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The epidemiological feedbacks critical to the evolution of host immunity.

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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, this introduces new ecological feedbacks to both the cost of resistance and the damage from infection. The multiple feedbacks in this case leads 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.

Key words: epidemiology, ecology, resistance, density dependence.

1. 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 feedback to change the selective pressures on the genotypes. These feedbacks can be complex even in simple models, but by 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 while on the other hand, 'resistance' mechanisms including avoidance, recovery and acquired immunity directly counter the parasite (Miller et al., 2007). Genes conferring resistance, since 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; Bowers et al., 1994; Antonovics & Thrall, 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; Dobzhansky, 1937; Cole, 1954; Maynard Smith

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₂₆ & Price, 1973; Lande, 1982; Charlesworth, 1994). In this study we use an evolutionary
₂₇ invasion analysis approach (Metz et al., 1996; Geritz et al., 1998) in which density-dependent
₂₈ ecological dynamics are explicitly modelled with feedbacks to fitness (but at the expense
₂₉ of genetic detail). The framework assumes a separation of ecological and evolutionary time
₃₀ scales as well as rare mutations of small effect with quantitative continuous phenotypes.
₃₁ The advantage of these simplifying assumptions is that density and frequency dependent
₃₂ selection emerge naturally from these eco-evolutionary models and this has proved effective
₃₃ in understanding how population level processes determine evolutionary outcomes. The
₃₄ assumption of quantitative continuous phenotypes is also a good one for the majority of
₃₅ immune mechanisms that are characteristically associated with quantitative trait loci (for
₃₆ example, cytokine activation in Dupuis et al. (2000), porcine leukocyte regulation in Edfors-
₃₇ Lilja et al. (1998) and rodent Th1 development in Gorham et al. (1996)).

₃₈   There is a large body of theoretical research focused on the evolution of resistance in
₃₉ the context of ecological feedbacks (Antonovics & Thrall, 1994; Bowers et al., 1994; Boots
₄₀ & Haraguchi, 1999; Boots et al., 2009). Nevertheless, understanding the patterns of CSS
₄₁ investment in host defence for different host-parasite systems remains a key challenge. For
₄₂ example, Van Boven & Weissing (2004) and Miller et al. (2007) showed that CSS investment
₄₃ in resistance in hosts with permanent immune memory can be low for long-lived species
₄₄ and Boots et al. (2013) demonstrated that this is due to low prevalence as a result of low
₄₅ population turnover at high lifespans. However, there are many counter-intuitive patterns in
₄₆ CSS resistance (Miller et al., 2007) and it remains unclear how ecological feedbacks determine
₄₇ these outcomes. For instance, the key dynamic feedback to resistance has been identified as
₄₈ force of infection in Van Baalen (1998), Boots & Haraguchi (1999) and Van Baalen (2002)
₄₉ yet disease prevalence is emphasised in Miller et al. (2007). Here, we determine the eco-
₅₀ evolutionary feedbacks for different host-parasite interactions and use these to explain how
₅₁ key differences in epidemiological context and mode of host defence leads to fundamentally
₅₂ distinct patterns in CSS resistance. Although our study is focused on host parasite systems
₅₃ the methods apply more generally and we emphasise that uncovering complex feedbacks is
₅₄ key to understanding the biological processes that underpin evolutionary behaviour.

2. Methods

(a) Epidemiological Model

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

$$\frac{dS}{dt} = a(S + \mu I + R) - q(S + \mu I + R)H - bS - \beta SI + (1 - \nu)\gamma I + \delta R \qquad (1)$$

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

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

All parameters are non-negative and μ, $\nu \in [0, 1]$. Hosts die at natural death rate b. Hosts produce susceptible offspring at rate a which is limited by intra-specific 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 non-zero host population. The parasite is maintained at endemic levels when the host-only equilibrium $\hat{H}_0$ becomes unstable. Analysis of the eigen-values 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, ν, acquire immunity to the pathogen which wanes at rate δ, while the remaining individuals return to a susceptible state.

This model captures several infection scenarios of interest. If $\nu = 0$ 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 $\nu = 1$ and $\delta = 0$ it represents a *Susceptible-Infected-Recovered* (SIR) model with life-long 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 (ν) or increases the expected duration of acquired immunity through changes in δ (Miller et al., 2007).

(b) 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, i.e.

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

In equation 4 r and m denote resident and mutant, and we are evaluating the resident population at its dynamic equilibrium (i.e. $H^r = \hat{H}^r$) while 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 sub-populations. The ODEs for the mutant strain differs to equations 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, dH^m/dt, is then the sum of the mutant equations, i.e.

8

$$\frac{dH^m}{dt} = S^m(a^m - qH^{tot} - b) + I^m(\mu(a^m - qH^{tot}) - b - \alpha) + R^m(a^m - qH^{tot} - b)\Big|_{H^r=\hat{H}^r, H^m=0}$$

(5)

where $H^{tot} = H^r + H^m$. The expressions in parentheses in equation 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

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

(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 equation 6 and noticing in equation 5 that $\sigma_S^m = \sigma_R^m$ leads to

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

(7)

Since the first term in equation 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 i.e.

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

(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, 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.

[114] We introduce a trait, ω, that is useful in the analysis, determining the phenotypic [115] value of quantitative resistance (i.e. $\omega = f(a)$ where mutant values of resistance are given [116] by $\omega^m = f(a^m)$) which can represent avoidance, recovery or acquired immunity. The host [117] population evolves in the direction of the mutant gradient of invasion fitness until it reaches an [118] evolutionary singularity. There, by definition, the fitness gradient is zero so that singularities, [119] a^*, satisfy

$$\left.\frac{\partial \Theta}{\partial a^m}\right|_* = 0 \qquad (9)$$

[120] where the vertical bar indicates that the expression is evaluated at the evolutionary equilibrium [121] where resident equals mutant (i.e. $r = m = *$). A singularity, a^*, is evolutionary stable (ES) [122] 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 [123] that is both ES and CS is uninvadable as well as attracting in an evolutionary sense (i.e. a [124] Continuously Stable Strategy, CSS, (Eshel, 1983) - an end point of evolution). In this study [125] we analyse the dependence of CSS investment in resistance on the underlying ecological model [126] for a range of model formulations. Our results are based on the assumption of diminishing [127] returns for a host investing in resistance, i.e. a continuous trade-off between resistance and [128] reproduction of any shape provided that reproduction is a decreasing function of resistance [129] and that costs accelerate. When the parasite causes a loss of fertility, CSS investment in [130] resistance with accelerating costs is a CSS (Hoyle et al., 2008), and hence an end-point of [131] evolution. When the parasite has no effect on fertility, CSS investment in resistance with [132] accelerating costs is a CSS when costs are sufficiently strongly accelerating (de Mazancourt [133] & Dieckmann, 2004; Bowers et al., 2005). The results presented in this study assume a trade- [134] off that makes the singularity studied a CSS (i.e. figures 1-4 are generated from trade-offs [135] with strongly accelerating cost structures), however, the analysis outlined in this work applies [136] more generally for any trade-off with an accelerating cost structure (but note that once the [137] singularity is reached branching can occur if costs accelerate only weakly).

[138] Solving equation 9 for the invasion fitness given by equation 7 and rearranging indicates [139] that evolutionary singularities of evolving resistance satisfy

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

$$= -\frac{C}{B}\bigg|_* \tag{11}$$

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

145 Equation 10 gives the position on the resistance-reproduction trade-off which corresponds
146 to a singularity. As a consequence of costs rising with increasing investment with diminishing
147 returns, any increase in the right hand side of equation 11 results in the location of the
148 singularity shifting to low values of mutant reproduction. This corresponds to high investment
149 in resistance, see figure $S1.1$ in *Supporting Information S1*. This implies that singular resistance
150 is the result of a cost benefit analysis so that CSS investment in resistance, ψ^* ($\omega(a)$ represents
151 the phenotypic value of resistance while ψ represents investment in the phenotype), is high
152 whenever the benefit is large relative to the cost, i.e.

$$\psi^* \sim \frac{B}{C}\bigg|_* \tag{12}$$

153 where we use the symbol $\sim$ to indicate that the left hand side is a *non$-$linear* monotonically
154 increasing function of the right hand side feedback, i.e. in equation 12, ψ^* increases when $\frac{B}{C}$
155 increases and similarly ψ^* decreases when $\frac{B}{C}$ decreases. A strength of our analysis is that the
156 results are not specific to a particular functional form of trade-off, but rather hold for any
157 trade-off that features diminishing returns on investment. Since our results allow for flexibility
158 in trade-off shape the relationship between feedback and CSS investment will not generally
159 be linear.

160 The exact expression for host fitness is key to explaining the role of costs and benefits.
161 However, the terms p_S^m and p_I^m that appear in cost and benefit (see equation 10) in practice
162 are too complex to calculate. A proxy for invasion fitness is a fitness criterion that shares
163 the same singularities and evolutionary behavior. Following the biologically inspired proxy of
164 Bowers & Turner (1997) we replace the proportion of mutants who are infected, p_I^m, with
165 the proportion of the expected lifespan a mutant spends infected, $\tilde{p}_I^m = T_I/T_H$, and similarly
166 $\tilde{p}_S^m$ for p_S^m. The proxy replacements, $\tilde{p}_S^m$ and $\tilde{p}_I^m$ allow CSS investment in resistance to be
167 expressed solely in terms of state variables and parameters of the epidemiological model. See
168 *Supporting Information S3* for an explanation of why this replacement produces a proxy for
169 invasion fitness.

170 *Example: avoidance resistance.* To provide a concrete example of how we determine the
171 feedback on investment we consider in detail the evolution of avoidance in a host population.
172 For simplicity we assume that the host has no ability to recover from infection ($\gamma = 0$) and
173 that an infected host does not reproduce ($\mu = 0$).

174 A mutant host will be born susceptible and will either die susceptible or become infected.
175 Infected individuals remain in that state until death. The average time a mutant host is
176 susceptible, denoted T_S, is the inverse of the rates at which individuals leave the mutant
177 susceptible class i.e. $T_S = 1/(b + \beta^m(I^m + I^r))$, see equation 1. The average time a mutant host
178 is infected, denoted T_I, is the probability the susceptible mutant becomes infected multiplied
179 by the average time the infected host remains infected i.e. $T_I = [\beta^m I^r/(b + \beta^m I^r)] \times [1/(\alpha +$
180 $b)]$, see equation 2.

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

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

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

12

183 Differentiating the proxy for prevalence, equation 14, with respect to resistance (in this case
184 transmission, β), and using equation 13 leads to

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

185 Therefore, substituting equation 15 into the expression for the benefit of resistance in equation
186 11 and using the definition of D in equation 8, the benefit for this model evaluated at the
187 singularity is

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

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

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

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

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

191 where equation 18 follows from equation 17 because of the equilibrium condition from equation
192 2, i.e. $\alpha + b = \beta S$. Furthermore, equation 19 follows from 18 since $S + I = H$ in the numerator
193 of 18 and this cancels with H in the denominator of p_I. On the other hand recalling the
194 definition of cost from equation 11, the cost evaluated at the singularity is

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

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

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

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

₂₀₁ ## 3. Results

202 Following the procedure outlined in the previous section we present expressions in table 1
203 for CSS investment in resistance for various host-parasite frameworks and the main routes
204 to resistance (more detail on deriving the expressions is provided in *Supporting Information*
205 *S2*). Table 1 indicates that CSS investment for each resistance model is governed by a simple
206 function of a single key population feedback. This leads to clear qualitative patterns for each
207 model. This is supported by plots of CSS investment against the dynamic feedback, see figures
208 1-4 *i*). We additionally show how CSS investment varies with life-history in figures 1-4 *ii*) (for
209 host lifespan, $1/b$), and figures 1-4 *iii*) (for host crowding, q). The closed circles and diamonds
210 represent results of ODE-solving simulations of the adaptive dynamics process throughout
211 (and the simulation results are in agreement with our analytical findings, see Boots et al.
212 (2012) for more information on the simulation procedure).

213 We first consider pathogens that both prevent host reproduction when infected (i.e. $\mu = 0$)
214 and increase mortality ($\alpha > 0$). Since previous model studies have often not considered loss
215 of fertility when infected we limit these results to innate resistance in hosts lacking immune
216 memory (i.e. $\nu = 0$). When the parasite prevents host fertility, CSS investment is governed
217 by a feedback consisting of equilibrium infecteds density, I, scaled by case mortality, ($\alpha +$

²¹⁸ $b)/(\alpha + b + \gamma)$, see table 1 $A2$ and figure 1 $(b)\,i)$. Both the cost and benefit of resistance vary

²¹⁹ with life-history parameters, see equation 10, and therefore the expressions in $A1$ and $A2$ of

²²⁰ table 1 reflect an interaction of cost and benefit.

²²¹ When the parasite has no effect on fertility, the dynamic feedback is disease prevalence for

²²² all forms of resistance, see table 1 $B1$-$B4$. In particular, when resistance is innate (through

²²³ either recovery or avoidance) in a host lacking immune memory, investment is always greatest

²²⁴ at intermediate prevalence, see table 1 $B1$ SIS and $B2$ SIS and figure 2 $(a)\,i)$ and $(b)\,i)$.

²²⁵ Here, when prevalence is low, few transmission events are occurring and enhancement to

²²⁶ avoidance or recovery has little impact on prevalence. When prevalence is high, the likelihood

²²⁷ of the transmission of infection is high for susceptible individuals so that it is relatively futile

²²⁸ to maintain or return individuals to a susceptible state. Therefore there is little benefit to

²²⁹ increased innate resistance when prevalence is either low or high and this lies at the heart

²³⁰ of the humpbacked dependence of investment on prevalence. Furthermore, when the parasite

²³¹ does not alter fertility, the direct cost of fitness is 1, see equation 10 (i.e. it does not depend

²³² on model details such as life-history values). Therefore the humpbacked relationship in table

²³³ 1 $B1$ SIS and $B2$ SIS reflects only variation in the benefit of innate resistance. The strongly

²³⁴ contrasting relationships seen between table 1 $A2$ (i.e. innate resistance with loss of fertility)

²³⁵ and table 1 $B1$ and $B2$ (i.e. innate resistance without loss of fertility) are a consequence of

²³⁶ costs also varying with life-history when the parasite reduces host fertility (where cost depends

²³⁷ on the proportion of mutants who are susceptible, as it is only they who pay the cost - infecteds

²³⁸ do not reproduce).

²³⁹ When acquired immunity evolves to counter pathogens that have no effect on fertility

²⁴⁰ investment is always higher for high prevalence, see table 1 $B3$ and $B4$. CSS investment

²⁴¹ is qualitatively the same whether resistance is through probability of acquiring immunity or

²⁴² through duration of acquired immunity, see figure 3 $(c)\,i)$ and 4 $(c)\,i)$ for illustration. Since the

²⁴³ parasite has no effect on fertility, direct cost does not vary with model parameters. However,

²⁴⁴ benefit now reflects an increase in proportion of immunes rather than an increase in proportion

²⁴⁵ of susceptibles (amounting to a reduction in prevalence in both cases). As long as prevalence is

246 not low it is always beneficial to boost immunity and this is particularly true when prevalence
247 is high.

248 In the absence of immune memory, CSS investment in the two modes of innate resistance
249 is qualitatively the same. However, with immune memory, investment patterns in avoidance
250 and recovery are markedly different, compare figure 3 $(b)\,i)$ and 4 $(b)\,i)$ with figure 3 $(a)\,i)$
251 and 4 $(a)\,i)$. This is because the benefit of recovery and avoidance is similar in an SIS
252 population since they both increase the susceptible frequency at the expense of infecteds
253 frequency. However, in an SIR or $SIRS$ population, recovery mainly boosts immune frequency
254 relative to prevalence while avoidance mainly boosts susceptible frequency. The parameter ν,
255 mediates between these two outlets (i.e. for low ν CSS recovery resembles avoidance, for high
256 ν it resembles acquired immunity).

257 The question of how CSS investment varies with life-history is entwined with how it varies
258 with the dynamic feedback. In some cases CSS investment features a density independent
259 coefficient term involving parameters from the host or parasite life-history, as, for example,
260 with the density independent case mortality coefficient in table 1 $A2$. Intra-host crowding,
261 q, which acts to reduce host births (or equivalently reduces juvenile survival), however, does
262 not appear directly in any of the expressions in table 1. It can be shown that prevalence and
263 infected density have a monotonic dependency on crowding (i.e. $\partial I/\partial q < 0$ and $\partial (I/H)/\partial q < 0$,
264 results not included). Therefore, the variation in CSS investment due to variation in crowding
265 mimics the relationship between CSS investment and the dynamic feedback (though the trend
266 will be opposite since the dynamic feedback decreases with crowding). The result is that CSS
267 investment has a humpbacked dependence on crowding when resistance is innate in an SIS
268 population or when it is innate through avoidance in an $SIRS$ population, see figure 2 $(a)\,iii)$,
269 2 $(b)\,iii)$, 3 $(a)\,iii)$ and 4 $(a)\,iii)$. Investment decreases with increasing crowding when infecteds
270 do not reproduce or when resistance is through acquired immunity or through recovery in an
271 $SIRS$ population, see figure 1 $A\,iii)$, 1 $(b)\,iii)$, 3 $(b)\,iii)$, 3 $(c)\,iii)$, 4 $(b)\,iii)$ and 2 $(c)\,iii)$.

272 Wherever CSS investment depends on the natural mortality parameter through a
273 coefficient term and not just through its implicit role in the dynamic feedback, there are
274 distinct curves depending on the level of natural mortality, see figure 1 $(b)\,i)$, 2 $(b)\,i)$, 3

275 $(b)\,i) - (c)\,i)$ and $4\ (b)\,i) - (c)\,i)$. As natural mortality changes, and hence host lifespan

276 changes, a conflict may arise between the directions of change of the coefficient term and the

277 dynamic feedback term. This is one reason for maximal investment at intermediate lifespan, see

278 figure 1 $(b)\,ii)$, 3 $(b)\,ii)$ and 3 $(c)\,ii)$. Another reason is the natural hump-backed relationship

279 between CSS investment and the population feedback, see figure 2 $(a)\,ii)$, 2 $(b)\,ii)$ and 3 $(a)\,ii)$.

280 Yet another reason requires life-long immunity, for then prevalence can be low at high lifespans

281 (as immunes dominate the population), see figure 3 $(b)\,ii)$ and 3 $(c)\,ii)$. Of course maximal

282 investment can occur for a combination of these reasons, see figure 3 $(a)\,ii)$.

283   Finally, the results can be extended to models incorporating age structure. For simplicity

284 we do not include this material in the main body of the text but we outline the direction of

285 the analysis in *Supporting Information S*4 through the example of evolving innate resistance

286 in a host population incapable of immune memory. The analysis indicates that our results are

287 broadly generalisable to models incorporating age structure, see equation $S4.12$ which is the

288 analogue of equation 10 for an age structured host (with no immune class for simplicity). The

289 bigger the reduction of prevalence in each of the age classes, scaled by infection damage in

290 those age classes, the higher the level of resistance that we expect to evolve. However, they

291 also highlight that there are additional, distinct interactions that arise from the inclusion of

292 age structure. In particular, if resistance shifts the age profile of the host population in favour

293 of classes with a greater contribution to overall mutant growth then we predict selection for

294 higher CSS investment. Similarly, a shift in favour of classes with lower contribution to mutant

295 growth then we expect this to select for lower investment than would otherwise be the case.

296 This analysis indicates that our techniques are generalisable to other more complex model

297 frameworks.

4. 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 recognised that host resistance will impact on parasite prevalence, and that prevalence impacts the selection for resistance (Haldane, 1949; Bowers et al., 1994; Antonovics & Thrall, 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 varies with force of infection. While, in contrast, when infection causes only increased death rate, investment varies with disease prevalence. A striking result, which can be explained simply by our analysis, is that when it is prevalence that determines investment in innate resistance (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 while 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 emphasises 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 emphasises 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 anti-predator traits in Abrams (1990)). Therefore, the hump-backed 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 (since recovering infecteds are functionally similar to new-borns/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: a) through increased probability of recovering to a permanent immune state (for convenience we call this *CSS life-long immunity*) or b) 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 life-long 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), 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.

413 However, intuitive understanding is inevitably gained at the expense of model complexity. It
414 is important to consider the likely effect of additional key interactions like parasite diversity
415 and host age structure on the phenomena that we describe. For example, the hallmark of
416 innate resistance i.e. the lowering of prevalence and increase of susceptible frequency, is likely
417 to be complicated by the presence of additional pathogens and their community dynamics. We
418 have also pointed the way to a fuller model of the host population by including age structure.
419 Our analysis indicates that the main results generalise to age-structured host populations
420 but we additionally identify distinct feedbacks arising due to the age-structure. Therefore,
421 although the results that we present here give a thorough explanation of CSS investment
422 in host resistance in standard epidemiological models, they are only a foundation for the
423 understanding of resistance in real world scenarios.

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<div style="text-align: center;">**References**</div>

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	SIS	SIR		$SIRS$
	$\nu = 0$	$\nu = 1$	B3	$\nu(a)$ & $\delta = 0$
			or B4	$\delta(a)$ & $\nu = 1$
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	$\psi^* \sim \alpha \frac{I}{H} \left(1 - \frac{I}{H}\right)$	$\psi^* \sim \alpha \frac{I}{H}(1 - (\frac{b+\gamma}{b})\frac{I}{H})$		—
B2 recovery	$\psi^* \sim \alpha \frac{I}{H} \left(1 - \frac{I}{H}\right)$	$\psi^* \sim \alpha \frac{I}{H} \left(\frac{\alpha I}{bH} + 1\right)$		—
B3 acquired immunity (prob.)	—	—		$\psi^* \sim \frac{\alpha\gamma}{b} \left(\frac{I}{H}\right)^2$
B4 acquired immunity (length)	—	—		$\psi^* \sim \alpha\gamma \left(\frac{I}{H}\right)^2$

Table 1. Feedbacks to CSS investment in resistance, ψ^*. We define $a \sim b$ to represent $non-linear$ monotonic dependence of a on b i.e. 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 $\nu = 0$ for $A1$-$B4$ column 1. Column 2 corresponds to host populations with immune memory and for simplicity immunity is life-long and therefore $\nu = 1$ and $\delta = 0$. In $B4$ column 3 $\nu = 1$ with $\delta > 0$ while in column 3 $\delta = 0$ with $\nu > 0$.
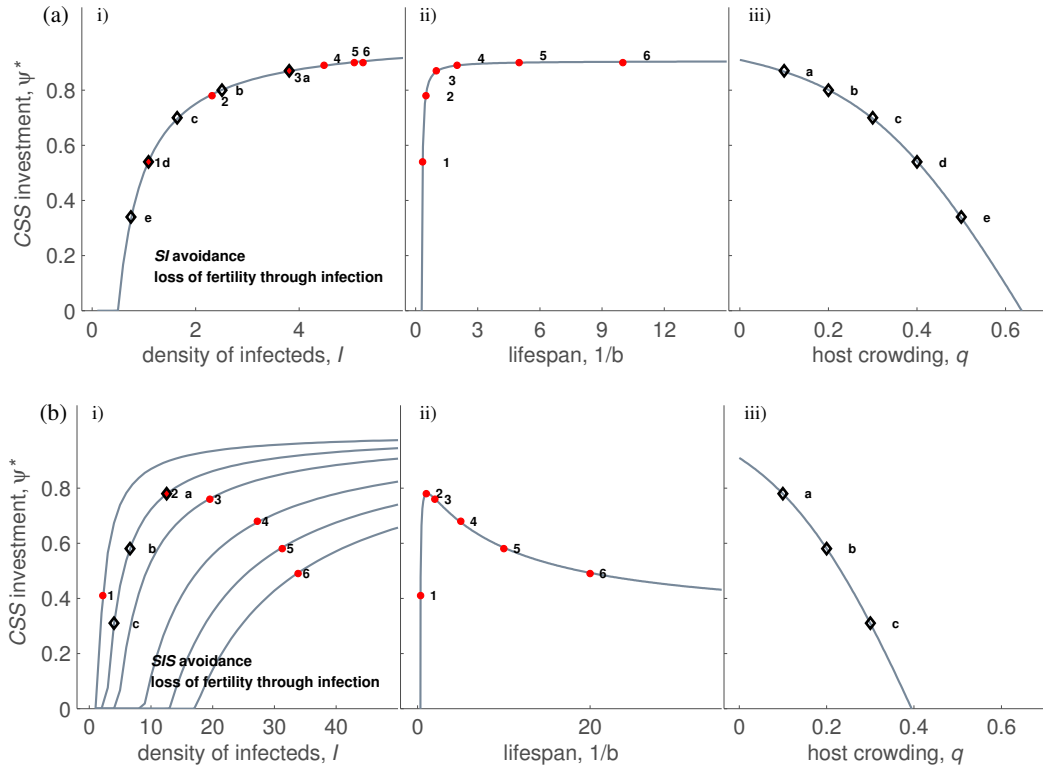
Figure 1. *CSS investment in innate resistance to an infection associated with loss of fertility.* In (a) there is no recovery from infection i.e. $\gamma = 0$. In (b) there is recovery from infection $\gamma = 5$. In both (a) $i)$ and (b) $i)$ CSS investment depends on the density of infecteds, I, while $ii)$ 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: $\mu = 0$ $\beta_0 = 1$ 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 red simulation marker in (b) $ii)$, i.e. 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 $1/b$.
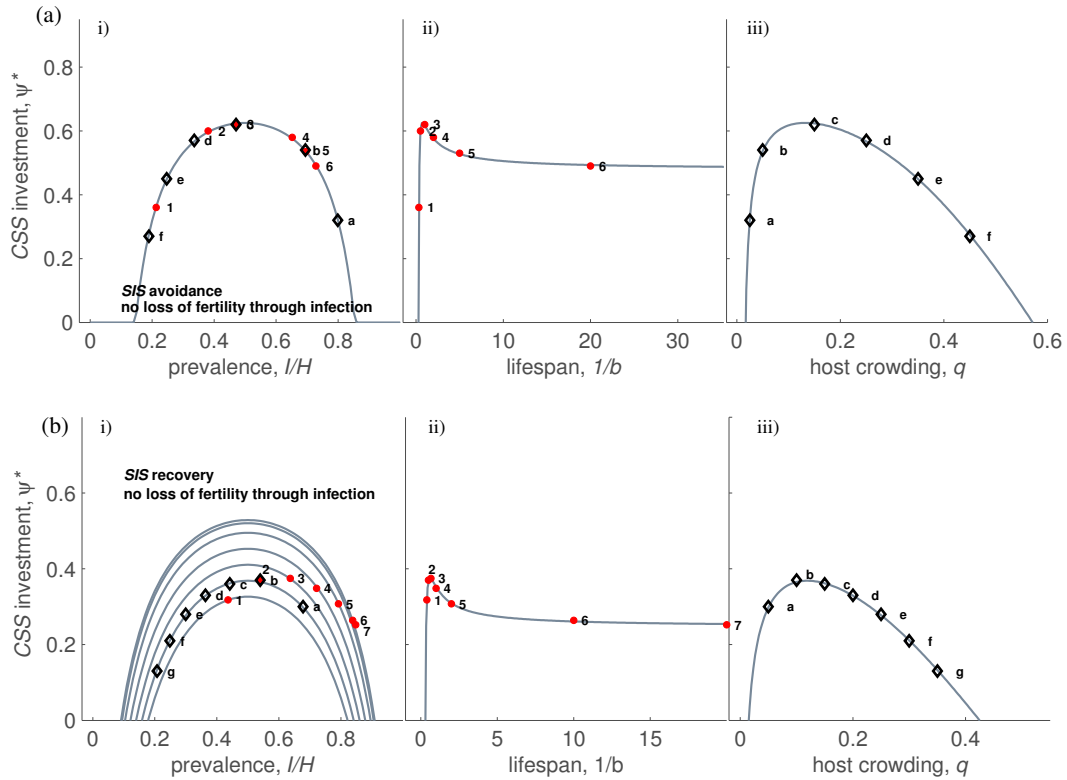
Figure 2. *CSS investment in innate resistance to an infection that has no impact on host fertility where the host has no capacity for immune memory i.e. SIS population.* In (a) the resistance is through avoidance while in (b) it is through recovery. In both (a) $i)$ and (b) $i)$ CSS investment depends on disease prevalence, I/H, while $ii)$ 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 red simulation marker in (b) $ii)$, i.e. 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 $1/b$.
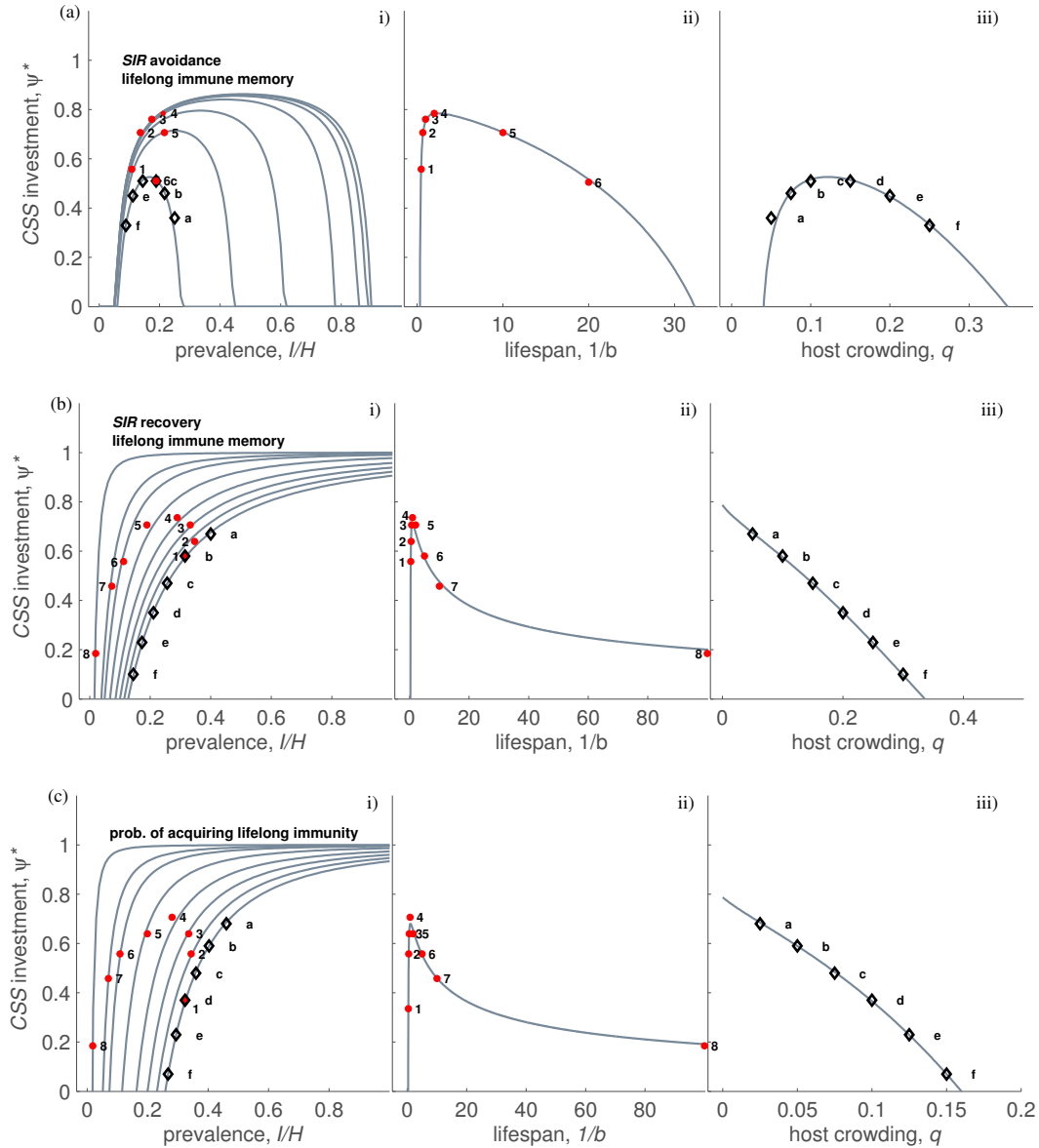
Figure 3. *CSS investment in resistance to an infection that has no impact on host fertility where the host possesses life-long immune memory i.e. SIR population except in (c) which is SIRS (in the sense that an SIR or SIS route is taken depending on ν) since recovereds return to a susceptible state 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 red simulation marker in figure $(a)\,ii)$, i.e. 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 red markers also correspond to values of lifespan i.e. 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.
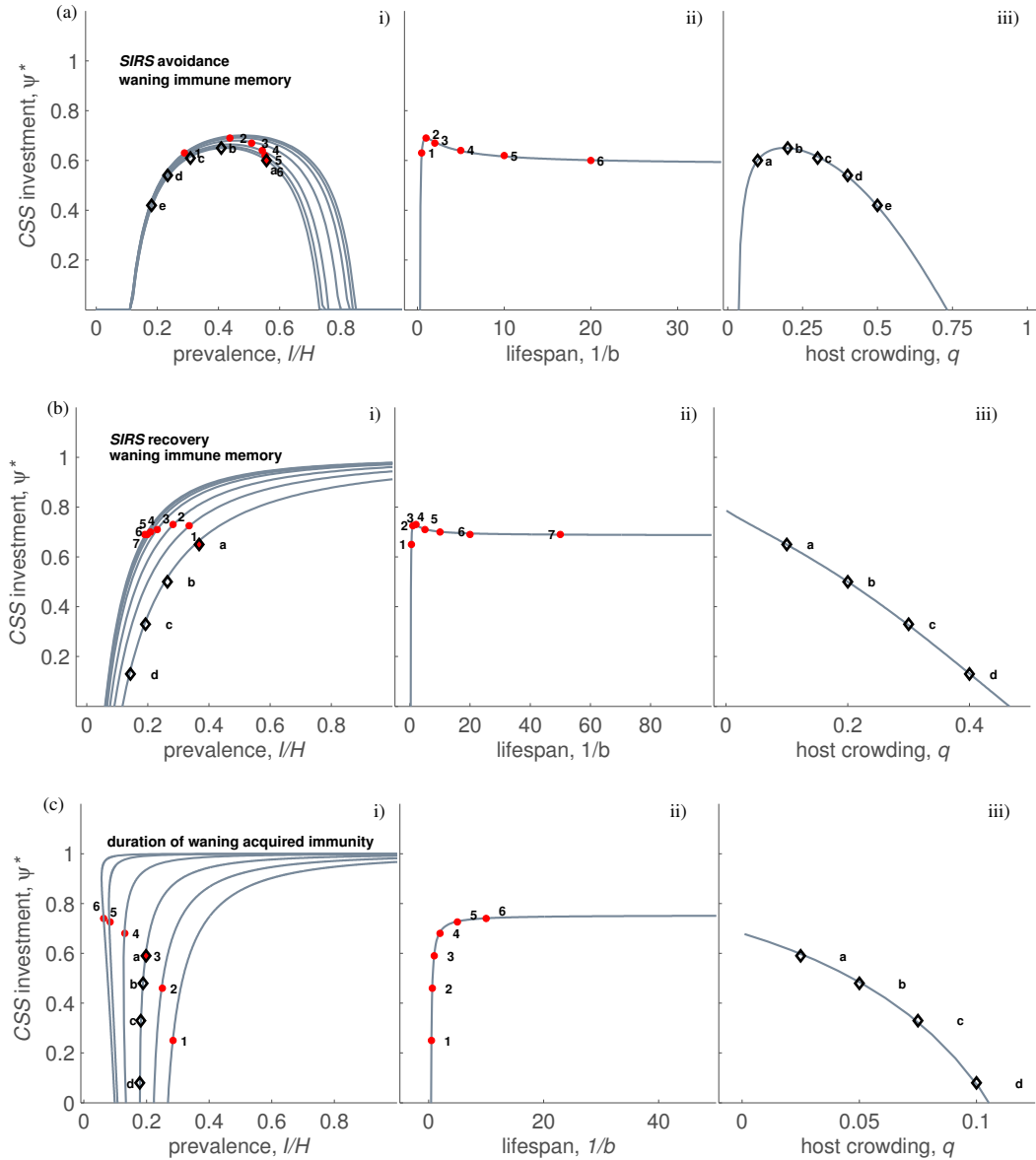
Figure 4. *CSS investment in resistance to an infection that has no impact on host fertility where the host possesses waning immune memory i.e. SIRS population.* In panel (a) resistance is through avoidance, in (b) through recovery, and in (c) through duration of acquired immunity. Note that while waning 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 red simulation marker in figure $(a)\,ii)$, i.e. 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 red markers also correspond to values of lifespan i.e. 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.

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

1   In main text equation 10 we show that,

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = -\left.\frac{C}{B}\right|_{a^*} \tag{S1.1}$$

2   which reveals the correspondence between the singular trait value (through its gradient value

3   $d\omega^m/da^m|*$) and the underlying epidemiological processes. Any resistance singularity on a

4   trade-off with accelerating costs represents CSS investment, ψ^*. The graphical argument in

5   figure S1.1 illustrates why this implies

$$\psi^* \sim \left.\frac{B}{C}\right|_{a^*} \tag{S1.2}$$

6   Where the relation $\sim$ is as defined in the main text. Our intention is to show how CSS

7   investment decreases or increases with changes in the parameters and population dynamics

8   of the underlying epidemiological model. One approach would be to specify a trade-off form

9   and derive exact expressions for CSS investment in resistance. However, our emphasis here is

10 on generality and therefore our results are not limited to specific trade-off forms. Our results

11 imply that for different trade-offs the qualitative patterns are the same, though naturally

12 there will be quantitative differences for different trade-off shapes. This is why our results are

13 expressed as feedback expressions (through a graphical argument) and not exact proportional

14 forms (through implicit differentiation), see equation S1.2.

15 **Appendix S2, CSS investment in resistance when the pathogen has no effect on fertility**

16 In the main text we consider pathogens who prevent fertility in infected hosts (i.e. $\mu = 0$).

17 In this appendix we consider both innate and acquired resistance to pathogens who have no

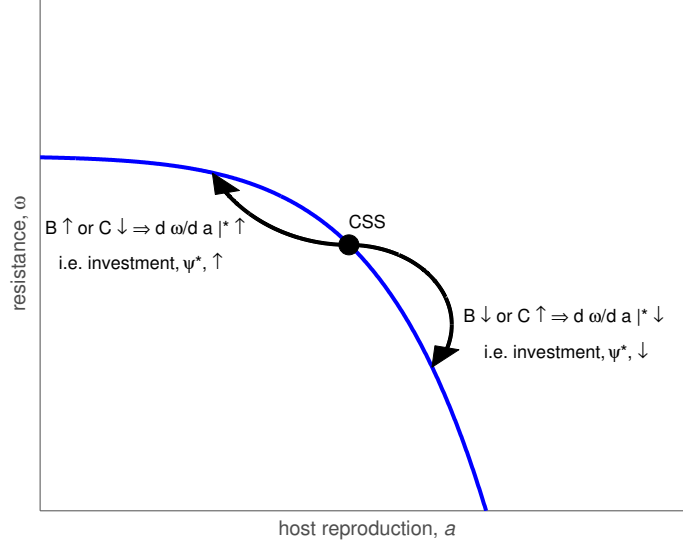18 impact on host fertility (i.e. $\mu = 1$). We assume that recovery leads to waning immunity and

Figure S1.1. The gradient of the resistance reproduction trade-off where the singularity can be found is expressed in terms of parameters of the ecological model in the equation $d\omega/da|* = -C/B|*$. The gradient is negative everywhere (investment is costly) and takes large negative values for high reproduction and small negative values for low reproduction (costs are accelerating). CSS investment, ψ^*, is therefore high or low depending on the ratio of benefit to cost.

never in an immediate return to a susceptible state (i.e. $\nu = 1$). Equation 10, main text, with $\mu = 1$ is,

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = \left.\frac{1 - D\frac{\partial p_I^m}{\partial a^m}}{D\frac{\partial p_I^m}{\partial \omega^m}}\right|_{a^*} \tag{S2.1}$$

The next step is to use the proxy for mutant prevalence $\tilde{p}_I^m = T_I/T_H$. When $\gamma > 0$ a mutant can make infinitely many return visits to the epidemiological states i.e. $T_I/T_H = \sum_{i=1}^{\infty} T_{I_i}/T_H$ where the i's represent the mutant host's successive visits to the infected state. However, following Van Baalen (1998), the equations for the probability that the rare mutant invader is in each of the classes, i.e.

$$\frac{d\vec{p}}{dt} = A\vec{p}$$

are linear, where $\vec{p}$ is the vector of these probabilities ordered according to S, I, R, and the expected times spent in each class are the elements of

$$\int_0^\infty \vec{p}(t)dt = -A^{-1}\vec{p}(0)$$

where

$$A = \begin{pmatrix} -b - \beta^m I^r & (1 - \nu^m)\gamma^m & \delta^m \\ \beta^m I^r & -(\alpha + b + \gamma^m) & 0 \\ 0 & \nu^m\gamma^m & -(b + \delta^m) \end{pmatrix}$$

Since we are interested in $\tilde{p}_S^m$, $\tilde{p}_I^m$ and $\tilde{p}_R^m$ and since $p(0)$ is necessarily $(1\ 0\ 0)^T$, it follows (for the SIR model) that we need only calculate certain cofactors of the matrix A. In particular, denoting the ith row and j^{th} column entry of A as a_{ij}

$$\begin{aligned}
\tilde{p}_S^m &= \frac{a_{22}a_{33} - a_{23}a_{32}}{(a_{22}a_{33} - a_{23}a_{32}) + (a_{23}a_{31} - a_{21}a_{33}) + (a_{21}a_{32} - a_{22}a_{31})} \\
&= \frac{(\alpha + b + \gamma^m)(b + \delta^m)}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r(b + \delta^m) + \nu^m\gamma^m\beta^m I^r}
\end{aligned} \tag{S2.2}$$

$$\begin{aligned}
\tilde{p}_I^m &= \frac{a_{23}a_{31} - a_{21}a_{33}}{(a_{22}a_{33} - a_{23}a_{32}) + (a_{23}a_{31} - a_{21}a_{33}) + (a_{21}a_{32} - a_{22}a_{31})} \\
&= \frac{(\beta^m I^r)(b + \delta^m)}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r(b + \delta^m) + \nu^m\gamma^m\beta^m I^r}
\end{aligned} \tag{S2.3}$$

4

$$\tilde{p}_R^m = \frac{a_{21}a_{32} - a_{22}a_{31}}{(a_{22}a_{33} - a_{23}a_{32}) + (a_{23}a_{31} - a_{21}a_{33}) + (a_{21}a_{32} - a_{22}a_{31})}$$

$$= \frac{\nu^m \gamma^m \beta^m I^r}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r(b + \delta^m) + \nu^m \gamma^m \beta^m I^r} \qquad (S2.4)$$

so that,

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = -\left(\alpha \frac{\partial \tilde{p}_I^m}{\partial \omega^m}\right)^{-1} \qquad (S2.5)$$

for $\omega \in (\beta, \gamma, \delta)$, since the proxy for mutant prevalence does not depend directly on a^m.

Differentiating equation S2.3 with respect to the various forms of resistance leads to,

$$\frac{\partial \tilde{p}_I^m}{\partial \beta^m} = \frac{1}{\beta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{\beta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{\beta^m}\tilde{p}_R^m = \frac{1}{\beta^m}\tilde{p}_I^m \tilde{p}_S^m \qquad (S2.6)$$

$$\frac{\partial \tilde{p}_I^m}{\partial \gamma^m} = -\tilde{p}_I^m \frac{1}{\alpha + b + \gamma^m}\tilde{p}_S^m - \tilde{p}_I^m \frac{1}{\gamma^m}\tilde{p}_R^m = -\frac{1}{\alpha + b + \gamma^m}\tilde{p}_I^m(\tilde{p}_S^m + \frac{\alpha + b + \gamma^m}{\gamma^m}\tilde{p}_R^m) \qquad (S2.7)$$

$$\frac{\partial \tilde{p}_I^m}{\partial \delta^m} = \frac{1}{b + \delta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{b + \delta^m}\tilde{p}_S^m - \tilde{p}_I^m \frac{1}{b + \delta^m}\tilde{p}_I^m = \frac{1}{b + \delta^m}\tilde{p}_I^m \tilde{p}_R^m \qquad (S2.8)$$

and substituting into equation S2.5 leads to CSS investment in the different routes to resistance.

Avoidance

$$\left.\frac{d\beta^m}{da^m}\right|_{a^*} = -\left(\alpha \frac{\partial \tilde{p}_I^m}{\partial \beta^m}\right)^{-1}$$

$$\iff \left.\frac{1}{\beta^m}\frac{d\beta^m}{da^m}\right|_{a^*} = -(\alpha \tilde{p}_I^m \tilde{p}_S^m)^{-1}$$

$$\implies \psi^* \sim \alpha \tilde{p}_I^m \tilde{p}_S^m \qquad (S2.9)$$

38 where investment, ψ^*, is in the natural logarithm of avoidance resistance (since

39 $1/\beta^m(d\beta^m/da^m) = d\ln\beta^m/da^m$) but the log transformation has only a quantitative effect

40 and not a qualitative one since it is monotonic with respect to its argument. Equation S2.9

41 for CSS investment in avoidance resistance appears as the $B1$ SIR in table 1, i.e. $\nu = 1$ so

42 recovery always results in immunity (but note that equation S2.9 is correct regardless of the

43 value of ν). The SIS entry requires analogous work for the model which assumes that $\nu = 0$).

44 *Recovery*

45 In the case of recovery, for the $SIRS$ model, we also assume that $\delta = 0$ (i.e. recovery to a

46 permanent immune state)

$$\left.\frac{d\gamma^m}{da^m}\right|_{a^*} = -\left(\alpha\frac{\partial\tilde{p}_I^m}{\partial\gamma^m}\right)^{-1} \tag{S2.10}$$

$$\iff \frac{1}{\alpha+b+\gamma^m}\left.\frac{d\gamma^m}{da^m}\right|_{a^*} = -(\tilde{p}_I^m(\tilde{p}_S^m + \frac{\alpha+b+\gamma^m}{\gamma^m}\tilde{p}_R^m))^{-1}$$

$$= -(\tilde{p}_I^m\tilde{p}_S^m(1 + \frac{\alpha+b+\gamma^m}{\gamma^m}\frac{\tilde{p}_R^m}{\tilde{p}_S^m}))^{-1}$$

$$= -(\frac{1}{b}\tilde{p}_I^m\tilde{p}_S^m(b+\beta I)^{-1}$$

$$= -(\frac{1}{b}\tilde{p}_I^m\tilde{p}_S^m(b\frac{H}{S} + \alpha\frac{I}{S})^{-1}$$

$$= -(\tilde{p}_I^m(1 + \frac{\alpha}{b}\tilde{p}_I^m)^{-1}$$

$$\implies \psi^* \sim \tilde{p}_I^m(\frac{\alpha}{b}\tilde{p}_I^m + 1) \tag{S2.11}$$

47 where investment, ψ^*, is in the natural logarithm of the infectious period and hence recovery

48 resistance (since $1/(\alpha+b+\gamma^m)(d\gamma^m/da^m) = d\ln(\alpha+b+\gamma^m)/da^m$). Equation S2.11 for

49 CSS investment in recovery resistance appears as $C1$ SIR in table 1 (the SIS entry requires

50 analogous work for the model which assumes that $\nu = 0$).

6

Duration of immunity

$$\frac{d\delta^m}{da^m}\bigg|_{a^*} = -\left(\alpha\frac{\partial\tilde{p}_I^m}{\partial\delta^m}\right)^{-1}$$

$$\iff \frac{d\delta^m}{da^m}\bigg|_{a^*} = -\left(\frac{\alpha\gamma}{(b+\delta)^2}\tilde{p}_I^m\tilde{p}_I^m\right)^{-1}$$

$$\implies \psi^* \sim \alpha\gamma\tilde{p}_I^m\tilde{p}_I^m \tag{S2.12}$$

where investment, ψ^*, is in the duration of immunity, $1/(b+\delta)$. Equation S2.12 for CSS investment in avoidance resistance appears as $B4$ in table 1 ($B3$ in table 1 requires analogous work for the model that assumes that $\delta = 0$ and $\nu = \nu(a)$).

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

In this section we demonstrate that replacing mutant prevalence by the expected proportion of lifespan invading mutants spend infected (and similarly for susceptible frequency and immune frequency) is a proxy for invasion fitness.

Firstly, if the *lifetime reproduction* of an invading mutant phenotype, R, is greater than 1, then the invading mutant population will grow. Therefore the condition, $R > 1$, must be met for a mutant to succeed and for this reason it is an established proxy for invasion fitness Hurford et al. (2010). The full condition for the model given by equations $1 - 3$, main text, is

$$R = T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) > 1 \tag{S3.1}$$

On the other hand, we have the actual expression for invasion fitness, see equation 6 main text. Here we show that equivalence of the two criteria implies that we can replace the rare mutant frequencies with the expected proportion of the rare mutant's life that is spent in the various classes.

Beginning with the *lifetime reproduction* criteria:

$$T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) > 1 \tag{S3.2}$$

$$\Leftrightarrow T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) - 1 > 0 \tag{S3.3}$$

$$\Leftrightarrow T_S^m(a^m - qH^r - b) + T_I^m(a^m - qH^r - b - \alpha) + T_R^m(a^m - qH^r - b)$$
$$+ T_S^m b + T_I^m(b + \alpha) + T_R^m b - 1 > 0 \tag{S3.4}$$

$$\Leftrightarrow \frac{T_S^m}{T_H^m}(a^m - qH^r - b) + \frac{T_I^m}{T_H^m}(a^m - qH^r - b - \alpha) + \frac{T_R^m}{T_H^m}(a^m - qH^r - b)$$
$$+ \frac{T_S^m}{T_H^m}b + \frac{T_I^m}{T_H^m}(b + \alpha) + \frac{T_R^m}{T_H^m}b - \frac{1}{T_H^m} > 0 \tag{S3.5}$$

$$\Leftrightarrow \frac{T_S^m}{T_H^m}(a^m - qH^r - b) + \frac{T_I^m}{T_H^m}(a^m - qH^r - b - \alpha) + \frac{T_R^m}{T_H^m}(a^m - qH^r - b)$$
$$b + \frac{T_I^m}{T_H^m}\alpha - \frac{1}{T_H^m} > 0 \tag{S3.6}$$

68 It can now be seen that replacing T_S^m/T_H^m with S/H (and similarly for the other frequencies)
69 links the *lifetime reproduction* criteria, $R > 1$, and invasion fitness. This is the case because
70 the final term of S3.6 (the inverse of the mutant lifespan) is the death rate of mutant hosts.
71 Once the frequency replacements are made, the preceding terms in the second line of equation
72 S3.6 are also the death rate of mutant hosts and the terms cancel leading to

$$\frac{T_S^m}{T_H^m}(a^m - qH^r - b) + \frac{T_I^m}{T_H^m}(a^m - qH^r - b - \alpha) + \frac{T_R^m}{T_H^m}(a^m - qH^r - b) > 0 \tag{S3.7}$$

73 which upon making the frequency replacements is the invasion fitness split into classes as per
74 equation 6 of the main text. Therefore, assuming the equivalence of the *lifetime reproduction*
75 criteria (evaluated at rare invasion) and invasion fitness is consistent with replacement of rare
76 mutant frequencies with the expected proportion of a rare mutant's lifespan spent in those
77 classes.

Appendix S4, Ecological feedbacks due to host age structure

79 In this appendix we illustrate the extension of our results to a host population structured by

80 C age classes, using the example of evolving innate resistance. We assume that recovery leads

81 to immediate return to a susceptible state. A model of C age classes is given by,

$$\frac{dS_1}{dt} = a \sum_{j=1}^{C} \kappa_j (S_j + \mu_j I_j) - q \sum_{j=1}^{C} \kappa_j (S_j + \mu_j I_j) H - b_1 S_1 - \beta_1 S_1 \sum_{j=1}^{C} I_j + \gamma_1 I_1 - q_1 S_1 \quad \text{(S4.1)}$$

$$\frac{dI_1}{dt} = \beta_1 S_1 \sum_{j=1}^{C} I_j - (\alpha_1 + b_1 + \gamma_1) I_1 - q_1 I_1 \quad \text{(S4.2)}$$

$$\frac{dS_n}{dt} = q_{n-1} S_{n-1} - b_n S_n - \beta_n S_n \sum_{j=1}^{C} I_j + \gamma_n I_n - q_n S_n, \qquad (2 \leq n \leq C-1) \quad \text{(S4.3)}$$

$$\frac{dI_n}{dt} = q_{n-1} I_{n-1} + \beta_n S_n \sum_{j=1}^{C} I_j - (\alpha_n + b_n + \gamma_n) I_n - q_n I_n, \qquad (2 \leq n \leq C-1) \quad \text{(S4.4)}$$

$$\frac{dS_C}{dt} = q_{C-1} S_{C-1} - b_C S_C - \beta_C S_C \sum_{j=1}^{C} I_j + \gamma_C I_C \quad \text{(S4.5)}$$

$$\frac{dI_C}{dt} = q_{C-1} I_{C-1} + \beta_C S_C \sum_{j=1}^{C} I_j - (\alpha_C + b_C + \gamma_C) I_C \quad \text{(S4.6)}$$

82 i.e. a total of C age classes, all of which are vulnerable to infection with different levels

83 of susceptibility. For simplicity, the transmission rate, β_j, depends on the age class of the

84 susceptible host but not the age class of the infected host. The rate q_l governs age transitions

85 of individuals between the $l-1^{th}$ and the lth age classes. $0 \leq \kappa_j \leq 1$ is the proportion of the

86 maximum reproduction rate, a, that is achieved by individuals of age class j. $0 \leq \mu_j \leq 1$ is the

87 reduction of host fertility (of age class j) due to infection. All other parameters are as described

88 in the main text, though now they are particular to the age class represented by the subscript

89 that they bear. As per *Appendix S*2, equations S4.1-S4.6 can be extended to represent mutants

90 in a population of residents. Where mutants bear a small phenotypic change along a trade-off

91 axis between resistance, ω and maximum reproduction, a. As per the main text, by taking a

92 rare mutant approximation, the invasion fitness can be written as

$$\Theta_r(m) = \frac{1}{H^m}\frac{dH^m}{dt}\bigg|_{H^r=\hat{H}^r, H^m=0} \tag{S4.7}$$

$$= \sum_{j=1}^{C}\left(\frac{S_j^m}{H^m}(a^m\kappa_j - q\kappa_j H^{tot} - b_j) + \frac{I_j^m}{H^m}(\kappa_j\mu_j(a^m - qH^{tot}) - b_j - \alpha_j)\right)\bigg|_{H^r=\hat{H}^r, H^m=0} \tag{S4.8}$$

$$= \sum_{j=1}^{C}\left(p_{A_j}^m\sigma_j - p_{I_j}^m((1-\kappa_j\mu_j)(a^m - qH^{tot}) + \alpha_j)\right)\bigg|_{H^r=\hat{H}^r, H^m=0} \tag{S4.9}$$

$$= \sum_{j=1}^{C}\left(p_{A_j}^m\sigma_j - p_{I_j}^m D_j\right)\bigg|_{H^r=\hat{H}^r, H^m=0} \tag{S4.10}$$

93 where p_{A_j} is the proportion of time a mutant spends in the jth age class (i.e. regardless of

94 infection status). Where σ_j represents the instantaneous host growth rate when the mutant is

95 uninfected and in age class j. Additionally, $D_j = (1 - \kappa_j\mu_j)(a^m - qH^{tot}) + \alpha_j$, represents the

96 damage caused by infection to hosts of age class j. Applying the singularity equation

$$\frac{d\Theta_r(m)}{da^m} = 0\bigg|_{a^*} \tag{S4.11}$$

97 to invasion fitness S4.9 yields the following expression describing the position of the CSS

98 singularity

$$\frac{d\omega^m}{da^m}\bigg|_{a^*} = \frac{\sum_{j=1}^{C}(\kappa_j p_{S_j}^m + \kappa_j\mu_j p_{I_j}^m)}{\sum_{j=1}^{C}(D_j\frac{\partial p_{I_j}^m}{\partial\omega^m} - \sigma_j\frac{\partial p_{A_j}^m}{\partial\omega^m})}\bigg|_{a^*} \tag{S4.12}$$

99 Note that we have omitted terms relating to derivatives of frequencies with respect to a^m

100 since it should be clear from *Appendix S*2 that the proxy terms are always independent of

[101] reproduction rate (because they represent the proportion of its life that the new mutant spends [102] in the particular classes).

[103] The next step would be to calculate the proxies for mutant prevalence $\tilde{p}_{I_j}^m = T_{I_j}/T_H$ and for [104] mutant age profile $\tilde{p}_{A_j}^m = (T_{S_j} + T_{I_j})/T_H$, but we omit these workings here. As per *Appendix* [105] *S2* they can be calculated by reference to elements of the vector $-A^{-1}\vec{p}(0)$ (A is a CxC [106] vector and $\vec{p}(0)$ is Cx1). All the elements of the column vector $\vec{p}(0)$ are zero except for the [107] first (representing birth of hosts into only the first age class and no vertical transmission) [108] and therefore one needs only to calculate the first column of A^{-1}. The elements of the vector [109] $-A^{-1}\vec{p}(0)$ represent expected duration of the mutant in each class and we therefore divide [110] each element by the sum of all the elements in order to calculate the frequencies. This means [111] that we do not need to calculate the determinant of A but only three of the *minors* of A [112] (results omitted here).

[113] From equation S4.12 we see that if there is no effect of the infection on fertility and if birth [114] rate does not vary between classes (i.e. setting $\kappa_j = 1$ and $\mu_j = 1$ for all $j \in C$), then

$$\psi^* \sim \sum_{j=1}^{C} (\alpha_j \frac{\partial p_{I_j}^m}{\partial \omega^m} - \sigma_j \frac{\partial p_{A_j}^m}{\partial \omega^m}) \bigg|_{a^*} \tag{S4.13}$$

[115] Equation S4.13 shows that the single age class result of equation S2.5 in *Appendix S2* is [116] generalisable to multiple age classes (i.e. see the first term on the right hand side of equation [117] S4.13). However, now there is an additional term due solely to age structure (i.e. the second [118] term on the right hand side of equation S4.13) which indicates that CSS investment is relatively [119] greater when resistance alters the age profile of the population in such a way that ages with [120] a greater contribution to instantaneous growth of the overall mutant population are more [121] favoured.

References

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