Maintenance of host variation in tolerance to pathogens and parasites

A. Best[a,1], A. White[b], and M. Boots[a]

[a]Department of Animal and Plant Sciences, University of Sheffield, Sheffield S10 2TN, United Kingdom; and [b]Department of Mathematics and the Maxwell Institute for Mathematical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom

Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved November 10, 2008 (received for review September 24, 2008)

Tolerance and resistance provide hosts with two distinct defense strategies against parasitism. In resistance the hosts ''fight'' the parasite directly, whereas in tolerance the hosts fight the disease by ameliorating the damage that infection causes. There is increasing recognition that the two mechanisms may exhibit very different evolutionary behaviors. Although empirical work has often noted considerable variance in tolerance within hosts, theory has predicted the fixation of tolerance due to positive frequency dependence through a feedback with disease prevalence. Here we reconcile these findings through a series of dynamic game theoretical models. We emphasize that there is a crucial distinction between tolerance to the effects of disease-induced mortality and tolerance to the effect of the disease-induced reductions in fecundity. Only mortality tolerance has a positive effect on parasite fitness, whereas sterility tolerance is neutral and may therefore result in polymorphisms. The nature of the costs to defense and their relationship to trade-offs between resistance and tolerance are crucial in determining the likelihood of variation, whereas the co-evolution of the parasite will not affect diversity. Our findings stress that it is important to measure the effects of different mechanisms on characteristics that affect the epidemiology of the parasite to completely understand the evolutionary dynamics of defense.

tolerance | resistance | genetic variation | evolutionary branching

Defense against parasites and pathogens by plant and animal hosts can be divided into two broad classes: resistance and tolerance. Resistance mechanisms actively reduce the parasite burden, whereas tolerance mechanisms limit the impact of disease caused at any particular burden. The distinction is not merely an issue of semantics: theory predicts that there are important differences in the evolutionary ecology of resistance and tolerance (1–4). By directly inhibiting infection and reducing parasite growth rate (''fighting the parasite''), resistance reduces parasite prevalence. Resistance genes therefore have a negative feedback on their own fitness as they spread through the population, because resistance becomes less beneficial as parasite prevalence falls (1). In contrast, tolerance ameliorates the damage that parasites cause. When this allows infected hosts to live longer, it increases the infectious period and therefore increases rather than decreases parasite prevalence, leading to a positive feedback (2). However, tolerance mechanisms to herbivore damage are often considered not to affect herbivore fitness (5), despite differing findings (6), and we have no theory on the evolutionary implications of tolerance mechanisms to parasites that reduce host fecundity. Identifying and understanding the evolutionary dynamics of these different defense mechanisms is, however, crucial to our understanding of host–parasite interactions.

The distinction between resistance and tolerance has been particularly well studied in a number of plant systems in response to both herbivory and infectious disease (7–11). However, these mechanisms are likely to be just as important in animal parasite interactions, and a recent study has shown variation in both tolerance and resistance to malaria in a rodent model system (12). It could be argued that because of their very different feedback mechanisms, it is unlikely that resistance and tolerance mechanisms would exist together within an individual. Highly resistant genotypes do not benefit from tolerance, as they experience little damage; in contrast, highly tolerant genotypes need no resistance, as the damage caused has little impact upon host fitness. Despite this, empirical studies have found both defense mechanisms present within a single population (13, 14). Furthermore, there is a large body of empirical evidence for considerable genetic variation in resistance and tolerance in both plant and animal populations (9, 12, 15).

Theory on the evolution of host defenses initially focused on resistance mechanisms (1, 3, 16, 17), but there has been a recent surge of interest in the evolutionary properties of tolerance (2, 4, 18, 19). A key focus of the theory concerns the potential for variation and polymorphisms in defense to arise due to ecological feedbacks. The reduction in prevalence caused by the spread of resistance in host populations leads to negative frequency dependence, and therefore polymorphisms of host strains can arise (3, 20). In contrast, the ecological feedback that occurs with tolerance to mortality increases parasite fitness, leading to positive frequency dependence, and therefore evolutionary branching and polymorphisms of tolerant strains are not found (2, 4). Given the empirical evidence for variation in tolerance, there is a need to develop more theory that can explain this apparent discrepancy.

Our aim is to understand how the ecological feedbacks of different types of tolerance may lead to the evolution and maintenance of variation. We therefore develop theory using the dynamic game theoretical techniques of adaptive dynamics that explicitly models how ecological dynamics generate selection pressures. We identify the conditions that lead to negative frequency dependence and to disruptive selection that will generate and maintain variation from the conditions for evolutionary branching with the adaptive dynamics framework. In particular we highlight the importance of understanding where the costs of tolerance are incurred, the effects of host–parasite co-evolution and in particular emphasize an important distinction between tolerance to mortality and sterility effects of the parasite. We demonstrate the importance of tolerance in animal as well as plant parasite interactions, and the need for further empirical work that distinguishes between tolerance to mortality and sterility and determines the nature of the costs to defense.

Results

Trade-Offs Between Resistance and Tolerance. Previous theoretical studies on the evolution of tolerance to the mortality effects of

Author contributions: A.B., A.W., and M.B. designed research, performed research, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. E-mail: a.best@shef.ac.uk.

This article contains supporting information online at www.pnas.org/cgi/content/full/0809558105/DCSupplemental.

infection have assumed that increased defense is costly in terms of host reproduction (2, 4). There is also, however, the potential for trade-offs between different components of the defense system, and there are empirical studies that have shown tolerance and resistance to be negatively correlated (7, 8, 12), although such correlations are by no means universal (21). Theory shows that there is the potential for evolutionary branching (through disruptive selection caused at an attracting strategy that is a fitness minimum) leading to polymorphism in resistance (3, 20), and therefore variation in tolerance may be due to a correlation with resistance. We examine here a host that can evolve increased tolerance (to parasite-induced mortality) at a cost to resistance through clearance/recovery of the infection. There are, of course, a range of differing resistance mechanisms that could be examined, including not only clearance (increased recovery) but also avoidance (lowered transmission) and control (lowered parasite replication rate) (3, 4). The other resistance mechanisms give qualitatively similar results to those reported in this study (they are not shown here but can be reproduced by simply altering the choice of parameter in the trade-off).

In our modeling framework, the potential for evolutionary branching is determined by a single quantity, M, which determines whether distinct strains are mutually invadable. When $M<0$ evolutionary branching can occur for some trade-off (see *Materials and Methods* section for details). For our model set-up with a straightforward trade-off between resistance and tolerance, we find that $M = 0$ for all parameter values and therefore branching cannot occur. When other ecological assumptions are made that modify the model set-up, as shown in equations (1) and (2), such as allowing infected individuals to reproduce, making the natural host death rate density-dependent, or the parasite-induced death rate (virulence) density-dependent, we find that the sign of M remains non-negative. Therefore, for a wide range of model assumptions, a trade-off between tolerance and resistance does not in itself allow branching to occur. The population will either evolve to some intermediate allocation between resistance and tolerance or one of the mechanisms will become fixed.

Trade-offs between resistance and tolerance alone do not lead to polymorphism but it is likely that the overall level of investment in defense will be costly to host fitness. This relationship between defense and overall fitness is intrinsic to the previous theory on resistance (1, 3) and tolerance (2, 4) because it is unlikely, at least in theory, that defense is cost free (22), although in practice such costs may not necessarily be detected. Therefore we again assume a trade-off between resistance and tolerance but also assume that higher overall investment in defense results in lower host fecundity. Specifically, we assume an additional relationship between birth rate and the overall level of defense, such that an increase in total defense (tolerance and resistance) causes a reduction in birth rate, as in Equation (7). Fig. 1 shows the relationship between the birth and recovery rates. We now find that there are parameter values which give $M<0$, and that therefore evolutionary branching can occur. This occurs even though the costs to defense are relatively small (the birth rate is only slightly altered compared to its fixed value under the previous analysis).

In Fig. 2 we show numerical simulations of this system following the methods outlined in (23). The population initially moves to an intermediate level of tolerance before branching into two strains—one of which evolves to minimal tolerance and high resistance, the other to minimal resistance and high tolerance. Alongside the simulation output is a pairwise invadibility plot (PIP). This graphic tool plots mutant fitness as a function of the resident strategy with shaded areas denoting those combinations where the mutant can invade (24). Given small mutations, the evolving population will move up or down the diagonal depending on the fitness of the mutant invader. In Figure 2, A and B mark two singular strategies (see *Materials and Methods* for definitions of terms); A is the evolutionary branching point (an attracting point that is invadable), whereas B is a repelling strategy (an invadable, repelling point). A trade-off with resistance can therefore lead to polymorphisms in tolerance if there is also a cost of defense in terms of host fitness.

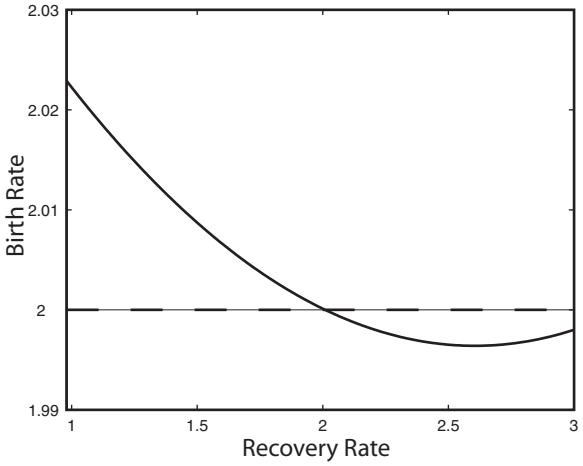

Fig. 1. Relationship of birth rate with recovery (resistance), where resistance is traded off with mortality tolerance but overall defense incurs a cost in birth rate. Parameter values are as in the simulation in Fig. 2. The dashed line shows the birth rate as a constant function when it was not involved in the trade-off.

Types of Tolerance. Until this point we have been dealing only with tolerance to the mortality effects of disease (mortality tolerance). However, it is important to note that the host may also be able to tolerate the damage that infection causes to the reproductive ability of infected individuals ("sterility tolerance"). There have been few theoretical investigations that consider the evolutionary and ecological implications of sterility tolerance (18). The distinction is also not always made in experimental studies, although in plant systems the effects on yield and therefore sterility rather than mortality tolerance are often examined (7, 14, 15). There is an important difference between mortality and sterility tolerance in terms of their effect on parasite fitness. Mortality tolerance increases parasite fitness and thereby increases prevalence, leading to an effective boost in its own utility as a defense strategy. However, sterility tolerance will most likely be neutral to a horizontally transmitted parasite's fitness, and the lack of a positive epidemiological

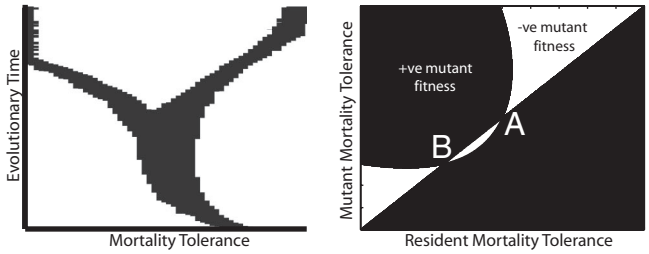

Fig. 2. Simulation output of the evolutionary dynamics of a host population where increased mortality tolerance is achieved at a cost to recovery resistance, and further costs are incurred in the birth rate (Fig. 1). Also shown is a pairwise invadibility plot (PIP). With small mutations the resident population will move up or down the diagonal depending on whether the mutant's fitness is positive (black) or negative (white) relative to the resident. A and B mark two singular strategies. Parameter values: b = 0.5, q = 0.5, $\beta = 2$, f = 0, $(\gamma^*, \alpha^*) = (2,2)$, $(\gamma_{min}, \alpha_{min}) = (0.977, 1)$, $(\gamma_{max}, \alpha_{max}) = (3, 2.998)$, p = −0.0203.

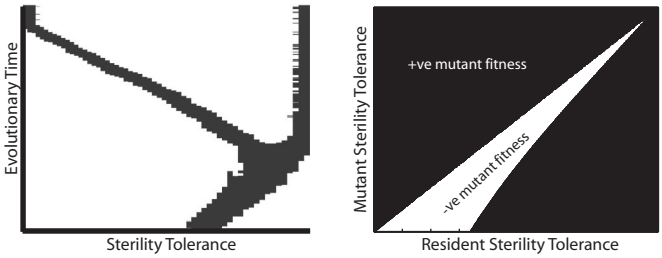

Fig. 3. Simulation output of the evolutionary dynamics of a sterility tolerance-death rate trade-off. Again shown is a pairwise invadibility plot or PIP (see Fig. 2 and text for details). Parameter values: a = 2, q = 0.5, $\beta = 2$, $\alpha = 1.5$, $\gamma = 0$, (b* , f*) = (1, 1), (b_{Min}, f_{min}) = (0.73, 0), (b_{max}, fmax) = (1, 1), p = −0.158.

feedback on the spread of tolerance may lead to different evolutionary outcomes.

In Fig. 3 we show simulation output and a PIP for the evolutionary dynamics when the investment in sterility tolerance is bought at a cost of increased host death rate. Here, there is an evolutionary branching point at maximum infected fecundity: when infected and uninfected reproduction are equal. The population evolves toward the singular strategy and, when nearby, undergoes disruptive selection leading to the maintenance of two co-existing strains—one of high and one of low tolerance. (This result can be confirmed analytically as a range of parameters exist for which $M<0$.) Recent work has suggested that sterility tolerance is more likely to evolve than resistance to the sterility effects of parasites, and that it is therefore important to distinguish between tolerance to the mortality and fecundity effects of disease (this work will be discussed elsewhere). Moreover, in our model framework, polymorphism occurs only when the costs to sterility tolerance are paid through higher host death rate (rather than, say, host reproduction), and therefore it is important to understand which life history characteristics are affected by investment in tolerance.

Co-evolution. Most host–parasite theory considers only the evolution of either the host or the parasite. Of course, most natural systems will be co-evolutionary (although not all agricultural ones in which, for instance, resistant or tolerant crops are planted). Recent theory has suggested that the outcomes of co-evolutionary systems can depart significantly from those of their evolutionary counterparts (25). It is therefore important to ask whether, in situations in which evolutionary models predict no branching, co-evolution with the parasite can cause branching in host tolerance levels.

The evolutionary dynamics of a species can be disrupted by the co-evolution of an antagonistic species (25, 26). However, for evolutionary branching to occur, we must still have $M<0$; otherwise a dimorphic population can never become established (24). Therefore, as we found in our baseline model that the host always has a strictly non-negative M, we can conclude that the co-evolution of the parasite cannot force branching to occur (see *Materials and Methods*).

Clearly, there may be genetic variation in the parasite (12), and it is important to ask whether this may lead to branching in the host in terms of tolerance. We can consider a model framework in which the host evolves in a system with two or more parasite strains by simply adding an extra equation for each parasite type to the model described by Equations (1) and (2). Using the same analysis we again find that $M>0$ and branching is not possible. Furthermore, this result confirms that two host strains can never coexist.

Discussion

There has been an apparent discrepancy between experimental studies of tolerance in which considerable genetic variance is exhibited (9, 12, 15) and previous theoretical studies in which it is predicted that tolerance will be fixed when it evolves (2, 4). Here, we have sought to resolve this conflict by examining a series of theoretical models. In particular, using our modeling framework we have identified the following: (*i*) sterility tolerance can lead to polymorphic populations and so has distinct evolutionary properties compared to mortality tolerance; (*ii*) trade-offs between mortality tolerance and resistance alone do not allow evolutionary branching to occur; but (*iii*) trade-offs between mortality tolerance and resistance, which also include a cost to the investment in total defense, can lead to genetic variation; and (*iv*) the co-evolution of the parasite cannot in itself explain variation in tolerance. As such, our work emphasizes the need to understand where tolerance acts (i.e., mortality or sterility) and the nature of the costs involved to fully understand the maintenance of variation in tolerance in natural populations.

There is an increasing recognition within both the experimental and theoretical literature that resistance and tolerance present a host with two distinct evolutionary defense strategies. Resistance mechanisms can be classified further into avoidance (lowered transmission), clearance (increased recovery), or control (lowered parasite reproductive rate) (3, 4). What has not been widely appreciated, however, is that tolerance can itself be manifested in two very different forms: mortality tolerance and sterility tolerance. Both forms of tolerance induce an increase in infected host health, but they have different consequences to parasite fitness and therefore ecological feedbacks that underpin their evolution. In combating parasite-induced death (generally defined as virulence), mortality tolerance may increase parasite fitness by lengthening the infectious period and, in so doing, can create a positive feedback to its own utility as a defense strategy. In contrast, by combating parasite-induced loss of reproduction, sterility tolerance is completely neutral to a horizontally transmitted parasite. However, when the cost of sterility tolerance is to lifespan, the infectious period is reduced and thus a negative feedback emerges. Because of these differing effects, unlike with mortality tolerance the evolution of sterility tolerance can, depending on its trade-off structure, result in genetic variation within a host population. Of course, it may often be the case that these two types of tolerance will be positively correlated, and it is easy to show that then tolerance will not necessarily be fixed. It follows from our study that tolerance to parasites and pathogens that have significant effects on fecundity are more likely to show variation in nature. Given the variance found in tolerance studies that measure plant yield (7, 14, 15), this could well be the case.

This distinction between mortality and sterility tolerance highlights a subtle issue in the measure of tolerance used in many experimental studies. Generally, tolerance is understood as the reaction norm of fitness across a damage gradient. However, achieving a reasonable estimate of this property in practice is far from simple (7, 10). Many studies essentially correlate host fitness with yield (7, 14, 15), whereas others limit themselves to a general term of health (12). Clearly, if fitness is being determined in terms of yield, defense against sterility will be of primary importance. Health, too, is likely to be made up of some combination of each component of tolerance. Potential mechanisms of tolerance to parasites in animals have been suggested, including tissue repair and immunological mechanisms (27). However, there is a clear need for studies to isolate the effects of mortality tolerance and sterility tolerance to fully elucidate the evolutionary dynamics of the host. Given that we may expect these two defense mechanisms to be positively correlated, this is

not an easy task; but important consequences of the evolutionary ecology may be missed if this distinction is not made.

A number of experimental studies have found a negative correlation to exist between resistance and tolerance (7, 8, 12). Despite this, few theoretical studies have investigated the evolutionary dynamics when hosts can achieve greater tolerance at a cost to resistance, and none have considered the consequences of such a trade-off on the potential for polymorphisms. We have found that a simple trade-off between resistance (through increased recovery) and mortality tolerance alone can never cause genetic variance to arise through a process of evolutionary branching. We know that the resistance mechanisms of avoidance and recovery can lead to branching only when they are traded off against another life-history trait, otherwise they will always evolve to fixation (3). Assuming a cost to high defense by correlating birth rate with the investment in resistance and mortality tolerance leads to the possibility of evolutionary branching in both tolerance and resistance. Underlying trade-offs both between defense components and other life-history traits may therefore be responsible for much of the genetic variance found in host defenses.

Given the differing effects that resistance and tolerance cause on parasite fitness, there is considerable interest in how defenses evolve, given that parasites are co-evolving (12, 19). Some recent theory has provided the tools with which to study such co-evolutionary systems in a dynamic context with ecological feedbacks under different trade-off assumptions (25). These advances show that co-evolution can have a significant impact upon the evolutionary behavior of the system. However, we have found here that the co-evolution of the parasite cannot force a host population to branch that did not do so when evolving in isolation.

Theory on mortality tolerance tends to predict its fixation in a host population (2, 4), which has led to work investigating how the parasite evolves in response to tolerant hosts (19). Tolerance often selects parasites to increase their transmission and thus their virulence, as they gain extra infections for very little extra cost. This work also concluded that tolerance may therefore be difficult to measure in many cases, as the host–parasite interaction may appear to be commensal. Also, although a fully tolerant host may coexist with a highly virulent parasite, this apparent commensalism will be devastating for any nontolerant hosts that subsequently enter the population (19).

For evolutionary branching to occur, there must be negative frequency dependence in the evolving trait leading to disruptive selection. Because of the relatively simple structure of our particular modeling framework, only one branching occurs (1, 3, 4, 20), but this result is not a general property of adaptive dynamics models; there are many examples of multiple branching and a resulting array of types in other ecological scenarios (28, 29). Our models describe a very simplistic one host–one parasite interaction, but of course in nature most hosts are part of a much more complex, multispecies interaction with competitors as well as other parasites. These more complex ecological scenarios lead to more complex fitness landscapes and therefore the potential for more branching. In addition, nonadaptive processes may lead to the production and maintenance of variation, particularly when selection is weak and mutation rates are high. Although not explicitly sexual, the predictions of our models should hold whenever the phenotypic effects are the result of additive effects of a number of alleles. In this case, heterozygotes falling between the homozygotes at a branching point may be maintained in the population but have lower fitness (30–32). Our key result is that the processes we describe that lead to disruptive selection have the potential to generate variation of types in nature. There is a long tradition of explicitly genetic gene-for-gene (33–35) or "matching alleles" models (36, 37), in which hosts are resistant to more or less of a range of parasite types. These do not link phenotype to ecological (life-history) parameters and, as such, they do not include explicit ecological feedbacks; but they emphasize that genetic recognition systems may also generate variation in host and parasite genotypes (38, 39).

There is considerable commercial interest in the development of host defenses in agricultural crops (40–42). Given their different epidemiological feedbacks, understanding and identifying the alternative defense mechanisms of resistance and tolerance is crucial to any applied success. We have identified here important areas in which experiments need to be carried out and theory developed to gain a fuller understanding of the evolution of tolerance. The relative simplicity of many theoretical models means that, despite the advantage of tractability, some of the more subtle behavior found in natural systems may be missed. There is also a need for experimental studies that use a more precise measure of tolerance, as this may be expressed not only in mortality but also in reproduction. In particular, we predict that variation in tolerance will be much more prevalent in systems in which the effects of parasitism are on reproduction rather than mortality, and where the costs of tolerance are expressed not only in resistance. It is therefore crucial that experiments are carried out that distinguish between parasite effects on reproduction of the host and mortality. In addition, the correlations between resistance and tolerance need to be better understood, as does the nature of costs to defense. Our work has shown how and why we may indeed expect variation in tolerance in natural populations; however, more detailed experimentation is required to understand the causes of this variation in particular systems.

Materials and Methods

Model Framework. Our baseline model is a susceptible–infected–susceptible (SIS) system. The population dynamics of uninfected hosts, X, and infected hosts, Y, can be described by the following coupled differential equations:

$$\frac{dX}{dt} = (a - qN)(X + fY) - bX - \beta XY + \gamma Y, \qquad [1]$$

$$\frac{dY}{dt} = \beta XY - (\alpha + b + \gamma)Y, \qquad [2]$$

where N is the total population ($X+Y$). Hosts are born free of infection with birth rate a, which is modified by a crowding parameter, q, which accounts for host self-regulation. Births from infected hosts occur at a fraction, f, of the rate for uninfected hosts (in the baseline model we assume $f = 0$). The natural death rate of hosts is b. The parasite is transmitted between hosts at rate β and induces additional host mortality for infected individuals (virulence) at rate α. Infected hosts can recover at rate γ.

We assume α and γ are linked through a trade-off such that an increase in tolerance (lowered α) causes a reduction in resistance (lowered γ). We assume a smooth curve that links the maximum values ($\alpha_{max}, \gamma_{max}$) and the minimum values ($\alpha_{min}, \gamma_{min}$). We introduce a parameter p that controls the shape of the trade-off: if $P < 0$ the trade-off is accelerating (convex); if $P > 0$ it is decelerating (concave); and if $P = 0$ it is linear (23). Analytically we can express this trade-off as:

$$\frac{\alpha - \alpha_{\min}}{\alpha_{\max} - \alpha_{\min}} = 1 - \frac{\left(1 - \dfrac{\gamma - \gamma_{\min}}{\gamma_{\max} - \gamma_{\min}}\right)}{\left(1 + p\dfrac{\gamma - \gamma_{\min}}{\gamma_{\max} - \gamma_{\min}}\right)}. \qquad [3]$$

This can then be rearranged into the form $\alpha = g(\gamma)$. Although this appears to be a rather complicated functional form, this trade-off function avoids mathematical complications of discontinuity that can arise with simpler power laws.

Adaptive Dynamics. The evolutionary behavior can be determined by assessing the fitness—the long-term exponential growth rate—of a rare, mutant strategy, y, attempting to invade an environment set by a resident strategy, x, at its dynamic attractor (24, 26). By analyzing the Jacobian of equations (1) and

(2), we find that the fitness of a mutant host, with strategy, $y = (\bar{\gamma}, \bar{\alpha})$, trying to invade the resident equilibrium strategy, $x = (\gamma,\alpha)$, (with resident equilibrium densities denoted by *s) is:

$$s = (a - qN^* - b - \beta Y^*)(\bar{\alpha} + b + \bar{\gamma}) + \beta Y^*(af - qfN^* + \bar{\gamma}). \quad [4]$$

The theory of adaptive dynamics shows how, over time, the population will evolve in the direction of the local selection gradient, $\partial s/\partial y$, until a *singular strategy* is reached whereby $\partial s/\partial y = 0$. In some sense, the singular strategy can be viewed as a (potentially temporary) ''stopping point'' of the evolutionary process. The evolutionary outcome at the singularity is governed by two key properties—evolutionary stability (ES) and convergence stability (CS). Evolutionary stability determines whether a strategy can be invaded by nearby mutant strains, whereas convergence stability determines whether selection directs the population toward or away from a strategy. Analytically, we can express the conditions for evolutionary stability and convergence stability respectively as:

$$E = \frac{\partial^2 s}{\partial y^2} < 0, \quad [5]$$

$$E + M = \frac{\partial^2 s}{\partial y^2} + \frac{\partial^2 s}{\partial x \partial y} < 0 \quad [6]$$

Attracting strategies (both ES and CS) are end points of evolution, which attract all nearby strategies and are fitness maxima. *Repelling strategies* (neither ES nor CS) are the exact opposite, being fitness minima and causing all nearby strategies to evolve away. *Evolutionary branching* occurs where a certain strategy is convergent-stable but not evolutionarily stable. In such a case, selection will direct the population to evolve to the singularity, but will then undergo disruptive selection and diverge into two distinct strains. In terms of Equations (5) and (6), we thus require $E>0$ and $E+M<0$. With some manipulation, we can express E and M as functions of the trade-off described in Equation 3 (25). The term E is a function of the trade-off curvature (its second derivative), whereas M is not. Hence, so long as we can find parameter values where $M<0$, we will always be able to construct a trade-off to meet the branching conditions. (*SI Appendix* provides a detailed description of the analysis.)

The analytic equations for E and M are somewhat lengthy, and we omit the explicit expressions for brevity. However, for sample parameters, $a = 2$, $f = 1$, $b = 0.5$, $q = 0.5$, $\beta = 2$, $(\gamma^*, \alpha^*) = (2,2)$, we find that $E = -0.35g''$ and $M = 0.05$. Clearly E depends on the curvature (g'') of the trade-off between α and γ. However, because M is positive, no trade-off will be able to satisfy the branching conditions. (We found that M was positive for all of the [wide-ranging] parameters tested.)

More Complex Trade-Offs. We include the birth rate in the trade-off by assuming:

$$a = (\alpha - \alpha_{\min}) + (\gamma_{\max} - \gamma). \quad [7]$$

An increase in either form of defense would cause a reduction in the birth rate. The trade-off between resistance and tolerance will, of course, lead to a complex relationship between the two defense traits and the birth rate. In particular, the shape of the trade-off will dictate how a varies with defense. If both tolerance and resistance are high, birth rate will be low. If both tolerance and resistance are low, birth rate will be high. By substituting Equation (7) into Equation (4), we can analyze the adaptive dynamics of this system as before.

Co-evolution. Calling the host's invasion fitness s and the parasite's r, a co-evolutionary singular point will occur when the host and parasite selection gradients are simultaneously zero, i.e., $\delta s/\delta y_H = 0$ in the host and $\delta r/\delta y_P = 0$ in the parasite. Assuming equal mutation rates, the convergence stability at this fixed point is determined by the eigenvalues of the Jacobian

$$\begin{pmatrix} E_H + M_H & A_H \\ A_P & E_P + M_P \end{pmatrix} \quad [8]$$

The diagonal terms are simply the convergence stability conditions of the host (subscript H) and parasite (subscript P), whereas the off-diagonals are the cross-effect of the resident population of one species on the mutant population of the other species (26). A singularity is convergence stable provided both eigenvalues are negative, which is guaranteed provided:

$$(E_H + M_H) + (E_P + M_P) < 0 \quad [9]$$

$$(E_H + M_H)(E_P + M_P) - A_H A_P > 0$$

Clearly, even though $M_H = 0$, if the parasite has strong convergence (i.e., ($E_P + M_P$) is very negative) and the cross-terms (A_H,A_P) have opposite signs, in co-evolution the host may be convergent-stable and evolutionarily unstable. However, even though the host would here be forced to evolve to a fitness minimum, without mutual invadibility ($M < 0$) hosts near the singularity will be unable to coexist with one another (24). This means that evolutionary branching cannot occur, and the host will simply remain at a fitness minimum.

ACKNOWLEDGMENTS. We thank the editors and two anonymous reviewers for their comments on a previous version of this manuscript. AB was supported by a Natural Environment Research Council studentship.

1. Boots M, Haraguchi Y (1999) The evolution of costly resistance in host-parasite systems. *Am Naturalist* 153:359–370.
2. Roy BA, Kirchner JW (2000) Evolutionary dynamics of pathogen resistance and tolerance. *Evolution* 54:51–63.
3. Boots M, Bowers RG (1999) Three mechanisms of host resistance to microparasites—avoidance, recovery and tolerance—show different evolutionary dynamics. *J Theor Biol* 201:13–23.
4. Miller MR, White A, Boots M (2005) The evolution of host resistance: Tolerance and control as distinct strategies. *J Theor Biol* 236:198–207.
5. Tiffin P (2000) Are tolerance, avoidance and antibiosis evolutionarily and ecologically equivalent responses of plants to herbivores? *Am Naturalist* 155:128–138.
6. Stinchcombe JR (2002) Can tolerance traits impose selection on herbivores? *Evolut Ecol* 15:595–602.
7. Simms E, Triplett J (1994) Costs and benefits of plant responses to disease: Resistance and tolerance. *Evolution* 48:1973–1985.
8. Fineblum W, Rausher M (1995) Tradeoff between resistance and tolerance to herbivore damage in a morning glory. *Nature* 377:517–520.
9. Tiffin P, Rausher, M (1999). Genetic constraints and selection acting on tolerance to herbivory in the common morning glory *Ipomoea purpurea. Am Naturalist* 154:700–716.
10. Stowe K, Marquis R, Hochwender C, Simms E (2000) The evolutionary ecology of tolerance to consumer damage. *Annu Rev Ecol System* 31:565–595.
11. Rausher M (2001) Co-evolution and plant resistance to natural enemies. *Nature* 411:857–864.
12. Råberg L, Sim D, Read A (2007) Disentangling genetic variance for resistance and tolerance to infectious diseases in animals. *Science* 318:812–814.
13. Lye B, Smith C (1988) Evaluation of rice cultivars for antibiosis and tolerance to fall armyworm (Lepidoptera: Noctuidea). *Florida Entomol* 71:254–261.
14. Stowe K (1998) Experimental evolution of resistance in Brassica rapa: Correlated response of tolerance in lines selected for glucosinolate content. *Evolution* 52:703–712.
15. Hochwender C, Marquis R, Stowe K (2000) The potential for and constraints on the evolution of compensatory ability in Asclepias syriaca. *Oecologia* 122:361–370.
16. Antonovics J, Thrall PH (1994) The cost of resistance and the maintenance of genetic polymorphism in host-pathogen systems. *Proc R Soc London B: Biol Sci* 257:105–110.
17. Bowers RG, Boots M, Begon M (1994) Life-history trade-offs and the evolution of pathogen resistance: Competition between host strains. *Proc R Soc London B: Biol Sci* 257:247–253.
18. Restif O, Koella JC (2004) Concurrent evolution of resistance and tolerance to pathogens. *Am Naturalist* 164:E90–E102.
19. Miller MR, White A, Boots M (2006) The evolution of parasites in response to tolerance in their hosts: The good, the bad and apparent commensalism. *Evolution* 60:945–956.
20. Boots M, Bowers RG (2004) The evolution of resistance through costly acquired immunity. *Proc R Soc London B: Biol Sci* 271:715–723.
21. Mauricio R, Rausher M, Burdick D (1997) Variation in the defence strategies of plants: Are resistance and tolerance mutually exclusive? *Ecology* 78:1301–1311.
22. Stearns SC (1992). *The Evolution of Life Histories.* (Oxford University Press, Oxford).
23. White A, Greenman JV, Benton TG, Boots M (2006) Evolutionary behaviour in ecological systems with trade-offs and non-equilibrium population dynamics. *Evolut Ecol Res* 8:387–398.
24. Geritz SAH, Kisdi E, Meszéna G, Metz JAJ (1998) Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolut Ecol* 12:35–57.
25. Kisdi E (2006) Trade-off geometries and the adaptive dynamics of two co-evolving species. *Evolut Ecol Res* 8:959–973.
26. Marrow P, Dieckmann U, Law R (1996) Evolutionary dynamics of predator-prey systems: An ecological perspective. *J Math Biol* 34:556–578.
27. Råberg L, Graham A, Read A (2008). Decomposing Health: Tolerance and resistance to parasites in animals. *Phil Transact R Soc B*, 364:37–49.
28. Kisdi E (1999) Evolutionary branching under asymmetric competition. *J Theor Biol* 197:149–162.
29. Geritz SAH, van der Meijden E, Metz JAJ (1999) Evolutionary dynamics of seed size and seedling competitive ability. *Theor Popul Biol* 55:324–343.

30. Kisdi E, Geritz SAH (1999) Adaptive dynamics in allele space: Evolution of genetic polymorphism by small mutations in a heterogeneous environment. *Evolution* 53:993–1008.
31. Geritz SAH, Kisdi E (2000) Adaptive dynamics in diploid, sexual populations and the evolution of reproductive isolation. *Proc R Soc London B: Biol Sci* 267:1671–1678.
32. Matessi C, Gimelfarb A, Gavrilets S (2001) Long-term buildup of reproductive isolation promoted by disruptive selection: How far does it go? *Selection* 2:41–64.
33. Flor HH (1956) The complementary genic systems in flax and flax rust. *Advanced Genet* 8:29–54.
34. Burdon JJ (1987). *Diseases and Plant Population Biology* (Cambridge University Press, Cambridge).
35. Thompson JN, Burdon JJ (1992) Gene-for-gene co-evolution between plants and parasites. *Nature* 360:121–125.
36. Grosberg RK, Hart MW (2000) Mate selection and the evolution of highly polymorphic self/nonself recognition genes. *Science* 289:2111–2114.
37. Agrawal A, Lively CM (2002) Infection genetics: Gene-for-gene versus matching-allele models and all points in between. *Evolut Ecol Res* 4:79–90.
38. Ebert D, Hamilton W (1996) Sex against virulence: The co-evolution of parasitic diseases. *Trends Ecol Evolut* 11:79–82.
39. Frank S (2000) Polymorphism of attack and defense. *Trends Ecol Evolut* 15:167–171.
40. Stuiver M, Custers J (2001). Engineering disease resistance in plants. *Nature* 411:865–868.
41. Campbell MA, Fitzgerald HA, Ronald PC (2002) Engineering pathogen resistance in crop plants. *Transgenic Res* 11:599–613.
42. Gurr SJ, Rushton PJ (2005) Engineering plants with increased disease resistance: What are we going to express? *Trends Biotechnol* 23:275–282.