RESISTANCE IS FUTILE BUT TOLERANCE CAN EXPLAIN WHY PARASITES DO NOT ALWAYS CASTRATE THEIR HOSTS

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The disease caused by parasites and pathogens often causes sublethal effects that reduce host fecundity. Theory suggests that if parasites can "target" the detrimental effects of their growth on either host mortality or fecundity, they should always fully sterilize. This is because a reduction in host fecundity does not reduce the infectious period and is therefore neutral to a horizontally transmitted infectious organism. However, in nature fully castrating parasites are relatively rare, no doubt in part because of defense mechanisms in the host. Here, we examine in detail the evolution of host defense to the sterilizing effects of parasites and show that intermediate levels of sterility tolerance are found to evolve for a wide range of cost structures. Our key result arises when the host and parasite coevolve. Investment in tolerance by the host may prevent castration, but if host defense is through resistance (by controlling the parasite's growth rate) coevolution by the parasite results in the complete loss of infected host fecundity. Resistance is therefore a waste of resources, but tolerance can explain why parasites do not castrate their hosts. Our results further emphasize the importance of tolerance as opposed to resistance to parasites.

KEY WORDS: Coevolution, resistance, sterility, tolerance.

The disease that parasites cause can have a variety of harmful effects on their hosts. From an evolutionary and ecological perspective, it is important to distinguish between disease effects that increase host mortality, thereby decreasing the infectious period and fitness of the parasite, and those that reduce host fecundity, which in contrast do not directly affect the fitness of a horizontally transmitted parasite (Jaenike 1996; O'Keefe and Antonovics 2002). There is also an important distinction to be made between resistance mechanisms and tolerance mechanisms (Boots and Bowers 1999; Roy and Kirchner 2000; Miller et al. 2005). Understanding the coevolutionary dynamics associated with this potentially complex interaction between host and parasite fitness

therefore remains an important challenge. Here we examine how host defense mechanisms evolve in response to parasite-induced loss of fecundity and thus address the question of why parasites do not always castrate their hosts.

There is extensive theoretical literature on the evolution of parasites that suggests that under simple assumptions parasites should evolve to maximize the epidemiological R_0 (Levin and Pimentel 1981; Bremermann and Thieme 1989; Nowak and May 1994; Miller et al. 2006). Often a trade-off in the parasite is then assumed to occur between transmission and disease-induced mortality (Frank 1992; Caraco et al. 2006; Miller et al. 2006). This trade-off assumption has increasing empirical support (Mackinnon and

Read 1999; de Roode et al. 2005; Wickham et al. 2007; de Roode et al. 2008) and can be intuitively understood in that if the parasite reproduces more rapidly and thereby produces more transmission stages; it also causes more damage to the host. However, damage due to parasite growth may be as likely to affect host fecundity as host mortality (Antonovics et al. 1996; Feore et al. 1997; Little et al. 2002). Theory suggests that when the negative effects of parasite growth can be directed toward either host reproduction or mortality the parasite will evolve to completely sterilize its host in well-mixed populations (Jaenike 1996; O'Keefe and Antonovics 2002). Host fecundity does not affect the parasite R_0 wheareas increased mortality reduces it; thus there are no fitness costs for the parasite in sterilizing the host.

Clearly, a reduction in fecundity caused by infection will lead to a strong selective pressure on the hosts. There have been a large number of theoretical studies focused on understanding the evolution of hosts in response to parasitism (Antonovics and Thrall 1994; Bowers et al. 1994; Boots and Bowers 1999; Boots and Haraguchi 1999; Boots and Bowers 2004; Miller et al. 2005, 2007), but again the majority of these studies limit the parasite's negative effects on the host to an increase in mortality (defined in this literature as virulence). However, Gandon et al. (2002) considered how investment in reproduction and survival evolve in response to parasitism, wheareas Bonds (2006) extended this by assuming that the parasite takes some of the host resources to aid its own transmission. Interestingly, Gandon et al. (2002) concluded that the host will increase reproduction upon infection whilst Bonds (2006) predicted that fecundity will fall. In both cases, the changes in fecundity were not due to any direct sterilizing effects of the parasite, but rather the result of host resources being redirected to ameliorate an increased mortality rate. Perhaps the clearest study of evolution of defenses to a sterilizing parasite is by Restif and Koella (2004), who examined how tolerance to sterility evolves simultaneously with resistance through increased recovery. They found that due to the differing feedbacks between tolerance and resistance, defense against sterility will be greater at high parasite growth rates.

This last study highlights an important distinction in host defense mechanisms between resistance and tolerance. Resistance mechanisms directly inhibit infection—either by the avoidance of infection, recovering faster once infected, or slowing the within-host growth rate of the parasite—whilst tolerance mechanisms act to compensate for/limit parasite damage but do not limit the within-host growth rate of the parasite (Roy and Kirchner 2000; Miller et al. 2005). By inhibiting infection resistance mechanisms reduce parasite fitness, whilst in compensating for parasite damage tolerance mechanisms may increase parasite fitness. These two forms of host response can lead to markedly different evolutionary outcomes, because resistance reduces disease prevalence whilst tolerance to mortality increases disease prevalence

by lengthening the average infectious period. In this definition of resistance and tolerance, one mechanism reduces parasite fitness wheareas the other increases it (Simms and Triplett 1994; Tiffin and Rausher 1999; Råberg et al. 2007).

Here we examine the evolution of sterility tolerance, which we define as the reduction of the parasite's impact on host fecundity whilst infected. It is important to note that this form of sterility tolerance, in contrast to mortality tolerance, does not increase parasite fitness (unless there is vertical transmission). This is because mortality tolerance increases the infectious period, wheareas sterility tolerance does not (Best et al. 2008). We begin by assuming that the host evolves defenses against a constant (nonevolving) parasite, and show that some level of reproduction whilst infected is often favored. We then discuss the outcome when the parasite coevolves with the host. Our key finding is that sterility tolerance may prevent parasites from castrating their hosts, wheareas resistance is not likely to be effective.

Modeling and Results
THE MODEL

We construct our baseline model within an SI (susceptible–infected) framework (Anderson and May 1981), denoting the uninfected density as X and the infected density as Y. The intrinsic birth rate of the host population is a, which can be reduced due to a crowding term q. Infected hosts reproduce at a proportion, f, of that of uninfected hosts. The natural death rate of the population is b. The parasites transmission coefficient is β and its virulence (parasite-induced mortality) is denoted by α. Calling the total host population $N = X + Y$, we write down our system as the following set of differential equations:

$$\frac{dX}{dt} = a(X + fY) - qN(X + fY) - bX - \beta XY, \quad (1a)$$

$$\frac{dY}{dt} = \beta XY - (\alpha + b)Y. \quad (1b)$$

(The host and parasite will always coexist provided $\beta > (\alpha + b)/X^*$, where X^* is the equilibrium density of hosts [in the absence of the parasite]). Increased fecundity can be achieved through tolerance of the parasite, meaning that parasite transmission and virulence from mortality remain constant (were we to instead consider sterility resistance we would assume that fecundity (f), transmission (β), and virulence (α) were all linked to the parasite growth rate (ε) and allow host evolution to control, or suppress, the parasite's growth rate (Miller et al. 2006)—sterility resistance is discussed further in the coevolution section). Tolerance incurs costs in the form of increased susceptibility to crowding (q) or increased death rate (b), which we assume to be linked by a trade-off function. For example, when the cost is to death rate, the trade-off is expressed as

$$f = g(b) = f_{\max} - (f_{\max} - f_{\min}) \frac{1 - \left(\dfrac{b - b_{\min}}{b_{\max} - b_{\min}}\right)}{1 + p\left(\dfrac{b - b_{\min}}{b_{\max} - b_{\min}}\right)},$$

which links the maximum and minimum values of f and b with a smooth function, the shape of which is controlled by p. We use this flexible trade-off relationship because qualitative evolutionary outcomes are crucially dependent on the shape of the trade-off assumed (de Mazancourt and Dieckmann 2004; Bowers et al. 2005; Hoyle et al. 2008).

The analysis of the evolutionary outcomes is performed using the game theoretical method of adaptive dynamics (see Metz et al. 1996; Geritz et al. 1998) and we calculate the invasion fitnesses using a Jacobian method (Boots and Bowers 1999; Miller et al. 2005). Adaptive dynamics considers the invasion of a rare mutant into an equilibrium population, where the mutant has a level of tolerance and associated cost slightly different from the resident population. The invasion fitness determines the success of the rare (mutant) host type (with traits $(\bar{f}, \bar{\tau})$, where for generality we call the costly trait τ) attempting to invade an established equilibrium (resident) host population (with traits (f, τ)), and is given by (see the Appendix)

$$s(\bar{\tau}, \bar{f}, \tau, f) = (a - \bar{b} - \bar{q}(X^* + Y^*) - \beta Y^*)(\alpha + \bar{b})$$
$$+ \beta Y^*(a\bar{f} - \bar{q}\bar{f}(X^* + Y^*)). \quad (2)$$

Note that the costly trait τ may refer to either crowding or death rate. Over evolutionary time the population will evolve in the direction of the local selection gradient, $\partial s / \partial \bar{\tau}$, until an evolutionary singularity, a potentially temporary "stopping point" of evolution, is reached where $\partial s / \partial \bar{\tau} = 0$. We found one such singularity to exist for a wide range of parameters and trade-offs.

EVOLUTIONARY BEHAVIOR

Through further analysis we can derive the evolutionary behavior at the singularity (see the Appendix). One outcome would be for a CSS (continuous stable strategy), where the population will evolve to the singularity, which is a local fitness maximum, and subsequently remain at that strategy. Alternatively, the singularity could be a repeller, in which case the population will always evolve away to either maximum or minimum investment. Thirdly, the singularity could be an evolutionary branching point, where the population evolves to the singularity but it is a local fitness minimum, leading to disruptive selection and the establishment of two independent, coexisting strains. Here we use a geometric form of adaptive dynamics, where we consider the evolutionary behavior for any shape of trade-off (de Mazancourt and Dieckmann 2004; Bowers et al. 2005; Kisdi 2006; Best et al. 2008, 2009; Svennungsen and Kisdi 2009). In particular we can understand whether evolutionary branching is possible for any trade-off or

parameter set by considering the sign of one term, M, which gives the mutual invadibility of two strains at a singularity. If M is negative, then evolutionary branching can occur for certain trade-off shapes whereas if it is positive or zero, then no branching can ever occur.

Analyzing the model, in general we find that whether the cost of sterility tolerance is to competitive ability (q) or natural death rate (b), if tolerance is "increasingly" costly —the costs accelerate relative to the benefits—then the singularity will always be a CSS and the host population will become fixed with some intermediate level of sterility tolerance. Strongly decelerating trade-offs will always cause the singularity to be a repeller, and infected individuals will evolve to have either minimum or maximum reproduction. When the cost of sterility tolerance is to competitive ability, we find that $M = 0$, meaning that evolutionary branching can never occur. However, when the cost is to death rate, we find that $M < 0$ and as such branching will be possible for certain trade-offs. In particular, when costs are to lifespan, then for a range of weakly decelerating trade-offs evolutionary branching can occur and a dimorphic host population will emerge, one with full sterility tolerance and one with zero tolerance.

We can study the outcomes graphically for a particular parameter set-up by the use of trade-off and invasion plots (Boots and Bowers 2004; Bowers et al. 2005; see the Appendix). Such a TIP for our system is shown in Fig. 1. The two traits, in this case sterility tolerance and death rate, form the state space of the plot.
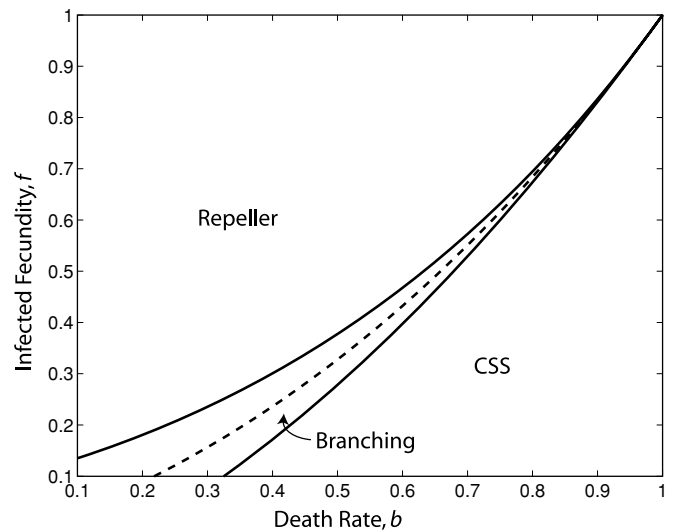

Figure 1. A trade-off and invasion plot (TIP) of the baseline model where increased fecundity can be achieved at a cost to the natural death rate. When a trade-off is chosen it must be tangential to the invasion boundaries at the singular point $(f^*, b^*) = (1,1)$. If the trade-off enters the singularity from a particular region of the TIP (separated by the invasion boundaries) the annotated behavior will occur. Parameter values are $a = 2$, $q = 0.5$, $\beta = 2.5$, $\alpha = 1$, $(b^*, f^*) = (1, 1)$.

We choose our singularity to be at the maximum level of sterility tolerance where infected reproduction is equal to susceptible reproduction ($f^* = 1$), and this therefore occurs in the top-right corner of the TIP. The solid lines represent the invasion boundaries and the dashed line represents the average of the two boundaries. When the trade-off is added to the TIP, theory dictates that it must be tangential to the invasion boundaries at the singularity (Bowers et al. 2005). If the trade-off enters the singularity from below (if it has accelerating or very weak decelerating costs), then it is a CSS, whereas if it enters from above (strong decelerating costs), it is a repeller. Branching will occur for those trade-offs that enter the singularity between the dashed line and the right-most invasion boundary. If we were to plot the corresponding TIP for where the costs are incurred in the competitive ability, we would find that the two invasion boundaries exactly coincide, emphasizing that only a CSS or a repeller can occur.

VARIATION IN INVESTMENT

We now examine how the evolutionarily stable level of investment in sterility tolerance (i.e., the singular value of f) varies with certain characteristics of the host-parasite interaction. In particular, we examine variation in the CSS level of investment in the SI model for a fixed trade-off with accelerating costs to susceptibility to crowding (results for the lifespan trade-off are qualitatively similar).

Investment in sterility tolerance increases as parasite transmission increases (Fig. 2A). Higher transmission rates lead to higher prevalence and therefore it becomes more important to
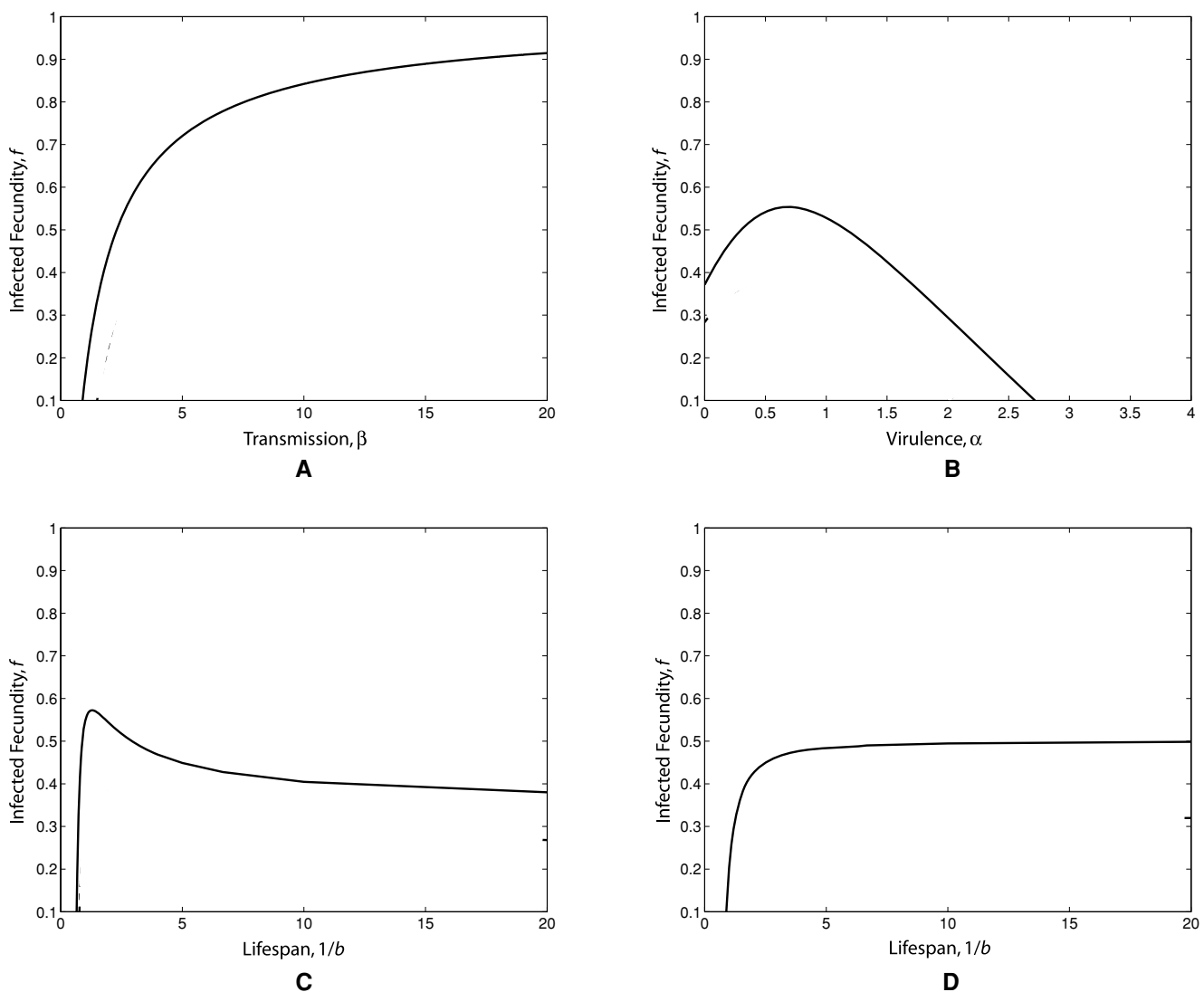

Figure 2. The variation in the singular level of sterility tolerance as a function of the model parameters. Tolerance is an increasing function of transmission, β (panel A), but a humped function of virulence, α (B). Tolerance is also a humped function of lifespan, $1/b$, when virulence is low ($\alpha = 0.5$, C). However, if virulence is relatively high ($\alpha = 1.5$), then tolerance is a saturating function of lifespan (D). Except where marked, parameter values are $a = 2$, $b = 0.5$, $\beta = 2.5$, $\alpha = 1$, $(f_{min}, f_{max}) = (0.1, 1)$, $(q_{min}, q_{max}) = (0.1, 1)$, $p = 2$.

tolerate the negative effects of the parasite. Some further work (not shown) finds that this relationship is essentially identical to that of recovery resistance, and indeed mortality tolerance (Miller et al. 2005). Whatever the form of defense, as transmission increases, the prevalence increases and so defense whilst infected is of increasing importance. In contrast, sterility tolerance is maximized at intermediate levels of virulence (mortality) (Fig. 2B). Initially as virulence increases there is some benefit to increased fecundity, but as virulence rises further and the lifespan of an infected individual is reduced prevalence falls making it less worthwhile to pay the costs of tolerance. The relationship between recovery resistance and virulence (again not shown) again displays a relationship similar to that of sterility tolerance (Fig. 2B). This contrasts to avoidance resistance where investment increases to avoid becoming infected with more virulent parasites (Boots and Haraguchi 1999). Recovery resistance and sterility tolerance act after infection and therefore are faced with high virulence.

As host lifespan, $1/b$, increases, when virulence (mortality) is low, investment in tolerance initially rises sharply but then falls (Fig. 2C; clearly, this relationship cannot be studied when the cost of sterility tolerance is to lifespan). If virulence is low, then long-lived individuals will not invest as much in tolerance because they will be able to reproduce for a longer period of time before death. For higher virulence rates (Fig. 2D), investment in tolerance remains higher because high virulence increases the chance of death meaning fecundity must be higher to achieve the same reproductive output before death. Investment in sterility tolerance with lifespan at different virulence rates is again most closely matched to that of recovery resistance (Miller et al. 2007). The key effect of both sterility tolerance and recovery resistance is that the infected class contributes to the uninfected host population, through current or future reproduction. This explains the similarity in the evolutionary properties of these two forms of defense.

Further work (not shown) shows that when recovery (SIS) or immunity (SIR) is introduced, the host becomes less likely to invest in tolerance. This relationship is intuitive: if a host has a strong chance of recovering (or becoming immune) from infection, then its fecundity whilst infected is of less importance than if infection is final.

COEVOLUTION

In natural systems we would expect the parasite to coevolve with the host. As such, the degree of fecundity loss of a host faced with a sterilizing parasite will be dictated by the interaction between the two organisms. In general, it is possible to predict coevolutionary dynamics by extending the analytic and numerical techniques we outlined for the evolution of the host (Marrow et al. 1996; Kisdi 2006; Best et al. 2009). However, encapsulating the complexity of a coevolutionary host-parasite system where selection is acting on the same trait (infecteds' fecundity) for both species

presents many difficulties as the outcome will be extremely sensitive to the relative mutation rates, fitness, and selection pressures of both species. For simplicity, many studies predict coevolutionary outcomes by plotting both the host and parasite's own CSSs in parameter space and calculating the point of intersection. We have shown that for a wide range of ecological scenarios we would expect a host to evolve to a positive level of infected reproduction. Yet both Jaenike (1996) and O'Keefe and Antonovics (2002) have shown that if a parasite can allocate the harm it causes subject to a trade-off between virulence and host fecundity, the optimal strategy will always be to fully sterilize. Under some circumstances, when for example the costs to host defense are very high, the optimum for both host and parasite is complete castration. Other than this, the optimal strategies of host and parasite will never coincide and we cannot find a CoCSS by this method.

Using graphical tools we present a general argument for the coevolutionary outcome when the host can defend itself to the sterility effects of the parasite, and we also show simulations of the coevolutionary process described. In particular we look to understand when the parasite may allow infected reproduction ($f > 0$) as part of its strategy and when it will insist on fully sterilizing ($f = 0$). Let us first summarize the arguments concerning the parasite's strategy. In Fig. 3A we assume that infected host fecundity, f, and virulence, α, are simple functions of the parasite's growth rate, ε. The studies of Jaenike (1996) and O'Keefe and Antonovics (2002) suggest that the parasite should always target its detrimental effects to host sterilization rather than mortality. Thus we see in Fig. 3A that as ε increases the parasite incurs the costs of a greater growth rate by causing the fecundity (f) of infected hosts to fall, reaching zero at reproductive rate ε_0. As the parasite's growth rate continues to increase, we should expect the parasite to cause further negative effects to its host. As such we presume that at growth rates above ε_0 the parasite must start to cause mortality, and so beyond this point in Fig. 3A we see virulence (α) increase with increased growth rate. If we assume that selection acts on the parasite's growth rate, ε, and that a higher growth rate leads to greater transmission (through some saturating function), then its CSS will occur at some intermediate growth rate ε^* (note that this is a more general case than O'Keefe and Antonovics (2002) where there was no relationship between transmission and growth rate, in which case ε^* would occur at ε_0). Therefore in this situation, the optimum strategy for the parasite causes complete sterility in the host.

Suppose that a host coevolves defenses through sterility tolerance, as described in the previous section. Tolerance by definition does not directly inhibit the parasite, but rather ameliorates the damage caused. By compensating for the sterility effects in another life-history trait, sterility tolerance will allow a slightly higher level of infected reproduction, f, at any given parasite reproductive rate, ε. In Fig. 3B we show this increase in tolerance
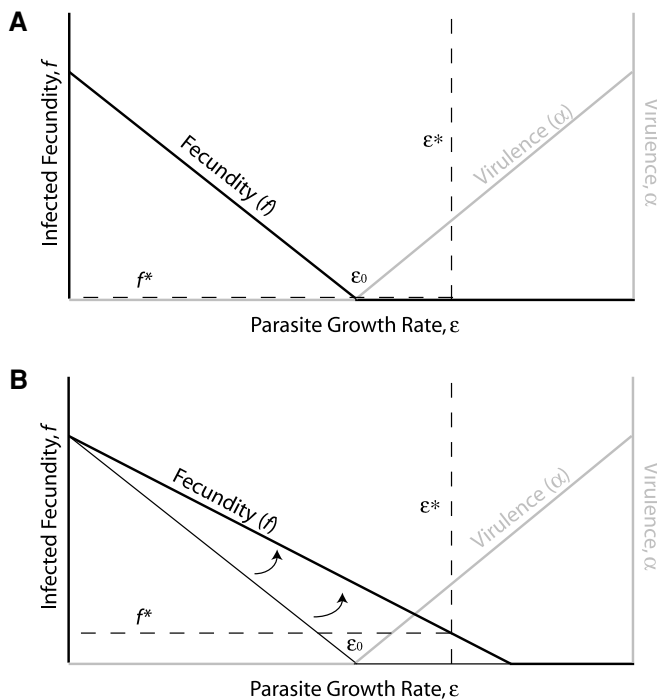
Figure 3. Plots showing how infected fecundity (*f*) and virulence (α) are related to the parasite growth rate (ε). **(A)** Initially, at any given growth rate the parasite incurs its damage in host fecundity, and so we see fecundity (*f*) fall with increasing ε whilst virulence (α) stays constant at zero. Once the host is fully sterilized any higher growth rates must incur further damage, and so we see virulence begin to increase. The parasite's CSS is at ε* which corresponds to complete sterilization (infected fecundity *f**). **(B)** By investing in tolerance the host can increase the level of infected reproduction at any given growth rate. As such the fecundity line shifts upward. The parasite continues to grow at rate ε* to incur zero virulence but this now allows some positive level of infected reproduction, shown by *f** shifting to a positive level of infected reproduction.

by shifting the sterility line, $f(\varepsilon)$, upward. Because we assume that the parasite cannot change the intrinsic relationships of α and β with the growth rate ε, but can only evolve the growth rate itself, the parasite continues to grow at rate ε*—because the CSS, the growth rate with optimal transmission and virulence, has not changed—and so the host can achieve reproduction from infected individuals. Therefore in a coevolutionary system, sterility tolerance can prevent a host from becoming fully sterilized by its parasite.

Suppose that we now allow the host to coevolve defenses through a resistance mechanism (with some associated cost). Resistance acts to decrease the growth rate, ε, of the parasite to a level where the sterility effects are lessened and therefore for both the host and parasite selection is acting on the parasite's growth rate. We know that a CSS exists for the parasite at $f = 0$, whilst a CSS for the host can occur at some $f > 0$ determined by the

relative costs of resistance. Clearly the resulting coevolutionary dynamics around these two CSSs depend on which species has the stronger selection pressure at any particular parasite growth rate and which has the greater mutation rate. When a mutant host appears (with selection toward lower values of ε), it will lead to a change in those parameters controlled by the parasite growth rate: fecundity (*f*), virulence (α), and transmission (β), and also in the trait in which costs are incurred (*q*, say). Similarly, when a mutant parasite appears (with selection toward higher values of ε), it will cause changes in fecundity, virulence, and transmission, but not in the host's costly trait because the host has made no change in its level of defense. As such, whenever the parasite moves back toward higher ε (and therefore lower *f*), for the host to return to the previous lower ε (and higher *f*) it must pay the cost again. Over time, this pattern will result in the host having to pay infinite costs to resist the parasite. As such we would expect the parasite to win the contest and therefore cause complete sterility. Resistance to the sterilizing effects of parasites is therefore futile when the parasites also evolve.

In Figure 4 we show simulations of the evolution of tolerance and resistance as described above. In Fig. 4A the host evolves tolerance (i.e., the gradient of the $f(\varepsilon)$ line) at a cost to competitive ability (*q*) whilst the parasite coevolves its growth rate (ε). Initially the parasite's growth rate is so high that no host types near the starting value achieve positive reproduction, so tolerance is dropped to recoup the cost in competitive ability. The parasite, however, soon evolves toward its CSS at an intermediate growth rate, at which point the host population (even with its low tolerance) can begin to have positive reproduction. At this point the level of tolerance then increases toward an intermediate CSS value (giving infected reproduction of roughly $f = 0.2$ in this instance). In Fig. 4B the host evolves resistance, and as such both species are selecting on parasite growth rate ε (we are forced to choose a specific function for how the host and parasite interact here). Initially the parasite's low growth rate allows infected reproduction and so the host increases its resistance. However, once the parasite reaches its CSS infected reproduction is forced to be zero, and thereafter resistance does not evolve in the host.

Discussion

There is a clear conflict and asymmetry between hosts and their sterilizing parasites. Parasites will always castrate, whilst the host must balance lost reproduction while infected against the costs of defense. The fact that infected hosts can reproduce (or recover to reproduce later) is something that ecologically distinguishes parasites from predators (Godfray 1993; Boots 2004), and it is therefore important to understand why parasites do not always castrate their hosts, or, put another way, why parasites are not ecologically predators. In our models, the outcome of the coevolutionary
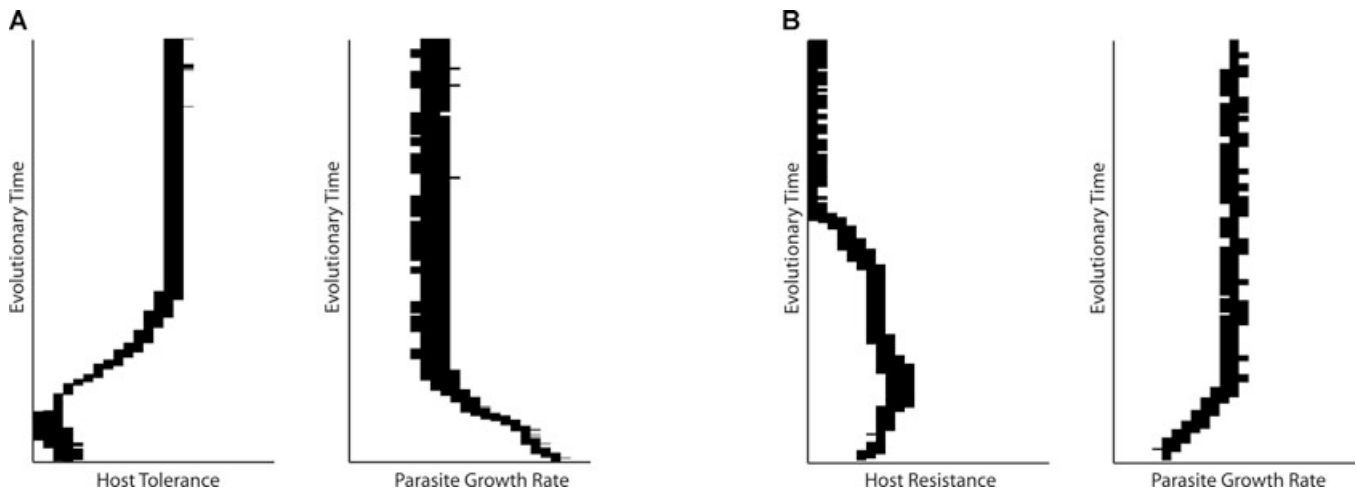
Figure 4. Simulations of the coevolutionary process. The simulations approximate the adaptive dynamical results by assuming a mutation-replacement process occurs in a system of ordinary differential equations (in practice the differential equations are solved for a sufficient length of time and then a nearby mutant type is introduced at low density and the process is repeated—see Best et al. (2009) for full details of the simulation procedure). In (A) the host evolves tolerance to the parasite by increasing the level of infected reproduction (f) for any parasite growth rate (ε) at a cost to its competitive ability (q). Simultaneously the parasite is coevolving its growth rate, which is linked to the transmission rate (β), the virulence (α) and infected reproduction (f), as in Fig. 3A. Initially tolerance is dropped by the host, but as the parasite evolves to a lower growth rate at its CSS the host increases its tolerance and achieves positive reproduction from infecteds. In (B) we decompose the overall level of infected reproduction in to a multiplicative function of the host and parasite's strategies. Initially the host invests in resistance but as the parasite evolves to its CSS it forces there to be zero infected reproduction, at which point resistance becomes futile and is dropped by the host.

interaction depends crucially upon the nature of the host defense mechanism. If the host can tolerate the damage caused by parasite growth, the coevolutionary stable outcome is often for some level of reproduction while infected. In contrast if the host instead invests in a resistance mechanism that controls the parasite's growth we should still expect complete sterilization. We therefore argue that resistance may be a futile strategy for the host, but that host tolerance may explain why parasites do not castrate their hosts.

Many parasites have strong effects on their infected host's fecundity in nature. There are a large number of castrating parasites including the well-studied Daphnia bacterial parasite *Pasteuria ramosa* (Little et al. 2002; Ebert et al. 2004), the *mycrobotryum* smut infections in *Silene* species (Antonovics et al. 1996), the *Portunion* isopod on *Grapsidae* crabs (Brockerhoff 2004) and insect baculoviruses (Boots and Begon 1993; Boots and Mealor 2007). Many more parasites have effects on fecundity short of complete castration. In particular, reduced fecundity effects due to parasitic nematodes are well studied in red grouse (Dobson and Hudson 1992; Hudson et al. 1992), common voles (Deter et al. 2007) and Svalbard reindeer (Albon et al. 2002). Furthermore, it is likely that such effects are largely under-recorded in the field as they can be difficult to recognize without in-depth longitudinal studies. In one such detailed study of bank voles and wood mice infected with the cowpox virus, Feore et al. (1997) found that despite having little observable impact upon mortality, infection does cause a profound loss of fecundity. Theory shows why this

is not surprising: reducing host fecundity is not as costly to the parasite as the reduction in the length of the infectious period that increased virulence through mortality causes (Jaenike 1996). Our work argues that host tolerance to the effects of sterilization may be crucial in many of the systems in which there is not full castration. The presence of full castration may reflect either the lack of these tolerance mechanisms or the cost of them being too high to pay. Given that reductions in fecundity (sublethal) effects are well known to be crucial to the likelihood of destabilization of host populations by parasites (Dobson and Hudson 1992; Boots and Norman 2000; Smith et al. 2008), perhaps more attention needs to be paid to the evolutionary dynamics of disease effects on fecundity.

We have confirmed that the optimal strategy for a parasite if it can allocate where damage is caused is to incur no mortality by fully sterilizing its host (Jaenike 1996; O'Keefe and Antonovics 2002) and that this can only be prevented in the host by tolerance mechanisms. It is also important to point out though that we would expect mortality as well as fecundity effects in most circumstances. For one, it may often be the case that parasites are not able to allocate damage to either mortality or fecundity. Different types of damage will often depend on the details of the pathogenicity of the parasite. Also, we assumed here that host fecundity has no direct link to parasite transmission. Of course in many cases a reduction in host fecundity will lead to greater parasite transmission—for example in the *Silene*'s anther smut

we may expect that transmission increases with the number of infected anthers. Furthermore, the relationship between transmission, virulence and growth rate may be such that R_0 is maximized at a growth rate at which the parasite is likely to cause virulence as well as reduce its host's fecundity (Bremermann and Thieme 1989). This is likely to result in a mixture of reduced fecundity and increased mortality and in some cases both castration and mortality. However, our key result that defense through tolerance to the damaging effects of parasite growth on fecundity may prevent castration still holds.

Importantly, we found that it is tolerance rather than resistance to a sterilizing parasite that is an effective host strategy. Tolerance mechanisms compensate for the detrimental effects of a parasite without attempting to control it in any way. Both host and parasite are therefore able to achieve optimal allocations of resources without compromising the other's strategy. Contrastingly, resistance mechanisms attempt to restrict a parasite's within-host growth. However, through repeatedly paying a cost to control the parasite's growth rate resistance comes at infinite costs, and as such we expect the host to become fully sterilized. As yet there has been little empirical research that attempts to identify hosts exhibiting sterility tolerance and more work is needed to find systems where it is present. Our work does, however, highlight the importance of tolerance more generally. There has been a recent increase in interest in tolerance to mortality effects in the theoretical literature (Boots and Bowers 1999; Roy and Kirchner 2000; Restif and Koella 2004; Miller et al. 2005, 2006) and empirical evidence of tolerance to mortality effects has been demonstrated in many plant populations (Simms and Triplett 1994; Tiffin and Rausher 1999). There is also increasing evidence of tolerance to mortality effects in animal populations (Råberg et al. 2007) and we suggest that sterility tolerance may be an equally important aspect of host-parasite dynamics. It should be noted however that the sterility tolerance considered here is different to tolerance to mortality effects (Roy and Kirchner 2000) in that it does not increase the parasite fitness. Without vertical transmission, sterility tolerance is neutral to parasite fitness and therefore has very different feedbacks to mortality tolerance. The way in which these different defense mechanisms feedback into the ecology of the interaction leads to very different evolutionary outcomes and therefore it is important to make these distinctions between different forms of tolerance both empirically and theoretically (Best et al. 2008).

Previous theoretical work on host defenses to parasites has focused on mechanisms of avoidance of infection, increased clearance and tolerance of mortality effects (Boots and Bowers 1999, 2004; Roy and Kirchner 2000; Miller et al. 2005). It is interesting to note that our work has shown that the dynamics of sterility tolerance are perhaps most closely matched to those of resistance through increased clearance. Unlike avoidance resistance or mortality tolerance, the epidemiological advantage of both sterility

tolerance and increased clearance is in contributing to the susceptible population rather than countering the effects of parasitism directly. Sterility tolerance has no direct effect upon parasite fitness, unlike resistance (negative feedback) and mortality tolerance (positive feedback). However, evolutionary branching can occur for sterility tolerance if its cost is to lifespan because this leads to a reduction in the infectious period, causing a negative feedback to parasite fitness and negative frequency dependence (Best et al. 2008).

Our work has emphasized the importance of examining coevolutionary processes (Best et al. 2009). In isolation, models of parasite evolution predict that they should always castrate their hosts, however, the evolution of sterility tolerance can prevent the loss of fecundity in the host. The importance of tolerance to mortality to host-parasite dynamics is being increasingly recognized (Miller et al. 2005; Råberg et al, 2007; Boots 2008). Here we have shown that tolerance may also be crucial in protecting hosts from the effects of a sterilizing parasite. Given that sterility tolerance has different evolutionary dynamics from mortality tolerance, it is important that we get more experimental data and a greater mechanistic understanding of tolerance in natural systems.

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Supporting Information

The following supporting information is available for this article:

Appendix: Mathematical Details.

Supporting Information may be found in the online version of this article.
(This link will take you to the article abstract).

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