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HOST LIFE SPAN AND THE EVOLUTION OF RESISTANCE CHARACTERISTICS

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There is a wide variety of resistance mechanisms that hosts may evolve in response to their parasites. These can be functionally classified as avoidance (lower probability of becoming infected), recovery (faster rate of clearance), tolerance (reduced death rate when infected), or acquired immunity. It is commonly thought that longer lived organisms should invest more in costly resistance. We show that due to epidemiological feedbacks the situation is often more complex. Using evolutionary theory we examine how the optimal investment in costly resistance varies with life span in a broad range of scenarios. In the absence of acquired immunity, longer lived populations do generally invest more in resistance. If hosts have acquired immunity, the optimal resistance may either increase or decrease with increasing life span. In addition, there may be evolutionary bistability with high and low investments in avoidance or tolerance. The optimal investment in the duration of acquired immunity always increases with life span, and due to bistability, shorter lived hosts may commonly not evolve any immunity. In contrast, the optimal investment in the probability of acquiring immunity initially increases and then decreases with life span. Our results have important implications for the evolution of invertebrate and vertebrate immunity, and for the evolution of acquired immunity itself.

KEY WORDS: **Acquired immunity, bistability, evolution, life span, parasites, resistance, tolerance.**

Given the abundance of natural parasites, the ability of an organism to defend against parasitism is an important life-history trait. There is a wide range of theoretical models investigating the evolution of host resistance traits (Antonovics and Thrall 1994; Bowers et al. 1994; van Baalen 1998; Boots and Bowers 1999, 2004; Boots and Haraguchi 1999; Bowers 1999, 2001; Gandon and Michalakis 2000; Roy and Kirchner 2000; Gandon et al. 2002; Restif and Koella 2003; Miller et al. 2005). Much of this work broadly defines "resistance" as any mechanism that inhibits or reduces infection (Antonovics and Thrall 1994; Bowers et al. 1994; Roy and Kirchner 2000; Gandon et al. 2002), whereas mechanisms that offset pathogen damage but do not limit infection are often known as "tolerance" (Boots and Bowers 1999; Roy and Kirchner 2000). Recently, models have also investigated the evolution of mechanisms that increase the rate of clearance of the pathogen (van Baalen 1998; Boots and Bowers 1999), or confer long-lasting acquired immunity (Boots and Bowers 2004). It is also recognized that "true" tolerance, which offsets pathogen damage but does not inhibit pathogen growth, may have different evolutionary dynamics from apparently similar "control" mechanisms that reduce damage by limiting parasite replication within infected hosts (Miller et al. 2005). In these models, the evolution of resistance is typically associated with a fitness cost in terms of other advantageous life-history traits (e.g., fecundity, competitive ability). There are good theoretical reasons to suppose that such costs exist (Roff 1992; Stearns 1992), through mechanistic,

physiological, or genetic causes associated with pleiotropy. Such trade-offs with resistance to parasites have also been demonstrated experimentally (Boots and Begon 1993; Kraaijeveld and Godfray 1997; Fellowes et al. 1998; Webster and Woolhouse 1999).

Because resistance is likely to have costs, there is widespread interest in the conditions under which it will evolve in populations (Zuk and Stoehr 2002; Schmid-Hempel 2003; Schmid-Hempel and Ebert 2003). Obviously, in the absence of parasites, resistance will tend to be selected against, due to the associated fitness cost (Boots and Begon 1993). Even where parasites are endemic, the investment in resistance will depend on the epidemiology of the particular host–parasite interaction, which in turn depends itself on the life histories of hosts and parasites (Zuk and Stoehr 2002). One aspect of life history that has attracted a great deal of recent attention in this context is the life span of the host organism. Shorter lived populations are generally expected to invest relatively less in costly resistance (Medzhitov and Janeway 1997; Rinkevich 1999; Zuk and Stoehr 2002). This is based on the idea that when fitness is correlated with reproduction and/or survival, shorter lived organisms will have a lower mortality cost of parasitism. However, selection for resistance is dependent on both epidemiological and demographic processes. Demographic turnover is lower in long-lived populations, and this may lead to unexpected patterns of selection. In particular, analysis of the basic susceptible-infective-removed (SIR) model has revealed that, under certain conditions, there may be a nonmonotonic relationship between life span and the optimal immune investment (van Boven and Weissing 2004). In addition, there can also be bistability in the evolutionary outcomes (van Baalen 1998; Boots and Bowers 1999; Restif and Koella 2003; van Boven and Weissing 2004), where the level of resistance that actually evolves depends on the initial conditions of the system.

It is therefore important to recognize that the evolution of resistance traits occurs within an adaptive context, which encompasses a dynamic ecological feedback loop. The life histories of the host and pathogen determine the population dynamics, which in turn determine the evolutionarily stable resistance and the evolution of life-history characteristics (Frank 1996; van Baalen 1998; Day and Burns 2003; van Boven and Weissing 2004). We therefore develop fitness expressions depending on both resident and "mutant" strategies, which incorporate the feedbacks between life-history traits and population dynamics. This expression is to determine the evolutionarily stable strategy (ESS; Maynard Smith and Price 1973) that cannot be invaded by any other genotype and also whether this strategy is attainable. In this study, we use this theoretical approach to investigate the conditions under which longer lived host populations will evolve more or less resistance to their parasites and examine a variety of different forms of resistance. Particular emphasis is given to how acquired immunity affects the evolutionary dynamics. We also investigate the evolution of acquired immune memory itself.

Models and Analysis

We consider three types of host–parasite interaction for a directly transmitted microparasite. The first model (I) describes a susceptible-infective-susceptible (SIS) interaction. Infected individuals are able to recover but then immediately return to being susceptible and may be subsequently reinfected. The dynamics are described by the following differential equations:

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + \gamma I \tag{1}$$

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

Here S is the density of susceptible individuals, I is the density of infecteds, and $H = S + I$ is the total population density. The parameter a represents the birth rate, and b is the natural death rate. We assume the population experiences intra-specific crowding that limits its growth rate. For simplicity, density-dependent crowding is assumed to act directly to reduce the birth rate. The severity of crowding is measured by the parameter q, which is related to the carrying capacity, K, by the relationship $K = (a - b)/q$. Susceptibles become infected through contact with infected hosts, at a rate determined by the transmission efficiency, β. Infected hosts have an increased death rate (virulence, α) due to pathogen replication and/or toxicity. Infected hosts are still able to reproduce, and recover at a rate γ.

Model II corresponds to a susceptible-infective-removed-susceptible (SIRS) interaction, in which infected hosts acquire immunity to the disease upon recovery. While immune, hosts do not become infected or transmit the disease to susceptibles. Immunity is lost at a constant rate, δ, whereupon individuals revert to being susceptible. The dynamics are then described by the equations:

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + \delta R \tag{3}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + \gamma + b)I \tag{4}$$

$$\frac{dR}{dt} = \gamma I - (\delta + b)R \tag{5}$$

The third model (III) gives an alternative formulation for an SIRS interaction. We assume that a proportion, v, of recovered hosts acquire permanent immunity, and the remaining proportion, $1 - v$, immediately return to being susceptible. The dynamics are described by the equations

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + (1 - v)\gamma I \quad (6)$$

$$\frac{dI}{dt} = \beta SI - (\alpha + \gamma + b)I \quad (7)$$

$$\frac{dR}{dt} = v\gamma I - bR. \quad (8)$$

Note that in models II and III, the total population density is given by $H = S + I + R$. We investigate the evolution of resistance in these models. We assume resistance evolves through the alternative mechanisms of avoidance, recovery, tolerance, or acquired immunity (Boots and Bowers 2004). "Avoidance" reduces the probability of becoming infected, and resistant hosts therefore have a lower transmission rate (β). "Recovery" increases the rate of clearance (γ), whereas "tolerance" reduces virulence (α) but does not affect the transmission rate. Finally, "acquired immunity" evolves as either a lower rate of loss of immunity (δ), or a higher probability of acquiring immunity (v). The different forms are summarized as follows (where x denotes the host's investment in resistance):

$$\text{Avoidance :} \quad \beta = \beta_1(1 - x)^h + \beta_0 \quad (9a)$$

$$\text{Recovery:} \quad \gamma = \gamma_1 x^h + \gamma_0 \quad (9b)$$

$$\text{Tolerance:} \quad \alpha = \alpha_1(1 - x)^h + \alpha_0 \quad (9c)$$

$$\text{Immunity (model II):} \quad \delta = \delta_1(1 - x)^h + \delta_0 \quad (9d)$$

$$\text{Immunity (model III):} \quad v = v_1 x^h + v_0. \quad (9e)$$

We assume an explicit trade-off such that increased resistance corresponds to a reduction in the intrinsic birth rate of the host:

$$a = a_0(1 - cx). \quad (10)$$

This trade-off is such that the benefit from an increase in resistance is bought at an ever-increasing cost in terms of a reduction in the birth rate (a trade-off with accelerating costs). In the absence of any resistance, the intrinsic birth rate is given by a_0. The parameter c provides a measure of the cost: to avoid negative birth rates, we assume $0 \leq (1 - cx) \leq 1$. This trade-off is chosen as there is empirical evidence that an investment in resistance leads to a reduced birth rate (i.e., an increased development time; Boots and Begon 1993). There are clearly a number of other potential trade-offs with resistance in terms of other life-history traits. One alternative that has empirical support (Kraaijeveld and Godfray 1997; Fellowes et al. 1998) would be a trade-off with intra-specific competitive ability (q in our models). Previous studies have shown that the evolutionary outcomes are qualitatively similar for both of these trade-off choices (see Bowers et al. 1994), and hence we focus on a trade-off between resistance and birth rate. We assume an accelerating trade-off because there are good mechanistic reasons to assume that benefits saturate faster than costs in many host–parasite systems (Boots and Haraguchi 1999). An accelerating trade-off also results in an evolutionarily stable (ES) level of resistance. A trade-off with decelerating costs would lead to maximization or minimization of the resistance or disruptive selection leading to protected polymorphisms in resistance (Boots and Haraguchi 1999). Because our aim is to see how the ES resistance level, and therefore the optimal investment in resistance, is altered by life span, we focus our analysis on situations where there is an ESS.

We begin by examining the evolution of avoidance (9a), recovery (9b), and tolerance (9c) for the basic SIS interaction (model I). Acquired immunity is then added as described by models II and III, and the evolutionary dynamics investigated. We then examine the evolution of acquired immunity itself, as described by equations (9d) and (9e). Because the natural death rate is b, the average life span of uninfected (susceptible) hosts can be taken as $1/b$. Our method is to examine how the level of investment in resistance (x^*) that evolves is affected by changes in life span ($1/b$). This is achieved using the method of adaptive dynamics (Metz et al. 1996; Geritz et al. 1998), which allows the position and nature of evolutionary singular points to be determined (see the appendix).

Results

SUSCEPTIBLE-INFECTIVE-SUSCEPTIBLE

When resistance evolves as reduced transmission rate (avoidance), the relationship between host life span ($1/b$) and the optimal investment, x^*, is dependent on the virulence, α (Fig. 1A). For intermediate or high virulence ($\alpha = 2, 2.75$), the optimal strategy, x^*, is an increasing saturating function of life span. Here, we define the optimal strategy as the level of avoidance that is both evolutionarily and convergence stable (i.e., x^* is a continuously stable strategy [CSS]; see Geritz et al. 1998). We therefore expect longer lived hosts to evolve more avoidance, although this is not always the case. At low virulence ($\alpha = 1.75$), resistance initially increases and then decreases marginally. Reducing virulence still further ($\alpha = 1.67$), longer lived hosts may in fact evolve much less avoidance than shorter lived ones; in this case, the optimal avoidance, x^*, is nonmonotonic, but mainly decreasing with life span. Over a range of intermediate life spans ($10 < 1/b < 43$) we observe bistability in the evolutionary outcomes: there evolves either a locally stable level of avoidance ($x^* > 0$), or no avoidance ($x^* = 0$), the outcome being determined by the initial conditions. If the initial level of avoidance is above a particular threshold (determined by the position of an evolutionary repellor; see Fig. 1A), then avoidance evolves to the stable positive level. If the initial level of avoidance is below this threshold, then the population evolves to

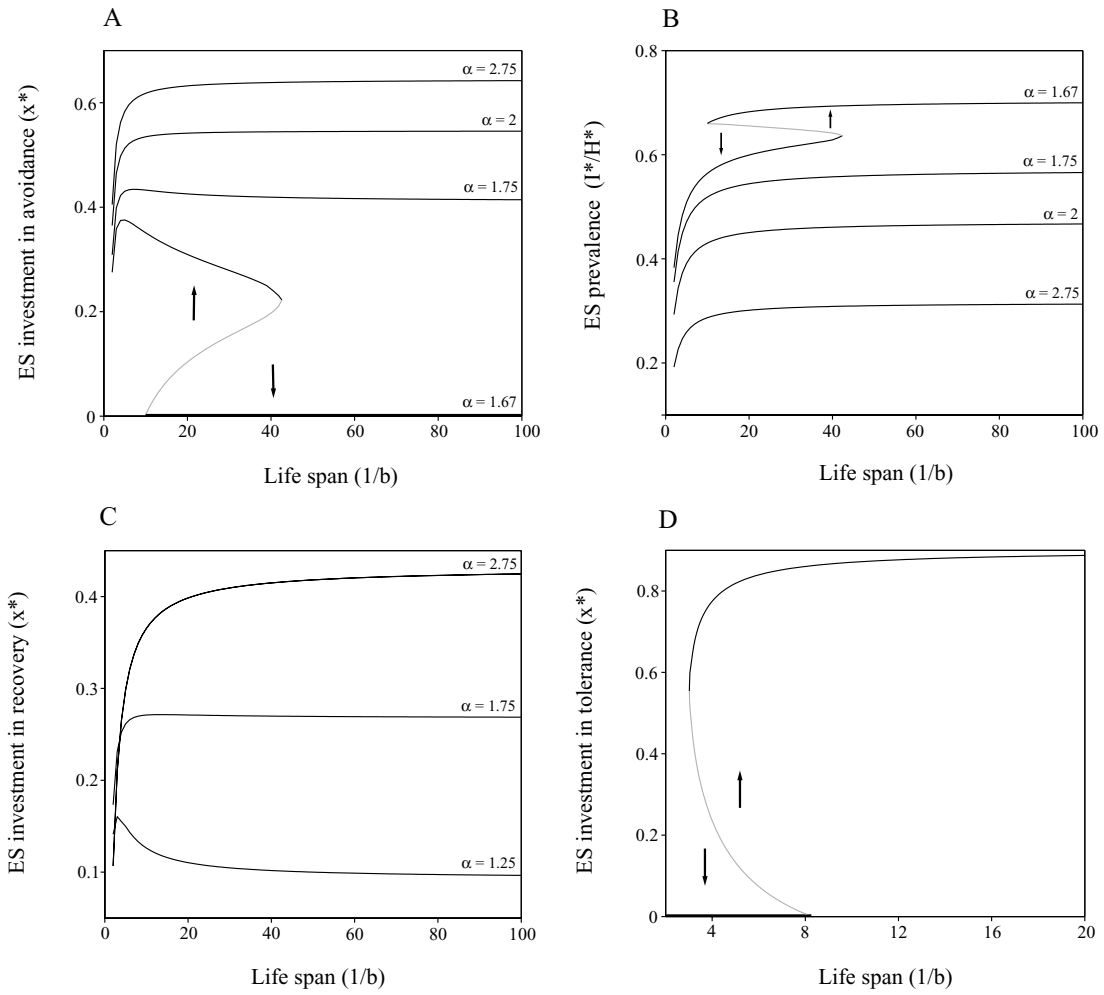

Figure 1. The effect of life span on the evolutionarily stable investment in immunity (avoidance, tolerance, and recovery) in susceptible-infective-susceptible (SIS) host–parasite interactions. (A) Evolutionarily stable investment in avoidance, and (B) the corresponding prevalence of infection, as a function of host life span; parameters are $\gamma = 0.25$, $\beta_1 = \beta_0 = 1$, and $h = 2$. (C) Evolutionarily stable investment in recovery as a function of host life span; parameters are $\beta = 1.5$, $\gamma_1 = 2.5$, $\gamma_0 = 0.1$, and $h = 0.9$. (D) Evolutionarily stable investment in tolerance as a function of host life span; parameters are $\beta = 1$, $\gamma = 0.25$, $\alpha_1 = 1.5$, $\alpha_0 = 1$, and $h = 1.5$. In all figures the black lines correspond to evolutionary attractors (Continuously Stable Strategies) and the gray lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. Other parameters are $a_0 = 1.5$, $q = 0.1$, and $c = 0.25$.

zero avoidance. Hosts with a sufficiently high life span ($1/b \geq 43$) will evolve zero avoidance. This evolutionary behavior only occurs over a small range of low virulences (α), between the regions where avoidance is worthwhile at all life spans ($x^* > 0$ at $\alpha = 1.7$), and is never worthwhile ($x^* = 0$ for $\alpha \leq 1.5$). That avoidance should generally increase with life span can be explained by the higher prevalence of infection in longer lived populations (Fig. 1B). Longer lived susceptibles encounter more parasites, whereas longer lived infecteds have more opportunities to infect susceptibles. Provided the virulence (α) is not too low, the higher prevalence in longer lived populations increases the selection for avoidance (Fig. 1A). Importantly, there is an underlying negative relationship between virulence and disease prevalence (Fig. 1B). Lower mortality of infected hosts increases the average infectious period, $1/(\alpha + \gamma + b)$, and therefore increases the opportunities for transmission. Assuming virulence (α) and the death rate (b) are low, a given level of avoidance may only marginally reduce the prevalence of infection. Consequently, longer lived populations may evolve relatively less avoidance, but only if the pathogenic effects on fitness are relatively small. When life span increases at low virulence, there exists a threshold at which prevalence (and therefore transmission) becomes so high that there is no investment in avoidance (particularly because the low virulence means the effects of infection are lessened). At intermediate life spans we observe bistability up to this threshold. Hence there exists a conflict between individuals that accept the fact that they are

going to be infected and therefore do not invest in avoidance, and those who make a relatively large investment and attempt to avoid infection during their (intermediate length) lifetimes.

We now investigate the evolutionary dynamics when resistance evolves as recovery (increased rate of clearance) (Fig. 1C). At intermediate to high virulences ($\alpha = 1.75,2.75$), the optimal recovery rate is an increasing and saturating function of life span. At low virulence ($\alpha = 1.25$), the optimal investment, x^*, initially increases with life span and then decreases toward a positive asymptote. As with avoidance, we find that the prevalence of infection increases monotonically with life span. This higher prevalence generally increases the selection for resistance in the population. At low virulence, because the mortality costs of infection are low and disease prevalence is high, recovered hosts are highly likely to be reinfected. Consequently, longer lived populations sometimes evolve lower recovery rates in response to parasitism. Note, however, that there is no bistability in evolutionary outcomes.

We now assume that resistance evolves as reduced virulence (tolerance). Here, very short-lived hosts do not invest in any tolerance (Fig. 1D). As life span increases, we observe a range of bistable strategies, where the host either evolves no tolerance ($x^* = 0$), or some positive level, $x^* > 0$, that increases with life span. As with avoidance, at intermediate life spans there is a conflict between whether individuals can escape infection during their lifetime and hence do not invest in tolerance, or else prepare for infection through a relatively large investment in tolerance. Note that investing in tolerance will increase prevalence, making infection more likely and further increasing the benefit of tolerance. As life span further increases, the positive ES tolerance also increases and the local optimum at $x^* = 0$ vanishes. We also find that, once again, disease prevalence increases with life span. Longer lived populations invest more heavily in tolerance in response to these higher prevalences.

SUSCEPTIBLE-INFECTIVE-RECOVERED-SUSCEPTIBLE

We now assume that individuals become immune upon recovery, and return to being susceptible at a constant rate, δ (model II). If there is a sufficiently high rate of loss of immunity ($\delta = 5$), then optimal avoidance increases and saturates with life span (Fig. 2A). With longer lasting immunity ($\delta = 0.5$), the optimal investment initially increases with life span and then marginally decreases toward a positive asymptote (Fig. 2A). For lower rates of loss of immunity ($\delta = 0.325$), investment tends to fall with life span and there is bistability over an intermediate range (a positive optimum, $x^* > 0$, and the zero strategy, $x^* = 0$). Furthermore, above a threshold life span ($1/b \geq 50$), hosts do not evolve any avoidance (Fig. 2A). Comparing the three examples, we note that hosts invest relatively less in avoidance (at any life span) as the length of immunity ($1/\delta$) increases.

These results can again be explained by the way in which the epidemiology of the interaction feeds back on the competition between strains with different investments in immunity. At moderate or high rates of loss of immunity (δ), the prevalence of infection always increases with life span (Fig. 2B). Interestingly, disease prevalence is almost the same for a moderate rate of loss ($\delta = 0.5$) as for a high rate ($\delta = 5$). In the former case, however, a greater proportion of the population is immune to infection (Fig. 2C), which significantly reduces the selection for avoidance. This lower level of avoidance balances the reduction in the susceptible population due to the immune class, leading to a similar level of prevalence. Provided the rate of loss of immunity (δ) is not too small, longer lived populations will exhibit higher prevalences, and consequently there is selection to evolve relatively greater avoidance. Even at low rates of loss ($\delta = 0.325$), prevalence generally increases with life span, although it is constant when the host does not invest in any resistance (Fig. 2B). The proportion of immunes always increases with life span and with the duration of immunity (Fig. 2C). Longer lived hosts are more likely to become infected, and to recover from infection before (natural) death. They will also live longer while immune. If immunity is sufficiently durable, it becomes more advantageous to invest in reproduction rather than resistance, as this outweighs the advantage of avoiding infection in the first place (i.e., avoiding virulence).

Next we examine the situation where the proportion, v, of hosts that acquire permanent immunity varies (model III). We find that optimal avoidance is always maximal for an intermediate life span; as life span increases from low values, the ES avoidance initially increases and then decreases (Fig. 2D). There always exists a narrow region of bistability, and a threshold life span above which hosts do not evolve any avoidance. As expected, at higher probabilities of acquiring immunity (v), hosts always invest relatively less in avoidance (Fig. 2D). The proportion of immunes always increases with life span and with the probability of becoming immune, v (Fig. 2F). Moving from a low to intermediate life span, the prevalence of infection also increases (Fig. 2E). Longer lived species have higher prevalences and a higher proportion of immunes; for sufficiently high life span, this always reduces selection for avoidance. This contrasts with variation in waning immunity (model II), where optimal avoidance may be monotonic ($\delta = 5$ in Fig. 2A), nonmonotonic and reach a positive asymptote ($\delta = 0.5$ in Fig. 2A), or nonmonotonic becoming zero for a sufficiently high life span ($\delta = 0.325$ in Fig. 2A). The relative importance of the immune class and its attendant density-dependent effects are more important when immunity is permanent (model III), as selection for avoidance always decreases at a higher life span. Furthermore, where the host does not evolve any avoidance, prevalence is seen to decrease with increasing life span (Fig. 2E). In model II, immunity always wanes eventually

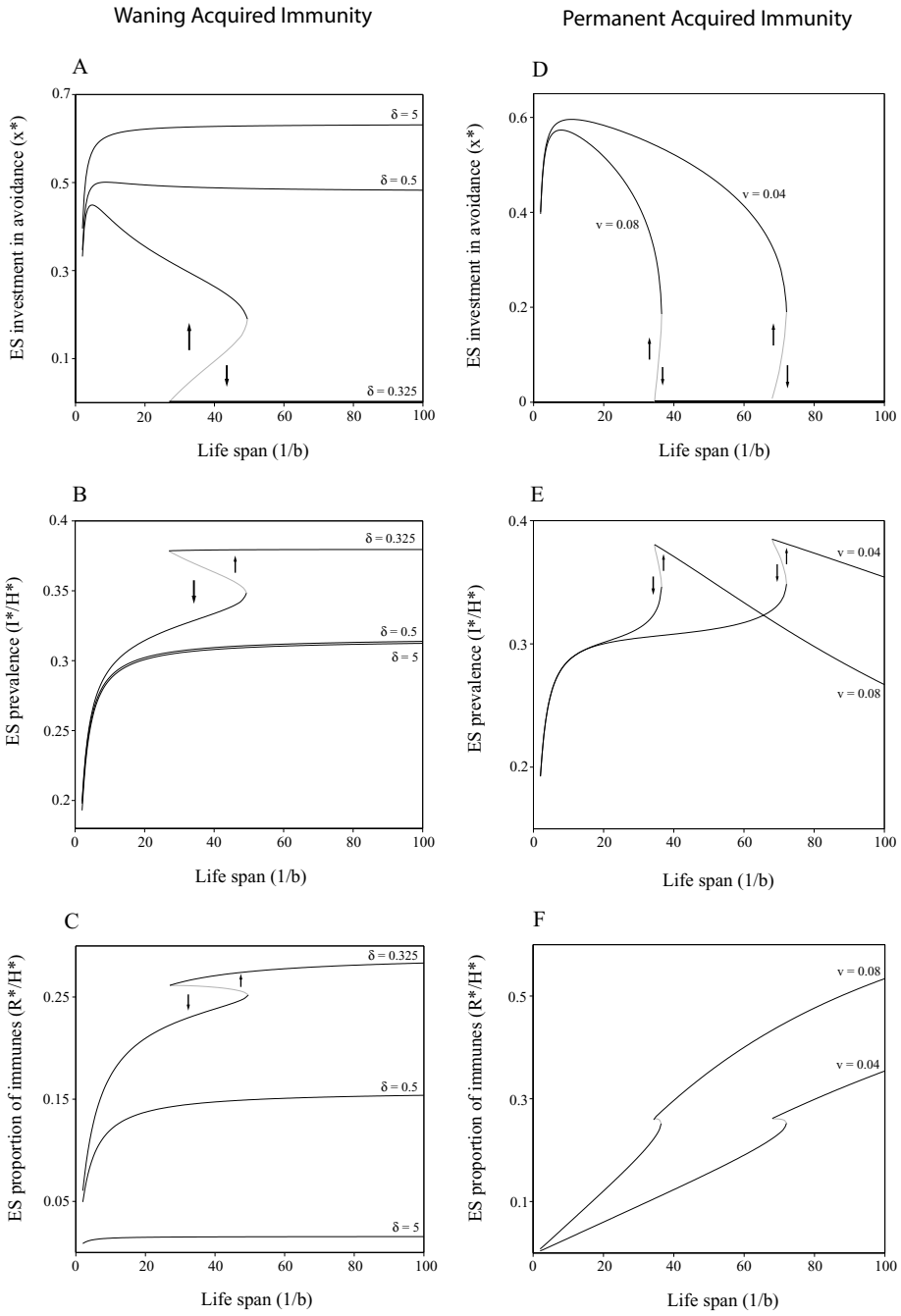

Figure 2. **The evolutionary investment in avoidance in susceptible-infective-recovered-susceptible (SIRS) host–parasite interactions. (A) and (D): evolutionarily stable investment in avoidance; (B) and (E): the corresponding prevalence of infection; and (C) and (F): proportion of immune individuals, as a function of host life span. In all figures the black lines correspond to evolutionary attractors (Continuously Stable Strategies) and the gray lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A)–(C) recovered hosts lose immunity at a constant rate, δ (model II); in (D)–(F) the probability of acquiring immunity upon recovery is v (model III). Other parameters are $a_0 = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = 2.75$, $\gamma = 0.25$, $\beta_1 = \beta_0 = 1$, and $h = 2$.**

(at rate δ), and the density-dependent effects are weaker. Note also that the nonmonotonic response described for both models is quantitatively dependent on the host's recovery rate (γ). As γ decreases, a lower rate of loss of immunity (or a higher probability of acquiring immunity) is required for selection for avoidance to decrease due to the relative importance of the immune class.

We now examine the evolutionary dynamics of recovery, assuming immunity wanes at a constant rate, δ (model II). At high rates of loss of immunity ($\delta = 5$), we tend to recover the results

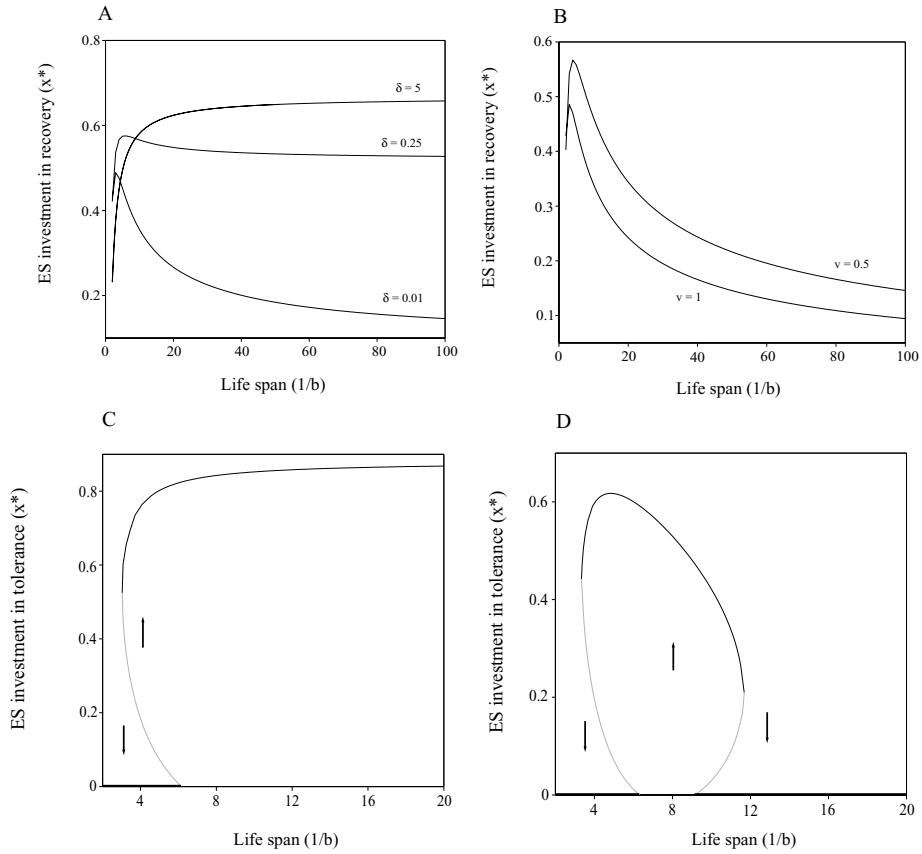

Figure 3. The evolutionary investment in recovery and tolerance in susceptible-infective-recovered-susceptible (SIRS) host–parasite interactions. (A) and (B): evolutionarily stable investment in recovery; (C) and (D): evolutionarily stable investment in tolerance. In all figures the black lines correspond to evolutionary attractors (continuously stable strategies) and the gray lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A), (C), and (D) recovered hosts lose immunity at a constant rate, δ (model II); in (B) the probability of acquiring immunity upon recovery is v (model III). In (A) and (B) parameters are $a_0 = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = 2.75$, $\beta = 2$, $\gamma_1 = 2.5$, $\gamma_0 = 0.1$, and $h = 0.9$. In (C) $\delta = 1$ and (D) $\delta = 0.05$, with other parameters $a_0 = 1.5$, $q = 0.1$, $c = 0.25$, $\beta = 1$, $\gamma = 0.25$, $\alpha_1 = 1.5$, $\alpha_0 = 1$ and $h = 1.5$.

for an SIS interaction: optimal investment increases and saturates with life span (Fig. 3A), as recovered hosts quickly lose their immunity and prevalence increases monotonically with life span. At intermediate rates of loss of immunity ($\delta = 0.25$), the optimal recovery initially increases with life span, then decreases toward a positive asymptote. When immunity wanes very slowly ($\delta = 0.01$), the ES recovery is again nonmonotonic with life span but shows a stronger decrease. Here, the proportion of immunes is much greater, and in long-lived species comprises the majority of the population. This reduces the proportion of susceptibles and, due to the density-dependent effects, may also reduce their absolute density. This acts to indirectly reduce the prevalence of infection, and therefore the selection for recovery.

Assume now that a proportion (v) of recovered hosts acquire permanent immunity (model III). Here the optimal recovery, x^*, initially increases and then decreases with higher life span, tending toward the zero asymptote; recovery is always maximal for an intermediate life span (Fig. 3B). At lower probabilities of acquiring immunity ($v = 0.5$), there is a stronger initial increase, but investments always tend to zero for sufficiently long life span. Again, the dynamics are explained by density-dependent effects and by the relative importance of immunes. The prevalence of infection was found to decrease as life span increased (for low values of v, prevalence may initially increase, but always decreases for a sufficiently high life span), whereas the proportion of immunes always increased with life span. At a sufficiently high life span, the long-lived immune population induces a higher level of density-dependent crowding. Disease prevalence is therefore lower and longer lived populations invest less in recovery. The immune class has a greater effect in model (III) due to the fact that immunity is permanent: even for very low v, prevalence and the selection for recovery always decrease for a sufficiently high life span. Note, however, that at a low life span (models II, III) and/or high rates of loss of immunity (model II), the optimal recovery rate is much higher than in the absence of acquired immunity (compare Fig. 1C with 3A, 3B). The added benefit of becoming

immune increases selection for recovery. Provided the overall proportion of immune hosts remains relatively low, individuals may therefore evolve higher recovery rates if they also have acquired immunity.

We now investigate the evolution of tolerance, firstly, when hosts lose immunity at a constant rate (model II). Provided this rate of loss of immunity (δ) is sufficiently high, the optimal investment increases and saturates with life span (Fig. 3C). Below a certain life span ($1/b \leq 3$), hosts do not invest in any tolerance. For higher life spans, hosts may evolve a positive level of tolerance, $x^* > 0$. However, over part of the range there is bistability whereby either a positive level of tolerance or zero tolerance will evolve: the outcome is dependent on the initial level of tolerance. Disease prevalence and the proportion of individuals with immunity both increase with life span. Here the increase in prevalence dominates, and selection for tolerance increases because the immune class is too small to significantly influence the dynamics.

At lower rates of loss of immunity (δ) or when immunity is permanent (model III), neither very long-lived nor very short-lived hosts invest in any tolerance (Fig. 3D). At intermediate life spans, there exists a locally stable level of tolerance, $x^* > 0$, which is globally stable over a reduced range; otherwise, there also exists a locally stable investment at $x^* = 0$. The level of investment ($x^* > 0$) initially increases and then decreases with life span, which is again due to the effect of the immune class. As life span increases, the proportion of immunes also increases, eventually causing disease prevalence to fall. Indeed, there is found to be a clear positive relationship between disease prevalence and the optimal investment in tolerance. At a high life span, the large immune class increases the density-dependent effects, reducing the proportion of susceptibles and therefore disease prevalence. Thus, longer lived populations may often evolve zero tolerance (Fig. 3D). However, as with avoidance, the decrease in investments occurring at high life spans is quantitatively dependent on the recovery rate, γ. If there is a lower rate of clearance, then lower rates of loss of immunity (δ) and/or higher host life spans are required before the investment in tolerance will decrease.

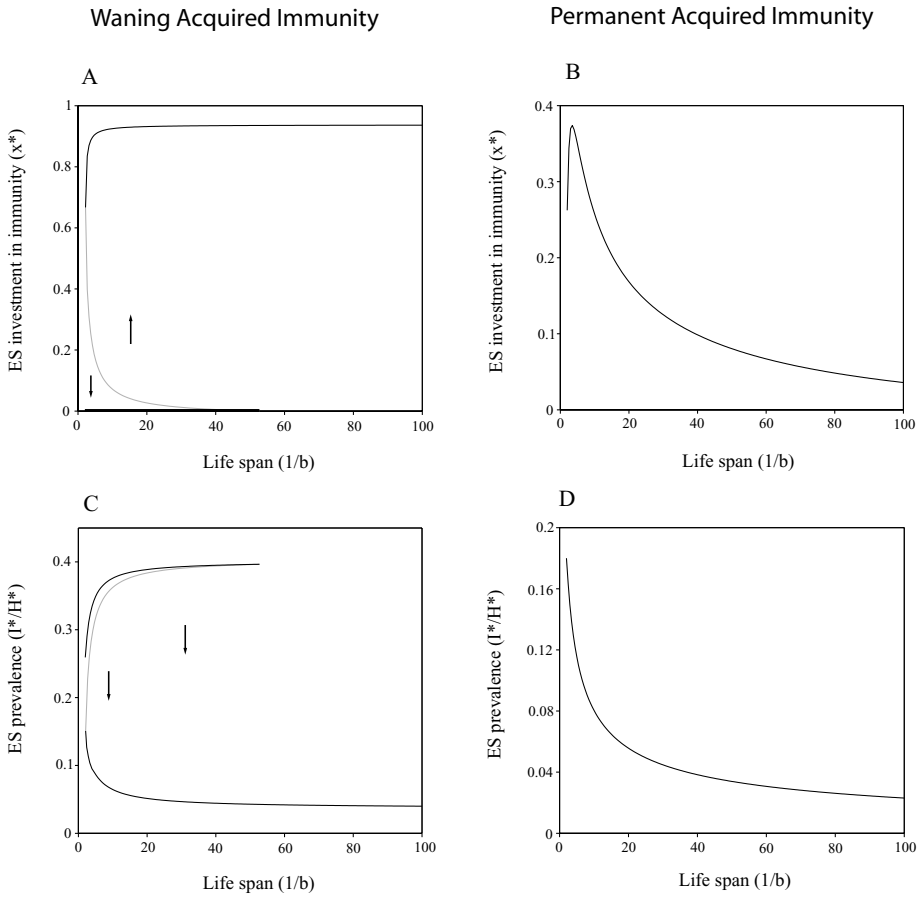

Figure 4. **The evolutionary investment in acquired immunity in susceptible-infective-recovered-susceptible (SIRS) host–parasite interactions. (A) and (B): evolutionarily stable investment in acquired immunity; (C) and (D): the corresponding prevalence of infection as a function of host life span. In all figures the black lines correspond to evolutionary attractors (continuously stable strategies) and the gray lines correspond to evolutionary repellors; the arrows indicate the direction of evolution. In (A) and (C) $\delta_1 = 5$, $\delta_0 = 0.1$, and $h = 2$ (model II); in (B) and (D) $v_1 = 0.9$, $v_0 = 0.1$, and $h = 0.9$ (model III). Other parameters are $a_0 = 1.5$, $q = 0.1$, $c = 0.25$, $\alpha = \gamma = 2.5$, and $\beta = 2.5$.**

EVOLUTION OF ACQUIRED IMMUNITY

We now investigate the evolution of acquired immunity itself, in terms of a reduced rate of loss of immunity, δ, or a higher probability, v, of gaining acquired immunity. If immunity increases the duration of the immune period (model II), then very short-lived hosts do not invest in resistance at all (Fig. 4A), as they are highly likely to die before the benefits of immunity can be realized. Above this threshold, there is bistability with an intermediate ES level of immunity, x^*, that rapidly attains a very high level, and an alternate ES strategy at $x = 0$ (zero investment). Here there is a conflict between individuals that die from the disease, and therefore would not benefit from investing in immunity, and those that recover, and would therefore invest heavily in acquired immunity to prevent reinfection. This is reflected in the fact that if hosts do not invest in any immunity, prevalence increases monotonically with life span, whereas if they do invest in immunity, prevalence decreases with a higher life span (Fig. 4C). For a sufficiently high life span, populations always evolve high levels of immunity (Fig. 4A). Here, individuals cannot affect the chance of initially becoming infected, but once recovered from infection. it is beneficial to retain immunity over their (long) lifetime.

The situation is very different when we consider the evolution of acquiring immunity (model III). Here, the ES level of immunity, x^*, increases initially and then decreases at a higher life span (as life span tends to infinity, x^* asymptotes toward zero; Fig. 4B). This contrast is due to differences in the effect of the immune class on the epidemiology, and therefore the selection for immunity. As life span increases, the proportion of individuals with acquired immunity increases, becoming very large at a high life span. In contrast, disease prevalence decreases with increasing life span to low levels (Fig. 4D). Density dependence from the long-lived immune class reduces the proportion of susceptibles and therefore the prevalence of infection. This reduces the selection for immunity at high life span.

Discussion

We have shown that longer lived species relying only on innate resistance to defend against parasites generally invest more in costly resistance. This increased investment occurs whether resistance reduces the probability of infection, increases the recovery rate, or reduces virulence. Longer lived individuals are more likely to become infected, and therefore tend to have a higher disease prevalence. This increases the selection for costly defenses that avoid infection or tolerate pathogen damage. In the examples given, infected hosts were able to recover from infection, but we found the results also hold if the disease is invariably fatal. In contrast, if hosts benefit from immunological memory and therefore acquire immunity, the optimal investment in innate resistance may often be maximal for an intermediate life span. If immunity is permanent (the classic susceptible-infective-removed dynamic), the optimal immunity is always maximal for an intermediate life span. Similarly, if immunity wanes over time, longer lived individuals may invest more in innate defenses, but this is not always the case: depending on the epidemiology, hosts of an intermediate life span may again invest in relatively more resistance. These effects occur because longer lived individuals are more likely to recover from infection, and may therefore invest relatively less in mechanisms that reduce transmission. Populations of longer lived hosts have a higher proportion of immune individuals and, due to intra-specific crowding, a lower prevalence of infection. Selection for mechanisms that reduce virulence or increase recovery may therefore also be lower in such longer lived species.

We commonly find bistability in the evolutionary outcomes. This bistability is due to the existence of a local fitness minimum, or evolutionary "repellor" (Metz et al. 1996; Geritz et al. 1998), occurring between two locally stable strategies (CSSs). Bistabilities tend to occur when the two strategies involved each affect the environment to their own advantage. As such, only large changes in the trait can alter the environment to the extent that the other strategy is favored. Consider the evolution of avoidance (Fig. 1A), where bistabilities between low and high investments occur due to the manner in which they affect the prevalence of the disease. When there is a low investment in avoidance, disease prevalence is relatively high. A small investment in resistance is not beneficial at such a high prevalence because individuals are likely to become infected in any case. Conversely, a high investment reduces prevalence and therefore further increases the chance of avoiding infection, making the cost of resistance worthwhile. An important implication for life spans in this bistable range is that if individuals are initially susceptible to a novel parasite, with local mutation, they will not evolve any resistance. However, if global mutations occur, even an initially susceptible population may evolve resistance. This type of bistability is also observed for the evolution of tolerance (Figs. 1C, 3C, 3D). When acquired immunity is long-lasting there is also bistability in tolerance for long-lived populations (Fig. 3D). Therefore, assuming local mutation, only hosts of an intermediate life span will evolve tolerance to a novel pathogen.

Evolutionary bistability is related to the phenomenon of hysteresis. Consider, for example, the evolution of tolerance (Fig. 1D). Assuming the population initially has zero tolerance, as life span increases the optimal investment remains at this level up to a critical threshold (at approximately $1/b = 8$ in this example). After this threshold is passed, the population evolves a positive level of tolerance, retaining this as life span increases further. If life span is then reduced, the population retains this positive level of tolerance until the threshold at approximately $1/b = 3$ is passed (note this is significantly below the level at which the switch to positive tolerance occurred). Thus, a small change in life span

when near a threshold can cause a dramatic change in the level of evolved tolerance; crucially though, a reversal in the change in life span does not reverse the change in the level of evolved tolerance. This phenomenon is known as hysteresis and has been observed for a diverse range of biological situations, ranging from the population dynamics of insect outbreaks (Ludwig et al. 1978) to the regulation of temperature due to land–atmosphere feedbacks (Watson and Lovelock 1983). The examples given in this study suggest hysteresis may also be important for determining the evolutionary dynamics of host–parasite systems.

We have shown that the evolution of acquired immunity depends on whether immunity is permanent or temporary. When the resistance mechanism operates by allowing the probability of gaining permanent immunity to evolve, then as life span increases, the optimal investment rises to a maximum and then falls toward zero (Fig. 4B). If, instead, resistance increases the length of the immune period, the optimal investment always increases with life span, although there is bistability at short and intermediate life spans with possibly zero investment. Given local mutation, shorter lived species may therefore not evolve any acquired immunity, whereas longer lived species are predicted to invest heavily (Fig. 4A). Acquired immunity is also most likely to evolve in response to high transmission rates and intermediate rates of recovery (Boots and Bowers 2004). We may therefore only expect acquired immunity to evolve in response to very strong selective pressure, where prevalence is high and the advantage of immunity is large (i.e., organisms have a good chance of recovering and also live long enough to benefit from immunity).

The possession of an acquired immune system has important implications: we have shown that longer lived populations may invest in relatively more, or relatively less, innate resistance if they have acquired immunity. Given that innate and acquired immunity are costly to maintain, hosts may be expected to balance the investment between the two defenses in each, to minimize the total cost. Often, different forms of resistance may be traded off (Mallon et al. 2003). In particular, investment in specific forms of defense may be negatively correlated with investment in nonspecific defense (Frank 2000), where the optimal allocation between the two forms will depend on the prevalence of infection (Moret 2003). This also crucially depends on the life span of the host, which selects for innate and acquired immunity differentially.

It is well established that population density may affect the evolution of resistance characteristics (Svensson et al. 2001; van Boven and Weissing 2004). We have shown that increased crowding due to a long-lived immune class may indirectly reduce disease prevalence and therefore the selection for innate or (model III) acquired immunity. We also investigated the evolution of resistance characteristics without density-dependent effects, assuming a constant birth rate (i.e., the parameter $q = 0$ in the previous models). In this case, when resistance evolved as increased recovery or reduced virulence (tolerance), the optimal investment always increased with life span. However, the optimal investment in reduced susceptibility (avoidance) was found to be maximal at an intermediate life span. Density-dependent effects alone therefore cannot explain the reduction in avoidance occurring in longer lived populations. Optimal avoidance may be lower in long-lived populations because here individuals are highly likely to become infected, but have a sufficiently high chance of recovering (and therefore acquiring long-lasting immunity). This outweighs the advantage of investing in costly avoidance.

We have assumed constitutive costs throughout this study. Resistant hosts therefore always had a reduced birth rate (whether infected, susceptible, or immune). Evolutionary costs are strictly constitutive in that they are genetically determined and can change only through natural selection (Schmid-Hempel 2003, 2005). Energetic or physiological costs of resistance may also be constitutive, where the organism is forced to expend valuable resources to maintain its immune system in a state of readiness (Schmid-Hempel 2003, 2005). However, there are also likely to be other "induced" costs associated with activating and/or maintaining the immune response (Zuk and Stoehr 2002). Importantly, the selective pressures may be very different under the assumption of induced costs. For example, Day and Burns (2003) have shown that longer lived hosts should invest relatively less in recovering from infection when there is no acquired immunity. In contrast, in assuming constitutive costs, we have shown that longer lived individuals will generally evolve higher recovery rates if they lack acquired immunity (Fig. 1C). Recent theoretical work has investigated when organisms should switch between constitutive and inducible forms of defense. Assuming constitutive defenses act more rapidly, hosts should invest in constitutive defenses whenever parasites are highly virulent and transmissible, although pathogens that grow quickly within the host may favor a mixed response (Shudo and Iwasa 2001). It would be interesting to see how host life span affects this response.

Our results suggest that in long-lived species, the presence of long-lasting immunological memory may reduce selection for less specific, innate resistance. This is more likely if the species is particularly prone to intraspecific crowding, although internal or external (i.e., behavioral) mechanisms that reduce the probability of infection may be selected against even in the absence of such a density dependence. Both invertebrates and vertebrates possess an innate immune system, which uses germ-line encoded receptors to recognize microbial pathogens (Medzhitov and Janeway 1997). Vertebrates also benefit from acquired immunity, which uses antigen-specific lymphocytes to invoke a specific response (Medzhitov and Janeway 1997). Invertebrates lack lymphocytes and are therefore thought to have no acquired immunity as such (Medzhitov and Janeway 1997; Rinkevich 1999; Zuk and Stoehr 2002). There is, however, evidence for immunological memory in

many invertebrate species (reviewed by Schmid-Hempel 2005). Our results may therefore be applicable to both vertebrate and invertebrate systems. However, it is important to note that longer lived species in particular may be exposed to many different pathogens. Acquired immunity is antigen specific and is activated by signals from the innate immune system (Medzhitov and Janeway 1997; Menezes and Jared 2002). As the diversity of parasites increases, the value of a given defense option becomes less effective and may be selected against (Jokela et al. 2000). It therefore seems likely that high levels of acquired immunity will only select for less innate resistance in long-lived organisms if these have relatively few parasites.

The main aim of this study has been to investigate how host life span affects the evolution of resistance characteristics, and the related implications of having an acquired immune system. The selective pressures affecting optimal allocation to resistance have been shown to depend on a variety of epidemiological and ecological factors. In particular, the effects of density dependence and the immune class on the epidemiology may produce counterintuitive patterns of selection. Fundamentally, life span not only affects the exposure to a pathogen, it also affects the amount of infection that occurs, and the level of competition between individuals. Ultimately, it is the combination of these factors that determines the optimal investment in immunity.

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Appendix

ADAPTIVE DYNAMICS

We establish the conditions for a mutant host to invade and replace an established resident host. It is assumed that all host strains are capable of supporting the parasite at an endemic equilibrium. This requires that births exceed deaths ($a > b$), and that the carrying capacity exceeds a threshold density, $K \geq H_T = (\alpha + \gamma + b)/\beta$. The analysis below is presented in detail for model II and summarized for the other models.

Consider the stable endemic equilibrium (S^*, I^*, R^*) in model II with the resident host strategy, x, and the associated total density $H^* = S^* + I^* + R^*$. Suppose a mutant strain characterized by x_m evolves at an initially low density (in the following the subscript m denotes the mutant parameters). For this mutant strain to invade, its marginal growth rate must be positive. This means the average contribution per mutant individual to the population must be greater than zero.

Assume the mutant is initially in the susceptible state, and remains uninfected for an average time period T_S, and let T_I and T_R denote the average times spent in the infected and recovered (removed) states. The average contributions while in the respective states are denoted ρ_S, ρ_I, and ρ_R. From the arguments given in Boots and Bowers (2004), the following identities can be derived (we omit the details for the sake of brevity):

$$\rho_S = a_m - b - qH^* \tag{A.1}$$

$$\rho_I = a_m - b - qH^* - \alpha_m \tag{A.2}$$

$$\rho_R = a_m - b - qH^* \tag{A.3}$$

$$T_S = \frac{1}{(b + \beta_m I^*)} \tag{A.4}$$

$$T_I = \frac{\beta_m I^*}{(b + \beta_m I^*)(\alpha_m + \gamma_m + b)} \tag{A.5}$$

$$T_R = \frac{\gamma_m \beta_m I^*}{(b + \delta_m)(b + \beta_m I^*)(\alpha_m + \gamma_m + b)}. \tag{A.6}$$

Let $\phi(x_m/x)$ denote the marginal growth rate of the rare mutant strain, x_m, in the resident population, x. This is equal to the sum of the average time periods (A.4)–(A.6), weighted by the corresponding contributions (A.1)–(A.3):

$$\phi(x_m/x) = \rho_S T_S + \rho_I T_I + \rho_R T_R. \tag{A.7}$$

Substituting in the values for (A.1)–(A.6) and eliminating the positive common factor, $1/(b + \beta_m I^*)$, the condition for a positive marginal growth rate is

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*(a_m - b - qH^* - \alpha_m)}{(\alpha_m + \gamma_m + b)} + \frac{\gamma_m \beta_m I^*(a_m - b - qH^*)}{(\delta_m + b)(\alpha_m + \gamma_m + b)} > 0. \tag{A.8}$$

If (A.8) is satisfied, then a rare mutant strain characterized by x_m can invade the resident strain x; otherwise, the mutant strain has a negative growth rate and will become extinct.

Two points need to be mentioned. First, successive periods of infection are possible (assuming the rates of recovery, γ_m, and loss of immunity, δ_m, are non-zero). Taking this into account scales (A.8) by a positive constant and can therefore be ignored. Second, invasions by infected or recovered individuals may also occur. It can be shown, however, that infected or recovered individuals cannot prosper unless susceptibles do. Equation (A.8) therefore sufficiently determines the growth rate of a rare mutant strain and can be taken as the invasion criterion (or fitness function). Using the same technique, the invasion criterion for model (I) is obtained as

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*}{(\alpha_m + \gamma_m + b)} \times (a_m - b - qH^* - \alpha_m) > 0. \tag{A.9}$$

The invasion criterion for model (III) is similarly given as

$$\phi(x_m/x) = a_m - b - qH^* + \frac{\beta_m I^*(a_m - b - qH^* - \alpha_m)}{(\alpha_m + \gamma_m + b)} + \frac{v_m \gamma_m \beta_m I^*(a_m - b - qH^*)}{b(\alpha_m + \gamma_m + b)} > 0. \tag{A.10}$$

The theory of adaptive dynamics (Metz et al. 1996; Geritz et al. 1998) is used to determine the evolutionary behavior and the

level of investment in resistance that will evolve. We assume explicit trade-off functions such that a given investment in resistance (9a)–(9e) is associated with a given reduction in birth rate (10). This trade-off is incorporated into the fitness functions (A.8)–(A.10). Adaptive dynamics states that the population will evolve in the direction of the local fitness gradient (Metz et al. 1996; Geritz et al. 1998), $[\partial\phi/\partial x_m]_{x=x_m}$, and that singular points of evolution occur where this fitness gradient is equal to zero:

$$[\partial\phi/\partial x_m]_{x=x_m} = 0. \tag{A.11}$$

Evolutionary singular points may exhibit a number of evolutionary properties. A full classification is given in Geritz et al. (1998), but here we limit our attention to two particular properties. First, a singular point is an "evolutionarily stable strategy" (ESS) if, once resident, it resists invasion by all other strains. Second, a singular point is "convergence stable" (CS) if local evolution proceeds toward it. A singular point that is both an ESS and CS is called a continuously stable strategy (CSS). Note that a singular point that is neither CS nor ESS corresponds to an evolutionary repellor because local evolution proceeds away from it. The results in this study often exhibit evolutionary bistability where two CSSs are separated by an evolutionary repellor (i.e., there are multiple solutions to [A.11]). The evolutionary outcome will then depend on the initial conditions in relation to the evolutionary repellor.

In this study we identified the singular points by solving (A.11). We also identified the behavior at the singular points. In the models analyzed, the singular points that were local fitness maxima corresponded to CSSs, whereas those that were fitness minima corresponded to evolutionary repellors. The evolutionary behavior at the singular points was checked by constructing pairwise invadability plots for specific parameter choices (Geritz et al. 1998) and by undertaking simulations of the mutation-selection process (see Bowers et al. 2005).