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The evolution of host resistance: Tolerance and control as distinct strategies

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Abstract

In response to parasitic infection, hosts may evolve defences that reduce the deleterious effects on survivorship. This may be interpreted as a form of resistance, as long as infected hosts are able to either recover or reproduce. Here we distinguish two important routes to this form of resistance. An infected host may either: (1) *tolerate* pathogen damage, or (2) *control* the pathogen by inhibiting its growth. A model is constructed to examine the evolutionary dynamics of tolerance and control to a free-living microparasite, where both forms of resistance are costly in terms of other life-history traits. We do not observe polymorphism of tolerant genotypes. In contrast, the evolution of control may lead to disruptive selection, and ultimately dimorphism of extreme strains. The optimal host genotype also varies with the type of resistance—individuals invest more in tolerance and pay a greater cost. The free-living framework used makes the distinction between tolerance and control explicit but the distinction applies equally to directly transmitted parasites. Due to the evolutionary differences exhibited, it is important to design experiments that distinguish between the two forms of resistance.

Keywords: Resistance; Tolerance; Control; Free-living pathogen; Polymorphism

1. Introduction

Faced with a wide variety of infectious agents, organisms have developed a diverse array of defence mechanisms (Roy and Kirchner, 2000). It is useful to clarify these different mechanisms in terms of their epidemiological role. Resistance can be achieved by avoiding infection in the first place, recovering faster once infected, or remaining immune for longer. In addition, mechanisms allowing infected individuals to survive for longer also lead to resistance, provided these infected hosts may still reproduce or are able to recover (Boots and Bowers, 1999; Roy and Kirchner, 2000). This ability to reduce the negative effects of infection on survivorship is often known as tolerance. However, we show that a reduction in pathogenicity (disease-induced mortality) through 'true' tolerance has very different evolutionary outcomes to when reduced pathogenicity is due to control of the parasite's growth rate.

There have been several theoretical studies investigating the evolution of resistance to pathogens (Antonovics and Thrall, 1994; Boots and Bowers, 1999, 2004; Boots and Haraguchi, 1999; Bowers, 1999, 2001; Bowers et al., 1994; Restif and Koella, 2003, 2004; Roy and Kirchner, 2000). Epidemiological models typically assume a haploid host, where increased resistance correlates with lower investment in some other advantageous trait. Resistance therefore incurs a cost that manifests as reduced fitness in the absence of disease. The existence of costs is supported by both theoretical arguments (Stearns, 1992) and empirical evidence (Boots and

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Begon, 1993; Kraaijeveld and Godfray, 1997). A common assumption is that costs arise due to antagonistic pleiotropy, where the allele encoding for resistance has other detrimental effects on fitness in the absence of disease (Simms, 1992). Bowers et al. (1994) and Antonovics and Thrall (1994) examined very similar models of the evolution of resistance to a directly transmitted pathogen where resistant hosts had a reduced probability of becoming infected, but experienced a lower birth rate or greater vulnerability to crowding. Polymorphism was shown to be unlikely between similar strains, and highly virulent parasites selected against resistance. Indeed, when the degree of difference between susceptible and resistant strains is large enough, polymorphism may be feasible even with very low costs of resistance. Boots and Bowers (1999) subsequently investigated the evolution of costly resistance through three different mechanisms. Resistance manifested as avoidance (a reduction in the probability of being infected), recovery (faster rate of clearance) or tolerance (a reduction in pathogen-induced mortality). In all three cases, resistance was most likely to evolve in hosts with a high intrinsic growth rate and low susceptibility to crowding. With resistance through avoidance or recovery, polymorphism was predicted between very dissimilar strains, over a wide range of costs, but polymorphism was found to be highly unlikely through a tolerance mechanism. Roy and Kirchner (2000) also argued that tolerant genotypes will increase disease incidence and hence the selection for tolerance; polymorphism is therefore only possible when there are other factors influencing selection.

Here we recognize that the evolution of resistance conferred through reduced pathogenicity may arise through different biological mechanisms. We distinguish between two forms which we term 'tolerance' and 'control'. Tolerance is defined as a reduction in pathogenicity that has no effect on the growth of the pathogen. Control is defined as a reduction in pathogenicity obtained by reducing within-host growth (effectively, the replication rate of the pathogen within infected hosts). We consider a free-living microparasite, such that transmission of the disease occurs through long-lived infective particles external to the host. This formulation makes the distinction between the two forms of pathogenicity-reducing resistance explicit. In addition, we can examine the implications of free-living stages, per se, to the evolution of resistance. In both cases we assume a pleiotropic cost of resistance in terms of a reduced intrinsic growth rate.

2. Model

We consider the dynamics of two host genotypes (susceptible and resistant) and a free-living pathogen. Our algorithm uses a structure adapted from model G of Anderson and May (1981) and a methodology derived from host-host-pathogen models for directly transmitted infection (Boots and Bowers, 1999). The variables are defined as follows:

X_S	density of uninfected individuals of the susceptible strain
Y_S	density of infected individuals of the susceptible strain
Z	density of infective particles
X_R	density of uninfected individuals of the resistant strain
Y_R	density of infected individuals of the resistant strain.

We assume that host strains share the same environment and become infected through contact with a common pool of infective particles. The dynamics are described by the following differential equations:

$$\frac{dX_S}{dt} = r_S(X_S + Y_S) - qH(X_S + Y_S) - \beta X_S Z + (\gamma + b)Y_S, \quad (1)$$

$$\frac{dY_S}{dt} = \beta X_S Z - (\alpha_S + \gamma + b)Y_S, \quad (2)$$

$$\frac{dZ}{dt} = \lambda_S Y_S + \lambda_R Y_R - \mu Z, \quad (3)$$

$$\frac{dX_R}{dt} = r_R(X_R + Y_R) - qH(X_R + Y_R) - \beta X_R Z + (\gamma + b)Y_R, \quad (4)$$

$$\frac{dY_R}{dt} = \beta X_R Z - (\alpha_R + \gamma + b)Y_R, \quad (5)$$

($H = X_S + Y_S + X_R + Y_R =$ Total host density).

The subscripts S and R denote the susceptible and resistant strains respectively (resistance manifests as either control or tolerance). Here r_i gives the intrinsic growth rate of host genotype i, equal to the birth rate a_i, minus the common death rate b. The quantity q measures susceptibility to crowding and represents density-dependence acting on the birth rate of the host. It is related to the carrying capacity $K_i = r_i/q$. The transmission rate of infection, the recovery rate, and the rate of pathogenicity (disease-induced mortality) are denoted β, γ and α_i, respectively. Once infected, hosts produce free-living particles at a rate λ_i, until they either die or recover. These infective particles persist in the external environment with a background mortality rate μ. We follow the approach of Dwyer (1994) and assume that infective particles are lost only through this natural decay rate; the reduction in pathogen density due to host consumption is assumed to be negligible.

We assume a uniform pathogen with a fixed level of 'potential' virulence that is only fully expressed as pathogenicity in susceptible hosts. The actual pathogenicity experienced is the potential virulence of the pathogen that is not compensated for by a resistance mechanism. In tolerant hosts, resistance reduces pathogenicity but this does not affect the growth of the pathogen. Control limits viral replication in infected hosts, reducing both pathogenicity and the production rate of free-living particles. The assumptions are therefore:

$$\text{Tolarance}: \quad \alpha_R < \alpha_S \quad r_R < r_S, \quad \lambda_R = \lambda_S = \omega, \tag{6}$$

$$\text{Control}: \quad \alpha_R < \alpha_S, \quad r_R < r_S, \quad \phi\,\alpha_R = \lambda_R < \lambda_S = \phi\,\alpha_S. \tag{7}$$

The parameter ω represents the rate of production of particles from infected hosts in the tolerance scenario, while ϕ determines the production rate (for a given level of pathogenicity) in the control scenario. All parameters are assumed to be positive.

3. Analysis

There are six equilibrium solutions of Eqs. (1)–(5). Taking the variables in the order $(X_S,\ Y_S,\ Z,\ X_R,\ Y_R)$ the equilibria are:

$$(0,\ 0,\ 0,\ 0,\ 0), \tag{8}$$

$$(K_S,\ 0,\ 0,\ 0,\ 0), \tag{9}$$

$$(0,\ 0,\ 0,\ K_R,\ 0), \tag{10}$$

$$(X_S^*,\ Y_S^*,\ Z_S^*,\ 0,\ 0), \tag{11}$$

$$(0,\ 0,\ Z_R^*,\ X_R^*,\ Y_R^*), \tag{12}$$

$$(X_S^+,\ Y_S^+,\ Z^+,\ X_R^+,\ Y_R^+). \tag{13}$$

The first equilibrium is always unstable for positive parameters. The second corresponds to an uninfected susceptible strain at its carrying capacity, $K_S = r_S/q$. This equilibrium is stable only when the threshold density required to support the pathogen exceeds the carrying capacity ($H_{T,S} > K_S$). This threshold density is given as $H_{T,S} = \mu(\alpha_S + \gamma + b)/\lambda\beta$. The third equilibrium similarly corresponds to an uninfected resistant strain at its carrying capacity $K_R = r_R/q$. Under our trade-off assumptions (6)–(7) this equilibrium is never stable, since in the absence of infection the susceptible strain has a higher growth rate. The fourth and fifth equilibria correspond to a single infected strain (susceptible or resistant) supporting the pathogen. The final solution corresponds to a dimorphic equilibrium where a susceptible and a resistant strain jointly support the pathogen.

Throughout our analysis we assume the susceptible carrying capacity always exceeds the threshold density ($K_S > H_{T,S}$). Equilibria (8)–(10) are therefore always unstable and we need only consider the stability criteria with respect to the infected states (11)–(13). We apply an invadability analysis that determines the specific conditions for a rare mutant strain to invade a resident equilibrium. These conditions are derived in Appendix A using a traditional Jacobian analysis, but we present here a more biologically motivated derivation.

Consider an initially rare mutant of the resistant strain, attempting to invade the susceptible equilibrium (11). To successfully invade, the resistant mutant must have a positive growth rate. This means that the net contribution of a single resistant individual must be greater than zero. On average, a single resistant mutant will remain uninfected for a period T_X, during which time it makes a contribution ρ_X to the total population, and will be infected for an average time T_Y, making a contribution ρ_Y. Letting I_R denote the overall contribution, this gives

$$I_R = \rho_X T_X + \rho_Y T_Y. \tag{14}$$

This term must be greater than zero for the genotype to invade. From Eqs. (1)–(5) the uninfected contribution is

$$\rho_X = r_R - q(X_S^* + Y_S^*). \tag{15}$$

Similarly, the contribution while infected is

$$\rho_Y = r_R - q(X_S^* + Y_S^*) - \alpha_R. \tag{16}$$

The average period an individual stays uninfected is determined by the natural mortality rate and the probability of becoming infected through contact with an infective particle. Since there are Z_S^* such particles, the probability of an infection is βZ_S^* and we have

$$T_X = 1/(b + \beta Z_S). \tag{17}$$

The probability of dying while uninfected is $b\,T_X$. The only other possibility is to become infected and then either die or recover, with probability $(\alpha_R + \gamma + b)\,T_Y$. Logically, this gives:

$$b\,T_X + (\alpha_R + \gamma + b)T_Y = 1. \tag{18}$$

Note that successive periods of infection and recovery are possible, but this only serves to scale the results by a positive common factor. Also, infected individuals cannot prosper unless uninfected individuals do. It is therefore sufficient to consider only a single cycle, where an initially uninfected individual either remains so, or becomes infected and then dies or recovers (Boots and Bowers, 1999).

Combining Eqs. (17) and (18):

$$T_Y = \frac{\beta Z_S^*}{(b + \beta Z_S^*)(\alpha_R + \gamma + b)}. \tag{19}$$

Substituting the terms into (14) we obtain an expression for the growth rate I_R of the resistant strain:

$$I_R = \{r_R - q(X_S^* + Y_S^*)\} \times \frac{1}{(b + \beta Z_S^*)} + \{r_R - q(X_S^* + Y_S^*) - \alpha_R\} \times \frac{\beta Z_S^*}{(b + \beta Z_S^*)(\alpha_R + \gamma + b)}. \quad (20)$$

To invade the susceptible equilibrium, I_R must be greater than zero. Eliminating a positive common factor, the condition for the resistant strain to invade is

$$I_R = r_R - q(X_S^* + Y_S^*) - \frac{\beta Z_S^*}{(\alpha_R + \gamma + b)} \times \{\alpha_R - (r_R - q(X_S^* + Y_S^*))\} > 0. \quad (21)$$

If this condition is not satisfied then the susceptible equilibrium (11) resists invasion and a resistant mutant will be eliminated. By symmetry, the condition for a susceptible strain to invade the resistant equilibrium (12) is

$$I_S = r_S - q(X_R^* + Y_R^*) - \frac{\beta Z_R^*}{(\alpha_S + \gamma + b)} \times \{\alpha_S - (r_S - q(X_R^* + Y_R^*))\} > 0. \quad (22)$$

We can now classify the equilibria according to these two invasion criteria. When only condition (21) holds, the resistant strain can invade the susceptible equilibrium but the resistant equilibrium resists invasion by the susceptible strain. In this case the susceptible strain is eliminated and equilibrium (12) is stable. Conversely, when only condition (22) holds, the susceptible equilibrium (11) is stable and the resistant strain is eliminated. If both (21) and (22) hold, then neither strain is favoured and the only stable equilibrium is the dimorphic state (13). The remaining situation occurs when neither condition holds, in which case both single equilibria ((11) and (12)) are locally stable, and the outcome is contingent on the initial conditions. Within our evolutionary context, this scenario favours the susceptible strain that is initially confronted with the parasite.

The dynamics are illustrated using Reciprocal Invasion Plots (Boots and Bowers, 1999; Bowers et al., 1994). We assume a resident susceptible strain characterized by (α_S, r_S) and a range of possible resistant mutants (α_R, r_R). The susceptible strain is paired with each resistant genotype and the invasion criteria (21) and (22) evaluated in each case. This allows us to determine the relative costs and benefits that favour resistance (for a given level of susceptibility). Resistance takes the form of either tolerance (6) or control (7).

First, we allow resistance to evolve as tolerance. Fig. 1(a) partitions the parameter space into regions where I_S and I_R are positive and negative. The solid lines therefore correspond to equality in (21) and (22). We do not observe polymorphism: either the susceptible or the tolerant strain is eliminated. There does exist a limited region where the outcome is contingent on initial conditions, but this also results in monomorphism. This appears to be the general case: we did not find polymorphism for any parameter combinations. The addition of free-living stages therefore does not alter the prediction for a directly transmitted microparasite, namely, that polymorphism is unlikely to evolve through tolerance (Boots and Bowers, 1999; Roy and Kirchner, 2000).

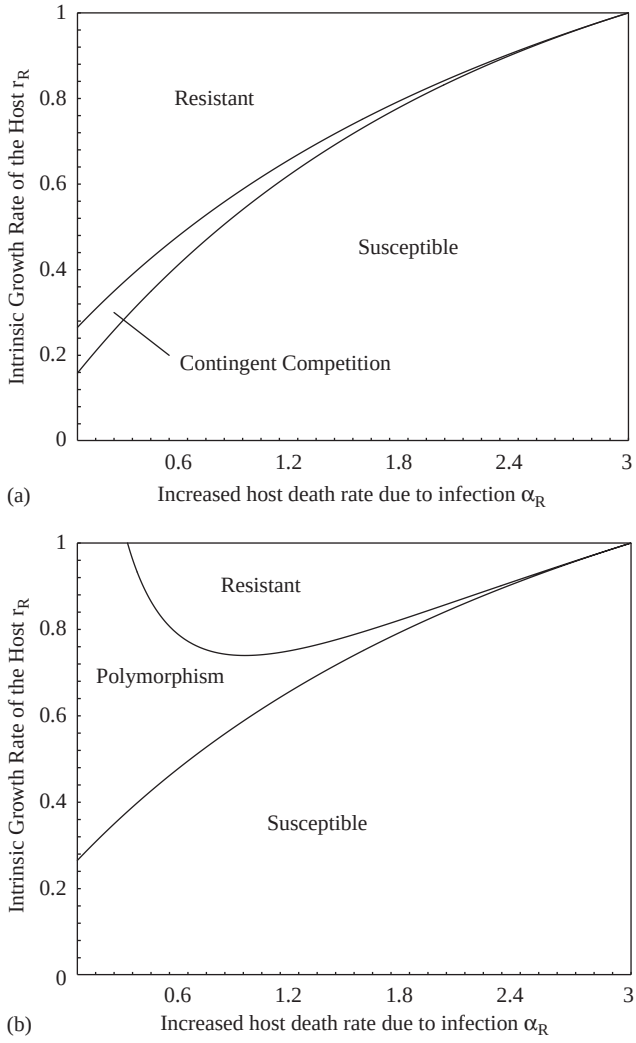

Fig. 1. Outcomes in trade-off space when a resistant mutant characterized by (α_R, r_R) attempts to invade a resident susceptible strain. The susceptible strain has intrinsic growth rate $r_S = 1$ and pathogenicity $\alpha_S = 3$. Resistance evolves as either: (a) tolerance, or (b) control. The 'resistant' region corresponds to $I_R > 0$, $I_S < 0$; the 'susceptible' region to $I_R < 0$, $I_S > 0$; 'contingent competition' corresponds to $I_R < 0$, $I_S < 0$, and polymorphism to $I_R > 0$, $I_S > 0$. Other parameters are: $q = 0.1$, $\beta = 0.25$, $\gamma = 1.5$, $b = 0.5$, $\mu = 1$, $\omega = 10$ (tolerance) and $\phi = 10/3$ (control).

When resistance evolves as control, polymorphism occurs over a significant region (Fig. 1(b)). It is most likely to occur between dissimilar strains, such that the

resistant strain possesses a much smaller pathogenicity. The region of polymorphism becomes increasingly narrow as the degree of similarity between the resistant and susceptible strain increases. Note the only difference between the two diagrams lies in the position of the $I_S = 0$ line. In Fig. 1(a) this lies below the $I_R = 0$ line, whereas in Fig. 1(b) it lies above it. Examining the resistant equilibrium (12) we find that a lower value of λ_R (due to control) increases the total host density $X_R^* + Y_R^*$, and reduces the density of infective particles Z_R^*. A putative susceptible invader therefore faces an increased level of resource competition, but a reduction in the force of infection. The overall effect on I_S may theoretically be either positive or negative. However, our results indicate that I_S will increase under control (as compared to tolerance with the same parameters). Faced with a controlling rather than a tolerant competitor, the susceptible strain experiences a reduced force of infection that outweighs the increase in resource competition. Graphically, this shifts the $I_S = 0$ line upwards, reducing the region of parameter space where the susceptible strain is eliminated and precluding contingent competition as an outcome. Interpreted biologically, the presence of a control strain reduces the density of infective particles, the opportunities for new infections, and hence the selective pressure for resistance.

4. Adaptive dynamics

In the preceding analysis, the susceptible strain was assumed to be resident and putative invaders had higher resistance and a lower growth rate. If a resistant strain was able to invade, it was shown to either eliminate the susceptible strain or coexist with it in a dimorphism. However, after an initial invasion has taken place, further mutations may occur to challenge the new equilibrium. There may indeed be many evolutionary steps before the final equilibrium is reached. We therefore embed our single-step algorithm within an adaptive dynamical framework. This assumes that mutations are small and rare and that the system reaches its attractor before a new mutation occurs. This approach allows us to determine whether the evolutionary behaviour outlined for the 'susceptible-resistant' analysis can occur as a result of many evolutionary steps. In particular, it enables us to examine whether polymorphism can evolve from an initially monomorphic resident. We assume explicit trade-offs for tolerance and control, such that a given level of resistance is associated with a particular reduction in growth rate.

The invasion exponent I_R gives the fitness of a resistant mutant in the environment determined by the susceptible strain. In the general case, the resident strain is not necessarily susceptible, but may have any level of resistance with associated growth rate (assuming a particular trade-off). Nearby mutants may be either more or less resistant and are also subject to the trade-off constraint. The invasion exponent for a given mutant (α_M, r_M) attempting to invade a resident strain (α_E, r_E) at equilibrium is:

$$I_M = r_M - q(X_E^* + Y_E^*) - \frac{\beta Z_E^*}{(\alpha_M + \gamma + b)} \times \{\alpha_M - (r_M - q(X_E^* + Y_E^*))\} > 0. \quad (23)$$

This is identical to the invasion exponent (22), except that the subscripts M and E are now used to identify the mutant and the resident strain, respectively.

The theory of adaptive dynamics (Geritz et al., 1998; Metz et al., 1996) uses fitness expressions to determine the position and nature of singular (fixed) points of evolution. Typically, singular points are determined from Pairwise Invadability Plots (PIPs), which display graphically the sign of the fitness function of a mutant strain. The way in which the parameter space is partitioned into fitness regions can be used to assess whether a singular point exhibits a number of evolutionary properties. At present, we restrict ourselves to two particular properties. Firstly, if nearby resident strategies not at the singular point may be invaded by those closer to it, we say it is convergence stable (CS), as local mutation proceeds towards it. Second, a singular point is an evolutionarily stable strategy (ESS) if, once resident, it resists invasion by all local mutants (a global ESS resists invasion by all possible mutants). For a fuller explanation of adaptive dynamics and the technique of pairwise invadability plots, see Geritz et al. (1998).

We assume explicit trade-offs between pathogenicity (α) and intrinsic growth rate (r). When resistance evolves as control, this implies an additional relationship between host growth and the pathogen's production rate (λ). In this study we restrict our consideration to nonlinear trade-off curves (Fig. 2). For example, with a decelerating trade-off, the cost (the reduction in growth rate) of a given increment of resistance becomes less as the investment in resistance increases (i.e. there are increasing benefits of resistance). Given a particular cost structure, we generate the corresponding pairwise invadability plot and determine the outcome of evolution.

We assume a weakly decelerating trade-off (Fig. 2(b)) and compare the pairwise plots when resistance evolves as control (Fig. 3(a)) and tolerance (Fig. 3(b)). The pathogenicity of the resident strategy is given on the horizontal axis and the mutant's pathogenicity on the vertical axis. Where the region contains a plus (+) sign this indicates the mutant strain has a positive fitness and may invade the resident equilibrium. A minus (−) sign indicates the fitness is negative such that the mutant will

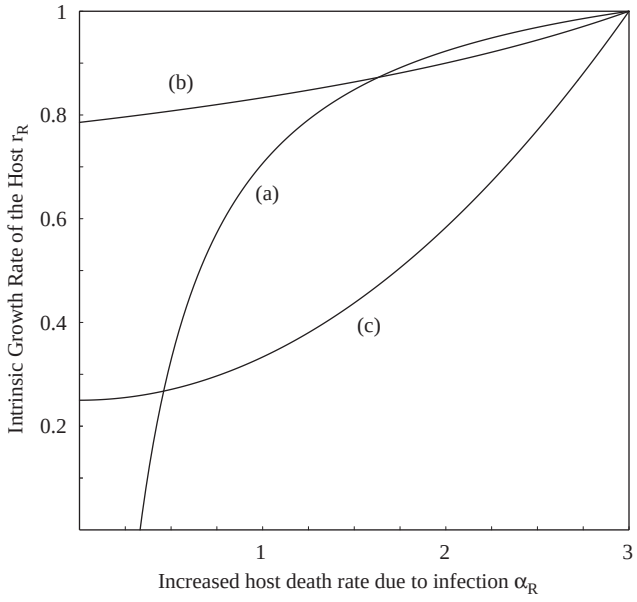

Fig. 2. Nonlinear trade-off curves. Here, there is a cost of reduced pathogenicity (resistance) in terms of a lower intrinsic growth rate. Resistance evolves from the initial susceptible strain defined by $\alpha = 3$ and $r = 1$. The examples shown are: (a) accelerating costs, (b) weakly decelerating costs, and (c) strongly decelerating costs.

be eliminated. In (a) resistance evolves as control; the intersection at $\alpha^* = 0.39$ indicates a singular strategy at which the local fitness gradient is zero. At resident values of α below this singular point, mutants with bigger α have positive fitness (indicated by the positive (+) region to the left of α^* and directly above the main diagonal). Similarly, given a resident above the singular point, mutants with smaller α have negative fitness (the (−) region to the right of α^* and below the main diagonal). Directional selection therefore moves towards the singular strategy at $\alpha^* = 0.39$ and the fixed point is convergence stable. However, the singular strategy does not itself resist invasion by mutants with larger or smaller pathogenicity (the vertical through α^* lies entirely in a positive (+) region). Once the fixed point is reached (or very near to it) we observe disruptive selection. Here the resident can be invaded by strains on either side of the singular point, and a process of evolutionary branching occurs. This leads ultimately to a dimorphic equilibrium composed of two subpopulations, one highly resistant ($\alpha^* = 0$) and the other highly susceptible ($\alpha^* = 3$). This is seen in evolutionary time by simulating the mutation-selection process and tracking the resident strategy (Fig. 3(c)). In

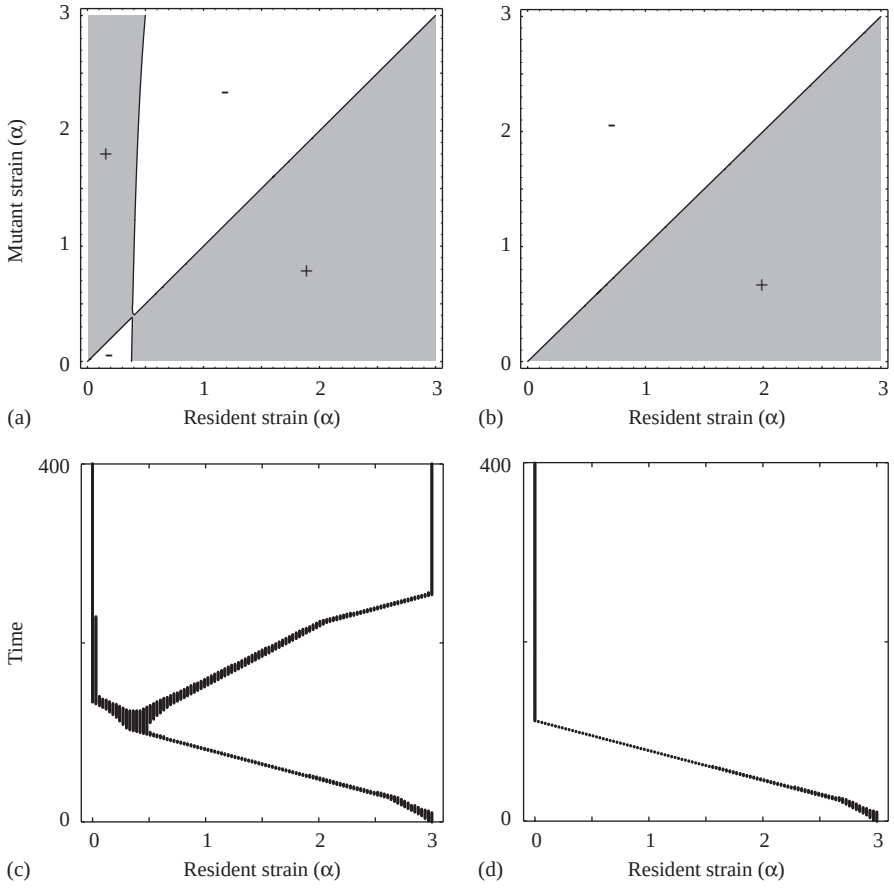

Fig. 3. Pairwise invadability plots (PIPs) when resistance evolves as: (a) control, and (b) tolerance. In both cases, there is a decelerating trade-off, such that $r = 0.5 + 2/(7 - \alpha)$. Other parameters are: $q = 0.1$, $\beta = 0.25$, $\gamma = 1.5$, $b = 0.5$, $\mu = 1$, $\omega = 10$ and $\phi = 10/3$. The corresponding plots of how α changes in evolutionary time are shown in (c) for control, and (d) for tolerance.

Fig. 3(b) resistance evolves as tolerance under the same trade-off. There is no internal strategy at which the fitness gradient is zero and the optimal fitness occurs at the minimum value. The evolutionary process converges at $\alpha = 0$ (Fig. 3(d)).

Applying a different trade-off, we investigated how the optimal investment in resistance differs with control and tolerance. We defined the optimal investment in resistance to be the difference in pathogenicity between optimally resistant (ESS) and susceptible hosts. We assumed an accelerating trade-off (Fig. 2(a)), applicable to both types of resistance. Using the method of pairwise invadability plots we checked that the singular strategies were both convergence and evolutionarily stable (CS and ESS). The optimal strategies are plotted as a function of the transmission rate (Fig. 4(a)). As transmission increases, the investment in both types of resistance increases. Hosts therefore invest more in defence when faced with highly infectious pathogens. We also investigated the effect of the natural mortality rate (Fig. 4(b)). As lifespan increases, resistance becomes increasingly beneficial and the optimal investments are higher: longer-lived hosts invest more in defence.

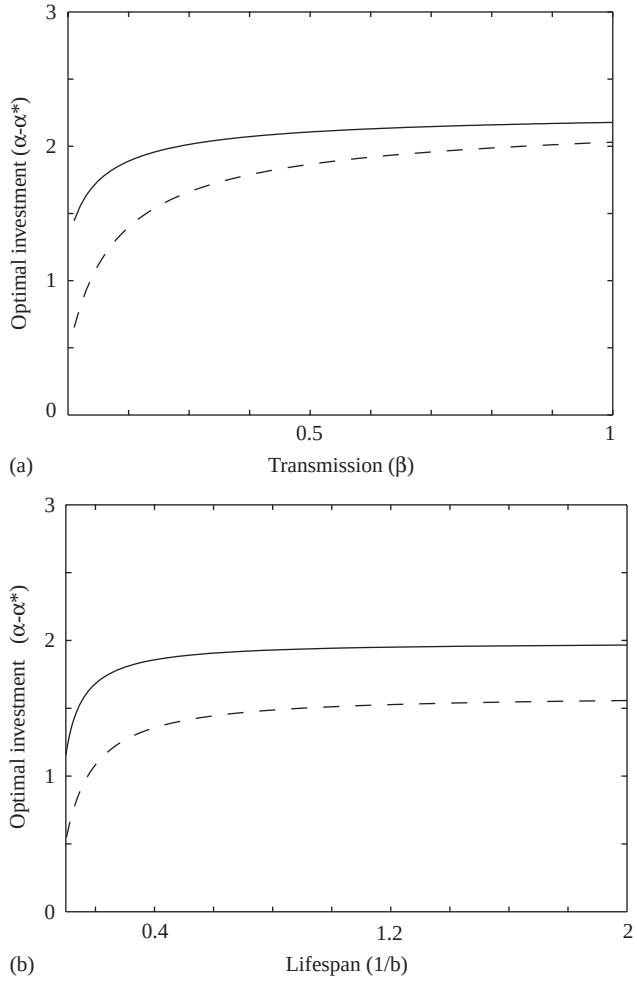

Fig. 4. Optimal investments in resistance, defined as the reduction in pathogenicity achieved by an optimally resistant host, from that experienced by the initial susceptible strain. The optimal investment in resistance is therefore $(\alpha_S - \alpha^*)$ where α_S is the pathogenicity of the susceptible strain and $\alpha*$ is the optimal pathogenicity. The solid line corresponds to the optimal strategy when resistance evolves as tolerance, and the dotted line to the optimal investment in control. In both cases there are accelerating costs of resistance such that $r = 72/62 - 1/[2(\alpha + 0.1)]$ and the optimal strategy is convergence and evolutionarily stable (both CS and ESS). The susceptible host is defined by $\alpha_S = 3$. In (a) there is a constant natural mortality rate $b = 0.5$; in (b) there is a constant transmission rate $\beta = 0.25$. Other parameters are: $q = 0.1$, $\gamma = 1.5$, $\phi = 10/3$, $\omega = 10$ and $\mu = 1$. Note that $\phi\ \alpha_S = \omega$ to allow comparison between tolerance and control (susceptible strains are defined by $\lambda_S = 10$ in each case).

Looking at Figs. 4(a) and (b), the optimal investment in tolerance is always greater than the investment in control. This is because control also reduces the prevalence of infective particles, the force of infection, and the selective pressure for further resistance. However, as transmission rate increases, the difference between the investments becomes smaller (Fig. 4(a)). There is stronger pressure on the host to reduce the force of infection, and resistance mechanisms conferring reduced transmission increase their benefits at a faster rate. Despite the cost of resistance, it is still worth allocating more resources to controlling the pathogen. By contrast, in response to greater host longevity, the two defences increase their benefits equally. As the average lifespan increases, the difference between the optimal allocations remains roughly constant (Fig. 4(b)).

5. Discussion

We have shown that different host defences lead to different evolutionary outcomes. As a general rule, tolerance will result in monomorphism. In contrast, the evolution of control may lead to dimorphism of extreme strains. Dimorphism is achieved when two distinct strategies are able to invade each other, and this is only likely when resistance evolves as control. Tolerance does not restrict the growth of the pathogen: on average, the longer-lived infected hosts produce more free-living infective particles, increasing the force of infection βZ_R^* and hence the selective pressure for further tolerance. This acts as a form of 'positive feedback' such that resistant hosts are better able to resist invasion by susceptible genotypes. The evolutionary dynamics of tolerance to a free-living pathogen are therefore analogous to those observed for a directly transmitted microparasite (Boots and Bowers, 1999).

A control strategy reduces pathogenicity, not through 'tolerating' the deleterious effects of disease, but rather by limiting pathogen reproduction. Biologically, the pathogen's growth rate inside the host is likely to correlate with tissue damage; in 'controlling' the virus, the host necessarily reduces this growth rate.

This corresponds to lower viral productivity, reducing the force of infection and hence the selective pressure for more resistance. This 'negative feedback' may allow a susceptible host to invade a more resistant one, promoting dimorphism of extreme strains. The free-living model employed here makes the mechanism of control explicit, by reducing the production rate of infective stages. The analysis, however, is not strictly limited to indirectly transmitted pathogens. There is often assumed to be a positive relationship between transmission rate and virulence (Anderson and May, 1982; Bremermann and Pickering, 1983; Lenski and May, 1994; Restif and Koella, 2003, 2004; van Baalen and Sabelis, 1995). Alternatively, virulence may be negatively correlated with the recovery rate (Anderson and May, 1982). In both these cases, resistance mechanisms that reduce pathogenicity may also inhibit pathogen transmission. The evolution of control may therefore be a likely host response to parasitism.

There is evidence that tolerance and avoidance may not be mutually exclusive adaptive traits. Roy and Kirchner (2000) showed that a single gene providing both types of resistance can be maintained or become fixed in a population. Restif and Koella (2004) modelled the simultaneous evolution of tolerance and recovery (faster clearance of the pathogen) as distinct traits. When investment in either trait incurred accelerating costs, in some cases the host split its defences between the two investments in order to reduce the total cost. This provides a parallel to our study, given that control may be viewed as a composite form of resistance combining the components of avoidance (lower density of infective particles) and tolerance (reduced effect of virulence). Where the previous study assumed accelerating costs of both avoidance and tolerance, we investigated accelerating and decelerating costs of control, where investment in one component of defence necessitated a given investment in the other (since there is a fixed relationship between pathogenicity and the production rate of infective particles).

In natural systems, it is clearly important to distinguish whether resistance is conferred by one or more defence mechanisms. Where resistant hosts exhibit both tolerance and avoidance components, this may be due to a single control trait. This may make it easier to predict the evolutionary outcome, particularly if we can determine the particular trade-off involved. It would also be interesting to investigate the consequences of decelerating trade-offs in Restif and Koella's model, since decelerating costs of avoidance are known to allow branching (Boots and Haraguchi, 1999). What balance of costs and benefits to avoidance and tolerance would select for polymorphism in the host? Extrapolating from previous results, polymorphism should be less likely when the overall bias is towards higher investment in tolerance (Roy and Kirchner, 2000).

When reduced pathogenicity exhibits equal (accelerating) costs for control and tolerance, hosts will invest relatively less in control (Fig. 4). This is because control lowers the force of transmission and therefore the selective pressure for resistance (Boots and Bowers, 1999). Where separate genes confer tolerance and avoidance, the overall cost of resistance may be either higher or lower, depending on how the individual costs combine (Restif and Koella, 2004).

We have shown that a weakly decelerating trade-off may lead to maximal investment in tolerance (Fig. 3(d)). However, different trade-offs (accelerating or strongly decelerating) were found to select for intermediate or even zero investment in tolerance. Tolerance is most likely to evolve in response to high transmission rates and low virulence (Boots and Bowers, 1999; Restif and Koella, 2003). In this context, virulence refers to the base pathogenicity experienced by susceptible, intolerant hosts. Also, the model of Restif and Koella (2003) predicted only locally stable investments in tolerance: a highly 'intolerant' host with high fecundity may be capable of invading the local ESS and driving the pathogen to extinction. Our model only considered host strains capable of supporting the pathogen—even susceptible (i.e. intolerant) hosts would exhibit a certain degree of innate resistance. Thus we fixed an upper limit on the level of pathogenicity experienced, which also implied a maximum growth rate (due to the trade-off). Pathogen extinction through invasion by a highly fecund and intolerant mutant was therefore assumed to be impossible. Nevertheless, we note that convergence towards the branching point (Fig. 3(c)) may be dependent on initial conditions: when the initial pathogenicity experienced by a susceptible host is high enough, evolution proceeds towards a monomorphic strategy with high fecundity and high pathogenicity. Whether dimorphism is actually attained as the result of selection may therefore be contingent on the level of susceptibility exhibited by the resident genotype, although in real systems there are likely to be constraints on the level of intolerance.

The dynamics in a free-living host-microparasite system can exhibit population cycles where those for a comparable directly transmitted system cannot (Boots and Bowers, 1999). The invasion analysis in this study assumed stable equilibrium behaviour. However, when the underlying dynamics are non-equilibrium our invasion exponents, (21) and (22), are not valid and need to be replaced by the largest Lyapunov exponent (Metz et al., 1992). However, it has been shown that the evolutionary behaviour predicted for equilibrium dynamics is robust to oscillatory dynamics provided the oscillations do not become extreme (White et al., submitted). Understanding how the introduction of

population cycles would affect the results of this study may form the basis of future work.

The chief aim of this study was to investigate the evolutionary dynamics of tolerance and control as distinct defence strategies in response to pathogenic infection. The two forms of resistance have been shown to attain different evolutionary optima. Control has been shown to promote a wider range of evolutionary outcomes, in particular dimorphism of extreme strains. This may go some way to explaining the high level of polymorphisms observed in nature.

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Appendix A

Here, we determine the invasion criterion (21) using a Jacobian analysis. Taking the variables in the order (X_S, Y_S, Z, X_R, Y_R) the associated Jacobian matrix evaluated at the susceptible equilibrium (11) has the form:

$$J = \begin{pmatrix} A & B \\ O & C \end{pmatrix}. \tag{A.1}$$

Here A, B, C are sub-matrices of size 3×3, 3×2 and 2×2 respectively, and O is the 2×3 zero matrix. Due to the linear independence of A and C, we can determine the stability conditions from two separate problems: a cubic equation corresponding to stability with respect to the pathogen (derived from A) and a quadratic corresponding to stability with respect to invasion by the resistant strain (derived from C). From our assumption that the susceptible strain is capable of supporting the pathogen, the stability conditions pertaining to A are known to be satisfied. It remains to consider the stability of C.

$$C = \begin{pmatrix} r_R - q(X_S^* + Y_S^*) - \beta Z_S^* & r_R - q(X_S^* + Y_S^*) + (\gamma + b) \\ \beta Z_S^* & -(\alpha_R + \gamma + b) \end{pmatrix}. \tag{A.2}$$

The matrix C has trace, τ, and determinant, Δ, given by

$$\tau(C) = r_R - q(X_S^* + Y_S^*) - \beta Z_S^* - (\alpha_R + \gamma + b), \tag{A.3}$$

$$\begin{aligned} \Delta(C) = {} & \{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}\{-(\alpha_R + \gamma + b)\} \\ & - \{\beta Z_S^*\}\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\}. \end{aligned} \tag{A.4}$$

The determinant (A.4) will certainly be negative unless the first term $\{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}$ is less than zero (if this term is greater than zero then the final term $\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\}$ is necessarily greater than zero and the determinant must be negative). If this first term is less than zero, we can see from (A.3) that the trace must also be negative. The equilibrium (11) is therefore stable, if and only if the determinant is greater than zero. If the determinant is negative, then the equilibrium is unstable and a resistant mutant characterized by $(\alpha_R,\ r_R)$ can invade. The condition for a stable equilibrium is therefore:

$$\begin{aligned} & \{r_R - q(X_S^* + Y_S^*) - \beta Z_S^*\}\{-(\alpha_R + \gamma + b)\} \\ & \quad - \{\beta Z_S^*\}\{r_R - q(X_S^* + Y_S^*) + (\gamma + b)\} > 0. \end{aligned} \tag{A.5}$$

Reversing the sign of this inequality gives the condition for a resistant mutant strain to invade. Some algebraic manipulation allows this condition to be expressed as

$$\begin{aligned} I_R = {} & r_R - q(X_S^* + Y_S^*) - \frac{\beta Z_S^*}{(\alpha_R + \gamma + b)} \\ & \times \{\alpha_R - (r_R - q(X_S^* + Y_S^*))\} > 0. \end{aligned} \tag{A.6}$$

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