JOURNAL OF Evolutionary Biology

doi: 10.1111/jeb.12719

The epidemiological feedbacks critical to the evolution of host immunity

R. DONNELLY*, A. WHITE* & M. BOOTS†

*Department of Mathematics and the Maxwell Institute for Mathematical Sciences, Heriot-Watt University, Edinburgh, UK
†College of Life and Environmental Sciences, University of Exeter Cornwall Campus, Penryn, UK

Keywords:

density dependence;
ecology;
epidemiology;
evolution;
resistance.

Abstract

We examine in detail how epidemiological feedbacks combine with costs and benefits to determine the evolution of resistance by systematically analysing continuously stable strategies (CSS) for different host–parasite frameworks. The mode of resistance (innate versus acquired), the nature of the host (i.e. life-history and immunological memory) and the nature of the disease (effects on fertility or mortality) all impact on the feedbacks that are critical to the evolution of resistance. By identifying relationships between CSS investment and the underlying epidemiological feedback for each mode of resistance in each framework, we distil complex feedbacks into simple combinations of selection pressures. When the parasite does not affect fertility, CSS investment reflects only the benefit of resistance and we explain why this is markedly different for innate and acquired resistance. If infection has no effect on host fertility, CSS investment in acquired immunity increases with the square of disease prevalence. While in contrast for evolving innate resistance, CSS investment is greatest at intermediate prevalence. When disease impacts fertility, only a fraction of the host population reproduce, and this introduces new ecological feedbacks to both the cost of resistance and the damage from infection. The multiple feedbacks in this case lead to the alternative result that the higher the abundance of infecteds, the higher the investment in innate resistance. A key insight is that maximal investment occurs at intermediate lifespans in a range of different host–parasite interactions, but for disparate reasons which can only be understood by a detailed analysis of the feedbacks. We discuss the extension of our approach to structured host populations and parasite community dynamics.

Introduction

During evolution, changes in the dominant genotypes within a population lead to phenotypes that may alter population ecological dynamics. Such ecological changes can in turn feed back to change the selective pressures on the genotypes. These feedbacks can be complex even in simple models, but using an ecologically explicit approach to modelling evolution, it is possible to distill complex feedbacks into simpler combinations of biologically meaningful selection pressures. In this study, we analyse host resistance by reference to these feedbacks and systematically compare how ecology feeds back to CSS investment for different combinations of host and parasite interactions.

There is substantial variation in host defence and this is likely to reflect the wide range of interactions between hosts and parasites. For example, parasites can damage their hosts by causing a loss of fertility or increasing mortality and hosts may differ in their capacity for immune memory. Despite the immunological complexity of defence, functionally it is achieved through just a few routes (Boots & Bowers, 1999; Schmid-Hempel, 2002). 'Tolerance' mechanisms reduce the damage that infection causes, whereas on the other hand, 'resistance' mechanisms including avoidance, recovery and acquired immunity directly counter the parasite (Miller *et al.*, 2007). Genes conferring resis-

Correspondence: Ruairi Donnelly, Department of Plant Sciences, University of Cambridge, CB2 3EA Cambridge, UK.
Tel.: 00441223330228; e-mail: rd501@cam.ac.uk

tance, as they reduce parasite fitness, in addition to increasing host fitness, cause the prevalence of infection, a dynamic ecological variable, to decline and so reduce the advantage of resistance (Haldane, 1949; Antonovics & Thrall, 1994; Bowers *et al.*, 1994; Boots & Haraguchi, 1999). On the other hand, genes conferring tolerance may cause prevalence to rise, if they lengthen the infectious period, increasing the advantage of tolerance as it spreads through the population (Roy & Kirchner, 2000; Miller *et al.*, 2007). This is a clear instance of the central role that ecological feedbacks play in the evolution of immune defence.

Approaches to modelling evolution by natural selection differ in their treatment of explicit ecology and genetics (Haldane, 1927; Cole, 1954; Lande, 1982; Maynard Smith, 1982; Charlesworth, 1994). In this study, we use an evolutionary invasion analysis approach (Metz *et al.*, 1996; Geritz *et al.*, 1998) in which density-dependent ecological dynamics are explicitly modelled with feedbacks to fitness (but at the expense of genetic detail). The framework assumes a separation of ecological and evolutionary time scales as well as rare mutations of small effect and quantitative continuous phenotypes. The advantage of these simplifying assumptions is that density-dependent and frequency-dependent selection emerge naturally from these eco-evolutionary models and this has proved effective in understanding how population level processes determine evolutionary outcomes. The assumption of quantitative continuous phenotypes is also a good one for the majority of immune mechanisms that are characteristically associated with quantitative trait loci [for example, cytokine activation in Dupuis *et al.* (2000), porcine leucocyte regulation in Edfors-Lilja *et al.* (1998) and rodent Th1 development in Gorham *et al.* (1996)].

There is a large body of theoretical research focused on the evolution of resistance in the context of ecological feedbacks (Antonovics & Thrall, 1994; Bowers *et al.*, 1994; Boots & Haraguchi, 1999; Boots *et al.*, 2009). Nevertheless, understanding the patterns of CSS investment in host defence for different host–parasite systems remains a key challenge. For example, Van Boven & Weissing (2004) and Miller *et al.* (2007) showed that CSS investment in resistance in hosts with permanent immune memory can be low for long-lived species, and Boots *et al.* (2013) demonstrated that this is due to low prevalence as a result of low population turnover at high lifespans. However, there are many counter-intuitive patterns in CSS resistance (Miller *et al.*, 2007) and it remains unclear how ecological feedbacks determine these outcomes. For instance, the key dynamic feedback to resistance has been identified as force of infection in Van Baalen (1998), Boots & Haraguchi (1999) and Van Baalen (2002) yet disease prevalence is emphasized in Miller *et al.* (2007). Here, we determine the eco-evolutionary feedbacks for different host–parasite interactions and use these to explain how key differences in epidemiological context and mode of host defence lead to fundamentally distinct patterns in CSS resistance. Although our study is focused on host–parasite systems, the methods apply more generally and we emphasize that uncovering complex feedbacks is key to understanding the biological processes that underpin evolutionary behaviour.

Materials and methods

Epidemiological model

Following the methods of Anderson & May (1979), we consider a system of nonlinear ordinary differential equations that compartmentalizes total host population density, H into susceptible, S, infected, I and immune/recovered, R, densities

$$\frac{\mathrm{d}S}{\mathrm{d}t} = a(S+\mu I+R) - q(S+\mu I+R)H - bS - \beta SI + (1-v)\gamma I + \delta R \quad (1)$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - (\alpha + b + \gamma)I \quad (2)$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = v\gamma I - (b+\delta)R \quad (3)$$

All parameters are non-negative and $\mu, v \in [0,1]$. Hosts die at natural death rate b. Hosts produce susceptible offspring at rate a which is limited by intraspecific crowding, q, so that the carrying capacity in the absence of disease is given by $K = (a-b)/q$. It follows from this host-only equilibrium (i.e. $\hat{H}_0 = K$) that $b > a$ is a necessary condition for a nonzero host population. The parasite is maintained at endemic levels when the host-only equilibrium $\hat{H}_0$ becomes unstable. Analysis of the eigenvalues shows that this occurs when $R_0 > 1$ where $R_0 = \beta\hat{H}_0/(\alpha + b + \gamma)$. Pathogens alter the fecundity of infected hosts such that hosts do not reproduce while infected when $\mu = 0$ or there is no effect on host reproduction when $\mu = 1$. Transmission of infecteds is a mass action process between susceptible and infected types, with transmission coefficient β. Infected hosts suffer additional disease-induced mortality (virulence) at rate α. Infected hosts recover at rate γ, and a proportion of these recoveries, v, acquire immunity to the pathogen which wanes at rate δ, whereas the remaining individuals return to a susceptible state.

This model captures several infection scenarios of interest. If $v = 0$ the model represents a *Susceptible-Infected-Susceptible* (SIS) framework, where there is no immune memory and recovered individuals are completely susceptible to the infection. On the other hand, if $v = 1$ and $\delta = 0$, it represents a *Susceptible-Infected-Recovered* (SIR) model with lifelong immunity (or *SIRS* with waning immunity if $\delta > 0$). Host resistance can be

achieved through the following routes: Avoidance, which decreases the rate of transmission (β); Recovery, which increases the rate of clearance of infection (γ). Finally, acquired immunity, which either increases the probability of inducing acquired immunity (v) or increases the expected duration of acquired immunity through changes in δ (Miller *et al.*, 2007).

Evolutionary model

The association of resistance with physiological costs through the development and maintenance of resistance capability has a firm empirical basis (Fuxa & Richter, 1989; Boots & Begon, 1993; Kraaijeveld & Godfray, 1997; Poulsen *et al.*, 2002). Following these studies, we assume that costs are paid through decreased host fecundity (i.e. we make avoidance, recovery and acquired immunity decreasing functions of host reproduction rate).

In evolutionary invasion analysis (Metz *et al.*, 1996; Geritz *et al.*, 1998), invasion fitness, Θ, is the asymptotic growth rate of a population of mutant hosts introduced at low density into an environment set by a population of resident hosts at equilibrium, that is

$$\Theta_r(m) = \frac{1}{H^m}\frac{\mathrm{d}H^m}{\mathrm{d}t}\bigg|_{H^r = \hat{H}^r, H^m = 0} \tag{4}$$

In eqn 4, r and m denote resident and mutant, and we are evaluating the resident population at its dynamic equilibrium (i.e. $H^r = \hat{H}^r$), whereas in contrast the mutant population is so rare, it has no impact on the dynamics (i.e. $H^m = 0$). Equations 1–3 can be extended to encompass both resident and mutant subpopulations. The ODEs for the mutant strain differs to eqns 1–3 in two respects. Infection occurs upon contact with both resident and mutant infecteds (i.e. $\beta^m(I^r + I^m)$), and host birth rate is reduced by a factor depending on total host density (i.e. $q(S^m + \mu I^m + R^m)(H^r + H^m)$). The rate of change of the mutant host population, $\mathrm{d}H^m/dt$, is then the sum of the mutant equations, that is

$$\begin{aligned}\frac{\mathrm{d}H^m}{\mathrm{d}t} = (&S^m(a^m - qH^{tot} - b) + I^m(\mu(a^m - qH^{tot}) - b - \alpha) \\ &+ R^m(a^m - qH^{tot} - b))|_{H^r = \hat{H}^r, H^m = 0}\end{aligned} \tag{5}$$

where $H^{tot} = H^r + H^m$. The expressions in parentheses in eqn 5 are the per capita growth rates of the mutant host population when the rare mutants are in the respective classes, denoted σ_S^m, σ_I^m and σ_R^m. Invasion fitness can therefore be written

$$\Theta_r(m) = (p_S^m\sigma_S^m + p_I^m\sigma_I^m + p_R^m\sigma_R^m)|_{H^r = \hat{H}^r, H^m = 0} \tag{6}$$

where p_S^m is the proportion of mutant hosts who are susceptible (i.e. $p_S^m = S^m/H^m$ and similarly for p_I^m and p_R^m). Substituting the relation $p_S^m = 1 - p_I^m - p_R^m$ into eqn 6 and noticing in eqn 5 that $\sigma_S^m = \sigma_R^m$ leads to

$$\Theta_r(m) = (\sigma_S^m - p_I^m((1-\mu)(a^m - qH^r) + \alpha))|_{H^r = \hat{H}^r, H^m = 0} \tag{7}$$

As the first term in eqn 7 is equivalent to the fitness of uninfected hosts, the second term provides an exact expression for the fitness loss due to infection. It is equal to the product of prevalence in the mutant population and harm caused by infection, henceforth denoted D, that is

$$D = (1-\mu)(a^m - qH^r) + \alpha \tag{8}$$

This shows that infection can be fought with two distinct strategies that offset fitness loss, $p_I^m D$. Resistance reduces prevalence, p_I^m, and on the other hand, tolerance reduces damage D (by alleviating either disease-induced mortality or loss of fertility). For simplicity, we henceforth omit the $|_{\hat{H}}$ notation, but it will be understood that all resident densities are evaluated at their endemic attractor and any mutant density is small enough to be evaluated as zero.

We introduce a trait, ω, that is useful in the analysis, determining the phenotypic value of quantitative resistance (i.e. $\omega = f(a)$ where mutant values of resistance are given by $\omega^m = f(a^m)$) which can represent avoidance, recovery or acquired immunity. The host population evolves in the direction of the mutant gradient of invasion fitness until it reaches an evolutionary singularity. There, by definition, the fitness gradient is zero so that singularities, a^*, satisfy

$$\frac{\partial\Theta}{\partial a^m}|_* = 0 \tag{9}$$

where the vertical bar indicates that the expression is evaluated at the evolutionary equilibrium where resident equals mutant (i.e. $r = m = *$). A singularity, a^*, is evolutionary stable (ES) if $\partial^2\Theta/\partial a^{m2} < 0$ and convergence stable (CS) if $\partial^2\Theta/\partial a^{r2} - \partial^2\Theta/\partial a^{m2} > 0$. A singularity that is both ES and CS is uninvadable as well as attracting in an evolutionary sense (i.e. a Continuously Stable Strategy, CSS, (Eshel, 1983) - an end point of evolution). In this study, we analyse the dependence of CSS investment in resistance on the underlying ecological model for a range of model formulations. Our results are based on the assumption of diminishing returns for a host investing in resistance, that is a continuous trade-off between resistance and reproduction of any shape, provided that reproduction is a decreasing function of resistance and that costs accelerate. When the parasite causes a loss of fertility, singular investment in resistance with accelerating costs is a CSS (Hoyle *et al.*, 2008), and hence an end point of evolution. When the parasite has no effect on fertility, singular investment in resistance with accelerating costs is a CSS when costs are sufficiently strongly accelerating (de Mazancourt &

Dieckmann, 2004; Bowers *et al.*, 2005). The results presented in this study assume a trade-off that makes the singularity studied a CSS (i.e. Figs 1–4 are generated from trade-offs with strongly accelerating cost structures); however, the analysis outlined in this work applies more generally for any trade-off with an accelerating cost structure (but note that once the singularity is reached, branching can occur from the singular point we describe if costs accelerate only weakly).

Solving eqn 9 for the invasion fitness given by eqn 7 and rearranging indicates that evolutionary singularities of evolving resistance satisfy

$$\left.\frac{d\omega^m}{da^m}\right|_* = \left.\frac{(p_S + \mu p_I + p_R) - D\frac{\partial p_I^m}{\partial a^m}}{D\frac{\partial p_I^m}{\partial \omega^m}}\right|_* \tag{10}$$

$$= -\left.\frac{C}{B}\right|_* \tag{11}$$

where the numerator in eqn 10 represents net cost and is therefore denoted by C; that is, C represents the change in fitness induced by a reduction in reproduction that follows from an increased investment in resistance. As $\partial p_I^m/\partial \omega^m < 0$, that is, prevalence is a decreasing function of resistance, the denominator in eqn 11 represents minus benefit and is denoted $-B$, i.e. B represents the change in fitness induced by an increased resistance capability.

Equation 10 gives the position on the resistance–reproduction trade-off which corresponds to a singularity. As a consequence of costs rising with increasing investment with diminishing returns, any increase in the right-hand side of eqn 10 results in the location of the singularity shifting to low values of mutant reproduction. This corresponds to high investment in resistance, see Fig. S1.1. This implies that singular resistance is the result of a cost benefit analysis so that CSS investment in resistance, ψ^* ($\omega(a)$ represents the phenotypic value of resistance, whereas ψ represents investment in the phenotype), is high whenever the benefit is large relative to the cost, that is

$$\psi^* \sim \left.\frac{B}{C}\right|_* \tag{12}$$

where we use the symbol $\sim$ to indicate that the left-hand side is a *nonlinear* monotonically increasing function of the right-hand side feedback, that is in eqn 12, ψ^* increases when $\frac{B}{C}$ increases and similarly ψ^* decreases when $\frac{B}{C}$ decreases. A strength of our analysis is that the results are not specific to a particular functional form of trade-off, but rather hold for any trade-off that features diminishing returns on investment. As

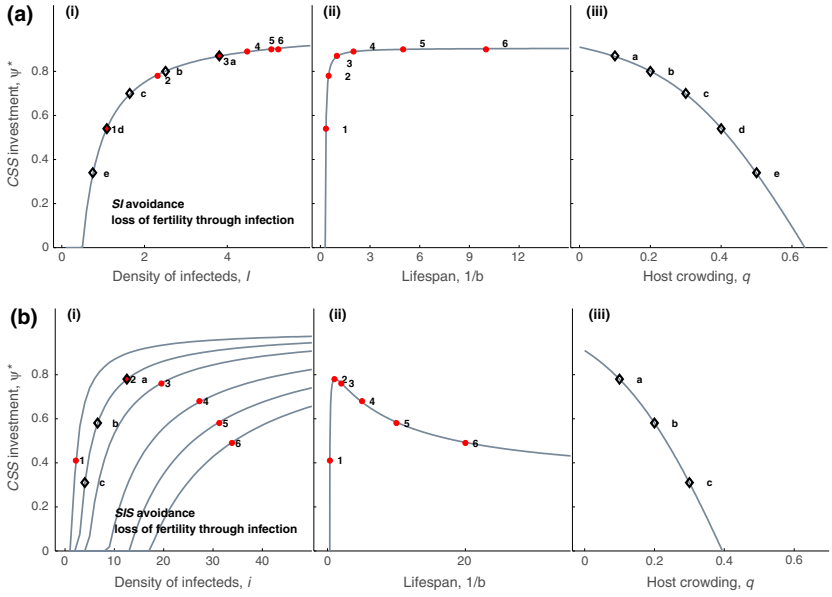

Fig. 1 CSS investment in innate resistance to an infection associated with loss of fertility. In (a), there is no recovery from infection, that is $\gamma = 0$. In (b), there is recovery from infection $\gamma = 5$. In both (a) (i) and (b) (i), CSS investment is driven by density of infecteds, I, whereas (ii) and (iii) throughout show the variation in investment as lifespan and crowding change. Closed circles and diamonds in each figure represent the final level of evolved resistance from ODE simulations of the evolutionary process. The resistance–reproduction trade-off was $\omega(a) = (1 - exp(-Q^*(amax - a)))/(1 - exp(-Q^*(amax - amin)))$ with $Q = 5$, $amax = 5$, $amax = 3$ for $\beta = \beta_0(1 - 0.4\omega(a))$. Parameters were: μ=0 $\beta_0 = 1$ in (a) and (b) and $\alpha = 4$ in (a) and $\alpha = 0.1$ in (b). *CSS* investment relies on case mortality which is always 1 when $\gamma = 0$ but depends on natural mortality when $\gamma > 0$ leading to curves for different values of natural mortality in (b) (i). The value of b for each curve corresponds to the location of the circular simulation marker in (b) (ii); that is, 1 corresponds to L=0.5, 2 to L=1, 3 to L=2, 4 to L=5, 5 to L=10 and 6 to L=20 where lifespan, L, equals $1/b$.

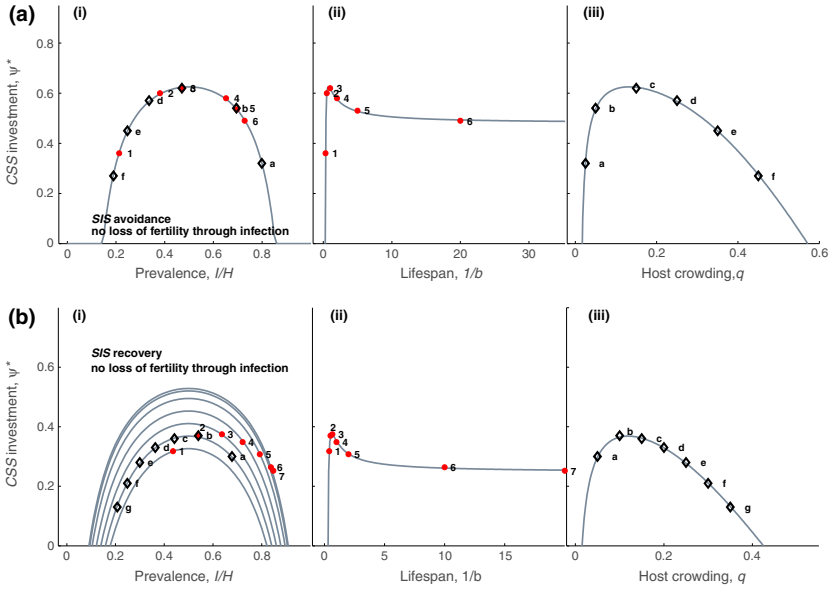

Fig. 2 CSS investment in innate resistance to an infection that has no impact on host fertility where the host has no capacity for immune memory, that is SIS population. In (a), the resistance is through avoidance, whereas in (b), it is through recovery. In both (a) (i) and (b) (i), CSS investment is driven by disease prevalence, I/H, whereas (ii) and (iii) throughout show the variation in investment as lifespan and crowding changes. Closed circles and diamonds in each figure represent the final level of evolved resistance from ODE simulations of the evolutionary process. See caption of figure 1 for the trade-off, $\omega(a)$ which affects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$ and affects recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$. In both (a) and (b) $\mu = 1$. In (a): $\beta_0 = 1$, $\alpha = 4$, $\gamma = 0.1$ and $b = 1$. In (b): $\alpha = 3$, $\gamma_0 = 2.5$ and $b = 2$. In the case of recovery, CSS investment is in the length of the infectious period which depends on natural mortality leading to curves for different values of natural mortality in (b) (i). The value of b for each curve corresponds to the location of the circular simulation marker in (b) (ii); that is, 1 corresponds to $L = 1/4$, 2 to $L = 1/2$, 3 to $L = 1/1.5$, 4 to $L = 1$, 5 to $L = 2.5$, 6 to $L = 10$ and 7 to $L = 20$ where lifespan, L, equals $1/b$.

our results allow for flexibility in trade-off shape, the relationship between feedback and CSS investment will not generally be linear.

The exact expression for host fitness is key to explaining the role of costs and benefits. However, the terms p_S^m and p_I^m that appear in cost and benefit (see eqn 10) in practice are too complex to calculate. A proxy for invasion fitness is a fitness criterion that shares the same singularities and evolutionary behaviour. Following the biologically inspired proxy of Bowers & Turner (1997), we replace the proportion of mutants who are infected, p_I^m, with the proportion of the expected lifespan a mutant spends infected, $\tilde{p}_I^m = T_I/T_H$, and similarly $\tilde{p}_S^m$ for p_S^m. The proxy replacements, $\tilde{p}_S^m$ and $\tilde{p}_I^m$, allow CSS investment in resistance to be expressed solely in terms of state variables and parameters of the epidemiological model. See Supporting Information S3 for an explanation of why this replacement produces a proxy for invasion fitness.

Example: avoidance resistance

To provide a concrete example of how we determine the feedback on investment, we consider in detail the evolution of avoidance in a host population. For simplicity, we assume that the host has no ability to recover from infection ($\gamma = 0$) and that an infected host does not reproduce ($\mu = 0$), but see Supporting Information S2 for a comprehensive account of our results when infected hosts reproduce.

A mutant host will be born susceptible and will either die susceptible or become infected. Infected individuals remain in that state until death. The average time a mutant host is susceptible, denoted T_S, is the inverse of the rates at which individuals leave the mutant susceptible class, that is $T_S = 1/(b + \beta^m(I^m + I^r))$, see eqn 1. The average time a mutant host is infected, denoted T_I, is the probability the susceptible mutant becomes infected multiplied by the average time the infected host remains infected i.e. $T_I = [\beta^m I^r/(b + \beta^m I^r)] \times [1/(\alpha + b)]$, see eqn 2.

From the expressions for T_S and T_I, we find proxy terms for prevalence and susceptible frequency (Boots & Bowers, 1999)

$$\tilde{p}_S^m = \frac{T_S}{T_S + T_I} = \frac{\alpha + b}{\alpha + b + \beta^m I^r} \tag{13}$$

$$\tilde{p}_I^m = \frac{T_I}{T_S + T_I} = \frac{\beta^m I^r}{\alpha + b + \beta^m I^r} \tag{14}$$

Differentiating the proxy for prevalence, eqn 14, with respect to resistance (in this case transmission, β), and

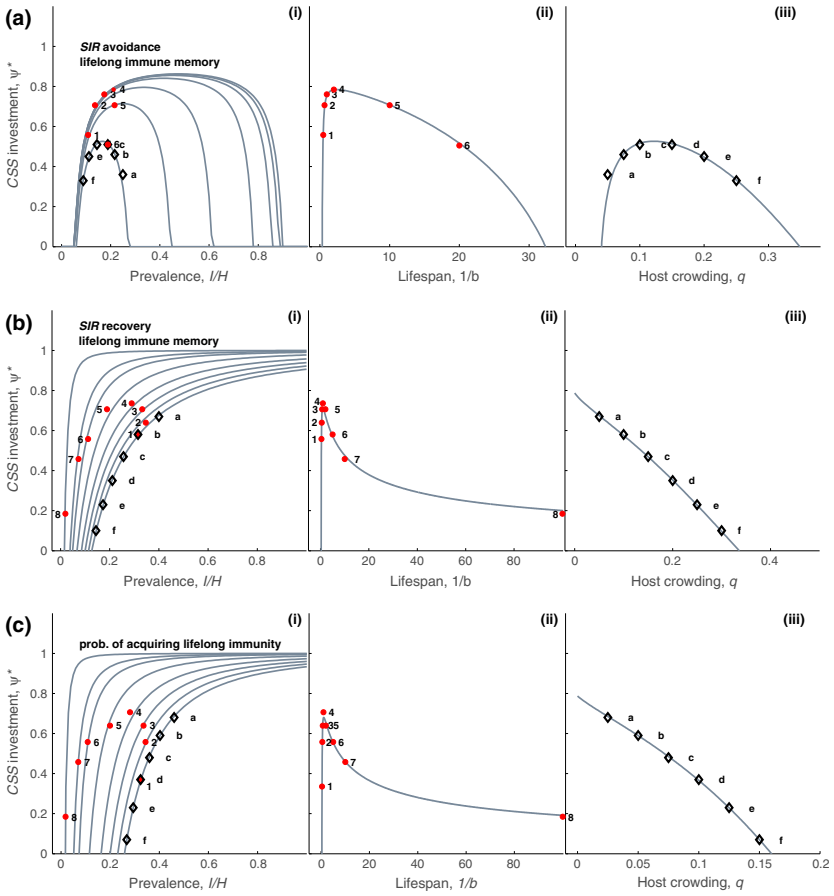

Fig. 3 CSS investment in resistance to an infection that has no impact on host fertility where the host possesses lifelong immune memory, that is SIR population except in (c) which is *SIRS* (in the sense that an SIR or SIS route is taken depending on ν as recovereds return to a susceptible state with a probability that is evolving. In panel (a), resistance is through avoidance, in (b) through recovery, and in (c) through the probability of acquiring immunity. See caption of figure 1 for the trade-off, $\omega(a)$ which effects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$, recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$ and the probability of recovering to immunity in (c) according to $\nu = \nu_0(1 + \omega(a))$. In (a), (b) and (c): $\mu = 1$. In (a): $\beta_0 = 1$, $\alpha = 10$ and $\gamma = 0.1$, $\nu = 1$, $q = 0.1$, $b = 0.05$. In (b) $\alpha = 3$, $\gamma_0 = 2.5$, $\nu = 1$, $q = 0.1$ and $b = 2.5$. In (c): $\alpha = 3$, $\gamma = 2.5$, $\nu_0 = 1$, $q = 0.1$, and $b = 2.5$. CSS investment relies directly on natural mortality when avoidance or recovery evolves in a host population containing immune individuals or when acquired immunity evolves. This leads to curves for different values of natural mortality in figure (a) (i), (b) (i), and (c) (i). The value of b for each curve corresponds to the location of the circular simulation marker in figure (a) (ii); that is, 1 corresponds to $L = 1/2$, 2 to $L = 1/1.5$, 3 to $L = 1$, 4 to $L = 2$, 5 to $L = 10$ and 6 to $L = 20$. In (b) (ii) and (c) (ii), the circular markers also correspond to values of lifespan; that is, 1 corresponds to $L = 1/4$, 2 to $L = 1/2$, 3 to $L = 1/1.5$, 4 to $L = 1$, 5 to $L = 2.5$, 6 to $L = 5$, 7 to $L = 10$ and 8 to $L = 100$ where lifespan, L, equals 1/b. Closed circles and diamonds in each figure represent the final level of resistance from ODE simulations of the evolutionary process.

using eqn 13 leads to

$$\frac{\partial \tilde{p}_I^m}{\partial \beta^m} = \frac{1}{\beta^m} \tilde{p}_S^m \tilde{p}_I^m \tag{15}$$

Therefore, substituting eqn 15 into the expression for the benefit of resistance in eqn 11 and using the definition of D in eqn 8, the benefit for this model evaluated at the singularity is

$$B = \frac{(a - qH + \alpha)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{16}$$

where for simplicity we have dropped the mutant symbol, m, from the mutant frequency expressions. The equilibrium condition for eqn 1 with $\gamma = 0$ and $\mu = 0$ is $a - qH = b + \beta I$, so that benefit can be further simplified to

$$B = \frac{(\alpha + b + \beta^* I)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{17}$$

$$= \frac{(\beta^* S + \beta^* I)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{18}$$

$$= I \tilde{p}_S \tag{19}$$

where eqn 18 follows from eqn 17 because of the equilibrium condition from eqn 2, that is $\alpha + b = \beta S$. Furthermore, eqn 19 follows from 18 since $S + I = H$ in the numerator of

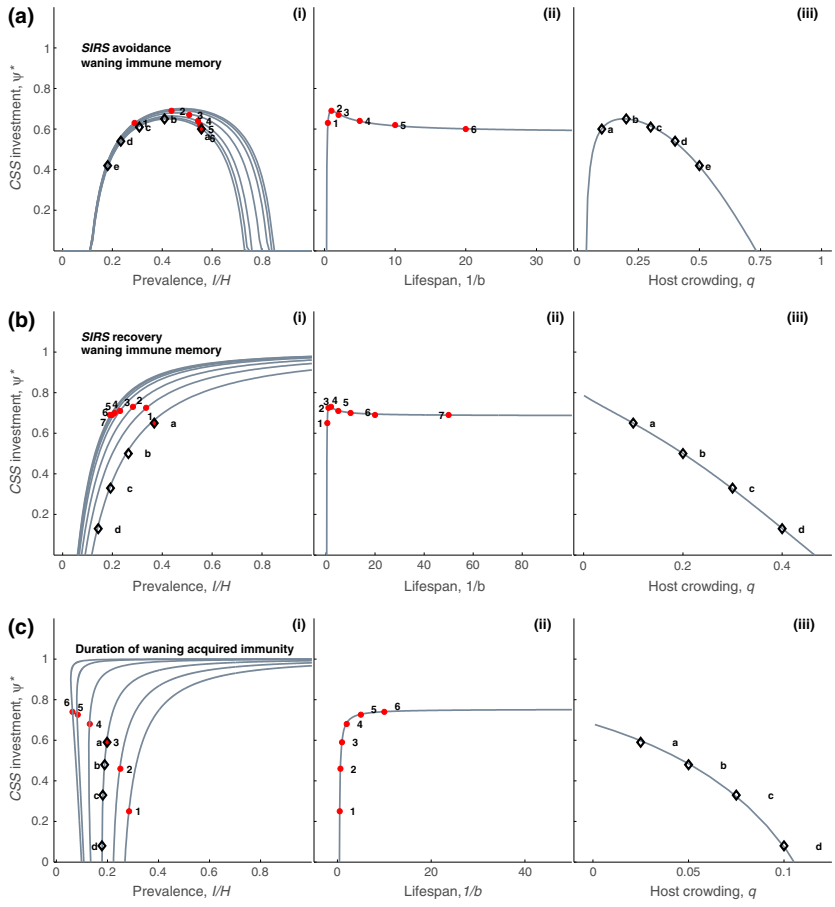

Fig. 4 CSS investment in resistance to an infection that has no impact on host fertility where the host possesses waning immune memory, that is SIRS population. In panel (a), resistance is through avoidance, in (b) through recovery, and in (c) through duration of acquired immunity. Note that while waning immunity is by necessity variable in (c), it is fixed in (a) and (b) (i.e. $\delta = 0.5$) and $\nu = 1$ throughout. See caption of figure 1 for the trade-off, $\omega(a)$, which effects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$, recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$ and waning immunity in (c) according to $\delta = \delta_0(1 - \omega(a))$. In (a), (b) and (c): $\mu = 1$. In (a): $\beta_0 = 1$, $\alpha = 5$, $\gamma = 5$, $\nu = 1$, $q = 0.1$ and $b = 0.05$. In (b): $\alpha = 3$, $\gamma_0 = 2.5$, $\nu = 1$, $q = 0.1$ and $b = 2$. In (c): $\alpha = 5$, $\gamma = 5$, $\nu = 1$, $q = 0.025$, $\delta_0 =$ and $b = 1$. CSS investment relies directly on natural mortality when avoidance or recovery evolves in a host population containing immune individuals or when acquired immunity evolves. This leads to curves for different values of natural mortality in figure (a) (i), (b) (i), and (c) (i). The value of b for each curve corresponds to the location of the circular simulation marker in figure (a) (ii); that is, 1 corresponds to $L = 1/2$, 2 to $L = 1$, 3 to $L = 2$, 4 to $L = 5$, 5 to $L = 10$ and 6 to $L = 20$. In (b) (ii), the circular markers also correspond to values of lifespan; that is, 1 corresponds to $L = 1/2$, 2 to $L = 1$, 3 to $L = 2$, 4 to $L = 5$, 5 to $L = 10$, 6 to $L = 20$ and 7 to $L = 50$ and in (c) (ii), 1 corresponds to $L = 1/2$, 2 to $L = 1/1.5$, 3 to $L = 1$, 4 to $L = 2$, 5 to $L = 5$ and 6 to $L = 10$ where lifespan, L, equals $1/b$. Closed circles and diamonds in each figure represent the final level of resistance from ODE simulations of the evolutionary process.

18 and this cancels with H in the denominator of p_I. On the other hand recalling the definition of cost from eqn 11, the cost evaluated at the singularity is

$$C = \tilde{p}_S \tag{20}$$

as $\mu = 0$ and as $\tilde{p}_I^m$ is independent of a (see eqn 14). Finally, as CSS investment in resistance is a cost benefit analysis,

$$\psi^* \sim \frac{B}{C} = I \tag{21}$$

Equation 21 indicates that CSS investment in avoidance is governed by a density of infecteds feedback. As long as costs increase with resistance such that diminishing returns apply, then the relationship depends on the exact form of the trade-off in a quantitative sense only. It has no qualitative impact on the pattern of CSS investment with respect to life history which in the above example increases when the density of infecteds increases and decreases whenever that density decreases.

Results

Following the procedure outlined in the previous section, we present expressions in Table 1 for CSS investment in resistance for various host–parasite frameworks and the main routes to resistance (more detail on deriving the expressions is provided in *Supporting Information S2*). Table 1 indicates that CSS investment for each resistance model is governed by a simple function of a single key population feedback. This leads to clear qualitative patterns for each model. This is supported by plots of CSS investment against the dynamic feedback, see Figs 1–4 (i). We additionally show how CSS investment varies with life history in Figs 1–4 (ii) (for host lifespan, $1/b$), and Figs 1–4 (iii) (for host crowding, q). The closed circles and diamonds represent results of ODE-solving simulations of the adaptive dynamics process throughout (and the simulation results are in agreement with our analytical findings, see Boots *et al.* (2012) for more information on the simulation procedure).

We first consider pathogens that both prevent host reproduction when infected (i.e. $\mu = 0$) and increase mortality ($\alpha > 0$). As previous model studies have often not considered loss of fertility when infected, we limit these results to innate resistance in hosts lacking immune memory (i.e. $v = 0$). When the parasite prevents host fertility, CSS investment is governed by a feedback consisting of equilibrium infecteds density, I, scaled by case mortality, $(\alpha+b)/(\alpha+b+\gamma)$, see Table 1 A2 and Fig. 1 (b) (i). Both the cost and benefit of resistance vary with life-history parameters, see eqn 10, and therefore, the expressions in A1 and A2 of Table 1 reflect an interaction of cost and benefit.

When the parasite has no effect on fertility, the dynamic feedback is disease prevalence for all forms of resistance, see Table 1 B1–B4. In particular, when resistance is innate (through either recovery or avoidance) in a host lacking immune memory, investment is always greatest at intermediate prevalence, see table B1 SIS and B2 SIS and Fig. 2 (a) (i) and (b) (i). Here, when prevalence is low, few transmission events are occurring and enhancement to avoidance or recovery has little impact on prevalence. When prevalence is high, the likelihood of the transmission of infection is high for susceptible individuals so that it is relatively futile to maintain or return individuals to a susceptible state. Therefore, there is little benefit to increased innate resistance when prevalence is either low or high and this lies at the heart of the humpbacked dependence of investment on prevalence. Furthermore, when the parasite does not alter fertility, the direct cost of fitness is 1, see eqn 10 (i.e. it does not depend on model details such as life-history values). Therefore, the humpbacked relationship in Table 1 B1 SIS and B2 SIS reflects only variation in the benefit of innate resistance. The strongly contrasting relationships observed between Table 1 A2 (i.e. innate resistance with loss of fertility) and Table 1 B1 and B2 (i.e. innate resistance without loss of fertility) are a consequence of costs also varying with life history when the parasite reduces host fertility (where cost depends on the proportion of mutants who are susceptible, as it is only they who pay the cost - infecteds do not reproduce).

When acquired immunity evolves to counter pathogens that have no effect on fertility investment is always higher for high prevalence, see Table 1 B3 and B4. CSS investment is qualitatively the same whether resistance is through probability of acquiring immunity or through duration of acquired immunity, see Fig. 3 (c) (i) and 4 (c) (i) for illustration. As the parasite has no effect on fertility, direct cost does not vary with

Table 1 Epidemiological feedbacks to evolving resistance.

Resistance Mechanism	SIS	SIR	SIRS
	$v = 0$	$v = 1$	B3 $v(a)$ & $\delta = 0$ or B4 $\delta(a)$ & $v = 1$
Avoidance infertile infecteds			
A1 no recovery	$\psi^* \sim I$	–	–
A2 with recovery	$\psi^* \sim \frac{\alpha+b}{\alpha+b+\gamma} I$	–	–
All forms fertile infecteds			
B1 avoidance	$\psi^* \sim \alpha \frac{I}{H}(1-\frac{I}{H})$	$\psi^* \sim \alpha \frac{I}{H}(1-(\frac{b+\gamma}{b})\frac{I}{H})$	–
B2 recovery	$\psi^* \sim \alpha \frac{I}{H}(1-\frac{I}{H})$	$\psi^* \sim \alpha \frac{I}{H}(\frac{\alpha I}{bH}+1)$	–
B3 acquired immunity (prob.)	–	–	$\psi^* \sim \frac{\alpha\gamma}{b}(\frac{I}{H})^2$
B4 acquired immunity (length)	–	–	$\psi^* \sim \alpha\gamma(\frac{I}{H})^2$

Feedbacks to CSS investment in resistance, ψ^*, for a range of model assumptions. We define $a \sim b$ to represent *nonlinear* monotonic dependence of a on b; that is, any increase in b results in an increase in a, and any decrease in b results in a decrease in a. In the case of evolving recovery, ψ^* represents investment in reducing the infectious period. In the case of evolving acquired immunity through the waning immunity rate, ψ^* represents investment in the duration of immunity. Column 1 corresponds to host populations without immune memory and therefore $v = 0$ for $A1-B4$ column 1. Column 2 corresponds to host populations with immune memory and for simplicity immunity is lifelong and therefore $v = 1$ and $\delta = 0$. In $B3$ column 3: $\delta = 0$ with $v > 0$ (i.e. a model of permanent immunity) whereas in B4 column 3: $v = 1$ with $\delta > 0$ (i.e. a model of waning immunity).

model parameters. However, benefit now reflects an increase in proportion of immunes rather than an increase in proportion of susceptibles (amounting to a reduction in prevalence in both cases). As long as prevalence is not low, it is always beneficial to boost immunity and this is particularly true when prevalence is high.

In the absence of immune memory, CSS investment in the two modes of innate resistance is qualitatively the same. However, with immune memory, investment patterns in avoidance and recovery are markedly different, compare Fig. 3 (b) (i) and 4 (b) (i) with Fig. 3 (a); (i) and 4 (a); (i). This is because the benefit of recovery and avoidance is similar in an SIS population as they both increase the susceptible frequency at the expense of infecteds frequency. However, in an SIR or SIRS population, recovery mainly boosts immune frequency relative to prevalence, whereas avoidance mainly boosts susceptible frequency. The parameter v mediates between these two outlets (i.e. for low v, CSS recovery resembles avoidance; for high v, it resembles acquired immunity).

The question of how CSS investment varies with life history is entwined with how it varies with the dynamic feedback. In some cases, CSS investment features a density-independent coefficient term involving parameters from the host or parasite life history, as, for example, with the density-independent case mortality coefficient in Table 1 A2. Intrahost crowding, q, which acts to reduce host births (or equivalently reduces juvenile survival), however, does not appear directly in any of the expressions in Table 1. It can be shown that prevalence and infected density have a monotonic dependency on crowding (i.e. $\partial I/\partial q < 0$ and $\partial(I/H)/\partial q < 0$, results not included). Therefore, the variation in CSS investment due to variation in crowding mimics the relationship between CSS investment and the dynamic feedback (although the trend will be opposite as the dynamic feedback decreases with crowding). The result is that CSS investment has a humpbacked dependence on crowding when resistance is innate in an SIS population or when it is innate through avoidance in an SIRS population, see Fig. 2 (a) (iii), 2 (b) (iii), 3 (a) (iii) and 4 (a) (iii). Investment decreases with increasing crowding when infecteds do not reproduce or when resistance is through acquired immunity or through recovery in an SIRS population, see Fig. 1 A (iii), 1 (b) (iii), 3 (b) (iii), 3 (c) (iii), 4 (b) (iii) and 2 (c) (iii).

Wherever CSS investment depends on the natural mortality parameter through a coefficient term and not just through its implicit role in the dynamic feedback, there are distinct curves depending on the level of natural mortality, see Fig. 1 (b) (i), 2 (b) (i), 3 (b) (i)-(c) (i) and 4 (b) (i)-(c) (i). As natural mortality changes, and hence host lifespan changes, a conflict may arise between the directions of change of the coefficient term and the dynamic feedback term. This is one reason for maximal investment at intermediate lifespan, see Fig. 1 (b) (ii), 3 (b) (ii) and 3 (c) (ii). Another reason is the natural humpbacked relationship between CSS investment and the population feedback, see Fig. 2 (a) (ii), 2 (b) (ii) and 3 (a) (ii). Yet another reason requires lifelong immunity, for then prevalence can be low at high lifespans (as immunes dominate the population), see Fig. 3 (b) (ii) and 3 (c) (ii). Of course, maximal investment can occur for a combination of these reasons, see Fig. 3 (a) (ii).

Finally, the results can be extended to models incorporating age structure. For simplicity, we do not include this material in the main body of the text, but we outline the direction of the analysis in Supporting Information S4 through the example of evolving innate resistance in a host population incapable of immune memory. The analysis indicates that our results are broadly generalizable to models incorporating age structure, see eqn S4.12 which is the analogue of eqn 10 for an age-structured host (with no immune class for simplicity). The bigger the reduction in prevalence in each of the age classes, scaled by infection damage in those age classes, the higher the level of resistance that we expect to evolve. However, they also highlight that there are additional, distinct interactions that arise from the inclusion of age structure. In particular, if resistance shifts the age profile of the host population in favour of classes with a greater contribution to overall mutant growth, then we predict selection for higher CSS investment. Similarly, if there is a shift in favour of classes with lower contribution to mutant growth then we expect this to select for lower investment than would otherwise be the case. This analysis indicates that our techniques are generalizable to other more complex model frameworks.

Discussion

It is clear that evolutionary change impacts population dynamics and that this in turn alters selection pressures. Such ecological feedbacks are particularly clear in host–parasite interactions where it is recognized that host resistance will impact on parasite prevalence and that prevalence impacts the selection for resistance (Haldane, 1949; Antonovics & Thrall, 1994; Bowers *et al.*, 1994; Boots & Haraguchi, 1999; Roy & Kirchner, 2000). However, we have shown here that the details matter, so, for example, the relationship between resistance and prevalence is contingent on the epidemiological scenario. For instance, when infection causes a loss of fertility CSS investment in resistance is driven by force of infection. Whereas, in contrast, when infection causes only increased death rate, investment is driven by disease prevalence. A striking result, which can be explained simply by our analysis, is that when it is prevalence that determines investment in innate resis-

tance (i.e. when there is no effect of infection on fertility), CSS investment does not always increase with prevalence. In cases where infection has no effect on fertility, investment in innate resistance (i.e. avoidance or recovery in an SIS model or avoidance in an SIR model) is highest at intermediate prevalence, whereas investment in immune memory (i.e. recovery, duration of immunity as well as probability of clearance to immunity in SIR and SIRS models) always increases with prevalence. Therefore, our work emphasizes the importance of ecological feedbacks to evolutionary outcomes and shows that quite distinct feedbacks arise for different ecological interactions between host and parasite. We now discuss the insights and implications from this work.

A key finding is that the presence of parasite-associated loss of fecundity radically alters the way that the epidemiology feeds back into the evolutionary process. Specifically, CSS investment in immunity is the result of a cost–benefit analysis in host fitness. The cost is proportional to the fraction of hosts who experience the loss of fecundity associated with costly resistance. When infected individuals reproduce normally, all individuals experience the costs of resistance equally, and crucially therefore, CSS investment reflects only variation in the benefit of resistance. When only susceptibles experience the cost (i.e. infected individuals do not reproduce), the cost is proportional to the frequency of susceptibles so that variation in the cost as well as the benefit determines the outcome (a similar result holds if infecteds reproduce at a reduced rate).

When infecteds reproduce normally and it is innate resistance that evolves, the humpbacked relationship between CSS investment and prevalence that arises reflects a humpbacked relationship between the benefit of resistance and prevalence. In our model framework with no immune class, the patterns of investment in innate resistance are the same whether the route is through avoidance or recovery and this emphasizes that the feedback differs with the type of immunity but not the precise mechanism. The benefit of resistance is the reduction in prevalence weighted by the damage from infection (when infecteds reproduce normally, damage equals disease-induced mortality, i.e. virulence). Innate resistance through recovery or avoidance achieves only a very slight reduction in prevalence, and hence has little benefit, if prevalence is already low or high. If prevalence is low, few transmissions occur because there are relatively few infecteds; therefore, neither avoidance nor recovery has a big effect on prevalence. If prevalence is high, returning individuals to a susceptible state (i.e. recovery) or maintaining them in a susceptible state (i.e. avoidance) only serves to feed the flames of future transmission and therefore has little effect on prevalence. This is an effect that has been noted in Van Baalen (1998), in relation to the force of infection in a model with no reproduction of infecteds or density dependence in host demography (Van Baalen (1998) describe this as a 'give-up-hope effect' and point out a corresponding effect in optimal antipredator traits in Abrams (1990)). Therefore, the humpbacked relationship between CSS investment and prevalence is actually a hallmark of the evolutionary dynamics of innate resistance.

The more complex cost–benefit relationship of investment in immunity when infection causes a loss of fertility has received less attention. Once again, the benefit of resistance follows a humpbacked relationship with prevalence. However, cost is now proportional to the frequency of susceptibles (as compared to unity when infecteds reproduce). Furthermore, damage consists of the rate of disease-induced mortality plus the density-dependent rate of reproduction whose loss now also constitutes damage due to infection. When we look at the evolution of avoidance, the interplay between the cost and benefit reduces this complexity so that CSS investment is a simple increasing function of the abundance of infecteds. This result echoes that of Boots & Bowers (1999) whose model features a parasite causing a loss of fertility and SI dynamics without recovery that are analogous to a predator–prey system. However, a key factor that distinguishes between predator–prey and disease interactions is the possibility of recovery from an infected state to a susceptible state. At first sight, the inclusion of recovery (i.e. SIS dynamics) might be thought to lead to dynamics that are more like the case where infection has no impact on fertility (as recovering infecteds are functionally similar to newborns/juveniles coming from infected adults). However, this is not the case. In fact, the more general pattern is that CSS investment is governed by a complex interaction of cost, damage and benefit, all of which vary with the equilibrium state of the host population (and obscure the humpbacked relationship of the benefit of resistance with prevalence). Instead, these factors combine to produce the deceptively simple increasing relationship between CSS investment and the abundance of infecteds scaled by case mortality.

We model investment in immune memory in two ways: (i) through increased probability of recovering to a permanent immune state (for convenience, we call this CSS lifelong immunity) or (ii) by an increased duration of immunity when recovery always leads to immunity (for convenience, CSS waning immunity). We show that in both of these cases, CSS investment always increases with disease prevalence. However, it is important to note that despite the expressions for CSS waning and CSS lifelong immunity being the same, the models in which they evolve produce different patterns in equilibrium prevalence at high lifespans due to the impact of waning immunity. In particular, a waning immunity term means that there is no very long-lived class and this means that it is harder for the host density to approach the carrying capacity which would

reduce prevalence (by reducing the supply of susceptibles). Avoidance and recovery exhibit remarkably similar CSS investment relationships when the host lacks immune memory yet markedly different relationships when immune memory is present. The key result is that recovery without immune memory is functionally different to recovery with immune memory (i.e. recovery to an immune state is a route to acquired immunity). In the former case, it acts to increase the proportion of susceptible hosts who are vulnerable to reinfection (and therefore follows a humpbacked relationship with disease prevalence), and in the latter case, it increases the proportion of immunes (and therefore increases with increasing prevalence). This highlights the generality of our results. There are very clear patterns to CSS investment in resistance that are distinct for innate and acquired immunity but within these categories the route is unimportant.

CSS investment has a complex relationship with host lifespan. Accounts of how the various forms of resistance respond to lifespan have been given in Van Boven & Weissing (2004) and Miller *et al.* (2007) and this has been reviewed in Boots *et al.* (2013). Maximal CSS investment at intermediate lifespans appears to be a result that is found across models and across resistance forms (though see also the acute cost scenario of Van Boven & Weissing (2004) which leads to maximal investment at long lifespans). The key exception is the duration of acquired immunity where CSS investment always increases with increasing host lifespan, see Miller *et al.* (2007) and Boots *et al.* (2013). Our analysis makes it clear that this consistent pattern is not an outcome inherent to the evolution of resistance for any one reason. For example, it occurs for innate resistance when immune memory is lacking and the parasite has no effect on fertility because investment responds to benefit which is small at low and high prevalence, and in general, high lifespan means high prevalence. In contrast, when resistance is through permanent acquired immunity, prevalence can be low when hosts have long lifespans (long-lived populations become dominated by immunes) leading to maximal investment at intermediate lifespans. In a third, contrasting example when innate resistance evolves to combat parasites causing a loss of host fertility, investment is governed by the abundance of infecteds scaled by case mortality. As lifespan increases abundance increases, but case mortality decreases, so that investment can be maximal at intermediate lifespan. This is an important point, although the findings such as maximal investment at intermediate lifespan that we see may be consistent, these three examples show that they result from very different combinations of cost and benefit that arise through ecological feedbacks.

We have shown how the combination of host and parasite characteristics and the ecological interactions between them lead to distinct ecological feedbacks to the evolution of host resistance. Understanding the ecological feedback is essential in accounting for the role that variation in life-history characters such as host lifespan plays in patterns of host resistance. However, intuitive understanding is inevitably gained at the expense of model complexity. It is important to consider the likely effect of additional key interactions like parasite diversity and host age structure on the phenomena that we describe. For example, the hallmark of innate resistance, that is the lowering of prevalence and increase of susceptible frequency, is likely to be complicated by the presence of additional pathogens and their community dynamics. We have also pointed the way to a fuller model of the host population by including age structure. Our analysis indicates that the main results generalize to age-structured host populations, but we additionally identify distinct feedbacks arising due to the age structure. Therefore, although the results that we present here give a thorough explanation of CSS investment in host resistance in standard epidemiological models, they are only a foundation for the understanding of resistance in real world scenarios.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 CSS investment is governed by a benefit/cost feedback.

Appendix S2 CSS investment in resistance when the pathogen has no effect on fertility.

Appendix S3 Fitness criteria and the proxy replacements for mutant frequencies.

Appendix S4 Ecological feedbacks due to host age structure.

Received 21 March 2015; revised 6 July 2015; accepted 6 August 2015