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Protective microbiomes can limit the evolution of host pathogen defense

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Abstract

The evolution of host immunity occurs in the context of the microbiome, but little theory exists to predict how resistance against pathogens might be influenced by the need to tolerate and regulate commensal microbiota. We present a general model to explore the optimal investment in host immunity under conditions in which the host can, versus cannot easily distinguish among commensal versus pathogenic bacteria; and when commensal microbiota can, versus cannot protect the host against the impacts of pathogen infection. We find that a loss of immune vigilance can occur due to the challenge of discriminating between pathogenic and other microbe species. Further, we find the greater the protective effect of microbiome species, acting either directly or via competition with a pathogen, or the higher the costs of immunity the more likely loss of immune vigilance is. Conversely, this effect can be reversed when pathogens (or microbiome species) increase host mortality. Generally, the magnitude of costs of immunity required to allow evolution of decreased immune vigilance are predicted to be lowest when microbiome and pathogen species most resemble each other (in terms of host recognition), and when immune effects on the pathogen are weak. Our model framework makes explicit the core trade-offs likely to shape the evolution of immunity in the context of microbiome / pathogen discrimination. We discuss how this informs interpretation of patterns and process in natural systems, including the distribution of immune function across life histories, and vulnerability to pathogen emergence.

Impact Summary

Evidence for impacts of the microbiome on host health is accumulating. Despite this, little theory has been developed to delineate the evolutionary trajectories that might lead to observed host-microbiome associations. One particularly important theoretical gap is evaluating how the presence and effects of microbiome species modify selection pressure on immune system function. We develop a simple model of host fitness given both immune discrimination and microbiome and pathogen effects on survival, in the context of an interaction between the microbiome and pathogen species. We use this framework to delineate when and to what degree the presence of microbiome species might lead to loss of immune vigilance. Positive microbiome effects can drive loss of immune vigilance, whether the microbiome acts directly on pathogen growth or indirectly by reducing the impacts of pathogens; and high costs of immunity will amplify this effect. Our results provide a first set of predictions regarding how immunity

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should evolve given the challenge of discriminating pathogen and microbiome species, and reveals the ways in which this might leave hosts vulnerable to novel pathogens.

Introduction

Bacterial species making up the microbiome are increasingly recognized to play an important role in host health, including via microbiome-mediated protection against pathogens (Friesen et al. 2011). An important implication is that the evolution of host immunity must have occurred in the context of balancing tolerance of commensals and resisting pathogens (Littman and Pamer 2011). Both underlying ecological features of hosts and bacteria, and aspects of immune system functioning will shape this process of immune selection. For example, microbiome-mediated protection might evolve very rapidly, due to both shorter microbial generation times and greater standing genetic variation. The resulting protection against pathogens enjoyed by the host might hinder the evolution of host genetic resistance. Growing evidence also suggests that the microbiome plays a critical role in shaping the breadth and specificity of host immunity. This will also shape selection pressures on host immunity to resist pathogens. Despite increasing recognition of the importance of the microbiome in host ecology and health, mathematical models of core processes remains rare, and there is little theory to guide expectations (Koskella, Hall, and Metcalf 2017).

To adequately reflect natural systems of interest, mathematical models must reflect several interlocking aspects of the ecology and co-evolution underpinning microbiome-mediated protection. Critically, pathogens and commensal microbiota are likely to have overlapping expression of molecules used by the host in detection of pathogens (Levy et al. 2018; Vogel et al. 2016), ranging from conserved Microbe Associated Molecular Patterns (MAMPs), to convergent ‘effectors’ designed to interact with host immune functioning (Carella, Evangelisti, and Schornack 2018), to molecules selected in bacteria for mimicry of host proteins (Levy et al. 2018). The decision to trigger an immune system must therefore discriminate between the presence of pathogens and (neutral or even beneficial) microbiota despite these similarities. One might predict, therefore, that hosts should evolve a highly specific immunity to differentiate pathogenic bacteria from commensals, blocking colonization of the former while allowing growth of the latter. However, such host evolution should then feedback on selection in pathogen populations to evade recognition by becoming indistinguishable from related commensal bacteria. This dual role of the immune system, to both defend against pathogens and tolerate commensals, is achieved in part by the ability of cells to release ‘safety’ versus ‘danger’ signals depending on tissue damage rather than recognition per se (Lathrop et al. 2011). However, there exists a fundamental tension between maintaining a diverse microbiome and defending against pathogens that remains poorly understood,

The problem is further complicated by the the ability of many commensal microbiota to play a role in host defense by either excluding pathogen colonization and growth or reducing the impact of pathogens on host health (Snelders et al. 2018). This might (or might not) echo molecular signatures underlying detection by immunity, for example if phylogenetically related pathogenic and commensal bacteria were more likely to compete for shared resources and were recognized by the immune system through shared mechanisms. In this case, reducing immune vigilance may allow for proliferation of particular commensal microbiota that directly compete with invading pathogens, reducing the need for hosts to invest in immunity. Many lines

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of evidence suggest that triggering an immune reaction is likely to be costly (Hanssen et al. 2004; Sheldon and Verhulst 1996) and thus walking the line between effective pathogen defenses and regulating microbiome homeostasis should be a ubiquitous but non-trivial challenge.

Here, we ask how host immunity might evolve in the presence of a microbiome community with the potential to diminish pathogen impact on the host via competition. As our focus is on host evolution, and since many molecules used by hosts to trigger immunity (like MAMPs) are evolutionarily constrained, we initially assume that evolution in pathogen and microbiome communities is negligible. From this, we explore outcomes across a range of static configurations of microbiome and pathogen species in terms of detection by host immunity, captured via a single axis along which the microbiome and pathogen species are distributed. The axis represents a range from a 'small' to a 'large' signal detectable by the immune system, which might reflect aspects such as the number of CpG repeats (detectable by Toll-like-receptor 9 (Pohar et al. 2015)) or immunogenically variable aspects of flagellin (Felix et al. 1999), or the integration of a variety of signals, some of which reflect positioning along a 'safe' to 'dangerous' axis (Swiatczak and Cohen 2015). From this, we develop a model framework constructed around core principles from epidemiology to better understand drivers of the evolution of host defense in the context of pathogen-microbiome interactions. We aim in particular to delineate conditions under which the presence of microbiome species may result in loss of immune vigilance altogether. Our results show that loss of vigilance driven by microbiome protective effects is possible, and its likelihood increases as similarity between the microbiome and pathogen communities increases, and when immune effectiveness against the pathogen is weak. We discuss how evolution by pathogen and microbiome communities might modulate outcomes for the host, and how these consequences might play out across host life histories.

Methods and Results

A discrimination trade-off

The problem faced by the immune system in discriminating between 'good' commensals and 'bad' pathogens is analogous to a classic result from epidemiology. Overlap between two categories along a continuum means that choosing where to draw a line to discriminate between them results in a trade-off between falsely allocating individuals to one or the other category (Figure 1). Here, the immune strategy under selection corresponds to the problem of where to draw the line above which an immune reaction is triggered. If we define 'microbiome' as the community of microbial species with purely neutral or positive effects, ideally, the line would have all individuals from the microbiome community to its left, where no immune response is triggered, and all pathogen species to its right, where immunity acts to clear microbial species. However, the predicted overlap between these two communities means that this would be impossible. Drawing the line to the far left of the plot corresponds to a strategy of 'total vigilance,' where every single microbe along the continuum triggers a reaction (with associated costs of immune response). Drawing the line to the far right of the plot corresponds to a strategy of 'no vigilance' where no microbe elicits an immune reaction. If there is overlap between the two distributions, drawing the line towards the middle of the plot (e.g., the intermediate strategy illustrated in Figure 1) inevitably mis-classifies some individuals: some

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members of the microbiome community will be above the line, and some members of the pathogen community below it. The strategy that maximizes fitness will balance costs of immunity with costs and benefits of pathogens and microbiome species, and the effect of their overlap, i.e., the impact of the microbiome on the pathogen relative to outcomes for the host. In what follows, we relax the definition of microbiome to encompass species with neutral or even slightly detrimental effects on host survival, with the condition that they are less deleterious than pathogen species.

Defining survival probability in the context of a discrimination trade-off

To move from our conceptual mapping of the challenge faced by the immune system (Figure 1) to a measure of fitness, we express host survival as the outcome of mortality hazards associated with each context. We can express the hazard of mortality for an individual as:

$$\mu = \mu_b + A \quad \mu_d + B\mu_d c + C\mu_d r_p + D\mu_d r_p c + E\mu_m + F\mu_m r_m \; + (C + D + F)I \qquad [1]$$

where the quantities *A*, *B*, *C*, *D*, *E*, and *F* refer to areas as shown on Figure 1 (*A*+*B*+*C*+*D* captures the areas occupied by the pathogen, and *E*+*F* areas occupied by the microbiome); μ_b is a baseline mortality hazard, μ_d is the mortality hazard associated with the presence of the pathogen, μ_m is the mortality hazard associated with the presence of the microbiome species (and can be negative, in the case of beneficial microbiome species).The parameter r_p captures the host's resistance to the pathogen, e.g., its ability to reduce the mortality hazard associated with the presence of pathogen species to the right of the immune threshold line. This parameter is contained between 0 and 1, where $r_p = 1$ indicates no effect of the host on the pathogen, and $r_p = 0$ indicates that the host completely eliminates the effects of the pathogen. Similarly, r_m captures how much the host reduces the effect of the microbiome. Where the microbiome has beneficial effects on survival ($\mu_m < 0$) this will translate into the host tolerating their microbiome if $r_p = 1$, and eliminating the beneficial effects if $r_p = 0$. The parameter c captures the degree to which the presence of microbiome species reduces the mortality hazard by the pathogens (e.g., by outcompeting or interfering with them) in a manner dependent on their overlap along the continuous axis used by the host, and is also contained between 0 and 1. The parameter I captures the cost of an immune response, and is multiplied by all contexts where an immune reaction has been triggered (e.g., area above the vertical line, shaded yellow, Figure 1).

To evaluate the outcome of different scenarios for the host, each mortality hazard must be multiplied by the relevant area reflecting the combination of the distribution of microbiome and pathobiome distributions, and the positioning of the immune threshold, as labelled on Figure 1; with A, the area below the threshold for immunity consisting of only the pathogen; B the area below the threshold where the pathogen overlaps with the microbiome; C, the area above the threshold where only the pathogen is present; D, the area above the threshold where both the pathogen and the microbiome are present (Figure 1); E, the area where the microbiome is below the threshold; and F, the area where the microbiome is above the threshold and thus potentially eliciting an immune response (the latter two are left off Figure 1 for clarity). An

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individual's probability of survival, as a function of the presence of the pathogen and its immune threshold can then be expressed by $s = exp(-\mu)$.

Selection on the immune threshold

Assuming that fertility is not affected by either the pathogen or the immune strategy adopted by the host, maximising survival will maximize host fitness. We can evaluate evolutionary outcomes schematically, mapping out how different contributions to the hazard change as the threshold moves from left (complete immune vigilance) to right (no immune vigilance), and from this characterize how increases in each of the contributions to the mortality hazard modulates the optimal immune threshold, which is defined by the strategy corresponding to the lowest summed hazard and thus highest survival (Figure 2). This indicates that high costs of immunity, or positive effects of the microbiome could shift the optimal towards 'no vigilance' (i.e., drive hosts towards the evolution of no immunity). Indirect effects of the microbiome on pathogen growth, for example, whereby microbiome competition reduces pathogen hazard, could also have this effect.

Detecting that there could be an effect of competition in the unusual context of complete overlap does not speak to the magnitude of the effect across a broader array of scenarios. To assess this, we can also evaluate the outcome quantitatively. Using basic probability, we can calculate the areas A-F. For simplicity, we can first evaluate outcomes where the two distributions are perfectly overlapping. This also captures the scenario where the pathogen has evolved to be indistinguishable from the microbiome. In this situation, $A = C = 0;\ B = E$ and $D = F = 1 - B$. The equation becomes:

$$\mu = \mu_b + B[\mu_m(1 - r_m) + \mu_d\, c(1 - r_p) - 2I] + \mu_m r_m + \mu_d r_p c + 2I \quad [2]$$

As the immune threshold moves from left to right, reflecting a transition from complete vigilance by the immune system to no vigilance at all, the magnitude of the area denoted *B* increases (Figure 1). As a result, the sign of the factor multiplying *B* will determine whether the outcome of evolution in the presence of a microbiome is effectively the absence of an immune response (we expect purely binary outcomes in this simple scenario). From this, selection for no vigilance requires that:

$$0.5[\mu_m(1 - r_m) + \mu_d\, c(1 - r_p)] > I \quad [3]$$

This relationship indicates that the cost of immunity (I)required to drive evolution in the host towards a strategy of no immune vigilance will increase: (i) as the hazards increase; (ii) when the effect of competition from the microbiome on the pathogen community is reduced (reflected by increased values of *c*); or (iii) if the impact of immunity on the hazards is increased (reflected by decreased values of either r_m or r_p).

Focussing on the magnitude of immune cost *I* required to drive complete loss of immune vigilance provides a tractable focus for understanding life history constraints (given the array of potential parameters), as well as being of biological interest. Extending results presented in eqn

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[3] numerically (Figure 3A), we can plot the magnitude of the cost of immunity (I)required for evolution to the point of no immune vigilance across a spectrum of microbiome and disease-mediated hazards, and across a range of overlaps between microbiome and pathobiome communities (Figure 3B, x axis, illustrated by the distributions at the bottom). The required immune cost associated with loss of all immune vigilance increases as overlap declines (Figure 3B, y axis), with higher costs required for lower pathogen hazards (Figure 3B, colours), or in the presence of a beneficial microbiome (Figure 3B, line types); and costs decline with diminishingly effective pathogen immunity r_p (Figure 3B, top row).

How will competition shape the evolution of immune vigilance? To explore this, we can evaluate survival at a range of immune thresholds in the absence ($c = 1$, Figure 4, left) versus presence ($c = 0$, FIgure 4, right) of competition across a spectrum of pathogen hazard and immune effectiveness against pathogens (Figure 4, line types, text) for different costs of immunity (purple colours indicate higher costs). If pathogen mortality is low, and/or immune effectiveness is high, the optimal strategy is no immune vigilance (Figure 4, dashed line peaks to the right) and is not much modulated by competition (compare top and bottom panels). For intermediate pathogen mortality / immune effectiveness, the optimal strategy is complete vigilance in the absence of competition (Figure 4, left, dotted line peaks to the left). The presence of competition between the microbiome and the pathobiome increases host survival across the range of thresholds, and slightly reduces the optimal immune vigilance (Figure 4, right, dotted lines increase with the dashed lines then decline at an intermediate threshold). For large pathogen mortality / low immune effectiveness, in the absence of competition, there is little difference in survival across a range of immune thresholds: complete vigilance results in very minor increases in survival for low costs of immunity, and vice versa (Figure 4, left solid line). The presence of competition results in larger survival across the board, and further, alters the optimal to being no immune vigilance, with this reflecting a considerable survival advantage (Figure 4, right, solid line peaks to the right).

Dysbiosis at high or low diversity

In many settings, reduced microbiome diversity has been linked to 'dysbiosis', or reduced health as a result of perturbed microbiome ecology. However, in others, such as the vaginal microbiome, evidence suggests that reduced diversity is in fact a sign of health. To better capture how the impacts of microbiome diversity shape selection on immune system response, we assume that the range of diversity left intact in the wake of immune activity affects the overall hazard. Diversity is measured using Simpson's diversity index,

$D = 1 - \sum \quad (n/N)^2$,

where *n* is the number of individuals of each species (identified as positions along the x axis) and *N* is the total number of individuals, in both cases taking only points below the threshold. This index thus represents the probability that two individuals randomly selected from a sample will belong to different species, and is thus essentially a saturating function of the position of the threshold from left to right, saturating at 1.

The effect of diversity on the hazard $\mu_{m.div}$ may be either negative or positive, and thus may increase or decrease the mortality hazard. The expression for the mortality hazard becomes:

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$$\mu = \mu_b + A\ \ \mu_d + B\mu_d c + C\mu_d r_p + D\mu_d r_p c + \mu_m E + \mu_m F r_m\ + (C + D + F)I + \mu_{m.div}[1 - \sum\ \ (n/N)^2]\square \qquad [4]$$

Conceptually, this corresponds to adding one more curve to the schematic in Figure 2, either increasing (where the hazard increases with diversity) or decreasing (where the hazard decreases with diversity). This illustrates that where dysbiosis increases as diversity declines (e.g., as in (Lawley et al. 2012)), this will select for a decline in immune vigilance; and vice versa.

Discussion

We provide a first framing of how the presence of microbiome species might modulate the evolution of host immunity where the immune system faces the challenge of discriminating between pathogenic and other microbe species (Figure 1). We separate out direct positive effects of the microbiome on reducing mortality (even in the absence of infection) with indirect effects from competing with and reducing mortality effects of pathogenic species (captured by our parameter *c*). We show that either effect can shift the evolution of host immunity towards loss of vigilance; that the effects are amplified as similarity between the microbiome and pathogen communities increases (Figure 3B, left hand side); and that when immune effectiveness against the pathogen is weak (Figure 3B, lower panel) immunity can be lost even when not very costly. The likelihood of loss of immune vigilance (Figure 2) will be further amplified if dysbiosis declines with diversity.

Our framework makes explicit the trade-offs which define whether microbiome species presence can drive loss of immune vigilance. A comparative framing provides one possible approach to testing the resulting predictions. Evidence for direct protective effects of the microbiome exists in a range of hosts, including against *Pseudomonas syringae* in horse chestnut trees (Koskella et al. 2017), tomato (Berg and Koskella 2018) and arabidopsis plants (Innerebner, Knief, and Vorholt 2011); against both salmonella (*Salmonella enterica typhimurium*) (Kubinak et al. 2015) and intestinal infection of *Entamoeba histolytica (Watanabe et al. 2017)* in mice; and against the the conjunctival bacterial pathogen *Mycoplasma gallisepticum* in house finches (Thomason et al. 2017). Furthermore, the role of individual defensive symbionts on host fitness has been demonstrated both empirically (Vorburger and Perlman 2018) and theoretically (King and Bonsall 2017). Under these scenarios, the immunity of the relevant host species (or genotype) might show diminished discrimination against pathogens, for example reduced sensitivity of pattern recognition receptors as reported in some plant species (Jones and Dangl 2006), or altered adaptive responses in vertebrates (Lee and Mazmanian 2010), relative to species or genotypes for which microbe communities do not play this protective role.

Across the field, a focus on host evolution relative to pathogen (or microbiome) characteristics remains relatively rare, as the expectation is that microbe evolution is likely to play out on much shorter time-scales than that of hosts. While our focus is on host evolution, we can also evaluate our results in the context of microbe evolution. In particular, the situation of completely overlapping pathogen and microbiome species distributions (equation [3]) captures the situation

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where the pathogen is evolving to be completely indistinguishable from the microbiome. A scenario where both the microbiome and the pathogen can evolve might reflect them evolving to evade the possibility of detection by immunity. This can be captured in our model by a lower bound on where the immune threshold can be drawn (Figure 1, the purple line can no longer go all the way to the right). This will bound the optimal strategy that the host can evolve, but does not qualitatively change the conclusions of the analyses.

Returning to the scale of the host, broad predictions can also be made across life-histories. Longer lived species might encounter a higher diversity of microbes, simply given longer exposure times during which microbe colonization can occur. If we assume that most microbial species have either neutral or slightly deleterious effects, then longer lived species might be predicted to be more likely to retain immune vigilance, all else being equal, since these cumulative costs will translate into a significant reduction in host reproductive value. An increase of dysbiosis with microbe diversity will tend to amplify this effect (noting, however, that the reverse pattern is often reported). Since many features, including costs of immunity might also covary with longevity, careful titration of selection pressures will be required to evaluate the strength of this prediction in natural systems.

The framing also makes explicit predictions about pathogen emergence. Since protective effects of microbiome species can drive the loss of host immune vigilance, hosts can be left vulnerable to attack by novel pathogens that too closely resemble allies that the host has been selected to ignore. In a similar vein, moving to time-scales of ontogeny, introduction of commensal species outside of a critical window of exposure could lead to a host either excluding a potentially protective microbiome species or mounting an immune defense against non-pathogenic bacteria in a way that leads to autoimmunity (Gensollen et al. 2016)

Finally, our model illustrates the types of interactions that may have lead to the intricate evolution of tolerance of microbiome species displayed by adaptive immunity in vertebrates (Cebula et al. 2013). While our focus so far has been on host evolution, emergent coevolutionary pressures may have driven selection for signalling by commensal microbiota to facilitate recognition by adaptive immunity (Ost and Round 2018), equivalent to increasing the separation between the two distributions in Figure 1. Similarly, these dynamics could lead to selection for pathogens to evade immunity by converging on signals of commensal microbiota, which could lead to interesting feedbacks on microbiome diversity.

To conclude, while our framework makes a number of simplifying assumptions (e.g., ignoring immune responses triggered by tissue-specific damage, a widely observed phenomenon; and collapsing of potentially multidimensional immune discrimination), it makes a first set of predictions about optimal immune discrimination, both as a function of overlap between pathogen and microbiome, and of microbiome-mediated protection. This initial framing lays a foundation for future work exploring the under-studied question of selection on host immunity in light of our expanding understanding of the microbiome. It also brings to light the need for more explicit data examining the overlap in host recognition of pathogens and commensal microbiota.

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Author Contributions: CJEM and BK developed the concept; CJEM developed the models; CJEM and BK wrote the paper.

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Figure 1: Schematic of overlap between microbiome (left, blue) and pathogen (right, red) communities along a continuous axis (x axis) reflecting intensity of some immune trigger (e.g., CpG ratio for TLR9), where the y axis captures species density. The purple line shows the threshold above which an immune response is triggered, also shaded yellow. Assuming a neutral or positive microbiome, areas of the microbiome distribution above the purple line are 'false positives' (inappropriately targeted by the immune system, are defined by E); areas of the pathogen distribution below the purple line are 'false negatives' (inappropriately ignored by the immune system, areas defined by C and D). Because both the presence or absence of the immune response, but also the presence or absence of microbiome species (via competition) define how pathogen species affect the host, there are four different categories (A-D, see labels) associated with the pathogen distribution; and two associated with the microbiome species (E and F, since we are assuming no effect of the pathogen on the microbiome). The optimization problem faced by host immunity is where to draw the immune threshold (purple line) to balance the costs of the pathogen and immunity, and the effects of the microbiome.

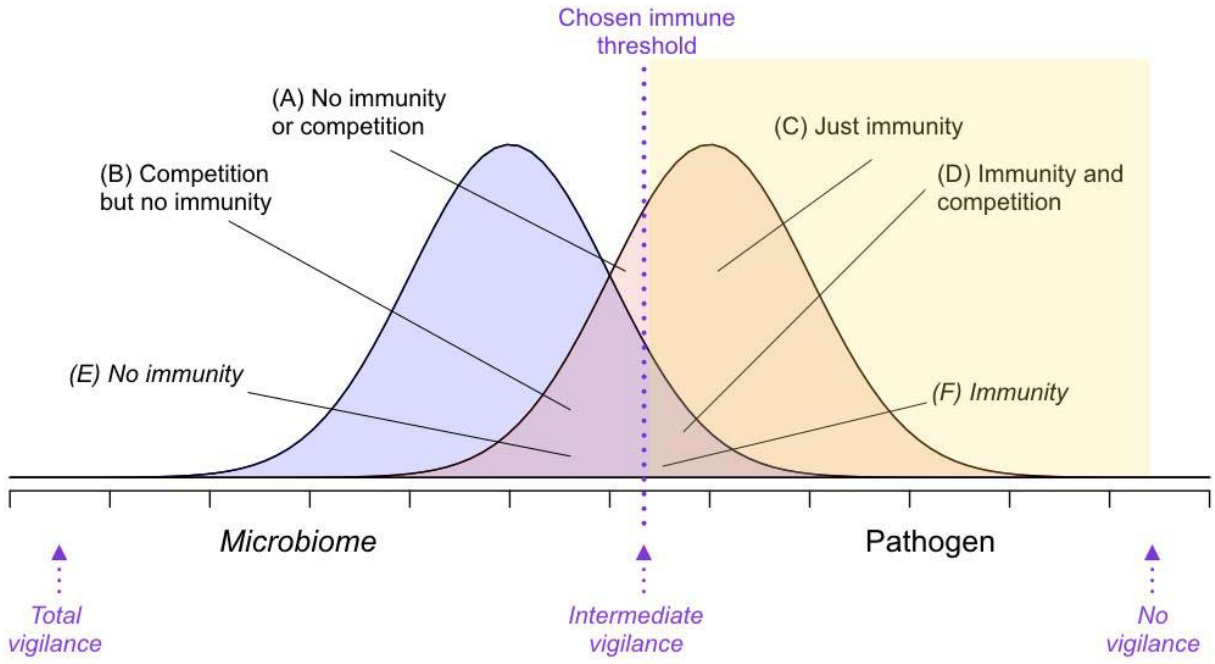

Figure 2: Schematic relationship between immunity and fitness, as a function of the position of the immune threshold (x axis), where a threshold on the far left reflects *total vigilance*

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(points all along the axis trigger a response), and to the far right reflect *no vigilance*. A) contributions to the hazard (y axis) from pathogens (red) which increase as immune vigilance declines, immune costs (purple) which decrease as immune vigilance declines, mildly detrimental microbiome species (blue) which increase as immune vigilance declines; and hazards associated with loss of a beneficial microbiome species (dashed blue line) which decrease as immune vigilance declines. B) The fitness landscape is defined by overall survival (y axis) as a function of the position on the immune threshold (x axis), which peaks when the sum the various contributions to the hazards is the smallest (grey line). Therefore, increases in pathogen (or detrimental microbiome) related hazards will shift the immune threshold left (see arrows), increasing vigilance; and increases in the costs of immunity, or loss of impacts of a beneficial microbiome will shift the threshold to the right, thus decreasing vigilance (see arrows). Both competition (parameter c) and immune effects (r_p and r_m) are not illustrated here, as their role effect may be context specific (see Figure 3).

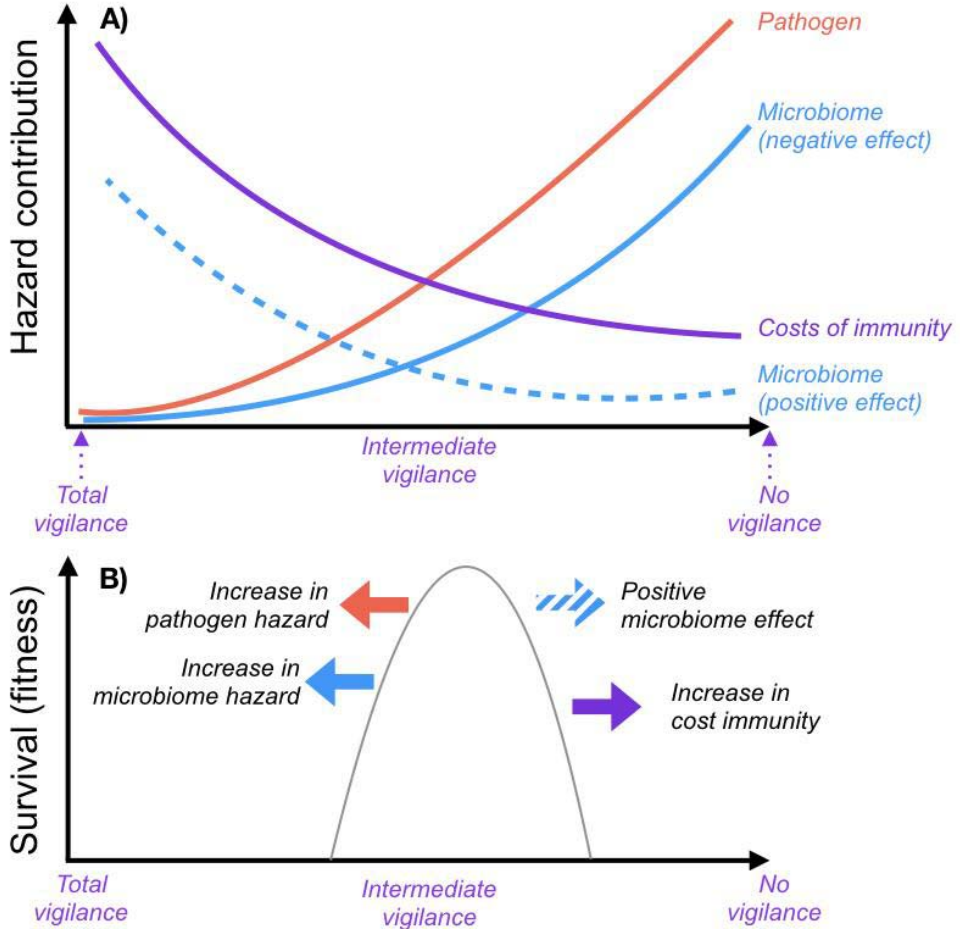

Figure 3: Cost of immunity required to drive evolution of loss of discrimination A) This cost is the value of I (purple box) required to tip the quantities on the right of the scales (i.e., the

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components of the hazard that decline as the immune threshold moves right), below the quantities on the left (i.e., components that increase in value as the immune threshold moves right). The effect of overlap between microbiome and pathogen distributions, governed by the competition parameter, c, contributes to both sides of the scale (pale red box). B) As the overlap between microbiome and pathogen communities declines (schematic left to right; x axis reflects increasing mean of the pathogen distribution), the cost of immunity required to drive evolution to no immune vigilance (y axis) increases, and is greatest for large pathogen hazards (darker red colours) and pathogenic microbiota (dotted line, corresponding to $\mu_m = 0.1$; with $\mu_m = 0$ for the dashed line, and $\mu_m = -0.1$ for the solid line; other parameters are $r_m = 0.3, r_p = 0.1, c = 0.5$). Reducing the effectiveness of pathogen immunity by setting $r_p = 0.7$ results in lower costs allowing loss of host immunity (lower panel).

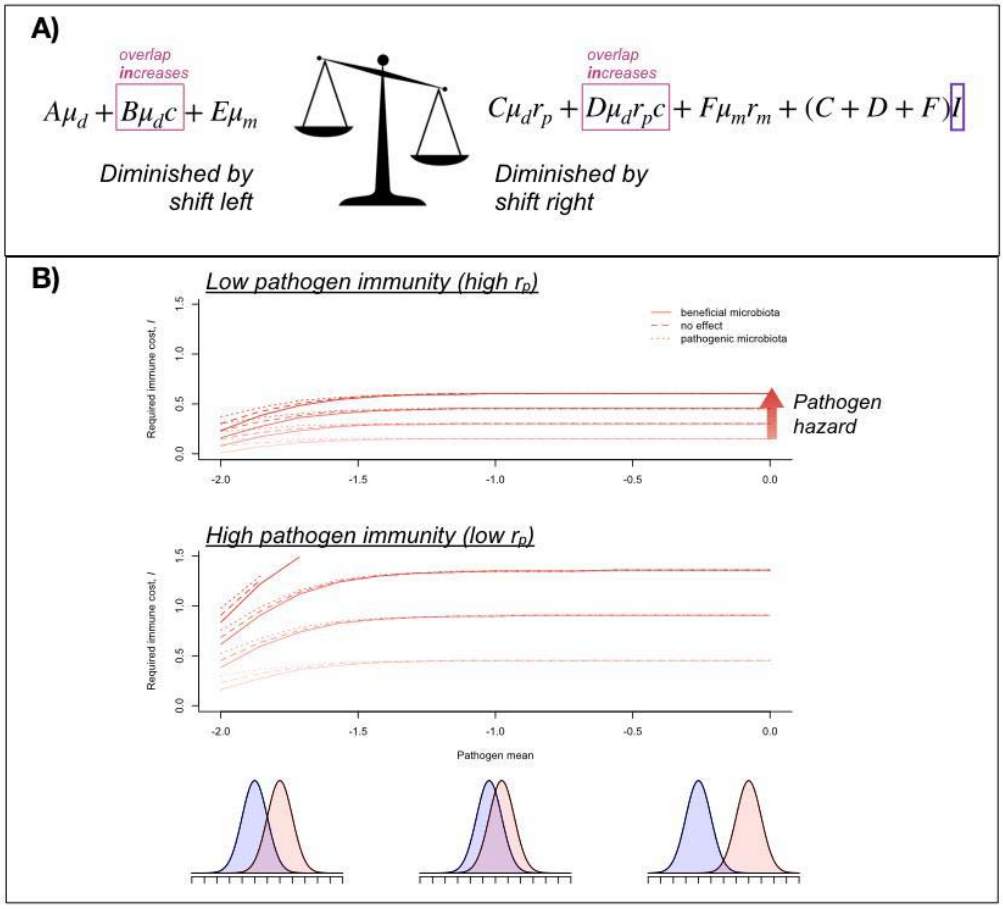

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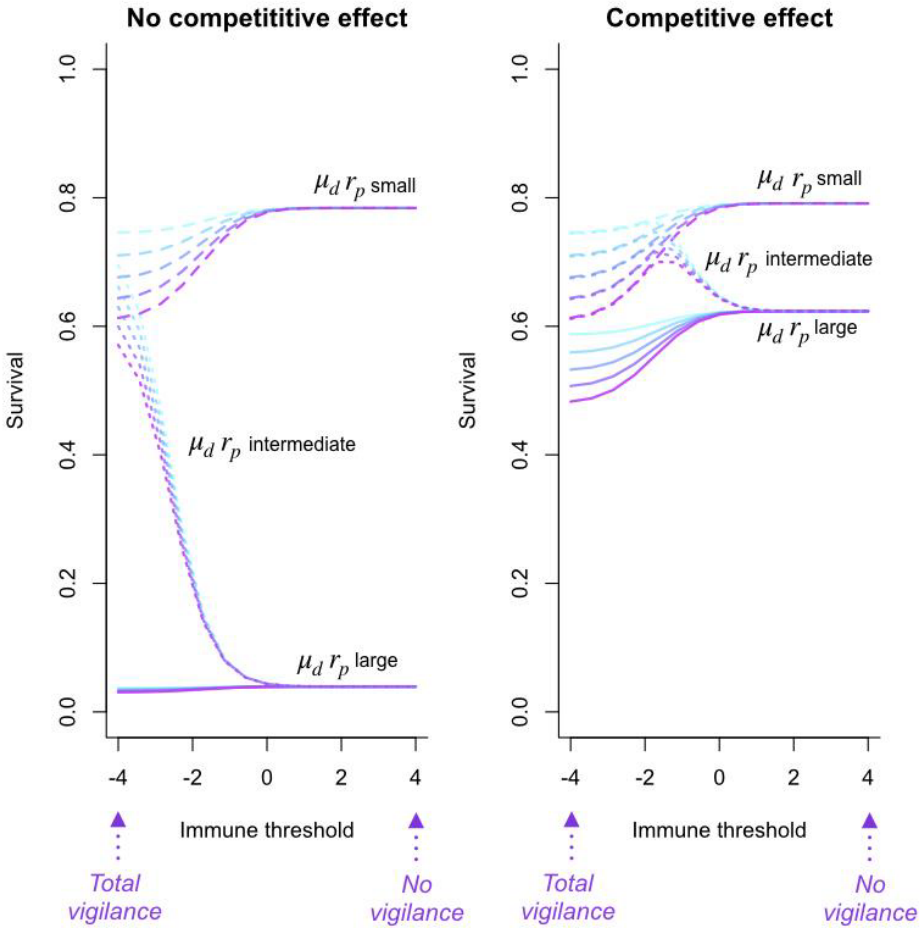
Figure 4: Effect of competition on survival (y axis) across a range of immune thresholds (x axis) in the absence (left, $c = 1$) and presence (right, $c = 0$) of competition for different combinations (text, line types) of the product of pathogen mortality ($\mu_d = 0.01$ or $\mu_d = 3$) and immune effectiveness ($r_p = 0.01$ or $r_p = 1$) for different costs of immunity ($I = 0.1$ to 0.2, light blue is the lowest cost, and purple is the highest cost, corresponding to the greatest reduction in survival). The presence of competition increases survival (right hand plot vs. left), but also can qualitatively change the outcome of selection on immune vigilance. For large pathogen mortality / low immune effectiveness (solid line) the outcome switches from close to no directional selection on vigilance to clear selection for no vigilance, while for intermediate pathogen mortality / immune effectiveness, selection shifts from favouring complete vigilance to intermediate vigilance.



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