

Protection Without a Component

Tuberculosis immunity read as a closure property

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Abstract. For a century, immunology has searched for a correlate of protection against Mycobacterium tuberculosis: some measurable component — an antibody titre, a cell count, a cytokine profile — whose presence would predict who is protected and who is not. The search has not succeeded, and its failure is usually described as a matter of insufficient resolution. This essay proposes that the failure is structural: that protection is a property of a trajectory that closes, not of a point on it. The argument is developed against published work on human immunity to tuberculosis, in particular the HLA-E and donor-unrestricted T-cell programme at Leiden, and is stated in the vocabulary of points, curves and connection points used in the Vacuum.Net framework. Because that proposal shares its negative prediction with the systems-immunology account it competes with, the essay gives closure an operational definition in terms of perturbation and return, names the competing explanation, and sets out two measurements that separate the two: transfer of a return measure against transfer of a cross-sectional multivariate signature, and dependence of outcome on the order of exposures. Both can fail, and the conditions under which they would be stated.

1. A question that stays open

Tuberculosis is the deadliest infectious disease caused by a single pathogen, and the only licensed vaccine against it is a century old. BCG protects infants against severe disseminated forms of childhood tuberculosis, but it does not reliably protect adolescents and adults against pulmonary disease, which is the form that sustains the epidemic. The standard account of why better vaccines have not arrived is given plainly in the field's own literature: development is held back by the absence of knowledge about what protection against Mycobacterium tuberculosis actually requires (Dijkman, Coler and Joosten, 2022).

This is an unusual sentence to find at the centre of a mature discipline. Immunology can enumerate the cells, sequence their receptors, measure their cytokines, and track them over time with spectral flow cytometry. What it cannot do is say which of these measurements means protected. The problem is not that the field lacks numbers. It is that the numbers do not converge on a quantity that behaves like protection.

There is a second anomaly beside the first. Roughly ninety-five per cent of people infected with Mtb never develop disease; about five per cent do, sometimes decades later. The containing majority are not cured — the organism persists — and they are not ill. They occupy a state that is stable for a lifetime and yet is not resolution. The vocabulary of the field registers this awkwardly, as latency, and the clinical boundary between latent infection and active disease is notoriously difficult to draw. A system that holds an unresolved condition stable for forty years is doing something that the language of presence and absence does not describe well.

2. The material

The empirical material for this essay is the programme of work on human anti-mycobacterial immunity associated with the Leiden University Center for Infectious Diseases, and specifically with Simone A. Joosten, whose group has worked for the past decade on host immunity to tuberculosis with a strong orientation towards clinical translation. Four features of that programme are relevant here. They are not selected because they are unusual; they

are selected because each of them is a move away from component thinking, made for empirical reasons, inside a field that is still organised around components.

2.1 A reading channel that is the same for everyone

Classical antigen presentation runs through HLA class Ia and class II molecules, which are among the most polymorphic loci in the human genome. Any vaccine that depends on them depends on a lock that differs from person to person. HLA-E is different: it is virtually monomorphic, it presents both self- and pathogen-derived peptides, and it is not downregulated in HIV co-infection. T cells that recognise HLA-E-presented peptides through their T-cell receptor are therefore called donor-unrestricted, because the restricting element barely varies across the population (Ruibal et al., 2021; Voogd et al., 2024b).

The significance of this is architectural rather than merely immunological. Beside the individual-specific reading layer there runs a second reading layer that is invariant across the species. Vaccine design aimed at HLA-E is design aimed at the invariant layer; vaccine design aimed at classical HLA is design aimed at the variable one.

2.2 Many paths, one connection point

When CD8+ T cells recognising HLA-E tetramers folded with Mtb-derived peptides were sorted from twenty-one individuals and their receptors sequenced, the repertoire turned out to be highly diverse (Voogd et al., 2024a). One nearly invariant presenting molecule; an open-ended variety of receptors arriving at it. Earlier work had already shown that the functional phenotype of these cells is unorthodox relative to classical HLA class I-restricted T cells, in that they can secrete cytokines associated with both of the conventional helper programmes.

Read as a diagram rather than as a mechanism, this is a connection point with many curves terminating on it. The point is fixed; the approaches are not. What has to be the same is the junction, not the route taken to reach it.

2.3 Function rather than quantity

In tuberculosis, antibody titres have long been a poor guide to anything. The recent consensus review from the same group reframes the question around functional capacity — what antibodies do rather than how much of them is present — with glycosylation and effector function carrying the discriminating information (van Meijgaarden et al., 2026; see also Rijnink, Ottenhoff and Joosten, 2021). Joosten's own statement of method is explicit on the general point: evaluate the sum of immune responses rather than isolated components, and assess that sum from a functional perspective.

2.4 The granuloma as a held state

In the granuloma, the local architecture of cellular interaction tracks with outcome: interactions between natural killer cells and macrophages correlate with limited pathology (Niewold et al., 2025). The granuloma is not a storage container for bacteria. It is a configuration under tension that neither resolves into clearance nor collapses into disease, maintained by continuous activity, and capable of persisting for decades before it does one or the other.

3. The reading

Take the elementary vocabulary of the Vacuum.Net framework in its positional form: points in a position space, curves running between them, and connection points where curves meet and a path can close. Nothing in what follows requires any physical claim; the vocabulary is used here as a geometry of relation.

In that vocabulary, a component measurement is the measurement of a point. A functional assay is the measurement of a segment of curve. Protection, on the reading proposed here, is neither: it is the property that a particular trajectory closes. Closure is not located anywhere on the trajectory. It is not a sum of the properties of the points, and it cannot be recovered by measuring them more precisely, because precision at a point says nothing about whether the circuit returns.

Three things follow, and all three are observed. No single correlate of protection will be found, because the thing being correlated is not a quantity carried by any element. The same intervention will protect in one host state and not in another, because the trajectory includes the state of the system at the moment of the attempt — BCG in an infant and BCG in an adolescent are not one agent on one path but two different paths. And invariant presentation elements will be unusually productive targets, because they are the junctions that every individual shares, which is the design logic of the HLA-E programme, arrived at independently.

Latency, on the same reading, is not a weak form of disease and not a cured state. It is a trajectory held open under tension that has not discharged. Disease is the discharge. The latent-active boundary is then not a defect of diagnostics: the two are not two states but two positions on one curve, which is why no test cleanly separates them.

4. Closure made operational

Everything in section 3 is a redescription, and a redescription that forbids nothing is worth nothing. The first objection to be met is therefore not that the reading is wrong but that it is idle: that protection is a property of interacting components rather than of isolated ones is the standing position of systems immunology, which predicts the absence of a single correlate just as confidently and without any geometry. If closure is to earn its place, it must say what counts as a closed trajectory, and it must differ somewhere from that account in a way that can be measured.

4.1 What counts as a closed trajectory

A first attempt would define closure as return: the system, displaced by a perturbation, comes back to where it was. That definition is wrong, and its being wrong is informative. Immunological memory is precisely a displacement that does not reverse — the system settles at a new set point and that new set point is the protective outcome. A definition requiring return to the original state would classify successful immunisation as failure.

The definition therefore splits in two. Take a defined perturbation — a vaccination, a controlled antigenic challenge in vitro — applied at time zero, and measure the response in two compartments: the transient compartment of activation (activation markers, effector cytokines, acute-phase and complement readouts such as C1q, proliferating effectors) and the registering compartment in which a lasting change is recorded (memory populations, antibody repertoire and its functional qualities, trained-innate reprogramming).

A trajectory has closed when both of the following hold: the transient compartment, having been displaced, returns within a characteristic time to within a defined neighbourhood of its pre-perturbation values; and the registering compartment carries a stable offset that persists after that return. A trajectory has failed to close when the transient compartment does not come back — when activation persists, differentiation runs to exhaustion, and inflammation continues without resolution. Closure is in other words the discharge of what the perturbation opened, together with the record that the discharge happened.

Two numbers follow directly: the fraction of the displacement in the transient compartment that is recovered, and the time constant over which it is recovered. Both require at least two time points. Neither can be read from a cross-section, and that is the whole of the difference being claimed.

This definition is not invented for the occasion. It describes what is already reported in the clinical literature of tuberculosis, where active disease is characterised by activation and terminal-differentiation phenotypes that do not resolve, and where successful treatment is followed by normalisation of compartments that were dysfunctional during disease. What the definition adds is the instruction to treat the non-resolution itself as the measured quantity rather than as a descriptive feature of the sick.

4.2 The competing explanation, stated fairly

The competitor is the multivariate account: protection is a joint function of many interdependent components, and no single one predicts because the function is high-dimensional. On this account the correlate of protection does exist — it is a signature over enough variables — and the research programme that follows is to measure more components at once and find the signature. This is not a straw position. It is the working assumption of most current correlate-of-protection work, and it explains the historical failure of single markers at least as well as the reading proposed here.

The negative prediction is therefore shared, and an earlier version of this essay was wrong to present it as a discriminating test. The absence of a single correlate separates nothing.

4.3 The measurement that separates them

The accounts differ on whether a cross-section can suffice. The multivariate account says a static signature generalises once it has enough dimensions. The closure account says no static signature generalises at any dimensionality, because the quantity is not in the snapshot; what generalises is the return measure of 4.1.

The test is a transfer test, and it is within reach of existing cohorts. On a single cohort, construct two predictors of subsequent outcome: the best available cross-sectional multivariate signature, and the pair of return numbers measured after a standardised perturbation. Then apply both, without refitting, to a second cohort differing in age, prior mycobacterial exposure and co-infection status. Three outcomes are possible, and they are not symmetrical in what they mean. If the cross-sectional signature transfers, the multivariate account is sufficient and the geometry adds nothing. If only the return measure transfers, closure has done work that the competing account did not do. If neither transfers, the reading proposed here is refuted along with its competitor, since it claims the return measure is the thing that carries across.

4.4 Order as a second separator

A joint function of component values is indifferent to history: the same values give the same output however they were reached. A trajectory property is not. The two accounts therefore come apart wherever outcome depends on the order of exposures while the component values at the endpoint match.

The relevant observation already exists in outline — repeated exposure to Mtb and to environmental mycobacteria shapes later responses and can move vaccine efficacy in either direction — but it has not been used as a test, because the endpoint components have not been matched across orders. The controlled form is straightforward in a model system: administer the same set of exposures in different sequences, match the resulting component profiles as closely as the data allow, and ask whether protection still differs. Sustained order-dependence at matched component values is something the multivariate account has to absorb as an additional hidden variable and the closure account predicts outright.

5. What this is and is not

Nothing in the Leiden work refers to any of this, and no part of the argument above is evidence for the Vacuum.Net framework as a whole. The claim is local: that a well-developed

experimental programme can be restated without remainder in the language of points, curves and connection points; that the restatement turns two standing anomalies into consequences; and that it yields an operational quantity and two measurements that could show it to be empty.

Until those measurements are made, the honest status of the reading is that it is compatible with the evidence and not yet distinguished by it. That is a weaker claim than the one made in the first version of this essay, and the reason for the retreat is given in 4.2.

6. The constructive side

If protection is closure, the design question for a vaccine is not which antigen to present but which junction to make reachable from the largest number of starting states. An invariant, population-wide presentation element with many routes converging on it is exactly such a junction. That is an argument for the HLA-E direction which does not depend on any mechanism specific to HLA-E, and it would carry over to any other invariant element that is found.

It also reorders the clinical question. If what distinguishes containment from disease is whether an opened response discharges, then the quantity worth monitoring in a treated or vaccinated person is not how much immunity is present but whether the activation that was raised has come down and left a record. That is a measurement the field is already equipped to make, and is not currently making as its primary endpoint.

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