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Insect Host Defense Depends on the Balance Between Limiting Pathogen Burden and Tolerating the Physiological Cost of Infection

Mikko Lahtinen[1]*, Elina Salo[1], Juhani Virtanen[2]

[1]Department of Host Defense and Pathogen Limitation, Faculty of Life Sciences, University of Helsinki, Helsinki, Finland.
[2]Department of Infection Tolerance and Physiological Costs, Faculty of Biosciences, University of Eastern Finland, Kuopio, Finland.

***E-mail** ✉ mikko.lahtinen@helsinki.fi

ABSTRACT

Insect infection outcomes are often interpreted through pathogen clearance, survival, or immune activation considered separately. This separation can obscure whether a host survives because it restricts pathogen burden, limits the damage associated with a given burden, or preserves function despite the physiological expense of defense. This article develops a proposed immunophysiological framework in which resistance, damage tolerance, immunopathology, and metabolic cost are treated as distinct but interacting dimensions of host defense. Evidence from *Drosophila*, mosquitoes, silkworms, and honey bees shows that pathogen control can depend on immune-cell metabolic reprogramming, systemic resource mobilization, mitochondrial state, and taxon-specific immune pathways, whereas survival can also improve without lower pathogen burden through tissue protection, damage repair, or metabolic support. Immune activity can itself generate tissue injury and energetic opportunity costs, preventing stronger activation from being interpreted automatically as better defense. The framework therefore treats pathogen burden, host damage, and physiological cost as jointly necessary observables rather than interchangeable proxies. It is proposed as a qualitative architecture for organizing experiments and predictions, not as a validated universal optimum across insects.

Keywords: Disease tolerance, Resistance, Immunopathology, Immunometabolism, Pathogen burden, Host damage

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Introduction

An insect that survives infection is not necessarily highly resistant. Resistance is expressed through the capacity to restrict or eliminate pathogen burden, whereas tolerance concerns the host consequence of infection at a given burden. Quantitative-genetic work in *Drosophila melanogaster* shows that these dimensions can vary partly independently, making survival alone an insufficient descriptor of defense [1]. Disease-tolerance theory likewise separates damage limitation from pathogen control, and insect-focused synthesis places tissue maintenance, repair, and physiological compensation within that distinction [2, 3]. The consequence is methodological as well as conceptual: an increase in postinfection survival can arise from lower burden, reduced host damage at similar burden, greater baseline vigour, or combinations of these processes.

A second source of ambiguity is the energetic and biochemical organization of immunity. In *Drosophila*, immune function is tightly linked to nutrient sensing, carbohydrate and lipid metabolism, and tissue-to-tissue signaling rather than being an isolated consumer of a fixed energy reserve [4]. Metabolic change can therefore be part of

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the mechanism of defense, a consequence of infection, or a cost that constrains later performance. These possibilities should not be collapsed into a generic statement that immunity is "expensive."

The need for separation is reinforced by viral infection. During *Drosophila C virus* infection, host vigour, viral load, and disease-tolerance phenotypes vary among genotypes and can depend on sex and dose [5]. Such variation cautions against assigning a single defense ranking to a genotype from one terminal outcome.

This article therefore proposes an immunophysiological framework in which pathogen burden, host damage, and physiological cost are tracked as distinct state variables. Resistance and tolerance are treated as response dimensions operating on these variables, while immunopathology and metabolic reallocation can alter the cost of achieving a particular infection outcome. The framework is intended to reconcile mechanistic findings across insect systems without implying that one optimal allocation, pathway, or burden–damage relationship is universal.

Resistance mechanisms

Resistance becomes biologically informative when a mechanism can be linked to altered pathogen control rather than merely to immune activation. In *D. melanogaster*, macrophages switch toward aerobic glycolysis during bacterial infection, and disruption of this metabolic program impairs antibacterial defense [6]. This result shows that cellular metabolism can be mechanistically constitutive of resistance. It does not, however, establish that stronger glycolytic flux always improves whole-organism performance, because the same metabolic resources participate in other physiological functions.

Nutrient-sensing pathways can also modify resistance in vectors. In *Anopheles stephensi*, rapamycin treatment altered mTOR-linked immune signaling and reduced *Plasmodium* development through enhanced antiplasmodial responses [7]. The finding supports a causal role for the manipulated pathway within that vector–parasite system, but pharmacological pleiotropy and taxonomic specificity preclude treating mTOR inhibition as a general route to increased insect resistance.

Resistance also depends on systemic resource coordination. During bacterial infection in *D. melanogaster*, macrophage-derived ImpL2 antagonizes insulin signaling and promotes lipoprotein mobilization [8]. The important distinction is that mobilization is an observable physiological response, not proof that the reallocation is cost-free or fitness maximizing. At the molecular level, *Bombyx mori* provides a different resistance mechanism: a single von Willebrand factor C-domain protein contributes to antibacterial defense through pathogen-associated molecular-pattern binding and downstream immune functions [9]. This Lepidopteran example supports mechanistic diversity rather than conservation of one insect-wide pathway.

Mosquito studies further show that intracellular physiological state can influence parasite control. In *A. stephensi*, host serotonin affected *Plasmodium* transmission through changes in mitochondrial homeostasis and reactive-oxygen-associated processes [10]. In *Anopheles gambiae*, TNF-related signaling promoted cellular immune activity and malaria-parasite killing [11]. Together, these systems show that resistance can emerge from metabolic, mitochondrial, humoral, and cellular mechanisms, but the evidence remains pathway-, pathogen-, and species-specific. Within the proposed framework, resistance is therefore assigned only when burden control is demonstrated; immune activation without a corresponding pathogen measurement remains mechanistically suggestive but insufficient for classification.

Damage-tolerance mechanisms

Tolerance requires a different evidential question: how well does the host maintain survival or function for the pathogen burden it carries? In *D. melanogaster* challenged orally with *Pseudomonas entomophila*, genes associated with damage prevention, signaling, and repair altered tolerance phenotypes, with effects dependent on mechanism and sex [12]. These results make tissue protection and repair experimentally distinguishable from pathogen restriction.

Immune priming illustrates why this distinction matters. Prior exposure of *D. melanogaster* to *Enterococcus faecalis* increased survival after challenge without a corresponding improvement in bacterial control, supporting tolerance rather than enhanced resistance as the proximate explanation in that system [13]. The result should not be generalized to all forms of immune priming; instead, it demonstrates that a survival advantage must be decomposed before its mechanism is named.

Tolerance can also involve protection from host-derived injury. A humoral stress response in *Drosophila* protects tissues from antimicrobial-peptide toxicity, showing that the host can require defensive mechanisms against collateral effects of its own immune effectors [14]. This does not make antimicrobial peptides intrinsically

detrimental. It instead places their antimicrobial benefit and their potential tissue cost on separable physiological axes.

Metabolic support provides another route to maintaining host function. During severe bacterial infection in *Drosophila*, infection-induced ketogenesis supports brain physiology and survival [15]. Such support is tolerance-like because maintenance of vulnerable tissue can improve outcome without being equivalent to increased pathogen killing. Conversely, exposure to nonreplicating *P. entomophila* material can produce mortality and reproductive damage in *Drosophila*, demonstrating that substantial host injury need not require ongoing pathogen proliferation [16]. Sex, microbiota, and virulence-factor context modify this response, emphasizing that "damage at a given burden" is itself conditional.

The proposed framework therefore treats tolerance as an outcome relation rather than a named molecular pathway. Repair, tissue protection, metabolic support, and damage buffering can all contribute, but only when their effects are interpreted relative to pathogen burden and host condition.

Immunopathology

An effective immune response can become a source of pathology when host effectors injure tissues or when inflammatory regulation destabilizes physiology. In *Drosophila* renal tubules, the antimicrobial peptide Attacin-D can accumulate intracellularly and mediate inflammatory organ damage; genetic manipulation of this process links an immune effector directly to tissue pathology in that organ context [17]. This result establishes a concrete mechanism of immunopathology, but it does not justify treating antimicrobial peptides generally as harmful because their antimicrobial functions and tissue effects depend on localization, dose, tissue state, and infection context.

Pathogens can also alter host damage without producing a simple one-to-one change in burden. In a *Drosophila–Mycobacterium abscessus* model, microbial metabolism modified cytokine-related and metabolic host responses, changing survival-related physiology without a proportionate explanation from pathogen load alone [18]. The implication is not that burden is unimportant, but that burden and damage are linked through pathogen traits and host signaling rather than by a universal fixed function.

Within the proposed architecture, immunopathology therefore forms a constraint on interpreting maximal immune activation as maximal defense. When stronger effector activity lowers burden but simultaneously increases tissue injury, the host can move toward greater resistance while losing net physiological integrity. That relationship is a proposed synthesis of the evidence, not a demonstrated universal optimum or conserved threshold.

Metabolic costs

The physiological cost of infection cannot be represented adequately by a single depletion term. Immune signaling can reorganize the host economy itself. In *Drosophila*, the TNF receptor Wengen couples gut immune state to systemic lipid expenditure, indicating that inflammatory regulation can alter the distribution and use of energetic resources [19]. Such metabolic expenditure is relevant to cost, but a change in lipid use should not automatically be equated with a demonstrated loss of fitness.

Immune activation can also redirect anabolic priorities. Toll signaling in the *Drosophila* fat body shifts lipid metabolism away from triglyceride storage and toward phospholipid synthesis needed for immune function [20]. This supports a resource-allocation interpretation in which defense may require biochemical restructuring rather than simple caloric consumption. The physiological consequence depends on what alternative functions lose access to those resources and when that loss occurs.

External nutritional state changes the same problem. Controlled macronutrient manipulation alters infection survival and immune phenotypes in *Drosophila* [21], showing that host defense operates within a resource environment rather than against a constant energetic background. At the pathway level, glutamate metabolism coordinates mitochondrial and systemic energetic trade-offs that shape susceptibility to bacterial infection [22]. These findings make "metabolic cost" mechanistically plural: it can arise through substrate diversion, signaling-mediated mobilization, altered storage, tissue support, or competition among physiological demands.

Chronic infection provides an important boundary. In *D. melanogaster*, persistent bacterial infections impose metabolic and starvation-related costs, but immune activation alone does not account for all pathogen-specific differences [23]. Cost therefore cannot be assigned solely to the host response; pathogen burden and pathogen physiology may contribute directly. A larval parasitoid model adds another layer: glucose and trehalose metabolism through the cyclic pentose phosphate pathway supports cellular defense and host protection, yet the

same carbohydrate reorganization can carry physiological consequences outside the immediate immune benefit [24]. Finally, high-sugar diets can increase bacterial susceptibility in *Drosophila*, with pathogen-dependent effects on growth and antimicrobial-peptide responses [25]. Nutrient abundance is therefore not synonymous with greater defensive capacity.

For this article, metabolic cost is defined operationally as a measurable physiological consequence of sustaining infection, activating defense, reallocating resources, or supporting damaged tissues; it is not inferred from immune activity alone. The proposed synthesis distinguishes at least four nonexclusive cost routes: immune-production cost, regulatory reallocation cost, pathogen-associated metabolic cost, and opportunity cost to storage or other functions. Their relative importance is expected to vary with tissue, developmental stage, diet, pathogen identity, infection duration, and the defense mechanism engaged.

Because these routes can produce similar survival outcomes while implying different mechanisms and experimental predictions, a prediction-and-test ledger is more informative than another narrative summary.

Table 1. Metabolic-cost routes that change how insect host defense should be interpreted and tested

Interpretive limit and decisive check	Biological context with observed basis	Interpretation for host defense
	Immune-cell fuel switching	
	Evidence-supported class	
Pathway and infection route are system-specific **Manipulate the pathway while measuring both burden and whole-host condition**	Adult Drosophila antibacterial defense Infection-linked change in immune-cell carbohydrate metabolism together with altered pathogen control	Metabolic flux is part of the resistance mechanism, not merely a downstream cost
	Systemic resource mobilization	
	Evidence-supported class	
Mobilization does not demonstrate net fitness benefit **Pair resource-mobilization measures with later storage, starvation, reproductive, or tissue-function outcomes**	Drosophila bacterial infection Immune-cell signaling alters insulin-related control and circulating lipid availability	Resistance can recruit resources from nonimmune tissues
	Anabolic reprioritization	
	Evidence-supported class	
Consequences depend on stage, tissue, and duration **Measure both immune-supporting synthesis and displaced physiological functions**	Drosophila fat-body immune activation Lipid synthesis shifts from storage toward immune-supporting phospholipids	Defense may impose opportunity cost through altered allocation rather than absolute energetic depletion
	Pathogen-associated metabolic drain	
	Evidence-supported class	
Causal partition between host and pathogen demand can be difficult **Compare matched burden, immune activation without live pathogen, and pathogen identity**	Chronic Drosophila bacterial infection Persistent burden coincides with altered energy stores or starvation resistance and differs among pathogens	Some infection cost originates from pathogen presence or pathogen-specific physiology, not from immune activation alone
	Nutritional-context limitation	
	Evidence-supported class	
Direction can reverse among diets, pathogens, and times **Factor diet into resistance and tolerance assays instead of treating it as background noise**	Diet-manipulated Drosophila and other insect infection systems Survival, burden, or immune outputs change with macronutrient or sugar context	Available resources modify the feasible resistance–tolerance response rather than uniformly strengthening immunity
	Tissue-support expenditure	
	Evidence-supported class	

Benefit may be tissue- and severity-specific **Separate tissue-function rescue from pathogen-control endpoints**	Severe infection with vulnerable-organ support Metabolites are redirected to maintain organ function during infection	A metabolic response may increase tolerance even if it does not reduce burden
	Composite physiological-cost state ***Proposed synthesis***	
No validated universal weighting exists **Test costs as separate observables rather than collapsing them into one score**	Any infection in which several routes operate simultaneously Joint changes in burden, tissue condition, storage, and systemic metabolism	The same survival phenotype can conceal different mixes of resistance benefit and physiological cost

Pathogen burden and host damage

Pathogen burden and host damage are related variables, but they are not interchangeable measurements. Burden estimates the amount or activity of the infectious agent, whereas damage describes deterioration of host tissue, physiological function, reproduction, or survival. The distinction becomes experimentally important when hosts with similar burdens experience different outcomes. Immune priming against *Enterococcus faecalis*, for example, can improve *Drosophila* survival without increasing bacterial clearance [13]. Conversely, pathogen metabolic state can modify host signaling and survival without a proportional change in microbial load [18]. These cases prevent a single burden measurement from identifying the mechanism responsible for host outcome.

Damage can also persist when replicating pathogen burden is absent or reduced. Nonreplicating *P. entomophila* material produces measurable host injury in *Drosophila* [16], while the antimicrobial peptide Attacin-D can itself generate renal pathology under inflammatory conditions [17]. These findings distinguish pathogen-associated damage signals from immune-mediated collateral damage. Neither mechanism implies that burden is irrelevant; rather, they demonstrate that different biological processes can occupy the causal interval between infection and organismal deterioration.

Chronic infection introduces a further complication because pathogen burden can contribute to continuing metabolic demand. Persistent bacterial infections in *D. melanogaster* differ in their physiological costs, and immune activation alone does not reproduce every pathogen-associated metabolic consequence [23]. Thus, even where greater burden predicts greater cost within a particular system, the slope and mechanism of that relationship cannot be assumed to transfer among pathogens, tissues, stages, or environments.

The proposed framework therefore reconciles three observables rather than collapsing them: pathogen burden, host damage or functional state, and physiological cost. Resistance is inferred primarily from changes in pathogen control; tolerance is inferred from changes in host condition relative to burden; and cost records what must be physiologically expended, displaced, or damaged in producing that outcome. A single terminal survival value cannot identify these dimensions.

This reconciliation is summarized visually because the central problem is not a sequence of events but the coexistence of parallel burden, damage, and cost trajectories whose relationships can change with mechanism and context.

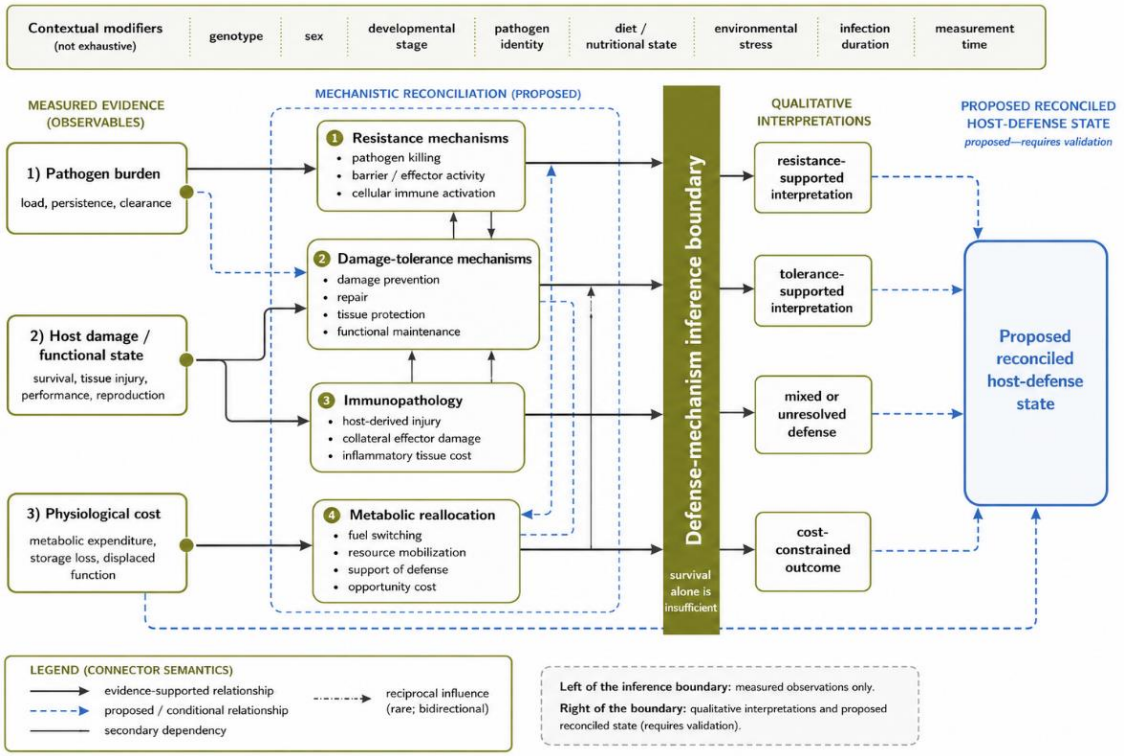


Figure 1. Reconciling pathogen burden with host damage when survival does not identify the defense mechanism

Resistance–tolerance trade-off surface

Resistance and tolerance are not necessarily opposing ends of one allocation axis. A natural Metchnikowin polymorphism in *D. melanogaster* produces infection-related benefits alongside sex- and pathogen-dependent life-history consequences [26]. This illustrates why a resistance advantage cannot be assumed to be cost-free, but it does not establish an invariant immunity–reproduction trade-off.

Experimental evolution makes the dimensionality clearer. Selection for improved postinfection survival increased resistance without a detectable corresponding increase in tolerance in one *Drosophila* system, whereas another oral-infection regime produced evolved changes involving both resistance and tolerance [27, 28]. Survival selection can therefore reach improved outcome through different combinations of pathogen control and damage management.

The article consequently proposes a resistance–tolerance trade-off surface rather than a fixed trade-off line. The term "surface" is qualitative: any defense state is located conceptually by the degree of burden restriction, host damage at that burden, and physiological cost required to achieve the state. A host may therefore become more resistant while remaining poorly protected from collateral damage, or may tolerate substantial burden while paying a large metabolic cost. No empirical evidence in the present synthesis supports assigning universal weights, thresholds, or an optimal point.

The resulting inference states are best treated as conditional categories rather than ranked defense scores.

Table 2. Qualitative defense states generated when resistance, tolerance, damage, and physiological cost do not change in parallel

Observable pattern and warranted reading	Proposed surface state with evidential standing	Defense interpretation, critical boundary, and discriminating experimental test
Burden decreases and host condition improves **Cost may be low or high and must be measured independently**	Resistance-dominant improvement Proposed classification	Greater pathogen control plausibly contributes strongly to outcome Better baseline vigour or simultaneous tolerance could contribute Manipulate resistance mechanism and track burden, damage, and cost through time

Burden is similar but host damage or functional loss decreases **Physiological support may itself be costly**	Tolerance-dominant improvement Proposed classification	Improved outcome is consistent with greater tolerance Unmeasured spatial or temporal differences in burden could mimic tolerance Use repeated burden measurement with independent tissue or functional endpoints
Burden decreases but substantial host damage persists **Immunopathology or irreversible pathogen injury may dominate**	Resistance with unresolved pathology Proposed classification	Pathogen control improves without equivalent restoration of host integrity Damage may predate burden reduction Resolve timing of clearance, tissue injury, and immune-effector activity
Burden remains substantial while function is maintained **Maintenance can require persistent metabolic expenditure**	Compensated high-burden state Proposed classification	Tolerance may buffer infection consequences Apparent health may be temporary Measure later functional decline, storage state, and persistent burden
Burden or damage improves while physiological reserves or other functions deteriorate **Storage, starvation resistance, reproduction, or organ function may be displaced**	Cost-constrained defense Proposed classification	Effective defense has a measurable opportunity cost Cost may arise from pathogen demand rather than immunity Compare live infection, matched immune activation, and metabolic perturbation
Burden and damage remain high and physiological condition declines **Multiple costs accumulate**	Joint defense failure Proposed classification	Neither burden control nor damage limitation is sufficient under tested conditions Host vigour, dose, route, or environmental stress may dominate Partition baseline vigour from induced resistance and tolerance

Life-stage and environmental modifiers

The proposed surface is context dependent rather than a fixed species property. In honey bees, nutritional state, pesticide exposure, and viral infection interact to produce outcomes whose direction depends on the combined exposure context [29]. Such interactions caution against extrapolating defense measured under one laboratory resource regime to environmentally stressed hosts.

Time can also change the classification itself. In adult female *Aedes aegypti*, sugar restriction and blood ingestion generate divergent immune-defense trajectories after bacterial challenge [30]. A host characterized as relatively resistant at one sampling point could therefore appear less resistant or more tolerant at another if burden and host condition change asynchronously.

Intrinsic modifiers are similarly important. Sex-dependent tolerance occurs in experimental *Drosophila* systems [12], viral defense varies with genotype and sex [5], larval carbohydrate metabolism influences parasitoid defense [24], and immune-allele costs can reverse with sex or pathogen context [26]. These examples do not establish one predictable modifier direction. They establish that pooling across stage, sex, genotype, or environment can conceal biologically distinct host-defense states.

Accordingly, the framework treats stage, sex, nutritional condition, infection route, pathogen identity, and measurement time as stratification variables. Broader environmental or field generalization requires direct testing rather than assuming that a laboratory-defined resistance–tolerance relation persists unchanged outside the experimental setting.

Experimental predictions

Testing the proposed framework requires designs that measure defense dimensions independently. Methods developed for *Drosophila* innate-immunity research demonstrate why pathogen load, survival, cellular activity, and humoral responses answer different questions and should not substitute for one another [31]. Equivalent pathogen-appropriate measurements are required in other insect systems.

Four predictions follow. First, experimentally increasing a resistance mechanism should not be expected to improve host condition monotonically. Tissue-protection data predict that burden reduction can coexist with collateral damage when immune-effectors are harmful to host tissues [17]. Second, improving metabolic support

may increase tolerance without reducing burden, as illustrated by infection-associated tissue support [15]. Third, interventions that strengthen defense should be evaluated for displaced physiological functions because immune-driven lipid and carbohydrate reorganization can generate opportunity costs [20]. Fourth, estimated resistance and tolerance should change when genotype, sex, stage, diet, or observation time changes; this is a prediction about conditional measurement, not a forecast of the direction of those changes.

A decisive experiment would therefore measure baseline vigour, repeated pathogen burden, tissue or functional damage, and at least one independent physiological-cost endpoint while manipulating a mechanistically justified resistance or tolerance process. Factorial replication across host state and environment would test whether the inferred defense state is stable or context dependent. Replication beyond *Drosophila* and mosquito models is particularly important before interpreting the framework as characteristic of insects generally.

These tests could falsify central parts of the proposal. If burden alone consistently predicts damage and physiological cost across contexts, the added dimensions would provide little explanatory value. If resistance and tolerance always covary in the same direction after independent manipulation, treating them as partially separable axes would be unnecessary. The framework therefore provides testable distinctions rather than a claim of prospective predictive performance.

Conclusion

Insect host defense is more accurately interpreted as the joint outcome of pathogen restriction, damage limitation, and the physiological cost of producing or sustaining those responses than as the magnitude of immune activation or survival alone. Resistance can depend on metabolic, cellular, humoral, and mitochondrial processes, while tolerance can arise through tissue protection, repair, or physiological support. Immunity can simultaneously protect and damage the host, and infection costs can originate from immune allocation, pathogen demand, displaced metabolism, or combinations of these processes.

The principal contribution of this article is the proposed separation and reconciliation of pathogen burden, host damage, and physiological cost within a qualitative resistance–tolerance trade-off surface. The surface is not an empirically validated optimum, quantitative fitness landscape, or universal insect defense rule. Its state depends on what is measured, when it is measured, and the host, pathogen, developmental, nutritional, and environmental context.

The framework is therefore most useful as an experimental discipline: burden and damage should be measured separately, physiological costs should be demonstrated rather than assumed, and survival should be interpreted only after alternative resistance and tolerance mechanisms have been tested. Broader validity will require comparative work across insect orders, life stages, environments, and naturally relevant infections.

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