injured patients, where the effect is confined to mild-to-moderate injury and the overall result was null; the figures are in the traumatic brain injury entry.

7. Rehabilitation — physiotherapy, prosthetics, orthotics, and the long-term care of brain and cord injury.

Simple means.

- **A helmet. Reduces death risk more than 6-fold and brain injury risk by up to 74 per cent**. A manufactured object costing tens of dollars, requiring no infrastructure, no power and no training. **Nothing in this book has a better ratio of protection to cost and complexity.**

- **A seat belt**, already fitted to most vehicles. **Up to 50 per cent reduction in occupant death**, and the intervention is the act of fastening it.
- **A child restraint — 71 per cent reduction in infant deaths**.
- **Direct pressure on a bleeding wound, and a tourniquet.** Bystander haemorrhage control has the shortest possible chain: hands, cloth, and in the limb case an improvised or commercial tourniquet. **A commercial windlass tourniquet costs tens of dollars; a cloth and a stick costs nothing.** The military and civilian evidence for prehospital tourniquets in limb exsanguination is strong.
- **The recovery position.** An unconscious breathing casualty placed on their side does not aspirate or obstruct. **It costs nothing, requires no equipment, and is taught in minutes.**
- **Not moving a casualty with suspected spinal injury, and manual in-line stabilisation.**
- **Splinting a fracture with whatever is at hand** — a board, a rolled newspaper, a padded stick, the other leg.
- **Lay first responder training.** Programmes training taxi drivers, bus drivers, police and community volunteers in basic trauma first aid — airway, bleeding, position, transport — have been evaluated in Ghana, Uganda, Cambodia and elsewhere with reported reductions in prehospital mortality. **The intervention is a two-day course and a small kit.** The evidence is pre-post and observational rather than randomised.
- **Organised transport** — a radio, a phone number, and an agreement with whoever owns a vehicle. **In most of the world the ambulance is a taxi**, and formalising that is a real intervention.
- **High-visibility clothing and reflectors** for pedestrians and cyclists, and daytime running lights on motorcycles.
- **Separating pedestrians from traffic with a kerb, a bollard or a painted footway.**
- **Speed humps.** Concrete, and they enforce the single most powerful variable above without any enforcement personnel.

The minimum chain: a helmet, a belt, hands on a wound, and a side-lying position. For the survivable abdominal and limb injuries, laparotomy and fracture care, and that is the Bellwether requirement with no substitute.

Gaps. The global age-standardised rate has not fallen significantly, and no analysis located separates implementation failure from exposure growth. **Two WHO pages give different death totals for the same quantity — approximately 1.16 million on the standalone fact sheet and approximately 1.47 million implied by the cross-cutting injuries sheet — and the 2023 status report gives 1.19 million; all three stand, unresolved**, because the pages use different and unstated data years. The road traffic injuries fact sheet carries no legislation coverage data at all, and the status report's figures are given by number of risk factors covered rather than per factor, so the per-factor country counts remain unsourceable from reachable pages. WHO gives no effect size for drink-driving legislation, for infrastructure measures, for vehicle standards or for post-crash care, though all are recommended. The 92 per cent and "over 90 per cent" low- and middle-income share figures differ within the same WHO page; both printed. CRASH-2's cost-effectiveness was not reported by the trial, and the cost-per-life-year figures in circulation are modelled. CRASH-2's timing subgroup results are not on the page consulted and are reported as the collaboration's published position. Lay first responder training evidence is pre-post, not randomised. Non-fatal injury is given as a 20-to-50 million range. Disability outcomes after road injury in low- and middle-income settings are very thinly measured.

> **Depth.** Starts in: the body (collision). Size: 1.7 m†; depth +15.87. First complaint: about 1 second († instant); time depth 33.15. One untreated course: no number.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names a late stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Falls and fragility fracture

What it is. A person falls to the ground. In children it is usually from a height; in older people it is usually from standing. In an older person with weak bone the fall breaks the hip, the wrist or the spine, and a broken hip at eighty is frequently the end of independent life.

Measured. Annual fatal falls: an estimated **684,000**. **The second leading cause of unintentional injury death worldwide**, after road traffic injuries. Non-fatal falls requiring medical attention: about **37.3 million** a year.

The DALY figures differ roughly two-fold between the two main sources and both are printed. The WHO falls fact sheet gives **over 38 million DALYs** a year, of which **nearly 40 per cent occur in children**, and notes explicitly that this may **understate** the impact on older adults, who have fewer life years to lose. GBD 2023 gives **74.3 million DALYs (58.9 to 95.0), the 8th leading DALY cause**, and **53.1 million years lived with disability (38.4 to 72.2), the 4th leading such cause**. The age-standardised DALY rate is down 11.8 per cent (6.1 to 16.3) since 2010.

Over 80 per cent of fall-related deaths occur in low- and middle-income countries, and the Western Pacific and South-East Asia regions account for **60 per cent** of these deaths. Death rates are highest among adults over 60 in all regions. In the United States, **20 to 30 per cent of older people who fall suffer moderate to severe injuries**.

Costs: the average health system cost per fall injury in people aged 65 and over is **US$3,611 in Finland and US$1,049 in Australia**. In China, per fatal child fall, there are 4 permanent disabilities, 13 hospitalisations over 10 days, 24 hospitalisations of 1 to 9 days, and 690 cases seeking care or missing school or work.

Falls are a leading cause of traumatic spinal cord injury alongside road traffic injuries, and a leading cause of traumatic brain injury in older people.

Where it starts. Age: risk of death or serious injury rises with age and is highest over 60 in every region, through the combination of higher fall frequency and lower bone strength. Osteoporosis and low bone mineral density are the fragility in fragility fracture, with fracture risk rising steeply as bone density falls. Previous fall and previous fracture are among the strongest predictors. Muscle weakness, impaired gait and balance, and sarcopenia contribute.

Psychotropic medication — benzodiazepines, antipsychotics, antidepressants, sedatives — is one of the most consistently measured and most modifiable risks. Polypharmacy, orthostatic hypotension and antihypertensives raise risk. Visual impairment contributes, including treatable cataract, and multifocal spectacles increase outdoor fall risk. Cognitive impairment and dementia, Parkinson's disease, stroke and peripheral neuropathy all raise risk, as does vitamin D deficiency in deficient individuals and alcohol. Environmental hazards — loose rugs, poor lighting, no handrails, slippery floors, uneven ground — are the proximate causes. In children: developmental stage, unguarded windows and balconies, roofs, trees, stairs, and in low-income settings work at height. In workers: construction and work at height. **No effect sizes are given for any risk factor on the WHO falls fact sheet**.

Two things are not known. How much of the fall risk in an individual older person is modifiable, and in what order to address it: the multifactorial interventions below work, and which component carries the effect is not established, because the trials bundle gait training, home modification, medication review and vision correction and the components have not been reliably separated. And **why the global burden is so heavily concentrated in low- and middle-income countries**, at over 80 per cent of deaths, when the condition is framed in the literature as a problem of ageing high-income populations. WHO itself notes that the DALY metric misrepresents the age distribution.

Cure status. Two things must be separated and they have different statuses. The fracture: CURABLE. A broken wrist, a broken hip, a vertebral compression fracture — these unite. Surgical fixation or arthroplasty of a hip fracture restores walking in the majority, and the bone heals. The underlying osteoporosis: CONTROLLABLE. Bisphosphonates and the other agents reduce fracture risk substantially and do not restore normal bone. The deviation remains and the treatment is long-term. The fall tendency: CONTROLLABLE. Multifactorial intervention reduces fall rate; it does not remove the propensity.

But the outcome of a hip fracture at advanced age is not the outcome of the fracture. One-year mortality after hip fracture in older people is substantial in every published cohort, and a large share of survivors never regain their previous mobility or independence. **The fracture is cured and the person does not recover**, and that is the honest statement.

Prevention. WHO's falls fact sheet lists interventions and reports no effect sizes for any of them. The gradings below note that, and the effect sizes come from the wider trial literature and are flagged.

For older people, WHO's list:

- **Gait, balance and functional training — STRONG.** The best-evidenced single component. The Cochrane reviews of exercise for fall prevention in community-dwelling older people report reductions in fall rate of the order of 20 to 25 per cent†; no effect size appears on the WHO page.
- **Tai Chi — MODERATE.** Named specifically by WHO. Trials report reduced fall rate and effect sizes vary.
- **Home assessment and modification — MODERATE**, with the effect concentrated in those at higher risk.
- **Reducing or withdrawing psychotropic drugs — STRONG.** Among the clearest modifiable causes, and deprescribing trials report reduced falls. **It costs nothing and saves drug expenditure.**
- **Multifactorial interventions — MODERATE**, with the component-attribution problem above.
- **Vitamin D supplements for those who are deficient — MODERATE.** WHO specifies "for those who are deficient", which is the current and narrowed position: high-dose and universal supplementation has not reduced falls and in some trials increased them.

For children and adolescents, WHO's list:

- **Parenting programmes for low-income and marginalised families — MODERATE.**
- **Informing parents about fall risks and supporting home risk reduction — MODERATE.**
- **Window guards — STRONG on the available evidence, and they are the specific measure with the best-documented history.** New York City's window-guard programme from 1972 combined guard distribution and legislation with public education and reported a very large fall in child falls from windows in the targeted districts — an often-cited reduction of the order of 95 per cent in the intervention area, and a 35 per cent city-wide decline in child fall deaths over the programme period. **These figures are from the programme-evaluation literature and were not verifiable against a source fetched in the retrieval round**. New York City's Health Code has required window guards in apartments with children under 11 since 1976, and similar requirements exist elsewhere. **A window guard costs tens of dollars; the alternative is a child falling several storeys.**
- **Balcony and stair gates; roof parapets.**

For workers:

- **Stricter workplace safety regulation in high-risk occupations such as construction — MODERATE.**
- **Multicomponent workplace safety programmes — MODERATE.**
- **Harnesses and fall-arrest systems for work at heights.**

Basic environmental measures, which WHO describes as prudent even without strong research support: fencing off dangerous areas; **playground standards requiring soft surfaces and limited fall heights**; building standards and landlord-required home modifications; accessible neighbourhoods and public spaces; and adequate staff-to-resident ratios in residential care.

The only quantified prevention outcome on the WHO page is a modelled Canadian estimate: a 20 per cent reduction in fall incidence among children under 10 could produce net savings of over US$120 million a year. A model, not a result.

For the fracture rather than the fall:

- **Bisphosphonates in osteoporosis — STRONG.**

- **Calcium and vitamin D in the deficient — MODERATE.**
- **Hip protectors — CONTESTED.** They reduce hip fracture in nursing-home residents in some trials; adherence is poor and the pooled effect is uncertain.
- **Smoking cessation and reducing alcohol — MODERATE** for bone density.

Treatment. 1. Surgical fixation or replacement of the fractured hip, early. Internal fixation for undisplaced intracapsular and for extracapsular fractures; hemiarthroplasty or total hip replacement for displaced intracapsular fractures. **Early surgery, within 24 to 48 hours, is associated with lower mortality and better function** in the cohort and registry literature. It requires orthopaedic surgery, anaesthesia and an implant — **the implant is the cost, and implant availability is the constraint in low-resource settings.**

2. Fracture management generally.

3. Bisphosphonates for osteoporosis — alendronate, risedronate, zoledronic acid. **Reductions in vertebral fracture of the order of 40 to 70 per cent and in hip fracture of the order of 40 to 50 per cent** in the pivotal trials in women with osteoporosis†; those figures are from the trial literature and were not verified against a source fetched in the retrieval round.

No bisphosphonate is on the WHO Essential Medicines List for osteoporosis, and this must be stated precisely. Alendronate is not on the list at all: a live query of the electronic list returns zero recommendations, zero medicines and zero therapeutic equivalents for it, with every filter count on the page at zero, so the result is not a filter artefact. Zoledronic acid is listed only under Supportive medicines, section 8.2.5, on the complementary list, for malignant neoplasm metastasis in bone or bone marrow and for osteogenesis imperfecta. The word osteoporosis does not appear on its record. Both are off-patent. Cost is a few US dollars a month for oral alendronate, and zoledronic acid is a once-yearly infusion and now cheap as a generic.

A 40 to 50 per cent reduction in hip fracture for a few dollars a month is one of the better effect-per-euro results in the chapter, and treatment rates after a first fragility fracture are low everywhere, which is the measured failure.

4. Denosumab, teriparatide, romosozumab — more effective in some comparisons, substantially more expensive, not off-patent for all, and not EML-listed in the sections reachable.

5. Calcium and vitamin D in the deficient. EML-listed, off-patent, cents.

6. Analgesia — paracetamol, non-steroidal anti-inflammatory drugs with caution in older people, opioids sparingly. Vertebral fracture pain is often undertreated.

7. Rehabilitation and early mobilisation. As important as the operation for function, and labour rather than technology.

8. Orthogeriatric co-management. Joint orthopaedic and geriatric care of the hip fracture patient reduces mortality and length of stay in trial and registry evidence.

9. Delirium prevention, pressure-area care, nutrition and thromboprophylaxis in the admitted older patient.

Simple means.

- **Exercise: standing on one leg, sit-to-stand repetitions, heel-toe walking, Tai Chi.** The best-evidenced fall-prevention intervention in the world requires no equipment and no facility. **A group of older people doing balance exercises in a courtyard is the intervention**, and WHO names Tai Chi specifically.
- **Stopping a psychotropic drug.** Free, and it saves money. One of the clearest modifiable causes.
- **Home modification with no purchased technology** — removing loose rugs and clutter, moving the bed, improving lighting, a nightlight on the route to the toilet, a chair in the washing area.
- **A grab rail and a handrail.** Wood or pipe, locally fitted, tens of dollars at most.
- **Non-slip footwear, and not walking in socks.**

- **Window guards and stair gates for children. Tens of dollars against a fatal fall**, and the measure is improvisable from bars or mesh.
- **A soft surface under playground equipment** — sand, wood chips, or earth rather than concrete. Free or nearly so, and it converts a fatal fall into a bruise.
- **Roof parapets and balcony railings.**
- **Vision: cataract surgery, and single-vision rather than multifocal spectacles for outdoor walking.** The second is free advice.
- **Splinting and immobilising a suspected fracture** before transport.
- **Getting the person up off the floor and keeping them warm.** A long lie after a fall causes hypothermia, pressure injury and rhabdomyolysis, and the intervention is being found — which is why a daily check on an older person living alone is a medical intervention.
- **Early mobilisation after a fracture** — walking the patient, which is labour rather than equipment, and is the strongest determinant of recovered function.
- **A stick or a locally made walking frame.**

The minimum chain: **nothing, for the exercise and the environmental measures that carry most of the prevention.** For the hip fracture, orthopaedic surgery and an implant, with no substitute — an unoperated displaced hip fracture in an older person means immobility, and immobility at that age means death.

Gaps. WHO and GBD differ roughly two-fold on DALYs, at over 38 million against 74.3 million, and both are printed. WHO reports no effect size for any prevention measure, and the only quantified figure on its fact sheet is a modelled Canadian cost saving; the effect sizes above come from the trial literature and are flagged as unverified. WHO states its own DALY figure may understate the impact on older adults, so the metric misrepresents the condition's main population. Nearly 40 per cent of fall DALYs occur in children and over 80 per cent of fall deaths are in low- and middle-income countries, which is at odds with the framing of falls as a geriatric high-income problem, and no analysis located reconciles this. The New York window-guard figures could not be verified. Multifactorial intervention components have not been separated, so the priority ordering for an individual is not established. Vitamin D's role has narrowed to the deficient only, after universal and high-dose supplementation failed and in some trials increased falls, so sources published before that shift give the opposite advice. Hip protectors are contested. Osteoporosis treatment rates after a first fragility fracture are low everywhere and the size of that gap is not quantified in any source reached. The falls fact sheet is the oldest in the WHO set, printed in April 2021, and gives **no data year** for most of its figures beyond "each year". Cost figures exist for only two high-income countries and none for the countries carrying 80 per cent of the deaths.

> **Depth.** Starts in: the hip or a bone. Size: 5 cm†; depth +12.66. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 8.6 weeks († bone healing 6–12 weeks); depth 47.23.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Burns

What it is. Skin and deeper tissue destroyed by heat, flame, hot liquid, electricity or chemicals. A burn kills by fluid loss and infection in the days after, not usually at the moment. Survivors are left with scars that contract and pull joints out of position.

Measured. Annual burn deaths: an estimated **180,000**. The share in low- and middle-income countries is given as the vast majority in the key facts and the majority in the body text — wording rather than a figure. **WHO gives no exact share.**

Non-fatal burns: no global count is given. WHO calls them a leading cause of morbidity. Country figures: **India, over 1 million people moderately or severely burned each year; Bangladesh, nearly 173,000 children; the United States, over 410,000 burn injuries in 2008 with approximately 40,000**

requiring hospitalisation. In Bangladesh, Colombia, Egypt and Pakistan, **17 per cent of children with burns have a temporary disability and 18 per cent a permanent disability**. In Nepal burns account for 5 per cent of disabilities and are the second most common injury.

Geography: almost **two thirds** of burn deaths occur in the WHO African and South-East Asia Regions. **Burn injuries requiring medical care are nearly 20 times more frequent in the Western Pacific Region than in the Americas**. Children under 5 in the African Region have **over twice** the burn death incidence of children under 5 worldwide, and boys under 5 in low- and middle-income countries of the Eastern Mediterranean Region are almost **twice** as likely to die from burns as boys in the European Region. **The child death rate from burns is over 7 times higher in low- and middle-income countries than in high-income countries**. Burns are the **fifth** most common cause of non-fatal childhood injuries.

Community surveys in Bangladesh and Ethiopia found 80 to 90 per cent of burns occur at home.

Healthcare cost: a 2014 systematic review gives a mean total cost per patient of **US$88,218, range US$704 to 717,306**, and South Africa an estimated **US$26 million** annually for kerosene cookstove burns.

GBD's fire, heat and hot substances DALY figure was not retrievable, in the current or the prior round.

Where it starts. Cooking. Open fires, three-stone stoves, unstable stoves at floor level, cooking at ground level with children nearby, loose clothing. The 80-to-90-per-cent-at-home finding identifies the kitchen as the site.

Scalds from hot liquids are the dominant mechanism in young children and the reason the under-5 figures are what they are: hot water, tea, cooking oil, water heated for washing. **Kerosene and paraffin appliances** — lamps, stoves and heaters, with adulterated fuel, unstable appliances and explosion. Open flame for lighting, candles, household fires. **Hot tap water**, a scald source entirely controlled by the thermostat setting. Electricity, through unsafe wiring, illegal connections and overhead lines. Chemicals, fireworks, industrial exposure.

Intentional burning, including acid attack and intimate-partner and dowry-related violence, is a recognised and substantial category in parts of South Asia.

Epilepsy — a seizure near an open fire — is a recognised and preventable route. Poverty, crowding, non-fire-resistant housing, and the absence of a smoke alarm or escape route complete the picture. **No effect sizes are given for any risk factor on the WHO burns fact sheet**.

What is not known is the non-fatal burden. WHO gives country figures and no global count, and the ratio of non-fatal to fatal burns differs by an order of magnitude between regions — the 20-fold Western Pacific and Americas difference is a statement about both exposure and ascertainment. Also not known: the share that is intentional, which is systematically under-ascertained because of how it is reported.

Cure status. Small and superficial burns: SELF-LIMITING with supportive care. A superficial burn re-epithelialises in days to weeks with nothing but cooling, cleaning and dressing. Deep and extensive burns: CURABLE, with survival a function of resources. Fluid resuscitation, infection control and skin grafting make them survivable, and burn mortality for a given burn size differs several-fold between well-resourced burn centres and settings without fluid, blood, antibiotics or grafting capacity. Hypertrophic and contractural scarring: RELIEF ONLY. Scar contracture across a joint or the neck is permanent without surgical release, and it recurs.

The survivor of a major burn is not restored. The functional, cosmetic and psychological burden is lifelong, and in children the contractures tighten with growth and require repeated surgery through childhood. **WHO provides no treatment outcome statistics** on the fact sheet, which is a gap for an entry whose cure status depends on them.

Prevention. WHO recommends the measures below and **gives no effect sizes for smoke alarms, water temperature regulation or cookstove safety**.

- **Smoke alarms — STRONG.** WHO names smoke detectors. **The effect size is not on the WHO page.** The standing position in the injury-prevention literature, from case-control and surveillance studies, is that a working smoke alarm **roughly halves the risk of death in a house fire**, and that

figure was not verified against a source fetched in the retrieval round. **A smoke alarm costs a few US dollars to tens of dollars and lasts years.** The documented failure mode is not absence but **non-functioning alarms with dead or removed batteries**, which is why installation programmes with ten-year sealed-battery alarms outperform give-away schemes. On the returns side, WHO's cross-cutting injuries sheet gives **US$1 spent on smoke detectors saving US$65**.

- **Lowering hot water tap temperature — STRONG.** WHO names it. Setting the domestic hot water thermostat to a maximum of about 50 °C, or fitting thermostatic mixing valves at the tap, prevents tap-water scalds, which are a meaningful share of childhood scalds in countries with piped hot water. **Cost: zero for a thermostat adjustment.** Jurisdictions with regulated maximum delivery temperatures report reductions in tap-water scald admissions. No effect size on the WHO page.
- **Safer cookstoves and enclosing fires — STRONG.** WHO names both. Raising the cooking surface above child height, enclosing the flame and stabilising the stove address the mechanism the at-home finding identifies. The clean-cookstove literature measures air pollution outcomes more than burn outcomes, and **the burn-specific effect size is not established.**
- **Fire-retardant sleepwear — MODERATE.** WHO names it. The historical evidence is the fall in childhood nightwear ignition injuries following flammability standards in the United States and the United Kingdom.
- **Sprinklers — STRONG** in the fire-engineering literature, for buildings.
- **Separating cooking from living and sleeping space; keeping hot liquids out of reach; not carrying a child while cooking; stove guards.**
- **Kerosene appliance safety, child-resistant fuel containers, and regulating fuel adulteration — MODERATE.**
- **Electrical safety regulation and residual current devices — MODERATE.**
- **Treating epilepsy**, which removes the seizure-near-fire route. Phenobarbital is EML-listed for epilepsy or seizures, off-patent, and works out at about US$0.017 a 30 mg tablet on October 2026 indicative prices, **about US$6.24 a patient-year at one tablet a day**. An unusually direct cross-chapter prevention.
- **Smoke-free policies and self-extinguishing cigarettes** for the fires they start.
- **Escape planning and building standards.**

Treatment. 1. Stop the burning, then cool with cool running water for about 20 minutes. WHO's first aid instruction, and it is a treatment with a time-dependent effect: cooling within the first hours reduces burn depth and the need for grafting. **Water, and twenty minutes.**

2. Fluid resuscitation, the intervention that converted major burns from uniformly fatal to survivable. Lactated Ringer's or Hartmann's solution by the Parkland or a modified formula for burns above about 15 to 20 per cent body surface area in adults and 10 per cent in children, and **oral rehydration where intravenous access is unavailable**, which is a genuine option for moderate burns. Compound sodium lactate is EML-listed, off-patent, at **a few US dollars a litre**.

3. Wound care and infection control. Cleaning, debridement, a topical antimicrobial dressing, and clean dressing changes. **Silver sulfadiazine** is the traditional topical agent, EML-listed, off-patent and cheap; **honey and paraffin gauze are evidenced alternatives**. **Systemic prophylactic antibiotics are not indicated**; antibiotics treat established infection.

4. Tetanus prophylaxis. A burn is a tetanus-prone wound. EML-listed, off-patent, cents.

5. Analgesia. Burns are among the most painful injuries and are routinely undertreated. Paracetamol, non-steroidal anti-inflammatory drugs, oral morphine. Morphine is EML-listed for pain, off-patent, and works out at **about US$0.57 an ampoule** of 10 mg/mL injection on October 2026 indicative prices — **its absence in most low-resource burn care is an access failure, not a cost one.**

6. Escharotomy for circumferential full-thickness burns compromising circulation or breathing, and **early excision and skin grafting** for deep burns, which shortens the course and improves outcome.

7. Nutrition. A major burn is a hypermetabolic state, and high-energy high-protein feeding is part of treatment and is deliverable with food.

8. Physiotherapy, splinting and pressure garments from early on, to limit contracture. This is the intervention that determines the survivor's function, and it is the one most often absent.

9. Reconstructive surgery for contracture release, often repeatedly through childhood.

10. WHO's explicit don'ts: no ice, no oils, no pastes, and do not open blisters. Named because the harmful traditional applications are widespread.

Simple means.

- **Cool running water for 20 minutes. The single most effective first aid act in this entry, free, and effective for hours after the burn.** It reduces depth, reduces pain and reduces grafting need.
- **Stop, drop and roll; smothering flames with a blanket.**
- **Removing hot wet clothing and jewellery** before swelling.
- **Covering the burn with a clean dry cloth or cling film.** Cling film is an excellent temporary burn dressing — sterile from the roll, transparent, non-adherent and universally available.
- **Oral rehydration solution.** For moderate burns where intravenous fluid is unavailable, oral rehydration is a real and evidenced route: the gut absorbs, and the burn's fluid requirement can be met by mouth in a conscious patient with a moderate burn. **Sugar, salt and water**, at about US$0.048 a sachet on October 2026 indicative prices.
- **Honey as a burn dressing.** Cochrane-reviewed evidence supports honey for partial-thickness burns, with faster healing than some conventional dressings in the pooled trials. **Cheap, locally available, antibacterial and non-adherent.** The evidence is of moderate quality and heterogeneous.
- **Boiled and cooled water, clean cloth and soap** for dressing changes.
- **Paraffin or petrolatum gauze** — cheap, non-adherent.
- **Splinting in the anti-contracture position with locally made splints** — plaster, wood, or moulded plastic. **The position in which a burn is immobilised determines whether the joint works afterwards**, and this is free knowledge applied with free material.
- **Range-of-movement exercises taught to the patient and family, done daily.** This is the whole of contracture prevention where no physiotherapist exists, and it works.
- **Pressure garments improvised from elastic bandage or tubular bandage.**
- **Raising the cooking fire off the ground; a stove guard; a separate cooking space.** The prevention is a change in the kitchen.
- **A smoke alarm** — a few dollars.
- **Turning down the water heater thermostat** — free.
- **Teaching the family not to apply ice, oil, paste, ash or toothpaste.** A conversation that prevents a deeper burn.

The minimum chain: water, clean cloth and oral rehydration salts. That set manages a moderate burn. For a major burn, intravenous fluid, blood, surgery and grafting, with no substitute.

Gaps. WHO gives no global non-fatal burn count and no exact low- and middle-income death share; the country figures are not a global estimate and the United States figure is from 2008. WHO gives no effect sizes for smoke alarms, hot water temperature regulation, cookstove safety or any other prevention measure, though it recommends all of them, and the smoke alarm figure could not be verified. WHO provides no treatment outcome statistics, so burn survival by burn size and setting — the figure that would quantify the resource gradient — is not available here. GBD's fire, heat and hot substances DALY figure was not retrievable, in the current or the prior round. The 20-fold Western Pacific and Americas difference in burns requiring medical care mixes real exposure difference with ascertainment difference, and the components are not separated. The intentional-burn share is systematically under-ascertained and no figure was located. The honey evidence is moderate-quality and heterogeneous. Contracture outcomes and long-

term function in survivors are almost unmeasured in low-resource settings, where most survivors are. Several WHO figures carry no year.

> **Depth.** Starts in: the skin. Size: 2 mm†; depth +9.73. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 17 days († 2–3 weeks); depth 46.09.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Drowning

What it is. Breathing is impaired by immersion or submersion in liquid. It happens silently and in minutes, often in shallow water, and most often to a small child who was out of sight for a short time.

Measured. Annual drowning deaths: about **300,000**. **The global drowning death rate fell 38 per cent since 2000, from 6.1 to 3.8 per 100,000 population**, and WHO states the decline falls short of what is needed for the related Sustainable Development Goals. This is one of the clearer measured declines in the chapter. DALYs: **17.0 million, the 40th leading DALY cause**.

Age: **children under 5 account for nearly a quarter of all drowning deaths** on the key facts, and the body text instead gives ages **0 to 29 as 57 per cent** of drowning deaths, with the highest rates among ages 0 to 4. Both are printed; the key facts figures appear nowhere in the body, which offers a different age cut. Drowning is the **4th leading cause of death for ages 1 to 4 and the 3rd for ages 5 to 14** globally; the cross-cutting injuries sheet instead gives it as the **sixth** leading cause of death for children aged 5 to 14.

Sex: the male drowning death rate is more than **twice** the female rate.

Geography: **over half of global drownings occur in the Western Pacific and South-East Asia regions**. The Eastern Mediterranean region has the highest under-5 drowning rate at **16.8 per 100,000**. In the Western Pacific, children aged 5 to 14 die from drowning more often than from any other cause. **92 per cent of drowning deaths occur in low- and middle-income countries**, where rates are more than **three times** higher than in high-income countries.

Fishers: more than **32,000** die while working each year, and **drowning accounts for 75 per cent of flood disaster deaths**.

WHO's investment case for day care plus basic swimming, scaled up to 2050: 774,000 fewer children drowning, 178,000 fewer severe non-fatal injuries, projected savings exceeding US$400 billion, and a return of 9 times the cost. These are model projections rather than measured results.

Where it starts. Age and developmental stage: toddlers are mobile, top-heavy, drawn to water and unable to self-rescue, which is where the under-5 quarter-share comes from. **Proximity of unprotected water to the home** — open wells, water storage vessels, ponds, irrigation ditches, rivers, flooded fields. In the high-burden rural settings this is the dominant exposure: the water is a few metres from the door and there is no barrier. **A lapse of supervision, typically brief**; the toddler-drowning literature consistently finds supervision interruptions measured in minutes. Inability to swim. Occupational and transport exposure — fishing, ferry and small-boat travel without flotation, overcrowded vessels. Flooding and extreme weather. Alcohol in adolescent and adult drowning. Male sex, through exposure and risk behaviour. **Epilepsy and some cardiac conditions** raise drowning risk substantially, including in baths. **No effect sizes are given for any risk factor on the WHO drowning fact sheet**.

What is genuinely not known is the effect sizes for the interventions. **WHO recommends barriers, supervised childcare and swimming instruction and gives no effect size for any of them**, which is remarkable for a condition with 300,000 annual deaths and a published investment case. The investment case figures are model outputs. The non-fatal burden, including drowning-related neurological injury, is addressed on the WHO page only through the modelled figure.

Cure status. The classification depends entirely on the interval, and that is the central fact. A rescued drowning victim who is breathing, or who is successfully resuscitated quickly: CURABLE. There is no residual condition. Water in the lungs clears, and the much-feared secondary drowning is largely a myth — a person who is well six to eight hours after immersion does not deteriorate later. A drowning victim resuscitated after prolonged hypoxia: RELIEF ONLY, for the hypoxic-ischaemic brain injury. Permanent, severe, and the reason drowning's non-fatal burden is so heavy. **The surviving child with severe neurological injury is the worst outcome of the condition, worse in burden terms than death.**

In between, the outcome is a function of minutes. This is why every item in prevention and simple means is about prevention and immediate rescue, and why there is no meaningful treatment section for the established injury.

One real exception that changes the rule: in cold-water submersion with rapid deep hypothermia, survival with intact neurology has been documented after very prolonged submersion, because the cold protects the brain. This is why prolonged resuscitation is attempted in cold-water drowning and not in warm-water drowning.

Prevention. WHO lists these interventions and says of the first two only that they greatly reduce or can reduce risk, giving no effect size for any of them.

- **Barriers and access control — STRONG.** WHO names **covering wells, doorway barriers, playpens and pool fencing**, and says these greatly reduce exposure and risk, with no effect size. The standing position in the injury-prevention literature is that **four-sided isolation pool fencing substantially reduces child drowning risk** compared with no fencing or with three-sided fencing; that was not verified against a source fetched in the retrieval round. **A well cover, a doorway barrier or a playpen costs a few dollars and is improvisable from local materials.**
- **Supervised childcare for pre-school children — STRONG.** WHO says it can reduce drowning risk, with no effect size. This is the intervention with the strongest field evidence in the high-burden settings: community crèches in rural Bangladesh that take toddlers for the high-risk daytime hours have reported very large reductions in drowning in the enrolled age group. **WHO's own investment case pairs day care with swimming instruction and projects 774,000 fewer child drownings to 2050**. Cost per child-place is low, of the order of tens of dollars per child per year in the published programme figures.
- **Basic swimming, water safety and safe rescue skills for school-age children — STRONG, with a specific caveat WHO attaches.** WHO recommends **safety-tested curricula** and gives no effect size. The evidence from the Bangladesh swimming programmes and comparable schemes supports a protective effect in the taught age group; WHO's cross-cutting injuries sheet gives swimming and rescue training in Bangladesh as returning **US$3,000 per death averted**. **The caveat matters: swimming instruction is recommended for school-age children, not as a substitute for barriers and supervision in the under-5 group, where it does not work.** A toddler who can swim a little still drowns, and teaching a young child to swim can increase exposure. Conflating the two age groups is the standard error in this field.
- **Safe rescue and resuscitation training for bystanders — STRONG** on mechanism, with no effect size given. WHO specifies "safe rescue", because **rescuer drowning is a documented and substantial cause of death** — the person who goes in after the child.
- **Boating, shipping and ferry regulation, and personal flotation devices — MODERATE**, described by WHO without quantified effects.
- **Flood early warning systems and flood risk management — MODERATE**, described without quantified effects.
- **National water safety strategies and coordinated policy** — recommended, unquantified.
- **Removing or draining unnecessary water hazards, and covering water storage vessels.**
- **Alcohol restriction around water — MODERATE** for the adolescent and adult share.
- **Treating epilepsy, and advising on bathing and swimming supervision** — a direct and cheap cross-chapter prevention.

Treatment. Treatment is rescue and resuscitation, and the window is minutes. No drug treats drowning.

1. Remove the person from the water, safely. Safely is load-bearing: **reach or throw, do not go**, because rescuer drowning is a major cause of death. A stick, a rope, a float, a boat.

2. Rescue breathing, immediately — and this is where drowning differs from cardiac arrest. Drowning is a **hypoxic** arrest, so **ventilation is the priority and should not be deferred.** Current resuscitation guidance for drowning specifies starting with **rescue breaths**, commonly five initial breaths, before chest compressions, and giving ventilations throughout — unlike the compression-only approach appropriate for adult cardiac arrest. **Compression-only bystander resuscitation is the wrong algorithm for a drowned child**, and that distinction is the most important piece of free knowledge in the entry.

3. Chest compressions where there is no pulse, with ventilations at the standard ratio.

4. Oxygen and airway management, with intubation and mechanical ventilation for those who remain unconscious or hypoxic.

5. Do not attempt to drain water from the lungs, and **abdominal thrusts are contraindicated** — they delay ventilation and cause aspiration of stomach contents. Another widely held belief that causes harm.

6. Rewarming in cold-water drowning, with prolonged resuscitation attempted because of the neuroprotection above.

7. Observation. A person who is fully well with normal oxygen saturation and no respiratory symptoms six to eight hours after immersion does not need admission. **Secondary drowning as a delayed deterioration in an asymptomatic person is not a real entity**, and reporting it as one generates unnecessary admissions and parental fear.

8. Supportive intensive care for established lung injury and for hypoxic brain injury. **No specific neuroprotective treatment has been shown to work**, and therapeutic hypothermia after drowning has not been established as beneficial.

9. Rehabilitation for the survivor with neurological injury. Relief only.

Simple means. This entry is almost entirely simple means, which is why its 38-per-cent decline since 2000 is credible and why the remaining burden is a failure of implementation rather than of technology.

- **A well cover.** Wood, metal or concrete over an open well. A few dollars, permanent.
- **A doorway barrier or a playpen.** WHO names both. A bamboo or wooden barrier at the threshold keeps a crawling toddler inside; a playpen keeps them in one place while the mother works. **Locally made from bamboo, wood or netting for a few dollars.**
- **Covering water storage vessels and draining unnecessary standing water.** Free.
- **A fence around a pond or a pool.** Four-sided isolation fencing is the evidenced form.
- **Community day care for toddlers during the high-risk daytime hours.** A room, a trained local woman, and a group of children. **Tens of dollars per child per year**, and it is the intervention WHO's investment case is built on.
- **Supervision as an explicit, assigned task** — naming who is watching, rather than assuming someone is. Free, and the toddler-drowning literature shows the lapse is usually brief and unassigned.
- **Swimming and safe-rescue instruction for school-age children**, taught in a pond or a fenced-off section of river by trained local instructors. Low cost, and WHO specifies safety-tested curricula.
- **Reach or throw, don't go.** A stick, a rope, an empty sealed plastic container as a float. **This single rule prevents rescuer drowning**, and it costs nothing to teach.
- **Rescue breathing.** Mouth-to-mouth, started at once, by anyone. **The highest-value free act in the entry.** Five initial breaths and continued ventilation — not compression-only.
- **Improvised flotation** — sealed plastic jerrycans or bottles in a net, used as life jackets on small boats in several river-transport settings.
- **Teaching that abdominal thrusts and draining water are wrong**, and that an asymptomatic child at eight hours is well.

- **A whistle, and a flood warning by radio or phone.**

The minimum chain: a well cover, a doorway barrier, an assigned pair of eyes, and the knowledge to blow into a child's mouth. Nothing in that list requires manufacture beyond local materials.

Gaps. WHO gives no effect size for any prevention measure — not for barriers, not for supervised childcare, not for swimming instruction — despite recommending all of them for a cause of 300,000 annual deaths; this is the largest evidential gap in the entry, and the gradings rest on programme evaluations and the injury-prevention literature rather than on figures from a WHO source. The investment case figures are model projections to 2050, not measured results, and the model's assumptions are not on the page. The pool fencing effect size could not be verified. **The non-fatal burden is not counted:** drowning's survivors with hypoxic brain injury — the worst outcome of the condition — appear only inside a modelled figure, and there is no measured global count. The 38 per cent rate decline since 2000 is not attributed to any intervention, and whether it reflects barriers, urbanisation, falling fertility, piped water or better reporting is not separated. Swimming instruction's age boundary is critical and routinely blurred. Rescuer drowning is named by WHO and not quantified. Ferry, small-boat and flood drowning are mentioned without figures and are likely substantially under-ascertained. The key facts and the body of the WHO page use different age cuts for the child share, and the cross-cutting injuries sheet gives a different rank for ages 5 to 14; both printed. The GBD DALY figure and the WHO death count are consistent in scale and come from different estimation frameworks.

> **Depth.** Starts in: the airway. Size: 25 cm†; depth +14.12. First complaint: about 1 minute ([B] in minutes); time depth 36.88. One untreated course: about 5 minutes ([B] in minutes); depth 38.34.
>
> **Model reading.** Way of ending: supply from outside. Layer: surround. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Poisoning

A note on the scope of this entry and its four sub-entries. These five entries report epidemiology, the **classes** of agent involved, and treatment — antidotes, decontamination and supportive care. They do not give lethal doses, do not compare agents by lethality or potency, and do not describe how exposure is achieved. Where the published prevention evidence turns on restricting access to a class of agent, the regulatory measure is reported as policy and population data and the mechanism of harm is not. This is a deliberate constraint, stated so that the omissions are not read as gaps in the evidence.

What it is. A substance taken into the body causes harm by its chemical action. It may be a medicine, an agricultural chemical, a household product, a gas, a metal, or venom from an animal. The harm may be immediate or build up over years.

Measured. GBD's poisonings external-cause death figure was not retrievable, in the current or the prior round. A WHO chemical safety page gives **unintentional poisoning deaths of 106,683 in 2016**, and states that **47 per cent of Member States have a poisons centre** as of 1 January 2023 and that **20 per cent of global suicides are due to pesticide self-poisoning**, with no year printed for the last. **The WHO poisoning fact sheet could not be read**: the URL returned a hard client error on four separate attempts and a search returned no such fact sheet, which suggests it may have been retired rather than merely being unreachable. The cross-cutting injuries and violence fact sheet gives no poisoning death total either.

Self-harm overall: **35.2 million DALYs, the 25th leading DALY cause**, and about **746,000 deaths** in 2021, 1.3 per cent of global deaths. Pesticide self-poisoning is a large component.

Lead: more than 3.5 million deaths globally in 2023, mainly from cardiovascular effects, and **more than 71.5 million DALYs**. **This is by far the largest single poisoning burden in the chapter and it dwarfs the acute poisoning figures.**

Pesticides: an estimated **1 million serious unintentional poisonings a year, plus about 2 million hospitalisations for pesticide suicide attempts**†, with the source stating these are likely undercounts. A survey in the Asian region suggested **up to 25 million agricultural workers in the developing world may**

have a poisoning episode each year. **Pesticide self-poisoning accounts for roughly one third of suicides worldwide**.

Carbon monoxide: described as the most common cause of injury and death from poisoning worldwide, and in many industrialised countries the cause of **more than 50 per cent of fatal poisonings**†. **No global figure exists.**

Snakebite: about **5.4 million bites, 1.8 to 2.7 million envenomings, and about 81,410 to 137,880 deaths each year**, with amputations and permanent disabilities roughly **three times** the number of deaths.

Where it starts. At class level:

- **Intent.** Poisoning divides into unintentional, which is overwhelmingly children and occupational; self-harm, which is overwhelmingly adults and the dominant mortality share; and occupational exposure. **The prevention evidence differs completely between them.**
- **Availability and storage.** The single most consistent determinant across all poisoning types: what is in the house, in what container, within what reach. This is the basis of the entire prevention section.
- **Occupation** — agricultural work is the dominant occupational exposure; mining, smelting, battery recycling and construction for lead.
- **Age** — under-5s for unintentional ingestion; working-age adults for self-harm and occupational exposure; children for lead's neurodevelopmental effects.
- **Poverty, informal industry, absent regulation and absent labelling.**
- **Alcohol co-ingestion** in adult self-poisoning.
- **Mental illness, acute interpersonal crisis and impulsivity** in self-harm — with the critical finding that **much self-poisoning is impulsive and low-planning**, which is why access restriction works.

What is genuinely not known is the true totals. **Every figure above is described by its own source as an undercount.** Poisoning is under-ascertained because many deaths occur at home without a cause being recorded, because self-harm is stigmatised and legally fraught in many jurisdictions, and because chronic poisoning — lead above all — is attributed to its downstream cardiovascular and neurological effects rather than to the exposure. **GBD's poisoning external-cause figure could not be retrieved at all**, which means this chapter has no verified global acute-poisoning denominator.

Cure status. Acute poisoning: CURABLE. With timely supportive care and, where one exists, an antidote, the great majority of acutely poisoned patients recover completely with no residual condition. Supportive care alone — airway, breathing, circulation, and time for the body to eliminate the substance — cures most poisoning, because most substances are eliminated. Organophosphate delayed neuropathy: RELIEF ONLY. Carbon monoxide delayed neurological effects, in up to 50 per cent of poisoned people: RELIEF ONLY once established. Snakebite tissue loss, at three times the death rate: RELIEF ONLY. Hypoxic brain injury from any poisoning causing respiratory arrest: RELIEF ONLY. Chronic lead exposure: CONTROLLABLE at best and substantially RELIEF ONLY. Removing the exposure stops further accumulation; **the neurodevelopmental deficit already caused in a child is permanent.** This is the single most important cure-status statement in the entry, because lead carries the largest burden.

Prevention. The prevention evidence for poisoning is unusually strong and it is almost entirely about **restricting access to the agent**, not about changing the person. Three measures carry nearly all of it.

1. **Pesticide regulation — STRONG, and the Sri Lanka data is the best natural experiment in the whole of injury prevention.** The figures are in the pesticide sub-entry below. As policy: successive national bans on named agents, implemented under a national pesticides control statute, with about 93,000 lives saved over twenty years at a direct government cost of under US$50 per life saved, and with national pesticide use rising over the same period.
2. **Child-resistant packaging — STRONG.** Containers that a young child cannot open within a reasonable time. The United States Poison Prevention Packaging Act of **1970** required it for specified hazardous household substances and medicines, and the subsequent surveillance literature attributes a very large fall in child poisoning deaths to it — the most commonly cited figure being a decline of the order of **45 per cent or more in child poisoning deaths** attributable to the regulation in the decades

following. **These figures are from the regulatory and surveillance literature and were not verified against a source fetched in the retrieval round**. The mechanism is a container design and **the marginal cost of a child-resistant closure is a few cents a unit**, borne by the manufacturer and requiring nothing of the household.

Related and evidenced: **blister or unit-dose packaging** of medicines, and **limits on the quantity sold in a single pack**. Both reduce the amount accessible in one episode, and national restrictions of this kind have been followed by measured falls in deaths and in liver transplant listings. WHO and the WHO and UN Environment Programme chemical safety framework recommend child-resistant packaging, safe storage and adequate labelling.

3. **Safe storage — STRONG.** Locked or out-of-reach storage of medicines, agricultural chemicals, fuels and household chemicals, keeping substances in their original labelled containers.

Other established measures:

- **Carbon monoxide alarms and appliance regulation — STRONG.**
- **Removing lead from petrol, paint, pipes, cookware, cosmetics and toys — STRONG. The global phase-out of leaded petrol, completed in 2021, is the largest single poisoning-prevention achievement in history by burden averted.**
- **Occupational controls** — personal protective equipment, training, cholinesterase monitoring, substitution of less hazardous agents, closed-transfer systems.
- **Labelling, and pictogram labelling for low-literacy settings — MODERATE.**
- **Poison information centres — MODERATE.** A telephone number staffed by people with a toxicology database prevents both under- and over-treatment. Cheap, and **47 per cent of Member States have one**, so it is absent in over half the world.
- **Means restriction as suicide prevention generally — STRONG.** The pesticide evidence is the clearest demonstration of a general principle: **restricting access at population level reduces deaths, and the reduction is not fully displaced.**
- **Reducing alcohol availability — MODERATE** for the co-ingestion share.
- **Mental health care and crisis support — MODERATE**, and much weaker as a population measure than means restriction, because much self-poisoning is impulsive.

Treatment. The general principles are here; agent-class specifics are in the sub-entries.

1. **Supportive care. This cures most poisoning and it is first, not last.** Airway protection, ventilation, oxygen, intravenous fluids, treatment of seizures, correction of acidosis and electrolytes, temperature control, and management of arrhythmia and hypotension. **Most poisons are eliminated by the body if the patient is kept alive**, and the great majority of poisoning deaths in low-resource settings are deaths from absent airway management rather than from absent antidotes.
2. **Seizure control** — lorazepam, diazepam, phenobarbital or phenytoin. All EML-listed, off-patent, cents; phenobarbital works out at about US$0.017 a tablet on October 2026 indicative prices.
3. **Decontamination, with its indications now narrow.**
   - **Skin and eye decontamination — do this, and do it early.** Remove clothing, wash with soap and water, shampoo the hair, **flush eyes with water for 10 to 15 minutes**. The dominant route of occupational pesticide exposure is the skin, so this is a high-yield measure.
   - **Activated charcoal** may reduce absorption **if given within 60 minutes**. It is not effective for all substances, and it is contraindicated where the airway is unprotected. EML-listed, off-patent, cheap.
   - **Gastric lavage — not routine.** Considered only for potentially life-threatening ingestion presenting within 60 minutes, and **contraindicated for hydrocarbons**.
   - **Syrup of ipecac — not recommended.** A settled negative, and it was standard household advice for decades.
   - **Urinary alkalinisation** — used for chlorophenoxy herbicide poisoning, **and the evidence is poor**.

   - **Haemodialysis** for specific dialysable substances.
4. **Antidotes, where one exists for the class** — see the sub-entries. **For most poisons there is no antidote**, which is why supportive care comes first.
5. **Observation and psychiatric assessment** after self-poisoning, with means restriction advice to the household as part of discharge. **This is the treatment step with the strongest prevention evidence attached and the one most often omitted.**

Simple means.

- **The recovery position and airway management by a bystander.** An unconscious poisoned person placed on their side does not aspirate. **This single free act is the highest-value simple means in the entry**, because aspiration and airway obstruction are what kill the unconscious poisoned patient before they reach care.
- **Washing the skin with soap and water, and flushing the eyes with water for 10 to 15 minutes.** The dominant occupational exposure route addressed with water.
- **Removing contaminated clothing.**
- **Removing the person from a contaminated atmosphere, without endangering the rescuer.** Carbon monoxide and other gas exposures kill rescuers.
- **Not inducing vomiting, and not giving salt water, milk or oil.** Teaching what not to do is free and prevents aspiration and delay.
- **Bringing the container.** Telling the family to bring the bottle, packet or plant to the clinic converts an unknown poisoning into a treatable one. Free.
- **Safe storage — a locked box, a high shelf, original labelled containers.** A lockable wooden box costs a few dollars. **The honest caveat: the large cluster-randomised trial of lockable household pesticide storage boxes in Sri Lanka did not demonstrate a reduction in self-poisoning**, which is an important negative and is why national bans rather than household storage carry the evidence.
- **Never decanting a chemical into a drink container.** Free, and it addresses the classic unintentional-ingestion mechanism.
- **Oral rehydration solution** for the vomiting and diarrhoea of many poisonings.
- **A poison information telephone number** written on the clinic wall.
- **Pictogram labelling** for low-literacy households.

The minimum chain: a side-lying position, water and soap, and the container brought with the patient. For the specific antidotes, manufactured drugs with no substitute — and for most poisons there is no antidote at all, so the simple means above are not second-best, they are the main treatment.

Gaps. GBD's global poisoning death figure could not be retrieved, in the current or the prior round, so the entry has no verified global acute-poisoning denominator; and **the WHO poisoning fact sheet itself could not be read on four attempts and may have been retired.** Every figure above is described by its own source as an undercount. The child-resistant packaging effect sizes could not be verified and are reported as the regulatory and surveillance literature position; for an intervention this important that is an unsatisfactory evidential basis. **The household pesticide storage box trial was negative while national bans are strongly positive**, so the level at which access restriction works is the national one, and household-level measures should not be presented as equivalent. Chronic poisoning is attributed to its downstream effects, so lead's 3.5 million deaths appear in the cardiovascular accounts and the poisoning figures understate the true burden by orders of magnitude. Gastric lavage, ipecac and urinary alkalinisation were all standard practice and are now not recommended or poorly evidenced, so older sources give the opposite advice. Occupational poisoning in informal agriculture and informal recycling is essentially unmeasured. Antidote availability, as opposed to antidote existence, is not quantified anywhere located.

> **Depth.** Starts in: the poison molecule. Size: 1 nm†; depth −3.48. First complaint: about 1 hour († minutes to hours); time depth 40.61. One untreated course: about 3 days († days); depth 44.50.
>
> **Model reading.** Way of ending: remove. Layer: surround. The book splits this entry by moment, early and late. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE,

> CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Pesticide poisoning

The constraint stated above applies in full: no lethal doses, no comparison of agents by lethality, no description of how exposure is achieved.

What it is. An agricultural chemical gets into the body. Most deaths worldwide follow deliberate self-poisoning rather than accidents at work, which is why the prevention evidence in this entry is about regulating availability rather than about treating exposure.

Measured. About **1 million serious unintentional poisonings a year, plus about 2 million hospitalisations for pesticide suicide attempts**, with the source stating these are likely undercounts. A survey in the Asian region suggested **up to 25 million agricultural workers in the developing world may have a poisoning episode each year**.

Pesticide self-poisoning accounts for roughly one third of suicides worldwide; a WHO chemical safety page gives **20 per cent of global suicides**, with no year printed. Both printed.

Canada records more than 6,000 acute poisoning cases†.

Occupational risk: agricultural workers face the highest risk, and **exposure is mainly through the skin**, with inhalation contributing in greenhouses, tractor cabs and closed spaces. Long-term exposure is linked to neurological disease, reproductive harm and some cancers, and **no global case counts** are given.

The mortality is overwhelmingly rural, agricultural, and in South and Southeast Asia, sub-Saharan Africa and parts of Latin America.

Where it starts. At class level:

- **Cholinesterase inhibitors, the organophosphates and carbamates: the most commonly reported class in occupational poisonings globally**. **Some organophosphates can cause delayed, often irreversible nerve damage**.
- **Organochlorines: persistent and bioaccumulative.** The source links one of them and its metabolite to endocrine disruption and tags that claim as needing a citation.
- **Chlorophenoxy herbicides**, relevant to treatment because of urinary alkalinisation.
- **Bipyridyl herbicides**, the class subject to the Sri Lankan restrictions of 2008 to 2011.
- **Availability in the household.** The determinant of the self-harm mortality: the agent is in the home or the field because it is an agricultural input, and the self-harm is frequently impulsive and low-planning.
- **Occupation, skin exposure, absence of protective equipment, mixing and loading, backpack sprayer leakage, re-entry to treated fields.**
- **Alcohol co-ingestion.**
- **No effect sizes are given for any risk factor on the source consulted**, apart from the prevention figures below.

What is not known is the true incidence. The headline figures date from 1990 and are described as undercounts, and the 25-million figure is a regional survey extrapolation. **Chronic health effects of long-term low-level occupational exposure are established as associations and not quantified**, which is the largest open question for the hundreds of millions of people who handle these chemicals for a living.

Cure status. Acute cholinesterase-inhibitor poisoning: CURABLE. Acute cholinergic crisis is survivable and reversible with atropine, airway management and ventilation, and a patient who survives the acute phase recovers. Deaths occur overwhelmingly where ventilators and atropine are not available and the interval to care is long. Organophosphate-induced delayed polyneuropathy, and in some agents a persistent neurobehavioural deficit: RELIEF ONLY. The source states plainly that some organophosphates can cause delayed, often irreversible nerve damage. Organochlorine and chlorophenoxy poisoning: CURABLE. Managed supportively, with recovery usual.

Prevention. This is the strongest prevention evidence in the whole of this chapter, and it comes from one country, as policy and population data.

The Sri Lankan regulatory sequence, under its Control of Pesticides Act:

Year	Measure
1984	Parathion and methyl-parathion banned
1992–1995	Methamidophos and monocrotophos banned
1998	Endosulfan banned immediately after a rise in deaths; WHO Class I pesticides and several Class II pesticides also banned from 1998
2008–2011	Dimethoate, fenthion and paraquat banned

The source gives two totals that do not agree, and both are printed: one statement says the bans resulted in **36 pesticides being phased out**; another says that as of 2018, **41 pesticides had been banned and 11 insecticides restricted**†.

The measured outcome, as population data:

- **Suicide rates rose about eight-fold from 1950 to the 1990s, peaking at 47 per 100,000 in 1995**†.
- **Pesticide poisoning accounted for more than two thirds of suicides** at that peak.
- **The overall suicide rate fell by 70 per cent over roughly two decades**†. The source gives no endpoint rate and no endpoint year. Applying 70 per cent to the 1995 peak gives about 14 per 100,000, and that is arithmetic rather than a figure from the source.
- **After the 2008 to 2011 bans, suicide rates fell by 50 per cent**†. The source does not state clearly whether this is pesticide-specific or overall.
- **About 93,000 lives saved over 20 years**†.
- **A direct government cost of less than US$50 per life saved**†.

That last figure is the single most important number in this chapter. A regulatory act, costing the government under US$50 per life saved, saved about 93,000 lives in one country over twenty years. No clinical intervention in this book approaches it.

Two further figures from the same source, reported because they address the standard objection: **pesticide use rose from 1,571 tons in 1990 to 2,260 tons in 2018**, so the bans did not reduce overall pesticide use — they removed specific agents; and **from 2002 to 2016 Class II pesticide products fell by 29 per cent**†. **In 1978, over 1,000 people died from pesticide poisoning in Sri Lanka**†. The agricultural-output question was studied, and the bans were implemented without the agricultural collapse that was predicted.

A provenance caveat, stated because it matters. The source carrying these figures **does not tie specific figures to specific studies.** Its reference list includes the relevant primary work — papers of 2007 on the impact of pesticide regulations on suicide, of 2017 on the impact of the 2008 to 2011 restrictions, of 2003 on the influence of regulation on acute poisoning deaths, of 2014 on suicide in Sri Lanka from 1975 to 2012, and of 2008 on effects on agricultural output — **and it does not state which study reports the 70 per cent decline, the 93,000 lives, or the under-US$50 cost.** Those primaries could not be fetched. The figures are reported with that provenance stated.

Other prevention:

- **Household storage boxes — NEGATIVE.** The large cluster-randomised trial of lockable household pesticide storage in Sri Lanka **did not demonstrate a reduction in self-poisoning**. **Access restriction works at the national-regulatory level and did not work at the household level in trial.** Reported as a negative because it is one.
- **Personal protective equipment and training — MODERATE. One study found a 55 per cent lower risk of acute poisoning among farmers who adopted extra protective measures and received education**.
- **Chemical-resistant gloves — STRONG for exposure. Gloves reduced contamination by 33 to 86 per cent**. A direct, measured, cheap intervention on the dominant dermal route.

- **Baseline cholinesterase monitoring** for regular users of carbamates or organophosphates, recommended, which detects exposure before symptoms.
- **Safe storage and labelling**, cited as ways to prevent accidental poisonings.
- **Bt cotton adoption in India was associated with 2.4 to 9 million fewer poisoning cases a year**† — a very wide range and an indirect mechanism, through reduced spraying.
- **Substitution with less hazardous formulations, closed-transfer systems, and restricting WHO Class I agents.** The WHO hazard classification is the instrument the Sri Lankan bans used.

Treatment. 1. Atropine, in adequate doses, for cholinesterase-inhibitor poisoning. The antidote, and the single most important drug in the entry. It reverses the muscarinic effects, and the endpoint is clearance of respiratory secretions and adequate oxygenation, reached by rapid dose escalation and then an infusion. **Under-dosing is the commonest treatment failure** in the published series. **Atropine is EML-listed under specific antidotes, for pesticide exposure**, and also under preoperative medication. Off-patent, **cents an ampoule** — and a full treatment course may require very many ampoules, so the practical constraint is stock depth at the clinic rather than unit price.

2. Airway management and mechanical ventilation. This determines survival. Respiratory failure from secretions, bronchospasm, central depression and muscle weakness is the mechanism of death, and **the 10-to-20-per-cent case fatality is largely a statement about ventilator and airway availability.**

3. Oximes — pralidoxime, obidoxime. They reactivate the inhibited enzyme in principle. **The evidence of clinical benefit is weak and contested:** randomised and quasi-randomised trials and the Cochrane review have not demonstrated a mortality benefit, and practice differs internationally. **Pralidoxime's EML status could not be confirmed** against the sections reachable. Reported as contested, not as standard. The source consulted does not discuss atropine or pralidoxime at all, which is itself notable; the atropine information above comes from the Essential Medicines List and standard toxicological practice.

4. Seizure control — lorazepam, phenytoin, phenobarbital or diazepam, with **diazepam particularly for organochlorines**. All EML-listed, off-patent, cents.

5. Decontamination.

- **Skin and eye: remove clothing, wash with soap and water, shampoo the hair, flush eyes with water for 10 to 15 minutes.** High-yield, because the skin is the main route.
- **Activated charcoal** within 60 minutes may reduce absorption, and it is **not effective for malathion**. EML-listed, off-patent, cheap.
- **Gastric lavage: not routine**, considered only within 60 minutes for life-threatening ingestion, and **contraindicated for hydrocarbons**, which many formulations are based on.
- **Syrup of ipecac: not recommended.**
- **Urinary alkalinisation** for chlorophenoxy herbicide poisoning, **and the evidence is poor** by the source's own statement.

6. Supportive care — fluids, oxygen, correction of acidosis and electrolytes, temperature control, and intensive care where available.

7. Psychiatric assessment and means restriction advice after self-poisoning.

Simple means.

- **The recovery position.** The patient is drowning in their own secretions, and **side-lying with the head dependent allows them to drain and prevents aspiration.** Free, immediate, and the highest-value bystander act.
- **Soap and water on the skin, and water in the eyes for 10 to 15 minutes.** It addresses the dominant exposure route with the cheapest possible material.
- **Removing and disposing of contaminated clothing**, including protecting the person who removes it.
- **Suctioning or wiping secretions, and positioning for drainage**, where no suction device exists.
- **Bag-and-mask ventilation.** The same self-inflating bag as the newborn resuscitation entry, costing tens of dollars, is what bridges a poisoned patient to a ventilator or substitutes for one during transport.

Hand ventilation by relays of family members has been described in the field literature as the practical reality in settings without ventilators, and it is the difference between the 10-to-20-per-cent case fatality and a much higher one.

- **Chemical-resistant gloves — reduced contamination by 33 to 86 per cent**†. A manufactured item costing a few dollars, with a measured effect on the main exposure route.
- **Bringing the container or the label.** Identifying the class determines whether atropine is indicated. Free.
- **Not giving milk, oil or salt water, and not inducing vomiting.**
- **Washing sprayer equipment away from water sources; not blowing out blocked nozzles; spraying downwind; covering the skin.**
- **Lockable storage**, with the honest caveat that the cluster-randomised trial of household storage boxes was negative, so this is reasonable practice rather than demonstrated prevention.
- **The regulatory act itself**, which is the cheapest intervention in this book at under US$50 per life saved, and which requires no supply chain at all — only a decision.

The minimum chain: a side-lying position and water as first aid; atropine ampoules and a means of ventilating for the cure. Atropine is cents and there is no substitute for it or for the airway.

Gaps. The Sri Lanka figures — the 70 per cent decline, the 93,000 lives, the under-US$50 cost per life — **are not tied to specific studies by the source consulted.** The relevant primaries are named in its reference list and could not be fetched, so the figures are reported with that provenance stated and should be verified against those primaries. The source gives two incompatible totals for pesticides banned, at 36 phased out and 41 banned with 11 restricted as of 2018; both printed. The 50 per cent fall after the 2008 to 2011 bans does not state whether it is pesticide-specific or overall, and the 70 per cent decline has no stated endpoint rate or year. The headline incidence figures are from 1990 and are described as undercounts, and the 25-million figure is a regional extrapolation. The source consulted does not discuss atropine or pralidoxime, the entry's two antidotes. Oxime benefit is unproven and contested, practice differs internationally on the same evidence, and pralidoxime's EML status could not be confirmed. The household storage box trial was negative while national bans are strongly positive, which is an important discrepancy in the level at which the intervention works. Chronic occupational exposure effects are associations without quantification, for a very large exposed population. The Bt cotton figure spans a nearly four-fold range and rests on an indirect mechanism. Urinary alkalinisation is used despite poor evidence, by the source's own statement.

> **Depth.** Starts in: an organophosphate molecule. Size: 1 nm†; depth −3.48. First complaint: about 1 hour († minutes to hours); time depth 40.61. One untreated course: about 3 days († days); depth 44.50.
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Carbon monoxide poisoning

The constraint stated above applies in full.

What it is. A colourless odourless gas produced whenever carbon burns incompletely. It binds to the blood's oxygen carrier far more tightly than oxygen does, so the blood circulates without delivering oxygen. The symptoms — headache, nausea, confusion — are mistaken for influenza, and the person does not know they are being poisoned.

Measured. Described as the most common cause of injury and death from poisoning worldwide, and in many industrialised countries the cause of **more than 50 per cent of fatal poisonings**†. **No global figure is given.**

United States, non-fire cases: more than **20,000 emergency visits a year and more than 400 deaths a year**†. A broader estimate gives more than **40,000 people a year** seeking medical attention†. Mortality figures: more than **500 unintentional deaths a year and more than 2,000 suicides a year**, with no year

stated on the source†. Between 1979 and 1988, **56,133 deaths were recorded, 25,889 of them suicides**†. About **200 deaths a year** are linked to home fuel-burning heating equipment, with no year stated.

Country examples: **New Zealand, 206 deaths in 2001 to 2002, 43.9 per cent of poisoning deaths; South Korea, 1,950 poisonings and 254 deaths from 2001 to 2003; Jerusalem, 3.53 poisonings per 100,000 people a year from 2001 to 2006; Australia, 95 per cent of carbon monoxide poisoning deaths attributed to gas space heaters**.

Cases rise in winter, largely from heating equipment, and **during power outages**, when people use fuel-burning devices indoors. **The true number is unknown because many non-lethal exposures go undetected**, by the source's own statement.

No global figure, no GBD series and no low- and middle-income data were located. Every figure above is from a high-income country.

Where it starts. At class level, the source's list:

- **Combustion heating and cooking** — furnaces, space heaters, stoves, wood-burning stoves, especially when faulty or poorly ventilated. Australia attributes 95 per cent of its deaths to gas space heaters.
- **Engines in enclosed or semi-enclosed spaces.**
- **Portable fuel-powered equipment** — propane devices and petrol-powered tools used in enclosed or semi-enclosed spaces. **Generator use indoors during a power outage is the classic cluster mechanism.**
- **Diving equipment** — faulty diving air compressors.
- **Confined natural and industrial spaces** — caves with decomposing organic matter, and coal mine afterdamp.
- **Tobacco smoke, and fires.**
- **Chemical metabolism: dichloromethane** in some paint strippers, **which the body metabolises into carbon monoxide** — an exposure route with no combustion at all. **The United States Environmental Protection Agency banned consumer use of dichloromethane in paint strippers, effective November 2019**.
- **Risk factors for delayed neurological effects: older age, loss of consciousness, and initial neurological abnormalities**.
- **No effect sizes** are given for any risk factor.

What is not known is the global burden. **There is no global figure, no retrievable GBD series, and no data from the low- and middle-income settings where solid-fuel and biomass cooking and heating are near-universal and the exposure is therefore likely highest.** The condition's epidemiology is described entirely from high-income countries with piped gas and automobiles. The source also acknowledges that the true number is unknown because non-lethal exposures go undetected, and the presentation mimics viral illness, so misdiagnosis is systematic rather than occasional.

Cure status. The acute poisoning: CURABLE. Oxygen displaces carbon monoxide from haemoglobin, and a patient treated before hypoxic injury has occurred recovers completely. The elimination is measurable: the gas's half-life falls **from about 320 minutes on room air to about 80 minutes on a non-rebreather mask, and to about 23 minutes at three atmospheres**. The delayed neurological sequelae: RELIEF ONLY, and this part is substantial. **Delayed neurological effects can develop in up to 50 per cent of poisoned people after 2 to 40 days** — cognitive impairment, personality change, movement disorder, parkinsonism. Follow-up and supportive care are often needed, and nothing reverses established injury.

A correction that must be stated, and it is a warning rather than a treatment option. The source consulted contains a sentence claiming that **an eight-to-twelve-week course of corticosteroids prevents delayed neurological effects. That sentence has no citation, the cited discussion does not support it, and the source itself flags it. It is not established practice and should not be acted on.** It is printed here only so that a reader who encounters the claim elsewhere knows its status.

Prevention.

- **Carbon monoxide alarms — STRONG, and they are the only reliable detection method because the gas has no smell.** The United States Consumer Product Safety Commission recommends at least one detector per home, preferably one per level, and states that they are as important to home safety as smoke detectors. Detectors sound an alarm at relatively high levels, allowing people to evacuate and ventilate, and **unlike smoke detectors they do not need to be near the ceiling**, because the gas mixes with air rather than rising. **The source does not report outcome studies quantifying how much detectors reduce deaths or injuries**, which is a significant gap for the entry's central intervention. **A carbon monoxide alarm costs tens of dollars and lasts years**.
- **Standards.** The 2009 edition of the relevant fire protection standard specifies: residential detectors on every level including basements and outside sleeping areas, with new mains-powered units needing battery backup and interconnection; and non-residential battery backup running notification devices for at least 12 hours, ceiling-mounted detectors in rooms with permanent fuel-burning appliances, and coverage on every habitable level and ventilation zone. **The standard is not necessarily enforced by law**.
- **Legislation — MODERATE where enacted, and patchy.** Massachusetts has required detectors in all residences with potential sources since April 2006, enforced by municipal inspectors, and **the law followed a 2005 death of a 7-year-old when snow blocked a heating vent**. Other jurisdictions may have no requirement, or may require detectors only for new construction or at sale.
- **Product regulation — STRONG where applied**, as in the 2019 dichloromethane ban.
- **Appliance measures — STRONG:** proper venting of gas appliances, cleaning chimneys, maintaining vehicle exhaust systems, and annual servicing of gas appliances.
- **Public education on safe use of heaters, generators and engines — MODERATE.** The specific messages with the highest yield: never run a generator or petrol engine indoors or in an attached garage; never use a charcoal or gas barbecue indoors; clear snow from vehicle exhausts and from heating vents.
- **No effect size is given for any of these on the source consulted**.

Treatment. 1. Remove the person from the source, without endangering others. The source states this first. **Rescuer poisoning is the documented hazard**, because the gas is undetectable.

2. Normobaric oxygen, high flow, by non-rebreather mask. The standard treatment. It shortens the gas's half-life from about 320 minutes on room air to about 80 minutes. Continue until symptoms resolve and carboxyhaemoglobin falls below about **3 per cent in non-smokers or 10 per cent in smokers**. **Pregnant patients receive oxygen for longer**, because fetal haemoglobin binds carbon monoxide more avidly and the fetus clears it more slowly. Oxygen is EML-listed and off-patent, and the cost is the cost of delivery — a concentrator, a cylinder or a piped supply. An oxygen concentrator runs on mains or solar power and removes the cylinder chain.

3. Cardiopulmonary resuscitation where the patient is unconscious and pulseless.

4. Hyperbaric oxygen — CONTESTED, and the evidence must be reported as mixed. At three atmospheres the half-life falls to about 23 minutes. **Of six randomised controlled trials comparing it with normobaric oxygen, four reported better outcomes with hyperbaric oxygen and two found no benefit, and some trials have methodological criticisms**. A 2005 review concluded the evidence neither confirms nor excludes a meaningful benefit and called for a large, well-designed multicentre trial, and two later authoritative sources state that the benefit over standard high-flow oxygen is unclear. The practical consequence: hyperbaric oxygen requires a chamber, which exists in very few places, and its benefit over the universally available alternative is not established. **The treatment that works is the high-flow oxygen above.**

5. Supportive care — intravenous fluids for hypotension, vasopressors for myocardial depression, standard advanced life support for arrhythmias, and management of seizures, pulmonary oedema and acidosis. Sodium bicarbonate for severe metabolic acidosis is controversial.

6. Follow-up for delayed neurological effects, in up to 50 per cent at 2 to 40 days. Supportive care and rehabilitation; nothing prevents or reverses them, and **the uncited corticosteroid claim above should not be acted on.**

7. Carboxyhaemoglobin measurement by co-oximetry on a blood gas. **A standard pulse oximeter reads falsely normal in carbon monoxide poisoning**, because it cannot distinguish carboxyhaemoglobin from oxyhaemoglobin. This is a trap and it belongs in the treatment section: **the reassuring saturation reading is wrong.**

Simple means.

- **Opening the windows and doors, and getting the person out into fresh air.** Free, immediate, and the first and most effective act. **Breathing air begins the elimination.**
- **Not entering an enclosed space to rescue someone without ventilating first.** Free knowledge that prevents the rescuer becoming the second casualty.
- **The recovery position** for the unconscious breathing casualty.
- **Mouth-to-mouth rescue breathing and cardiopulmonary resuscitation.**
- **Oxygen from a concentrator** — mains or solar powered, no cylinder chain. This is the actual treatment and it is close to a simple means in a clinic that has power.
- **A carbon monoxide alarm.** Tens of dollars, battery or mains, lasting years. **The gas has no smell, so there is no biological detection — the alarm is the only detection.**
- **Chimney sweeping and flue clearing.** A brush, and it addresses the dominant residential mechanism.
- **Ventilation openings in the cooking and heating space, kept unblocked.** In solid-fuel and biomass-using households this is the principal structural prevention and it costs nothing to keep clear.
- **Never running a generator, petrol engine, charcoal brazier or gas barbecue indoors or in an attached space.** A rule, taught in one sentence, that addresses the outage-cluster mechanism.
- **Keeping vehicle exhausts and heating vents clear.**
- **Suspecting it.** The presentation mimics influenza, and **a whole household with simultaneous headache and nausea is the pattern.** Asking whether others in the house are also unwell is free and is the diagnostic act.
- **Never using a charcoal or wood fire for indoor heating in a sealed room**, which is the dominant mechanism in cold-climate low-income settings.

The minimum chain: an open window and fresh air as first aid; an alarm for prevention; oxygen for treatment. The alarm is the only item that must be bought, and it is the only possible detection.

Gaps. There is no global figure. The condition is described as the most common cause of poisoning death worldwide and no global count exists in any source reached, and no GBD series was retrievable. **Every quantified figure is from a high-income country** — the United States, New Zealand, South Korea, Australia, Israel — and **there are no data from the low- and middle-income settings where solid-fuel and biomass heating and cooking are near-universal and the exposure is likely highest.** That is the largest gap in the entry. No outcome studies quantifying the effect of alarms on deaths or injuries are reported on the source consulted, for the entry's central preventive intervention. **The source contains an uncited and unsupported claim that corticosteroids prevent delayed neurological effects, flagged by the source itself, and it is printed here as a warning rather than as a treatment option.** Hyperbaric oxygen is genuinely unresolved after decades — four of six randomised trials positive, two null, methodological criticisms of some, and two authoritative reviews stating the benefit is unclear — and a definitive trial has been called for and not done. Several figures carry no year. Non-lethal exposures go undetected by the source's own statement, so all morbidity figures are floors. Delayed neurological effects occur in "up to 50 per cent", a wide and unbounded figure with no central estimate. Misdiagnosis as viral illness is systematic and unquantified.

> **Depth.** Starts in: the carbon monoxide molecule. Size: 0.11 nm†; depth −5.49. First complaint: about 30 minutes († minutes to hours); time depth 39.98. One untreated course: about 6 hours († hours); depth 42.24.

> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Lead poisoning

The constraint stated above applies in full.

What it is. Lead enters the body from paint, dust, water pipes, petrol residues, pottery glaze, cosmetics, cookware or battery recycling. It accumulates in bone over years. In a child it lowers intelligence permanently; in an adult it raises blood pressure and causes heart disease and strokes.

Measured. More than 3.5 million deaths globally in 2023, mainly from cardiovascular effects, and **more than 71.5 million DALYs lost worldwide in 2023**. Lead exposure ranks tenth among the top ten risks by health loss in 2023.

This is the largest single poisoning burden in this chapter by two orders of magnitude, and it is larger than road traffic injury deaths at about 1.16 million, falls at 684,000, drowning at 300,000 and burns at 180,000 combined.

Blood lead thresholds: **decreased intelligence, behavioural difficulties and learning problems may be associated with blood lead as low as 3.5 µg/dL in children**, and **WHO guidance recommends identifying and stopping the source of exposure at 5 µg/dL or above**†.

“There is no level of exposure to lead that is known to be without harmful effects”, verbatim.

WHO’s page states that lead can reduce IQ in children and gives no point figure. The standing figure in the literature is of the order of several IQ points lost per 10 µg/dL increment at low blood lead levels, with a steeper slope at the lowest concentrations; **no figure is asserted here**, because it could not be sourced.

WHO’s page gives no count of children with elevated blood lead. The widely cited figure of approximately 800 million children with blood lead at or above 5 µg/dL comes from a 2020 report and **was not verifiable against a source fetched in the retrieval round**, so the number of affected children is not asserted in this entry.

Main sources of exposure: mining, smelting, manufacturing and recycling; **lead-acid batteries, which account for most global lead consumption**; paint, solder, ceramic glazes, toys, jewellery, some traditional cosmetics and medicines, and lead plumbing. The routes are inhaling particles from burning lead-containing materials, and ingesting contaminated dust, soil, water or food.

Where it starts. WHO’s list, with the mechanisms it names:

- **Informal and unregulated lead-acid battery recycling.** WHO names lead-acid batteries as accounting for most global lead consumption, and informal recycling is the dominant modern point source in low- and middle-income countries.
- **Mining, smelting, manufacturing and recycling** — occupational and community exposure, including take-home dust on workers’ clothing.
- **Lead paint** — in housing stock, and still manufactured and sold in many countries.
- **Lead plumbing** — pipes, solder and brass fittings, with the leaching rate depending on water chemistry.
- **Ceramic glazes and cookware**, including lead-glazed pottery used for food and drink.
- **Some traditional cosmetics and medicines**, and **spices and foods adulterated with lead chromate for colour.**
- **Toys, jewellery and consumer goods.**
- **Contaminated soil and dust**, including the legacy of leaded petrol, which persists in urban soils for decades after the fuel is withdrawn.

- **Age: children absorb a far higher fraction of ingested lead than adults, and the developing brain is the vulnerable organ.** Hand-to-mouth behaviour and pica raise intake.
- **Nutritional status: iron and calcium deficiency increase lead absorption** — so the anaemic child absorbs more lead, which is a direct interaction between two entries in this book.
- **No effect sizes are given for any risk factor on the WHO page.**

What is not known is the shape of the dose-response at the lowest levels, which is the question that matters most. **WHO states there is no known safe level**, and the evidence is that the IQ slope is steepest at the lowest blood lead concentrations — meaning the harm per microgram is greatest where exposure is lowest, and there is no threshold to aim for. That makes the condition unusual: **the policy target is zero and there is no defensible intermediate standard.** Also not known: how much of the 3.5 million cardiovascular deaths is attributable to current against historical exposure, since bone lead is a decades-long internal reservoir.

Cure status. This must be stated plainly because it is the central fact of the entry and it is widely misunderstood. What has already happened: RELIEF ONLY. **The neurodevelopmental deficit in a child who has been exposed is permanent.** Lowered IQ, attention and behavioural problems, and reduced educational attainment do not reverse when the exposure stops and do not reverse with chelation. **No treatment recovers lost cognitive capacity.** Further accumulation: CONTROLLABLE. Removing the exposure stops it — which is why WHO's guidance at 5 µg/dL is to **identify and stop the source**, not to treat the child. That is control, not cure.

Chelation lowers blood lead and is used for severe poisoning. **It has not been shown to improve cognitive outcomes:** a randomised trial of succimer in children with moderately elevated blood lead **lowered blood lead and produced no improvement in cognitive, behavioural or neuropsychological outcomes**. **This is the decisive negative result in the entry and it is why lead poisoning is a prevention problem and not a treatment problem.** That finding is reported as the standing literature position; it is not on the WHO page and was not verified against the primary.

The adult cardiovascular burden — the 3.5 million deaths — follows from accumulated exposure and is addressed by treating the hypertension and cardiovascular disease, not the lead.

Prevention. Everything of value in this entry is here. Lead poisoning is the clearest case in the book of a condition where regulation is the whole of medicine.

- **Removing lead from petrol — STRONG, and it is the largest completed poisoning-prevention achievement in history by burden averted.** The global phase-out was **completed in 2021**, when the last country ceased sales. Population blood lead levels fell by large multiples in every country that did it — the United States recorded a fall of roughly 80 per cent in mean child blood lead across the 1976 to 1991 period spanning its phase-out†. **The figures could not be verified against a source fetched in the retrieval round** and are reported as the standing position. **The intervention was a regulatory act with no clinical component.**
- **Eliminating lead paint — STRONG.** WHO and the UN Environment Programme's alliance works toward legally binding controls in every country; a substantial number of countries still have none, and lead paint continues to be manufactured and sold. **The cost of reformulating paint is small and the measure is purely regulatory.**
- **Regulating and formalising lead-acid battery recycling — STRONG, and it is the highest-yield remaining action.** WHO names lead-acid batteries as most of global lead consumption. Informal recycling — smelting batteries in residential areas, often with children present — is the dominant modern point source. The measures are producer responsibility, licensed recycling, and closing informal smelters.
- **Removing lead plumbing, and controlling water chemistry where it remains — STRONG.** Pipe replacement, with corrosion control as the interim measure.
- **Regulating ceramic glazes, cookware, cosmetics, toys, jewellery and spices — STRONG** where enforced.

- **Occupational controls — STRONG.** Enclosure, ventilation, respiratory protection, changing facilities and laundering of work clothes on site to prevent take-home dust, and blood lead monitoring with removal from exposure above action levels.
- **Blood lead screening of children in high-risk areas — MODERATE**, as a case-finding tool, with the explicit purpose of finding and removing the source rather than treating the child.
- **Soil remediation, dust control, wet cleaning and hand-washing before eating — MODERATE** in contaminated areas.
- **Correcting iron and calcium deficiency — MODERATE.** It reduces lead absorption and it is cheap.
- **WHO's framing is explicit: identify and stop the source of exposure**. The prevention is the treatment.

Treatment. The honest ordering is source removal first, chelation a distant second. **1. Identify and remove the source of exposure.** WHO's recommendation at 5 µg/dL and above. **This is the treatment.** It is an environmental and regulatory act rather than a clinical one, and for the whole household and often the whole neighbourhood rather than the individual child.

2. Nutritional support — iron and calcium repletion, which reduces further absorption. EML-listed, off-patent, about a cent a tablet for iron on October 2026 indicative prices.

3. Chelation therapy, for severe poisoning — encephalopathy and very high blood lead. The agents are **succimer** orally, **sodium calcium edetate** parenterally, and **dimercaprol** for lead encephalopathy, given with edetate. **Dimercaprol and sodium calcium edetate are on the WHO Essential Medicines List under specific antidotes**. Off-patent, moderate cost, with availability the constraint. **The indication is severe poisoning, not moderate elevation:** the randomised trial above showed that chelating children with moderately elevated blood lead lowers the blood level and does not improve cognitive outcome. **Chelation is therefore not a treatment for the harm; it is a treatment for acute severe toxicity.** It carries real risks — nephrotoxicity, redistribution of lead to the brain with some agents, mineral depletion — and **chelation without removing the source is futile, because the child returns to the exposure.**

4. Supportive treatment of lead encephalopathy — seizure control, management of raised intracranial pressure, intensive care.

5. Treating the consequences — anaemia, hypertension and cardiovascular disease in adults, and educational and behavioural support for affected children. Relief, and it is where most of the lifetime cost falls.

6. Developmental and educational assessment and support for affected children. The permanent deficit is managed rather than cured, and early educational intervention is the only measure with a demonstrated effect on functional outcome.

Simple means.

- **Hand-washing before eating, and wet-wiping surfaces rather than dry sweeping.** Lead reaches children as dust on hands and food. Soap and a damp cloth, and in contaminated housing this is a real and measurable reduction in intake.
- **Wet mopping; damp dust control; removing shoes at the door; covering bare contaminated soil with grass, matting or clean soil.**
- **Not storing or cooking acidic food in lead-glazed pottery**, and not using leaded cookware. Free knowledge.
- **Workers changing and washing clothes before going home.** Take-home dust is a documented route to the worker's own children, and the countermeasure is a change of clothes and a wash.
- **Moving informal battery smelting away from homes and away from children** — and the honest statement is that the real measure is closing it, which is regulatory.
- **Iron-rich food and iron supplementation**, which reduces absorption and costs about a cent a tablet.
- **Breastfeeding and adequate nutrition generally.** A well-nourished child absorbs less.

- **Keeping children away from renovation and paint-stripping work**; wet-sanding rather than dry-sanding; not burning painted wood.
- **Running the tap before drinking where lead pipes are present**, and using cold water for drinking and cooking.
- **Avoiding lead-containing traditional cosmetics and medicines** — a conversation.
- **Checking what is in the house:** pottery, cosmetics, spices, paint, imported cookware.

What the chain minimally requires, stated plainly: nothing manufactured — and also, almost nothing that a household can do is sufficient. The simple means above reduce intake at the margin. **The interventions that produced the measured reductions in population blood lead were national regulatory acts: removing lead from petrol, from paint, from pipes and from recycling.** This is the entry where simple means matter least and policy matters most, and saying otherwise would misdirect effort.

Gaps. WHO gives no IQ point figure despite stating that lead reduces IQ in children: the dose-response figure most needed for policy is not on the page, and the literature figure could not be verified. WHO gives no count of children with elevated blood lead, and the widely cited figure of about 800 million could not be verified, so the number of affected children is not asserted here. The leaded petrol phase-out effect figures could not be verified and are reported as the standing position. The chelation trial finding is not on the WHO page and was not verified against the primary, and it is nonetheless the decisive statement for the entry's cure status. The dose-response at the lowest exposures is unresolved and WHO states there is no known safe level, so there is no defensible intermediate standard. The split between current and historical exposure in the 3.5 million cardiovascular deaths is not separated, because bone lead is a decades-long reservoir. The 3.5 million deaths are an attributable-burden estimate overlapping with the cardiovascular cause counts, and cannot be added to them. **WHO's two thresholds differ** — harm associated from 3.5 µg/dL, action recommended at 5 µg/dL — which is a policy gap rather than an evidential one and follows from there being no threshold. Lead burden is attributed to its downstream effects in the cause-of-death accounts, so it is invisible in the poisoning figures and visible only in the risk-factor accounts. No cost or cost-effectiveness figure for any lead intervention was located, for the largest poisoning burden in the chapter.

> **Depth.** Starts in: the lead atom. Size: 0.35 nm†; depth −4.43. First complaint: about 2 years ([B] builds up over years); time depth 49.50. One untreated course: no number ([B] permanent in a child).
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The bound applies. Lead is stored in bone. In a child the damage to the brain stays. So it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Snakebite envenoming

The constraint stated above applies in full, including no comparison of species by lethality.

What it is. A venomous snake bites, usually a farmer or a child in a rural area. The venom destroys tissue around the bite, or stops the blood clotting, or paralyses the breathing muscles. Treatment is an antiserum made by immunising horses or sheep, and in most of the places where the bites happen it is not available.

Measured. About 5.4 million people are bitten by snakes each year. Envenomings: **1.8 to 2.7 million cases** a year. Deaths: **about 81,410 to 137,880 each year. Amputations and permanent disabilities: roughly three times the number of deaths each year** — so of the order of 250,000 to 400,000 people permanently disabled annually. **The disability burden exceeds the mortality burden threefold, which is unusual among the entries in this chapter.**

Geography: most cases in Africa, Asia and Latin America. **Asia has up to 2 million envenomings a year. Africa has an estimated 435,000 to 580,000 bites a year that need treatment. The highest burden falls where health systems are weakest**.

Most affected: agricultural workers, children, women, and farmers in poor rural communities in low- and middle-income countries. **Children often suffer more severe effects**.

The WHO 2030 target is a 50 per cent reduction in snakebite envenoming mortality and disability, pursued through four objectives — empowering communities, ensuring safe and effective treatment, strengthening health systems, and increasing partnerships and resources. Snakebite envenoming was added to the WHO list of neglected tropical diseases in 2017, which is the institutional marker of how long it was absent from the global health agenda.

Where it starts. Agricultural work. Barefoot or sandalled work in fields, especially planting and harvesting, and especially in the rainy season. The exposure is occupational and it is unavoidable for the people who have it. **Walking at night without a light. Sleeping on the floor**, the dominant mechanism for bites by nocturnal species that enter dwellings, and the reason bed nets have an effect. **Children**, who have smaller body mass for a given envenoming and whom WHO states often suffer more severe effects. **Housing** — thatch, mud walls, stored grain and rodent presence, which attract snakes. **Monsoon and flooding**, which displace snakes into human dwellings and produce seasonal peaks. **Distance from a facility holding antivenom**, which is the determinant of outcome rather than of risk. **No effect sizes are given for any risk factor on the WHO page**.

What is not known is the true numbers. **The ranges WHO publishes are very wide — envenomings 1.8 to 2.7 million, deaths 81,410 to 137,880, a 1.7-fold span on mortality**† — because most deaths occur at home in rural areas without registration, and because many bitten people go to traditional healers and are never recorded. India's community-based mortality surveys have repeatedly found snakebite deaths an order of magnitude above official hospital-based figures, which is the best illustration available of how the under-ascertainment works. **The species distribution responsible for the burden is also incompletely mapped in much of Africa**, which matters directly because antivenoms are species- and region-specific.

Cure status. Systemic envenoming: CURABLE with antivenom. **Antivenom works and it works dramatically.** Neurotoxic envenoming with respiratory paralysis reverses — a patient being hand-ventilated regains breathing. Haemotoxic envenoming with incoagulable blood corrects. The effect is one of the clearest in medicine, and **it is time-dependent**: the earlier the antivenom, the more of the envenoming is reversible. Tissue already destroyed: RELIEF ONLY. Local necrosis, compartment syndrome and the limb loss that follows are established before or despite treatment, and **the amputations and permanent disabilities at three times the death rate are the measure of it.**

And the first classification is conditional on a supply that is failing. WHO's own account is that antivenom availability has declined or disappeared in some areas, that manufacturers have left the market, and that **many believe antivenom supply failure is imminent in Africa and parts of Asia**. **A condition is only curable if the cure exists where the patients are**, and for snakebite that is increasingly not the case.

Prevention.

- **Footwear — STRONG on mechanism, unquantified.** Boots or closed shoes for field work. **No effect size is given on the WHO page** and none was located. **Cost: a pair of boots.** The intervention is obvious, cheap and almost completely unstudied, which is itself a finding.
- **Sleeping on a raised bed, and using a bed net tucked in — MODERATE.** The bed net, distributed for malaria, is also a snakebite intervention for nocturnal species that enter dwellings. A rare case of one cheap item serving two unrelated conditions.
- **A torch or lamp when walking at night — MODERATE** on mechanism, unquantified.
- **Clearing vegetation and rubble around dwellings; controlling rodents; storing grain away from living space — MODERATE.** It removes what attracts snakes.
- **Not reaching into holes, under rocks or into grain stores without looking; using a stick ahead on paths — MODERATE.**
- **Community education.** WHO's first strategic objective is empowering communities, which in practice means teaching avoidance, correct first aid, and the necessity of going to a facility rather than a traditional healer. Unquantified.
- **Occupational measures** — protective clothing and timing of fieldwork.

- **WHO gives no effect size for any preventive measure**. For a condition with up to 137,880 annual deaths, the entire prevention evidence base is mechanism and plausibility.

Treatment. 1. Antivenom — the treatment, and the supply problem is the entry's defining feature. The mechanism is antibodies raised in horses or sheep against the venoms of the species of the region, which bind and neutralise circulating venom. **It must match the species or species group of the region:** an antivenom raised against Indian species does not reliably treat African envenoming. This is why antivenom is not one product and why the market fragments.

Antivenom immunoglobulin appears on the WHO Essential Medicines List under sera and immunoglobulins, and the snake-specific wording was not visible in the sections reachable. It is off-patent: these are biological products whose constraint is manufacturing capacity and venom supply, not patent. **WHO states that the price of some antivenom products has dramatically increased in the last 20 years, making treatment unaffordable for most people who need it, and gives no price figure**. Published figures for a full treatment course in sub-Saharan Africa have been reported in the range of tens to several hundred US dollars, often many times a household's monthly income, and **no figure is asserted here**.

Adverse reactions — early anaphylactoid reactions and late serum sickness — are common and manageable with adrenaline and antihistamines, and the fear of them is one reason antivenom is withheld. **Adrenaline must be drawn up before antivenom is given**, which is a procedural rule with a fatal failure mode.

The supply problems, in WHO's own terms:

- **Very few countries can produce snake venoms of adequate quality for antivenom manufacture, and many manufacturers rely on common commercial sources.**
- **Low demand has led several manufacturers to stop production.**
- **Antivenom availability has declined or disappeared in some areas.**
- **Inappropriate, untested or fake products have undermined confidence in antivenom therapy.** This is the mechanism of market collapse: ineffective products are sold, clinicians observe that antivenom does not work, demand falls further, and manufacturers exit.
- **Many believe antivenom supply failure is imminent in Africa and parts of Asia.**

2. Airway management and mechanical ventilation for neurotoxic envenoming with respiratory paralysis. **This is life-saving independent of antivenom** — a paralysed patient who is ventilated survives until the venom is cleared or neutralised, and **hand ventilation with a bag and mask has sustained patients for hours in field reports**.

3. Supportive care — intravenous fluids, transfusion and blood products for coagulopathy, renal replacement therapy for acute kidney injury, which is a major cause of death and of long-term morbidity after some envenomings, and management of shock.

4. Wound care, debridement and fasciotomy where indicated for compartment syndrome — with the caveat that fasciotomy is over-performed and should follow measured compartment pressures and correction of coagulopathy rather than clinical impression alone.

5. Tetanus prophylaxis. A bite is a tetanus-prone wound. EML-listed, off-patent, cents.

6. Antibiotics only for established infection, not prophylactically.

7. Analgesia — paracetamol and opioids. **Non-steroidal anti-inflammatory drugs are avoided** in haemotoxic envenoming because of the bleeding risk.

8. Rehabilitation, prosthetics and physiotherapy for the survivors with tissue loss — the group three times larger than the dead.

9. Psychological support. Post-traumatic symptoms after snakebite are documented and untreated.

Simple means.

- **Reassure, immobilise, and transport. The whole of correct first aid.** Keep the patient calm and still, immobilise the bitten limb with a splint or sling in a neutral position, keep it at or below heart level, and move the patient to a facility as fast as possible. **It costs nothing.**
- **Pressure immobilisation bandaging** — a broad firm bandage over the bitten limb plus a splint, for neurotoxic envenoming where transport will be prolonged. The evidence is strongest for Australian elapid bites and the technique is harder to apply correctly than it appears; **it is not recommended where local necrosis is expected**, because it concentrates the venom.
- **Removing rings, bangles and tight clothing** before swelling. Free, and it prevents digital ischaemia.
- **What not to do, and this is the highest-value free knowledge in the entry: no tourniquet, no cutting, no sucking, no suction devices, no electric shock, no ice, no cautery, no herbal application, no black stone, and no attempt to catch or kill the snake. Every one of these is harmful and all are widely practised.** Tight arterial tourniquets cause limb loss and contribute to the amputation figure above. **Teaching their abandonment is free and prevents disability.**
- **A photograph of the snake if it is already dead, from a safe distance.** Identification guides treatment and costs nothing. **Not pursuing the snake.**
- **Bag-and-mask ventilation.** The same self-inflating bag as the newborn resuscitation entry, costing tens of dollars. **A relay of family members hand-ventilating a paralysed patient is a documented practice and it keeps people alive without a ventilator and without antivenom.** For neurotoxic envenoming this is the single most valuable low-cost intervention available.
- **Organised transport** — a motorcycle, a phone number, a stretcher.
- **Boots, a torch, a tucked-in bed net, a raised bed, and a cleared yard** — the prevention, all of it cheap.
- **Knowing which facility holds antivenom**, and going there rather than to a nearer one that does not. A piece of local information that determines survival.
- **Not going to a traditional healer first.** The measured determinant is the interval to antivenom, and the detour is the commonest cause of its loss.

The minimum chain: a splint, calm, and transport as first aid; a bag and mask to sustain a paralysed patient; and antivenom, for which there is no substitute and whose supply is failing.

Gaps. The ranges are very wide — envenomings 1.8 to 2.7 million and deaths 81,410 to 137,880, a 1.7-fold span — because deaths occur at home and are not registered, and community surveys find figures an order of magnitude above hospital-based ones. **WHO gives no price for antivenom** while stating that prices have risen dramatically and that treatment is unaffordable for most who need it, so the central economic fact of the entry is unquantified. **WHO gives no effect size for any preventive measure:** footwear, torches and bed nets are recommended on mechanism alone, and for a condition of this size the prevention evidence base is essentially empty, which is a research gap rather than an evidential ambiguity. Antivenom supply failure is described as imminent in Africa and parts of Asia and is not quantified, with no figures for manufacturing capacity, market size or the number of facilities holding stock. Fake and untested products have undermined confidence and their market share is unquantified. The species distribution driving the burden is incompletely mapped in much of Africa, which directly limits antivenom development and procurement. The disability burden has no breakdown by type, limb or cause — venom necrosis against tourniquet against fasciotomy — so the preventable iatrogenic share is unknown. Pressure immobilisation bandaging's evidence is largely Australian and its applicability to African and Asian envenoming with local necrosis is contested. No cost-effectiveness analysis of antivenom provision was located, for a condition with a WHO 2030 target attached, and that target has no published baseline year on the fact sheet.

> **Depth.** Starts in: a venom protein. Size: 5 nm†; depth −2.01. First complaint: about 1 hour († minutes to hours); time depth 40.61. One untreated course: about 3 days († days); depth 44.50.
>
> **Model reading.** Way of ending: remove. Layer: surround. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Traumatic brain injury

What it is. A blow or jolt to the head damages the brain. The injury at the moment of impact is one thing; the swelling, bleeding and oxygen starvation over the following hours is another, and that second part is what treatment addresses. Most are mild and recover; the severe ones kill or disable permanently.

Measured. No global annual incidence figure, no global death count and no global DALY figure were located. The condition is described as a leading cause of death and disability around the globe without a number. Every quantified figure below is from a single high-income country or region.

United States: about **2 million people have a traumatic brain injury each year**, with roughly **675,000 emergency department visits and 500,000 hospitalisations**†.

Yearly incidence per 100,000: **180 to 250 in the United States; 281 in France; 361 in South Africa; 322 in Australia; 430 in England**†. **The European aggregate incidence of hospitalisations and fatalities is 235 per 100,000**†. **Mild traumatic brain injury incidence may be 100 to 600 per 100,000 a year**†.

Global incidence is rising, largely because of motor vehicle use in low- and middle-income countries Case fatality: **about 21 per cent by 30 days in the United States**†. Severe injury mortality in Iraq War soldiers was 30 to 50 per cent†. **The fraction of hospitalised patients who died fell from almost half in the 1970s to about a quarter in the early 2000s**†.

Severity split: a WHO study estimated **70 to 90 per cent of treated head injuries are mild**, and a United States study found moderate and severe injuries each make up 10 per cent with the rest mild.

Causes: in the United States the most common are violence, transportation accidents, construction mishaps and sports. **Falls are the leading cause in children aged 2 to 4**, with traffic accidents competing in older children†. **Abuse causes 19 per cent of paediatric brain trauma cases**†. Data for 2021 to 2025 show people aged 75 and over had the most deaths and hospitalisations†.

Sex: **men have about twice the rate of women and a fourfold risk of fatal head injury**. **Traumatic brain injury causes more years of disability in Europe than any other cause** — a statement of relative burden without a figure.

Where it starts. Falls, the leading cause in young children and in people over 75. Road traffic injury, with the rising global incidence attributed to motor vehicle growth in low- and middle-income countries. Violence, including firearms. **Child abuse, at 19 per cent of paediatric brain trauma**†. Sport and recreation; occupational injury including construction; military blast exposure. Male sex, at about twice the rate and fourfold fatal risk. The age extremes. Alcohol. Not wearing a helmet or a seat belt. Previous traumatic brain injury raises the risk of another.

A great deal is not known, and the gaps are consequential.

- **Why no treatment for the primary injury has succeeded.** Dozens of neuroprotective agents have reached phase III and failed. The primary injury is mechanical and immediate; the secondary cascade is understood in outline and has not proved druggable.
- **The relationship between repeated mild injury and chronic traumatic encephalopathy.** The association is established in autopsy series of exposed athletes, and the incidence, dose-response and attributable risk in the exposed population are not.
- **Why mild injury leaves a minority with persistent symptoms** while most recover in three weeks. No biomarker or imaging finding predicts it.
- **The global burden is not measured at all.** For a condition described as a leading cause of death and disability worldwide, the absence of a global figure is the single largest data gap in this chapter.

Cure status. Mild injury: SELF-LIMITING. **Most mild traumatic brain injury resolves within three weeks**. **Permanent disability is estimated at 10 per cent for mild injuries**, so a tenth do not, and nothing identifies them in advance. Moderate and severe injury, for the established injury: RELIEF ONLY. **Permanent disability is estimated at 66 per cent for moderate and 100 per cent for severe injuries**. Nothing reverses the damage, and everything in treatment limits the **secondary** injury — the swelling, raised pressure and hypoxia over the following hours.

What mitigation achieves is nonetheless large and measurable: **the fraction of hospitalised patients who died fell from almost half in the 1970s to about a quarter in the early 2000s**†, achieved by intensive care, surgery and systematised trauma management rather than by any treatment for the brain itself.

Recovery continues longer than is often assumed: **neurological improvement usually continues for two or more years after injury**. **Over 90 per cent of people with moderate injury live independently, and most people with severe closed head injury either die or regain independent living** — a bimodal outcome. Coma is a strong predictor of poor outcome, and subarachnoid haemorrhage roughly doubles mortality.

Prevention. Prevention of traumatic brain injury is prevention of its causes, and the effect sizes come from the road traffic injury and falls entries.

- **Helmets — STRONG. Correct helmet use reduces the risk of death in a crash by more than 6 times and the risk of brain injury by up to 74 per cent**. **The source consulted for this entry gives no quantified effect sizes for helmets or seat belts**, noting only that seat belts, child seats and motorcycle helmets reduce damage and that appropriate helmet use reduces incidence. **The 74 per cent figure is WHO's and is the number to use.**
- **Seat belts — STRONG. Up to 50 per cent reduction in occupant death. Child restraints — 71 per cent reduction in infant deaths**.
- **Speed management — STRONG.** One per cent more mean speed gives 4 per cent more fatal crash risk.
- **Vehicle safety laws — STRONG.** They have reduced traffic-related brain injury in high-income countries since the 1970s.
- **Fall prevention — STRONG** — exercise and balance training, psychotropic drug withdrawal, home modification, and window guards for children.
- **Restricting access to the means of injury — STRONG** where a population-level restriction has been evaluated. This is the same principle as the pesticide data, and the evidence for it is the measured fall in total deaths after a restriction, without full displacement.
- **Child abuse prevention — MODERATE** for the 19 per cent paediatric share; home visiting and parenting programmes have the evidence, and WHO's cross-cutting injuries sheet gives home visitation as returning **US$6 for every US$1** spent.
- **Sport rule changes, limiting contact exposure in youth sport, and graduated return-to-play protocols — MODERATE.** Rule changes such as banning head contact and limiting contact practice have measured effects on concussion incidence; whether they reduce long-term neurodegeneration is unknown.
- **Workplace fall protection and helmet requirements — MODERATE.**
- **Alcohol policy — MODERATE.**

Treatment. The single largest positive drug result is confined to a subgroup, and several once-standard treatments are now known to be harmful.

1. **Tranexamic acid within 3 hours — effective in mild-to-moderate injury, null overall.** The CRASH-3 trial randomised **12,737 patients** at 175 hospitals in 29 countries, recruiting from July 2012 to January 2019, with **9,127 analysed within 3 hours of injury** — 4,613 on tranexamic acid and 4,514 on placebo.
   - **Primary outcome, 28-day in-hospital head-injury death, treated within 3 hours: 18.5 per cent against 19.8 per cent. Relative risk 0.94 (95 per cent CI 0.86 to 1.02) — not statistically significant**†.
   - **Mild-to-moderate injury, Glasgow Coma Scale 9 to 15, a prespecified subgroup: 5.8 per cent against 7.5 per cent. Relative risk 0.78 (0.64 to 0.95). The source notes this may be a type I error**.
   - Severe injury: no separate severe-only relative risk is given, and the closest subgroup, excluding a Glasgow Coma Scale of 3 or bilateral unreactive pupils, showed **12.5 per cent against 14.0 per cent, relative risk 0.89 (0.80 to 1.00)**. **Timing had no effect in severe injury**.

  - Timing: under 1 hour, relative risk 0.96 (0.79 to 1.17); 1 to 3 hours, 0.93 (0.85 to 1.02). **Earlier treatment was more effective than later in mild-to-moderate injury, p = 0.005**†.
  - Vascular occlusive events: 1.6 per cent in both groups. Seizures: 3.2 against 3.0 per cent. No safety signal.

The honest summary: CRASH-3 was null on its primary outcome and positive in a prespecified mild-to-moderate subgroup, with the trial's own summary noting the subgroup result may be a false positive. That is a weaker result than CRASH-2 in general trauma, where the all-cause mortality effect was significant at a relative risk of 0.91 (0.85 to 0.97)†. Tranexamic acid is EML-listed, off-patent, **a few US dollars a gram**. The source consulted for this entry states only that tranexamic acid given within three hours of head injury decreases the risk of death, and **does not name CRASH-3**.

2. **Prevention of secondary injury — the core of management.** Maintaining oxygenation and blood pressure, avoiding hypoxia and hypotension, each of which independently worsens outcome, controlling intracranial pressure, maintaining cerebral perfusion pressure, and treating fever and seizures. **These are process measures rather than products, and they carry most of the mortality improvement above.**
3. **Surgical evacuation of an extradural or subdural haematoma. Time-critical and definitively life-saving** — an extradural haematoma evacuated early produces full recovery, and left alone it kills a patient whose brain was otherwise undamaged. **This is the clearest curative surgical intervention in the entry.** It requires neurosurgical capacity, or in its absence a trained general surgeon performing burr-hole drainage, which is done in some low-resource settings.
4. **Osmotic therapy — hypertonic saline or mannitol**, which appear similarly effective for intracranial pressure. Mannitol is EML-listed, off-patent, cheap.
5. **Decompressive craniectomy — CONTESTED.** Primary decompressive craniectomy is performed routinely during haematoma surgery. Secondary decompressive craniectomy, done for persistently raised intracranial pressure, lowers the pressure and shortens intensive care stay. **Compared with standard medical therapy, however, it is associated with worse Glasgow Coma Scale scores and higher rates of death, vegetative state or severe disability**. **That is the DECRA finding and it must be reported: the operation controls the pressure and the patients do worse.** The later RESCUEicp trial found lower mortality with more survivors in dependent states. **The trials disagree on the direction of benefit, and both are printed.**
6. **Seizure prophylaxis and treatment** — phenytoin or levetiracetam for early post-traumatic seizures. EML-listed, off-patent, cheap.
7. **Negative and harmful results, reported as such because they were once standard.**
   - **Corticosteroids are linked to higher death risk and are not recommended.** The CRASH trial of methylprednisolone in head injury, reported in **2004, found increased mortality** and ended decades of routine use. A definitive and important negative.
   - **Hypothermia** is not discussed on the source consulted, which notes only that body temperature is carefully regulated because fever raises metabolic demand. The trial literature on therapeutic hypothermia in traumatic brain injury has been null or negative for benefit.
   - **Hyperventilation**, once routine for raised intracranial pressure, causes cerebral ischaemia and is now restricted to brief use for impending herniation.
   - Some data support hyperbaric oxygen; the evidence is weak and it is not standard.
8. **Rehabilitation** — physical, occupational, speech, cognitive and behavioural. Neurological improvement usually continues for two or more years, so rehabilitation has a long window. This is where most of the function is recovered and where provision is thinnest.

Simple means.

- **A helmet. Up to 74 per cent reduction in brain injury risk and more than 6-fold reduction in death risk**. **This is the single highest-value item in the entry and in much of this chapter** — a manufactured object costing tens of dollars, requiring no infrastructure.
- **A seat belt and a child restraint.**

- **The recovery position**, for the unconscious breathing casualty. It prevents the aspiration and airway obstruction that cause the hypoxia that causes the secondary injury. **Free.**
- **Manual in-line stabilisation of the head and neck, and not moving the casualty unnecessarily.**
- **Keeping the airway clear and the patient breathing**, with bag-and-mask ventilation where needed. **Avoiding hypoxia and hypotension is the single most important thing done for a head-injured patient before they reach hospital**, and both are addressed with positioning, airway clearance, ventilation and fluids.
- **Elevating the head of the stretcher about 30 degrees**, where there is no spinal injury. Free, and it lowers intracranial pressure.
- **Observation and the warning signs.** A patient sent home after a head injury, with a written list — worsening headache, repeated vomiting, drowsiness, confusion, weakness, unequal pupils, seizure — and an instruction to return. **Free, and it is what detects the extradural haematoma in time for the surgery above.**
- **The Glasgow Coma Scale.** A bedside score requiring no equipment, which stratifies severity, guides transfer and is the entry criterion for most of the evidence above. **A laminated card.**
- **Pupil examination with a torch.**
- **Not giving alcohol or sedatives**, and documenting the level of consciousness serially so that deterioration is visible.
- **Organised transport to a facility with surgical capacity**, which is the determinant for the haematoma cases.
- **Rehabilitation delivered by family, taught by a therapist once** — range of movement, positioning, swallowing safety, graded activity, cognitive routine. Labour rather than technology, and in most of the world it is the only rehabilitation available.
- **Avoiding a second impact before recovery** in sport. A rule, and free.

The minimum chain: a helmet for prevention, a side-lying position and a clear airway for first aid, and a written list of warning signs on discharge. For the haematoma, surgery, with no substitute — and burr-hole drainage by a trained general surgeon is the low-resource form of it.

Gaps. There is no global incidence figure, no global death count and no global DALY figure, for a condition described as a leading cause of death and disability worldwide; **this is the largest data gap in this chapter**, and every quantified figure above is from a single high-income country or region. The source consulted gives no helmet or seat belt effect sizes, and those come from WHO. CRASH-3 was null on its primary outcome and its positive mild-to-moderate subgroup result is flagged by the trial's own summary as possibly a type I error, so it should not be reported as a straightforward positive. **Decompressive craniectomy: DECRA found worse outcomes and RESCUEicp found lower mortality with more dependent survivors; the trials disagree and both are printed.** No treatment for the primary injury exists, after dozens of failed phase III neuroprotection trials. The repeated-mild-injury and chronic traumatic encephalopathy relationship is unquantified — association established in selected autopsy series, with incidence and attributable risk unknown. Nothing predicts which 10 per cent of mild injury will not resolve. The permanent disability figures of 10, 66 and 100 per cent are from one source and are very round, and "100 per cent for severe" is a definitional statement as much as a measurement. Several figures carry no year. Hypothermia is not discussed on the source consulted despite being a major trial question. Long-term outcome and rehabilitation provision in low- and middle-income countries, where the rising incidence is, are essentially unmeasured.

> **Depth.** Starts in: the brain at the moment of impact. Size: 15 cm†; depth +13.66. First complaint: about 1 second ([B] at the moment of impact); time depth 33.15. One untreated course: about 3 weeks ([B] most mild injury resolves within three weeks); depth 46.27.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book splits this entry by moment, early and late. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Spinal cord injury

What it is. The spinal cord is damaged, so signals no longer pass between the brain and the body below the injury. Movement and sensation are lost below that level, and so is control of the bladder and bowel. The cord does not regenerate.

Measured. Prevalence: about **15.4 million people living with spinal cord injury in 2021**, which the key facts round to over 15 million. Disability burden: **over 4.5 million years lived with disability in 2021**.

Annual incidence: not reported on the WHO fact sheet. No global incidence figure was located, in the current or the prior round.

Males are more often affected, with consistently higher prevalence and years lived with disability, and **no ratio is given**.

Causes are ranked by WHO without percentage shares: traumatic causes lead, in the order **falls and road traffic injuries, then violence including self-harm and attempted suicide, then work- or sports-related injuries. Non-traumatic causes — tumours, degenerative and vascular conditions — are increasing, especially in ageing populations.**

Mortality is highest in the first year after injury and remains elevated relative to the general population. **In-hospital mortality is nearly three times higher in low- and middle-income countries than in high-income countries**. **This three-fold figure is the central measured inequality of the entry.**

Life expectancy is not quantified. WHO states it correlates strongly with neurological impairment and with **preventable secondary conditions** — and preventable is the operative word, because those are what kill.

Economic costs: no monetary figures. WHO states that global estimates are limited by data, that indirect costs such as lost earnings often exceed direct costs, and that direct costs peak in the first year.

Adults with spinal cord injury face unemployment rates above 60 per cent. Children with spinal cord injury are less likely to start school and less likely to advance once enrolled.

Wheelchair access: globally, only 5 to 35 per cent of people who need wheelchairs have access. **This single figure determines more of the burden than any clinical variable.**

Where it starts. WHO's ranking, without shares: falls, with the older-person low-energy fall onto a degenerative cervical spine an increasing mechanism; road traffic injuries; violence, including self-harm; and work- and sports-related injuries — diving into shallow water, rugby and other collision sport, horse riding, falls from height at work. Non-traumatic causes are increasing, especially in ageing populations, and include tuberculosis of the spine, which is a major non-traumatic cause in high-burden settings and is treatable. Male sex, alcohol, and the absence of protective measures — window guards, fall protection at work, helmets, seat belts — complete the picture. **WHO gives no figures for any risk factor**.

Three things are not known. The annual incidence globally: WHO does not report it. The shares attributable to each cause, so the targeting of prevention cannot be quantified. And the fundamental one: **why the mammalian central nervous system does not regenerate axons across a cord lesion.** Decades of work have produced an understanding of the inhibitory environment of the glial scar and no clinical treatment. **Every announced cure for spinal cord injury over fifty years has failed to replicate**, and that record should temper any statement about imminent regenerative therapy.

Cure status. RELIEF ONLY. The cord does not regenerate and no treatment restores function below the lesion. This is unambiguous and must be stated without hedging. Surgical decompression and stabilisation prevent further damage and allow mobilisation; they do not restore lost function. **Methylprednisolone**, given for decades on the basis of the NASCIS trials, has been withdrawn from most guidelines because the benefit was a post-hoc subgroup finding and the harms — infection, pneumonia, gastrointestinal bleeding — were real. **No pharmacological neuroprotective or regenerative treatment has succeeded.** Cell transplantation, epidural stimulation and brain-computer interfaces are research interventions with early-phase findings and no established clinical benefit.

What relief achieves is nevertheless the whole of the entry's value, and it is large. WHO's own framing says it: life expectancy correlates with **preventable secondary conditions**. **People with spinal cord injury die of pressure ulcers, urinary sepsis, respiratory infection and venous thromboembolism — all preventable with care that requires almost nothing manufactured.** The three-fold in-hospital mortality difference between low- and high-income countries is not a difference in the cord injury; **it is a difference in nursing, catheter care and turning.** And the 5-to-35-per-cent wheelchair access figure determines whether the person lives in a bed or in a community.

So the injury is RELIEF ONLY and the mortality is largely preventable. Those two statements are not in tension and both must be made.

Prevention. WHO names these interventions and gives no figures for any of them. The gradings draw on the effect sizes established in the road traffic injury and falls entries.

- **Road infrastructure and vehicle improvements — STRONG** (WHO names them). The underlying effect sizes are speed management, seat belts at up to 50 per cent reduction in occupant death, and helmets at more than 6-fold reduction in death risk.
- **Window guards — STRONG** (WHO names them specifically). Tens of dollars.
- **Alcohol policies — MODERATE** (WHO names them).
- **Firearm access controls — STRONG** for the violence share (WHO names them), on the means-restriction principle.
- **Violence and suicide prevention — MODERATE** (WHO names them).
- **Fall prevention in older people — STRONG** — exercise and balance training, psychotropic drug withdrawal, home modification. **With the ageing-population shift above, this is the growing preventive frontier for spinal cord injury.**
- **Fall protection at work — harnesses, guard rails, scaffold standards — MODERATE.**
- **Not diving into water of unknown depth — a rule, free, and it addresses a recognised cause in young men.**
- **Sports rule changes.** The banning of the spear tackle in rugby and of head-first tackling in American football followed measured clusters of cervical cord injury and were followed by measured reductions.
- **Treating spinal tuberculosis early — STRONG** for that non-traumatic cause, with cheap EML-listed drugs.
- **Prehospital spinal immobilisation — CONTESTED.** Long assumed essential, it is now recognised to carry harms — pressure injury, airway compromise, raised intracranial pressure, delay — and the evidence that rigid collars and backboards prevent secondary cord injury is weak. Current practice has moved toward **minimal handling and manual in-line stabilisation** rather than routine rigid immobilisation. Reported as contested because it is.

Treatment. The most valuable items are nursing and bladder care, not surgery or drugs.

1. Prevention of secondary conditions. This is first because it determines survival, and because WHO identifies preventable secondary conditions as the determinant of life expectancy.

- **Pressure ulcer prevention — turning every 2 to 3 hours, pressure-relieving surfaces, skin inspection, nutrition.** A pressure ulcer over the sacrum or ischium progresses to osteomyelitis and sepsis and is a leading cause of death. **It is prevented by turning a patient, which is labour.**
- **Bladder management — clean intermittent catheterisation. Urinary sepsis and renal failure were historically the leading cause of death in spinal cord injury, and intermittent catheterisation is what changed that.** Reusable catheters, clean water and soap.
- **Bowel management** — a scheduled programme with diet, fluid, suppositories and digital stimulation.
- **Respiratory care** — assisted coughing, positioning, breathing exercises. Pneumonia is a leading cause of death in cervical injury.
- **Venous thromboembolism prophylaxis** — low molecular weight heparin, early mobilisation, compression.

- **Nutrition.**

2. Surgical decompression and stabilisation. Early decompression within 24 hours is associated with better neurological outcomes in prospective cohort evidence, and the randomised evidence is limited. Stabilisation permits early mobilisation, which is what prevents the complications above. **It does not restore lost function.**

3. Maintaining spinal cord perfusion — avoiding hypotension, managing neurogenic shock, and treating **autonomic dysreflexia**, which is a hypertensive emergency triggered by a blocked catheter or an impacted bowel in injuries above T6 and which kills if not recognised. **Recognising it and removing the trigger is free and life-saving.**

4. Rehabilitation — the principal treatment. Physiotherapy, occupational therapy, transfer and wheelchair skills, functional electrical stimulation where available, and training for independent living. **This is the intervention with the largest effect on outcome and it is labour and time rather than technology.**

5. Spasticity management — baclofen, EML-listed, off-patent, cents; physiotherapy; positioning; and botulinum toxin and intrathecal baclofen in specialist settings.

6. Neuropathic pain management — amitriptyline, gabapentin or carbamazepine. Amitriptyline and carbamazepine are EML-listed, off-patent, cents a day. Neuropathic pain after spinal cord injury is common, severe and undertreated.

7. Bladder and bowel surgery, sexual and fertility care, and management of heterotopic ossification and syringomyelia as they arise.

8. Assistive technology — wheelchairs, cushions, transfer boards, orthoses. With 5 to 35 per cent access globally, this is the largest unmet need in the entry. A badly fitted wheelchair with no pressure-relieving cushion causes the ulcer that causes the death, so provision must include fitting and a cushion.

9. Methylprednisolone — not recommended. Withdrawn from most guidelines: the NASCIS benefit was a post-hoc subgroup finding and the harms were real. Reported because it was standard for twenty years.

Simple means. This entry is, in practice, almost entirely simple means — which is why the three-fold mortality difference between rich and poor settings is so damning.

- **Turning the patient every two to three hours, and inspecting the skin. The single highest-value act in the entry.** It prevents the pressure ulcer that causes the sepsis that causes the death. It requires hands, a clock and a willing family member, and it can be taught in one session. **A pressure-relieving mattress can be improvised from foam, and sheepskin, cushions and folded blankets are used to offload bony prominences.**
- **Clean intermittent catheterisation, taught to the patient or family.** Reusable catheters washed with soap and water. **This is what converted spinal cord injury from a condition that killed by renal failure into one in which people live for decades**, and it is improvisable to a degree that long-term indwelling catheters are not — indwelling catheters cause more infection and more stones.
- **A bowel programme** — timing, fluid, fibre, and digital stimulation. No equipment.
- **Assisted coughing** — a carer's hands on the abdomen timed with the patient's effort. It prevents pneumonia in cervical injury. Free.
- **Positioning, passive range-of-movement exercises and splinting** to prevent contractures, taught to the family and done daily. Free, and it determines whether a hand can be used.
- **Recognising autonomic dysreflexia** — sudden severe headache and very high blood pressure in an injury above T6 — **and the response: sit the person up, loosen clothing, check the catheter for a blockage, check for a loaded bowel. Free knowledge that prevents a stroke.**
- **A locally made wheelchair, with a pressure-relieving cushion.** Appropriate-technology wheelchairs built for rough ground from local materials, with the WHO wheelchair provision guidelines specifying fitting and a cushion as part of provision. **Tens to low hundreds of dollars against thousands for imported designs**. A cushion improvised from foam is better than no cushion.

- **A transfer board, a rope ladder on the bed, a grab rail** — plywood and rope.
- **Manual in-line stabilisation and minimal handling at the scene**, rather than rough transfer. Free, and the rigid-collar question is contested.
- **Drinking enough fluid**, which reduces stones and infection.
- **Peer support, and return to school and work.** With unemployment above 60 per cent and children less likely to start school, these are the measured outcomes, and inclusion is a decision rather than a resource.
- **Family training.** Everything above is deliverable by a trained family member, and in most of the world it has to be.

The minimum chain: **hands to turn the patient, a reusable catheter, soap and water, and a cushion.** That list is the difference between dying within a year and living for decades, and it contains nothing that cannot be had.

Gaps. WHO reports no annual incidence figure: prevalence and years lived with disability are given and incidence is not, and no global incidence estimate exists in any source reached. WHO gives no percentage shares for any cause, only a ranking, so prevention cannot be targeted quantitatively. WHO gives no effect size for any preventive measure, despite naming road infrastructure, window guards, alcohol policy, firearm controls, and violence and suicide prevention. There are no monetary cost figures at all, with WHO stating global estimates are limited by data. Life expectancy is not quantified, only described as correlating with impairment and preventable secondary conditions. **The wheelchair access figure spans 5 to 35 per cent — a seven-fold range, which is the measure of how poorly provision is counted.** Prehospital rigid immobilisation is contested and long-standing practice is not supported by good evidence either way. No pharmacological treatment works, and methylprednisolone was standard for twenty years on a post-hoc subgroup finding. Early surgical decompression rests largely on prospective cohort rather than randomised evidence. The three-fold in-hospital mortality difference between low- and high-income countries is reported and not decomposed: how much is nursing, how much surgery and how much intensive care is not established. Non-traumatic spinal cord injury is increasing and is not separately quantified anywhere located.

> **Depth.** Starts in: the spinal cord. Size: 1 cm†; depth +11.19. First complaint: about 1 second († instant); time depth 33.15. One untreated course: no number ([B] does not recover).
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The bound applies. The spinal cord does not regrow. So it is held, not ended. The book's status: RELIEF ONLY. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Fractures

What it is. A bone breaks. If the skin stays intact it is closed; if the bone or the wound communicates with the outside it is open, and then infection is the main danger. Most fractures heal if the ends are held in reasonable position for long enough.

Measured. 440 million prevalent fractures and 26 million years lived with disability, both on the 2019 burden study. **No global annual incidence figure and no deaths figure** specific to fractures were located. GBD reports injury burden by external cause rather than by lesion, so the mortality attaches to falls at 74.3 million DALYs and road injuries at 75.3 million DALYs rather than to fracture.

Traumatic amputation, as a related lesion: **180 million prevalent and 5.5 million years lived with disability** on the 2019 study.

The dominant causes are falls and road traffic injury, and the fragility-fracture burden in older people is covered in the falls entry.

Open fracture care is one of the three Bellwether procedures, alongside laparotomy and caesarean section — which is the clearest institutional statement of this lesion's importance: the capacity to manage an open fracture is treated as part of the irreducible minimum of surgical care.

The burden follows road traffic injury, where 92 per cent of deaths are in low- and middle-income countries, and falls, where over 80 per cent are.

Where it starts. Mechanical force exceeding bone strength, by two routes: **high-energy trauma on normal bone** — road crashes, falls from height, violence, crush — and **low-energy force on weak bone**, the fragility route.

Osteoporosis and low bone density dominate in older people and in women after the menopause. Age at both extremes matters: children's bones fail differently, with greenstick, buckle and physeal injuries, and older people's fail at low energy. Previous fracture is among the strongest predictors of the next. Falls and road traffic injury are the proximate causes, with occupational and sporting exposure behind them. **Pathological fracture** occurs through bone weakened by tumour, metastasis, infection, or metabolic bone disease including rickets and osteomalacia, the last nutritional and preventable with vitamin D. Stress fracture follows repetitive loading. Osteogenesis imperfecta and other genetic bone fragility account for a small share with very different management. **Malnutrition and vitamin D deficiency** produce rickets in children, with deformity and fracture, **and it is preventable for cents.** No effect sizes beyond those in the falls entry were located.

What is not known is the global incidence. GBD's structure gives prevalence and years lived with disability for fracture as a lesion and no incidence, and the cause-level accounting means a fracture's mortality is counted against the fall or the crash. **What proportion of the 440 million prevalent fractures were adequately treated is not known and not estimated anywhere located** — which is the number that would size the global orthopaedic gap. Also unresolved: optimal management for many specific fractures, where operative and non-operative treatment have been compared with surprising results.

Cure status. CURABLE. Fractures heal, and this is one of the most reliable cures in medicine. Bone is one of the few tissues that repairs itself with original tissue rather than scar. Held in reasonable alignment and given time, a fracture unites and the limb works. **The treatment requirement is reduction and immobilisation, not restoration** — the body does the healing.

The qualifications, each real:

- **Open fractures** carry infection risk, and an infected non-union is a limb-threatening and sometimes life-threatening problem requiring prolonged treatment. Early debridement, antibiotics and skeletal stabilisation are what prevent it, and this is why open fracture care is a Bellwether procedure.
- **Non-union and malunion** occur in a minority and need further surgery.
- **Intra-articular fractures** that heal with an irregular joint surface produce post-traumatic osteoarthritis — CONTROLLABLE, not cured.
- **The hip fracture in an older person is cured as a fracture and frequently not survived as an event.**
- **Growth plate injuries in children** can cause progressive deformity as the child grows.
- **Compartment syndrome and neurovascular injury** cause permanent loss if missed.

So the lesion is CURABLE, and the common failures are infection, missed compartment syndrome, and the frailty of the patient rather than the behaviour of the bone.

Prevention.

- **Everything in the road traffic injury entry — STRONG**, with the measured effect sizes: speed management at 1 per cent mean speed for 4 per cent fatal crash risk, helmets at more than 6-fold death reduction, seat belts at up to 50 per cent, child restraints at 71 per cent.
- **Everything in the falls entry — STRONG**: exercise and balance training, psychotropic drug withdrawal, home modification, window guards, playground surfacing, workplace fall protection.
- **Bisphosphonates in osteoporosis — STRONG. Reductions in vertebral fracture of the order of 40 to 70 per cent and hip fracture 40 to 50 per cent** in the pivotal trials in women with osteoporosis; those figures are from the trial literature and were not verified. **Alendronate is not on the WHO Essential Medicines List at all, and no bisphosphonate is listed for osteoporosis**. Off-patent, a few US dollars a month.

- **Calcium and vitamin D in the deficient — MODERATE.**
- **Vitamin D for rickets prevention — STRONG.** Cents a dose, EML-listed, and it prevents the deformity and fracture of nutritional rickets outright.
- **Fracture liaison services — MODERATE.** Systematically starting osteoporosis treatment after a first fragility fracture. **Treatment rates after a first fracture are low everywhere** and this is the identified gap.
- **Hip protectors — CONTESTED.**
- **Smoking cessation and reducing alcohol — MODERATE** for bone density and for fall risk.
- **Occupational safety regulation — MODERATE.**
- **Protective equipment in sport — MODERATE.**

Treatment. 1. For open fractures: early debridement, irrigation, antibiotics and skeletal stabilisation. This is the time-critical sequence and it is what prevents the infection that threatens the limb.

- **Antibiotics as early as possible** — a first-generation cephalosporin or equivalent, and **the evidence favours early administration over any particular agent.** EML-listed, off-patent, cheap.
- **Tetanus prophylaxis.** EML-listed, off-patent, cents.
- **Debridement of dead tissue and foreign material**, repeated as needed.
- **Stabilisation** — external or internal fixation depending on contamination and soft tissue.
- **Soft tissue cover** — flaps for exposed bone.
- **This is a Bellwether procedure**.

2. Reduction and immobilisation for closed fractures.

- **Closed reduction and casting or splinting** for the majority. **Plaster of Paris and a trained pair of hands.**
- **Traction** for selected femoral fractures, especially in children; Perkins and gallows traction are standing low-resource techniques.
- **Internal fixation** — plates, screws, intramedullary nails — where it gives better function or earlier mobilisation. **The implant is the cost and the constraint.** The SIGN intramedullary nail is specifically relevant: a nail system designed for use without an image intensifier, supplied free to surgeons in low- and middle-income countries, with a large published series. **An implant designed around the absence of the equipment the standard technique requires.**
- **Arthroplasty** for displaced intracapsular hip fractures in older people.

3. Analgesia. Paracetamol, non-steroidal anti-inflammatory drugs, opioids. **Regional nerve blocks** — a femoral or fascia iliaca block for a hip or femoral fracture — give excellent analgesia with cheap local anaesthetic and a needle, and reduce opioid need. Lidocaine and bupivacaine are EML-listed, off-patent, cents.

4. Early mobilisation and physiotherapy. It determines function, and it is labour.

5. Treatment of the underlying bone disease — osteoporosis, vitamin D deficiency, tumour.

6. Important instances where operative and non-operative treatment proved equivalent, reported because they bear on what is actually needed.

- **Displaced distal radius fractures in older people:** several trials have found no functional advantage of fixation over cast treatment at one year.
- **Many clavicle, humeral shaft and proximal humerus fractures:** trials and meta-analyses have found non-operative management equivalent in function for large subgroups.
- **Tibial shaft and ankle fractures in defined groups** have similar findings.
- **The general direction of the evidence is that fixation is used more widely than its demonstrated advantage supports**, which is relevant for settings where implants are unaffordable: **cast treatment is often not a compromise.**

7. Compartment pressure measurement and fasciotomy where compartment syndrome is suspected. Time-critical, and missed compartment syndrome causes permanent loss.

8. Amputation where the limb is unsalvageable, followed by prosthetic rehabilitation.

Simple means. This entry is rich in them, and several are also the best treatment.

- **Splinting with whatever is at hand.** A board, a rolled newspaper or magazine, a padded stick, a folded blanket, cardboard, or the opposite limb bound to the injured one. **Immobilising a fracture before transport reduces pain, bleeding and further soft tissue damage.** Free, and it is the single most useful first aid act for a fracture.
- **Plaster of Paris.** Rolls of plaster bandage and water — **a few US dollars of material** — and a trained pair of hands cure the large majority of fractures. **This is the same material as the Ponseti method**, and it is the backbone of orthopaedic care everywhere that implants are unaffordable. The equivalence evidence above means this is frequently not a second-best choice.
- **A sling and a broad arm bandage.**
- **Traction improvised with weights and a frame** — a standing technique for femoral fractures in children and adults where fixation is unavailable.
- **Direct pressure and a dressing for the bleeding open fracture; covering the wound with a clean dressing and not probing it.**
- **A tourniquet for catastrophic limb haemorrhage.** Commercial windlass tourniquets cost tens of dollars; a cloth and a stick costs nothing.
- **Elevation and ice** for swelling.
- **Checking the pulse, sensation and movement distal to the fracture, before and after splinting**, and loosening anything that compromises them. **This free examination detects the neurovascular injury and the developing compartment syndrome**, which are the catastrophic missable complications.
- **Nerve blocks with cheap local anaesthetic** — a syringe, a needle and a vial. Transformative analgesia for a hip fracture at almost no cost.
- **Early mobilisation and walking the patient** — labour, and the determinant of recovered function, especially after a hip fracture.
- **Locally made crutches, sticks and walking frames** from wood.
- **Clinical diagnosis without radiography.** Many fractures are diagnosed and managed adequately on examination where no X-ray exists, and the Ottawa ankle and knee rules are decision tools on a card that safely reduce the need for imaging.
- **Vitamin D for rickets** — cents.
- **Turning and skin care** for the immobilised patient.

The minimum chain: **plaster, water, a splint and trained hands.** For the open fracture, antibiotics, debridement and stabilisation — the Bellwether requirement, with no substitute.

Gaps. There is no global annual incidence figure and no deaths figure for fractures as a lesion; GBD's structure attributes mortality to the external cause, and the available figures of 440 million prevalent and 26 million years lived with disability are both from the **2019** burden study rather than 2023. **What proportion of the 440 million prevalent fractures received adequate treatment is not known or estimated anywhere located**, and that is the number that would size the global orthopaedic gap. The bisphosphonate effect sizes are from the trial literature and were not verified. The operative-against-non-operative equivalence findings are specific to defined fracture patterns and populations and are frequently over-generalised in both directions; they are printed because they bear directly on what low-resource settings need, and they should not be read as a general argument against fixation. Osteoporosis treatment rates after a first fragility fracture are low everywhere and the size of that gap is unquantified. Open fracture infection rates by setting are not globally reported, so the consequence of the Bellwether gap is not measured. Implant availability and cost in low- and middle-income settings are not quantified in any source reached, despite being the binding constraint. No cost or cost-effectiveness figures for fracture care were located

beyond the Lancet Commission framing. The SIGN nail programme's published series is large and is not a randomised comparison.

> **Depth.** Starts in: a bone. Size: 3 cm†; depth +12.19. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 8.6 weeks ([B] most heal; † 6–12 weeks); depth 47.23.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book's status: CURABLE, with CONTROLLABLE for a named stratum. Reading and status agree. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Open wounds

What it is. The skin is cut, torn or punctured so that the tissue underneath is exposed. Bleeding is the immediate danger, infection the one that follows. Most heal if cleaned, closed where appropriate, and protected.

Measured. No global incidence figure and no deaths figure for open wounds and lacerations were located, in the current or the prior round. GBD reports injury burden by external cause rather than by lesion, so the mortality attaches to road injuries at 75.3 million DALYs, falls at 74.3 million, interpersonal violence at 30.2 million and animal contact.

Oro-dental trauma: about 1 billion people affected — the only billion-scale lesion figure in the chapter, and it includes wounds to the mouth and lips.

Two open-wound consequences are counted: **neonatal tetanus, 7,700 deaths in 2021, down 84 per cent from 46,898 in 2000**; and **rabies, 15,800 deaths in 2023** on GBD against **44,203 in 2021** on WHO's Global Health Estimates. Non-neonatal tetanus deaths were not retrievable.

The relevant burden figure for this entry is not a wound count but a care-access count: about 5 billion people lack access to safe, affordable surgery and anaesthesia care when needed. Wound care is the lowest tier of that gap.

Where it starts. Road traffic injury, falls, interpersonal violence, occupational injury from machinery, blades and glass, animal and human bites, burns with open areas, agricultural injury, domestic injury. Crush and blast mechanisms produce wounds with far more devitalised tissue than their surface appearance suggests.

Contamination at the moment of wounding — soil, manure, saliva, seawater, organic material — determines infection risk far more than wound size does. **Delay to cleaning** is the single most consistent determinant of whether a wound becomes infected. Host factors raise risk: diabetes, peripheral vascular disease, malnutrition, immunosuppression, HIV, smoking, age. Absence of tetanus immunisation and a retained foreign body complete the picture. No effect sizes were located.

What is not known is the incidence. **This is among the most common lesions in human medicine and there is no global count of any kind.** Also genuinely contested: much of the standard wound-care practice. The optimal irrigation fluid, the optimal irrigation pressure, the time window beyond which a wound should not be closed primarily, the value of prophylactic antibiotics for most clean wounds, and whether tap water is as good as sterile saline — these have been studied and the answers are either no difference or insufficient evidence, which is a different situation from the risk factors being unknown.

Cure status. Most open wounds: CURABLE, and for most SELF-LIMITING with basic care. Skin heals. A clean wound closed or left to granulate heals, and the patient recovers completely apart from a scar. **The treatment requirement is cleaning, haemostasis and protection; the body does the repair.** Infection: CURABLE, with urgency. It converts a self-limiting wound into a condition requiring antibiotics and sometimes surgery, and in the extreme into necrotising infection or sepsis. Tetanus, from a contaminated wound in an unimmunised person: RELIEF ONLY, and frequently fatal. **A few cents of vaccine prevents it; an intensive care unit often cannot cure it.** Rabies, from an animal bite wound: RELIEF ONLY, and essentially always fatal once symptomatic. Post-exposure prophylaxis prevents it completely. Chronic wounds — in diabetes, venous disease or pressure injury: CONTROLLABLE rather than curable, and they

behave as a different condition. Scarring and contracture across a joint: RELIEF ONLY without surgical release.

So the great majority of open wounds are curable with soap, water and a dressing, and the deaths come from three specific preventable complications — haemorrhage, tetanus and rabies — each of which has a cheap countermeasure.

Prevention.

- **Prevention of the causing injury**, with the effect sizes in the road traffic injury and falls entries, plus occupational safety regulation.
- **Tetanus immunisation — STRONG, and it is the clearest preventive in this entry.** WHO recommends 6 doses over a lifetime, and neonatal tetanus deaths fell 84 per cent between 2000 and 2021 with immunisation scale-up. **Cents a dose, EML-listed, off-patent**. An immunised person does not get tetanus from a dirty wound.
- **Rabies pre-exposure and post-exposure prophylaxis, and dog vaccination — STRONG.**
- **Occupational measures** — machine guarding, gloves, eye protection, blade handling, footwear.
- **Removing hazards** — broken glass, sharp fencing, exposed machinery.
- **Footwear**, which prevents penetrating foot wounds, the classic tetanus route, and snakebite.
- **Hand hygiene and clean technique in any procedure** that creates a wound.
- **Treating the host conditions** — glycaemic control in diabetes, nutrition, smoking cessation.
- **Dog population management and bite prevention education.**

Treatment. 1. Haemorrhage control. First, because it is what kills within minutes.

- **Direct pressure** — the first and usually sufficient measure.
- **A tourniquet** for catastrophic limb bleeding. **Commercial windlass tourniquets cost tens of dollars; the improvised cloth-and-stick version costs nothing.** The military and civilian evidence for prehospital tourniquets in limb exsanguination is strong.
- **Wound packing and pressure** for junctional bleeding, with haemostatic dressings where available.
- **Tranexamic acid** for significant traumatic haemorrhage, **within 3 hours**: all-cause mortality 14.5 against 16.0 per cent, relative risk 0.91 (0.85 to 0.97); death due to bleeding 4.9 against 5.7 per cent, relative risk 0.85 (0.76 to 0.96), over 20,211 patients in 40 countries. EML-listed, off-patent, a few US dollars a gram.

2. Cleaning. The determinant of infection.

- **Irrigation with a large volume under moderate pressure. Potable tap water is as effective as sterile saline for cleaning most wounds** in the trial and Cochrane evidence, which is a finding of real practical consequence where saline is unavailable.
- **Removal of foreign material and devitalised tissue — debridement. This is the single most important anti-infective measure, more than any antibiotic.**
- **Soap and water for the surrounding skin.**

3. Tetanus prophylaxis. Vaccine, and tetanus immunoglobulin for high-risk wounds in inadequately immunised people. EML-listed, off-patent, cents for the vaccine.

4. Rabies post-exposure prophylaxis for animal bites — immediate thorough wound washing with soap and water for 15 minutes, vaccine, and rabies immunoglobulin for the most severe exposure category.

5. Closure, where appropriate.

- **Sutures, staples, adhesive strips or tissue adhesive. Adhesive strips and tissue adhesive are equivalent to sutures for many small low-tension wounds** and need no anaesthesia and no removal visit.
- **Delayed primary closure or healing by secondary intention** for contaminated wounds, bites, and wounds presenting late. **Closing a contaminated wound primarily causes the infection.**

- **Local anaesthetic — lidocaine.** EML-listed, off-patent, cents a vial. Suturing without anaesthesia is a real and avoidable cruelty, and the drug costs almost nothing.

6. Antibiotics — selectively, not routinely.

- **Prophylactic antibiotics are not indicated for most clean simple wounds.** They are indicated for bites, especially hand and cat bites, heavily contaminated wounds, open fractures, wounds with devitalised tissue, and immunocompromised or diabetic patients.
- **Amoxicillin-clavulanate** is the standard for bites, and a first-generation cephalosporin for other indications. EML-listed, off-patent, cheap.
- **Treating established infection**, and **recognising necrotising infection**, which requires immediate extensive surgical debridement and in which delay is lethal.

7. Dressing and protection. Simple non-adherent dressings are as good as expensive modern dressings for most acute wounds in the trial evidence. Moist wound healing for granulating wounds.

8. Elevation, immobilisation and analgesia.

9. Skin grafting and flap coverage for large tissue loss, and negative pressure wound therapy where available.

10. Nutrition. Wound healing is a metabolic demand and protein-energy support matters in large wounds.

Simple means. This entry is almost entirely simple means, and the treatment with the best evidence is among the simplest.

- **Direct pressure with a hand and a cloth. The single highest-value act in the entry**, and it stops most bleeding.
- **A tourniquet, improvised from a cloth and a stick, or commercial.** For catastrophic limb haemorrhage it is life-saving and it is improvisable.
- **Bystander haemorrhage control training.** Teaching pressure, packing and tourniquet use to lay people is a short course and a small kit. **The evidence is programme evaluation rather than randomised**, and the underlying intervention evidence for tourniquets and pressure is strong.
- **Washing the wound with clean running water and soap. Tap water is as good as sterile saline** for most wounds, which removes a supply chain.
- **Fifteen minutes of soap and water washing for an animal bite. This single act substantially reduces rabies risk and it is free**.
- **Removing visible foreign material.**
- **A clean cloth dressing**, boiled and dried where sterility matters. **Clean cotton cloth is adequate for most wounds**, and simple non-adherent dressings are as good as expensive ones.
- **Elevation and immobilisation.**
- **Honey as a wound dressing.** Cochrane-reviewed evidence supports it for partial-thickness burns and it is used for wounds: cheap, locally available, antibacterial, non-adherent. The evidence quality is moderate and heterogeneous.
- **Leaving a contaminated wound open** rather than closing it. **The intervention is not doing something**, and it prevents the infection that closure causes.
- **Adhesive strips, or clean cloth tape, for small low-tension wounds** — no needle, no anaesthetic, no removal visit.
- **The recovery position and keeping the patient warm** during transport.
- **Boiled water cooled, and clean containers.**
- **Teaching the warning signs of infection** — spreading redness, increasing pain, pus, fever, and the pain-out-of-proportion that signals necrotising infection. **Free, and it is what brings the patient back in time.**
- **Oral rehydration** for the patient with significant blood loss during transport.

- **Not applying earth, dung, ash, oil or herbal preparations** — the classic tetanus route and a cause of necrotising infection. **A conversation.**

The minimum chain: **water, soap, a cloth and a hand.** Those four cure the majority of open wounds. Beyond them, tetanus vaccine at cents, lidocaine at cents, antibiotics for the minority that need them, and surgical debridement for the contaminated and the necrotising.

Gaps. There is no global incidence figure of any kind for open wounds, one of the commonest lesions in medicine, and GBD's structure means they are counted only through their external causes. No deaths figure attaches to the lesion. Non-neonatal tetanus deaths were not retrievable, so the open-wound tetanus burden is only partially quantified. **Much standard wound-care practice is unsupported or shown to be equivalent to cheaper alternatives** — irrigation fluid, irrigation pressure, the closure time window, routine prophylactic antibiotics, and expensive dressings — which is a case where the evidence favours the simple option and practice has not fully followed. No effect sizes for any preventive measure specific to wounds were located. Bystander haemorrhage control programme evidence is pre-post, though the component interventions are well evidenced. The honey evidence is moderate-quality and heterogeneous. Chronic wounds — diabetic foot, venous ulcer, pressure injury — carry a very large global burden that is not quantified in any source reached and that behaves as a different condition from the acute wound described here. Necrotising infection incidence and mortality by setting are not reported anywhere located, despite being the wound complication with the highest case fatality.

> **Depth.** Starts in: the wound. Size: 1 cm†; depth +11.19. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 12 days ([B] most heal; † 1–3 weeks); depth 45.76.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Crush injury

What it is. A part of the body is compressed for a prolonged period — under rubble, machinery, or the person's own body weight after a long collapse. Muscle dies while compressed. When the pressure is released the dead muscle's contents flood the circulation, which can stop the heart and destroy the kidneys.

Measured. No global incidence figure and no deaths figure for crush injury were located, in the current or the prior round. GBD reports injury burden by external cause: the relevant causes are exposure to forces of nature, for earthquakes, and exposure to mechanical forces, and **no global figure was retrieved for either**.

The burden is **episodic rather than endemic.** It arrives in earthquakes, building collapses, landslides and conflict, and the published case series come from named events: the Marmara earthquake of 1999, Bam in 2003, Kashmir in 2005, Wenchuan in 2008, Haiti in 2010, Nepal in 2015 and Türkiye and Syria in 2023, and building collapses such as Rana Plaza in 2013. **Earthquake case series consistently report crush syndrome in a substantial minority of hospitalised survivors and acute kidney injury requiring dialysis in a large share of those**, with reported dialysis requirements in the range of roughly 10 to 50 per cent of crush syndrome cases depending on the event and the rescue interval. These are case-series figures from individual disasters and were not verified, so no pooled figure is asserted.

Geography: wherever buildings are not built to seismic standards, and wherever conflict destroys buildings with people inside.

Where it starts. The mechanism is well understood. **Prolonged compression of muscle:** skeletal muscle is the vulnerable tissue, compression beyond roughly an hour begins to produce irreversible damage, and the damage scales with duration.

Earthquakes and building collapse are the dominant cause, and the reason the burden is episodic. Landslides, mining accidents, industrial machinery, agricultural machinery and vehicle entrapment follow. Conflict and bombardment produce it.

Prolonged immobility against a hard surface — the long lie after a fall or a collapse, after a stroke, or after unconsciousness from alcohol, drugs or poisoning — produces the same syndrome without any external crushing force, and is the commonest non-disaster route in high-income settings.

Non-seismic building standards, unreinforced masonry and informal construction are the structural determinant of how many people are crushed by a given earthquake. **The rescue interval** determines the outcome, and the intervention that shortens it is organised rescue. No effect sizes were located.

What is not known is the burden. **The condition has no incidence figure, no deaths figure and no GBD series**, and the evidence base is a series of single-event case reports from which no pooled estimate has been constructed in any source reached. Also unresolved in the clinical literature: the optimal fluid regimen and rate, whether bicarbonate and mannitol add anything to volume alone, and the indications and timing for fasciotomy in crushed limbs, where over-aggressive fasciotomy causes infection and amputation.

Cure status. Crush syndrome, the systemic illness: CURABLE, with a time-dependence as sharp as any condition in this book and a mortal trap at the moment of rescue. It is survivable and fully recoverable if the patient is given fluid before and during extrication and dialysed where needed. The acute kidney injury of crush syndrome is typically **reversible**: survivors who are dialysed through the acute phase commonly recover renal function completely and come off dialysis. The crushed muscle, limb loss and nerve injury: RELIEF ONLY. That tissue is dead.

The trap is the central clinical fact: releasing the compression without first establishing fluid resuscitation can kill the patient within minutes. The potassium and myoglobin held in the crushed limb enter the circulation at the moment of release, producing cardiac arrest and overwhelming the kidneys. **People have been extracted alive from rubble, conscious and talking, and died on release.** This is why the intervention is given **before** the rescue rather than after it, and it is the single most important piece of knowledge in the entry.

Prevention.

- **Seismic building codes and their enforcement — STRONG, and it is the whole of the prevention.** Earthquakes do not kill people; buildings do. The measured evidence is comparative: earthquakes of similar magnitude produce death tolls differing by orders of magnitude between countries with enforced seismic codes and those without. **No effect size was retrievable**, and the comparison is the standing position in the disaster literature.
- **Retrofitting existing unreinforced masonry — STRONG**, and expensive.
- **Land-use planning** — not building on landslide-prone slopes or liquefiable ground.
- **Enforcement rather than legislation.** The repeated finding after every major earthquake is that codes existed and were not enforced, so **the preventive gap is inspection rather than knowledge.**
- **Machine guarding and lock-out procedures in industry and agriculture — MODERATE.**
- **Organised search and rescue capacity — STRONG for survival**, because the outcome is determined by the interval. This is preparedness rather than prevention.
- **Training first responders and community volunteers in the fluid-before-extrication rule — STRONG** on mechanism; this is the highest-yield piece of preparedness in the entry.
- **Preventing the long lie** — personal alarms for older people living alone, and a daily check. **A visit is the intervention.**
- **Earthquake drills and furniture anchoring**, which reduce injury inside surviving buildings.

Treatment. The order matters more here than in most entries.

1. Intravenous fluid, started BEFORE the compression is released, and continued at high volume. This is the treatment, and the sequence is the point. Isotonic saline, begun while the patient is still trapped if a limb can be reached, at high rates — the published disaster-nephrology guidance recommends starting before extrication and continuing with very large daily volumes under monitoring. Normal saline is EML-listed, off-patent, **a few US dollars a litre**. **A few litres of salt water, given in the right order, is the difference between death on release and full recovery.** Potassium-containing fluids are generally avoided, because hyperkalaemia is the killing mechanism.

2. Management of hyperkalaemia. Calcium gluconate or chloride to stabilise the myocardium, insulin-dextrose, salbutamol, and dialysis as the definitive measure. Calcium gluconate, insulin, dextrose and salbutamol are all EML-listed, off-patent and cheap; calcium gluconate was printed at US$10.66 and US$5.01 for the same material number on different pages of the October 2026 indicative catalogue, which is why these are indicative figures and not a price. **Continuous or frequent electrocardiographic monitoring, where available, detects the hyperkalaemia before the arrest.**

3. Renal replacement therapy — dialysis. The intervention that determines survival in established crush-related acute kidney injury. **Peritoneal dialysis is the low-resource form and has been used at scale in disaster settings**, requiring a catheter, fluid and no machine and no electricity — which is why it matters here. Dialysis demand after an earthquake arrives all at once in a place whose dialysis capacity has also been destroyed.

4. Urine output monitoring and alkalinisation — CONTESTED. Sodium bicarbonate to alkalinise the urine and mannitol to force diuresis are widely used and **their added benefit over adequate volume alone is not established.** Reported as contested.

5. Fasciotomy — CONTESTED and over-performed. Indicated for measured compartment syndrome. **Routine or prophylactic fasciotomy in crushed limbs is associated with infection, sepsis and amputation**, and the disaster literature is explicit that restraint improves outcomes. **Measured compartment pressures, not clinical impression.**

6. Wound care, debridement and antibiotics for the open and contaminated components, and **tetanus prophylaxis.**

7. Amputation where the limb is unsalvageable or the patient is dying from it, sometimes performed at the scene to permit extrication.

8. Analgesia. Crush injury is extremely painful and analgesia at the scene is routinely absent. Morphine is EML-listed, off-patent, and works out at about US$0.57 an ampoule on October 2026 indicative prices.

9. Treatment of hypothermia. People under rubble become cold, and hypothermia compounds coagulopathy and acidosis.

10. Rehabilitation for the surviving limb and for the amputee.

Simple means.

- **Fluid before release. The highest-value simple means in the entry and one of the highest in the chapter: a bag of salt water and the knowledge of the order in which to do things.** A litre of saline costs about a dollar. **A first responder who starts fluid before lifting the slab saves a life that is otherwise lost at the moment of rescue.** If no intravenous access is possible, **oral fluid, including oral rehydration solution, given to a conscious trapped person is a real and recommended fallback.**
- **Teaching the rule.** The whole intervention is a piece of knowledge, transmissible in a sentence, and its absence is the mechanism of death. **This is the clearest case in the chapter where information, not equipment, is the intervention.**
- **Not applying a tourniquet to a crushed limb as a routine measure.** The released-toxin logic that motivates it does not hold and the limb is lost. Tourniquets are for haemorrhage.
- **Keeping the trapped person warm, hydrated and talking.** Insulation from the ground, covering, and fluid by mouth. Free.
- **Marking the time of entrapment.** The rescue interval determines management, and writing it down costs nothing.
- **Community search and rescue with hand tools.** The great majority of people rescued alive after earthquakes are pulled out by neighbours in the first hours, before any organised team arrives. **Hands, levers, jacks and digging tools, used by trained community volunteers, save more lives after an earthquake than any medical intervention.**

- **Oral rehydration solution** — sugar, salt and water, for the conscious trapped or just-released patient, at about US$0.048 a sachet on October 2026 indicative prices.
- **Peritoneal dialysis** — a catheter and fluid, no machine and no electricity. The low-resource form of the definitive treatment.
- **Analgesia, including oral morphine or ketamine where available.**
- **Splinting the limb and wound dressing.**
- **Anchoring furniture and knowing where to shelter** — household earthquake preparedness, free.
- **A daily check on an older person living alone**, which prevents the long lie that produces the same syndrome without an earthquake.

The minimum chain: a bag of saline, or failing that oral rehydration solution, and the knowledge to give it before the weight comes off. For the established kidney injury, dialysis — and peritoneal dialysis is the form that works without a machine.

Gaps. There is no incidence figure, no deaths figure and no GBD series for crush injury: the evidence base is single-event case series from named disasters, and no pooled estimate has been constructed in any source reached. The dialysis-requirement figures are from individual event series and were not verified, and no pooled figure is asserted. The seismic building code effect size could not be retrieved, despite being the entire prevention. The optimal fluid regimen, rate and composition are not established by trial; the guidance is expert consensus from disaster nephrology experience. Bicarbonate and mannitol are widely used and their added benefit over volume alone is not established. Fasciotomy indications and timing are contested, and the disaster literature's position that it is over-performed and causes harm conflicts with general trauma practice. The burden is episodic, so it is absent from annual accounting frameworks and reappears as an emergency each time, which is itself a structural reason the data do not exist. Conflict-related crush injury is essentially unmeasured. The long-lie route in older people is recognised clinically and not quantified anywhere located.

> **Depth.** Starts in: skeletal muscle. Size: 10 cm†; depth +13.29. First complaint: about 1 hour ([B] after about 1 hour of compression); time depth 40.61. One untreated course: about 7 days († days); depth 45.27.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

Hypothermia and heat illness

What it is. Two opposite failures of the body's temperature control. In hypothermia the core cools below about 35 °C and the heart and brain slow until they stop. In heat stroke the core rises above about 40 °C and proteins and cells begin to fail. Both kill, and both are reversible if the temperature is corrected in time.

Measured. About 489,000 heat-related deaths a year, as a 2000 to 2019 average. **The source is unnamed in the compilation that carries this figure**, and it is printed with that caveat. **GBD's environmental heat and cold exposure cause series was not retrievable**, in the current or the prior round.

Neonatal hypothermia has no burden figure at all — no GBD cause line, no global prevalence estimate, and its mortality counted inside preterm birth complications and sepsis.

No global incidence figure for either hypothermia or heat illness as a clinical presentation was located. The available figures are mortality attributions to ambient temperature, which is a different measure: the attributable-burden literature estimates deaths attributable to non-optimal ambient temperature in the millions annually, with **cold-attributable deaths exceeding heat-attributable deaths** in most of that work. Those figures could not be verified and are not asserted; they measure temperature-attributable mortality across all causes, not cases of hypothermia and heat stroke.

Heat exposure is rising with the climate, and the attributable-burden literature reports rising heat-attributable and falling cold-attributable mortality, unverified here.

Cold-water drowning is relevant: in cold-water submersion with rapid deep cooling, survival with intact neurology has been documented after very prolonged submersion, which is why prolonged resuscitation is attempted in cold water and not in warm.

Where it starts. For hypothermia: **cold exposure, with wind and wet multiplying it**, and immersion cooling far faster than air. **The age extremes. The newborn is the most vulnerable human**: a large surface area to mass, no shivering, no fat, and no ability to move or dress itself. Older people have reduced shivering, reduced perception of cold and reduced mobility. **Alcohol and drugs** through vasodilatation and impaired judgement, the classic urban hypothermia death. **Immobility and the long lie** — a fall, a stroke, or unconsciousness on a cold floor. Hypoglycaemia, hypothyroidism, adrenal insufficiency, malnutrition and sepsis, and **in a newborn hypothermia may be the presenting sign of sepsis rather than its cause. Poverty** — inadequate heating, inadequate housing, homelessness, fuel poverty — is the determinant in high-income-country winter mortality. And **trauma**, where hypothermia, acidosis and coagulopathy form a lethal triad, and trauma patients become hypothermic even in warm environments through exposure, fluid and blood loss.

For heat illness: **ambient heat and humidity**, with humidity decisive, because evaporative cooling is the body's only mechanism at high temperature and above a wet-bulb threshold it fails entirely. **Exertional heat stroke** in athletes, soldiers and labourers occurs in moderate ambient conditions with high work rates and affects the young and fit. **Classical heat stroke** in older, chronically ill and isolated people during heatwaves produces the mortality spikes. The age extremes; chronic illness; cardiovascular and renal disease; obesity. **Medications** — anticholinergics, diuretics, beta blockers, antipsychotics — and drugs of abuse. Dehydration, lack of acclimatisation, occlusive clothing. **Urban heat island, living on a top floor, no shade, no fan, no air conditioning, and social isolation** — the 2003 European and 1995 Chicago heatwave analyses identified social isolation as a leading risk factor, which is a finding about society rather than physiology. And **outdoor and indoor manual labour** — agricultural and construction work in heat, which is the largest occupational exposure and is growing. **No effect sizes were located for any risk factor.**

What is not known is the burden, for either. **The 489,000 heat figure has no named source.** And the attributable-burden approach and the clinical-case approach measure different things: a heatwave kills mostly by precipitating cardiovascular and respiratory death in people who are never diagnosed with heat stroke, so the clinical incidence of heat illness and the mortality attributable to heat differ by orders of magnitude and neither is well counted. **The same applies to hypothermia: excess winter mortality is largely cardiovascular and respiratory, not diagnosed hypothermia.**

Cure status. Both conditions are CURABLE, with RELIEF ONLY for the organ damage and hypoxic injury established once the threshold is passed. Both have a time-dependent threshold beyond which they are not.

Hypothermia: CURABLE, and notably so. Rewarming reverses it and recovery is complete. **The maxim in the resuscitation literature — no one is dead until they are warm and dead — reflects a real finding: patients have survived with intact neurology after profound hypothermia with prolonged cardiac arrest, because the cold protects the brain while it protects nothing else**. Prolonged resuscitation and extracorporeal rewarming are therefore justified in hypothermic arrest in a way they are not in normothermic arrest. **Accidental hypothermia has one of the best outcomes of any cause of cardiac arrest, if the rewarming is achieved.**

Heat stroke: CURABLE if cooled fast, RELIEF ONLY for what the heat has already destroyed. Cooling rate is the determinant of outcome and the evidence is unusually clear: in exertional heat stroke, cooling to below about 39 °C within 30 minutes is associated with survival approaching 100 per cent in the military and athletic series, while delay produces multi-organ failure. What is not reversible is the established damage — hepatic failure, rhabdomyolysis with renal failure by the same mechanism as crush injury, disseminated intravascular coagulation, and permanent cerebellar and cognitive injury in a share of survivors.

So both conditions are, at the moment of presentation, temperature problems with temperature solutions, and both become organ-failure problems if the temperature is not corrected.

Prevention. For hypothermia:

- **The newborn warm chain — STRONG, free, and the highest-yield item**: immediate drying, skin-to-skin, a hat, delayed bathing, a warm room, keeping mother and baby together, warm transport. **Plastic wrapping of very preterm babies at birth is randomised-trial and Cochrane-supported** and costs a plastic bag.
- **Adequate home heating and insulation, and addressing fuel poverty — STRONG** for winter mortality, and it is a housing and income intervention rather than a medical one.
- **Winter fuel payments, cold weather alerts, and warm-space provision — MODERATE.**
- **Shelter for homeless people during cold weather — STRONG.**
- **Daily contact with isolated older people — MODERATE**, and it prevents the long lie.
- **Clothing, layering, head covering, and staying dry — STRONG** on mechanism.
- **Not drinking alcohol in the cold — MODERATE.**
- **Active warming of trauma patients and of surgical patients — STRONG.** Perioperative warming reduces wound infection, blood loss and cardiac events in randomised trials, and the measure is a blanket and warmed fluid.
- **Flotation and immersion protection for those working on water — STRONG.**

For heat illness:

- **Heat-health action plans and early warning systems — STRONG.** Introduced across Europe after the 2003 heatwave, and the evaluations report reduced heat mortality in subsequent comparable events. **No effect size retrievable**.
- **Checking on isolated older people during a heatwave — STRONG.** Social isolation was identified as a leading risk factor in the Chicago 1995 and Europe 2003 analyses. **A visit is the intervention.**
- **Cooling centres, shade, and access to a fan or air conditioning — STRONG.**
- **Urban greening, tree planting, reflective roofing and reducing the urban heat island — MODERATE**, slow-acting.
- **Housing design** — ventilation, shutters, insulation — **MODERATE.**
- **Acclimatisation protocols, work-rest cycles, hydration and shade for outdoor workers — STRONG** in the occupational literature, and the regulatory instrument is a heat standard with mandatory rest breaks.
- **Rescheduling work and sport away from the hottest hours, and cancelling events on high wet-bulb days — STRONG.**
- **Medication review before summer** for drugs that impair thermoregulation — **MODERATE**, and free.
- **Never leaving a child or an animal in a parked vehicle — STRONG**, and the mechanism is rapid interior heating.
- **Education on recognising heat illness — MODERATE.**

Treatment. For **hypothermia**:

1. **Remove from the cold, remove wet clothing, insulate, and prevent further loss.** First, and free.
2. **Passive external rewarming** for mild hypothermia — dry insulation, a warm environment, and the patient's own shivering, which is an effective heat source if fuel is available.
3. **Active external rewarming** — forced warm air, heating pads, radiant heat, warm water immersion.
4. **Active internal rewarming** — warmed humidified oxygen and warmed intravenous fluids, and in severe cases body-cavity lavage.
5. **Extracorporeal rewarming** for hypothermic cardiac arrest. **The best survival of any cardiac arrest aetiology, and it requires a centre.**
6. **Careful handling and minimal movement** in moderate and severe hypothermia; rough handling can precipitate ventricular fibrillation.

7. **Prolonged resuscitation.** Defibrillation and drugs are ineffective below about 30 °C, so **resuscitation is continued while rewarming proceeds**, sometimes for hours.
8. **Treating the cause** — glucose for hypoglycaemia, antibiotics for sepsis, thyroid hormone where indicated, and in a newborn treating the sepsis that the hypothermia may signal.
9. **Warming all fluids and blood** in the trauma patient.

For **heat stroke**:

1. **Cool immediately, and cool fast. Cooling rate determines survival.**
   - **Cold water immersion is the most effective method** and is the standard for exertional heat stroke — **cool first, transport second**, which inverts the usual order and is the key clinical instruction.
   - **Evaporative cooling** — spraying or sponging with water and fanning — where immersion is impossible. Effective, and it needs water and a fan or a piece of card.
   - **Ice packs to the neck, axillae and groin; cold intravenous fluids; iced gastric or rectal lavage** in extremis.
   - **Antipyretics do not work.** Paracetamol and non-steroidal anti-inflammatory drugs have no role in heat stroke, because the hypothalamic set point is not raised — this is not fever. **Giving them wastes time, and the anti-inflammatories harm the kidneys that are already at risk.**
2. **Airway, breathing, circulation, and intravenous fluid**, with care for the fluid status, which differs between exertional and classical heat stroke.
3. **Treating the complications** — rhabdomyolysis and acute kidney injury, by the same management as crush injury; hepatic failure; coagulopathy; seizures; electrolyte disturbance.
4. **Stopping the exertion and removing the clothing.**
5. **Monitoring core temperature** — rectal or oesophageal. **Axillary and tympanic readings are unreliable in heat stroke** and underestimate the core.
6. **Dantrolene does not work in heat stroke** — it is for malignant hyperthermia, a different condition. A negative worth stating because the two are confused.

Simple means. For **hypothermia**:

- **A dry cloth, a hat, and body contact. For the newborn this is the entire intervention and it carries the kangaroo mother care mortality effect, relative risk 0.75**†. Nothing in this book is cheaper or better evidenced.
- **Drying and removing wet clothing.** Evaporation is the largest heat loss.
- **Insulation from the ground** — a mat, cardboard, dry vegetation. Conduction to cold ground is a major loss and the countermeasure is anything dry underneath.
- **Shelter from wind; a blanket; a plastic sheet or survival bag.**
- **Warm sweet drinks** for a conscious shivering patient — fuel for shivering, which is the body's own rewarming mechanism.
- **Skin-to-skin contact between two people in a sleeping bag or blanket.**
- **Not rubbing the extremities, not giving alcohol, and handling the patient gently.**
- **Prolonged resuscitation in cold-water drowning and hypothermic arrest** — free, and justified by the neuroprotection.
- **Closing windows and doors; a single heated room; blankets and layered clothing** for an older person in a cold house.
- **A daily visit** to an isolated older person.

For **heat illness**:

- **Water, shade, and rest.** The three-word prevention and treatment.

- **Cold water immersion in anything that holds water** — a tub, a tarpaulin held by bystanders, a stock trough, a river. **This is the most effective treatment for exertional heat stroke and it needs only water and a container.**
- **Wetting the skin and fanning.** Evaporative cooling with a spray bottle or a wet cloth and a piece of card. **Free, and it works.**
- **Ice or cold packs to the neck, armpits and groin**, and wet cloths where there is no ice.
- **Removing clothing.**
- **Oral rehydration solution** — sugar, salt and water.
- **Working in the early morning and late afternoon; a work-rest cycle; a shaded rest place; a water container at the work site.**
- **A fan.** Where humidity is not extreme, a fan is an effective cooling intervention at very low power and very low cost, and it is the realistic alternative to air conditioning for most of the world's population.
- **Wetting clothing and skin, and wet cloths on the head and neck** during a heatwave.
- **Opening windows at night and shuttering by day; a wet sheet in a doorway; shading the roof.**
- **Checking on neighbours** during a heatwave. **Social isolation was a leading risk factor in the Chicago and European heatwave analyses, so a knock on a door is a medical intervention.**
- **Never leaving a child in a vehicle.**
- **Teaching that antipyretics do not work and that cooling comes before transport.**

The minimum chain: a dry cloth and body heat for hypothermia; water, shade and a container to sit in for heat stroke. Both conditions are reversible with materials that cost nothing, and both kill when those materials are not applied in time.

Gaps. The 489,000 heat-deaths-per-year figure has no named source in the compilation that carries it, and GBD's environmental heat and cold exposure series was not retrievable. There is no global incidence figure for either condition as a clinical entity. **The temperature-attributable mortality literature, reporting millions annually with cold exceeding heat, could not be verified and measures something different from clinical cases** — most heat and cold deaths are cardiovascular and respiratory deaths never diagnosed as heat or cold illness, and the two literatures are not reconciled anywhere located. Neonatal hypothermia has no burden figure at all, despite being prevented by a dry cloth. No effect sizes were retrievable for heat-health action plans, cooling centres, urban greening, home heating interventions or occupational heat standards. The cooling-rate evidence for heat stroke is from military and athletic series, which are young, fit and observed populations, and its applicability to classical heat stroke in isolated older people is an extrapolation. Occupational heat exposure is growing and is poorly measured, particularly in informal agriculture and construction. The wet-bulb threshold beyond which human thermoregulation fails is a physiological inference with limited direct human data. Trend statements about rising heat mortality rest on attributable-burden modelling that could not be verified here.

> **Depth.** Starts in: the body core. Size: 1.7 m†; depth +15.87. First complaint: about 2 hours († hours of exposure); time depth 41.24. One untreated course: about 6 hours († hours); depth 42.24.
>
> **Model reading.** Way of ending: supply from outside. Layer: surround. By the rule it ends when the shortage is supplied in time. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: supply from outside what is short. This is a reading. The status above stands.

Foreign body aspiration

What it is. An object — a piece of food, a small toy, a button battery — is breathed in instead of swallowed. If it blocks the windpipe the person cannot breathe and dies within minutes. If it lodges lower it causes coughing, wheeze and repeated chest infection, sometimes for months before it is found.

Measured. No global incidence figure and no deaths figure for foreign body aspiration were located, in the current or the prior round. GBD reports injury burden by external cause, and the relevant cause is other unintentional injuries, for which no figure was retrievable.

The condition is concentrated in **children under 3**, in whom it is a leading cause of unintentional injury death in the published national series. In the United States, choking causes of the order of **100 to 200 child deaths a year and tens of thousands of emergency department visits** for food and non-food choking in children, with nuts, seeds, hard sweets, grapes, hot dogs and popcorn the most frequently implicated foods and small toy parts, coins, button batteries and balloons the most frequent non-food items. **These are national-series figures reported as the standing literature position and they were not verified**. No figure is asserted.

Button batteries are a distinct and growing hazard with a different mechanism — electrical burn of the oesophagus within hours rather than airway obstruction — and national poison-centre series report rising incidence and a small number of deaths and severe injuries annually.

It occurs everywhere, and **the mortality is concentrated where bronchoscopy is unavailable**, because the lodged foreign body that does not fully obstruct requires rigid bronchoscopy to remove.

Where it starts. Age under 3 years is the determinant, and the mechanism is developmental: no molars, immature chewing and swallowing coordination, a narrow airway, hand-to-mouth exploration, and a tendency to run, laugh or cry while eating.

Food characteristics — round, hard, smooth, compressible or slippery items that match the paediatric airway diameter. **Nuts, seeds, whole grapes, hard sweets, raw carrot, popcorn, hot dogs and sausage pieces, and chewing gum** are the repeatedly implicated classes.

Small objects within reach — coins, marbles, small toy parts, pen caps, beads, pins, and deflated or burst balloons, a repeatedly identified cause of fatal obstruction because the latex conforms to the airway.

Button and coin cell batteries, where the mechanism is electrochemical burn, not obstruction, and the hazard window is hours.

In older children and adults: intellectual disability, neurological impairment with impaired swallow, dentures, sedation, alcohol, and eating while talking or lying down. **Stroke and neurodegenerative disease with dysphagia** produce the adult aspiration population, who aspirate food and fluid rather than objects, and whose consequence is pneumonia rather than obstruction. Absence of adult supervision at meals, and older siblings feeding younger ones. No effect sizes were located.

What is not known is the incidence and mortality globally. **This is a condition in which death occurs within minutes in front of a witness, and there is no global count.** Also not well characterised: the share of chronic childhood respiratory morbidity — recurrent wheeze, persistent cough, localised bronchiectasis — caused by an unrecognised retained foreign body. The published bronchoscopy series repeatedly report cases found months after the event, having been treated as asthma, which implies a misdiagnosed population of unknown size.

Cure status. Complete airway obstruction: CURABLE in seconds by a bystander, with back blows and abdominal thrusts, or chest thrusts in an infant. **Removing the object restores a completely normal child.** Not removing it causes death, or hypoxic brain injury in the resuscitated — RELIEF ONLY for that. Partial or lower airway obstruction: CURABLE by rigid bronchoscopy, with complete recovery in the large majority. **Delayed diagnosis leads to granulation tissue, persistent infection and localised bronchiectasis**, which is CONTROLLABLE and may require lobectomy — so the cure becomes progressively harder and more destructive with time. Button battery ingestion: CURABLE if removed within hours; catastrophic after. The burn perforates the oesophagus and can erode into the aorta. **The time window is the entire clinical issue and it is measured in hours, not days.** Aspiration pneumonia in the adult with dysphagia: CURABLE as an episode, CONTROLLABLE as a tendency.

Prevention. This entry is prevention-dominated, and the measures are cheap and specific.

- **Not giving high-risk foods to children under about 4 — STRONG** on mechanism, and it is the single highest-yield measure. **No nuts, whole grapes, hard sweets, popcorn, raw carrot sticks, or whole hot dog or sausage pieces. Cutting grapes lengthways into quarters, grating raw vegetables, and chopping sausage lengthways** removes the hazard. **Free.**

- **Supervision at meals; sitting still to eat; not eating while running, laughing or lying down — STRONG** on mechanism.
- **Small-parts regulation of toys — STRONG.** The small-parts cylinder test — a gauge approximating the throat of a child under 3, against which toy parts for that age group must not fit — is embodied in United States consumer product safety regulations and in the European and international toy safety standards. **A regulatory measure with a physical gauge**, and the surveillance literature attributes substantial reductions in toy-related choking deaths to it. **No effect size was retrievable**.
- **Labelling of choking hazards on toys — MODERATE.**
- **Balloon warnings and keeping latex balloons away from young children — MODERATE**, because burst balloon fragments are a recognised cause of fatal obstruction.
- **Button battery compartment regulation — STRONG where enacted.** Requiring screw-secured battery compartments in consumer products, child-resistant packaging for loose batteries, and warning labelling. Several jurisdictions have introduced mandatory standards following clusters of deaths, and **United States legislation of 2022 requires secured compartments and performance standards**†. **This is the clearest recent example of product regulation responding to a specific injury mechanism.**
- **Keeping small objects out of reach, and getting down to child height to survey a room** — free.
- **Child-resistant packaging** for small items.
- **Training parents and carers in choking first aid — STRONG** on mechanism. Free knowledge with a minutes-long window.
- **Dysphagia assessment, and modified diet and fluid consistency** after stroke or in neurodegenerative disease — **STRONG** for aspiration pneumonia, with the caveat that thickened fluids themselves have a contested evidence base.
- **Oral hygiene in the dependent patient — MODERATE** for aspiration pneumonia, and it is a toothbrush.
- **Dental care and well-fitting dentures.**

Treatment. The ordering by setting matters. **1. For complete obstruction with a conscious patient: back blows and abdominal thrusts, or chest thrusts in an infant, immediately.**

- **Adult and child over 1: up to 5 back blows between the shoulder blades, then up to 5 abdominal thrusts, alternating.**
- **Infant under 1: up to 5 back blows, then up to 5 chest thrusts. Abdominal thrusts are not used in infants**, because of the risk of visceral injury.
- **This is the treatment and it is delivered by a bystander with their hands.** The evidence is observational and mechanistic — a randomised trial is impossible — and the effectiveness in reported series is high.
- **Encourage coughing if the person can cough, speak or breathe.** An effective cough is better than any intervention and should not be interrupted.

2. If the patient becomes unconscious: start resuscitation. Chest compressions generate airway pressure and may expel the object.

3. Direct laryngoscopy and removal with Magill forceps, where equipment and a trained operator are present.

4. Rigid bronchoscopy. The definitive treatment for a lodged airway foreign body, with success rates above 95 per cent in the published series†. It requires a rigid bronchoscope, general anaesthesia and a trained operator — **and its absence is what makes this condition lethal or chronically disabling in low-resource settings.** Flexible bronchoscopy has a role for diagnosis and for some removals.

5. Emergency surgical airway — cricothyroidotomy for complete obstruction above the cricothyroid membrane that cannot be relieved. A scalpel and a tube; rarely indicated, and the obstruction is usually below the level it bypasses.

6. For button battery ingestion: immediate removal, endoscopic, within hours. Honey or sucralfate given before removal has been shown in animal and early clinical work to reduce oesophageal injury by neutralising the alkaline burn, and is now recommended as a holding measure in children over 12 months while transport to endoscopy proceeds†. **Honey, in this instance, is an evidenced emergency treatment.**

7. Antibiotics for the pneumonia distal to a retained foreign body, and for aspiration pneumonia. EML-listed, off-patent, cheap. **They do not substitute for removing the object.**

8. Chest physiotherapy and bronchodilators have no role in dislodging an airway foreign body and may convert a partial obstruction into a complete one. A negative worth stating.

9. Lobectomy for established bronchiectasis distal to a long-retained foreign body.

Simple means. This entry's treatment is almost entirely simple means, and so is its prevention.

- **Back blows and abdominal or chest thrusts. Hands, and nothing else. The highest-value simple means in the entry and among the highest in the chapter**, because the alternative within four minutes is death and the intervention is free.
- **Encouraging an effective cough, and not interfering with it.**
- **Teaching choking first aid to every parent, carer, teacher and food-service worker.** A twenty-minute demonstration. **The intervention is knowledge with a minutes-long window and no equipment.**
- **Cutting food up. Grapes quartered lengthways, sausage split lengthways, raw vegetables grated, nuts ground or withheld.** Free, and it is the single most effective preventive act.
- **Not giving nuts, hard sweets, popcorn or whole grapes to a child under four.** A rule.
- **Getting down to the floor and looking at what is within reach of a crawling child.** Free.
- **Taping or screwing shut battery compartments on household devices**, and keeping loose button batteries out of reach. A roll of tape.
- **Honey for a swallowed button battery** in a child over 12 months, while getting to hospital. A spoonful of honey, as an evidenced emergency measure.
- **Sitting the child down to eat, and supervising.**
- **A toothbrush.** Oral hygiene in the dependent patient reduces aspiration pneumonia.
- **Positioning for swallowing** — upright, chin slightly down, small mouthfuls, no talking while eating — taught to a family caring for someone with dysphagia. Free.
- **The recovery position** for the unconscious patient.
- **Thinking of it.** A child with persistent unilateral wheeze, chronic cough or recurrent pneumonia in one lobe, treated as asthma, may have a retained foreign body. **Asking whether they could have inhaled something costs nothing and is what prevents the lobectomy.**

The minimum chain: **two hands and a piece of knowledge.** For the lodged foreign body, rigid bronchoscopy, and there is no simple means that substitutes for it, which is why the chronic cases exist.

Gaps. There is no global incidence figure and no global deaths figure, for a condition that kills small children within minutes in front of witnesses, and the national figures above are reported as the standing literature position and were not verified. GBD has no retrievable series for foreign body effects. No effect size was retrievable for small-parts toy regulation, for food-cutting advice, for button battery compartment standards or for choking first aid training — the entire prevention set is recommended on mechanism. The share of chronic childhood respiratory morbidity caused by unrecognised retained foreign bodies is unknown, and the bronchoscopy series imply it is not negligible. **Back blows and thrusts cannot be randomised**, so the first-aid evidence is observational and mechanistic; that is an acceptable limitation and should be stated rather than glossed. Button battery injury incidence is rising and is counted only in national poison-centre series, with no global figure. The honey recommendation for button battery ingestion rests on animal work and early clinical data, and the age restriction above 12 months matters because of infant botulism risk. Thickened fluids for dysphagia have a contested evidence base, and the trial evidence has not supported the practice as strongly as its adoption implies. Bronchoscopy availability is not quantified anywhere located, despite being the determinant of outcome for the non-obstructing case.

> **Depth.** Starts in: an object in the airway. Size: 1 cm†; depth +11.19. First complaint: about 5 seconds († seconds); time depth 34.62. One untreated course: about 4 minutes ([B] death within minutes when the airway is closed); depth 38.14.
>
> **Model reading.** Way of ending: remove. Layer: mesh. The book names an early stratum. By the rule it ends when the foreign party is taken away in time. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: take the foreign party away, as early as possible. This is a reading. The status above stands.

Animal bites

What it is. An animal's teeth break the skin. The wound itself is usually minor; what matters is what was in the animal's mouth. A dog bite can transmit rabies, which is invariably fatal once symptoms begin, and is entirely preventable in the hours after the bite.

Measured. The rabies death figures differ roughly fourfold and both are printed. GBD 2023 gives **15,800 rabies deaths** for 2023. WHO's own page gives **44,203** for 2021 on its Global Health Estimates, while its key facts say only "tens of thousands" annually. WHO's long-standing published estimate, widely cited, is approximately **59,000** a year†. The difference arises because rabies deaths occur at home in rural areas with no diagnosis and no registration.

Dogs transmit 99 per cent of human rabies cases in WHO's key facts, and "up to 99 per cent" in the body of the same page. **Forty per cent of rabies deaths are children under 15** in the key facts, and the body states only that children aged 5 to 14 are frequent victims, with no percentage. Both printed; WHO's own page hedges between its key facts and its body on both figures.

Fatality once symptoms appear: 100 per cent in the key facts and "virtually 100 per cent" in the body.

Wound washing: at least 15 minutes. **Incubation: typically 2 to 3 months, with a range from one week to one year**; paralytic rabies accounts for about 20 per cent of human cases.

Over 29 million people receive human rabies vaccine annually, and **the average cost of post-exposure prophylaxis was US$108 in 2018**, against at-risk people living on US$1 to 2 a day. **Intradermal vaccination cuts the cost by 60 to 80 per cent**, and there were 3 WHO pre-qualified human rabies vaccines as of 2024. The global economic cost of rabies is about **US$8.6 billion a year**.

Three countries have been validated for eliminating dog-mediated human rabies — Bhutan, Chile and Mexico — as of September 2026, and 17 countries have self-declared rabies-free status, against a 2030 target.

Snakebite, covered separately, is by far the largest animal-inflicted mortality in this chapter at 5.4 million bites, 1.8 to 2.7 million envenomings and 81,410 to 137,880 deaths annually†.

No global incidence figure for animal bites as a lesion was located. The standing estimate is tens of millions of dog bites requiring medical attention annually, with children disproportionately affected and bitten more often to the head and neck.

Rabies deaths are concentrated in Asia and Africa, in rural areas and among the poor, and the disease has been eliminated from domestic dog populations in most of Europe, the Americas and parts of Asia by dog vaccination.

Where it starts. Dog bites are the dominant source of both bite injury and rabies. **Free-roaming and unvaccinated dog populations are the determinant**, and rabies elimination tracks dog vaccination coverage rather than human treatment coverage.

Children are disproportionately bitten, bitten to the face and neck because of their height, less able to avoid or fend off a dog, and less likely to report a bite. **Cat bites** are a small puncture with a high infection rate, because the tooth inoculates deeply and the wound closes over; cat bites to the hand have a particularly high rate of septic arthritis and tenosynovitis. **Monkey, bat and other wildlife exposure**: **bats are the principal rabies reservoir in the Americas and a recognised source elsewhere**, and bat bites and scratches may be unnoticed, which is why exposure history includes waking with a bat in the room. **Human**

bites have a high infection rate, and the clenched-fist injury over a knuckle inoculates a joint. **Livestock** — kicks, crushing and bites in agricultural work. **Occupational exposure** — veterinarians, animal handlers, abattoir workers, wildlife researchers, who are the pre-exposure prophylaxis population. Provoking behaviour, approaching an unfamiliar or feeding dog, and leaving a young child unsupervised with a dog. Poverty and rurality determine both exposure and whether prophylaxis is reached. No effect sizes were located.

What is not known is the incidence of animal bites globally as a lesion, and, more consequentially, **the true rabies mortality**: GBD's 15,800, WHO's 44,203 for 2021, and the widely cited approximately 59,000 span a fourfold range. **Community-based surveys in India and parts of Africa have repeatedly found rabies deaths far above official figures**, the same under-ascertainment pattern as snakebite.

Cure status. The bite wound: CURABLE. Cleaning, selective antibiotics, and delayed rather than primary closure. Recovery is complete apart from scarring, and facial bites in children may need reconstruction. Bite-wound infection: CURABLE with antibiotics and drainage. Rabies, before symptoms appear: CURABLE. **Post-exposure prophylaxis given promptly is close to completely effective.** Wound washing, vaccine, and rabies immunoglobulin for severe exposures prevent the disease in essentially all treated cases. Rabies, once symptomatic: RELIEF ONLY, and fatal. **Case fatality is 100 per cent once symptoms appear**. A handful of survivals have been reported in the world literature, most with severe neurological sequelae, and no treatment protocol has proved reproducible — the Milwaukee protocol has failed on repeated attempt and is not recommended. **Treatment is palliative: sedation and analgesia for one of the most distressing deaths in medicine.** Tetanus: RELIEF ONLY, and preventable by vaccine.

Rabies is the sharpest division in this book. Entirely preventable before symptoms; essentially 100 per cent fatal after. The incubation period is typically two to three months, which is the entire opportunity: a bite today can be rendered harmless this week and is untreatable once the symptoms arrive.

Prevention.

- **Mass dog vaccination — STRONG, and it is the intervention that eliminates the disease.** WHO's position is that **vaccinating 70 per cent of the dog population interrupts transmission**†, and this is the measure that removed canine rabies from Europe, most of the Americas and parts of Asia. **A dog vaccine dose costs of the order of a US dollar or less**, against **US$108 for a human post-exposure course in 2018** for every person that dog would otherwise bite. **The cost-effectiveness case is overwhelming and the intervention is veterinary, not medical** — which is precisely why it is under-funded, because it falls outside health budgets. Three countries have been validated for elimination of dog-mediated human rabies. The 70 per cent figure is WHO's standing position and was not verified against a source fetched in the retrieval round.
- **The global target is zero human deaths from dog-mediated rabies by 2030**.
- **Post-exposure prophylaxis availability — STRONG** for the individual, and it is treatment of an exposure rather than prevention of the disease in the population. **Expensive relative to dog vaccination, and required for every exposed person indefinitely as long as the dogs are unvaccinated** — over 29 million people receive the vaccine annually.
- **Pre-exposure prophylaxis for high-risk occupations and for children in high-burden areas — MODERATE.**
- **Dog population management — MODERATE**, and **culling is ineffective and counterproductive**; vaccination is the measure that works.
- **Education — STRONG on mechanism**, and specifically: do not approach unfamiliar, feeding or sleeping dogs; do not run from a dog; do not leave a young child alone with any dog; wash every bite immediately; report every bite. **Teaching children bite avoidance is free and the target population is the one WHO's key facts put at 40 per cent of the deaths**.
- **Tetanus immunisation — STRONG.**
- **Responsible pet ownership, leashing, and breed-independent dangerous-dog regulation — MODERATE. Breed-specific legislation has a weak evidence base**; bite-prevention programmes and owner liability have more.

- **Not handling bats, and not keeping wild animals — MODERATE**, and the exposure may be unnoticed.
- **Supervision of children around animals — STRONG** on mechanism.

Treatment. The first item is the most important and the cheapest.

1. Immediate thorough wound washing with soap and running water for at least 15 minutes. **This is the first-line rabies intervention and it is free.** Mechanical removal and the lipid-solvent action of soap on the virus envelope substantially reduce the risk of rabies before any vaccine is given, and the published animal and observational evidence supports it strongly. Povidone-iodine or another virucidal agent after washing, where available. **This single act, performed by the bitten person or their family within minutes, is the highest-value intervention in the entry.**

2. Rabies post-exposure prophylaxis, started as soon as possible.

- **Rabies vaccine**, by intramuscular or **intradermal** regimen. **The intradermal route uses roughly a fifth of the vaccine volume per dose and is WHO-recommended precisely because it makes a vial serve several patients**, which is the practical answer to cost and supply in high-burden settings: **WHO gives the cost reduction as 60 to 80 per cent**. The vaccine is EML-listed and off-patent, and **the average cost of a post-exposure course was US$108 in 2018**, which is catastrophic expenditure for a rural household living on US$1 to 2 a day.
- **Rabies immunoglobulin, or a monoclonal antibody, infiltrated into and around the wound**, for the most severe exposure category — transdermal bites, licks on broken skin, mucous membrane contact, bat exposure. EML-listed under sera and immunoglobulins, off-patent as a plasma-derived product. **Cost: the most expensive component, and the one most often unavailable.** Rabies monoclonal antibodies are now licensed and reduce dependence on plasma supply.
- **Category assessment determines the regimen**, and over-treatment of the mildest exposure category wastes scarce vaccine while under-treatment of the most severe kills.

3. Tetanus prophylaxis — vaccine and, for high-risk wounds in the inadequately immunised, tetanus immunoglobulin. EML-listed, off-patent, cents for the vaccine.

4. Antibiotics — for bites, more often indicated than for other wounds.

- **Amoxicillin-clavulanate** is the standard, covering *Pasteurella* from dogs and cats, *Capnocytophaga*, staphylococci, streptococci and oral anaerobes.
- **Prophylaxis is indicated for cat bites, hand bites, deep puncture wounds, bites requiring closure, bites in immunocompromised or diabetic patients, bites over a joint or tendon, and human bites.** Not routinely for superficial dog bites elsewhere.
- EML-listed, off-patent, cheap.

5. Wound management — irrigation, debridement, and delayed rather than primary closure. **Closing a bite wound primarily causes the infection**, with facial wounds the usual exception where cosmetic need and good blood supply justify careful primary closure with close follow-up.

6. Surgical exploration for hand bites, bites over joints and clenched-fist injuries. **Septic arthritis and tenosynovitis from an apparently trivial puncture is the classic missed injury.**

7. Reconstruction for facial and other disfiguring bites, particularly in children.

8. Palliative care for symptomatic rabies — sedation and analgesia. **Nothing else. The Milwaukee protocol is not recommended.**

9. Psychological support. Post-traumatic symptoms after a dog attack, particularly in children, are common and untreated.

Simple means.

- **Soap, running water, and fifteen minutes. This is the single highest-value simple means in this chapter by ratio of lives saved to cost**, because rabies is otherwise invariably fatal and the washing substantially reduces the risk before any vaccine is involved. **It costs a bar of soap and a quarter of**

an hour, and it must be done by the family within minutes of the bite, which means the intervention is knowledge.

- **Teaching every household that every animal bite must be washed and reported.** Free, and it is the bottleneck: people do not present, or present late, or wash inadequately.
- **Not closing the wound.** Leaving a bite open is both correct treatment and a simple means.
- **A clean cloth dressing.**
- **Dog vaccination.** Not a household simple means, and **the cheapest life-saving intervention in this entry by a wide margin** — about a dollar a dog, 70 per cent coverage, and the disease stops. The chain is a vaccine vial, a cold box and a volunteer with a syringe.
- **Teaching children how to behave around dogs** — do not approach, do not run, do not disturb a feeding or sleeping dog, do not put your face near one. **Free, and the target group carries the largest share of the deaths.**
- **Supervision of young children around animals.**
- **Confining and observing the biting dog for ten days** where possible: if the dog is alive and well after ten days it was not infectious at the time of the bite, which can spare a course of vaccine. **Free, and it is a diagnostic test performed by watching.**
- **Tetanus vaccine** — cents.
- **Not handling bats; not keeping wild animals as pets.**
- **Elevation and immobilisation of a bitten hand**, which is the limb where the trivial-looking bite causes the disabling infection.
- **Recognising the warning signs of wound infection** — spreading redness, pain out of proportion, pus, fever — and returning. Free.
- **Knowing which facility holds rabies vaccine and immunoglobulin**, and going there rather than to a nearer one that does not.

The minimum chain: **soap, water and knowledge** for the first and most important step; **vaccine and immunoglobulin** for the cure, with no substitute, and the intradermal regimen is what makes the vaccine reach more people from the same vial.

Gaps. The rabies death figures span roughly fourfold: GBD 2023's 15,800, WHO's own 44,203 for 2021, and the widely cited approximately 59,000. All printed. **WHO's own page also hedges between its key facts and its body on the dog-mediated share, at 99 per cent against up to 99 per cent, and on fatality, at 100 per cent against virtually 100 per cent; and its key facts assert that 40 per cent of deaths are children under 15, a figure the body nowhere supports.** Rabies deaths are under-ascertained, with community surveys finding figures far above official ones, the same pattern as snakebite. No global incidence figure for animal bites as a lesion exists, and no GBD series for animal contact beyond the rabies proxy. No effect sizes were retrievable for any preventive measure, including dog vaccination, which is the intervention that eliminates the disease, and the 70 per cent coverage threshold is a standing position that was not verified. Rabies immunoglobulin availability, as opposed to EML listing, is not quantified anywhere located, and it is the component most often absent. Breed-specific dog legislation has a weak evidence base and remains widely used, and bite-prevention programme evidence is thin. **No survivor has been reproducibly treated**, and the Milwaukee protocol's early reported success did not replicate — a reminder that a single reported survival is not a protocol. Dog bite morbidity, facial scarring in children and the psychological sequelae are essentially unmeasured.

> **Depth.** Starts in: the bite wound. Size: 1 cm†; depth +11.19. First complaint: about 1 second († instant); time depth 33.15. One untreated course: about 14 days († about 2 weeks); depth 45.90.
>
> **Model reading.** Way of ending: rebuild. Layer: mesh. The book names an early stratum. By the rule it ends when the structure is repaired and the cause has stopped. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: repair the body's own structure, or take the diseased part out. This is a reading. The status above stands.

What no longer holds

Six treatments in this chapter were standard practice and are now known not to work, or to harm. They are collected here because a reference work that records only what is currently recommended leaves the reader unable to recognise the older advice when they meet it.

Syrup of ipecac. Standard household advice for decades, kept in home medicine cabinets and recommended for suspected childhood poisoning. **Not recommended.** It delays effective treatment, it does not reliably remove what was swallowed, and the vomiting it induces carries its own aspiration risk.

Routine gastric lavage. Once the reflex intervention for poisoning on arrival at hospital. Now **considered only for potentially life-threatening ingestion presenting within 60 minutes, and contraindicated for hydrocarbons**. For most poisonings it adds risk and no benefit, and supportive care is what cures.

Methylprednisolone in spinal cord injury. Given for roughly twenty years on the basis of the NASCIS trials, and **withdrawn from most guidelines**: the apparent benefit was a post-hoc subgroup finding, and the harms — infection, pneumonia, gastrointestinal bleeding — were real. It is the clearest example in this chapter of a treatment sustained by a subgroup analysis.

Corticosteroids in head injury. Routine for decades. **The CRASH trial, reported in 2004, found increased mortality** with methylprednisolone in traumatic brain injury and ended the practice. Corticosteroids are now linked to higher death risk in this indication and are not recommended.

GM-CSF and intravenous immunoglobulin in neonatal sepsis. Both were given on mechanism. A 2009 randomised trial found GM-CSF **corrects the neutropenia and does not reduce sepsis or improve survival**, and the INIS trial of intravenous immunoglobulin **found no benefit**. Two clear negatives, in a condition where the cure remains an antibiotic given early.

Therapeutic hypothermia outside high-resource settings. This one is different in kind, because the treatment works where it was first tested and does not travel. **In high-income settings, meta-analysis of the major trials found reduced death or major disability with cooling for neonatal encephalopathy, at a number needed to treat of approximately 7†. The HELIX trial, conducted in India, Sri Lanka and Bangladesh, found no reduction in death or disability and an increase in mortality**. WHO does not recommend it outside settings with intensive care and the capacity to deliver it to protocol, and the low-cost adaptations designed for exactly those settings are therefore unsupported rather than merely unproven.

Three others in this chapter belong alongside them, as practices that are contested rather than superseded. **Antenatal thyrotropin-releasing hormone** for fetal lung maturation is a settled negative. **Universal ultrasound screening for hip dysplasia** produced an insignificant reduction in late diagnoses and is not recommended, while the clinical examination that is recommended was found insufficiently reliable by a 2024 review — both the recommended and the unrecommended strategy carry negative evidence. And **secondary decompressive craniectomy** controls intracranial pressure while the DECRA trial found worse outcomes and the later RESCUEicp trial found lower mortality with more dependent survivors; the trials disagree on the direction of benefit and both are printed.

Chapter 18 — Conditions Related to Sexual Health, the Non-Disease Chapters, and Three Cross-Cutting States

This chapter covers the last of the ICD-11 chapters and three states that cut across all of them.

Part A is ICD-11 chapter 17, conditions related to sexual health. Part B is the seven ICD-11 chapters and sections that do not classify diseases. Part C is three entries — multimorbidity, frailty and palliative care — that belong to no single chapter and govern the outcome of many.

On the burden basis. The book's burden basis is the Global Burden of Disease 2023 study, published in *The Lancet* on 12 October 2025 and presented at the World Health Summit in Berlin. It covers 292 causes of death, 375 diseases and injuries, 88 risk factors, 204 countries and territories and 660 subnational locations, from 1990 to 2023, on more than 310,000 data sources. Where a GBD 2023 figure for a particular category could not be obtained, this chapter uses a WHO figure and names it as WHO, with its reference year, in the text.

PART A — ICD-11 chapter 17: conditions related to sexual health

A standing note on this chapter

Cure status in Part A. The four labels — SELF-LIMITING, CURABLE, CONTROLLABLE, RELIEF ONLY — are statements about what a treatment does to the course of a condition. They are given for every entry here, as everywhere else in this book, and where they do not fit the entry says so and gives the reason.

They do not fit either gender incongruence category. The standing interventions there aim at alignment, at function, or at distress, and not at the removal of a lesion, and WHO does not hold the condition to be one of mental ill-health. Both entries say that in place of a label.

They do fit the dysfunctions, and the answer is often worth having. A desire or erectile difficulty caused by a medication is curable by changing the medication. The same difficulty arising from established arterial disease is not. A reader who is given seven sections here and eight everywhere else cannot tell whether the eighth was weighed and withheld or simply forgotten.

The finding that governs every entry here. Not a single category in chapter 17 has a prevalence estimate measured against the ICD-11 definition. Every figure in the literature comes from an instrument built for DSM-IV, for ICD-10, or for a bespoke survey question. The chapter has existed in released form for seven years and its epidemiology has not been measured.

The scale of that gap is visible in the chapter's best-evidenced category. Male erectile dysfunction carries a published global prevalence range of 3 to 76.5 per cent, and the systematic review reporting it attributes the range to instrument heterogeneity. A 25-fold spread is not a prevalence estimate. It is a measurement failure, and this book records it as one.

The structure of the chapter. Chapter 17 was newly created in ICD-11. The WHO ICD-11 fact sheet lists it as one of three new core chapters, alongside diseases of the immune system and sleep-wake disorders. It contains three blocks of clinical categories — sexual dysfunctions (HA00 to HA0Z), sexual pain disorders (HA20 to HA2Z) and gender incongruence (HA60 to HA6Z) — one aetiology axis (HA40), and two residual codes (HA8Y, HA8Z).

Every sexual dysfunction and HA20 carries the same five-way subdivision: lifelong generalised, lifelong situational, acquired generalised, acquired situational, unspecified. No study has validated that split against natural history, biology or treatment response. It is not repeated in the entries below.

The aetiology axis, HA40. This is not a disorder. It is a set of codes applied alongside a dysfunction code to record contributing factors: a medical condition, injury or effect of surgery or radiation (HA40.0); psychological or behavioural factors, including mental disorders (HA40.1); use of a psychoactive substance or medication (HA40.2); lack of knowledge or experience (HA40.3); relationship factors (HA40.4); cultural factors (HA40.5); and other specified (HA40.Y).

HA40 is the chapter's consequential design decision. ICD-10 split sexual dysfunction between an organic set in the genitourinary chapter and a non-organic set in the mental disorders chapter. ICD-11 abolishes that split. One diagnosis is made, and aetiology is recorded separately on its own axis, where it can be multiple. A single presentation may carry a medical, a medication, a knowledge, a relationship and a cultural code at once.

Read in the net: the five aetiology codes are not five candidate causes competing to be the true one. They are five depths at which the same failure to close can be described, and the axis lets all five stand together. This is a reading, not a mechanism.

What the chapter does not contain. Chapter 17 is not the complete set of sexual-health conditions. WHO places elsewhere, and lists as exclusions on the chapter page: paraphilic disorders (6D30 to 6D3Z, in the mental and behavioural disorders chapter); adrenogenital disorders (5A71); predominantly sexually

transmitted infections (1A60 to 1A9Z); contact with health services for contraceptive management (QA21); sexual dysfunction associated with pelvic organ prolapse (GC42); female dyspareunia (GA12); and pain related to the vulva, vagina or pelvic floor (GA34.0).

Infertility is also outside this chapter. WHO's infertility fact sheet of 28 November 2025 defines it as failure to achieve pregnancy after 12 months or more of regular unprotected intercourse, and gives a lifetime prevalence of approximately one in six people of reproductive age worldwide. That page gives no absolute count and no regional breakdown. WHO issued its first global guideline on infertility on the same date.

The residual codes. HA8Y, other specified conditions related to sexual health, and HA8Z, unspecified, carry no epidemiology and no treatment. HA8Z in particular absorbs poorly characterised presentations in routine coding, which inflates the unspecified count in any national dataset built on this chapter.

Where the evidence base is weakest. Ranked, weakest first:

1. **Gender incongruence of childhood (HA61).** No prevalence data of any kind. No established aetiology. No reliable persistence figure. Intervention evidence in which nine of ten studies were rated low quality by their own reviewers.
2. **Sexual pain-penetration disorder (HA20).** No prevalence data for the category as defined. The controlling Cochrane review found no demonstrated effect for systematic desensitisation, rated every included study at moderate or high risk of bias, and its literature search ends in August 2012.
3. **Female sexual arousal dysfunction (HA01.0).** No distress-qualified prevalence figure anywhere. The construct's two components correlate poorly.
4. **Orgasmic dysfunctions (HA02).** No distress-qualified prevalence. Sex-asymmetric classification by construction. Behavioural treatment evidence pre-modern in method.
5. **Ejaculatory dysfunctions (HA03).** Self-report prevalence of up to 30 per cent against clinically significant prevalence of under 5 per cent, a sixfold gap, with the guideline rejecting its own field's higher figure.
6. **Hypoactive sexual desire dysfunction (HA00).** Usable United States and Australian data, none elsewhere, none in men, none against the ICD-11 definition. Drug evidence graded very low by its own meta-analysts.
7. **Gender incongruence of adolescence or adulthood (HA60).** Self-identification data exist and are not prevalence of the diagnosis. Adolescent treatment evidence low quality by its reviewers' assessment.
8. **Male erectile dysfunction (HA01.1).** The best-evidenced category in the chapter, and still carrying a published global prevalence range of 3 to 76.5 per cent†.

Hypoactive sexual desire dysfunction (HA00)

What it is. Absence or marked reduction of desire or motivation for sexual activity. ICD-11 recognises three presentations: little or no spontaneous desire, with few sexual thoughts or fantasies; little or no responsive desire to erotic cues; or inability to sustain desire once activity has begun.

The pattern must be present episodically or persistently for at least several months and must cause clinically significant distress. The distress requirement does substantial work. Low desire without distress is not a diagnosis under ICD-11.

Measured. The largest study is the United States PRESIDE survey: 31,581 women aged 18 and over, drawn from 50,002 sampled households on a nationally representative research panel. Age-adjusted point prevalence was 43.1 per cent for any sexual problem, 22.2 per cent for sexually related personal distress on the Female Sexual Distress Scale, and 12.0 per cent for any distressing sexual problem. By age: 10.8 per cent under 45, 14.8 per cent at 45 to 64, and 8.9 per cent at 65 and over (Shifren et al., *Obstetrics & Gynecology* 2008;112(5):970–978).

Unadjusted component figures from the same survey circulate widely: low desire 39 per cent, arousal problems 26 per cent, orgasm difficulties 21 per cent, any problem 43 per cent, distress 12 per cent†. The 39

per cent low-desire figure and the 12.0 per cent distress-qualified figure differ by a factor of three and are routinely quoted interchangeably. Only the second is diagnostically relevant.

An Australian cohort of 1,548 women aged 65 to 79, mean age 71, found low sexual desire in 88.0 per cent (95 per cent CI 86.3 to 89.6), sexually related personal distress in 15.5 per cent (13.8 to 17.4), and the full diagnosis in 13.6 per cent (11.9 to 15.4)†. Within that cohort the diagnosis was present in 23.7 per cent of partnered women against 5.9 per cent of unpartnered women, and in 31.5 per cent of sexually active against 17.3 per cent of sexually inactive women† (Zeleke, Bell, Billah & Davis, *Menopause* 2017;24(4):391–399).

Low desire rises with age. Distressing low desire does not: it peaks in midlife and falls after. The Australian figures make the divergence plain. Desire is low in nearly nine women in ten at 65 to 79, and one in seven meets the distress-qualified definition.

Usable population data exist for the United States and Australia. Comparable nationally representative, distress-qualified data do not exist for most of the world, including almost all of Africa, South Asia, Latin America and the Middle East. There is no large distress-qualified prevalence study in men.

Where it starts. The PRESIDE regression identified poor self-assessed health, low education, depression, anxiety, thyroid conditions and urinary incontinence as correlates of distressing sexual problems. The study is cross-sectional, so direction is not established.

Partnership status and current sexual activity are strongly associated. Partnered women in the Australian cohort had about four times the prevalence of unpartnered women. The direction is the opposite of the naive expectation, and indicates that the distress criterion is partly measuring relational context.

Medication is a measured cause in one direction. Antidepressant-associated sexual dysfunction is established well enough to carry its own Cochrane review of management strategies: 23 trials, 1,886 participants (Taylor et al., Cochrane CD003382, 1 May 2022).

What is not known is more than what is. Whether hypoactive desire is a single entity. Whether the lifelong-acquired and generalised-situational subtypes correspond to anything with distinct natural history, biology or treatment response. Whether the association with depression runs in either direction or reflects a third factor. There is no established biomarker, no established endocrine threshold and no replicated neurobiological finding separating cases from controls.

Cure status. Distress traced to a removable cause: CURABLE. The cause may be a medication (HA40.2), a lack of knowledge or experience (HA40.3) or a relationship factor (HA40.4). Where the cause is removed, desire can return. No proportion has been measured, and the trial evidence quantifying the response is thin.

Persistent, with no removable cause: RELIEF ONLY. Flibanserin gave 0.49 more satisfying sexual events per month than placebo, about one every two months. Its authors graded the evidence very low and the overall improvement minimal to absent. The state is not held and nothing removes it.

Prevention. No evidence base. No trial has tested prevention of this condition as an outcome.

The one partial item is iatrogenic. Choosing an antidepressant with a lower sexual side-effect profile is a prevention-shaped decision. The comparative evidence addresses management once dysfunction is present, not its prevention — WEAK.

Treatment. Flibanserin is the best-quantified drug. A systematic review and meta-analysis pooled 8 randomised trials, 5 published and 3 unpublished, 5,914 women. The pooled mean difference for 100 mg against placebo was 0.49 satisfying sexual events per month (95 per cent CI 0.32 to 0.67). The Female Sexual Function Index desire score difference was 0.27 (0.17 to 0.38)†. That is one additional satisfying sexual event every two months.

Harms in the same analysis: dizziness RR 4.00 (2.56 to 6.27), somnolence RR 3.97 (3.01 to 5.24), nausea RR 2.35 (1.85 to 2.98), fatigue RR 1.64 (1.27 to 2.13). The authors graded the quality of evidence as very low and concluded that the overall improvement was minimal to absent against a substantially raised adverse-event risk (Jaspers, Feys, Bramer, Franco, Leusink & Laan, *JAMA Internal Medicine* 2016).

Testosterone in women is the other pharmacological option. The standing systematic review and meta-analysis of randomised trial data is Islam, Bell, Green, Page & Davis, *Lancet Diabetes & Endocrinology* 2019;7(10):754–766. Its pooled effect sizes are not quoted here; they were not obtained.

Clinical guidance differs by jurisdiction. Flibanserin and bremelanotide are approved by the United States Food and Drug Administration for this condition in premenopausal women. The European Medicines Agency has not approved flibanserin; the manufacturer withdrew its European application. The same evidence base supports a marketing authorisation in one jurisdiction and not in the other. Testosterone for women is approved for this indication in very few countries and is commonly prescribed off-label where it is used.

Simple means. Counselling, psychosexual therapy and couple-based interventions require no industrial chain. The measured effect is poorly characterised: no current high-quality systematic review of psychological interventions for hypoactive desire specifically was obtained.

Addressing a removable aetiology is both simple and directly supported by the chapter's own axis. Medication (HA40.2), lack of knowledge or experience (HA40.3) and relationship factors (HA40.4) are each coded causes with an available response. The trial evidence quantifying those responses is thin.

Gaps. No prevalence data measured against the ICD-11 definition. No large prevalence study in men. No population data outside high-income Western countries. The four-way subtyping is unvalidated. The 39 per cent and 12.0 per cent figures from one survey differ threefold and are quoted interchangeably. Pharmacological effect sizes are small and their own authors grade the evidence very low.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 40 years († onset about age 40); time depth 52.23. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Female sexual arousal dysfunction (HA01.0)

What it is. Absence or marked reduction of response to sexual stimulation. ICD-11 defines the parent category HA01 as covering difficulties with the physiological or the subjective aspects of arousal. The wording admits a presentation in which genital response is intact and subjective arousal absent, and the reverse.

Measured. PRESIDE reported arousal problems in 26 per cent of 31,581 United States women, unadjusted. That survey publishes its distress-qualified figure as a composite across problem types, 12.0 per cent, and not separately by type. A distress-qualified arousal-specific prevalence is therefore not available from the largest study.

No nationally representative, distress-qualified prevalence estimate for this condition exists for any country. There are no data outside high-income countries. The quality of the prevalence evidence is low.

Where it starts. Postmenopausal urogenital change is the best-established association. Its standing in this category is complicated by the classification itself: ICD-11 excludes from the sexual pain category what is entirely explained by postmenopausal or age-related change, and the analogous reasoning bears on arousal.

Antidepressant medication is an established cause (Taylor et al., Cochrane CD003382, 2022). Beyond these, aetiology is not known. The relationship between measured genital vasocongestion and reported subjective arousal is weak, which undermines the construct itself.

Cure status. Arousal difficulty on antidepressant treatment: CONTROLLABLE. Bupropion 150 mg twice daily added to the antidepressant gave SMD 1.60 (95 per cent CI 1.40 to 1.81) in 3 studies, pooled across men and women. The review's authors call the evidence rather limited. The added drug is continued, so the state is held and not removed.

All other presentations: RELIEF ONLY. No treatment has a measured effect on this category. Lubricants, psychosexual counselling and directed stimulation relieve, and their effect is not quantified. Arousal

difficulty explained by urogenital atrophy belongs to the genitourinary chapter, where oestrogen is standing treatment.

Prevention. No evidence base. No prevention target has been defined for this condition.

Treatment. For antidepressant-associated dysfunction, the Cochrane review found a benefit for added bupropion 150 mg twice daily, pooled across men and women: SMD 1.60 (95 per cent CI 1.40 to 1.81), 3 studies. Once-daily 150 mg showed no significant difference. The review's authors describe the available evidence as rather limited and the review carries no GRADE ratings (Taylor et al., Cochrane CD003382, 1 May 2022, 23 trials, 1,886 participants).

Topical and systemic oestrogen is standing treatment for urogenital atrophy. That indication sits in the genitourinary chapter, not here.

Simple means. Lubricants, which need no industrial chain of consequence. Psychosexual counselling. Directed stimulation approaches. The measured effect of each is not well quantified for this category.

Gaps. No distress-qualified prevalence figure exists. The construct's physiological and subjective components correlate poorly, and no study has established whether they belong in one diagnosis. This is among the weakest-evidenced categories in the chapter.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 50 years († onset about age 50); time depth 52.43. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Male erectile dysfunction (HA01.1)

What it is. Inability to attain or maintain an erection sufficient for sexual activity, present for at least several months and causing clinically significant distress. ICD-11 places it in the sexual health chapter rather than the genitourinary chapter. Aetiology — vascular, neurological, endocrine, drug-related, psychological — is coded separately on the HA40 axis rather than determining which chapter holds the diagnosis.

Measured. A systematic review of population-based studies in EMBASE and MEDLINE gives a global prevalence of 3 to 76.5 per cent. The review's own explanation for that range is instrument heterogeneity: screening tools in population-based studies are its named major source of discrepancy. Questionnaires derived from the International Index of Erectile Function and the Massachusetts Male Aging Study identified high prevalence even in young men (Kessler, Sollie, Challacombe, Briggs & Van Hemelrijck, *BJU International* 2019).

A 25-fold range is not a prevalence estimate. It is the measurement failure named in the standing note at the head of this part, and it occurs in the chapter's best-studied category.

Guideline-cited estimates circulate alongside it: up to 30 million men in the United States and 150 million men worldwide (American Urological Association erectile dysfunction guideline, 2018; *Journal of Urology* 2018;200:633). These are estimates and not survey measurements.

Figures with comorbidity are better behaved. From the same guideline: present in 38 to 42 per cent of men with hypertension, with about 35 per cent of hypertensive men having some degree of the condition. Diabetes-related prevalence 20 to 85 per cent depending on severity and duration. One study gave an age-adjusted 28 per cent in men with diabetes against 10 per cent without. Up to 72 per cent of affected men have lower urinary tract symptoms or benign prostatic hyperplasia. And 11 per cent report depression. European Association of Urology guidance adds two figures. The condition is common in metabolic syndrome and type 2 diabetes, in up to 70 per cent of patients. And 30 per cent of affected men have co-existing testosterone deficiency (EAU Guidelines on Sexual and Reproductive Health, 2024).

Prevalence rises steeply with age in every study. Age-specific figures from the Massachusetts Male Aging Study, the standard longitudinal source, are not reproduced here; they were not obtained. Population-based

studies exist across many countries and are not comparable, because the instruments differ. No harmonised global estimate exists.

The quality of the prevalence evidence is low for the absolute figure and high for the age gradient and the comorbidity associations.

Where it starts. The strongest established associations, with their measures. Diabetes, age-adjusted 28 per cent against 10 per cent. Hypertension, 38 to 42 per cent prevalence in hypertensive men. Metabolic syndrome, up to 70 per cent. Lower urinary tract symptoms or benign prostatic hyperplasia, up to 72 per cent co-occurrence. Testosterone deficiency, 30 per cent co-existence†.

The AUA guideline states that the condition is independently associated with cardiovascular disease and may be the first clinical sign of atherosclerosis in some men. That makes it diagnostically useful beyond itself.

What is not known: the relative contribution of vascular, neurogenic and psychological mechanisms in an individual case, which no available test determines; whether the condition is a causal step toward cardiovascular events or a marker only. Natural history without treatment is poorly described, because treatment is near-universal where it is available.

Cure status. Reversible single cause: CURABLE. A causative medication stopped or switched, a correctable endocrine deficiency, or a focal arterial lesion in a young man treated by reconstruction removes the cause, and the dysfunction goes with it. No proportion has been measured. Arterial reconstruction carries a Conditional, Grade C recommendation (AUA 2018).

Established vascular, diabetic or neurogenic disease, or no cause identified: CONTROLLABLE. Phosphodiesterase type 5 inhibitors, vacuum devices and injections restore function while they are used. In men with diabetes the inhibitors raised successful attempts by 26.7 percentage points over control (95 per cent CI 23.1 to 30.3). They do not alter the underlying disease. The condition may be the first sign of atherosclerosis, and that disease remains.

A penile prosthesis is in this stratum, not in the curable one. It replaces the function. It destroys the native erectile tissue and does not restore it.

Prevention. The evidence is indirect. The AUA 2018 guideline makes a Moderate Recommendation, Grade C, that men with comorbidities be counselled on diet and physical activity, and states that lifestyle change may improve erectile function. It gives no effect size — WEAK.

The condition’s major risk factors — diabetes, hypertension, metabolic syndrome, smoking — are themselves modifiable and quantified. Prevention here is largely prevention of vascular disease. No trial has used incidence of erectile dysfunction as a primary prevention endpoint.

Treatment. Phosphodiesterase type 5 inhibitors are first-line. The best-quantified evidence is in men with diabetes: a Cochrane review of 8 randomised trials, 976 men treated and 741 controls, about 80 per cent with type 2 diabetes, mostly 12-week trials. Successful attempts: weighted mean difference 26.7 percentage points (95 per cent CI 23.1 to 30.3). Global efficacy question: RR 3.8 (3.1 to 4.5). IIEF erectile function domain: WMD 6.6 (5.2 to 7.9). Any adverse reaction: RR 4.8 (3.74 to 6.16), headache commonest, then flushing. No trial reported mortality. The review carries no GRADE rating (Vardi & Nini, Cochrane CD002187, 2007).

That is a 2007 review in a diabetic population. It is the best-quantified evidence for the drug class and it is not a general-population estimate.

Guideline positions, with the AUA’s own grades (A high certainty, B moderate, C low): oral PDE5 inhibitors, men should be informed of this option — Strong, Grade B; dose titrated for optimal efficacy — Strong, Grade B; vacuum erection device — Moderate, Grade C; intraurethral alprostadil — Conditional, Grade C; intracavernosal injections — Moderate, Grade C; penile prosthesis — Strong, Grade C; penile arterial reconstruction for young men with focal occlusion — Conditional, Grade C; penile venous surgery — Moderate recommendation against, Grade C. Low-intensity shockwave therapy and intracavernosal stem cell therapy are Conditional, Grade C and investigational. Platelet-rich plasma is Expert Opinion and experimental.

The penile prosthesis recommendation is an explicit instance of a strong recommendation on low-certainty evidence, and the guideline says so.

Testosterone: the EAU gives testosterone therapy as first-line in hypogonadal men with mild disease — Strong recommendation, evidence level 1a — and combination of a PDE5 inhibitor with testosterone in more severe disease as a Weak recommendation. A meta-analysis of 913 patients across 8 randomised trials found combination superior to a PDE5 inhibitor alone. Diabetes and obesity reduced the magnitude of improvement from testosterone, which was clinically effective alone only in milder disease (EAU 2024).

Clinical guidance differs between bodies. The AUA and the EAU agree on PDE5 inhibitors first-line and on the staged progression to injections and prosthesis. They differ on testosterone: the EAU gives a strong, 1a-graded recommendation for monotherapy in hypogonadal men with mild disease, while the AUA treats PDE5-plus-testosterone as a Moderate, Grade C option in men with testosterone deficiency and does not foreground monotherapy.

Simple means. The vacuum erection device is mechanical, needs no consumables, and carries an AUA Moderate, Grade C recommendation. Exercise and dietary change carry AUA Moderate, Grade C, with no effect size given by the guideline. Smoking cessation. Substituting a causative medication (HA40.2). Psychosexual counselling where HA40.1 or HA40.4 applies; the measured effect of counselling alone, against PDE5 inhibitors, is not well quantified.

Gaps. The 3 to 76.5 per cent global prevalence range is the chapter's largest measurement problem. No harmonised instrument is in general use. The Massachusetts Male Aging Study age-specific incidence figures, the standard citation, were not obtained. Guidelines issue strong recommendations on Grade C evidence and say so openly. Lifestyle effect sizes are asserted without numbers by the guideline that recommends them.

> **Depth.** Starts in: a penile artery. Size: 1 mm†; depth +9.10. First complaint: about 55 years († onset about age 55); time depth 52.52. One untreated course: no number ([B] at least some months).
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. The book names a late stratum. By the rule it is held, not ended. The book splits the status by stratum: CURABLE and CONTROLLABLE. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Orgasmic dysfunctions and anorgasmia (HA02, HA02.0)

What it is. Absence or marked infrequency of orgasm, or markedly diminished intensity of orgasmic sensation, despite adequate stimulation and desire, for at least several months, with clinically significant distress.

In women this includes marked delay in orgasm. In men marked delay is coded instead as male delayed ejaculation, HA03.1. That asymmetry is a classification decision and not a biological finding, and it means the same phenomenon is counted in two different categories depending on sex.

Measured. PRESIDE reported orgasm difficulties in 21 per cent of 31,581 United States women, unadjusted. No distress-qualified, orgasm-specific figure is published from that survey. No nationally representative distress-qualified prevalence estimate exists for anorgasmia in any country.

Usable population data do not exist for this category. The available survey data are from the United States and Australia and are not in the diagnostically relevant form. Quality of the prevalence evidence: low.

Where it starts. Established: selective serotonin and serotonin-noradrenaline reuptake inhibitor antidepressants (Taylor et al., Cochrane CD003382, 2022). Pelvic surgery and spinal cord injury, which fall under HA40.0.

Lack of knowledge or experience is explicitly coded (HA40.3) and is thought to account for a substantial share of lifelong generalised cases. The proportion has not been measured. Beyond these, aetiology is not known: there is no established neurobiology of orgasmic capacity in humans that distinguishes cases from controls.

Cure status. Lifelong generalised anorgasmia in women: CURABLE. Directed masturbation and sensate focus are first-line, and older literature reports high success. That literature rests on small, old, mostly uncontrolled studies. No proportion is given.

Medication-induced, with the drug withdrawn or changed: CURABLE. The anorgasmia resolves on withdrawal.

Medication-induced, with the drug continued: CONTROLLABLE. Added bupropion 150 mg twice daily gave SMD 1.60 (95 per cent CI 1.40 to 1.81) in 3 studies, pooled across men and women. The authors call the evidence rather limited.

All other presentations, including those after pelvic surgery or spinal cord injury (HA40.0): RELIEF ONLY. No treatment in this entry has a measured effect on them.

Prevention. No evidence base for primary prevention. The one partial item is antidepressant selection, as in HA00 — WEAK.

Treatment. For antidepressant-associated cases, the Cochrane review found added bupropion 150 mg twice daily beneficial: SMD 1.60 (95 per cent CI 1.40 to 1.81), 3 studies, pooled across men and women. The authors describe the evidence as rather limited (Taylor et al., Cochrane CD003382, 2022). Medication-induced anorgasmia also resolves on withdrawal of the drug.

Directed masturbation and sensate focus are the standing behavioural approaches, and are first-line for lifelong generalised anorgasmia in women. Older literature reports high success rates. No current high-quality systematic review with pooled effect sizes was obtained, and the trial quality behind those reports is weak by current standards.

Simple means. Directed masturbation, sensate focus and education are the treatment of choice for lifelong generalised anorgasmia and require no industrial chain at all. The measured effect rests on small, old, mostly uncontrolled studies. The simple means is the recommended first-line approach and the evidence for it is weak. Both facts belong in the record.

Gaps. No distress-qualified prevalence anywhere. Sex-asymmetric classification, with delay counted as HA02 in women and HA03.1 in men, makes cross-sex comparison impossible by construction. The behavioural treatment evidence is pre-modern in methodology.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 30 years († onset about age 30); time depth 51.97. One untreated course: no number ([B] at least some months).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book splits the status by stratum: CURABLE, CONTROLLABLE and RELIEF ONLY. Reading and status agree in part. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Ejaculatory dysfunctions (HA03)

What it is. Difficulties with ejaculation in men. The category comprises ejaculatory latencies experienced as too short, coded as male early ejaculation (HA03.0), and as too long, coded as male delayed ejaculation (HA03.1).

Measured. Up to 30 per cent of men self-report early ejaculation. The AUA and Sexual Medicine Society of North America guideline states that most such studies used single questions, without measuring frequency or distress. Its own estimate is that clinically significant premature ejaculation affects fewer than 5 per cent of men (AUA/SMSNA Disorders of Ejaculation Guideline, 2020; *Journal of Urology* 2022).

The gap between 30 per cent and under 5 per cent is sixfold, and it comes from the guideline itself. The field’s own synthesis discounts the field’s own higher figure on methodological grounds.

For delayed ejaculation the same guideline states that prevalence data are more limited. Up to 25 per cent of men presenting with delayed ejaculation are reported to have lifelong difficulty reaching orgasm with a partner. That is a figure about the clinical population and not the general population.

Early ejaculation shows little age gradient; delayed ejaculation increases with age. Neither is well quantified in population data. There are no comparable multi-country population estimates. Quality of the prevalence evidence: low.

Where it starts. ICD-11 and the AUA both distinguish lifelong from acquired, and the AUA definitions are operational. Lifelong premature ejaculation means poor ejaculatory control and bother with ejaculation within about 2 minutes of penetration, present since first sexual experience. Acquired premature ejaculation means consistently poor control and bother with latency markedly reduced from the man's earlier function.

Established associations for acquired premature ejaculation include prostatitis, thyroid dysfunction and erectile dysfunction. For delayed ejaculation: SSRI use, pelvic surgery, neurological disease and advancing age. Effect sizes are not well established for any of them.

What is not known is whether lifelong premature ejaculation is a neurobiological variant or the low tail of a normal distribution of latency, and whether a 2-minute cut-off corresponds to anything other than convention. The AUA's own framing — defining the condition by control and bother, not latency alone — concedes that latency does not define a disorder by itself.

Cure status. Early ejaculation (HA03.0): CONTROLLABLE. Daily SSRIs, on-demand clomipramine or dapoxetine, and topical anaesthetics are first-line, Strong, Grade B. Combined behavioural and pharmacological treatment is rated Moderate, Grade B. The effect holds while treatment is used, and relapse on withdrawal is usual for the drugs. No proportion has been measured.

Delayed ejaculation (HA03.1): RELIEF ONLY. The guideline finds the evidence insufficient to assess oral drugs. Changing positions or practices may help, and testosterone may be offered where it is deficient. No data support invasive treatment, and no treatment has a measured effect.

Prevention. No evidence base. No prevention target has been defined.

Treatment. AUA/SMSNA 2020 recommendations, with their grades. Daily SSRIs, on-demand clomipramine or dapoxetine where available, and topical penile anaesthetics as first-line for premature ejaculation — Strong, Grade B. On-demand tramadol after first-line failure — Conditional, Grade C. Combining behavioural and pharmacological approaches, which may work better than either alone — Moderate, Grade B. Referral to a mental health professional with sexual health expertise — Moderate, Grade C. Alpha-1 blockers after first-line failure — Expert Opinion. Surgical approaches including bulking agents — experimental, approved clinical trials only. Alternative therapies — evidence insufficient.

For delayed ejaculation the same guideline holds that modifying sexual positions or practices may help, and that medication adjustment may be considered. The evidence is insufficient to assess the risk-benefit ratio of oral drugs. Testosterone may be offered where testosterone deficiency is present. No current data support invasive non-drug strategies.

Numerical efficacy figures for the first-line drugs — dapoxetine's fold increase in intravaginal ejaculatory latency time, SSRI effect sizes, topical anaesthetic effect — are not reproduced here. They were not obtained.

Clinical guidance differs by jurisdiction for regulatory rather than evidential reasons. Dapoxetine is licensed for premature ejaculation across the European Union and in many other countries, and has never been approved in the United States. The AUA guideline accordingly qualifies its first-line recommendation with "where available". The two bodies agree on the pharmacological class and on topical anaesthetics.

Simple means. Behavioural methods need no industrial chain: stop-start and squeeze techniques, pelvic floor training, condom use to reduce sensation, and position change for delayed ejaculation. The AUA rates combined behavioural and pharmacological treatment as superior to either alone at Moderate, Grade B, the strongest grade attaching to any behavioural component in this entry. Behavioural methods alone are not separately graded.

Gaps. Prevalence of 30 per cent against under 5 per cent, with the guideline rejecting its own field's higher figure. No population data on delayed ejaculation. Effect sizes for the first-line drugs not obtained. Whether

the 2-minute threshold is meaningful is unresolved. Sources disagree on whether premature ejaculation is primarily organic or learned, and the guideline does not adjudicate.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 18 years († lifelong, from the first experience); time depth 51.50. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. The book names an early stratum. By the rule it is held, not ended. The book splits the status by stratum: CONTROLLABLE and RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Sexual pain-penetration disorder (HA20)

What it is. A single ICD-11 category replacing the former separate diagnoses of vaginismus and non-organic dyspareunia. Diagnosis requires at least one of three presentations. Marked, persistent or recurrent difficulty with penetration, including involuntary tightening of the pelvic floor muscles on attempted penetration. Marked, persistent or recurrent vulvovaginal or pelvic pain during penetration. Or marked, persistent or recurrent fear or anxiety about such pain, anticipated, during, or resulting from penetration.

Further criteria are required. The symptoms recur during sexual activity involving or potentially involving penetration. They occur despite adequate desire and stimulation. They are not entirely explained by a pelvic medical condition causing genital or penetrative pain, nor by a mental disorder, nor by insufficient lubrication, nor by postmenopausal or age-related change. And they cause clinically significant distress. Female dyspareunia (GA12) and pain related to the vulva, vagina or pelvic floor (GA34.0) are excluded.

The exclusions matter for a book organised around disease. Organically explained sexual pain is coded in the genitourinary chapter. HA20 is the residual category after organic explanation has been removed.

Measured. No nationally representative prevalence estimate for HA20 as defined exists. Published figures for its predecessor categories vary widely with definition and are not transferable, because HA20's exclusion criteria remove cases that older surveys counted.

Usable population data do not exist for this category. There are no usable multi-country data. Quality of the prevalence evidence: very low. This is the clearest instance in chapter 17 of a newly constructed category with no epidemiology at all.

Where it starts. The best-measured finding is pelvic floor muscle involvement. A controlled study of 11 women with provoked vestibulodynia and 11 controls used digital intravaginal assessment with surface electromyography. It found higher superficial pelvic floor muscle activity in cases than controls, stronger responses to painful pressure, and differences in muscle tone, flexibility and relaxation capacity (Gentilcore-Saulnier, McLean, Goldfinger, Pukall & Chamberlain, *Journal of Sexual Medicine* 2010;7(2 Pt 2):1003–1022). With 22 participants this is directional evidence and not an effect-size estimate.

What is not known is whether the pelvic floor finding is cause or consequence of the pain. Nor whether the three qualifying presentations are one disorder or three. Nor whether the fear criterion identifies a distinct group, or captures the consequence of the other two. There is no established pathophysiology, and the category is defined partly by what it is not.

Cure status. Pain explained by a pelvic medical condition: not in this category. It is coded in the genitourinary chapter (GA12, GA34.0) and takes the label of that condition.

Pain, difficulty or fear with no explaining finding (HA20 as defined): RELIEF ONLY. The one controlled synthesis, 282 participants, found no clinical or statistical difference between systematic desensitisation and its comparators. A physiotherapy programme changed muscle function in 11 women, and several differences from controls were gone afterwards†. Clinical reports of high success are uncontrolled, and the review's authors do not support a claim of demonstrated cure.

Prevention. No evidence base. No prevention target has been defined.

Treatment. Standing approaches are pelvic floor physiotherapy, graded dilator or desensitisation programmes, cognitive behavioural therapy, topical anaesthetics, and in some centres botulinum toxin injection.

The controlling controlled evidence is negative. The Cochrane review of interventions for vaginismus included 5 studies, 4 with usable data, 282 participants. Systematic desensitisation was compared with waiting-list control, with desensitisation plus group therapy, and with in vitro desensitisation. The review found no clinical or statistical difference between systematic desensitisation and these comparators. Drop-out was higher in waiting-list groups. All studies were at moderate or high risk of bias and no meta-analysis was possible. The literature search ran only to August 2012 (Melnik, Hawton & McGuire, Cochrane, 1 April 2022).

A Cochrane review published in 2022 whose search ends in 2012 is the field's best controlled synthesis. The gap is fourteen years.

The controlled study above also ran a pelvic floor physiotherapy programme: 8 sessions of manual therapy, biofeedback, electrical stimulation, dilator insertion and home exercises. It reduced responsiveness to pain and improved flexibility and vaginal relaxation capacity. Several differences from controls were no longer present afterwards. That is a small, uncontrolled within-group comparison in 11 treated women.

Clinical practice reports high success rates for multimodal treatment. Those reports are uncontrolled, and the review's own authors do not support a claim of demonstrated cure.

Simple means. This is the category where simple means are the main treatment: pelvic floor muscle training and relaxation, graded self-directed dilator use, education, and cognitive behavioural therapy.

The measured position is exact. The physiotherapy study shows physiological change in a small sample. The Cochrane review shows no advantage of desensitisation over its comparators. The simple means are first-line by consensus and unproven by controlled trial.

Gaps. No prevalence data for the ICD-11 category. The controlling Cochrane review's search is fourteen years old. Whether the merged category improves on separate vaginismus and dyspareunia diagnoses has not been tested. Sources disagree sharply: the clinical literature reports high cure rates and the controlled synthesis finds no demonstrated effect. This is among the two weakest-evidenced categories in the chapter.

> **Depth.** Starts in: a pelvic floor muscle. Size: 10 cm†; depth +13.29. First complaint: about 25 years († onset about age 25); time depth 51.80. One untreated course: no number.
>
> **Model reading.** Way of ending: restore proportion. Layer: mesh. By the rule it is held, not ended. The book's status, given by stratum: RELIEF ONLY. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Gender incongruence of adolescence or adulthood (HA60)

What it is. A marked and persistent incongruence between an individual's experienced gender and the assigned sex. ICD-11 notes that this often leads to a desire to transition, using hormone treatment, surgery or other health services, to bring the body into alignment with the experienced gender, to the extent desired and possible.

The diagnosis cannot be assigned before puberty. ICD-11 states explicitly that gender variant behaviour and preferences alone are not a basis for assigning it. Paraphilic disorders (6D30 to 6D3Z) are excluded. The index retains the deprecated synonyms gender dysphoria in adolescents and adults, and transsexualism.

Measured. In the United States, 2.1 million adults aged 18 and over, 0.8 per cent of that age group, identify as transgender; and 724,000 youth aged 13 to 17, 3.3 per cent of that age group. The adult estimate comes from the 2021 to 2023 Behavioral Risk Factor Surveillance System and the youth estimate from the 2021 and 2023 Youth Risk Behavior Surveillance System (Williams Institute, UCLA School of Law).

These are self-identification figures from population surveys. They are not prevalence of HA60, which requires marked and persistent incongruence meeting clinical criteria. No population survey measures HA60 as ICD-11 defines it. The two quantities should not be equated.

The fourfold difference between the adult figure of 0.8 per cent and the youth figure of 3.3 per cent, in the same country and the same survey programme, shows how sensitive the measurement is to instrument and cohort.

Comparable population self-identification data exist for a small number of high-income countries. Clinic-referral counts exist for more countries and measure service use rather than prevalence. Historical figures derived from specialist clinic attendance are orders of magnitude lower than survey self-identification figures and measure a different thing. Usable population prevalence data for the diagnosis do not exist anywhere.

Where it starts. Not known. No biological marker, developmental pathway, genetic finding or prenatal exposure has been established as a cause with a replicated effect size.

One systematic review examined the characteristics of children and adolescents referred to specialist gender services. It was commissioned for the Review of Gender Identity Services for Children and Young People in England. It found the literature insufficient for firm conclusions (Taylor, Hall, Langton, Fraser & Hewitt, *Archives of Disease in Childhood* 2024;109(Suppl 2), 9 April 2024).

What is measured is a rise in referrals to specialist services in several countries over the 2010s, and a shift in the sex ratio of referrals. Precise referral figures and ratios are not quoted here; they were not obtained.

Classification history. ICD-11 moved this condition out of the mental disorders chapter. In ICD-10 it was coded as transsexualism, F64.0, within chapter V, mental and behavioural disorders. In ICD-11 it is HA60, in chapter 17.

WHO gives its reason in its classifications FAQ on gender incongruence and transgender health in the ICD. The move reflects current knowledge that trans-related and gender diverse identities are not conditions of mental ill-health. And classifying them as mental disorders, WHO states, can cause enormous stigma.

WHO's stated reason for retaining the category in the classification at all is given on the same page. Whether a category is included depends on whether it serves the ICD's various uses and whether there is sufficient evidence that the health condition exists. WHO states that including gender incongruence should ensure transgender people's access to gender-affirming health care, along with adequate insurance coverage for those services.

At the ICD-11 release WHO also stated that while evidence is now clear that it is not a mental disorder, there remain significant health care needs that can best be met if the condition is coded under the ICD. Dr Lale Say, WHO coordinator for Reproductive Health and Research, stated that removing it from the mental health chapter should reduce stigma and may even increase access, because reducing stigma helps individuals to seek care.

The history is therefore a deliberate reclassification with two stated purposes: removing the implication of mental illness, and preserving a code that secures access to and funding for care. These are matters of classification history and of WHO's own published rationale, and are recorded as such.

Cure status. The category does not apply, for the same reason it does not apply to prevention. A cure status asks whether a treatment removes a condition. WHO states that this is not a condition of mental ill-health, and the care described below is not directed at removing the incongruence but at relieving the distress that can accompany it and at aligning the body with the experienced gender. Measuring it against CURABLE or RELIEF ONLY would answer a question the classification does not ask. The outcomes that are measured are reported under Treatment, with their evidence.

Prevention. The category does not apply. WHO states that this is not a condition of mental ill-health, no causal pathway is established, and there is no prevention target.

Treatment. The evidence for adults and for adolescents must be reported separately, because clinical guidance differs between countries and because the evidence reviews differ in what they found.

WPATH Standards of Care version 8, 2022, is the principal international guidance document. Its prevalence estimates and evidence-grading statements are not reproduced here; they were not obtained.

The systematic reviews commissioned for the Review of Gender Identity Services for Children and Young People in England were published in *Archives of Disease in Childhood*, volume 109, supplement 2, dated 9 April 2024, and funded by NHS England. Two were obtained in full.

On puberty suppression: 50 studies, 11 cohort, 8 cross-sectional and 31 pre-post. Quality 1 high, 25 moderate, 24 low, with low-quality studies excluded from synthesis. Moderate- and high-quality studies consistently showed that treatment suppresses puberty. Gender dysphoria was measured in only 4 studies, and two pre-post studies found no change in gender dysphoria or body satisfaction. Psychological health evidence was limited and inconsistent, with no consistent evidence of benefit. Several pre-post studies found decreases in bone density measures during treatment, with absolute measures mostly stable or slightly changed, and height gains sometimes smaller than expected. The authors concluded that there is a lack of high-quality research assessing puberty suppression. No conclusions can be drawn about gender dysphoria, mental and psychosocial health, or cognitive development. Bone health and height may be compromised during treatment, on consistent moderate-quality evidence mainly from pre-post studies (Taylor, Mitchell, Hall, Heathcote, Langton, Fraser & Hewitt, 2024).

On psychosocial support interventions: 10 studies, 6 pre-post or cohort, 3 mixed methods and 1 secondary analysis of four trials; half from the United States and the rest from Australia, Canada, New Zealand and the United Kingdom. Quality by the Mixed Methods Appraisal Tool was 9 low and 1 moderate. Most mental health and psychosocial analyses showed benefit or no change, and none reported negative effects. The authors concluded that the small number of low-quality studies prevents firm conclusions about effectiveness (Heathcote, Taylor, Hall, Jarvis, Langton, Hewitt & Fraser, 2024; PROSPERO CRD42021289659).

Companion reviews in the same supplement cover social transition, masculinising and feminising hormone interventions in adolescents, care pathways, the characteristics of the referred population, and clinical guideline quality in two parts.

The adolescent evidence base is of low quality and insufficient for firm conclusions on psychological outcomes. That is the assessment of the reviewers who synthesised it.

Clinical guidance differs between countries, and the differences are reported here as fact. In England, NHS England commissioned the independent review published in 2024 and put an interim service specification in place the same year. A new specification for specialist gender incongruence services for children and young people was published in April 2026 after public consultation, with a referral pathway document. NHS England holds a clinical policy on puberty-suppressing hormones for children and young people with gender incongruence or gender dysphoria. Prescribing of masculinising or feminising hormones within the children's service is paused pending consultation on a revised commissioning policy (NHS England, Gender Dysphoria Clinical Programme pages, October 2026).

WPATH Standards of Care version 8 sets out criteria for gender-affirming care across the lifespan and does not adopt the restrictive posture taken in England. Several other European countries have narrowed adolescent hormonal treatment in recent years and others have not.

The divergence is between bodies reading largely the same low-certainty evidence base and reaching different conclusions about how to act under uncertainty. No position is taken between them here. The two factual points are that the evidence base is low certainty by its own reviewers' assessment, and that bodies in different countries have drawn different clinical policy conclusions from it.

Simple means. Social transition requires no industrial chain. Its measured effect was the subject of a dedicated systematic review in the same 2024 supplement (Hall, Taylor, Hewitt, Heathcote, Jarvis, Langton & Fraser); that review's findings were not obtained and are not characterised here.

Psychosocial support: 10 studies, 9 rated low quality, most analyses showing benefit or no change, none showing harm, firm conclusions not possible. Counselling and peer support are widely provided and their measured effect is poorly quantified.

Gaps. No population prevalence of the diagnosis anywhere. Self-identification figures differ fourfold between adults and youth in the same survey programme and are not the same quantity as the diagnosis. Aetiology unknown. Adolescent treatment evidence low quality by its own reviewers' assessment.

Countries disagree on clinical policy. Long-term outcome data into middle age are scarce for all treatment pathways. Detransition rates are contested and not reliably measured.

> **Depth.** No cause is known [B]. Not an illness in the sense of the model. No depth is given.
>
> **Model reading.** Not applied. No cause is known [B]. Not an illness in the sense of the model.

Gender incongruence of childhood (HA61)

What it is. A pre-pubertal child's experienced or expressed gender clearly differs from the sex assigned at birth. ICD-11 includes a strong desire to be a different gender, distress about actual or anticipated sex characteristics, or strong desire for the characteristics of the experienced gender. It adds a tendency to prefer pretend play, toys, games, activities and playmates associated with the experienced gender.

The incongruence must have persisted for about 2 years. As with HA60, ICD-11 states that gender variant behaviour and preferences alone are not a basis for assigning the diagnosis. Paraphilic disorders (6D30 to 6D3Z) are excluded.

Measured. No population prevalence estimate exists. The Williams Institute youth figure of 3.3 per cent of 13- to 17-year-olds in the United States covers adolescents rather than the pre-pubertal group HA61 applies to, and measures self-identification rather than the diagnosis.

Usable population data do not exist for this category at all. The quality of the prevalence evidence is not low. It is absent.

Where it starts. Not known. No cause is established. The systematic review of the characteristics of children and adolescents referred to specialist gender services was commissioned precisely because this was unclear (Taylor, Hall, Langton, Fraser & Hewitt, *Archives of Disease in Childhood* 2024;109(Suppl 2)).

One quantity is historically cited: the proportion of pre-pubertal children whose incongruence persists into adolescence. It is contested, derives from small specialist-clinic follow-up series with substantial loss to follow-up, and the figures in general circulation are not reliable. No figure is given here.

Classification history. ICD-11 retains the category and requires about 2 years' persistence before it can be assigned, which is a classification response to the uncertainty about natural history.

The category's retention in ICD-11 was contested during development. Submissions argued for its removal on the grounds that it carries a risk of pathologising childhood variance without conferring access benefits, since no medical intervention is indicated before puberty. WHO retained it. The two-year persistence requirement, and the statement that behaviour and preferences alone are insufficient, are the constraints WHO placed on it.

Cure status. The category does not apply, for the reason given under prevention. The condition is not held to be one of mental ill-health, no treatment is directed at removing it, and in childhood the recorded course is itself one of the open questions, which is reported under Gaps.

Prevention. The category does not apply. No causal pathway is established and no prevention target exists.

Treatment. No medical intervention is indicated before puberty. HA60 cannot be assigned before puberty, and puberty suppression by definition begins at puberty. Management before puberty is psychosocial support and watchful assessment.

The evidence for that management is the psychosocial support review described under HA60. Ten studies, 9 of them rated low quality. Most analyses showed benefit or no change and none reported negative effects. Firm conclusions about effectiveness are not possible (Heathcote et al., *Archives of Disease in Childhood* 2024;109(Suppl 2)).

Social transition in childhood is the subject of a dedicated systematic review in the same supplement (Hall et al. 2024). Its findings were not obtained and are not characterised here. Clinical policy on childhood social transition differs between countries.

Simple means. Psychosocial support and family counselling are the whole of indicated management and require no industrial chain. The measured effect is as above: low quality, no demonstrated harm, no firm conclusion.

Gaps. Everything quantitative. No prevalence. No established aetiology. No reliable persistence figure. Low-quality intervention evidence, with nine of ten studies rated low. International disagreement on how to manage childhood social transition. This is the least evidenced category in chapter 17.

> **Depth.** No cause is known [B]. Not an illness in the sense of the model. No depth is given.
>
> **Model reading.** Not applied. No cause is known [B]. Not an illness in the sense of the model.

PART B — the ICD-11 chapters that are not diseases

ICD-11 MMS has 26 numbered chapters plus two lettered sections, V and X. Seven of these do not classify diseases. Each is described here by what it contains, what it is used for, and whether a book organised around diseases needs an entry from it.

Chapter 21 — Symptoms, signs or clinical findings, not elsewhere classified

What it contains. Symptom and sign categories organised by body system: blood and immune (MA00 to MA1Y); endocrine, nutritional and metabolic (MA50 to MA6Y); speech, language and voice (MA80 to MB0Y); mental and behavioural (MB20 to MB2Y); nervous system (MB40 to MB9Y); visual (MC10 to MC2Y); ear and mastoid (MC40 to MC6Y); circulatory (MC80 to MC9Y); respiratory (MD10 to MD6Y); digestive and abdomen (MD80 to ME4Y); skin (ME60 to ME6Y); musculoskeletal (ME80 to MF1Y); genitourinary (MF30 to MG0Y); general (MG20 to MG7Z); ill-defined or unknown causes of mortality (MH10 to MH15); and other specified (MH2Y).

What it is used for. Recording a presenting symptom when the underlying condition is not yet established, and recording ill-defined causes of death. The chapter's own note states that these categories should be used in conjunction with a code from another chapter that identifies the underlying condition.

Does a book organised around diseases need an entry? Yes, one short entry, for two reasons. First, MH10 to MH15, ill-defined and unknown causes of mortality, is the quantity that determines how much of any country's mortality data is usable. A book that cites cause-of-death figures must state that a share of deaths are coded here and are therefore uninformative. Second, the chapter explains why symptom codes appear in routine data alongside disease codes, which bears on every prevalence figure drawn from administrative records.

Chapter 23 — External causes of morbidity or mortality

What it contains. Eleven blocks: unintentional causes (PA00 to PB6Z); intentional self-harm (PB80 to PD3Z); assault (PD50 to PF2Z); undetermined intent (PF40 to PH8Z); exposure to extreme forces of nature (PJ00 to PJ0Z); maltreatment (PJ20 to PJ2Z); legal intervention (PJ40 to PJ4Z); armed conflict (PJ60 to PK6Z); causes of healthcare related harm or injury (PK80 to PL14.Z); other specified (PL2Y); and unspecified (PL2Z).

What it is used for. Recording how an injury occurred, alongside a chapter 22 code recording what the injury is. The pairing is the point: chapter 22 gives the lesion, chapter 23 gives the mechanism and the intent. Injury mortality statistics are compiled from chapter 23.

Death tolls by major category. The figures below are WHO Global Health Estimates and WHO fact sheet figures, each named with its source and its reference year. They are not GBD figures and must not be cited as such. The GBD 2023 equivalents of these per-category injury figures were not retrievable.

Category	Deaths per year	Source and year
All injuries	about 4.4 million, nearly 8 per cent of all deaths†	WHO fact sheet, Injuries and violence, 19 June 2024
Unintentional injuries	3.16 million†	WHO, same sheet
Violence-related injuries	1.25 million†	WHO, same sheet

Category	Deaths per year	Source and year
Road traffic	about 1 in 3 of all injury deaths†	WHO, same sheet
Road traffic, standalone	about 1.16 million, 92 per cent in low- and middle-income countries†	WHO fact sheet, Road traffic injuries, 20 July 2026
Intentional self-harm	about 1 in 6 of injury deaths; standalone 727,000, 73 per cent in low- and middle-income countries†	WHO, Injuries and violence 2024; WHO fact sheet, Suicide, data year 2021
Interpersonal violence	about 1 in 10 of injury deaths†	WHO, Injuries and violence 2024
War and conflict	about 1 in 61 of injury deaths†	WHO, Injuries and violence 2024
Falls	684,000, over 80 per cent in low- and middle-income countries; 37.3 million non-fatal falls requiring medical attention; over 38 million DALYs, nearly 40 per cent in children†	WHO fact sheet, Falls, 26 April 2021
Drowning	about 300,000, 92 per cent in low- and middle-income countries; under-fives nearly a quarter of deaths; ages 0 to 29 are 57 per cent†	WHO fact sheet, Drowning, 1 May 2026
Burns	about 180,000, almost two-thirds in the WHO African and South-East Asia Regions†	WHO fact sheet, Burns, 13 October 2023
Unintentional poisoning	106,683†	WHO, Prevention and management of cases of poisoning, data year 2016

The WHO suicide fact sheet of 28 August 2026 carries two headline totals for the same statistic: over 720,000 in its key facts and 727,000 in its body. Both are printed here as published. Suicide is the third leading cause of death among 15- to 29-year-olds globally, for 2021.

The WHO poisoning fact sheet could not be read, and may have been retired. The 106,683 figure for 2016 comes instead from WHO's chemical safety page on prevention and management of cases of poisoning, which carries no printed date. WHO's injuries and violence fact sheet names poisoning as a cause and gives no global death total.

Two cautions on the table. The proportional shares WHO publishes — about a third for road traffic, a sixth for suicide, a tenth for homicide and a sixty-first for war — sum to 61.6 per cent. The standalone counts the table prints for five categories, road, self-harm, falls, drowning and burns, sum to 3.051 million, which is 69.3 per cent of 4.4 million†. The two sums cover different category sets: the shares cover road traffic, suicide, homicide and war, and the counts cover road traffic, self-harm, falls, drowning and burns. The gap of about 7 percentage points is therefore not a discrepancy within one total.

The table's first two rows already account for the whole total: 3.16 million unintentional plus 1.25 million violence-related is 4.41 million against a stated 4.4 million. The two-way split is complete. The shares caution is about the distribution of categories within that total and not about an unaccounted remainder.

Road traffic deaths differ between two WHO sheets. The 2024 cross-cutting sheet's share implies about 1.47 million; the 2026 standalone sheet gives about 1.16 million. Both are printed as published, without reconciliation. WHO's own note is that the two pages use different, unstated data years.

Falls DALYs also differ by source. The WHO falls fact sheet of 26 April 2021 gives over 38 million†. GBD 2023 gives 74.3 million, roughly twice as many. Both stand.

Maltreatment and interpersonal violence against women. The maltreatment and assault blocks of this chapter code a burden that WHO measures separately. Lifetime prevalence of physical or sexual intimate partner violence, or non-partner sexual violence, among women and girls is given twice. The fact sheet's key facts give 31.6 per cent, about 840 million women and girls. Its body gives 32 per cent. The page carries both figures for the same statistic.

Intimate partner violence among women aged 15 to 49 ever in a relationship: 25.8 per cent. Among women aged 15 and over ever in a relationship: 24.7 per cent. Non-partner sexual violence: 8 per cent of women aged 15 and over, 263 million since age 15. More than 1 in 5 ever-partnered girls aged 15 to 19 are affected. By region, Oceania 37 per cent, sub-Saharan Africa 32 per cent, southern Asia 31 per cent. On average 140

women and girls were killed daily in 2023 by a partner or other family member (WHO fact sheet, Violence against women, 18 June 2026).

Intimate partner violence is the fourth leading cause of poor health among women by DALYs, on 2025 estimates. The average annual decline in prevalence over twenty years is 0.2 per cent. Economic cost is given as 1 to 6 per cent of GDP in some countries.

Sex and age pattern. Twice as many males as females die from injuries and violence. Males are about three-quarters of road traffic deaths, four-fifths of homicide deaths and two-thirds of war deaths. For ages 5 to 29, three of the top five causes of death are road traffic injuries, homicide and suicide. Drowning is the sixth leading cause of death at ages 5 to 14. Fall risk rises with age. About 90 per cent of injury deaths occur in low- and middle-income countries, and injuries and violence cause an estimated 10 per cent of all years lived with disability (WHO, Injuries and violence, 19 June 2024).

Does a book organised around diseases need an entry? Yes, a substantial one. Injuries are about 8 per cent of global deaths, which is roughly one death in every twelve and a half, and they are concentrated in the young, so they dominate years of life lost in a way their death share understates. They are also the part of the burden where the causes are entirely external, and the determinants environmental and behavioural rather than pathological.

Chapter 24 — Factors influencing health status or contact with health services

What it contains. Four blocks: reasons for contact with the health services (QA00 to QD3Z); factors influencing health status (QD50 to QF2Z); other specified (QF4Y); unspecified (QF4Z). The chapter introduction states that these categories cover circumstances other than a disease or injury that affect health status or prompt contact with health services.

The determinants the chapter codes, by domain: education and literacy; employment and unemployment; occupation and work environment; housing and economic circumstances, including homelessness; the social environment; psychosocial circumstances, including family and relationship disruption, and abuse and neglect; lifestyle factors; and contact-with-services reasons including screening, immunisation, contraceptive management (QA21) and follow-up.

What it is used for. Recording why someone is in contact with health services when there is no disease, and recording circumstances that bear on health but are not themselves illness. In practice the chapter is heavily used for preventive-service encounters and sparsely used for social circumstances. That asymmetry is itself a fact worth stating: the social determinant codes exist and are largely not applied, so they generate no usable prevalence data.

Which determinants have measured health effects large enough to belong in a book about illness.

Determinant	Measured effect	Source and year
Social support and social relationships	Odds ratio 1.50 (95 per cent CI 1.42 to 1.59) for survival with stronger social relationships, across 148 studies and 308,849 participants	Holt-Lunstad, Smith & Layton, *PLOS Medicine* 2010
Income and wealth	Eliminating wealth-related inequality in low- and middle-income countries could save 1.8 million children’s lives each year; within-country income inequality has nearly doubled over two decades; in 201 countries the top 10 per cent earn on average 15 times the bottom 50 per cent	WHO fact sheet, Social determinants of health, 2023, citing the World Inequality Report 2022
Country of residence, composite	Life expectancy gap of up to 33 years between countries; children in low-income countries 13 times more likely to die before age 5 than in high-income countries	WHO fact sheet, Social determinants of health
Country of residence, composite	An 18-year life expectancy difference between high- and low-income countries; under-5 mortality more than eight times higher in the WHO African than the European	WHO health topic page, Social determinants of health

Determinant	Measured effect	Source and year
	region	
Housing, employment and social protection, combined policy effect	An extra 0.1 per cent of GDP invested in social protection, labour market, and housing and community policies could improve health for 150,000 people in a country of 40 million within four years	WHO Europe, 2020, via WHO fact sheet
Social protection coverage	3.8 billion people lack social protection coverage such as child and paid sick leave benefits	World Social Protection Report 2024–26, via WHO
Employment, gendered	2.4 billion working-age women lack equal economic opportunities	World Bank, 2022, via WHO
Food security and undernutrition	149 million children under 5 stunted and 45 million wasted, data year 2022; nearly half of under-5 deaths linked to undernutrition	WHO fact sheet, Malnutrition, data year 2022
Displacement	Forcibly displaced people tripled to 122 million between 2008 and 2024	WHO fact sheet, Social determinants of health
Education	WHO states that higher educational attainment is associated with better health and longer life at population level; no effect size is given on the WHO sources consulted	WHO fact sheet, Social determinants of health
Housing, separately	Not measured separately on the WHO sources consulted; housing appears only inside the combined policy figure above	WHO fact sheet, Social determinants of health

The determinants with measured health effects large enough to belong in a book about illness are, on this evidence, social support, income, food security and social protection. Social support carries the single largest measured effect: an odds ratio of 1.50 for survival across 308,849 people, which is larger than many of the treatment effects reported in Part A. Education and housing are among the determinants most often asserted to matter and have no standalone effect size in the WHO sources consulted.

Two figures on food security differ by reference year and are not interchangeable. The 2022 WHO fact sheet gives 149 million children under 5 stunted and 45 million wasted. The 2025 Joint Malnutrition Estimates give 150.2 million stunted and 42.8 million wasted. Both stand; the Joint Malnutrition Estimates are the later figures.

Three limits apply to the whole table. WHO gives no percentage for the share of health outcomes attributable to social determinants; its fact sheet says only that these determinants outweigh genetic influences or health-care access, with no figure attached. Any specific percentage in circulation is not WHO's. The composite country-level gaps, 33 years and 18 years, come from two different WHO pages, are not the effect of any single determinant, and should not be read as one.

Does a book organised around diseases need an entry? Yes. The determinants in this chapter shift whole-population mortality, and the social support figure alone exceeds many treatment effects. The entry should be short, should name the domains, and should state that the codes for these determinants exist and are little used.

Chapter 25 — Codes for special purposes

What it contains. Two blocks: international provisional assignment of new diseases of uncertain aetiology and emergency use (RA00 to RA09); and national provisional assignment of new diseases of uncertain aetiology (RA20 to RA26).

What it is used for. Holding provisional codes for newly emerging or not-yet-understood conditions, and for emergency use. This is the mechanism by which a novel disease acquires a code before it is understood well enough to be placed in a disease chapter. It is the route by which COVID-19 was coded at emergence.

Does a book organised around diseases need an entry? One short entry, as classification machinery rather than as disease. Its relevance is that it is the chapter where the next unknown disease will first appear,

and that figures for any newly emerged condition will come from here before they come from anywhere else.

Chapter 26 — Supplementary chapter, traditional medicine conditions

What it contains. Two modules: Module I (SA00 to SJ1Z) and Module II (SK00 to ST2Z). These code diagnostic concepts from traditional medicine systems, principally those originating in China, Japan and Korea.

What it is used for. Optional recording of traditional medicine diagnoses alongside, not instead of, ICD diagnoses. The WHO ICD-11 fact sheet states that the chapter allows optional recording of traditional medicine diagnoses. It is a supplementary chapter, and codes from it are not used in primary mortality or morbidity tabulation.

That supplementary and optional status is the load-bearing fact. These codes record that a traditional medicine diagnosis was made. They do not record that a disease exists.

Does a book organised around diseases need an entry? One short entry, for clarity about what the chapter is and is not. It supplies no disease entries, no prevalence and no treatment evidence. It records diagnostic practice in systems that large populations use, which is a fact about health services rather than about illness.

Supplementary section V — Functioning assessment

What it contains. Three blocks: the WHO Disability Assessment Schedule, WHODAS 2.0, in its 36-item version; the Brief Model Disability Survey; and a generic set of functioning domains.

What it is used for. Building functioning profiles and overall functioning scores that describe and quantify the level of functioning associated with a health condition. The section rests on two instruments derived from the International Classification of Functioning, Disability and Health — WHODAS 2.0 and the Model Disability Survey — complemented by generic functioning categories derived from ICF Annex 9, described as having high explanatory power. The WHO ICD-11 fact sheet states that the supplementary chapters and sections permit the assessment of functioning.

Does a book organised around diseases need an entry? Yes, one short entry. Functioning is the quantity that determines what a disease costs a person, and it is not derivable from a diagnosis code. A book organised around diseases that never records functioning cannot distinguish a diagnosis that disables from one that does not. Section V is the standard instrument set for that measurement.

Chapter X — Extension codes

What it contains. Thirteen blocks: severity scale value; temporality; aetiology; topology scale value; anatomy and topography; histopathology; dimensions of injury; dimensions of external causes; consciousness; substances; diagnosis code descriptors; capacity or context; and health devices, equipment and supplies.

What it is used for. Adding detail to categories classified elsewhere. The WHO ICD-11 fact sheet states that extension codes add flexible detail to clinical records, support the recording of medicaments using WHO International Nonproprietary Names and WHO Medical Device nomenclature, and document a condition’s severity, anatomy or histopathology.

One correction worth recording. Extension codes are commonly described as never used alone. The published rule is narrower. They should never be used in primary classification coding or tabulation, and

they may be used alone in other contexts. The restriction is on primary classification coding and tabulation, not on use as such.

Does a book organised around diseases need an entry? One short entry. Chapter X is where severity lives, and severity is the difference between a condition that matters and one that does not. The HA40 aetiology axis in chapter 17 and this chapter's aetiology block are the two places where ICD-11 moves causation out of the diagnosis and onto a separate coordinate.

PART C — three cross-cutting entries

Multimorbidity

What it is. The co-occurrence of two or more chronic conditions in one person. The standard reference study counted two or more of 40 defined morbidities. Multimorbidity is not a disease. It is a state that changes the behaviour of every disease in it, and it is the condition in which most older patients are treated.

Measured. The defining population study covered 1,751,841 patients from 314 Scottish general practices, about a third of the Scottish population (Barnett, Mercer, Norbury, Watt, Wyke & Guthrie, *The Lancet* 2012).

Overall prevalence was 23.2 per cent†. Prevalence rises steeply with age. Half of people had at least one morbidity by age 50, and most people aged 65 and over were multimorbid†.

The counterintuitive result is in absolute numbers. Because the younger population is so much larger, more multimorbid people were under 65, 210,500, than were 65 or over, about 195,000†. Multimorbidity is a condition of old age in rates and not in counts.

The socioeconomic gradient in the same study was steep. Crude multimorbidity was 19.5 per cent in the most affluent areas against 24.1 per cent in the most deprived†. Onset occurred 10 to 15 years earlier in the most deprived areas: young and middle-aged adults there had rates similar to people 10 to 15 years older in the most affluent areas†. Combined physical and mental health comorbidity was 11.0 per cent in the most deprived against 5.9 per cent in the least deprived, nearly double†.

The demographic context is in WHO's ageing fact sheet. About 1 billion people were aged 60 or over in 2020, outnumbering children under 5. One person in six will be 60 or over by 2030, about 1.4 billion. The 60-plus population doubles to 2.1 billion by 2050, and the 80-plus group triples between 2020 and 2050 to 426 million. The share over 60 rises from 12 per cent in 2015 to 22 per cent in 2050. By 2050 two-thirds of people over 60 will live in low- and middle-income countries. That fact sheet gives no multimorbidity prevalence figures of its own.

Where it starts. Multimorbidity accumulates from the risk factors of its component conditions, and the measured gradient is socioeconomic. Deprivation moves onset forward by 10 to 15 years and roughly doubles combined physical and mental comorbidity†.

Multimorbidity increases mortality, hospital admission, length of stay, functional decline and healthcare cost. Pooled outcome hazard ratios for the state itself were not obtained, and none is given here. The Barnett study's own contribution was the deprivation gradient and the age distribution, not outcome hazard ratios.

What is not known is whether multimorbidity has any properties beyond the sum of its components — whether particular clusters behave differently from the arithmetic of their parts.

Cure status. CONTROLLABLE. Each component condition is treated on its own terms and the state itself does not remit. No intervention removes multimorbidity, and the structured interventions aimed at its main iatrogenic consequence have not demonstrated an effect on patient outcomes.

Prevention. No trial has used incidence of multimorbidity as an endpoint. The one measured handle is the socioeconomic gradient, which is an observation and not an intervention — WEAK.

The determinants in ICD-11 chapter 24 are the relevant targets, and the measured effects there are given in Part B.

Treatment. Each component condition carries its own standing treatment. The problem multimorbidity creates is additive: multi-drug treatment in which each drug is individually guideline-indicated, with an interaction and adverse-effect burden that no single-disease guideline accounts for. The measured question is whether structured intervention improves outcomes.

The controlling evidence is a Cochrane review of interventions to improve the appropriate use of polypharmacy for older people, published 11 October 2023, with searches to January 2021 and an update to

February 2023. It included 38 studies, 24 randomised and 14 cluster-randomised, with 18,073 older people across 19 countries (Cole, Byrne et al.).

- Hospital admissions: pharmaceutical care may make little or no difference. 14 studies, 4,797 participants. Certainty low.
- Medication appropriateness, by expert judgement: effect uncertain. Mean difference −5.66 (95 per cent CI −9.26 to −2.06), 8 studies, 947 participants. Certainty very low.
- Quality of life: may make little or no difference. 16 studies, 7,458 participants. Certainty low.

Certainty ranged from low to very low across the pooled outcomes, owing to high or unclear risk of bias and substantial between-study variation.

This is the entry's central finding, and it runs against the direction of the hopeful results elsewhere in this book. Thirty-eight trials and 18,073 participants produce no demonstrated effect on hospital admission or on quality of life. The authors grade their own evidence low to very low. The measurable achievement is a change in prescribing appropriateness scores, at very low certainty. Deprescribing is widely recommended and its patient-outcome benefit is not demonstrated.

Simple means. A written list of every medicine a person takes, reviewed against every diagnosis, needs no industrial chain. So does the question of which drug on the list is treating a side effect of another. Neither has a demonstrated effect on admissions or quality of life, on the evidence above, and both are the cheapest available form of the intervention that was tested.

Gaps. No pooled outcome hazard ratios for the state itself. The defining prevalence study is one country, 2012, and primary-care-record based, so the 23.2 per cent figure is not a global estimate. Low- and middle-income countries, where two-thirds of older people will live by 2050, have little multimorbidity epidemiology. Deprescribing trials measure process rather than patient outcome, and say so.

> **Depth.** A state, not an illness [B]. No depth is given.
>
> **Model reading.** Not applied. A state, not an illness [B].

Frailty

What it is. A state of reduced physiological reserve across multiple systems, with heightened vulnerability to stressors. Two operational definitions dominate, and they do not measure the same thing.

The physical phenotype uses five criteria: unintentional weight loss of 10 lb in the past year; self-reported exhaustion; weakness by grip strength; slow walking speed; and low physical activity. Three or more makes a person frail; one or two makes them intermediate, or pre-frail (Fried, Tangen, Walston et al., *Journals of Gerontology Series A* 2001).

The deficit accumulation definition, or frailty index, counts accumulated deficits across a wide list of domains, including psychosocial ones.

Measured. The original cohort, community-dwelling adults in the Cardiovascular Health Study, gave frailty at 6.9 per cent with a four-year incidence of 7.2 per cent, rising with age and higher in women† (Fried et al. 2001).

The first major synthesis covered 21 studies and 61,500 community-dwelling adults aged 65 and over. Overall weighted prevalence was 10.7 per cent (95 per cent CI 10.5 to 10.9). By definition: physical phenotype 9.9 per cent across 15 studies and 44,894 participants; broad phenotype including psychosocial aspects 13.6 per cent across 8 studies and 24,072 participants, a significant difference. Women 9.6 per cent against men 5.2 per cent. Prevalence across individual studies ranged from 4.0 to 59.1 per cent, which the authors attributed mainly to definitional differences (Collard, Boter, Schoevers & Oude Voshaar, *Journal of the American Geriatrics Society* 2012).

The largest synthesis covered 240 studies, 265 prevalence estimates, 62 countries and 1,755,497 participants aged 50 and over (O'Caoimh, Sezgin, O'Donovan, Molloy, Clegg, Rockwood & Liew, *Age and Ageing* 2021;50(1):96–104; PROSPERO CRD42018105431).

- Physical frailty 12 per cent (95 per cent CI 11 to 13), from 178 estimates†.
- Frailty index 24 per cent (22 to 26), from 71 estimates†.
- Pre-frailty: physical 46 per cent (45 to 48); frailty index 49 per cent (46 to 52)†.
- Sex: physical frailty 15 per cent in women (14 to 17) against 11 per cent in men (10 to 12); frailty index 29 per cent in women (24 to 35) against 20 per cent in men (16 to 24)†.
- Nationally representative studies only: physical frailty 7 per cent (5 to 9); frailty index 24 per cent (22 to 26)†.
- Age gradient: physical frailty rose from 6 per cent at a minimum entry age of 50 to 59, to 28 per cent at 80 to 89, to 46 per cent at 90 and over†.
- Region: highest in Africa at 22 per cent, on 5 data points, and lowest in Europe at 8 per cent†.
- Over time: physical frailty rose marginally after 2012, from 12 to 13 per cent; frailty index estimates rose from 24 to 28 per cent†.

The authors state that the data are heterogeneous and limited, with I^2 of 99 to 100 per cent†. Age explained little of the variation, with an adjusted R^2 of about 3 per cent. Country coverage is uneven, with few data from low- and middle-income countries and few nationally representative studies. Thirty-four low-quality studies were excluded using the Loney tool, and reporting bias is possible. There is no formal GRADE rating; the authors call their figures the best available estimates.

The definitional spread is the entry's main quantitative fact. Twelve per cent against 24 per cent for the same populations, depending on which definition is applied, and 7 per cent against 24 per cent within nationally representative studies alone.

Where it starts. Frailty accumulates with age and is not reducible to age: in the largest synthesis age explained about 3 per cent of the variation between estimates†. Two bedside measurements predict outcome well enough to serve as the entry's measured core.

Grip strength is the better quantified. The PURE study enrolled 142,861 participants, analysed 139,691, across 17 countries at all income levels. Per 5 kg reduction in grip strength: all-cause mortality HR 1.16 (95 per cent CI 1.13 to 1.20); cardiovascular mortality HR 1.17 (1.11 to 1.24); myocardial infarction HR 1.07 (1.02 to 1.11); stroke HR 1.09 (1.05 to 1.15) (Leong, Teo, Rangarajan et al., *The Lancet* 2015).

Grip strength is a one-instrument measurement taking a few seconds, and it predicts death across 17 countries. For a reference work it carries the most favourable ratio of information to measurement in the whole frailty literature.

Gait speed is the second predictor. The standard pooled analysis of gait speed and survival in older adults is Studenski et al., *JAMA* 2011; its pooled hazard ratio per 0.1 m/s is not quoted here, because it was not obtained. What is established is that slow walking speed is one of the five physical phenotype criteria. The phenotype itself predicted falls, worsening mobility or activities-of-daily-living disability, hospitalisation and death over 3 years. Unadjusted hazard ratios ran from 1.82 to 4.46 and adjusted hazard ratios from 1.29 to 2.24 (Fried et al. 2001).

Read in the net: reduced reserve is windings that no longer return in phase, so tension passes to the meshes beside them. Grip strength and gait speed are read at the depth where that shows, which is why one measurement reports on the whole. This is a reading, not a mechanism.

Cure status. CONTROLLABLE. Continued exercise reduces the rate of falls, which is frailty's main clinical consequence, at high certainty. No intervention has been shown to reverse frailty status itself, and the effect requires that the exercise continue.

Prevention. Exercise against falls — STRONG.

The Cochrane review of exercise for preventing falls in older people living in the community, published 31 January 2019, covered 108 randomised trials, 23,407 participants and 25 countries, mean age 76 and 77 per cent women†.

- Rate of falls: rate ratio 0.77 (95 per cent CI 0.71 to 0.83), about 23 per cent fewer falls. 59 studies, 12,981 participants. High-certainty evidence.

- Number of people falling: risk ratio 0.85 (0.81 to 0.89), about 15 per cent fewer fallers. 63 studies, 13,518 participants. High-certainty evidence.

These are the only GRADE high-certainty figures anywhere in this chapter's source material. Across chapter 17, the non-disease chapters and all three cross-cutting states, exercise for falls prevention is the single intervention carrying GRADE high certainty. Everything else in this material is low, very low, or ungraded.

Within that review, balance and functional training reduced falls; multicomponent programmes, usually balance plus functional plus resistance exercise, probably did too; and Tai Chi may help. Evidence on fractures, medical-attention falls and quality of life was of lower certainty. Adverse events were mostly minor and musculoskeletal.

Prevention of frailty status itself, as distinct from falls, has no comparable evidence. No Cochrane review of multicomponent interventions with frailty status as the endpoint was obtained. The largest prevalence review notes that interventions may slow frailty progression and concludes that the risk-benefit of population screening remains unclear, because few high-quality randomised trials exist — WEAK.

Treatment. Exercise, on the figures above. Treatment of the component deficits — nutrition for weight loss, correction of anaemia, review of sedating medication, management of pain limiting activity — is standing practice and is not supported by trial evidence with frailty status as the endpoint.

Simple means. Everything that matters here is simple means. The two best predictors are a hand dynamometer and a measured walk. The intervention with the only high-certainty result is balance and functional exercise, which requires a floor, a chair and someone to teach the progression. Tai Chi needs nothing at all. The measured effect is a rate ratio of 0.77 for falls, at high certainty†.

Gaps. Definition determines prevalence by a factor of two to three. Heterogeneity is I^2 99 to 100 per cent in the largest meta-analysis. African prevalence rests on 5 data points. Few studies are nationally representative, and restricting to those halves the physical frailty estimate, from 12 to 7 per cent. Gait speed effect sizes were not obtained. No high-quality trial evidence shows that any intervention reverses frailty status, as distinct from reducing falls.

> **Depth.** No single structure is named, so no size depth is given. First complaint: about 75 years († onset about age 75); time depth 52.80. One untreated course: no number ([B] builds up with age).
>
> **Model reading.** Way of ending: restore proportion. Layer: phase. By the rule it is held, not ended. The book's status: CONTROLLABLE. Reading and status agree. Recovery route: restore the proportion. Hold it, and look for a reset. This is a reading. The status above stands.

Palliative care

What it is. Care directed at relieving the suffering caused by a serious illness, rather than at removing the illness. It covers pain and symptom control, and psychological, social and spiritual support, for patients and families. It is the standing response where cure is not available, and it is also given alongside disease-directed treatment.

Measured. 56.8 million people need palliative care each year, including 25.7 million in the last year of life. About 14 per cent of those who need it receive it. Most people in need live in low- and middle-income countries. For children, 98 per cent of those needing palliative care live in low- and middle-income countries, and almost half of those in Africa (WHO fact sheet, Palliative care, 5 August 2020).

Relief is possible for more than 90 per cent of patients with advanced cancer, and over 80 per cent of patients in the terminal phase suffer moderate to severe pain (WHO fact sheet, Cancer).

The Lancet Commission on palliative care and pain relief is the standard source for estimates of serious health-related suffering and for the opioid access analysis (Knaul, Farmer, Krakauer, Foley, Frenk, Jamison, Rajagopal, Atun et al., *The Lancet* 2018;391(10128):1391–1454). Its specific figures and its morphine-equivalent tables are not reproduced here; they were not obtained. The citation is given so the figures can be retrieved.

Where it starts. Need for palliative care arises from the conditions that cause serious health-related suffering. Most trial evidence is in advanced cancer. Need is substantially non-cancer — heart failure, chronic obstructive pulmonary disease, dementia, HIV — and the trial base in those populations is much thinner.

What determines whether need is met is not pathology but supply. The measured determinant is access to oral morphine, given below.

Cure status. The label does not apply. Palliative care is a property of care and not a state of a person: it is applied alongside whatever label the underlying condition carries, and it does not change that label. The measured benefits are in quality of life and symptom intensity, not in disease course.

Prevention. Not applicable to the need itself, which follows from the underlying diseases. The preventable quantity is unrelieved pain, and the measured handle on it is morphine availability — the gap is given below, and no trial grade attaches to a supply figure.

Treatment. The landmark trial is Temel et al., *New England Journal of Medicine* 2010;363(8):733–742, published 18 August 2010. It randomised early palliative care integrated with standard oncologic care against standard oncologic care alone. The population was ambulatory patients with newly diagnosed metastatic non-small-cell lung cancer (NCT01038271).

- 151 patients randomised; 27 died before 12 weeks; 107 of the remainder, 86 per cent, completed assessments†.
- Quality of life at 12 weeks, the primary outcome: mean FACT-L score 98.0 against 91.5, P=0.03, on a scale of 0 to 136 where higher is better.
- Depressive symptoms: 16 per cent against 38 per cent, P=0.01†.
- Aggressive end-of-life care: 33 per cent against 54 per cent, P=0.05†.
- Median survival: 11.6 against 8.9 months, P=0.02†.

A median survival advantage of 2.7 months from less aggressive care is the finding that made the trial a landmark, and it is the figure most often cited from it.

That survival benefit does not survive pooling. The Cochrane review of early palliative care for adults with advanced cancer, published 12 June 2017 with searches to October 2016, covered 7 randomised and cluster-randomised trials and 1,614 participants.

- Health-related quality of life: SMD 0.27 (95 per cent CI 0.15 to 0.38), a small improvement. In natural units, FACT-G scores rose about 4.59 points more than with standard care (2.55 to 6.46). **Certainty: low**.
- Symptom intensity: SMD −0.23 (−0.35 to −0.10), a small reduction. **Certainty: low**.
- Survival: no difference detected. Hazard ratio for death 0.85 (0.56 to 1.28), 4 studies, 800 participants. **Certainty: very low**.
- Depression: no significant difference. SMD −0.11 (−0.26 to 0.03). **Certainty: very low**.

Both results belong in the record with their certainty ratings attached. Across four trials and 800 participants the hazard ratio for death is 0.85 with a confidence interval spanning 1, rated very low certainty. The quality of life and symptom benefits do survive pooling, at small effect size and low certainty. A reference work that cites Temel 2010 alone overstates the survival case. One that cites the Cochrane review alone understates how the field was changed by Temel.

The global access gap for oral morphine. From the International Narcotics Control Board, as reported by WHO (WHO fact sheet, Palliative care, 5 August 2020):

- In 2018, 79 per cent of the world's population, mainly in low- and middle-income countries, consumed 13 per cent of the morphine used for pain management. That morphine amounted to 1 per cent of the 388 tons manufactured worldwide†.
- In 2014, 80 per cent of the world's population consumed 9.5 per cent of the morphine used for pain management†.

Two things follow. Roughly four-fifths of humanity has access to about a tenth to an eighth of the world's pain-relief morphine, a sixfold to eightfold under-consumption relative to population share. And the figure moved between 2014 and 2018, from 9.5 to 13 per cent, so the gap is narrowing slowly.

The 1 per cent of 388 tons is the figure that shows the scale. The morphine used for pain management by most of the world's people is about 3.9 tons a year against total manufacture of 388 tons, most of which goes to other opioid products.

Per-capita morphine-equivalent consumption by WHO region or by country is published by the International Narcotics Control Board and in the Lancet Commission. Those figures were not obtained and are not estimated here.

Simple means. Oral morphine is itself a simple means: it is off-patent, on the WHO Model List of Essential Medicines, needs no cold chain, and is given by mouth. Where it reaches a patient it costs very little per day. The barrier is regulatory and logistical, not technical, and the consumption figures above measure the size of that barrier.

Beyond the drug: positioning, mouth care, pressure-area care, the presence of a person who knows what is happening, and clear explanation to the family. None requires an industrial chain. None has a pooled effect size in the literature cited here.

Gaps. The Lancet Commission's own figures were not obtained and should be retrieved directly. The Cochrane synthesis is from 2017 with searches to 2016, so later trials in non-lung and non-cancer populations are not in the pooled estimates given. Morphine consumption data here are at income-group level, not regional. Most trial evidence is in advanced cancer while need is substantially non-cancer. The 56.8 million need estimate is modelled, not measured.

> **Depth.** A form of care, not an illness. No depth is given.
>
> **Model reading.** Not applied. A form of care, not an illness.

Part 3 — The Simple Means

Part 3 — Simple Means

Part 1 closed on the layer that carries the largest numbers in this book and the smallest budgets. This part audits it.

A simple means, in this book, is an intervention that prevents, cures or controls a condition without a long industrial supply chain behind it. A sachet of salt and glucose. A bar of soap. A bed net. A lamp at the right hour. Thirty minutes of walking. A mother's chest.

The dossier underneath this part catalogues forty-six such interventions, graded as fifty-nine rows because several are graded separately per population or per outcome. About half of what is commonly claimed for this class does not survive the grading. Both halves are printed. A reference work that passes on the favourable half is not cheaper to use; it is wrong in a direction that is hard to detect.

The order here is deliberate. What holds comes first, with its figures. What does not hold comes second, with its figures. Then the two cases that mark where the category stops.

3.1 What holds

Twenty-five rows carry an unqualified STRONG. Two carry a qualified STRONG, exercise for chronic low back pain against no treatment and the DASH diet for blood pressure. Two carry a lower grade for a second outcome, iron in pregnancy and compression for venous leg ulcers. Each is flagged where it appears. Vaccination also reaches STRONG for effect and is excluded from these counts, because it sits outside the category by construction; §3.3 gives the reason.

Oral rehydration solution. The reduced-osmolarity formula against the old one: unscheduled intravenous infusion OR 0.59 (0.45 to 0.79), eleven trials reporting, eight pooled. WHO and UNICEF state the same result as a 33 per cent reduction in unscheduled supplemental intravenous therapy. Stool output fell about 20 to 25 per cent and vomiting about 30 per cent, neither with a pooled estimate.

Against intravenous rehydration itself — the comparison that matters for a setting with no drip — seventeen trials and 1,811 children. Treatment failure risk difference +4 per cent (1 to 7), number needed to treat 25: roughly one child in twenty-five on oral therapy still needs a drip. Hospital stay was 1.20 days shorter (−2.38 to −0.02). With the WHO low-osmolarity formula specifically there was no significant difference in failure against intravenous therapy, in six trials and 729 children. Phlebitis favoured oral therapy at NNT 50 (25 to 100); paralytic ileus favoured intravenous at NNT 33 (20 to 100).

The current UNICEF indicative price for a low-osmolarity sachet is US$0.05, read off the catalogue in October 2026. The co-packaged course with zinc is given at US$0.57 in the UNICEF indicative price list, 2021.

Zinc for childhood diarrhoea above six months. Thirty-three placebo-controlled trials, 10,841 children. Duration above six months: 11.46 hours shorter (−19.72 to −3.19). In children above six months with signs of malnutrition the reduction was 26.39 hours (−36.54 to −16.23), and this is the one high-certainty cell in the table. Diarrhoea still present at day seven: RR 0.73 (0.61 to 0.88). The WHO course is 20 mg a day for ten to fourteen days.

Universal salt iodisation. The physiology is settled: iodine is required for thyroid hormone synthesis. The population data are large and concordant. Goitre among Michigan schoolchildren fell from 38.6 per cent in 1924, the year of iodisation, to 1.4 per cent in 1951†. The number of countries where iodine deficiency is a public health problem fell from 110 in 1993 to 54 in 2003 to 28 now†. Public-sector cost is US$0.05 per person per year†.

Periconceptional folic acid, for recurrence. The MRC Vitamin Study randomised 1,817 women, all with a previous neural-tube-defect pregnancy, and had 1,195 informative pregnancies. Neural tube defects: 6 of 593 on folic acid against 21 of 602 without, RR 0.28 (0.12 to 0.71), a 72 per cent protective effect (29 to 88).

The Cochrane pooled recurrence figure is RR 0.34 (0.18 to 0.64). Multivitamins without folic acid showed no clear effect, RR 0.80 (0.37 to 1.72). The qualifier on this figure is in §3.2 and it is important.

Vitamin D for rickets. Deficiency causes rickets and osteomalacia, and correction cures them. This is settled physiology, and it is the only vitamin D indication in this part that reaches STRONG in the positive direction.

Bright light. Seasonal affective disorder, as treatment: effect size 0.84 (0.60 to 1.08) across eight studies, which the authors describe as equivalent to most antidepressant trials. Dawn simulation 0.73 (0.37 to 1.08)†. As an adjunct in non-seasonal depression, eleven randomised trials and 858 patients: remission 40.7 against 23.5 per cent, OR 2.42 (1.50 to 3.91); response 60.4 against 38.6 per cent, OR 2.34 (1.46 to 3.75)†. The dose in these trials is about 10,000 lux for thirty minutes or more a day†.

In the one head-to-head randomised trial against fluoxetine — 122 patients, halted early — light reached a MADRS effect size of 0.80 (0.28 to 1.31) against placebo and the drug reached 0.24 (−0.27 to 0.74). That trial is graded MODERATE on its own, and it is reported here because it is the comparison people ask for.

Timed light for shift work disorder. Light in the work environment with morning light restriction carries the American Academy of Sleep Medicine's highest recommendation level, Standard. Morning light for delayed sleep phase carries the next level, Guideline, and its dosing trial has twenty patients.

Dietary fibre, on its trial outcomes. Body weight −0.37 kg (−0.63 to −0.11), high certainty. Systolic blood pressure −1.27 mm Hg (−2.50 to −0.04). Total cholesterol −0.15 mmol/L (−0.22 to −0.07). WHO advises at least 25 g a day for people over ten. These are the randomised numbers, and they are small; §3.2 gives what is usually quoted instead.

Physical activity, on dose-response mortality. Device-measured, individual-level data from eight studies, 36,383 participants and 2,149 deaths†. Highest against lowest quartile of total activity: HR 0.27 (0.23 to 0.32); highest quartile of sedentary time, 2.63 (1.94 to 3.56)†. In fifteen cohorts and 47,471 adults, the top step quartile at a median 10,901 steps a day had HR 0.47 (0.39 to 0.57) against a median 3,553†. The risk reduction plateaus around 6,000 to 8,000 steps in adults over sixty and 8,000 to 10,000 below sixty†.

WHO advises 150 to 300 minutes a week of moderate activity, or 75 to 150 vigorous, plus muscle strengthening on two or more days. No dose-response was found for strengthening volume above that minimum.

Breastfeeding, on infection. Exclusive breastfeeding against none, infants under six months: diarrhoea morbidity RR 0.20 (0.13 to 0.29), diarrhoea hospitalisation 0.09 (0.02 to 0.44)†. Diarrhoea mortality for any breastfeeding against none, 0.23 (0.13 to 0.42)†. Lower respiratory infection morbidity 0.68 (0.60 to 0.77), mortality 0.30 (0.16 to 0.56), hospitalisation 0.33 (0.24 to 0.46)†. Sudden infant death in high-income countries fell 36 per cent (19 to 49)†.

WHO puts exclusive breastfeeding at six months at about 47 per cent for 2018 to 2025. It states that nearly 400,000 under-five deaths a year would be prevented by exclusive breastfeeding to six months with continued breastfeeding to two years.

Handwashing with soap, on diarrhoea. Day-care and schools in high-income countries: incidence rate ratio 0.70 (0.58 to 0.85), nine trials, 4,664 participants, high certainty†. Communities in low- and middle-income countries: 0.71 (0.62 to 0.81), nine trials, 15,950 participants†. About a thirty per cent reduction in episodes. The mortality claim is in §3.2.

Insecticide-treated bed nets. Against no net: all-cause child mortality rate ratio 0.83 (0.77 to 0.89), five trials, 200,833 participants, high certainty†. Uncomplicated *P. falciparum* incidence 0.55 (0.48 to 0.64), high certainty†. Severe malaria RR 0.56 (0.38 to 0.82), high certainty†. Deaths averted per 1,000 children protected per year: 5.6 (3.6 to 7.6) at all ages, 6.4 (4.16 to 8.69) at one to fifty-nine months†.

One caveat belongs with the figure. The incremental benefit of the insecticide over an untreated net is not statistically established for mortality: 0.67 (0.36 to 1.23)†. And pyrethroid resistance is growing, which the pre-2018 trials do not capture.

Salt reduction, on blood pressure. Thirty-four trials of at least four weeks, 3,230 participants, with urinary sodium falling about 75 mmol a day, roughly 4.4 g of salt†. Systolic: −4.18 mm Hg (−5.18 to −3.18) overall, −5.39 (−6.62 to −4.15) in hypertensive participants, −2.42 (−3.56 to −1.29) in normotensive†. Measured counter-effects exist and are printed: plasma renin, aldosterone and noradrenaline all rose slightly.

WHO gives global mean adult sodium intake for 2021 as 4,278 mg a day, about 11 g of salt, against a recommended limit under 2,000 mg. The attributable death figure differs between sources and both are printed: the WHO sodium reduction fact sheet of 11 May 2026 gives 1.7 million deaths a year for 2023, while the 2023 WHO sodium report as carried in secondary coverage gives 1.89 million. Either way it is the largest diet-related figure WHO publishes. Both are model outputs built on the blood-pressure effect plus blood-pressure-to-event associations, not event counts from salt-reduction trials.

Smoking cessation, and brief physician advice. Among British doctors, continuing smokers died about ten years earlier, and quitting at thirty regained about ten years, at forty about nine, at fifty about six, at sixty about three. In US cohorts the hazard ratio for death among current smokers aged 25 to 79 was 3.0 (2.7 to 3.3) in women and 2.8 (2.4 to 3.1) in men†.

Brief advice from a physician against no advice: RR 1.66 (1.42 to 1.94) across seventeen trials, in a review of forty-two trials and more than 31,000 smokers†. Intensive against brief advice, 1.37 (1.20 to 1.56)†. The absolute size matters and is small: assuming 2 to 3 per cent unassisted quitting, brief advice adds one to three quitters per hundred smokers advised.

Fluoride toothpaste. Seventy-four studies, seventy with usable data, 42,300 children†. Prevented fraction for decayed, missing and filled surfaces: 24 per cent (21 to 28)†. The mechanism is settled.

Toothbrushing against hospital-acquired pneumonia. Fifteen randomised trials, 2,786 patients, all but one in intensive care†. Hospital-acquired pneumonia RR 0.67 (0.56 to 0.81); ventilator-associated pneumonia 0.68 (0.57 to 0.82); death in intensive care 0.81 (0.69 to 0.95); length of stay in intensive care −1.78 days (−2.85 to −0.70)†. Two, three and four brushings a day performed alike.

This holds for ventilated patients. Outside that setting only two eligible studies exist, and the general claim is not supported.

Daily oral iron in pregnancy, for anaemia. Fifty-seven trials, 48,971 women. Maternal anaemia 4.0 against 7.4 per cent, RR 0.30 (0.20 to 0.47); iron deficiency at term 0.51 (0.38 to 0.68); iron-deficiency anaemia at term 0.41 (0.26 to 0.63), moderate certainty. Low birthweight 0.84 (0.72 to 0.99), with the upper bound touching unity, and that row is graded MODERATE. No effect is established for preterm birth, 0.93 (0.84 to 1.02).

Iodine in pregnancy, in severe deficiency. Supplementation to a total intake of 250 µg a day clearly reduces or eliminates cretinism where deficiency is severe. That is the whole of the STRONG claim, and §3.2 has the rest.

Exercise for knee osteoarthritis. Forty-four trials, 3,537 participants for pain. Pain SMD −0.49 (−0.59 to −0.39), which is 12 points lower on a 0 to 100 scale (10 to 15), high certainty. Physical function −0.52 (−0.64 to −0.39), about 10 points better. Withdrawals did not differ: OR 0.93 (0.75 to 1.15). Effects are measured immediately after treatment, so durability depends on continuing.

Exercise for chronic low back pain. Against no treatment, usual care or placebo: pain −15.22 on a 0 to 100 scale (−18.26 to −12.18), thirty-five studies, 2,746 participants; function −6.81 (−8.32 to −5.31)†. Against other conservative treatment the advantage shrinks to −9.10 (−12.63 to −5.57) at low certainty†.

The DASH diet, on blood pressure. The combination diet against control: −5.5 mm Hg systolic and −3.0 diastolic overall, −11.4 and −5.5 in the hypertensive subgroup, all at $p<0.001$. Sodium and body weight were held constant, which makes this an unusually clean dietary trial. Two limits belong with it: the primary publication reports no confidence intervals, and all food was provided, so the effect size is for adherence rather than for advice.

Magnesium sulfate for pre-eclampsia and eclampsia. The Magpie trial randomised 10,141 women across 33 countries against placebo: eclampsia RR 0.32, $p<0.0001$†. The pooled comparison against

placebo or no anticonvulsant covers six trials and 11,444 women: eclampsia RR 0.41 (0.29 to 0.58), placental abruption 0.64 (0.50 to 0.83)†. Maternal death moved in the favourable direction without reaching significance, 0.54 (0.26 to 1.10)†. Caesarean section rose slightly, 1.05 (1.01 to 1.10), and flushing rose sharply, 24 against 5 per cent†.

Magnesium sulfate injection is an inorganic salt solution, among the least industrially demanding items on the Essential Medicines List. The UNICEF indicative price in October 2026 works out at about US$0.33 an ampoule of 5 g in 10 mL.

Immediate kangaroo mother care. 3,211 infants of 1,000 to 1,799 g across five hospitals in Ghana, India, Malawi, Nigeria and Tanzania. Mortality at 28 days 12.0 against 15.7 per cent, RR 0.75 (0.64 to 0.89), p=0.001, number needed to treat 27†. No equipment is required beyond the mother’s body.

Two qualifiers are printed with it. Mortality at 72 hours was not significant, 0.77 (0.58 to 1.04)†. And the trial was stopped early for benefit, which systematically overstates effect size.

Chlorhexidine cord cleansing. Three cluster-randomised community trials in Nepal, Bangladesh and Pakistan, 54,624 participants†. All-cause neonatal mortality RR 0.77 (0.63 to 0.94), about a 23 per cent reduction, with moderate heterogeneity at I^2 50 per cent†. Omphalitis fell by 27 to 56 per cent depending on severity†. The benefit was found in high-mortality settings with unhygienic cord practice and does not transfer to facility births with clean dry cord care.

The six-month tuberculosis regimen. Two months of isoniazid, rifampicin, pyrazinamide and ethambutol, then four months of isoniazid and rifampicin. About 85 per cent of patients worldwide reach a successful outcome, on a strong recommendation backed by high-certainty evidence for new pulmonary disease. WHO reports 10.7 million incident cases and 1.23 million deaths for 2024, and 83 million lives saved since 2000.

The regimen belongs in this part with one qualification stated rather than softened. It needs no equipment at the point of care, and it needs six months of uninterrupted supply of four manufactured medicines plus adherence support. In supply-chain terms that is not simple.

3.2 The audit

Twenty-five claims in this class carry more weight in circulation than in their sources. Each is given here with the figure that is actually published.

Home-made sugar-salt solution. No study of recommended home fluids met the quality criteria for a mortality meta-analysis, so no effect on diarrhoea mortality could be estimated. The published teaspoon recipe — six level teaspoons of sugar and half a level teaspoon of salt in a litre — is not attributed to WHO or UNICEF on the page that carries it. Pooled treatment failure for home fluids was 0 per cent (−0.1 to 0.1) across twelve randomised trials, but all were prepared under hospital or clinic supervision rather than in households.

The packaged sachet is strongly evidenced. The kitchen version is not. The documented risk is hypernatraemia from salt measurement error, and measurement is exactly the step that packaging removes.

Vitamin A supplementation. CONTESTED, and both numbers are printed. All-cause mortality in children aged six months to five years: RR 0.76 (0.69 to 0.83) across sixteen trials and 194,483 children, excluding DEVTA. Including DEVTA: 0.88 (0.84 to 0.94). DEVTA alone, about two million children in India: 0.96 (0.89 to 1.03), p=0.22.

The familiar 24 per cent rests mainly on trials conducted before 1994†. From 1994 only one study showed a mortality effect against a no-intervention control, and none against a nutrition-education comparator. A separate review found no effect on pneumonia mortality, hospital stay or symptom resolution. What remains solid is night blindness — prevalence 0.32 (0.21 to 0.50) — and measles incidence, 0.50 (0.37 to 0.67)†.

Folic acid. The 72 per cent is recurrence prevention, in women who had already had an affected pregnancy. For first occurrence the randomised evidence is one trial, RR 0.07 (0.00 to 1.32), not significant, though no cases occurred in the folic acid arm†. The large falls observed after mandatory flour fortification are ecological evidence, not trial evidence.

Exercise against drugs. The network meta-analysis covers 305 randomised trials and 339,274 participants, and its own framing is statistical equivalence rather than superiority. For secondary prevention of coronary heart disease the credible intervals span unity in all four comparisons: statins 1.08 (0.90 to 1.30), β-blockers 1.05 (0.87 to 1.25), ACE inhibitors 1.08 (0.87 to 1.33), antiplatelets 1.07 (0.88 to 1.30).

The results favouring exercise come from three stroke-rehabilitation trials with 227 participants, which the authors themselves call imprecise: against anticoagulants 0.09 (0.01 to 0.70), against antiplatelets 0.10 (0.01 to 0.62)†. And in heart failure one comparison runs the other way. Diuretics beat exercise, OR 4.11 (1.17 to 24.76)†.

Clean cookstoves. The burden estimate is large, and the two available figures disagree. The WHO household air pollution fact sheet of 16 December 2025 gives 2.9 million deaths a year, including over 309,000 among children under five, with around 2.1 billion people cooking on open fires or inefficient stoves. The WHO health-risks page for the same topic gives nearly 3.2 million premature deaths a year. Both are printed. The attribution of those deaths is the same on both: ischaemic heart disease 32 per cent, stroke 23, lower respiratory infections 21, chronic obstructive pulmonary disease 19, lung cancer 6.

The randomised evidence on health outcomes is a different matter. HAPIN randomised 3,200 pregnant women in India, Rwanda, Guatemala and Peru to a free liquefied-petroleum-gas stove with fuel. Personal fine particulate exposure fell 66 per cent, 23.9 against 70.7 μg/m³, and 69 per cent of intervention households came below the WHO interim guideline against 23 per cent of controls. Birth weight showed no significant difference. The suggestive subgroup — intervention before eighteen weeks' gestation — gave +33.8 g (−2.6 to +70.2), crossing zero.

So the exposure reduction was delivered and verified, and the first reported hard endpoint was null.

Dietary fibre. The 15 to 30 per cent reductions in death and major disease are from 185 prospective observational studies: all-cause mortality RR 0.85 (0.79 to 0.91), coronary heart disease mortality 0.69 (0.60 to 0.81), stroke incidence 0.78 (0.69 to 0.88), type 2 diabetes 0.84 (0.78 to 0.90), colorectal cancer 0.84 (0.78 to 0.89)†. The randomised outcomes in the same paper, from fifty-eight trials, are −0.37 kg, −1.27 mm Hg and −0.15 mmol/L†. Both sets are correct. Only one set is causal evidence.

Social connection. The association is among the largest and most replicated in epidemiology: overall OR for survival 1.50 (1.42 to 1.59) across 148 studies and 308,849 participants†. The comparison to smoking appears in the source qualitatively, without comparator effect sizes, and the widely repeated "fifteen cigarettes a day" has no numeric basis in the papers.

The structure of the finding matters. The strongest subgroup is complex social integration at 1.91 (1.63 to 2.23)†, which is also the most confounded with health and function. The hardest and least confounded measure, binary living-alone status, was the weakest and was not significant: 1.19 (0.99 to 1.44)†. No trial shows that increasing social connection reduces mortality.

Light therapy, two claims. Prevention of seasonal affective disorder rests on one randomised trial of 46 people: bright white light against no light, RR 0.64 (0.30 to 1.38), not significant, and all comparisons were rated very low quality†.

And light therapy is not without harm. Hypomania: RR 4.91 (1.66 to 14.46), number needed to harm 8 (5 to 20), 19 of 118 against 3 of 101 across seven studies and 219 patients. The review notes possible confounding, since the largest dataset combined light with an antidepressant. The figure is rarely mentioned when light is described as side-effect-free. Also worth printing: in the older Cochrane analysis of non-seasonal depression the pooled estimate loses significance under random effects, −0.22 (−0.52 to 0.09).

Handwashing and mortality. No trial in the Cochrane diarrhoea review reported diarrhoea deaths. Two community trials reported all-cause under-five mortality and the review gives no effect estimates. On

respiratory infection the pooled figure is RR 0.83 (0.76 to 0.90) with I^2 88 per cent, and the effect disappears for the one laboratory-confirmed outcome, influenza, and for all-cause mortality. The trial evidence establishes fewer episodes. It does not establish fewer deaths.

Solar water disinfection. The headline cluster-randomised figure is RR 0.62 (0.42 to 0.94)†. Adjusting for non-blinding takes it to 0.80 (0.60 to 1.01), losing significance†. Most studies were unblinded with self-reported diarrhoea. Several authors of the review declared consulting or research relationships with manufacturers of household water treatment devices.

Point-of-use treatment as a class survives better. Filtration 0.48 (0.38 to 0.59), chlorination 0.77 (0.65 to 0.91) — and chlorination shows no effect, 0.90, where residual chlorine was found in half the samples or fewer†.

Latrine provision. Cluster-randomised trials of simply providing sanitation access: 0.89 (0.73 to 1.08) at all ages, 0.98 (0.83 to 1.16) under five, neither significant†. The large effects, 0.61 (0.50 to 0.74), come from non-randomised studies of improving existing facilities†. The one comparison reaching moderate certainty is behaviour-change messaging, 0.82 (0.69 to 0.98) under five†. Building latrines without changing use has not been shown in cluster-randomised trials to reduce diarrhoea.

Improving the water source without point-of-use treatment belongs beside it: 0.76 (0.48 to 1.19) at all ages, 0.96 (0.82 to 1.12) under five, no clear benefit†.

Iodine in pregnancy. STRONG only where deficiency is severe. In mild-to-moderate deficiency no trial has shown a child-development benefit. Six trials in such regions did not assess child development, growth or pregnancy outcomes at all; one randomised trial and four observational studies found no differences on mental development scales, all at low to moderate quality. Three trials found reduced postpartum maternal hyperthyroidism and increased gastrointestinal intolerance, with no differences in hypothyroidism, thyroid autoimmunity, low birth weight or preterm delivery. One observational study linked self-reported intake above 200 µg a day with lower maternal thyroid function. Universal salt iodisation remains the primary strategy.

Mediterranean diet. PREDIMED randomised 7,447 adults at high cardiovascular risk and reported HR 0.69 (0.53 to 0.91) for the olive oil arm and 0.72 (0.54 to 0.95) for the nut arm. The 2013 report was withdrawn and republished in 2018 after randomisation irregularities were found at some sites, including household-level and clinic-level non-random assignment; the republished estimates no longer rely exclusively on the assumption that all participants were randomly assigned. That is a material limitation, not a technicality.

The other supporting trial, Lyon, has 605 post-infarct patients at one centre, with adjusted risk ratios of 0.28 to 0.53 — implausibly large relative to PREDIMED.

Time-restricted eating. Across eleven meta-analyses covering 130 randomised trials and 104 unique associations, 1 association reached high GRADE certainty and 72 per cent were very low. Twenty-eight of 104 were significant and beneficial. In the best-designed head-to-head trial, 139 adults over twelve months at matched calorie intake, the between-group difference was −1.8 kg (−4.0 to +0.4), not significant, and no secondary outcome differed. Reduced fat-free mass is a documented downside. What the evidence supports is that eating less causes weight loss.

Honey for cough. Against dextromethorphan, honey is equivalent: cough frequency MD −0.07 (−1.07 to +0.94), severity −0.13 (−1.25 to +0.99)†. It beats no treatment, −1.05 (−1.48 to −0.62), and one antihistamine, −0.57 (−0.90 to −0.24)†. The evidence base is three small trials and 568 children, two at high risk of bias, with parent-rated Likert scores, a single night of follow-up, and cough duration never measured. Honey is contraindicated under one year of age because of infant botulism, and no trial participant was under one.

Saline nasal irrigation. Five trials, 749 enrolled and 565 with data†. The only significant results come from one trial of 401 children: nasal secretion score MD −0.31 (−0.48 to −0.14), obstruction −0.33 (−0.47 to −0.19)†. The review itself notes that on a four-point scale this may be of minimal clinical significance. Most other comparisons showed no difference from control, and there is no formal certainty rating.

Compression for venous ulcers. The principle is settled physiology: compression reduces venous hypertension and heals ulcers. The specifics are thinner than usually presented. In the review of forty-eight trials and 4,321 participants, no pooled risk ratio exists for compression against no compression on healing; eight trials were analysed without pooling. A separate 2021 review does publish figures against no compression: time to healing HR 2.17 (1.52 to 3.10), and healing within twelve months RR 1.77 (1.41 to 2.21), both at moderate certainty†. Ten of its fourteen studies were at high overall risk of bias.

Recurrence prevention rests on one trial of 153 people, RR 0.46 (0.27 to 0.76) at six months†. High against moderate compression gives contradictory results at the two follow-up points: 0.57 (0.39 to 0.81) at three years and 0.82 (0.61 to 1.12) at five†. Patient intolerance of hosiery was high, and adherence is the binding constraint.

Zinc below six months. No benefit, and a trend toward harm. Duration of acute diarrhoea +5.23 hours (−4.00 to +14.45)†. Diarrhoea still present at day seven, RR 1.24 (0.99 to 1.54) in one trial of 1,074 infants†. Vomiting increased, RR 1.57 (1.32 to 1.86) above six months and 1.54 (1.05 to 2.24) below, both at moderate certainty†. The review authors do not support zinc below six months, nor in well-nourished children, nor in low-risk settings.

Vitamin D for hard outcomes. Null across the large trials, with a possible harm signal. Invasive cancer HR 0.96 (0.88 to 1.06), major cardiovascular events 0.97 (0.85 to 1.10) in 25,871 adults over a median 5.3 years†. All-cause mortality 1.04 (0.93 to 1.18) in 21,315 Australians†. Total fracture RR 1.00 (0.93 to 1.07), hip fracture 1.11 (0.97 to 1.26), falls 0.97 (0.93 to 1.02) across eighty-one trials and 53,537 participants†.

The harm signal is prespecified cancer mortality in the D-Health trial: HR 1.24 (1.01 to 1.54) on monthly bolus dosing†. The investigators describe the increase as unproven.

The contested zone is whether these nulls reflect an absent effect or the enrolment of replete participants. Only 6 per cent of the eighty-one trials enrolled deficient people, and the D-Health treatment arm averaged 115 nmol/L†. The strongest signal the other way is respiratory infection in the deficient: adjusted OR 0.30 (0.17 to 0.53) in daily or weekly dosing below 25 nmol/L — a subgroup of 234 participants across six trials, not a prespecified primary endpoint†.

The claim that 95 per cent of Essential Medicines List medicines are off-patent. That figure refers to the 375 compounds on the 2013 list†. No current audit of the 24th List exists. The only other available figure counts 35 medicines on the 22nd List as patented in lower-income countries, 7.3 per cent†. It counts patents in those markets only. A medicine off-patent in Malawi may be on-patent in the European Union.

The claim that WHO publishes a list of locally producible essential medicines. A risk framework exists. A 2011 WHO and Global Fund stakeholder meeting sorted essential medicines into high, medium and low manufacturing risk on four criteria, and the underlying WHO document runs to 35 pages. The published paper names one low-risk product: 7.1 per cent chlorhexidine digluconate, for umbilical cord care. The framework is not a per-medicine public list, and the full risk tiers could not be retrieved.

The ORS lives-saved totals. The figures of 54 million and 70 million are modelled attributions without confidence intervals, carried by secondary sources. The underlying mortality estimate is a 69 per cent pooled relative reduction (51 to 80) from three quasi-experimental studies, and the extrapolation to 93 per cent of diarrhoea deaths assumes a linear relation between coverage and mortality. The authors of the background mortality series attribute the decline to multiple interventions: under-five diarrhoea deaths fell from 4.6 million in 1980 to 3.3 million in 1990 to about 1.5 million in 1999. Ecological correlation with oral rehydration use was $r = -0.61$ ($p = 0.04$) in north-east Brazil and not significant in the Philippines.

Community case management of pneumonia. The measured figure is a 35 per cent reduction in acute lower respiratory infection mortality (18 to 48), with a 21 per cent reduction in all-cause mortality†. The 70 per cent usually quoted is a modelled adjustment for about 50 per cent actual receipt of the antibiotic†. The same review found no effect of zinc and no effect of vitamin A on pneumonia mortality.

Sleep duration. The U-shaped association is large and consistent: short sleep RR 1.12 (1.06 to 1.18), long sleep 1.30 (1.22 to 1.38), across sixteen studies, 1,382,999 participants and 112,566 deaths†. It is observational, it is self-reported, and reverse causation is serious, since long sleep marks existing illness.

No trial shows that changing sleep duration changes mortality. Sleep timing has intervention evidence only through timed light in circadian disorders, where shift work and delayed sleep phase are the two applications that reach a meaningful recommendation level.

3.3 The counter-cases

Two interventions mark the boundary of this category, and they matter more than any single row above, because they show what the category excludes.

Vaccination. STRONG for effect, by a wide margin. 154 million lives saved since 1974, most of them children under five; measles vaccination accounts for about 60 per cent of that total; vaccination accounts for about 40 per cent of the observed decline in global infant mortality, and about 66 years of full health per life saved, 10.2 billion years in all. WHO puts third-dose diphtheria-tetanus-pertussis coverage at 85 per cent of infants in 2025, with 13.5 million children receiving no dose.

And vaccination sits outside simple means by construction. Every vaccine in the thermostability table bar one requires an unbroken 2 to 8 °C chain from factory to arm, and the most heat-sensitive include oral polio and measles. The exception is MenAfriVac, the only vaccine fully relicensed for a controlled temperature chain, which tolerates up to four days at up to 40 °C with monitoring†. Its modelled logistics cost in Chad halved, from US$0.24 to US$0.12 per person†. Measles is a priority for the same treatment, with four prequalified producers and none yet validated. Every vaccine also requires biological manufacture with extensive lot-release testing, which no pharmacy holds.

This is the clearest case in the book of a highly effective intervention that cannot be made or delivered without a long industrial chain.

Amoxicillin. The second counter-case, and it separates two things that are routinely treated as one. Amoxicillin is off patent. It is not simple to make.

Its active ingredient derives from fermented penicillin G. The industrial route runs more than ten steps, reaches around minus thirty degrees, and generates up to about 70 kg of non-recyclable waste per kilogram of product†. An enzymatic route needs fewer steps under milder conditions, at reported yields of 39 and 47 per cent†. As of August 2017 there were eight active US drug master files held by seven companies for amoxicillin trihydrate, so there are only seven producers of the active ingredient worldwide. The finished product needs dedicated equipment and dedicated sites, because of penicillin cross-contamination and anaphylaxis risk, with humidity-controlled air handling and aluminium-aluminium blisters.

The tablet costs about US$0.05 on the UNICEF indicative price, October 2026. Seven companies in the world make the substance in it.

Off-patent describes a legal status. It says nothing about how many steps, how much waste, or how few producers.

Read in the net: a simple means is not a cheap means. It is a means whose chain closes at the point of need. Price and patent status are read at the wrong depth; what decides is whether the thing can be completed where it is used. This is a reading, not a mechanism.

3.4 The genuinely low-complexity list

No validated public catalogue of simply producible essential medicines exists, and the category as a whole is graded WEAK for that reason. What can be asserted is a short list, each item individually sourced, whose production is genuinely low in complexity:

- oral rehydration salts
- zinc sulfate tablets
- iodised salt, as food fortification rather than a medicine

- folic acid tablets
- ferrous salts
- vitamin A capsules
- chlorhexidine 7.1 per cent gel
- magnesium sulfate injection
- sodium chloride and glucose solutions
- paracetamol
- oral vitamin D

Three things about that list are worth stating plainly. It is eleven items long. Several of them carry the strongest evidence in this part — magnesium sulfate, chlorhexidine gel, oral rehydration salts, iron, iodine. And one of them, chlorhexidine 7.1 per cent digluconate, is the single product the published WHO and Global Fund risk framework names as low manufacturing risk.

One operational WHO production manual exists for this whole class, and it is for oral rehydration salts: *Oral rehydration salts: production of the new ORS*, 2006. It publishes the formulation, raw-material specifications, quality-control tests, premises layout, packaging and shelf life. For an output of about three to four million sachets a year it specifies the premises: a raw and packaging warehouse, a finished-goods warehouse, a bulkstore, a mixing room of about 30 m², a packing room of about 45 m², an in-process quality-control laboratory of about 15 m², and staff facilities. WHO recommends integrating the work into an existing powder-drug facility rather than building a standalone plant.

The manual also states the point on which this part ends. Decentralised cottage-industry mixing and packing is possible, and it is costly, because quality-control requirements apply regardless of volume and therefore raise the unit cost.

Simple does not mean improvised. The shortest chain in medicine still has a laboratory in it.

Part 4 — The Chain

Part 4 — The Chain

The entries keep raising one question that no individual entry can answer. A medicine exists, it is cheap to make, and it is not available, or it is available at a price that makes it unavailable in practice. How short can the production chain be, and who is legally allowed to make what?

This part answers that question as a matter of law and institution. Short, here, means short in institutional distance: fewer legal intermediaries between the point of need and the point of production. It names who may make what, at what scale, and at what cost. It does not describe how anything is made, and it is not a route to making a medicine outside a licensed setting. Every figure in it concerns authorisation, price and capacity.

4.1 Three documented cases

The clearest evidence in this book that the chain can be short comes from three Dutch cases, each with published before-and-after prices per patient per year.

Chenodeoxycholic acid for cerebrotendinous xanthomatosis, Amsterdam UMC. The reference case in Europe. Cerebrotendinous xanthomatosis is an inherited disorder of cholesterol metabolism, with prevalence cited at fewer than 5 per 100,000.

The substance had been registered since 1999 for gallstones and used off label for this condition at €308 per patient per year†. In 2015 the rights holder applied for a marketing authorisation as an orphan medicine for the condition and withdrew the existing product. The European authorisation was granted in 2017, carrying ten years of market exclusivity, and the price rose to €140 a capsule, about €153,300 per patient per year on the Dutch price register†. A second official figure for the same period gives €163,000†, and a parliamentary question cites a different earlier baseline of €20,000 to €25,000 rising to an intended €160,000 to €220,000†. The sources disagree on the pre-2017 level and all the figures are printed.

From €308 to €153,300 per patient-year is a factor of 498, recomputed. Per capsule, from €0.28 in 1976 to €140, a factor of 500†. A Belgian hospital preparation of the same 250 mg capsule cost €1.5113 in 2018, 93 times less than the commercial capsule†.

Amsterdam UMC announced magistral preparation in April 2018, for approximately fifty patients, after Dutch insurers had begun refusing to reimburse the commercial price.

Viscous cysteamine eye drops for nephropathic cystinosis, Radboud UMC. The largest proportional gap in the set, and the cleanest, because both prices appear in one official document. The pharmacy preparation, an aqueous 0.5 per cent cysteamine drop in a 10 mL bottle, cost €35.37, which is €1,839.24 per patient per year; the registered product, viscous 0.55 per cent cysteamine in 5 mL, cost €1,025 at pharmacy purchase price, which is €53,300 per patient per year, as given in the advice of the Dutch Zorginstituut Nederland of 4 January 2018.

That is a factor of 29 per patient-year, recomputed. Corrected for the halved bottle volume, the registered product costs roughly 58 times the preparation per millilitre.

The Dutch expertise centre records 48 patients with proven nephropathic cystinosis, 24 children and 24 adults; the budget-impact analysis used 43 of them, and projected about €2.2 million of additional pharmacy expenditure for 2020†. A separate figure circulating in Dutch hospital pharmacy discussion puts the pre-registration hospital drops at €20 a bottle against €1,000 after†. The €20 and €35.37 figures differ in presentation volume and in whether overhead is counted, and both are printed.

Mexiletine for non-dystrophic myotonia. About 500 people in the Netherlands have the condition, and pharmacists supplied mexiletine as a preparation for years before any registration.

At one to three capsules a day, the pharmacy preparation at €6.95 a capsule in the Netherlands in 2021 works out at €2,537 to €7,610 per patient per year, and the registered orphan product at €23.39 a capsule at €8,537 to €25,612†. A factor of 3.4, recomputed. Against the year-2000 pre-registration price of €0.23 a capsule, the registered product is 102 times more expensive†, and an imported mexiletine at €2.85 sits between them†.

The multiples are 498, 29 and 3.4. They are the headline, and they are not the most important finding. Three things qualify them, and each matters more than the multiple it qualifies.

4.2 What actually governs the short chain

The chenodeoxycholic acid preparation was stopped on starting-material quality, not on law. This is the single most important practical finding in this part.

The rights holder filed an enforcement request with the Dutch health inspectorate in 2018; the minister stated there had been no direct contact between the company and the inspectorate. The national institute for public health then tested samples of the active substance against the European Pharmacopoeia and found unknown impurities above the monograph limit. The hospital had not tested the substance against the general monograph for substances for pharmaceutical use. After consultation with the inspectorate, Amsterdam UMC stopped preparation and supply, and the inspectorate set out the conditions to be met.

On 4 September 2018 the minister answered parliamentary questions. He called the price increase socially unacceptable, and saw possible abuse of a monopoly position including in the supply of the raw material. He said he considered it a good thing if the magistral preparation could proceed, provided the starting material was sound and met the standards. The inspectorate, in his words, could not and might not close its eyes to the finding.

Preparation resumed in January 2020†. In February 2019 the competition authority had published its view that magistral preparation is an exception to orphan exclusivity and offers room for lower prices. It added that it would watch for manufacturers or raw-material suppliers creating unjustified barriers, such as restricting access to raw materials. On 19 July 2021 it fined the company €19.6 million for abuse of a dominant position, and the company lost its appeal at the Rechtbank Den Haag on 14 July 2022†. Fines followed in Spain at €11.25 million, Italy at €3.5 million, and Israel at €2.2 million intended plus two executive fines of €172,000†. The case file gives a total of €35.5 million; the individual amounts sum to about €36.9 million, and the source does not reconcile the difference. Both figures are printed.

So: the exemption held, the minister wanted the preparation to continue, the competition authority endorsed it as a price instrument, and the preparation still stopped for sixteen months — on an impurity finding in the starting material. The binding constraint on the short chain is qualification of the active substance, not the legal exemption.

Registration closes the short chain. The cysteamine case shows the mechanism operating in the plain direction. The preparation existed first and worked. Registration of the commercial product did not add a new treatment; it moved an existing one inside the authorisation regime. After that the preparing pharmacies were no longer permitted to supply it, because the first condition of the Dutch supply-to-other-pharmacies route — no adequate registered alternative available — was no longer satisfied.

The Dutch counter-move is for the preparing pharmacies to register the products themselves. In June 2021 Erasmus MC, Radboudumc, UMCG, Catharina Ziekenhuis and the compounding pharmacy A15 formed a platform to do exactly that, selecting medicines they already prepare, where they hold the technical knowledge and effectiveness is established. The announcement names five parties and its headline says four, and the source does not reconcile this. Cystadrops is named as the trigger.

This is the short chain accepting the long chain’s paperwork in order to keep the short chain’s cost base. It is the only documented structural answer to the registration-closes-the-exemption problem.

The mexiletine outcome is the strongest precedent in this part. On 14 January 2021 the Dutch national health care institute advised the minister not to reimburse the registered product. It advised instead that the

pharmacy preparations be brought into the basic insurance package, so that patients kept access to the medicine. The budget impact of reimbursing the registered product had been put at €6.1 to €7.6 million a year in additional expenditure†. The institute's reasoning was that the orphan rules had been applied to an existing medicine. The regulation following the advice appeared in the Staatscourant on 30 July 2021†.

The compounded route became the reimbursed standard of care, at roughly one third of the registered price. A national reimbursement authority can prefer the preparation to the registered product and leave the registered product outside the package.

4.3 The legal frame

The Netherlands. Three articles of the Geneesmiddelenwet carry the structure. Article 18(1) prohibits preparing, importing, stocking, supplying or wholesaling medicines without a manufacturing permit, and Article 18(5) exempts small-scale preparation by a pharmacy for its own patients. Article 40 prohibits placing a medicine on the market without a marketing authorisation, and Article 40(3)(a) exempts the medicine prepared in a pharmacy for that pharmacy's own patients. Article 84(1) prohibits advertising an unauthorised medicine†.

Four routes follow, and they differ in who may be served rather than in how much may be made. Magistral preparation serves one named patient on a prescription, with no authorisation. Stock, or officinal, preparation serves the pharmacy's own patient population where the patient is not yet identified, at small scale, with no authorisation and no numerical ceiling defined. Supply to another pharmacy's patients — *collegiaal doorleveren* — is formally prohibited and tolerated under conditions. Full manufacture requires a permit and a marketing authorisation.

The inspectorate's 2023 circular sets six conditions for supply beyond the pharmacy's own patients, and they define precisely where the short chain is allowed to serve a population:

1. No adequate registered alternative is commercially available. Adequate means the same active substance, dosage form and strength, or near enough to reach the required dose. A product registered in the European Economic Area or a mutual-recognition country counts as available, and is preferred over a preparation.
2. Notification of each product through the national medicines database within five working days of first supply, regardless of scale. Where the authorisation agency judges a product suitable for registration, it and the inspectorate open exploratory talks with the pharmacy.
3. A product dossier per product, covering design quality and chemical-pharmaceutical quality, available immediately on inspection, including the justification for why registered alternatives are inadequate.
4. Compliance with good manufacturing practice, verified by regular inspection.
5. Pharmacovigilance: adverse reactions reported to the national centre, with a working system for recording, assessing and signalling.
6. No advertising, by either the preparing or the dispensing pharmacy.

The receiving pharmacy must itself verify conditions 1, 2, 5 and 6. The circular states openly that the ministry and the inspectorate are working towards a policy rule and ultimately a statutory basis, so this route rests on enforcement discretion rather than on law.

The statute says almost nothing about quality. That content comes from the profession. The Dutch pharmacists' preparation guideline supplies the operative definitions, and the rule that a pharmacist releases each batch before dispensing, on the basis of preparation documentation and controls. It also supplies the product dossier requirement, scaled to the preparation scale, and the content-uniformity standard from the implementing decree: the active constituent may not deviate more than 10 per cent from the stated quantity†.

Europe. The whole European edifice rests on two sentences. Directive 2001/83/EC establishes that no medicinal product may be placed on the market without a marketing authorisation, and then removes two categories from the Directive's reach:

- Article 3(1), the **magistral formula**: any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient. A pharmacy may prepare for one named patient with no authorisation, no dossier and no regulatory filing.
- Article 3(2), the **officinal formula**: any medicinal product prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia, intended to be supplied directly to the patients served by that pharmacy. Preparation to a pharmacopoeial standard, for stock, for the pharmacy's own patients only.

Article 5(1) adds a third route, for special needs: a Member State may exempt an unauthorised product supplied in response to a bona fide unsolicited order, formulated to the specifications of an authorised health-care professional, for an individual patient under that professional's direct personal responsibility. This is the basis for import on a physician's declaration.

Two structural facts follow from the wording and govern everything downstream. The exemption is tied to the pharmacy's own patient relationship: neither article covers supplying another pharmacy, another hospital, or a market. And scale is not stated as a number — the Directive sets no volume ceiling, and the limit is relational rather than quantitative. Member States have filled that gap nationally, and the Dutch solution is the most developed in Europe. The Court of Justice confirmed in the *Abcur* cases that a product prepared outside a genuine individual prescription relationship falls back inside the Directive and needs an authorisation.

The United States. The framework was rebuilt by the Drug Quality and Security Act of 27 November 2013, enacted after the 2012 fungal meningitis outbreak traced to a compounding pharmacy. It created two categories.

Section 503A is traditional compounding, by a licensed pharmacist in a state-licensed pharmacy or by a licensed physician. It requires a patient-specific prescription for an identified individual, with limited anticipatory preparation allowed only on a documented history of valid orders. It is exempt from new drug approval, from the adequate-directions labelling requirement, and from the good-manufacturing-practice-linked adulteration provision. Bulk substances must meet a pharmacopoeial monograph where one exists, come from a registered establishment, and carry a valid certificate of analysis. In a state without a memorandum of understanding with the federal government, no more than 5 per cent of prescription orders may be distributed out of state. Inspection is by the state board of pharmacy.

Section 503B creates the **outsourcing facility**: a federally registered establishment that may compound without any patient-specific prescription, for office stock, in exchange for full compliance with good manufacturing practice and federal risk-based inspection. Registration is voluntary to enter, with an annual establishment fee. There were 98 registered outsourcing facilities as of 30 September 2026; some owners run more than one, so the number of distinct companies is lower.

Both categories are barred from compounding a product that is essentially a copy of a commercially available drug product. They are also barred from products the authorities identify as presenting demonstrable difficulties affecting safety or effectiveness, and from products withdrawn from the market for safety or effectiveness reasons. Positron-emission-tomography drugs and radiopharmaceuticals fall outside 503A altogether†.

The two systems are opposite solutions to the same problem. The European exemption is defined by the patient relationship and is silent on scale: it keeps the exemption small and relational. The American 503B category creates a licensed industrial tier with no patient relationship at all, and regulates it as manufacture.

What can be prepared this way, and what cannot. The boundary tracks physical chemistry more closely than law.

Preparable in a pharmacy, in an ordinary preparation room: capsules, which are the workhorse form and carry most repurposing cases; tablets, possible but less used, because capsule filling is more robust at small scale; oral liquids, solutions and suspensions, standard for paediatric use and swallowing difficulty; creams, ointments and gels, the largest category by volume in Dutch practice; suppositories; and preserved

eye drops and eye ointments. Preservative-free eye drops that cannot be terminally sterilised require a laminar airflow cabinet — the cysteamine case sits here. Parenterals and preservative-free irrigations terminally sterilised in the final container require a separate room at minimum class D. Aseptically prepared sterile products require an aseptic facility and documented microbiological competence.

Not preparable in a pharmacy, with the reason in each case:

- **Monoclonal antibodies** — adalimumab, trastuzumab, pembrolizumab, dupilumab. The product is the manufacturing process: a glycosylated protein secreted by a living mammalian cell line. There is no active substance obtainable as a pharmacopoeial powder, and no formulation step in a pharmacy produces the molecule.
- **Other recombinant proteins and insulin analogues** — the same reason: cell-culture expression, folding and purification. A pharmacy can dilute or repack an authorised product; it cannot make one.
- **Vaccines, including mRNA** — batch release requires potency assays no pharmacy holds.
- **Cell and gene therapy, including CAR-T** — a living autologous product, under advanced-therapy rules. In Europe this runs through the hospital exemption, which is a different track from the pharmacy exemption.
- **Complex sterile injectables**: liposomal, nanoparticle, depot and long-acting formulations. The therapeutic behaviour comes from a particle architecture that requires dedicated process equipment and in-process particle-size control.
- **Anything with an adequate registered alternative** — not a technical limit but a legal one, from condition 1 of the Dutch circular and the American essentially-a-copy prohibition. This is what ended the cysteamine preparation.

What a pharmacy can do with a biological is reconstitute, dilute, repack and split a dose from an authorised product. For biologicals the economic lever is therefore dose optimisation rather than compounding, and it is documented: dupilumab at €16,000 per patient per year at full dose in the Netherlands in 2024, with about 70 per cent of patients able to taper in early studies, in a programme that reports tens of millions less declared to insurers since 2021†.

4.4 What off-patent does and does not mean

Off-patent is routinely read as meaning many suppliers and therefore a secure supply. The census does not support that reading.

Counting valid Certificates of Suitability in the European pharmacopoeial database as of 30 April 2020, across 554 generic active ingredients: 56.3 per cent have five or fewer certified manufacturers worldwide. A further 23.1 per cent have six to ten, and only 1.4 per cent have more than twenty-five†. And 93 of the 554, about 17 per cent, have no certificate holder in Europe at all†. A European Parliament study carries the same finding from a second source.

The figures understate the concentration, because raw materials and intermediates are not counted, and those sit further upstream and are more concentrated than the active ingredients themselves.

Set that beside the shortage data. The Netherlands has the best national time series in Europe. In 2025, 1,134 medicines were in shortage, affecting 3.5 million people, roughly one medicine user in three†. The report prints 1,135 in one place and both figures are given. In 2024 the figures were 1,563 medicines and 4.5 million people†. The cause is unknown for 70 per cent of shortages, because suppliers do not disclose it; among known causes most are production problems — raw material availability, manufacturing, or final laboratory checks. Seventy-one per cent of shortages fall under insurer preferential policy and 14 per cent are definitive†.

The medicines the report highlights are levothyroxine, rifampicin, salbutamol, prednisolone, quetiapine, lithium and oxazepam. They are almost all old, cheap, off-patent and, in dosage-form terms, compoundable. Fifteen shortages reached the most serious category of the Dutch responsible-substitution

guideline, mainly lower strengths of levothyroxine, and nearly a hundred reached that category on the Dutch critical medicines list.

At European level the pattern is the same. The EU Critical Medicines List carried over 270 active substances in its December 2024 version, of which innovative medicines are 10 to 20 per cent. More than 90 per cent of reported critical-medicine shortages concern generics, and about two-thirds of generic shortages are linked to products with few suppliers. Sixty-two per cent of countries awarded tenders on price alone in 2022. Shortage notifications across fourteen OECD countries rose 60 per cent.

So the shortage list and the compoundable list substantially overlap. And pharmacy preparation appears once in the entire Dutch shortage report, for lithium, as one possible response alongside other manufacturers' products and imports. It is not in the report's general list of alternatives.

The overlap is unquantified in the official data. No published figure states what share of shortages could be met by pharmacy preparation, or what share is met by it now. That is a gap worth naming, because the two datasets describe the same medicines from opposite ends and have not been joined.

One further legal route belongs here. Where a registered product is unavailable in the Netherlands, the inspectorate can grant an exemption on a physician's declaration that treatment with available registered products is not possible. Pharmacies, wholesalers, manufacturers and dispensing general practitioners may apply, and three forms exist: application, extension, and a return of the number of patients treated.

4.5 Where the chain genuinely cannot be shortened

For each of these the chain is long because a step in it cannot be compressed. Regulation follows the physics rather than creating the constraint.

Monoclonal antibodies. The process defines the molecule. The chain contains, without an omissible step, a characterised master cell bank, a seed train, a bioreactor campaign, chromatographic capture, viral clearance, buffer exchange, sterile fill, and a release panel of potency, identity, purity and immunogenicity assays. Industry has brought drug substance cost of goods down from US$1,000 a gram to above US$50 a gram†. The target set for prophylactic use in low-income settings is US$10 a gram, which is break-even for a half-gram to one-gram dose priced US$5 to US$10†. Named cost drivers include cell culture medium, which can reach US$1 million a batch, and chromatography resin, which can cost millions of dollars for a large batch and falls per gram only with reuse.

Even at the US$10 target, a one-gram dose costs more in materials alone than a full six-month first-line tuberculosis course at an estimated US$38, or a year of first-line HIV therapy at an estimated US$82. The gap is not margin. It is biology. The available levers are biosimilar entry, dose optimisation and price regulation — not pharmacy preparation.

Cell and gene therapy. The product is the patient's own cells, modified. The chain is a logistics loop with a living product at its centre: apheresis, cryopreservation and transport, vector supply which is itself a separate manufacturing chain, transduction, expansion, formulation, cryopreservation, release testing and return transport, with the patient waiting throughout. It must be repeated per patient, so there is no batch to amortise.

Point-of-care manufacture is how far it compresses, and India has the documented case. An Indian CAR-T product approved in October 2023 is expected at about US$50,000 against about US$400,000 for commercial CAR-T in the United States. Across the combined trials, 64 people with B-cell lymphoma or leukaemia and 53 evaluable: 67 per cent overall response, about half of them complete; lymphoma 68 per cent, leukaemia 72 per cent and all complete.

That is a factor of 8, recomputed. It is not the factor of hundreds that compounding achieves for a small molecule, and it still requires a cell-processing facility, a vector supply and a release-testing laboratory inside the treating institution.

Radiotherapy. The treatment is a megavoltage beam, and the chain contains a linear accelerator, a shielded bunker, a planning system, dosimetry equipment, and three professions that take years to produce. The workforce, not the machine count, is the constraint. Against roughly 21,800 megavoltage machines needed in 2035, the workforce to be trained by then runs to 3,300 radiation oncologists, 2,400 medical physicists and 8,100 radiation technologists in low-income countries alone, and 9,900, 7,200 and 24,900 in lower-middle-income countries†. Between 40 and 60 per cent of cancer patients globally have access to radiotherapy, and over 90 per cent of the population of low-income countries does not†.

Scale-up across low- and middle-income countries for 2015 to 2035 is modelled at US$184.0 billion nominally and US$96.8 billion under an efficiency model, against 26.9 million life-years saved†. Under the human-capital approach the net benefit is US$16.9 billion nominal and US$104.2 billion efficiency — with a net deficit for low-income countries under both, −US$14.9 billion and −US$2.4 billion†.

This is the one intervention in this part whose own advocates' most conservative model does not pay back in the poorest settings over a twenty-year horizon. There is no short-chain version of radiotherapy.

Dialysis. Haemodialysis is not delivered once. It is delivered three times a week indefinitely, and each session consumes a sterile single-use dialyser, bloodlines, needles, and tens of litres of ultrapure water and dialysate. The chain is therefore a permanent per-patient consumables line, plus a machine, plus a water treatment plant, plus nursing time. The per-patient cost is dominated by the recurring consumable, which is exactly the component that cannot be amortised.

Dutch annual healthcare cost per patient, in 2014 euros: in-centre haemodialysis €92,616; peritoneal dialysis €77,566; kidney transplant in the year of transplantation €85,127 on average, €73,376 for a living donor and €99,450 for a deceased donor; first year after successful transplantation €29,612; second year €15,018†.

Transplantation is the chain-shortening intervention for renal failure. It replaces a permanent consumables line with a one-off procedure plus immunosuppression, at about a sixth of the dialysis cost by the second year. The constraint is organ supply, not manufacturing.

Complex surgery. Cardiac, neurosurgical, transplant and major oncological surgery require, simultaneously, a sterile theatre with controlled air handling; anaesthesia with monitoring and reliable oxygen and power; blood banking; intensive care with ventilation; imaging; a pathology laboratory; and surgical, anaesthetic and nursing teams that take a decade to train. The chain is the institution. No element can be removed without the procedure becoming unsafe.

The Lancet Commission's Bellwether framing exists to separate what can be done at district level from what cannot. The three Bellwether procedures are caesarean delivery, laparotomy and treatment of open fracture, and the capacity to perform all three is used as the proxy for a system's ability to deliver broad surgical care. The Commission's first indicator is the share of the population within two hours of a facility that can perform them, with a target of 80 per cent coverage by 2030. Procedures beyond the Bellwethers are explicitly not expected at district level; they require referral to an institution whose chain is long by construction.

4.6 The asymmetry: mRNA vaccines

The most interesting single result in this material is that mRNA vaccines are a narrow chain, not a long one.

The chain is irreducibly specific. It requires enzymatic nucleic acid synthesis from defined nucleotides, a template supply, enzymatic capping and purification, lipid nanoparticle formulation by controlled mixing with defined lipids including a proprietary ionisable one, sterile fill under cold chain, and release by potency assay. The lipids and the enzymes are each their own specialist supply chain.

The capacity requirement is modest. One facility with a single production line can make 100 million doses a year, in about 264 batches†. Modelled total manufacturing cost for 100 million doses, in a 2021 model, is US$270 million for a Moderna-equivalent product and US$127.1 million for a Pfizer-BioNTech-equivalent one, which works out at US$2.70 and US$1.27 a dose†. Fill-and-finish alone is US$0.27 a dose

in ten-dose vials and US$0.37 in five-dose vials†. The mRNA required per year is 10.53 kg and 3.16 kg respectively, and staff per line 80 and 75†. The modelled headcount was about 27 and 25; the authors raised it to 80 and 75 to cover quality control, warehousing and administration, against an industry report of over 70 employees per line†. Annualised facility capital, straight-line over ten years, enters operating costs at US$4.3 million and US$2.5 million a year†.

The model excludes facility construction, and the labour for construction, installation, validation and start-up. The per-dose figures are to be read with that exclusion in view.

An mRNA vaccine cannot be made in a pharmacy, and it does not need a global industry either. It needs a facility of seventy-five to eighty people. The chain is short in headcount and footprint and long in technical specificity. The binding constraint is technology transfer, not scale, which is why the WHO mRNA technology transfer hub model exists.

4.7 Human insulin, which is not the analogues

These two are routinely spoken of as one product and they sit on opposite sides of the line.

Human insulin is a recombinant protein with the native human sequence, off patent for decades, and manufacturable by multiple producers. The analogues — glargine, lispro, aspart, degludec — are sequence-modified proteins with later patents, proprietary formulation and device-coupled delivery. Both require fermentation and purification. Neither is compoundable. Their cost and competitive structures differ.

Production cost and estimated biosimilar price, as modelled in a 2018 study, per 10 mL, 1,000-unit phial, with the annual figure at 40 units a day†:

Insulin	Production cost per phial	Estimated biosimilar price per phial	Estimated price per patient-year
Regular human insulin	US$2.28–3.37	US$3.29–4.86	US$48–71
Glargine	US$3.69–5.13	US$5.32–7.38	US$78–108
Lispro	US$4.52–6.16	US$6.51–8.87	US$95–130
Aspart	US$4.51–6.16	US$6.50–8.86	US$95–129

The paper’s abstract gives a broader analogue range of US$78 to US$133 a year, and both are printed†.

Now the comparison that carries the finding. Median current prices as a multiple of those estimates: regular human insulin 1.2 to 1.8 times; glargine 5.6 to 7.8 times; lispro 2.7 to 3.7; aspart 2.6 to 3.5†. The comparison covers any presentation, phial, pen or cartridge, while the estimates are for phials only.

Human insulin is already priced close to its production cost. Glargine is priced at between five and eight times its own. The economic problem is in the analogues, not in insulin.

A second and lower estimate exists and is printed beside it: one presentation puts the production cost of insulin at US$1 a vial against up to US$240 in the United States†. The two estimates disagree and neither is resolved here.

The market structure is the binding constraint rather than the manufacturing. Three companies hold over 90 per cent of the global insulin market by value, with some sources putting the figure near 99 per cent. Of 108 countries in scope, only 29 have all WHO-listed insulins registered and 24 have none at all.

4.8 The dead end

One source must be recorded as dead, because four of this book’s research lines named it as the reference that would settle its weakest data.

The MSH International Medical Products Price Guide no longer exists as a live product. Its own publisher's page states that the last edition is the 2017 edition, and that the publisher itself now describes the data as nine years old. The same page states that the website was retired and would no longer be accessible after 30 June 2024. Free PDF editions covered 1996 to 2015 only. A citation to the guide must therefore be dated 2017 at the latest and labelled as such. It cannot retire this book's price debt.

The UNICEF Supply Catalogue is the working substitute, and it was read on 19 October 2026, so the figures it supplies in this book are current as at October 2026. It is the supplier's own catalogue, it gives indicative prices in US dollars per pack, and it carries material numbers so that any row can be rechecked.

It has one property that governs how its figures are printed here. Its pagination returned different indicative prices for the same material number on different pages. Ferrous sulfate oral solution appeared at 0.71 and at 0.61; folic acid at 5.41 and 5.39; iron 60 mg at 1.43 and 1.60; furosemide injection at 2.05 and 1.84; benzathine benzylpenicillin at 29.49 and 29.12; calcium gluconate at 10.66 and 5.01; thiamine at 1.29, 1.42 and 5.55; ibuprofen 400 mg at 2.23 and 1.43; glucose 50 per cent at 62.90 and 56.00. These are indicative prices refreshed against live tenders, so the spread is real movement rather than transcription error. Where two values were seen, both are given in the entries.

A catalogue that quotes two numbers for one material number is still the best available source. It is not a price list. Its figures are printed in this book as indicative and dated, and never as a price.

Appendices

Appendix A — The Register of Contradictions

A reference work inherits the disagreements of its sources. This appendix records them rather than smoothing them, for one practical reason: a book that silently picks one of two published figures passes on a choice its reader cannot see, and a reader who later meets the other figure has no way of knowing it was considered.

The register has three parts. First, the places where a single source contradicts itself. Second, the places where two sources of comparable standing disagree. Third, the places where this book's own research lines disagreed with each other, and how each was settled.

A.1 Where one source contradicts itself

All of these were read off the page in October 2026. They are numbered A1 to A31, and the chapters cross-reference them by those numbers. Both numbers are given with their position on the page. None is an error of transcription by this book.

World Health Organization fact sheets

A1 — Malaria. The share of African deaths in children under five appears as 75 per cent in Key Facts, and as 76 per cent and then 75 per cent in consecutive paragraphs of one section of the body.

A2 — Malaria, date. Printed 4 December 2025, with a 2026 copyright line and 2026 linked items.

A3 — Hepatitis B. Ten million on treatment against 240 million infected gives 4.2 per cent; the page states 4.3 per cent, with no denominator explained.

A4 — Hepatitis C. Key Facts gives about 47 million chronic infections. The body's own regional figures sum to 50 million.

A5 — Dengue. Key Facts puts half the world at risk, about four billion. The body gives 5.6 billion.

A6 — Dengue, date. Printed 21 August 2025, with a 2026 copyright line and an item dated 11 June 2026.

A7 — Rabies. Key Facts asserts flatly that 99 per cent of cases are dog-mediated and that the disease is 100 per cent fatal. The body says "up to 99 per cent" and "virtually 100 per cent". Key Facts also states that 40 per cent of deaths are in children under fifteen, which the body does not support anywhere.

A8 — Neglected tropical diseases. The metadata says twenty conditions. The page's own footnote lists twenty-one.

A9 — Soil-transmitted helminths. The metadata gives 836 million children needing treatment. The body's own figures sum to about 914 million (260 plus 654). The figure 836 million appears neither in Key Facts nor in the body.

A10 — Lymphatic filariasis. The country counts do not reconcile: 81 minus 10 leaves 71 treated, while 39 plus 14 plus 21 gives 74. The overlap is unexplained.

A11 — Trachoma. Endemic countries appear as 29 in Key Facts and 32 in the page metadata.

A12 — Sexually transmitted infections. Syphilis appears as 8 million for 2022 in Key Facts and 7.1 million for 2020 in the body. Two magnitudes, two years, unreconciled.

A13 — Cardiovascular diseases. The share in lower- and middle-income countries is "over three quarters" in Key Facts and "approximately 80 per cent" in the body.

A14 — Hypertension. 630 million treated is given as 44 per cent of 1.4 billion, which is 45 per cent. And 44 per cent is assigned to both the unaware group of 600 million and the treated group of 630 million.

A15 — Cancer. The infection-attributable share is about 30 per cent of cases in lower- and middle-income countries in Key Facts, and about 10 per cent globally in the body.

A16 — Suicide. Key Facts gives over 720,000; the Overview gives 727,000. The depression fact sheet also gives 727,000.

A17 — Tobacco. The number of Parties to the Framework Convention appears as 182 plus the European Union in one place and 183 in another.

A18 — Physical activity. Adolescent inactivity is 80 per cent in Key Facts and 81 per cent in the body, for ages 11 to 17.

A19 — Deafness and hearing loss. The same figure of 700 million is attached to two different metrics: "will require hearing rehabilitation" in Key Facts, and "will have disabling hearing loss" in the body.

A20 — Musculoskeletal health. The headline is 1.71 billion. The condition-by-condition figures total about 2.5 billion. Comorbidity is never stated.

A21 — Osteoarthritis. The share older than 55 is 73 per cent in Key Facts and 70 per cent in the body.

A22 — Low back pain. Key Facts says prevalence rises up to 80 years. The body says it is greatest at 80 to 85.

A23 — Maternal mortality. The 40 per cent decline in the maternal mortality ratio is global in Key Facts and sub-Saharan Africa only in the body, with no global figure given against which to check it.

A24 — Maternal mortality, share. The share in lower- and middle-income countries is "just over 90 per cent" in one place and "approximately 92 per cent" in another.

A25 — Newborn mortality. Key Facts states flatly that midwife-led care makes a preterm birth 24 per cent less likely. The body says "by up to 24 per cent" and only where midwifery programmes function well. Key Facts drops both qualifiers.

A26 — Stillbirth. The page text projects 15.9 million stillbirths. An infographic on the same page gives more than 19 million.

A27 — Congenital disorders. The share in lower- and middle-income countries is nine in ten, about 90 per cent, in Key Facts, and about 94 per cent in the body.

A28 — Road traffic injuries. The share in lower- and middle-income countries is 92 per cent in Key Facts and "more than 90 per cent" in the body.

A29 — Drowning. The body says the 2024 status report shows a fall while also describing that report as planned for release in 2024; the page is dated 1 May 2026. The page also carries a printing error in a rate.

A30 — Violence against women. The headline prevalence appears as 31.6 per cent with "about one in three", and as 32 per cent with "nearly one in three".

A31 — Violence against women, date. Key Facts says the estimates were published in 2023. The page's own reference and its linked news item indicate 2025.

Two pages that are not fact sheets

The expected fact-sheet addresses for neglected tropical diseases and for stillbirth return navigation shells with no Key Facts and no body. Their figures come from health- topic pages instead, and those pages carry no printed date at all. Any work citing a "WHO fact sheet" for either is citing a document that does not exist.

In the published literature

EPIC-Oxford, diverticular disease. The top-against-bottom fibre fifth appears as hazard ratio 0.59 (0.46 to 0.78) in one place and 0.58 (0.46 to 0.73) in the paper's own results section.

The clubfoot cost range. The source paper's abstract and results give figures that do not match each other. The arithmetic closes against the printed range, so the inconsistency is the paper's and not a computational error.

A 2024 review of emollients for eczema prevention describes a significant benefit that its own printed confidence interval contradicts, and reports one trial's participant number inconsistently.

A neonatal sepsis source renders United States early-onset incidence per 100,000, which is inconsistent by two orders of magnitude with the low-birth-weight figures beside it. It is reported here per 1,000.

A.2 Where two sources of comparable standing disagree

These are printed both ways throughout the book, at both ends, with no winner picked.

Quantity	One figure	The other
Maternal deaths, 2023	260,000, UN interagency group	239,900, GBD
Total deaths, 2023	60.04 million, GBD	about 61 million, WHO
Neonatal jaundice deaths	30,300, GBD	more than 100,000, published series
Rabies deaths	15,800, GBD	about 59,000, WHO
Fall DALYs	38 million, WHO	74.3 million, GBD
Road traffic deaths	1.16 million, WHO 2026 sheet	1.47 million, WHO 2024 sheet
Liver cancer deaths	732,000, WHO	507,700, GBD
Stomach cancer deaths	642,000, WHO	935,900, GBD
COVID-19 rank, 2023	20th, 797,600, GBD	14th, about 0.9 million, WHO
Hepatitis B chronic infections	240 million, 2024	254 million, 2022
Adult obesity	940 million	890 million
Multiple sclerosis	1.8 million, WHO	2.8 million, MS Atlas
Antimicrobial resistance, 2050	10 million deaths, O'Neill	1.91 million attributable and 8.22 million associated, GBD
Cervical cancer cases	662,301, GLOBOCAN 2022	604,196, GLOBOCAN 2024
Preterm births	13.4 million, text	15 million, metadata
Obstructed labour deaths	23,000 for 2015; 19,000 for 2013; 12,200 for 2023 — non-monotonic across GBD rounds	

Four of these are not disagreements about the world but about method or vintage. The cervical cancer pair is a methodological revision between GLOBOCAN releases, not a trend. The hepatitis B pair, the obesity pair and the road traffic pair are different reference years. They are listed here because a reader meeting one figure in one chapter and the other elsewhere is entitled to know which kind of difference it is.

A.3 Where this book's own research lines disagreed

Six disagreements arose inside the preparation of this book. Each was settled by going back to the source, and each is recorded because the settlement changed what the book says.

Whether GBD 2023 exists. One line reported that no 2023 release existed and substituted WHO estimates throughout. It does exist: published in *The Lancet* on 12 October 2025 and presented at the World Health Summit in Berlin. The substituted WHO figures were kept, labelled and tagged, and the claim was struck.

Which edition of the Essential Medicines List governs. One line used the 23rd, another the 24th. The 24th List, 2025, governs. Every status checked against the 23rd was marked for rechecking rather than carried across.

Whether a bisphosphonate is listed for osteoporosis. Two lines asserted that one is. A live check of the electronic list shows alendronate returns nothing and zoledronic acid is listed only as a supportive medicine, for bone metastases and for osteogenesis imperfecta. The assertions were wrong and were corrected.

Whether permethrin is on the list. One line asserted it; another doubted its own source. Section 13.5 lists both benzyl benzoate and permethrin. The doubt was struck and the claim kept.

The 53.1 million figure. It appears both as hearing-loss years lived with disability and as falls years lived with disability, with different intervals, and was flagged as a suspected transcription error. It is not an error: the two are adjacent rows of one table, ranked fourth and fifth, each 5.4 per cent of all-cause years lived with disability. The flag was withdrawn.

Whether a published number needed to treat exists for aspirin in secondary prevention. A figure of about 50 over two years circulated in the preparation. The source paper publishes 6.7 against 8.2 per cent a year and no number needed to treat at all. The figure had no origin. Recomputed from the published rates, it is 67 a year and 33 over two years.

That last one is the reason this appendix exists. The figure was plausible, it was in the right range, and nobody had derived it.

A.4 Where the book contradicted itself

The contradictions above are between sources. These were between two places in this book, and they are the more dangerous kind, because no reader can find them. A reader consults one entry. Only someone reading two chapters side by side would see that they disagree, and nobody reads a reference work that way.

They were found by listing every entry heading in the book and comparing them for near matches. Three conditions turned out to have a complete entry in two different chapters, each written by a different hand from a different dossier.

A32 — Uterine fibroids, in the neoplasms chapter and in the genitourinary chapter. The only flat contradiction of the three. One entry labelled myomectomy CURABLE; the other labelled it CONTROLLABLE. Their recurrence figures differed — roughly 15 to 30 per cent within five to ten years against about 15 per cent at five years and 25 to 50 per cent at ten — and the two figures carried different provenance tags, one unreachable and one named. Both entries were internally coherent and both were defensible. Resolved to one entry, in the neoplasms chapter, where ICD-11 codes uterine leiomyoma. Myomectomy is CURABLE of the fibroids it removes, which is how this book labels the excision of a localised tumour everywhere else; new fibroids are new clonal growths and not regrowth, and the entry says so and gives the better-sourced figures. Embolisation, which shrinks rather than removes, is CONTROLLABLE.

A32a — What the fibroid merge actually found. The cure-status conflict was visible from outside. Merging the two entries found eight more disagreements that were not. The incidence by age fifty in Black women stood at above 80 per cent in one entry and 80 to 90 per cent in the other, with different tags. The hysterectomy share was a third to 40 per cent in the United States against 30 to 40 per cent across many countries — different scopes presented as the same statistic. Tranexamic acid reduced blood loss by roughly a third in one and by 40 to 50 per cent in the other. The levonorgestrel system gave 80 to 90 per cent in one and 70 to 95 per cent in the other. Neither of those last two figures carried a provenance tag in either entry. The risk that a presumed fibroid is in fact a sarcoma ran to one in 1,000 to one in 2,000 in one entry and to one in 10,000 in the other. All are now printed side by side, with both values and both tags, and the entry says the sources disagree.

The lesson is not about fibroids. Two competent writers, working from two dossiers on one condition, produced nine disagreements, and only one of them was a disagreement about the headline answer. The other eight were in the detail, where nobody was looking.

A32b — The default tag, denied and restored. When the two fibroid entries were merged, eight figures in the second carried no tag. The reviewer gave them all the dagger tag, on the rule that a dossier figure with no tag of its own takes one. That is the book's rule, written in its own conventions, and the reviewer was right.

The coordinating session said otherwise. It searched the house style for the word "default", did not find it — the style states the rule in different words — and told two further reviewers that no default existed and that an untagged figure must be struck. One of them struck twenty-five figures in the digestive, genitourinary and musculoskeletal chapters on that instruction: cure proportions for gallstone surgery, appendicitis treated with antibiotics, osteomyelitis, glomerulonephritis, obstetric fistula repair and others. All are restored with daggers.

Six of the original eight fibroid figures do appear in no dossier at all, and those remain struck. That is the real distinction, and it is worth stating plainly because it is the distinction the whole provenance scheme rests on. A figure sitting untagged in a dossier has a research line behind it that did not record where it came from; it is printed with a dagger, which says exactly that. A figure appearing in no dossier has nothing behind it at all. Nobody consulted anything. It is not published.

A33 — Allergic rhinitis, in the immune chapter and in the respiratory chapter. Not a flat contradiction. The respiratory entry carried a CURABLE stratum — avoidance, where a single removable allergen is responsible — that the immune entry did not have at all. One question, two answers, in one book.

A34 — Erectile dysfunction, in the genitourinary chapter and in the sexual health chapter. The labels agreed once both were written. The genitourinary entry, however, called a penile prosthesis "a mechanical cure", which this book's own definition does not allow: the native erectile tissue is destroyed and its function substituted, so the deviation remains. It also filed treated hypogonadism under CURABLE although the testosterone must be continued. Both were corrected against the book's own rules.

A35 — Two figures with no origin at all. The same genitourinary entry gave 60 to 80 per cent success for first-line drug treatment and 80 to 90 per cent satisfaction with a prosthesis. Neither figure carried a provenance tag, and neither appears in any dossier behind this book. They were not taken from a source and then mis-tagged. They were never taken from anything. They are struck, and the text says in words what is known.

The sexual health chapter, meanwhile, had excused itself from the cure status entirely, on the argument that its categories are not diseases in the sense the rest of the book uses. That argument holds for gender incongruence and fails for a dysfunction with a removable cause — and the book had already refuted it against itself, by giving erectile dysfunction a full cure status in another chapter.

A36 — Trachoma, in the infectious chapter and in the eye chapter. Found only after a fault in the checking was corrected: chapter 1 headed its entries one level higher than every other chapter, so an automated comparison of entry titles had been skipping all forty-two of them. The two entries disagree on the answer. The infectious entry splits trachoma three ways — active infection CURABLE, trichiasis corrected by surgery CURABLE, established corneal opacity and blindness RELIEF ONLY. The eye entry says CURABLE, without qualification. For a book whose subject is what can and cannot be cured, that omission is the whole of the matter. Merged into the infectious chapter, where ICD-11 codes it.

A37 — Scabies, in the same two chapters. No contradiction; both say CURABLE. Merged for the same reason, with the eye chapter's population-scale data carried over.

Appendix B — What Is Not Known, and What Was Not Checked

This appendix states the limits of the book. It has two parts: gaps in the measured record itself, and gaps in this book's verification of it.

B.1 Where the measured record is silent

These are not failures of this book. They are absences in the data the world has.

Conditions with no global burden figure

The Global Burden of Disease study carries no global figure for any of the following, although several affect tens or hundreds of millions of people.

Heart failure as a syndrome, which affects about 64 million. Venous thromboembolism. Aortic aneurysm. Infective endocarditis. Pericarditis. Pulmonary hypertension, affecting about one per cent of the world population. Cardiac arrest. Varicose veins, in 20 to 35 per cent of adults. Arrhythmias other than atrial fibrillation. Bronchiectasis. Chronic rhinosinusitis, in about 10 per cent of adults. Allergic rhinitis, affecting about 400 million. Pleural effusion. Pneumothorax. Acute respiratory distress syndrome. Cystic fibrosis.

And the whole of ICD-11 chapter 07, sleep-wake disorders, has no condition that is a level-three cause in the burden study — including obstructive sleep apnoea, which affects about 936 million adults aged 30 to 69. A chapter of the classification exists for which no burden series exists at all.

ICD-11 chapter 17, conditions related to sexual health, is in the same position, and worse: not one of its categories has a prevalence estimate measured against the ICD-11 definition. Every figure in the literature comes from an earlier classification or a bespoke instrument.

Figures with no data year

Four WHO fact sheets give their headline figure with no year attached: diarrhoeal disease, falls, epilepsy and kidney disease. The injuries and violence overview states no data year for any of its main statistics.

Quantities that have never been measured

Overdiagnosis is quantified for breast, prostate, thyroid, lung, melanoma and neuroblastoma. It has never been quantified for gastric, liver, kidney or bladder cancer, for cervical intraepithelial neoplasia, for colonic adenoma, for uterine fibroids, for incidental meningioma, for monoclonal gammopathy or for monoclonal B-cell lymphocytosis — several of which have reservoirs as large or larger.

No trial has ever randomised dietary fibre for diverticular disease, which is why the contradiction between the two best observational findings cannot be resolved.

No trial shows that changing sleep duration changes mortality.

The two-hourly repositioning interval for pressure ulcer prevention has never been established by trial.

The lifetime risk that diverticulosis becomes diverticulitis is given as 10 to 25 per cent in textbooks and 1 to 4 per cent in recent estimates. The tenfold gap is unresolved.

Whether diverticulitis is primarily an infective process at all remains open.

The overlap between the medicines that are in short supply and the medicines a pharmacy could prepare itself is not quantified anywhere in the official record. The Dutch shortage report for 2025 names 1,134 medicines short and 3.5 million people affected, with the cause unknown for 70 per cent. The medicines it names are almost all old, cheap, off-patent and preparable. Pharmacy preparation appears once in that entire report. How much of the shortage the short chain could absorb is therefore unknown, and no published source has asked.

This is the only question raised by the material in Part 4 that has no published answer at all.

B.2 Where this book did not verify

Every numeric claim in this book was checked against a named source while it was compiled, as the front matter describes. This section says what that checking added up to, so the reader can weigh a figure by where it sits.

The honest summary is this: a minority of the figures in this book were read off their source during its preparation. The majority name a source and a year that were not re-opened. A substantial block could not be reached at all.

No single percentage is given for the book as a whole, and that is deliberate. The research lines counted different units — some counted a figure, some a sentence — so any corpus-wide rate would be an invented number, which is the thing this book is trying not to produce.

What could not be reached, and why

Three classes of source resisted retrieval throughout.

The GBD Results Tool is a browser application. It does not render as text, so the per-condition burden table — the single largest outstanding item for this book — could not be queried. The GBD 2023 release notes, the headline totals and the published rankings were obtained; the per-cause detail was not.

PubMed Central returns a bot-detection challenge. Several landmark trials could therefore be cited only from repository copies or from their own abstracts.

The Cochrane Library returned errors. Six effect sizes that are central to their entries — compression for venous ulcers and antibiotics for acute otitis media among them — rest on secondary reporting as a result, and carry daggers.

The published capstone table of causes of death truncates at the same row on every retrieval route attempted. That is a property of the table, not of any one host, and it is why the death counts for cardiovascular, respiratory, digestive, neurological and injury causes in this book come from WHO estimates rather than from the burden study.

A source that no longer exists

Four of this book’s research lines independently named the MSH International Medical Products Price Guide as the source that would settle its weakest class of figure. It has not been updated since 2017, and its site was retired after 30 June 2024.

The working substitute is the UNICEF Supply Catalogue, which returns different indicative prices for the same material number on different pages. Its figures therefore appear in this book as indicative and dated, never as a price.

Figures that were removed rather than published

A number of drug prices in the preparation of this book were order-of-magnitude estimates for which no source had ever been consulted. They are not in the published text. Each was either replaced by a sourced figure or struck and written in words.

A reference work may say it does not know a price. It may not print a number it invented and let the reader take it for a measurement.

B.3 The outstanding list

For a later edition, or for anyone who wishes to close these, the following would settle the largest number of figures that carry daggers, in this order.

1. The GBD 2023 Results Tool, for per-condition deaths, DALYs, years lived with disability, prevalence and incidence. It would retire more daggers than any other single source, and it would also settle the injury block and several of the disagreements in Appendix A.2.
2. One reachable international drug price source. Prices are the weakest data class in four of this book’s chapters.
3. The Essential Medicines List statuses in the blood, immune and metabolic chapter, rechecked against the 24th List. They were originally checked against the 23rd.
4. The Cochrane reviews named above, for the six effect sizes that currently rest on secondary reporting.
5. The ICD-11 simple tabulation, for the per-chapter category counts. The counts in this book are of code blocks, which are a coarser unit.

Appendix C — How This Book Was Checked, and What That Found

A reference work is only as good as its weakest unchecked number. This appendix records what checking was done, what it found, and what it did not reach. It is here so that a reader can weigh the book by its method rather than by its confidence.

C.1 The method

The book was written from research dossiers, and the dossiers were written from sources. Three separate passes then ran over the result, each by a reader who had not produced what it was reading.

The first pass read the dossiers and reported defects without fixing them. The second applied the decisions that pass produced. The third read the finished chapters against both the dossiers and the decisions.

That separation is the whole of the method, and it rests on one observation: a writer checking their own work finds a fraction of what a separate reader finds. Every round of this book confirmed it.

The reviewers were allowed to correct only what has exactly one possible answer — arithmetic, a figure that does not match its own source, a provenance tag set higher than its source supports, a classification contradicting a live check, a word used outside the scheme the book defines. Everything requiring a judgement was referred back rather than resolved, on the principle that a reviewer who resolves a judgement becomes the author of that resolution, and then nobody has checked it.

C.2 What the checking found

The totals, across the nine chapters and the four parts:

Corrections recorded, all four rounds	3,388
of which provenance tags set too high, in the third round	about 1,480
Cure-status labels using a word outside the four	29
Compound prevention grades, resolved to the lower	239
Items referred for a decision	over 170
Passages removed or generalised on safety grounds	10

Every one of those corrections is in *The Review Record*, the companion to this book, with the wording it replaced.

The dominant finding is the first one, and it is worth stating plainly: **the book systematically presented itself as better sourced than it was.** Not in one chapter, not by one writer, but everywhere, by every hand that worked on it, in the same direction. Figures acquired a higher provenance tag than their sources supported, and no individual step in that drift was large.

Correcting it changed the book’s shape. In one chapter the share of figures marked as unreachable rose from 74 to 77 per cent; in another the count of figures carrying a named but unread source fell from 566 to 144, with 461 moving down to the lowest tag. Nothing was discovered to be false by this. What was discovered is that the book did not know what it knew.

C.3 Six findings worth their own sentence

An invented number. A number needed to treat for aspirin in secondary prevention circulated through the preparation at a plausible value, in the right range, with a correct citation attached. The cited paper publishes two event rates and no number needed to treat at all. The figure had no origin. Recomputed from the published rates it is 67 a year and 33 over two years.

A ruling that was wrong. One figure appearing twice with different uncertainty intervals was flagged as a transcription error and ordered corrected. It was not an error: the two are adjacent rows of one table, correctly quoted, each 5.4 per cent of the same denominator. The order was withdrawn.

A compliance figure measuring the wrong rule. A review reported that 30 per cent of entries complied with the cure-status format. It had measured against a rule that had already been superseded. Against the rule actually in force, compliance was 84.5 per cent and the defect count was 57 rather than 250.

Two prices that looked like a contradiction and were not. Tamoxifen at US$80 to 250 for five years, and the same entry's per-tablet price implying US$785 to 1,241. Both are correct: one is a generic international price, the other high-income retail. The defect was that neither named its market. The book now requires every price to name its market and its year, or to be written in words.

A source that no longer exists. Four research lines independently named one international price guide as the source that would settle the book's weakest data. It has not been updated since 2017 and was retired in 2024.

Entries written to close a gap. Three entries were written by the coordinating session itself, quickly, after a writer stopped mid-chapter. The review found in them the same defects it found elsewhere: tags above their sources, a grade of STRONG resting on a trial the entry itself said it could not open, a claim that sources disagreed where only one range was ever given, and a procedural instruction written into a section meant for household measures. Writing an entry oneself is no protection at all.

C.4 What the checking did not reach

Three classes of source resisted retrieval throughout, and they are the reason this book carries as many unreachable figures as it does.

The burden-of-disease results tool is a browser application and does not render as text, so the per-condition table — the single largest outstanding item — could not be queried. A major article repository returns a bot-detection challenge. A major review library returned errors, which is why six effect sizes central to their entries rest on secondary reporting.

One block was recorded here as unresolved, and the record was wrong. About ninety figures in the circulatory and respiratory chapter were said to carry the highest provenance tag while appearing in none of the verification files, and to need their sources re-read. They were checked again at the end of the fourth round. Of the 110 figures in that chapter carrying the highest tag, 24 are indeed absent from the two verification files — but all of them stand in the chapter's own research dossier, and that dossier records a verified read for every one.

The earlier count came from comparing the chapter against the wrong corpus: the two verification files, which hold the retrieval work, rather than the dossier the chapter was written from. Nothing was wrong with the figures. The check was wrong, and it is left described here rather than quietly deleted, because a reader weighing this book should see that its own accounting needed correcting twice.

Appendix B lists what would close these, in the order that would retire the most.

C.5 The fourth round, and what it cost to get right

A fourth pass ran after the three described above. It was not planned. It happened because the third pass left twenty-four questions its readers could not settle, and because settling them turned up errors the earlier passes had introduced.

An over-correction, reversed. The book requires every price to name its market and its year, or to be written in words. Applied strictly, that rule converted 1,261 prices from digits into words in a single pass. That was too much. A price whose market and year stand in the same paragraph is properly sourced, even if they are not repeated in the same clause. A source that gives a market but no year gives a usable price. Both cases had been swept up. The rule was rewritten in three parts, and each converted price was read again against the dossier it came from.

What that re-reading found is worth stating plainly, because it is a fact about this book rather than about the rule. Many of those prices could not be restored. In the circulatory and respiratory chapters, 462 of 489 stayed in words, because the dossier behind them gives only order-of-magnitude bands drawn across three different reference classes that differ by factors of three to fifty. There is no single market behind such a figure. Printing digits would have claimed a precision the source never had.

A mark that was disappearing. Assembling the book revealed a fault in the assembly itself. The source text is hard-wrapped. Where a provenance mark happened to fall at the start of a new line, the tool that moved those marks could not see the sentence they belonged to, and dropped them. 541 unconfirmed figures would have reached the page looking confirmed. The marks are counted now: 2,361 of them, against 6,352 figures read off a named source.

A chapter that had excused itself. The chapter on conditions related to sexual health carried a note explaining that the cure status was not applied to any of its entries, because its categories are not diseases in the sense the rest of the book uses. The argument holds for gender incongruence and does not hold for a dysfunction with a removable cause — and the book proved as much against itself, because erectile dysfunction carries a full cure status in another chapter. Eight entries were written. Two of them say the label does not apply, and say why. The blanket exemption was withdrawn.

Three conditions entered twice. Uterine fibroids, allergic rhinitis and erectile dysfunction each had a complete entry in two different chapters, written by different hands from different dossiers. The fibroid entries disagreed: one called myomectomy curable, the other controllable, and their recurrence figures differed and carried different marks. No reader comparing two chapters would have found that, and no reader reading one chapter would have known to look. Each condition now has one entry and one answer.

Every figure made to carry its provenance. The book states that each numeric claim carries exactly one provenance mark. At the end of the fourth round that was measured rather than assumed, and 382 figures carried none. Each was looked up in the dossier its chapter was written from and given the mark its source supports. Two hundred and forty-one were marked; the rest proved to be covered already by a mark at the end of their list or table, or were restatements of a figure marked elsewhere in the same entry, or were thresholds and definitions rather than findings. Not one had to be struck: every figure was traceable to a research line.

What this did not reach: figures written out in words — “one in seven”, “a third”, “twentyfold” — were not swept, because the sweep looked for numerals. They are a small minority and they carry no false precision, but the gap is real and is recorded here rather than left for a reader to find.

A check that was blind, and what it was hiding. The duplicate entries above were found by listing every entry heading in the book and comparing them. That list was incomplete, and nobody noticed, because chapter 1 headed its forty-two entries one level higher than every other chapter. The comparison looked for one heading level and silently skipped the whole of the infectious diseases — the largest chapter in the book and the one most likely to share conditions with the chapters on the eye and the skin.

The entries themselves were sound: all forty-two carried the eight sections. The fault was in the checking, not the content. But correcting it immediately produced two more duplicate conditions, trachoma and

scabies, and trachoma turned out to be one of the disagreements that matters — one entry splitting it three ways and reserving RELIEF ONLY for established blindness, the other saying simply CURABLE.

That is the shape of this whole round. Each time a check was found to be blind in some respect, correcting it turned up something real. A reader has no way to audit the checking, only the result, which is why the blind spots are recorded here alongside what they hid.

A rule corrected against itself. One ruling written during this round — that a vague quantifier may never be replaced by a figure — was tested against the whole book before being applied. It would have destroyed thirty-four properly sourced numbers. The rule was wrong as written and was rewritten before it did any damage. The point of testing a rule against the text before enforcing it is exactly this.

C.6 What a reader should do with this

Read the daggers. They are there for exactly this reason.

A figure without a dagger rests on a named source. Some of those sources were opened during the preparation of this book and some were named but not opened again, which is ordinary for a reference work. A figure with a dagger is reported as commonly carried, and its source could not be opened at all. The distinction is not between true and false. It is between checked and taken on report, and a reader is entitled to know which is which.

No figure in this book is published as a bare number that someone invented. Where a value had no source, it was removed and the text says in words what is known without it.

That is the standard this book holds itself to, and this appendix exists so the reader can check whether it was met.

Appendix D — The Record of the Trials

On 25 and 26 November 2026 seven trials and one later count were run on the text of this book. Their purpose was to find a model into which an illness can be put, and to see whether the Trit Tile carries it. This appendix records each trial as it was run, with what failed.

D.1 The method

The input was the text of the first edition, split into its entries. The outcome was the book's own cure status. An entry "ends" when the book gives SELF-LIMITING or CURABLE.

For trials 1 to 7 a protocol was written first: the coding rules, the test, the direction and the bound. The protocol was then hashed with SHA-256. The run came after. The first characters of each hash are printed below; the files travel with this edition. Trial 8 had no protocol. It is a count made afterwards.

Where a result looked good, it was checked for three ways in which it could be empty. There may be too few distinct values. One group may carry the whole effect. Or the phase of the tile may do no better than a random phase. Those checks are reported with the result.

Three limits apply to all eight trials.

- The entries were read from the printed file of the first edition. Fourteen entries could not be read from it at that time (see *About the second edition*). The trials therefore ran on 361 entries, not on 375.
- The status was taken from the entry by a simple search for the four words. A stricter reading, made for this edition, gives a different set of labels for 29 of the 361. The trial numbers below are those of the runs as made.
- One coder did all the coding.

D.2 The trials in one table

Trial	Question	Entries	Outcome	Verdict
1	Does the path of the tile, from five levels coded by keyword, give the status?	30	6 of 30 right; the largest class gives 9	Rejected
2	Does a depth from a table of sizes, with the tile, order the status?	101	rho −0.22, p 0.012; did not survive the checks	Rejected
3	Does a depth from a time in the text, with the tile, order the status?	32, then 53	rho −0.31, p 0.043; not repeated in the second set	Not confirmed
4	Building against upkeep; layer; tile with the *Depth* field	145	Layer passed; building did not; tile rho −0.02 and +0.01	Layer holds; tile rejected
5	Do four ways of ending, coded blind, order the status of split entries?	212	Differences +0.05 and −0.09	Not passed
6	Way of ending and moment together	145 and 783 strata	Early 87 per cent, late 19 per cent; rule 80 per cent	Moment holds
7	Do illnesses tied to the month of birth share a way or a layer?	15	p 0.88 and p 0.51	Nothing found
8	The rule with six ways, applied to all entries	361	83 per cent on single-status entries	Not a test

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D.3 Each trial

Trial 1. Protocol hash 842643428f1a. Thirty entries with one status were drawn at random. Five levels were chosen by the coder. Each level got a trit by keyword from *What it is* and *Where it starts*. The five trits gave a point, the tile gave its path, and the path gave a status. Six of 30 were right. Always choosing the largest class gives 9 of 30. The permutation test gave p 0.75 and kappa was −0.03. The cause was in the design: over all 243 possible inputs the scheme can only give SELF-LIMITING (111 times) or CURABLE (132 times). The book has four labels; the path of the tile has three ends.

Trial 2. Protocol hash 75c0eda338ea. Each of 101 other entries got a depth from a table of sizes, by the structure named in *Where it starts*. Fourteen entries without a recognisable structure were left out. Depth alone: rho −0.185, p 0.064. Depth with the tile: rho −0.220, p 0.012. The second passed the bound and then failed four checks. The table gives only 11 distinct depths. With the groups kept whole the permutation test gave p 0.13. Without the one group of 22 gene products rho was −0.05. And 26 per cent of random phases did as well as the phase of the tile.

Trial 3. Protocol hashes 8bb7ad498c53 and 4e1e3003faa6. A time was searched in the text of each entry and turned into a depth. In 32 entries: depth alone rho 0.06, p 0.74; with the tile rho −0.31, p 0.043. The times that the search found were often not the illness's own time. The trial was repeated on 53 other entries, with the time taken from *Measured*. With the tile: rho +0.05, p 0.64. The first result was not repeated. Depth alone gave rho +0.56 in the second set, but 23 of the 53 times were exactly one year, taken from phrases such as "per year". That number says that what lasts long is cured less often. It is not a test of the net.

Trial 4. Protocol hash 13939dc5a966. The *Depth* field was first built by hand for all 361 entries. Four tests were fixed, with a bound of p below 0.0125 for each. Data: the 145 entries with one status.

Test	Result	p	Verdict
Building years against upkeep	7 of 18 against 3 of 25 end	0.046	Not passed
Layer: mesh against reading and phase	40 of 68 against 5 of 48 end	below 0.0001	Passed
Tile, with the size depth	rho −0.02	0.41	Failed
Tile, with the time depth	rho +0.01	0.56	Failed

Share that ends, by layer: mesh 0.59; word 1.00, with only three entries; chain 0.08; reading 0.10; phase 0.11; surround 0.11. Two checks that were not fixed beforehand: without Chapter 01 the layer test gave 51 against 10 per cent, and without Chapters 01 and 17 it gave 41 against 5 per cent. One further count was also not fixed beforehand. In the mesh, entries with a foreign party or an injury end in 29 of 31 cases. Entries of the body's own structure end in 11 of 37. That count led to the next trial.

Trial 5. Protocol hash a6e51317f880. The four ways of ending from the author's text were coded by keyword from *What it is* alone. The outcome was the share of ending labels in the status. The main test used the 212 entries with a split status, which had not been used before. Remove 0.56 (61 entries), supply 0.41 (15), restore proportion 0.51 (136). Remove against proportion: +0.05, p 0.077. Supply against proportion: −0.09, p 0.91. Neither passed. In 67 of the 212 entries the share was exactly one half. The book splits these entries by moment or by means, not by kind of illness. On the 145 single-status entries, as a second look: remove 0.62, supply 0.25, proportion 0.23.

Trial 6. Protocol hash 2e69f9135969. Two axes. The way of ending was taken from the first sentence only, and supply was split into outside and inside. The moment was coded blind for each stratum of a split entry, from words such as early, localised, late and established. Of 783 strata, 70 were early, 89 late and 624 gave no moment.

Test	Result	p
Within one entry, 31 entries	Early better 25, late better 1, equal 5	below 0.00001
All strata	Early 61 of 70 end; late 17 of 89 end	below 0.000001

The rule gave the right class for 465 of 783 strata (0.59; the largest class gives 0.53) and for 116 of 145 single-status entries (0.80; the largest class gives 0.65). By way, on the single-status entries: remove 23 of

27; supply from outside 4 of 5; supply from inside 0 of 8; restore proportion 24 of 105. The first axis had been adjusted after trial 5 on these same 145 entries.

Trial 7. Protocol hash 4f0e66d94364. A study of 1.7 million patient records found 55 of 1,688 conditions tied to the month of birth (Boland and others, 2015). Fifteen entries of this book could be linked to conditions that the study names. Their ways of ending did not differ from the rest of the book (chi-square 0.95, p 0.88). Nor did their layers (chi-square 4.16, p 0.51). The test is weak. Only 15 of the 55 could be linked, the selection is heavy with conditions of the heart, and the effects in the study are small. Such links are also unsteady. A later study used the same method on three cohorts with 11.8 million people. Of thirty new links that it found, six held in more than one cohort (Borsi, 2017).

Trial 8. Not a test. After trial 6 two ways were added, rebuild and let close, and the rule was applied to all 361 entries. Single-status entries: 0.83 right (largest class 0.65). Split entries, taken whole: 0.57 (largest class 0.70). All entries: 0.68 (0.56). The count by way was: restore proportion 177, rebuild 70, remove 68, supply from inside 19, let close 15, supply from outside 12. Rule and book agreed for 241 entries, agreed in part for 91, and disagreed for 25. Four entries carry no status. The 25 are the first review points of Appendix E.

D.4 What the record shows

Three things hold on the text of this book: the moment, the layer, and, less firmly, the way of ending. None of the three comes from the Trit Tile. They come from the layer edition of this book and from two texts of the author.

The phase of the Trit Tile did not order the cure status in any of five runs. The first of those runs failed by design, and the next two by the way depth was measured. The last two used a depth of its own for each illness, and still found nothing.

The record does not show that the model foretells anything outside this book. Every count is the book set against itself.

D.5 What a next round needs

1. A second coder who does not know the statuses, for the way of ending, the layer and the *Depth* field.
2. The fourteen restored entries added, and the stricter reading of the status used throughout.
3. The ladder test of section 0.8 repeated with the period of the tile.
4. For the blueprint: the trial of section 1b.7, with persons and with a protocol fixed beforehand.

Appendix E — Review Points for a Next Edition

This appendix lists what the work on the second edition turned up and did not settle. Nothing here has been changed in the entries. The author decides.

E.1 Where the model and the book differed

In trial 8 the rule and the book disagreed for 25 entries with a single status. Each was read again. They fall into four groups.

The coding was wrong (9). The keyword was missing from the first sentence. Clubfoot, fractures, retinal detachment, chronic suppurative otitis media, chronic wounds and obstructed labour are rebuild. Peptic ulcer with *Helicobacter pylori* and cholera are remove. Acute pancreatitis is let close. In *Model reading* these are coded by reading. The book was right.

Remove that does not reach (5). HIV, the dust diseases of the lung and neonatal tetanus: the party cannot be reached in full. That is a bound. Allergic rhinitis and gout were coded remove by keyword; read again, they are restore proportion.

A bound on rebuild (6). Spinal cord injury, diabetic neuropathy, ischaemic heart disease, ischaemic stroke, peripheral arterial disease and chronic obstructive pulmonary disease: the tissue does not regrow, or the process goes on.

Other (5). Von Willebrand disease is supply from inside, not from outside. Myasthenia gravis and functional dyspepsia are restore proportion. Preterm labour does not close by itself; it is read as restore proportion. The complications of preterm birth do close, as the organs ripen.

E.2 One entry where reading and status still differ

Congenital hypothyroidism. The entry says CURABLE. It also says that the treatment is lifelong and is the replacement of a missing hormone. *How to use this book* says that a treatment which must be continued for life does not cure, and gives phenylketonuria on a lifelong diet as CONTROLLABLE. By that rule this entry would read CONTROLLABLE, with the damage to the brain fully prevented. The model reads it the same way: supply from inside.

E.3 Open-angle glaucoma: a split may be due

The entry says CONTROLLABLE and adds that nothing restores lost visual field. The literature read for this edition suggests that the lost field has two parts.

- A part that sleeps. Ganglion cells pass through a stage in which they still live and no longer signal. In early glaucoma their electrical response improved after the pressure was lowered (Ventura and Porciatti, 2005, a pilot study). In a small trial, nicotinamide with pyruvate gave more improving points in the visual field than placebo over about two months (De Moraes and others, 2022). A larger trial of nicotinamide, NAMinG, has finished recruiting and has not reported.
- A part that is dead. Nothing replaces it yet.

Two further points are absent from *Where it starts*. In mice a short rise in pressure lets T cells into the retina. The damage then goes on after the pressure is normal again. Mice raised without gut bacteria do not show this (Chen and others, 2018). And a first trial in people of a therapy that resets the epigenetic state of the

ganglion cell reported on three participants in October 2026. It was tolerated. Two of the three showed better points in the visual field. The company itself states that efficacy cannot be concluded from this.

A next edition could split the status as the entry on angle-closure glaucoma already does: living cells that do not signal, and dead cells. In the terms of section 0.6 the sleeping cell is the third outcome, 0: it is there and it is not read. That last sentence is a reading.

Each of these sources should be opened again before the entry is changed. They are listed in Appendix F.

E.4 Conditions with two entries

Appendix C reports that three conditions had been entered twice: uterine fibroids, allergic rhinitis and erectile dysfunction. It says that each now has one entry. For the first two that is so. Erectile dysfunction still has a full entry in two chapters. Appendix C also names trachoma and scabies. For each of these the second entry is now a cross-reference.

In all, eleven conditions still have a full entry in two chapters. For five of them the two entries give different labels.

Condition	First entry	Second entry
Gestational diabetes	Gestational diabetes: SELF-LIMITING	Gestational diabetes mellitus: SELF-LIMITING and CONTROLLABLE
Burns	Burns and their skin consequences: CURABLE and RELIEF ONLY	Burns: SELF-LIMITING, CURABLE and RELIEF ONLY
Spinal cord injury	Spinal cord injury consequences: CONTROLLABLE and RELIEF ONLY	Spinal cord injury: RELIEF ONLY
Stroke	Stroke: CURABLE and RELIEF ONLY	Ischaemic stroke (ICD-11 8B11): CONTROLLABLE, with RELIEF ONLY for named strata
Congenital heart disease	Congenital heart disease (ICD-11 LA80–LA8Z): SELF-LIMITING, CURABLE, CONTROLLABLE and RELIEF ONLY	Congenital heart defects: SELF-LIMITING, CURABLE and CONTROLLABLE

The others agree with each other: pneumonia, cystic fibrosis, gout, osteoporosis, erectile dysfunction and obstructive sleep apnoea. Some of these pairs look at one condition from two sides and may be meant to stand. The labels should then be made to match, or the difference explained in one of the two.

E.5 The daggers of the Depth field

Every size in *Depth* is a typical value, and its source was not opened. The same holds for 260 of the 348 times to a first complaint and for 78 of the 138 lengths of a course. A depth moves by one step when a size is wrong by a factor of three, so the order of the entries is sturdier than any single value. A next edition should open a source for each value, as the first edition did for its figures.

Where the book names several agents or structures, one was chosen and the choice is stated. For entries that are a class, an overview, a state or a form of care, no depth is given.

E.6 Points on the side of the theory

1. **Closure is defined twice.** Section 0.4 and the Trit Tile use two rules (section 1b.2). A next edition of the theory could state how they relate.
2. **Decay against going on for ever.** Section 0.5 and the Trit Tile differ on what happens to what does not close.

3. **Editions.** Part 0 cites the eighth edition of the theory. The Trit Tile cites the ninth.
4. **Which structure is measured.** The author’s text of 10 October 2026 on Parkinson disease and dementia places amyloid four layers down. The *Depth* field of this edition uses the size of the molecule, which gives −2.21. One convention should be chosen.
5. **The ladder test.** Section 0.8 can be repeated with the period √3 (section 1b.2).

E.7 Repairs of setting made in this edition

Repair	Count
Pages on which text stood in a column one word wide	268
Entries restored from that column	14
Section and chapter headings restored from that column	8
Paragraphs in which a list had run together	234
List items restored	1,662
Paragraphs in which the star of an allele name had been taken for a mark of setting, for example HLA-B*57:01	13
Stray spaces before a comma, semicolon or full stop	40
Words broken at the end of a line in the printed file and set whole again	about 13,700

Broken words were set whole again by rule, against the words of the book itself and a word list. The rule also decides whether a hyphen at the break belongs to the word. In about 230 cases the rule had little to go on, mostly long names of medicines. A hyphen may be wrong or missing in a few of them. No figure is affected.

E.8 Sources behind the blueprint that need a second look

Section 1b.7 rests on the paper *The Biofield Monitor*. Before that paper is used further, five of its statements should be checked against their sources.

1. A citation given as Cell volume 184 with the year 2024. That volume is from 2021.
2. A citation of a paper on small living constructs made from human cells, given as Nature volume 618.
3. A statement that bone is lost within hours of leaving the magnetic field of the Earth.
4. The size given for the field of the heart.
5. A statement that ties a number series to an algebra. The paper gives no proof for it.

Appendix F — Sources of the Second Edition, with Notes

These are the sources of the new material only. The sources of the entries are named in the entries. For each source a line says why a reader would open it. Titles of texts on constable.blog are given as they were read on 25 November 2026.

F.1 The theory and the author's own texts

Konstapel, J. (2026). *The Trit Tile. A reference work on a number system that never settles.* Reference v1.1, 21 November 2026. Constable Research, Leiden. *Why read:* it holds the definition, the proof and the measurements that section 1b.1 only names. Its section 21 gives the procedure for finding a cycle in a series.

Konstapel, J. (2026). *The Vacuum.Net Theory: Foundational Paper*. Eighth edition, version 8.1, 17 October 2026. constable.blog. *Why read:* Part 0 of this book rests on it.

Konstapel, J. (2026). *Vacuum.Net Theory, Ninth Edition: Foundations 9.2 and Physics 9.0.* Constable Research, Leiden. *Why read:* the Trit Tile rests on it. A reader who wants to see where the two editions differ in wording needs both.

Konstapel, J. (2026). *Where Illness Comes From.* Ninth edition, September 2026. *Why read:* the short edition of this book. Its chapter 13 gives the six layers of treatment. Its chapters 7, 8 and 14 give the difference between the building years and upkeep that trial 4 tested.

Konstapel, J. (2026). "Research directions to cure all diseases." constable.blog, 29 October 2026. *Why read:* the source of the ways of ending.

Konstapel, J. (2026). "Why some infections end and others do not." constable.blog, 1 November 2026. *Why read:* the race of two clocks, and the statement that closure belongs to the pair of host and agent.

Konstapel, J. (2026). "Why reuse of old medicine is possible." constable.blog, 3 November 2026. *Why read:* the measure of return, as a fraction and a time.

Konstapel, J. (2026). Text on old medicines and the net. constable.blog, 14 November 2026. *Why read:* five kinds of failure that line up with the layers.

Konstapel, J. (2026). "Oorzaak en genezing van Parkinson" (in Dutch). constable.blog, 10 October 2026. *Why read:* it places amyloid on the ladder in another way than the *Depth* field does (Appendix E.6).

Konstapel, J. (2026). The maze-doctor. constable.blog, 20 October 2026. *Why read:* the three sentences on the blueprint, and the four classes of failure.

Konstapel, J. (2026). *The Biofield Monitor*. 22 May 2026. *Why read:* the definition of the state, the blueprint and the number S(t). Read it with Appendix E.8 at hand.

F.2 Sources of the trials

Boland, M. R., Shahn, Z., Madigan, D., Hripcsak, G. and Tatonetti, N. P. (2015). Birth month affects lifetime disease risk: a phenome-wide method. *Journal of the American Medical Informatics Association* 22(5), 1042–1053. doi:10.1093/jamia/ocv046. *Why read:* the one large study that asks, without a prior guess, which conditions hang on the month of birth. It found 55 among 1,688.

Borsi, J. P. (2017). Hypothesis-free search for connections between birth month and disease prevalence in large, geographically varied cohorts. *AMIA Annual Symposium Proceedings* 2016, 319–325. PubMed Central PMC5333224. *Why read:* the same method on three cohorts with 11.8 million people. Of thirty new links, six held in more than one cohort. It shows how unsteady such links are.

Wikipedia. Incubation period (table of incubation periods). Opened 25 November 2026. *Why read:* the source behind the mark [W]. It is a secondary source, and each value in it should be traced to its own.

F.3 Sources of the review point on glaucoma

Ventura, L. M. and Porciatti, V. (2005). Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. *Ophthalmology* 112(1), 20–27. PMID 15629815. *Why read:* the first evidence in patients that a ganglion cell can stop signalling and start again.

De Moraes, C. G., John, S. W. M., Williams, P. A., Blumberg, D. M., Cioffi, G. A. and Liebmann, J. M. (2022). Nicotinamide and pyruvate for neuroenhancement in open-angle glaucoma: a phase 2 randomized clinical trial. *JAMA Ophthalmology* 140(1), 11–18. PubMed Central PMC8603231. *Why read:* a small trial, short in time, with a measured gain in the visual field.

Nicotinamide in Glaucoma (NAMinG). University College London, Comprehensive Clinical Trials Unit. ISRCTN16435278; NCT05405868. *Why read:* the large trial that will say whether the small one holds. It randomised 378 patients; recruitment closed in April 2026.

Chen, H., Cho, K.-S., Vu, T. H. K. and others (2018). Commensal microflora-induced T cell responses mediate progressive neurodegeneration in glaucoma. *Nature Communications* 9, 3209. doi:10.1038/s41467-018-05681-9. *Why read:* the work in mice that makes glaucoma, in part, an illness of the reading layer.

Life Biosciences (2026). First data in people from the phase 1 trial of ER-100 in optic neuropathies. Press release, 8 October 2026. Trial registered as NCT07290244. *Why read:* three participants, no control. It is a first signal and no more.