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The evolution of host defence when parasites impact reproduction

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ABSTRACT

Question: How does the evolution of host defences to parasitism depend on the level of disease-induced sterility?

Mathematical methods: Evolutionary invasion analysis (adaptive dynamics) applied to susceptible-infected host–parasite model.

Key assumptions: Hosts can evolve defence through avoidance (lower transmission), clearance (higher recovery) or tolerance (lower virulence), in isolation or simultaneously, at a cost to their reproductive rate. Separation of ecological and evolutionary timescales and mutations of small phenotypic effect.

Conclusions: Avoidance and clearance are maximized when sterility is high, but tolerance is greatest when sterility is low. However, when clearance and tolerance co-evolve there is greater tolerance at high sterility, as this boosts the effectiveness of clearance. Patterns of investment along other environmental gradients can change as the level of sterility changes. Evolutionary branching to co-existence in avoidance and clearance is most likely when sterility is high.

Keywords: adaptive dynamics, evolution, host–parasite, sterility.

INTRODUCTION

Understanding the evolution of host defences to parasitism, and specifically the ecological feedbacks that drive the patterns of selection, is a major area of theoretical inquiry (van Baalen, 1998; Boots and Bowers, 1999, 2004; Boots and Haraguchi, 1999; Roy and Kirchner, 2000; Restif and Koella, 2003, 2004; Miller *et al.*, 2005, 2007; Best *et al.*, 2008, 2009; Toor and Best, 2014). For the most part, these theoretical studies have assumed that the main fitness impact of parasitism is through disease-induced mortality, generally defined to be 'virulence'. However, it is also well understood that parasitism can cause sub-lethal effects, specifically through sterilizing effects that reduce the reproduction rate of infected hosts. Indeed, many parasites are known to cause complete

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castration in their hosts, such as *Pasteuria ramosa* in *Daphnia* (Little *et al.*, 2002; Ebert *et al.*, 2004), anther smut infections in *Silene* (Antonovics *et al.*, 1996), and insect baculoviruses (Boots and Begon, 1993; Boots and Mealor, 2007). Many more parasites cause reduced fecundity in their infected hosts, for example in red grouse (Dobson and Hudson, 1992; Hudson *et al.*, 1992) and vole (Feore *et al.*, 1997; Deter *et al.*, 2007) populations due to parasitic nematodes.

A few theoretical studies have considered the evolution of defence traits that combat parasite-induced sterility directly – that is, sterility itself is being selected on (Restif and Koella, 2004; Bonds, 2006; Best *et al.*, 2008, 2009). These have shown that tolerance mechanisms that reduce the degree of sterility may be a more effective defence strategy for the host than resistance (Best *et al.*, 2009), and that investment in such a tolerance mechanism will be greatest against parasites with a high growth rate (Restif and Koella, 2004). More generally, theoretical studies focus on defences that combat epidemiological processes of transmission or virulence, and this will also be our focus here. Commonly, these studies consider the investment in these defences along environmental gradients. Yet, the majority of these studies have not allowed sterility to vary but instead assumed that sterility is either complete (such that infected hosts do not reproduce at all) or absent (such that infected hosts reproduce at the same rate as susceptible hosts). It is important for us to assess how these assumptions might impact the predicted outcomes of host evolution.

Boots and Haraguchi (1999) showed that resistance (through 'avoidance') is maximized against the least virulent parasites, while van Baalen (1998) showed that resistance (through 'clearance') is highest when virulence is intermediate. However, these two studies made very different assumptions about disease-induced sterility, with either complete (Boots and Haraguchi, 1999) or no sterilizing effects (van Baalen, 1998). Donnelly *et al.* (2015) recently offered some insight into this difference by showing that the main driver of selection alters between disease exposure (castrators) and disease prevalence (non-castrators) depending on whether sterility is complete or absent. A few studies of host defence evolution have explored investment in host defences along a gradient of sterility. For example, while exploring the effects of host plasticity, McLeod and Day (2015) showed that avoidance increases as the level of sterility is increased, a result that Toor and Best (2014) showed remains true when a (dynamic) predator is also present. In a separate study, McLeod and Day (2014) also considered the impact of sterility on host reproductive strategy as a defence against sexually transmitted disease, while we showed that investment in immune priming in invertebrates would be highest when parasites are sterilizing (Best *et al.*, 2012). Thus, while we have some knowledge of how parasite-driven sterility impacts host evolution in specific circumstances, we still lack a general overview of its role in the evolution of host defences.

A key finding has been the distinction between resistance and tolerance mechanisms due to their ecological feedbacks. Resistance mechanisms directly reduce parasite fitness (i.e. through lowered transmission or increased clearance) creating negative frequency-dependence. Therefore, when these mechanisms are costly to the host there can be evolutionary branching to co-existence of host strains (Boots and Bowers, 1999; Boots and Haraguchi, 1999). In contrast, tolerance mechanisms generally increase parasite fitness (i.e. through reduced virulence, and therefore increased infectious period) creating positive-dependence (Roy and Kirchner, 2000; Miller *et al.*, 2005). When tolerance is to the sterilizing rather than mortality effects of parasitism, parasite fitness is not impacted directly, and depending on where the costs of sterility tolerance are incurred branching can arise (Best *et al.*, 2008, 2009). In another study, Ashby and Gupta (2014) showed that castration may be crucial to the maintenance of temporal diversity through co-evolutionary cycles in gene frequencies between hosts and

parasites, but it remains an open question as to how static diversity (co-existence due to evolutionary branching) in resistance depends on the degree of sterility.

In this study, we consider the evolution of three forms of host defence: avoidance, clearance, and mortality tolerance, in a similar manner to the study of Miller *et al.* (2007) on the effects of host lifespan. Our focus here is on how investment in each type of defence varies with the sterilizing effects of the parasite, as well as on how this interacts with variation along other environmental gradients. We also consider the effects of sterility on the potential for diversity through evolutionary branching and on the outcome when two of the defence mechanisms co-evolve together.

MODEL

For consistency with many earlier studies, and in particular Boots and Haraguchi (1999), we use a standard SIS epidemiological model with emergent density-dependence on births, with the population dynamics of susceptible (S) and infected (I) hosts given by

$$\frac{dS}{dt} = (a - q(S+I))(S + fI) - bS - \beta SI + \gamma I \tag{1}$$

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

All hosts reproduce at rate a, which is reduced due to crowding, q. All hosts die at natural death rate b, with infected hosts suffering additional mortality (virulence) at rate α. Transmission is a mass-action term with parameter β. Again for consistency with earlier studies, notably Boots and Haraguchi (1999) and van Baalen (1998), we assume that transmission is density-dependent. We note, however, that because many sexually transmitted infections induce infertility in their hosts (Lockhart *et al.*, 1996), frequency-dependent transmission would be an equally relevant assumption, but we leave this for future work. Infected hosts may recover back to susceptibility at rate γ. The key parameter is that infection may reduce the reproduction rate of infected hosts by a fecundity factor f. We note that a low value of f indicates high sterility (with $f = 0$ representing full castration), and high f low sterility (with $f = 1$ meaning infected hosts reproduce at the same rate as susceptibles).

We model evolution of host defence through an evolutionary invasion (adaptive dynamics) framework (Geritz *et al.*, 1998). As such, we assume that a rare mutant type attempts to invade a resident population at its dynamic attractor ($\hat{S}$, $\hat{I}$) with $\hat{N} = \hat{S} + \hat{I}$. We will consider three forms of host defences: (i) avoidance (lowered susceptibility to infection, β), (ii) clearance (increased recovery, γ), and (iii) tolerance (lowered virulence, α).

In each case, we will assume that there is a cost to higher defence through reduced reproduction, as is commonly assumed in the theoretical literature (e.g. Boots and Bowers, 1999; Boots and Haraguchi, 1999; Restif and Koella, 2003; Miller *et al.*, 2007) and for which there is empirical support (Boots and Begon, 1993). For example, let us assume that defence is through avoidance (the other cases can be expressed similarly), where a mutant host has strategy (β_m, $a(\beta_m)$). We emphasize that this implies a reduced likelihood of a susceptible host becoming infected, not a reduced rate of infection by infected hosts. For the first part of the study we use a generic trade-off function of the form,

$$a(\beta) = a_{\max} - (a_{\max} - a_{\min}) \left(1 - \frac{\beta - \beta_{\min}}{\beta_{\max} - \beta_{\min}}\right) \Big/ \left(1 + p\,\frac{\beta - \beta_{\min}}{\beta_{\max} - \beta_{\min}}\right), \tag{3}$$

which links maximum and minimum birth and avoidance (defence) values through a smooth function the shape of which is controlled by parameter p (the trade-off is concave for $p > 0$ and convex for $-1 < p < 0$). We note that for the recovery trade-off, the values of $a_{\max}$ and $a_{\min}$ must be swapped for the trade-off to be decreasing rather than increasing. We emphasize that in all cases, including the evolution of recovery and tolerance, the costs of reduced reproduction are paid both by susceptible and infected hosts. An alternative approach might be to assume that induced defences are plastic, and are only 'switched on' once a host is infected, and therefore only infected hosts would pay the costs. Here we assume that all defence mechanisms are constitutive and always present.

By considering the transversal stability of the resident equilibrium, specifically the determinant of the mutant's Jacobian, it can be found that host fitness is given by [for the derivation, see http://www.evolutionary-ecology.com/data/3071Appendix.pdf]

$$s = [a(\beta_m) - q\hat{N} - b - \beta_m \hat{I}][\alpha + b + \gamma] + \beta_m \hat{I}[\gamma + f(a(\beta_m) - q\hat{N})]. \tag{4}$$

If $s > 0$, then the mutant can invade to replace or co-exist with the resident, whereas if $s < 0$, the mutant will die out. Through a mutation-substitution sequence the population will evolve in the direction of the local selection gradient (e.g. $\partial s/\partial \beta_m|_{\beta_m = \beta}$ for avoidance) until this gradient is zero and an evolutionary 'singular point' has been reached. Here, the evolutionary outcome depends on two second-order derivatives: evolutionary stability (ES), $\partial^2 s/\partial \beta_m^2|_{\beta_m = \beta}$ (is the point evolutionarily invadable?), and convergence stability (CS), $\partial^2 s/\partial \beta_m^2|_{\beta_m = \beta} + \partial^2 s/\partial \beta_m \partial \beta|_{\beta_m = \beta}$ (is the point evolutionarily attracting?). If both expressions are negative, the point is said to be a 'continuously stable strategy' (CSS), a long-term attractor of evolution. As our main focus here is on how sterility impacts quantitative investment in defence mechanism, we shall concentrate on examining the location of CSSs. We shall also look at 'evolutionary branching points' where a dimorphic population emerges at a singular point that is CS (second expression is negative) but not ES (first expression is positive).

DIRECT EFFECTS

We first consider the direct effects of varying the fecundity of infected hosts, f, on the evolutionary outcome, focusing on whether investment at an attracting singular point (a CSS) will increase or decrease. We plot numerical examples for each case in Fig. 1. For consistency, we plot $B^* = \beta_{\max} - \beta^*$ for avoidance and $A^* = \alpha_{\max} - \alpha^*$ for tolerance, such that in all cases high values indicate high defence and low values low defence. These show the general patterns that avoidance decreases with increasing fecundity (Fig. 1a), clearance decreases with increasing fecundity (Fig. 1b), and tolerance increases with increasing fecundity (Fig. 1c). Therefore, we see that resistance (avoidance or clearance) is highest when fecundity is low (sterility high), while tolerance is highest when fecundity is high (sterility low). In the Appendix, we demonstrate analytically that this pattern is always true for clearance [3071Appendix.pdf]. Numerical exploration suggests that the patterns are also always true for the other two cases, but we cannot prove this analytically.

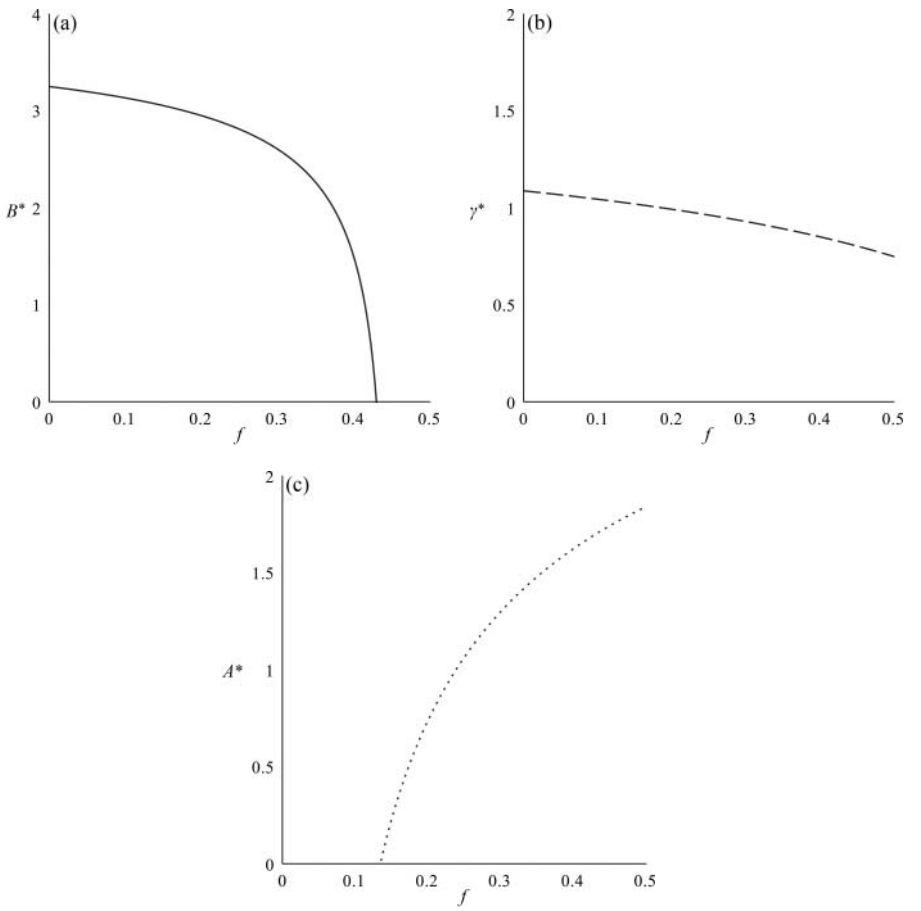

Fig. 1. Direct effects of varying infected fecundity, f, on host investment. (a) Avoidance (for consistency we plot $B^* = \beta_{max} - \beta^*$); (b) clearance ($\gamma^*$); (c) tolerance (for consistency we plot $A^* = \alpha_{max} - \alpha^*$). Parameter values: $\beta = 2$, $b = 1$, $q = 0.1$, $\alpha = 1$, $\gamma = 1$. Trade-offs: (a) $a(\beta) = 2.76 - 1.18(1.25 - 0.25\beta)/(0.84 + 0.16\beta)$; (b) $a(\gamma) = 1.70 + 0.50(1 - 0.5\gamma)/(1 - 0.17\gamma)$; (c) $a(\alpha) = 2.14 - 0.54(1 - 0.5\alpha)/(1 + 0.91\alpha)$.

The pattern for resistance is to be expected. As the level of sterility is increased, the fitness contribution from infected hosts is reduced. Thus selection for resistance mechanisms, which act to keep or move more of the population into the more fecund susceptible state, will 1increase. The pattern for tolerance, in contrast, may not have initially been expected but in fact follows similar reasoning. At high rates of sterility, there is almost no contribution to fitness by infected hosts (due to both the direct effect of reduced reproduction and the indirect effect of a reduced infected density), meaning that there is very little reason to invest in tolerance mechanisms. However, when infected hosts do reproduce, they can still make a significant contribution to fitness, as contribution that can be increased by investing in tolerance and thus lengthening the infectious period.

It is clear from the fitness expression given above that there is a special case where $f = 0$. Here, a part of the fitness term disappears. This has an important simplifying effect when calculating the fitness gradient of each case. For example, in the case of avoidance, the full fitness gradient is,

$$\left.\frac{\partial s}{\partial \beta_m}\right|_{\beta_m=\beta} = [a'(\beta) - \hat{I}][\alpha + b + \gamma] + \hat{I}[\gamma + f(a(\beta) - q\hat{N})] + fa'(\beta)\beta\hat{I}. \quad (5)$$

If $f = 0$, this expression simplifies to

$$\left.\frac{\partial s}{\partial \beta_m}\right|_{\beta_m=\beta} = [a'(\beta) - \hat{I}][\alpha + b + \gamma] + \hat{I}\gamma, \quad (6)$$

such that the total population size, $\hat{N}$, no longer appears in the fitness gradient and thus does not have an effect on the location of the singular point. In this case, $\hat{I}$, that is the density of infecteds, is the key driver of evolution. However, in the more general case, both $\hat{I}$ and $\hat{N}$ impact the location of the singular point. The same argument can be applied to the other two cases [see 3071Appendix.pdf, section A3].

COMBINED EFFECTS

In this section, we look at how investment across other environmental gradients is affected by altering the amount of sterility. We limit our study to the range $f \in [0, 0.5]$, noting that further investigation found no further qualitative changes of behaviour occur when $f > 0.5$.

Parasitic characteristics

We first focus on how fecundity interacts with virulence [note that we cannot consider the case of tolerance here, as this selects on virulence. The respective plots will be absent when considering recovery (clearance) and transmission (avoidance) also]. In Fig. 2a we plot the CSS level of transmission as α (horizontal axis) and f (vertical axis) vary. Blue hues indicate high defence (low β) and yellow hues low defence (high β). Here we see that for very low f, defence is highest when virulence is lowest. However, as f increases the pattern shifts so that defence is maximized against parasites with intermediate virulence. Once f is reasonably high, the pattern has completely reversed and defence is highest against the most virulent parasites. The changes in behaviour can be seen as line plots for the cases of $f = 0$ and $f = 0.5$ in Fig. A1 [3071Appendix.pdf].

We now look at the relationship, α and f, when defence is through clearance. In Fig. 2b, once more yellow hues denote low defence (low γ) and blue hues high defence. Here we see a similar pattern as with avoidance. Defence is maximized against parasites with low virulence when there is low fecundity (high sterility), but against parasites with intermediate virulence when fecundity is higher. Again, the behaviour at the extremes of $f = 0$ and $f = 0.5$ is shown in Fig. A1.

Next we look at varying recovery. For avoidance (Fig. 2c), we see that investment always decreases with increasing clearance, but that the strength of this effect lessens at higher fecundity. For tolerance (Fig. 2d), we again see that the level of fecundity alters the pattern of investment. When fecundity is low (sterility high), tolerance is greatest at high clearance rates. However, as fecundity increases, tolerance is instead maximized at intermediate and

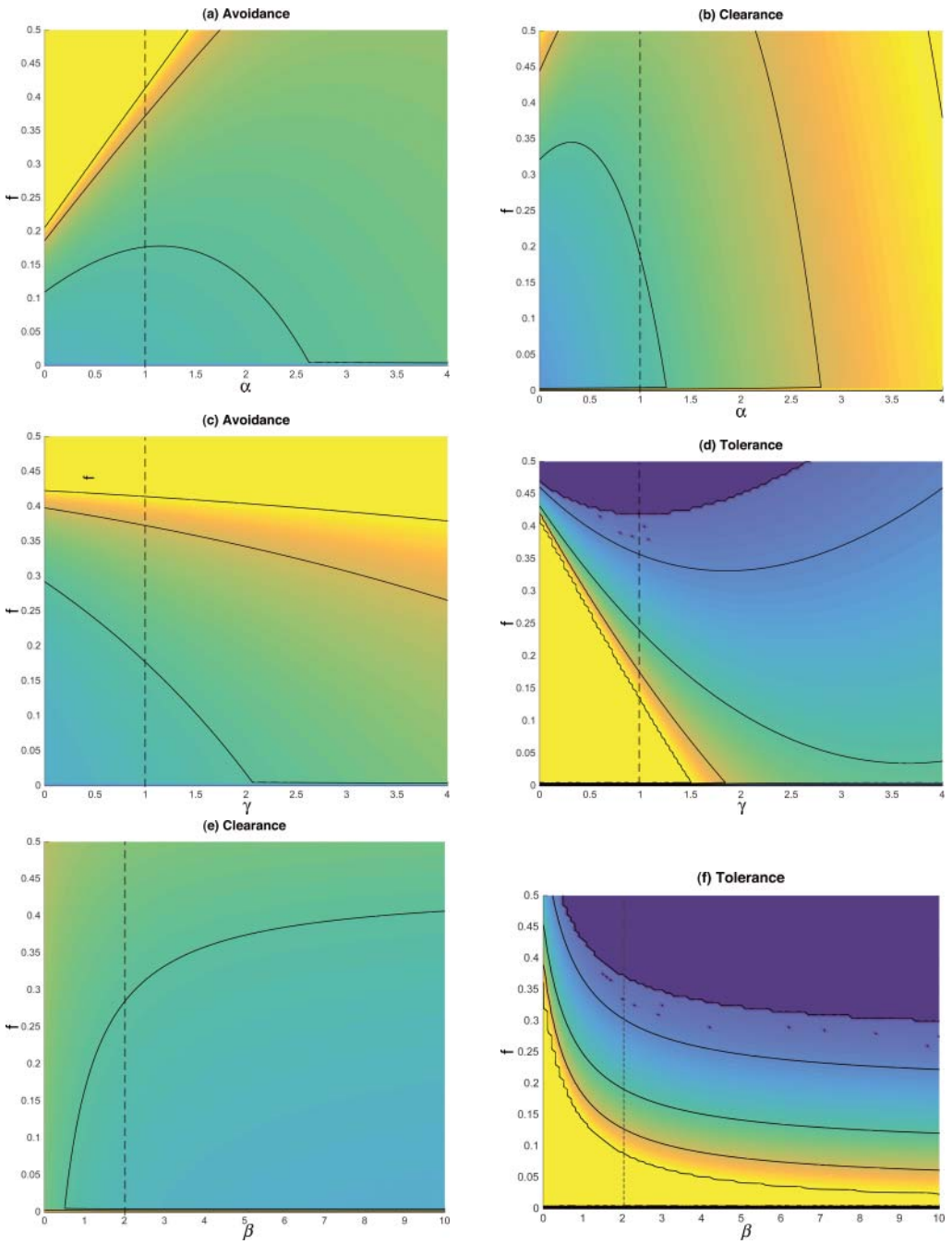

Fig. 2. Combined effects of varying fecundity, f (y-axis) with virulence (α, top row), recovery (γ, middle row), and transmission (β, bottom row). Plots are of investment in avoidance (a and c), clearance (b and e), and tolerance (d and f). In each case, blue hues indicate high defence and yellow hues low defence. Contours are added for clarity. The dashed line marks the gradient along which the single variable plots from Fig. 1 are taken. Parameter values are as in Fig. 1.

then low rates of recovery. Finally, we show the patterns for varying transmission for defence in clearance and tolerance (Fig. 2e,f). In both cases, fecundity has no qualitative effect on the relationship, with investment increasing with transmission.

Host characteristics

We now consider the variation in investment against different host characteristics, starting with lifespan. In general, Fig. 3 (top row) shows investment is highest (blue hues) in all three defence mechanisms for high lifespans (low death rates). However, at intermediate rates of fecundity we see that for the resistance mechanisms of avoidance (Fig. 3a) and clearance (Fig. 3b), investment may be maximized at intermediate lifespans. (Note that the solid black region in Fig. 3a represents a repelling singular point that is neither ES nor CS instead of an attractor. In this case, evolution will lead to the host either maximizing or minimizing avoidance depending on the initial conditions.) We also consider investment as the competition coefficient q is varied. Figure 3 (bottom row) shows that for all three defence mechanisms, investment is highest when competition is low and therefore the population density is high.

STABILITY AND EVOLUTIONARY BRANCHING

We now examine how fecundity impacts the potential for dimorphism through evolutionary branching, in particular through the evolutionary and convergence stability of a fixed singular point. At such a point, the population is attracted to the singular point (it is CS), but once there it finds it is a local fitness minimum (it is not ES). This results in disruptive selection and the emergence of two co existing strains either side of the singular point (Geritz *et al.*, 1998). We now fix the singular point to be at a particular level of defence (and related cost). We no longer choose a fixed trade-off function, but the existence of the singular point at the chosen values requires us to fix the gradient of the trade-off. We then consider the change in behaviour at the singular point as we vary the curvature (second derivative) of the trade-off at the singular point (de Mazancourt and Dieckmann, 2004; Bowers *et al.*, 2005). Specifically, we plot the boundaries of evolutionary stability (ES) and convergence stability (CS) at a fixed singular point in terms of the trade-off curvature (y-axis) at that point, as a function of sterility (x-axis) in Fig. 4. Figure 4a shows the relationship for avoidance, Fig. 4b that for clearance, and Fig. 4c that for tolerance. In each case, curvatures below the solid line are ES and those below the dashed line are CS. As is known to be generally true from earlier work (Hoyle *et al.*, 2008), trade-offs with strongly negative ('accelerating') curvatures tend to produce CSS points (both ES and CS), those with strongly positive ('decelerating') curvatures tend to produce repelling points (neither ES nor CS), with branching and 'Garden of Eden' points (ES but not CS) generally occurring for near-linear trade-offs.

In the first two cases, avoidance and clearance, we see that when fecundity is not too high (sterility not too low), there are a range of trade-off curvatures for which the singular point is CS but not ES, and therefore an evolutionary branching point. However, for both cases we see that the potential for branching decreases with increasing f, with no branching predicted for this parameter set when reproduction is unaffected by infection. We explored a range of parameter values and found that this qualitative pattern, of a decreasing range of trade-offs that allows branching as f increases, is generally preserved [3071Appendix.pdf,

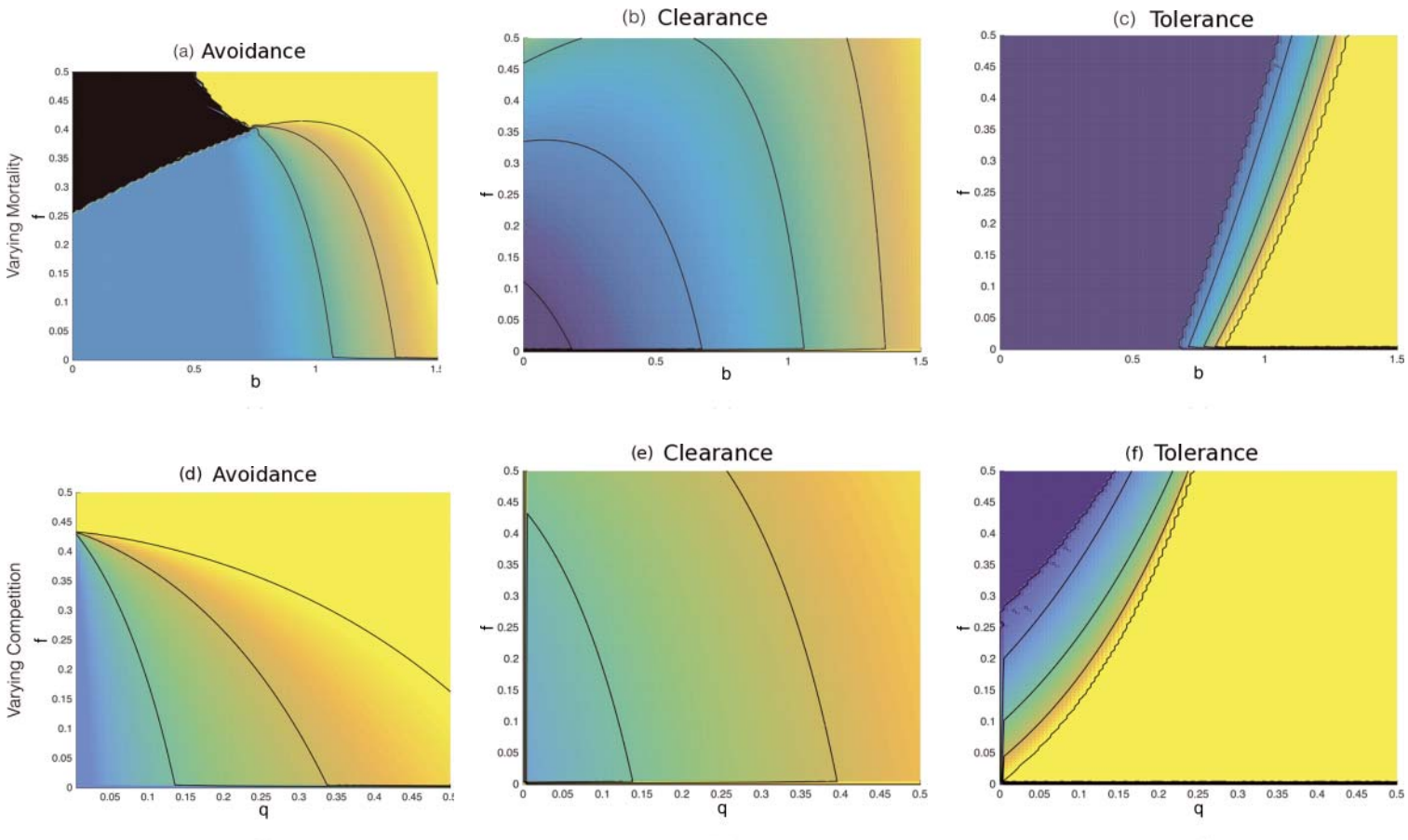

Fig. 3. Combined effects of varying fecundity, f (y-axis) with host mortality (b, top row) and competition (q, bottom row). Plots (a) and (d) are for avoidance, plots (b) and (e) for clearance, and plots (c) and (f) for tolerance. Again, blue hues indicate high defence and yellow hues low defence. Note that the solid black region of the top-left plot in fact denotes an evolutionary repeller. Parameter values are as in Fig. 1.

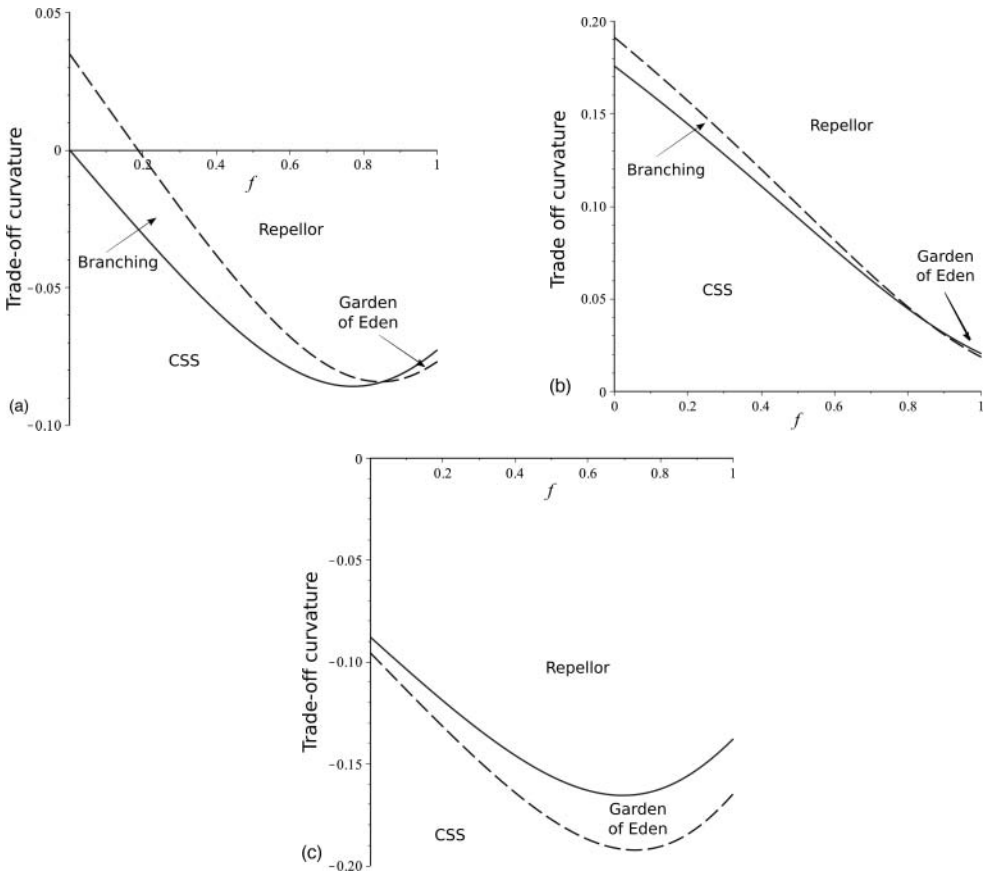

Fig. 4. Boundaries of evolutionary stability and convergence stability at a fixed singular point when the host evolves (a) avoidance, (b) clearance, and (c) tolerance. Below the solid line the singular point is evolutionarily stable (ES), while below the dashed line the singular point is convergence stable (CS). Evolutionary branching occurs for points that are CS but not ES. Parameters are as in Fig. 1 with respective singular points chosen at $\beta^* = 2$, $\gamma^* = 1$, $\alpha^* = 1$, and $a^* = 2$ for all three cases.

section A.5, Figs. A.2, A.3]. For the final case, tolerance, we see that there is never any evolutionary branching. It is well known that branching of tolerance mechanisms is not possible in standard models, as the derivatives are such that a singular point can never simultaneously be CS but not ES (Roy and Kirchner, 2000; Miller *et al.*, 2005). After branching has occurred, for most standard trade-off forms (such as that used earlier in this study) the two strains would evolve to the maxima/minima of evolution leaving two co-existing extreme strains [though we note more complex trade-offs may lead to extinction of one of the strains (Best *et al.*, 2015)].

CO-EVOLUTION OF DEFENCES

Direct trade-offs

We now consider the outcome when two of the defence mechanisms co-evolve. We first assume that the two defences are directly traded off against one another, for example where increased avoidance is costly to clearance, $\gamma = \gamma(\beta)$, with no further life-history costs. Let us consider the selection gradient, for example, in the case for $\gamma(\beta)$:

$$\left.\frac{\partial s}{\partial \beta_m}\right|_{\beta_m=\beta} = -\hat{I}[\alpha + b + f(a - q\hat{N})] + \gamma'(\beta)[a - q\hat{N} - b]. \tag{7}$$

In this specific case, the level of fecundity has no impact on the evolutionary singular point, and thus allocation between the two defence mechanisms of avoidance and recovery will remain the same whatever the degree of sterility. This can be shown to be the case by noting that at equilibrium,

$$\frac{dN}{dt} = (a - q\hat{N})(\hat{S} + f\hat{I}) - b\hat{N} - \alpha\hat{I} = 0 \tag{8}$$

$$\Rightarrow \hat{S} = \frac{\hat{I}[\alpha + b - f(a - q\hat{N})]}{a - q\hat{N} - b}, \tag{9}$$

yet we also know that = $(\hat{S} = (\alpha + b + \gamma)/\beta$. By comparing this to equation (7) we see that the first term of (7) can be re-written without f appearing explicitly. We can then factor out the term $[a - q\hat{N} - b]$, noting that this term must be positive at the endemic equilibrium (as $\hat{S} < (a - b)/q$, the disease-free equilibrium), meaning that the solution to equation (7) is independent of f.

For the other two possibilities, this is not the case. When clearance and tolerance are linked (e.g. $\alpha = \alpha(\gamma)$), we find that hosts favour recovery at low levels of fecundity and tolerance at higher levels (Fig. 5b). When avoidance and tolerance are linked (e.g. $\alpha = \alpha(\beta)$), we find that hosts favour avoidance (low transmission, β^*) at low levels of fecundity and tolerance at higher levels (Fig. 5c). Thus, in each case, tolerance is favoured more strongly relative to resistance at higher rates of fecundity, as we might have predicted from the initial results in Fig. 1. However, if the two resistance mechanisms are traded off, there is no impact of sterility.

Simultaneous evolution

We now assume that the two defences are not directly traded off against one another, but instead evolve together simultaneously (i.e. co-evolution). We assume both defences incur costs to the birth rate, as above, with the resulting birth rate being a linear combination of the two cost structures [similar to the approach by Restif and Koella (2004); see the legend of Fig. 6 for the trade-off functions used].

We plot the results of the three cases in Fig. 6. As when the two resistance mechanisms were directly traded off, we find that investment in avoidance and recovery remains relatively constant for varying levels of sterility when they evolve simultaneously, suggesting that the balance of investment in resistance mechanisms is largely independent of sterility.

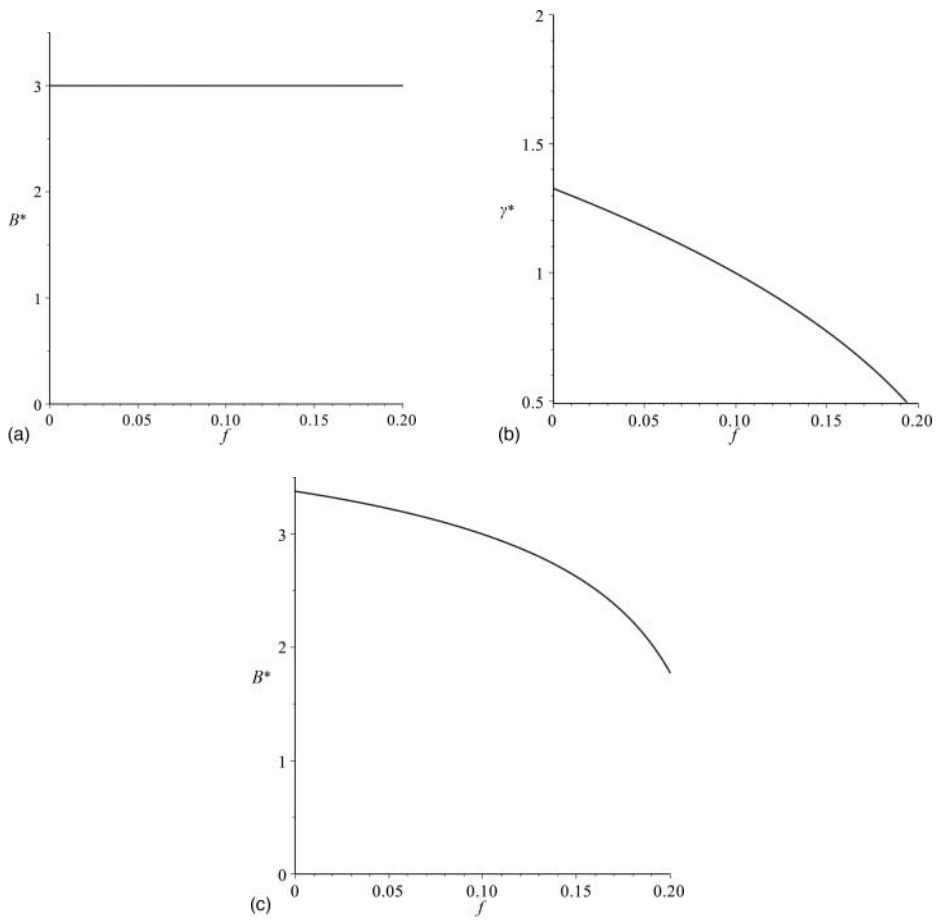

Fig. 5. Singular levels of investment for varying fecundity when defence mechanisms are traded off against one another. Parameter values are as in Fig. 1, with (a) $\gamma = 4 - 4.8(5/4 - \beta/4)/(0.8 + 0.2\beta)$; (b) $\alpha = 3.29 - 3.46(1 - \gamma/2)/(1 - 0.244\gamma)$; (c) $\alpha = -0.26 - 3.30(5/4 - \beta/4)/(3.97 - 2.97\beta)$.

We find that when tolerance and clearance co-evolve in this way, both defence mechanisms are favoured at low rates of fecundity (we are again plotting here $A^* = \alpha_{max} - \alpha^*$ such that high A^* means high tolerance). This is of interest, since it reverses the result from the first part of this study for tolerance (i.e. Fig. 1c). When tolerance evolved in isolation, there was little benefit of defence when sterility was high, whereas now increased tolerance boosts the effectiveness of increased recovery. Finally, when avoidance and tolerance co-evolve, we find that both defences retain the patterns of investment as when they evolved in isolation, with high avoidance at low fecundity and high tolerance at high fecundity. In particular, we note that the pattern of tolerance differs markedly from its co-evolution with clearance due to the differing feedbacks of the two resistance mechanisms.

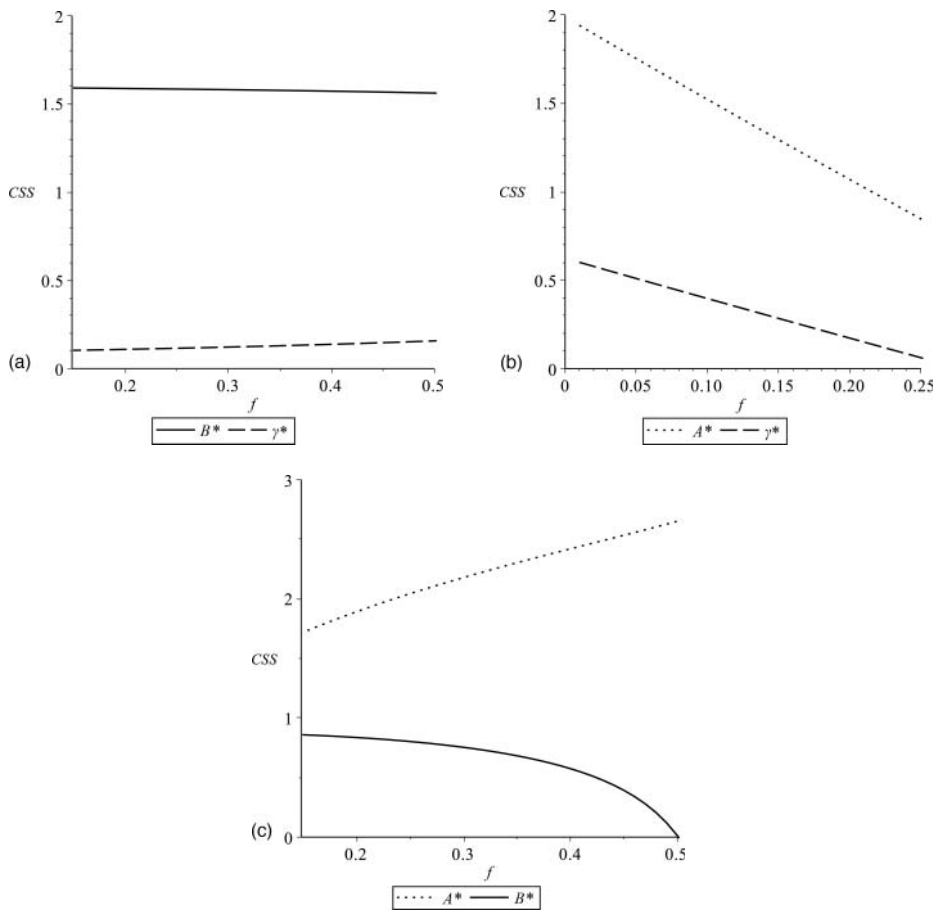

Fig. 6. Singular levels of investment for varying fecundity when defence mechanisms evolve simultaneously. As before, we plot $B^* = \beta_{max} - \beta^*$ and $A^* = \alpha_{max} - \alpha^*$. Parameter values are as in Fig. 1, with (a) $a = 0.5(1.5 + 0.5(1 - 0.5\gamma)/(1 - 0.25\gamma)) + 0.5(2.8 - 1.15(1.25 - 0.25\beta)/(0.84 + 0.25gb))$; (b) $a = 0.5(1.7 + 0.5(1 - 0.5\gamma)/(1 - 0.05\gamma)) + 0.5(2.14 - 0.54(1 - 0.5\alpha)/(1 + 0.9\alpha))$; (c) $a = 0.5(2.14 - 1.5(1 - 0.5\alpha)/(1 + 4\alpha)) + 0.5(2.76 - 1.5(1.25 - 0.25\beta)/(0.5 + 0.75\beta))$.

DISCUSSION

While the sterilizing effects of disease are known to be important to host–parasite interactions, few studies have specifically studied the impact this will have on host evolution (Best *et al.*, 2012; McLeod and Day, 2014, 2015; Toor and Best, 2014; Donnelly *et al.*, 2015). We have shown here that higher sterility selects for higher resistance [reduced transmission (see also McLeod and Day, 2015) or increased clearance], but lower tolerance (increased virulence). For resistance, this is because when sterility is high selection drives individuals to maximize their time in the susceptible state, as this becomes the only source of reproduction. However, understanding the pattern for tolerance needs more consideration. As sterility increases, infected hosts contribute less to fitness and there is therefore less selection to extend the infectious period through tolerance. We find that these results largely hold even when two of the defence

mechanisms evolve simultaneously, except that high clearance leads the host to invest in high tolerance to boost the effectiveness of increased recovery. The present study therefore not only further highlights the importance of the distinction between resistance and tolerance mechanisms due to their feedbacks to population densities, but stresses how these feedbacks can influence the simultaneous evolution of one another.

An important result from previous studies is that host resistance may not be highest against the most virulent parasites as might be intuitively expected, owing to the ecological feedbacks. Specifically, Boots and Haraguchi (1999) showed that avoidance is greatest against the least virulent parasites, while van Baalen (1998) showed that clearance is maximized at intermediate rates of virulence. However, these studies focused on specific cases of full and no sterility respectively. Here we have explored in finer detail how these patterns depend on the degree of sterility. In general, if sterility is very high, resistance through either mechanism will be greatest against the least virulent parasites (cf. Boots and Haraguchi, 1999). This is because the key effect of reduced virulence is increased exposure (since reduced disease-induced mortality naturally leads to higher infected densities), which leads to increased selection for resistance. However, as sterility decreases there is a shift to maximize resistance at intermediate levels of virulence (cf. van Baalen, 1998) and then, for avoidance, at the highest virulence rates. Now, infected hosts are able to make a significant contribution to fitness through reproduction. Not only does reduced virulence lead to increased exposure, but also a greater contribution from infected hosts. The balance of these two feedbacks is such that resistance is now greatest at higher rates of virulence. These conclusions fit with the findings of McLeod and Day (2015) and Donnelly *et al.* (2015), the latter of who showed that for castrating diseases ($f = 0$) the driver of selection is purely parasite exposure (i.e. the density of infected hosts) whereas for non-castrators ($f = 1$) the driver is disease prevalence (i.e. the proportion of infected hosts). Our work extends the findings of Donnelly *et al.* (2015) by showing the range of behaviours as sterility varies from one extreme to the other (see also McLeod and Day, 2015).

In addition to virulence, we have seen similar shifts in behaviour when sterility is small or large as other parameters are varied with the same reasoning applying. For example, we observed such a relationship as host lifespan is varied for both avoidance and clearance evolution. This pattern was again discussed by Donnelly *et al.* (2015) in more detail for the specific cases of $f = 0$ and $f = 1$. We also saw that as recovery is varied, tolerance is highest at high recovery rates when parasites are sterilizing, but at intermediate or low recovery rates when infected fecundity is higher. When $f = 0$, infected hosts contribute little to fitness. If in addition recovery rates are high, however, increased tolerance gives infected hosts more chance of recovering to susceptibility where they can contribute more. For larger f, when there is low recovery, tolerance may seem beneficial in order to extend the time producing offspring, but in this case the costs of reduced reproduction are not worth paying. For high f at high recovery rates, hosts are likely to return to susceptibility quickly, making reproduction more important than tolerance. We therefore emphasize how important the degree of sterility is to the evolution of host defences due to the feedbacks to population dynamics.

It is well known that resistance mechanisms can create negative frequency-dependence leading to evolutionary branching and co-existence (Boots and Bowers, 1999) but that tolerance mechanisms cannot (Roy and Kirchner, 2000; Miller *et al.*, 2005), and we have recovered those patterns here. However, we have also shown that branching in resistance is more likely (that is, possible for a wider range of trade-offs) when sterility is high. High rates of sterility act to

increase the dichotomy between extreme strategies of a slow but long-lasting reproductive strategy (high resistance) and a fast but short reproductive strategy (low resistance), which makes diversity more likely. We found these results held across different parameter sets, and we have previously found that branching in invertebrate immune priming is also most likely for high levels of sterility (Best *et al.*, 2012). Interestingly, Ashby and Gupta (2014) also showed that the maintenance of temporal diversity (co-evolutionary cycles) similarly required a high degree of sterility. It therefore appears that both static and temporal forms of diversity are far more likely to evolve in host–parasite systems where the disease is sterilizing.

We found that if two of the defences co-evolved, there was little change to our general predictions. There were, however, some key differences. First, when tolerance co-evolves with clearance, increased tolerance boosts the effectiveness of evolving higher clearance. Second, we found that when the two resistance mechanisms co-evolve, whether directly or by evolving simultaneously, the relative investment in each mechanism stays constant no matter the level of sterility. Here we have focused purely on the role sterility plays in the evolution of host defences. It is, of course, very likely that parasites would co-evolve with their hosts to combat these defences. Previous theory has shown that if the parasite can target its negative impacts towards either host mortality or reproduction, it will always evolve to completely sterilize its host, since fecundity has no impact on the parasite's R_0 but mortality does (Jaenike, 1996; O'Keefe and Antonovics, 2002). It is for this reason that in a previous study we argued that tolerance to sterility is likely to be a better defence strategy for the host than resistance, since resistance mechanisms cannot prevent a parasite co-evolving to sterilize its host but tolerance can (Best *et al.*, 2009). McLeod and Day (2015) showed that for avoidance resistance, the pattern of investment along a sterility gradient found here is qualitatively the same when the parasite co-evolves, but further study is needed to explore this question more generally.

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