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Review Article

Optimal immune defence in the light of variation in lifespan

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SUMMARY

There is good evidence for costs to both the uses of immune defences and their development and maintenance. The optimal defence will be a balance of these costs with the risk of infection and the virulence of the disease. It is therefore clear that the life-history characteristics of both host and parasite will impact the optimal level of defence, and that this may in part explain the variation in immune defence against different pathogens and parasites. For instance, it has traditionally been suggested that long-lived hosts should invest in immune memory. Ecological evolutionary theory can be used to examine in detail how different host characteristics will affect the optimal immune response that evolves. Here, we review theoretical studies on the impact of host lifespan on various immune defence characteristics including acquired immunity and highlight the importance of population-level epidemiological feedbacks on the outcome. In particular, we discuss when longer-lived hosts may invest less in acquired immunity and develop new theory to highlight the importance of the mechanism of host population regulation to the outcome. We finish by discussing where more theory is needed and how comparative and experimental studies may test the theory.

Keywords *costs, ecological feedbacks, evolutionary game theory, immunity, models, theory*

INTRODUCTION

Parasites and pathogens are ubiquitous and by definition harm the individuals that they infect. As a consequence, a wide range of constitutive and induced, innate as well as adaptive, defence mechanisms, ranging from behavioural avoidance and mechanical barriers to complex humoral and cellular immune systems, have evolved (1, 2). However, these responses are far from uniform. There is considerable variation between individuals in their immune investment, and more broadly hosts respond very differently to their various diseases (1, 2). This is perhaps particularly noticeable in terms of whether long-lasting immune memory occurs to different diseases in vertebrates. Life-long immunity is far from the normal outcome of recovery with partial and/or waning immune memory found in response to many infectious diseases, such as syphilis, while no immune memory occurs to other infections, such as rotaviruses and many bacterial infections of humans (1, 2). These outcomes may be considered as failures of the immune system, but the burgeoning evolutionary immunity research community has shown the importance of understanding both the level and the type of immune investment as an intrinsic outcome of the ecological and evolutionary interactions between the host and the infectious organism (1–3). From this point of view, we need to understand the considerable variation in immune investment in the context of both the overall fitness of the host and the population-level impacts of immunity. The ecological/epidemiological impacts of immunity may be critical as they feed back into the evolution of host defence. In particular, investment in immunity will tend to reduce the prevalence of disease, thereby reducing the risk of infection and as a consequence the relative importance of investment in stronger immunity. As such, infection risk is a result of the dynamics of the host–parasite interaction and it is the nature of these interactions that define the benefits of different immune strategies.

A key epidemiological driver of immune memory is the chance of future exposure to the same infection and as such, host lifespan has been discussed as a key driver of immune investment within the evolution of life-history literature (4–6). Within this conceptual framework, it is often argued longer-lived species should invest more in

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acquired immunity while shorter-lived species should invest more in innate relative to acquired immunity (7). There are a number of empirical studies in vertebrates that have looked for evidence for this pace of life hypothesis including meta-analyses (8, 9) and single studies with both non-specific (10–12) and specific challenges and/or immune measures (13–17). When the more specific challenges or measures are used, evidence for the pace of life hypothesis is often found (14–16). While the acquired immune system of vertebrates is well studied, a traditional view is that vertebrates have evolved immune memory in part due to their relatively long lifespans. However, it is becoming increasingly apparent that in invertebrates, previous exposure to parasites can also lead to increased protection on subsequent challenge (18–20). Furthermore, there are many vertebrate and invertebrate host–parasite interactions where long-lived hosts do not acquire long-lived immunity (1, 2). Ecoevolutionary theory has been recently developed with a focuss on understanding the impact of the interactions between individual life-history characteristics such as lifespan and ecological dynamics on the evolutionarily optimal outcome. Here, we review the insights of this theory on the implication of host lifespan into the evolution of immunity.

Fundamental to the idea that there is an optimal level of defence is that there are costs to defence. It is now clear that there may be costs through either the use of the defence mechanisms (21–26) or through the costs of their development and maintenance in the absence of infection (27–30). For example, the activation of the immune system following challenge with a pathogen has been shown to be costly (25, 31, 32), and much of the virulence of many diseases may be due to some form of such immunopathology (22, 26, 33). However, it is the costs of having a strong immune system in the absence of disease that is critical to determining the optimal level of defence. Such evolutionary constitutive costs to high immune defence have been demonstrated directly using selection experiments in a number of systems (27–30), and it is clear that the nature of these costs may depend on the host environment (34). Constitutive costs may be manifested in other life-history traits such as slower development rates (27, 34) or decreased competive ability (29) or through trade-offs between different components of defence (2). When defence against infectious disease is costly, not only is there an optimal level of defence, but the level of immunity is a fundamental component of the life histoy and fitness of the host. Such evolutionary costs may also help to generate and maintain the considerable variation in the level of defence within host populations seen in nature (32, 35–38). Ecoevolutionary theory has been developed to allow us to understand the factors that lead to different levels of investment in different forms of defence.

In addition to the importance of costs in the immune system, there are also likely to be important ecological feedbacks to the evolution of defence against infectious organisms. Ecological feedbacks result from the impact that changes in defence have on the epidemiology of the disease that in turn feed back to influence the evolution of defence. Intuitively, the level of the defence invested in by hosts will affect the prevalence of the parasite in the population. Because this prevalence defines the risk that an individual will be challenged, it influences the selection pressure for defence in the first place. For example, consider a mutation that reduces the chance that an individual becomes infected in the first place, but this defence is costly such that it is traded off against another component of the hosts life history (for example, higher defence results in a slower development time and therefore a lower rate of reproduction). If the benefits of this costly resistance in terms of a reduced risk of infection is relatively high, the cost is worth paying and the mutation will spread through the population. However, as the frequency of the resistance allele increases in the population, more individuals are resistant to infection leading to a lower prevalence of the infectious disease in the population. Because the prevalence is lower, there is less selective advantage for the resistant allele. This negative frequency-dependent selection results from the feedback between the ecological dynamics (the prevalence) and the evolutionary ones (the spread of costly resistance genes). Any defence mechanism that reduces the prevalence of the parasite (e.g. avoiding infection in the first place, recovering more rapidly from infection or controlling the growth rate of the parasite within the host) leads to this form of feedback. Furthermore, as these defence mechanisms reduce the parasites prevalence, they also reduce parasites fitness and are therefore classified as forms of resistance (39–42). In contrast, a defence mechanism that ameliorates the damage that a parasite causes its host, such that it reduces an individuals disease-induced mortality, will lengthen the infectious period of the parasite. As such, this type of defence mechanism increases parasites prevalence as it spreads through the host population, leading to positive frequency dependence. This form of defence is known in the evolutionary literature as tolerance (39–42), and due to its different ecological feedback, it leads to very different evolutionary outcomes (39, 42, 43).

The contrasting ecological feedbacks between resistant and tolerant traits are a fairly intuitive example of the phenomenon. However, as ecological scenarios become more complex with, for example, multiple infections, different transmission functions or long-lasting acquired immunity, the ecological feedbacks in turn become complex and less straightforward to understand intuitively.

Formal theory, is then useful in order to make predictions on the impact of different biological mechanisms to the evolution of defence and to guide our understanding of the processes that underlie these predictions.

THEORY

One of the main reasons for developing a mathematical model is that it clearly defines the processes that we are considering and the ones that we are not. Using these models, we can define a number of different mechanisms of host defence from their impact on the epidemiology of the disease. Consider a general infectious disease model

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + (1-\nu)\gamma I + \delta R \quad (1)$$

$$\frac{dI}{dt} = \beta SI - (\alpha + b + \gamma)I \quad (2)$$

$$\frac{dR}{dt} = \nu\gamma I - (b + \delta)R \quad (3)$$

that compartmentalizes a host population into densities of susceptibles, S, infecteds, I and immunes, R and where the dynamics of these densities and hence the total host density, given by $H = S + I + R$, are described by nonlinear ordinary differential equations. All parameters are non-negative and $\nu \in [0,1]$. Hosts produce susceptible offspring at rate a that is limited by intraspecific crowding, q, so that the carrying capacity is given by $K = (a - b)/q$. Hosts die at natural death rate b. Transmission of infections is a mass action process between susceptible and infected types, with transmission coefficient β, and infected hosts suffer additional disease-induced mortality (virulence) at rate α. Infected hosts recover at rate γ, and a proportion ν of these individuals become immune to the pathogen while the remaining individuals return to a susceptible state. Recovered hosts lose immunity at rate δ. This general model form can capture a wide range of classical infectious scenarios. For example, if $\nu = 0$ (or $\delta = \infty$), the model represents a susceptible–infected–susceptible (SIS) framework, where there is no immune memory and recovered individuals are completely susceptible to the disease, while if $\delta = 0$, we have the susceptible–infected–removed (SIR) model with lifelong immunity.

The model can be used to investigate a number of different classes of defence based on their epidemiological impacts. The fundamental forms of host defence can be defined as follows: (i) avoidance reduces the probability of becoming infected, and resistant hosts therefore have a lower transmission rate (β), (ii) recovery increases the rate of clearance of infection (γ), whereas (iii) tolerance reduces virulence (α). Finally, acquired immunity evolves as either (iv) a higher probability of acquiring immunity (ν) or (v) a lower rate of loss of immunity (δ).

The costs associated with defence can either be due to trade-offs with other defence mechanisms or through other determinants of fitness in the host. Trade-offs within the immune system can be examined by correlations within defence traits such that, for example, high avoidance results in lower recovery, $\beta = f(\gamma)$. However, there is relatively little theory on optimal levels of defence given trade-offs between different immune components (44), with most of the work focused on constitutive costs manifested in other components of the host life history (35, 44–49). Generally, the costs are assumed to be manifested in the rate of reproduction, a, which includes both the number of offspring produced and the rate of maturation. As such, there are a wide range of mechanisms that may underpin these costs.

The theoretical approach of evolutionary invasion analysis is useful when we want to examine evolutionary dynamics in response to ecological feedbacks. In Box A, the mathematical details of this approach are outlined in the context of the evolution of acquired immunity. It is assumed that traits are continuous and that the level of immunity is determined due to the action of many alleles at many loci. This type of modelling is therefore less appropriate when there are major genes that encode for large changes in immune responses. When we use mathematical analysis to predict the outcome, we also assume that evolution proceeds through rare mutations of small effect. However, the robustness of the predictions of the theory to a relaxation of this assumption can be examined through simulation. In this analysis, we vary parameters such as host lifespan and predict the optimal investment in different types of immunity – for example, avoidance and recovery – given different ecological scenarios. For this reason, it is an appropriate theoretical framework in which to address our question of how host lifespan should impact on optimal investment in defence.

Using the approach outlined in Box A for the evolution of immunity, Miller *et al.* (50) investigated the evolution of resistance traits in the general model of host–parasite dynamics given by equations 1–3. They showed that longer-lived individuals relying only on innate immunity to defend against parasites do generally invest more in immunity as increased lifespan often leads to higher disease prevalence. The first take-home message of this paper and indeed a number of other theoretical papers whose focus was not just on the impact of host lifespan (35, 44–49) is that longer-lived hosts should invest more in innate immunity. It is interesting to reflect on this result in the context of the generally held idea that immune memory is selected for in longer-lived hosts. The theory tells us that longer lifespans promote more immune investment in organisms that only have innate immunity.

Box A: Adaptive dynamics of acquired immunity

Model 1: Evolution of probability of clearance to immunity (ν),

$$\nu = f(a) \text{ with } \frac{d\nu}{da} < 0 \text{ under SIR dynamics}, \delta = 0 \quad (A.1)$$

Model 2: Evolution of waning immunity (δ),

$$\delta = g(a) \text{ with } \frac{d\delta}{da} > 0 \text{ under SIRS dynamics}, \nu = 1 \quad (A.2)$$

A criteria for a successful mutant invasion of a resident population is that the average change in the mutant population per invader is positive,

$$\theta = \rho_s T_s + \rho_I T_I + \rho_R T_R > 0, \quad (A.3)$$

where ρ_i is the per capita growth rate of mutant hosts (i.e. hosts with trait $\nu_m(a_m)$ in model 1 and $\delta_m(a_m)$ in model 2), when an individual mutant, whose epidemiological state is given by i, invades a population consisting solely of individuals with the resident trait. T_i is the average time spent by the mutant in state i.

The invasion criteria given by equation A.3 is a proxy for invasion fitness when it involves only growth rates from an invader who has entered class i for the first time (43). The proxy can be used to assess evolutionary behaviour in both model 1 and model 2.

Applying the methods of adaptive dynamics (53, 54), which assumes monomorphic trait distributions and small mutations, the evolutionary dynamics of models 1 and 2 can be analysed. This approach assesses properties of the fitness of a new mutant strain attempting to invade a resident population at its dynamic attractor.

From the invasion fitness, it is possible to determine the position (located at the zeros of the fitness gradient) and nature of evolutionary singularities. A singularity that is both convergence stable (CS, i.e. the population evolves towards the singularity) and evolutionary stable (ES, that is, a population in the vicinity of the singularity cannot be invaded) is known as a continuously stable singular strategy [CSS, (55)].

Here, we consider only trade-offs with a suitable (accelerating) cost structure to ensure that the singularity is a CSS. We examine how the position of the CSS, and hence the level of optimal immunity, varies with model parameters.

Once the host has the potential for immune memory, the relationship between investment in immunity and lifespan becomes more complicated. Firstly, once there is immune memory investment in the components of innate immunity no longer necessarily increases with lifespan. When there is long-lived acquired immunity, investment in avoidance tends to increase with investment initially, but in very long-lived hosts, investment may fall to low levels (50) fig. 2A,D and an earlier paper van Boven and Weissing (51) that examined some of the same questions in a different framework fig. 5). A similar pattern can be observed for both recovery and tolerance [see (50) fig. 3B,D, although for some parameter combinations, investment increases with lifespan see (50) fig. 3A,C and (51) fig. 3 and 4)]. These results can be understood due to the effects of immune individuals on the prevalence of the disease: immune individuals may lead to lower prevalence and therefore less investment in other components of the immune system. It must also be borne in mind that long-lived individuals bear the costs of higher investment in immunity over their relatively longer lifespan.

Perhaps the key results of the (50) paper were found when they considered the investment in immune memory itself. In the case of acquired immunity, there are two traits that can be considered as measures of the investment in immunity. The first of these is the propensity to acquire immune memory in the first place. A second trait is how long immune memory lasts before individuals revert to susceptibility. Miller *et al.* (50) showed that there is a distinction between the effects of lifespan on optimal immune investment in acquired immunity measured in these two ways. For clarity, we repeat and extend the analysis of Miller *et al.* (50) here (Figure 1). Investment in the rate of waning immunity always increases with host lifespan (Figure 1c). As such, immune memory is

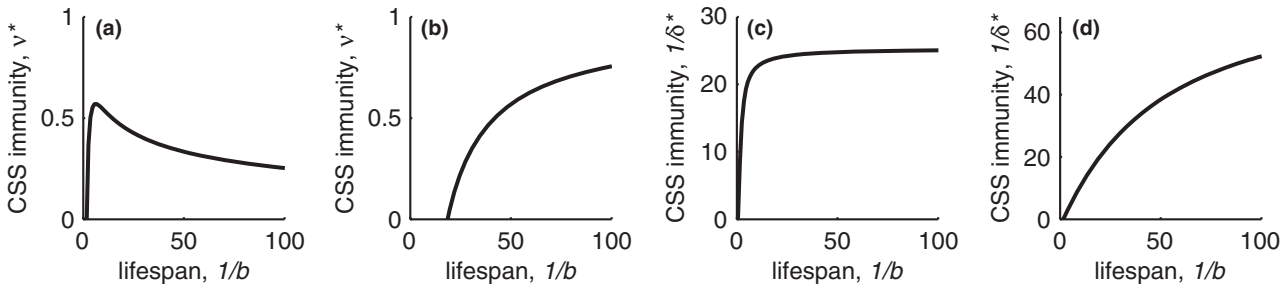

Figure 1 The results of the mathematical models described in the text that predict the optimal investment in immunity against lifespan under different assumptions of density dependence in the hosts. In (a) and (b) – evolution of the probability of acquiring immunity, v^* against host lifespan where in (a), regulation of host population occurs through host self-regulation ($q = 0{\cdot}02$), and in (b), where there is no density dependence in the host and regulation only occurs through the pathogen ($q = 0$). In (c) and (d) – evolution of waning immunity, δ^* against host lifespan where in (c), regulation of host population occurs through host self-regulation ($q = 0{\cdot}02$), and in (d), there is no density-dependent self-regulation in the host ($q = 0$). The figures presented in (a) and (c) are reproductions of Miller *et al.* (50) using alternative trade-offs and parameter values. The trade-off and parameter values for evolution of the probability of acquiring immunity, v^*, were $\nu = 1 - a^4/2^4$ and $\alpha = 5$, $\gamma = 1$, $\beta = 1$ in (a) and $\nu = 1 - a^4/1^4$ and $\alpha = 10$, $\gamma = 0{\cdot}15$, $\beta = 1$ in (b). The trade-off and parameter values for evolution of waning immunity, δ^*, were $1/\delta = 100 - 100\,a^4/2^4$ and $\alpha = 5$, $\gamma = 1$, $\beta = 1$ in (c) and $1/\delta = 100 - 100\,a^4/1^4$ and $\alpha = 10$, $\gamma = 0{\cdot}15$, $\beta = 1$ in (d).

predicted to last longer in longer-lived organisms. However, optimal investment in the probability of clearance to immunity is maximal for an intermediate lifespan (Figure 1a). This is a critical result as it shows that investment in acquiring immunity in the first place is not selected for by longer lifespans. We now develop some more general theory in order to highlight how epidemiological feedbacks drive this result.

Miller *et al.* (50) assumed that there was density dependence in the host population such that it is self-regulating ($q > 0$ in equations 1–3) and discussed that this may be critical to their key result that optimal probability of acquiring immunity, ν^*, is maximal for an intermediate lifespan when immunity is permanent, see Figure 1(a). van Boven and Weissing (51) also speculated on the importance of such density dependence and stated that determining the evolution of immunity when the host is not self-regulated is an open question. Here, we examine this question in detail and use models to explain the processes that underpin the results. When there is no density dependence in the host population ($q = 0$ *in* equations 1–3), it can be shown analytically that the optimal probability of acquiring immunity, ν^* always increases with lifespan, see Figure 1(b). Therefore, the additional population feedback generated by intra-specific crowding has a significant qualitative impact on how the optimal probability of acquiring immunity varies with lifespan. In Box B, we present an analytical exploration of the conditions leading to decreasing optimal acquired immunity with increasing lifespan.

Biologically, increasing lifespan results in an increasing total host density. When $q > 0$ this brings the system closer to carrying capacity and hence reduces net births that in turn lowers equilibrium prevalence given by,

$$\frac{I}{H} = \frac{1}{\alpha}(\alpha - qH - b) \tag{4}$$

The lower prevalence that results selects for decreased acquired immunity. But there is always a further selective pressure for increased immunity due to the increased exposure to infection that longer lifespan entails. When lifespan is sufficiently long, the former pressure dominates the latter. Thus, investment in the probability of acquiring immunity is increasing for lower lifespans and decreasing for higher lifespans, see Figure 1(a). When $q = 0$ and the host population is regulated by the infection, the prevalence no longer decreases with increasing host density and therefore optimal immunity can only increase with host lifespan, see Figure 1(b).

When it is the length of immunity that evolves (the rate of waning immunity, δ^*) against host reproduction, optimal investment has a similar form to equation B.1. Here too, total host density increases with lifespan leading to a decrease in prevalence when $q > 0$. However, in this model, exposure to the infection increases more rapidly with increasing lifespan because this time, immunity is not permanent. Thus, the selection for increased immunity is far stronger in this model. This effect dominates the selective pressure for decreasing investment from the prevalence feedback, and hence, optimal investment in immunity increases with lifespan, see Figure 1(c). The results presented here [and in van Boven and Weissing (51) and Miller *et al.* (50)] show that investment in immunity has a complex relationship with lifespan. In particular, density-dependent demography that limits the host turnover and therefore impacts on prevalence can lead to a reduction in investment in immunity as host lifespan increases.

Box B: Density dependence and optimal probability of acquiring immunity, ν*

Evolutionary invasion analysis of the probability of acquiring immunity in the SIR model [i.e. equations 1–3 with $\delta = 0$, $\nu = \nu(a)$] indicates that the trait will evolve in the direction of the fitness gradient until,

$$\frac{\partial \nu(a^*)}{\partial a} = -\frac{1}{L\alpha\gamma}\left(\frac{I^*}{H^*}\right)^{-2}, \tag{B.1}$$

where a^* denotes reproductive rate on the evolutionary attractor, and $L = 1/b$ is a measure of host lifespan. We assume costly immunity ($\nu(a)$ is a decreasing function of a) and accelerating costs (in order to ensure the singularity is a CSS).

Equation B.1 identifies the singular strategy by giving the value of the slope of the tangent to the trade-off curve at the singularity, see figure B1. It is composed of a term that depends directly on lifespan and a term that depends on equilibrium prevalence (the term in brackets, I/H) that can indirectly depend on lifespan.

Equation B.1 implies that high equilibrium prevalence selects for high acquired immunity, ν. Also, in the absence of the ecological feedback (i.e. holding prevalence constant so that only the lifespan term varies), longer lifespan selects for increased immunity.

The effect of increasing host lifespan is a balance of these selective pressures (i.e. the selective pressure through the lifespan term and the selective pressure through the prevalence term), resulting in increasing optimal immunity when the selective pressures are in agreement ($\partial/\partial L(I^*/H^*) > 0$) and potential for decreasing immunity with lifespan when the selective pressures are in opposition ($(\partial/\partial L(I^*/H^*) < 0$). Therefore, a necessary (but not sufficient) condition for decreasing immunity with increasng lifespan is

$$\frac{\partial}{\partial L}\left(\frac{I^*}{H^*}\right) = \frac{\partial a^*}{\partial L} - q\frac{\partial H^*}{\partial L} + \frac{1}{L^2} < 0, \tag{B.2}$$

where prevalence at equilibrium is given by equation 4.

When $q = 0$, equation B.2 can only hold when $\partial a^*/\partial L < 0$, and hence, investment in immunity always increases with lifespan. Because total host density increases with increasing host lifespan, the term $q\partial H^*/\partial L$ in equation B.2 contributes to a decrease in prevalence but only when $q > 0$. Therefore, once intraspecific crowding limits host reproduction, prevalence can decrease with lifespan leading to a selective pressure for decreasing immunity.

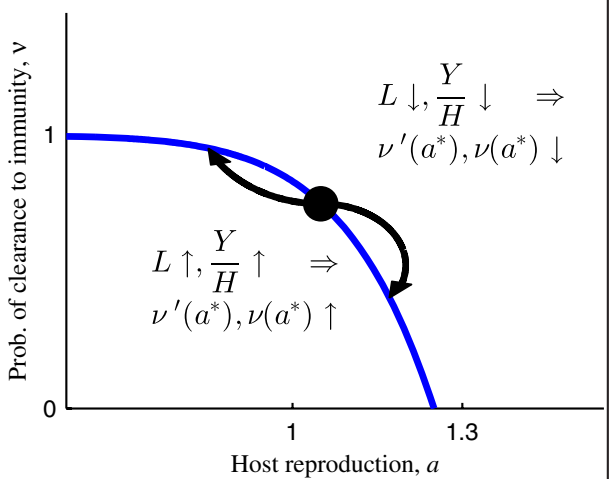

Figure B1 The trade-off between host reproduction, a, and probability of clearance to immunity, ν.

PARASITE 'LIFESPAN'

Clearly therefore, the lifespan of the host is important to the optimal immune defence, but what can we say about the lifespan of the parasite? The lifespan of macroparasitic worms are likely to have an impact on the optimal level of immunity, but there is, however, very little theoretical work that considers the impact of macroparasites on optimal immune investment. In one sense, however, the lifespan of microparasites (pathogens such as viruses, bacteria etc.) can be considered to be the infectious period, which is determined by a combination of the recovery rate and the host death rate due to infection (virulence). Clearly, these two parameters are influenced by both the host and the parasite, but a useful simplification is that the recovery rate is a host trait while virulence can be defined as a parasite trait (52). From this point of view, acute parasites with a short lifespan have a high virulence while chronic long-lived parasites have a low virulence. Generally, the highest level of immunity will be invested against parasites with intermediate virulence (43, 48). In this sense, parasites of intermediate lifespan promote the highest investment in immunity in their hosts. This is intuitively straightforward to under-

stand. Chronic parasites causing low virulence are relatively harmless to individuals, and therefore, there is less selection for costly immunity. Highly pathogenic acute parasites are dangerous to individuals, but the prevalence of the disease in the population reduces at higher virulence (due to their short infectious period). Generally, therefore, low virulence results in a high risk of challenge with disease but a low-impact infection, while high virulence has a high individual impact on fitness but there is a relatively low risk of challenge. As such, intermediate virulence leads to the greatest combination of risk of exposure and fitness reduction and therefore the highest investment in costly immunity. From this perspective, parasites of intermediate life-span promote the highest investment in immunity.

DISCUSSION

The existing models have therefore given us some important insights into the impact of host and parasite lifespan on investment in immunity. Like all models, they are wrong. The models make simplifying assumptions and by definition look at particular epidemiological processes. This is the key strength of simple models: they make the assumptions we are making in our arguments on optimal immune investment explicit. As discussed previously, it has been classically assumed that longer-lived organisms should be selected to invest in long-lived immune memory. The explicit theory that we have discussed has shown that the outcome is more nuanced, and in many situations, immune memory is optimized at intermediate lifespans. However, the classical verbal arguments may implicitly assume a number of different mechanisms while the theory that we have reviewed makes very general explicit assumptions. In particular, the current theory assumes that hosts are faced with an endemic disease. If in contrast organisms are faced with recurring epidemics, the impact of being a longer-lived host and therefore being subject to repeated epidemics are potentially considerable. The theory should therefore be extended to examine the impact of epidemic pathogens. Furthermore, the theory has made the assumption that hosts are faced with one genetically identical infectious disease agent. Clearly, a longer-lived organism faced with multiple pathogens or multiple strains of the same pathogen is more likely to face the same pathogen/strain repeatedly than a short-lived organism. It is therefore important to examine theoretically the impact of longevity on investment in immune defence in the face of multiple and/or diverse pathogens. These are just two of a number of possible important extensions of the theory that would help us to gain a better understanding of the role of host lifespan on the optimal level of immune investment. Furthermore, the burgeoning empirical literature on the impact of lifespan on immune function (10–12, 9, 14–16) is creating an exciting opportunity to link the theory more directly to empirical results, driving both the theory and experimental tests of the theory. The current work emphasizes that it is important to develop explicit theory in the face of potentially complex ecological feedbacks that define optimal immunity.

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REFERENCES

1 Frank SA. *Immunology and Evolution of Infectious Disease*. Princeton, Princeton University Press, 2002.
2 Schmid-Hempel P. *Evolutionary Parasitology*. Oxford, Oxford University, 2011.
3 Viney ME, Riley EM & Buchanan KL. Optimal immune responses: immunocompetence revisited. *Trends Ecol Evol* 2005; **20**: 665–669.
4 Norris K & Evans MR. Ecological immunology: life history trade-offs and immune defense in birds. *Behav Ecol* 2000; **11**: 19–26.
5 Ricklefs RE & Wikelski M. The physiology/life-history nexus. *Trends Ecol Evol* 2002; **17**: 462–468.
6 Zuk M & Stoehr AM. Immune defense and host life history. *Am Nat* 2002; **160**: S9–S22.
7 Lee KA. Linking immune defenses and life history at the levels of the individual and the species. *Integr Comp Biol* 2006; **46**: 1000–1015.
8 Tella JL, Scheuerlein A & Ricklefs RE. Is cell-mediated immunity related to the evolution of life-history strategies in birds? *Proc Biol Sci* 2002; **269**: 1059–1066.
9 Versteegh MA, Schwabl I, Jaquier S & Tieleman BI. Do immunological, endocrine and metabolic traits fall on a single Pace-of-Life axis? Covariation and constraints among physiological systems. *J Evol Biol* 2012; **25**: 1864–1876.
10 Ardia DR. Individual quality mediates trade-offs between reproductive effort and immune function in tree swallows. *J Anim Ecol* 2005; **74**: 517–524.
11 Lee KA, Wikelski M, Robinson WD, Robinson TR & Klasing KC. Constitutive immune defences correlate with life-history variables in tropical birds. *J Anim Ecol* 2008; **77**: 356–363.
12 Tieleman BI, Williams JB, Ricklefs RE & Klasing KC. Constitutive innate immunity is a component of the pace-of-life syndrome in tropical birds. *Proc Biol Sci* 2005; **272**: 1715–1720.
13 Addison B, Klasing KC, Robinson WD, Austin SH & Ricklefs RE. Ecological and life-history factors influencing the evolution of maternal antibody allocation: a phylogenetic comparison. *Proc Biol Sci* 2009; **276**: 3979–3987.
14 Garnier R, Ramos R, Staszewski V, *et al.* Maternal antibody persistence: a neglected life-history trait with implications from albatross conservation to comparative immunology. *Proc Biol Sci* 2012; **279**: 2033–2041.

15 Martin LB, Weil ZM & Nelson RJ. Immune defense and reproductive pace of life in Peromyscus mice. *Ecology* 2007; **88**: 2516–2528.
16 Previtali MA, Ostfeld RS, Keesing F, Jolles AE, Hanselmann R & Martin LB. Relationship between pace of life and immune responses in wild rodents. *Oikos* 2012; **121**: 1483–1492.
17 Russo J & Madec L. Linking immune patterns and life history shows two distinct defense strategies in land snails (Gastropoda, Pulmonata). *Physiol Biochem Zool* 2013; **86**: 193–204.
18 Little TJ, OConnor B, Colegrave N, Watt K & Read AF. Maternal transfer of strain-specific immunity in an invertebrate. *Curr Biol* 2003; **13**: 489–492.
19 Moret Y & Siva-Jothy MT. Adaptive innate immunity? Responsive-mode prophylaxis in the mealworm beetle, *Tenebrio molitor*. *Proc R Soc London B Biol Sci* 2003; **270**: 2475–2480.
20 Tidbury HJ, Pedersen AB & Boots M. Within and transgenerational immune priming in an insect to a DNA virus. *Proc Biol Sci* 2011; **278**: 871–876.
21 Bonneaud C, Mazuc J, Gonzalez G, *et al.* Assessing the cost of mounting an immune response. *Am Nat* 2003; **161**: 367–379.
22 Graham AL, Allen JE & Read AF. Evolutionary causes and consequences of immunopathology. *Annu Rev Ecol Evol Syst* 2005; **36**: 373–397.
23 Klasing KC. Nutritional modulation of resistance to infectious diseases. *Poult Sci* 1998; **77**: 1119–1125.
24 Lochmiller RL & Deerenberg C. Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos* 2000; **88**: 87–98.
25 Moret Y & Schmid-Hempel P. Survival for immunity: the price of immune system activation for bumblebee workers. *Science* 2000; **290**: 1166–1168.
26 Sadd BM & Siva-Jothy MT. Self-harm caused by an insects innate immunity. *Proc Biol Sci* 2006; **273**: 2571–2574.
27 Boots M & Begon M. Trade-offs with resistance to a granulosis-virus in the indian meal moth, examined by a laboratory evolution experiment. *Funct Ecol* 1993; **7**: 528–534.
28 Fuxa JR & Richter AR. Reversion of resistance by *Spodoptera-frugiperda* to nuclear polyhedrosis-virus. *J Invertebr Pathol* 1989; **53**: 52–56.
29 Kraaijeveld AR & Godfray HCJ. Trade-off between parasitoid resistance and larval competitive ability in *Drosophila melanogaster*. *Nature* 1997; **389**: 278–280.
30 McKean KA, Yourth CP, Lazzaro BP & Clark AG. The evolutionary costs of immunological maintenance and deployment. *BMC Evol Biol* 2008; **8**: 76.
31 Armitage SAO, Thompson JJW, Rolff J & Siva-Jothy MT. Examining costs of induced and constitutive immune investment in *Tenebrio molitor*. *J Evol Biol* 2003; **16**: 1038–1044.
32 Schmid-Hempel P. Variation in immune defence as a question of evolutionary ecology. *Proc R Soc London B Biol Sci* 2003; **270**: 357–366.
33 Long GH & Boots M. How can immunopathology shape the evolution of parasite virulence? *Trends Parasitol* 2011; **27**: 300–305.
34 Boots M. The evolution of resistance to a parasite is determined by resources. *Am Nat* 2011; **178**: 214–220.
35 Boots M & Haraguchi Y. The evolution of costly resistance in host-parasite systems. *Am Nat* 1999; **153**: 359–370.
36 Frank SA. Ecological and genetic models of host pathogen coevolution. *Heredity* 1991; **67**: 73–83.
37 Frank SA. Evolution of host-parasite diversity. *Evolution* 1993; **47**: 1721–1732.
38 Juneja P & Lazzaro BP. Population genetics of insect immune responses. In Rolff J, Reynolds CS (eds): *Insect Infection and Immunity: Evolution, Ecology and Mechanisms*. Oxford, Oxford University press, 2009: 206–224.
39 Miller MR, White A & Boots M. The evolution of parasites in response to tolerance in their hosts: the good, the bad, and apparent commensalism. *Evolution* 2006; **60**: 945–956.
40 Raberg L, Graham AL & Read AF. Decomposing health: tolerance and resistance to parasites in animals. *Philos Trans R Soc Lond B Biol Sci* 2009; **364**: 37–49.
41 Restif O & Koella JC. Concurrent evolution of resistance and tolerance to pathogens. *Am Nat* 2004; **164**: E90–E102.
42 Roy BA & Kirchner JW. Evolutionary dynamics of pathogen resistance and tolerance. *Evolution* 2000; **54**: 51–63.
43 Boots M & Bowers RG. Three mechanisms of host resistance to microparasites-avoidance, recovery and tolerance – show different evolutionary dynamics. *J Theor Biol* 1999; **201**: 13–23.
44 Best A, White A & Boots M. Maintenance of host variation in tolerance to pathogens and parasites. *Proc Natl Acad Sci USA* 2008; **105**: 20786–20791.
45 Antonovics J, Boots M, Abbate J, Baker C, McFrederick Q & Panjeti V. (2011). Biology and evolution of sexual transmission. Evolution of Infectious Agents in Relation to Sex. A. Nahmias, D. Danielsson and S. B. Nahmias. 1230: 12–24.
46 Best A, White A & Boots M. Resistance is futile but tolerance can explain why parasites do not always castrate their hosts. *Evolution* 2010; **64**: 348–357.
47 Boots M, Best A, Miller MR & White A. The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Philos Trans R Soc Lond B Biol Sci* 2009; **364**: 27–36.
48 Boots M & Bowers RG. The evolution of resistance through costly acquired immunity. *Proc R Soc London B Biol Sci* 2004; **271**: 715–723.
49 Boots M, White A, Best A & Bowers R. The importance of who infects whom: the evolution of diversity in host resistance to infectious disease. *Ecol Lett* 2012; **15**: 1104–1111.
50 Miller MR, White A & Boots M. Host life span and the evolution of resistance characteristics. *Evolution* 2007; **61**: 2–14.
51 van Boven M & Weissing FJ. The evolutionary economics of immunity. *Am Nat* 2004; **163**: 277–294.
52 van Baalen M. Coevolution of recovery ability and virulence. *Proc R Soc London B Biol Sci* 1998; **265**: 317–325.
53 Geritz SAH, Kisdi E, Meszena G & Metz J. Evolutionary singular strategies and the adaptive growth and branching of the evolutionary tree. *Evol Ecol* 1998; **12**: 35–57.
54 Metz JAJ, Geritz SAH, Meszena G, Jacobs FJA & Heerwaarden JSV. Adaptive dynamics: a geometrical study of the consequences of nearly faithful reproduction. In Van Strien SJ, Verduyn LS (eds): *Stochastic and Spatial Structures of Dynamical Systems*. Amsterdam, Elsevier, 1996: 183–231.
55 Eshel I. Evolutionary and continuous stability. *J Theor Biol* 1983; **103**: 99–111.