

## THE EVOLUTION OF PARASITES IN RESPONSE TO TOLERANCE IN THEIR HOSTS: THE GOOD, THE BAD, AND APPARENT COMMENSALISM

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**Abstract.**—Tolerance to parasites reduces the harm that infection causes the host (virulence). Here we investigate the evolution of parasites in response to host tolerance. We show that parasites may evolve either higher or lower within-host growth rates depending on the nature of the tolerance mechanism. If tolerance reduces virulence by a constant factor, the parasite is always selected to increase its growth rate. Alternatively, if tolerance reduces virulence in a nonlinear manner such that it is less effective at reducing the damage caused by higher growth rates, this may select for faster or slower replicating parasites. If the host is able to completely tolerate pathogen damage up to a certain replication rate, this may result in apparent commensalism, whereby infection causes no apparent virulence but the original evolution of tolerance has been costly. Tolerance tends to increase disease prevalence and may therefore lead to more, rather than less, disease-induced mortality. If the parasite is selected, even a highly efficient tolerance mechanism may result in more individuals in total dying from disease. However, the evolution of tolerance often, although not always, reduces the individual risk of dying from infection.

**Key words.**—Adaptive dynamics, apparent commensalism, evolution, evolutionarily stable strategies, parasites, theory, tolerance.

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There are a variety of different mechanisms that hosts can evolve to defend themselves against parasites and pathogens (Boots and Bowers 1999; Gandon and Mickalakis 2000; Roy and Kirchner 2000). Avoiding infection in the first place (avoidance), increasing the rate of clearance (recovery), or remaining immune for longer (immunity) have broadly similar evolutionary dynamics when hosts pay a cost for these mechanisms (Boots and Bowers 2004). If infected individuals can still reproduce or have a chance of recovering from infection, then mechanisms that reduce the death rate due to the disease (virulence) will also increase fitness (Boots and Bowers 1999; Roy and Kirchner 2000). Such mechanisms are often called “tolerance,” but it is important to distinguish between two distinct processes that may reduce virulence. A control mechanism that limits the growth of the pathogen/parasite within infected hosts may evolve. With the usual assumption that host mortality due to infection is proportional to the within-host parasite replication rate (Read and Harvey 1993; Ebert 1998; Mackinnon and Read 1999a,b; Ebert and Bull 2003; Gandon et al. 2003), this controlling mechanism acts to reduce virulence. Alternatively, a true tolerance mechanism that reduces the damage that parasite growth causes to the host may evolve. In this situation, there is no control of the parasite’s growth and reproduction by the host.

However, evolution of the host may also select the pathogen. This has been considered in several contexts (van Baalen 1998; Gandon and Mickalakis 2000; Gandon et al. 2001, 2002a, 2002b, 2003; Restif and Koella 2003). In particular, control of the parasite’s growth by the host has been shown to select for more exploitative parasites (Gandon and Mickalakis 2000). In this study, we focus on how tolerance, once fixed in a host population, will select the parasite.

We classify three generic types of tolerance mechanism

and consider the implications in terms of the parasite’s evolution. Our approach is to examine the evolution of parasite growth (or replication) rate within the host, assuming that this relates to transmission and causes virulence. An explicit account of the epidemiological feedbacks in the system is taken and the consequences of tolerance evolution in terms of disease prevalence and mortality at the level of the population are considered. We develop a formal model that examines the evolution of parasites in response to tolerance with different characteristics, and we show that higher or lower parasite growth rates can be selected, depending on the nature of the tolerance mechanism. Roy and Kirchner (2000) showed that tolerance will tend to become fixed in populations, with no possibility of polymorphism. We therefore assume that selection acts on the parasite after the evolution of tolerance. This is a realistic simplifying assumption for tolerance mechanisms, but less so for resistance through avoidance, recovery, or control of the parasite, where a full coevolutionary model may be more appropriate. The evolution of tolerance is assumed to be costly in terms of a reduction in the host’s intrinsic growth rate.

### THE MODEL

The following equations describe a host-pathogen interaction for a directly transmitted microparasite. Here  $X$  denotes the density of uninfected individuals,  $Y$  denotes the density of infected individuals, and  $H = X + Y$  gives the total host density:

$$\frac{dX}{dt} = rH - qH^2 - \beta XY + (\gamma + b)Y \quad \text{and} \quad (1)$$

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

where  $r$  is the intrinsic growth rate of the host genotype, equal to the birth rate ( $a$ ) minus the natural death rate ( $b$ ). Density dependence is assumed to act directly on the birth rate, where the parameter  $q$  measures the host population's susceptibility to crowding. The transmission rate of infection, the recovery rate, and the virulence are denoted by  $\beta$ ,  $\gamma$ , and  $\alpha$ , respectively. All parameters are assumed to be positive.

We assume virulence ( $\alpha$ ) is determined by the parasite within-host replication rate ( $\varepsilon$ ). In the wild-type host that has not evolved any tolerance, the relationship between increased death rate and parasite growth rate takes the form  $\alpha = \varepsilon v_W$ . Here,  $v_W$  scales the damage that within-host growth causes the host, and may be interpreted as the intrinsic virulence of the parasite.

Tolerance mechanisms reduce the damage caused for a given rate of replication. With type I (complete) tolerance, we assume the host is able to completely tolerate a given rate of parasite replication,  $\rho$ , below which it suffers no damage. Above this level, virulence increases at the same constant rate that occurs in nontolerant hosts, such that  $\alpha = 0$  for  $\varepsilon \leq \rho$ , and  $\alpha = \alpha(\varepsilon) = (\varepsilon - \rho)v_W$  for  $\varepsilon \geq \rho$  (Fig. 1A). Type II (constant) tolerance reduces virulence by a constant factor across the range of parasite growth rates, such that  $\alpha = \alpha(\varepsilon) = \varepsilon v_T$ , where  $v_T < v_W$  (Fig. 1B). Type III (saturating) tolerance causes virulence to increase at a nonlinear rate. This form is able to ameliorate host damage well at lower rates of replication, but is less effective at higher rates, which swamp the tolerance mechanism. We assume the relationship  $\alpha = \alpha(\varepsilon) = v_W m(\varepsilon/m)^a$ , where  $a \geq 1$  and there is a maximum rate of replication ( $m$ ) attainable by the pathogen (Fig. 1C). For all three forms, tolerant host genotypes pay a cost in terms of a reduction in their intrinsic growth rate ( $r$  is a decreasing function of tolerance).

In line with previous work, transmission is assumed to be a bounded increasing function of parasite replication rate (Anderson and May 1982; van Baalen and Sabelis 1995; Restif and Koella 2003):

$$\beta = \beta(\varepsilon) = \frac{K\varepsilon}{\varepsilon + \eta}. \tag{3}$$

Transmission and virulence are therefore traded off from the point of view of the parasite. The parameter  $K$  gives the upper bound of the transmission rate. The parameter  $\eta$  measures the rate at which transmission approaches this upper bound as  $\varepsilon$  increases (smaller values of  $\eta$  correspond to faster rates of saturation). Tolerance reduces the virulence that a particular growth rate causes but does not affect the transmission rate.

We investigate how the parasite is selected in response to the different forms of tolerance, compared to a wild host. In each case, we determine the evolutionarily stable (ES) par-

asite replication rate  $\varepsilon^*$  (Figs. 1, 2) and the corresponding level of virulence  $\alpha$  (Fig. 3). We then examine the effect on the epidemiological dynamics when a tolerant host replaces the wild type in two scenarios: one in which the parasite replication rate remains fixed (at the wild-type rate  $\varepsilon_W^*$ ) and one in which the replication rate evolves to its new optimum ( $\varepsilon_T^*$ ). The epidemiology is described by the prevalence of infection (Fig. 4), the total number of hosts dying from infection  $\alpha Y^*$  (Fig. 5), and the relative number of hosts dying from infection  $\alpha Y^*/H^*$  (Fig. 6). This last gives the average mortality due to infection (virulence,  $\alpha$ ) scaled by the probability that a given individual becomes infected (prevalence,  $Y^*/H^*$ ).

RESULTS

The ES parasite strategies are determined in the Appendix and summarized in Table 1. Here, we reproduce the key results and discuss their implications. Against the wild-type host that has not evolved tolerance, the optimal parasite strategy  $\varepsilon_W^*$ , and the corresponding virulence  $\alpha_W^*$  are given as (see eqs. A1–A7):

$$\varepsilon_W^* = \sqrt{\eta(\gamma + b)/v_W} \quad \text{and} \tag{4}$$

$$\alpha_W^* = \varepsilon_W^* v_W = \sqrt{v_W \eta(\gamma + b)}. \tag{5}$$

The optimal replication rate therefore increases with the recovery rate,  $\gamma$ , and the natural death rate,  $b$  (Lenski and May 1994; van Baalen and Sabelis 1995; Ebert and Mangin 1997; Restif and Koella 2003). Higher rates of loss from the infected class decrease the average duration of infection and therefore diminish the benefit of reduced virulence (van Baalen 1998).

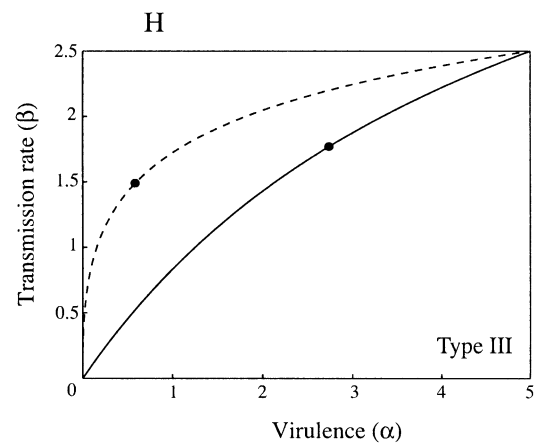
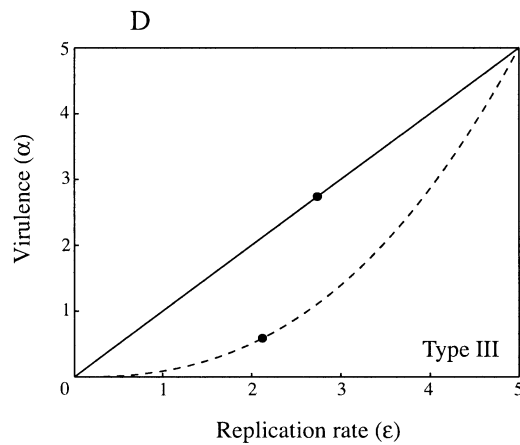
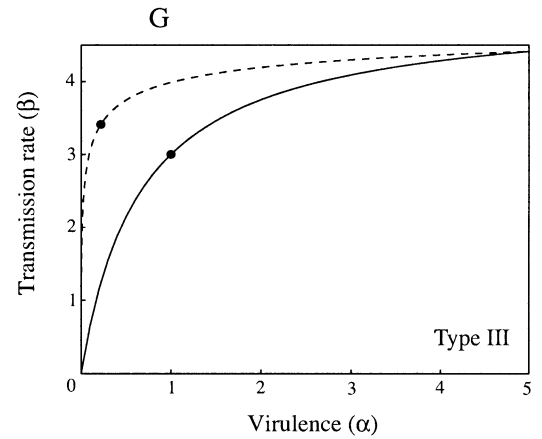
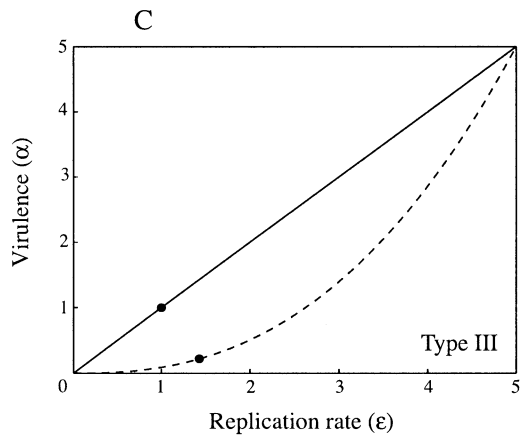
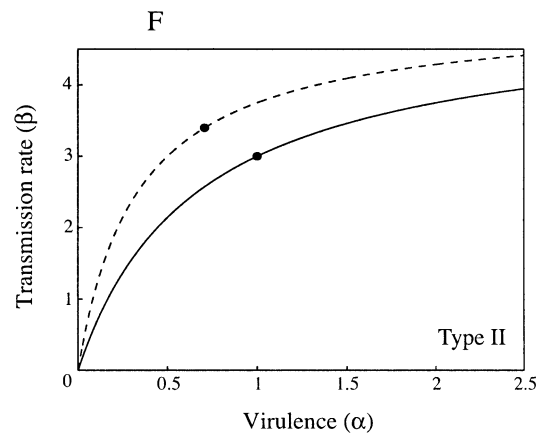
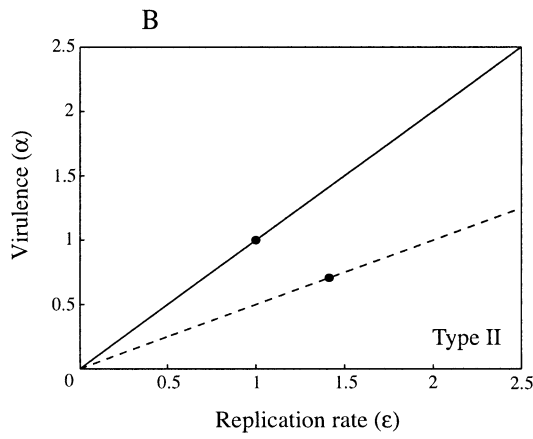
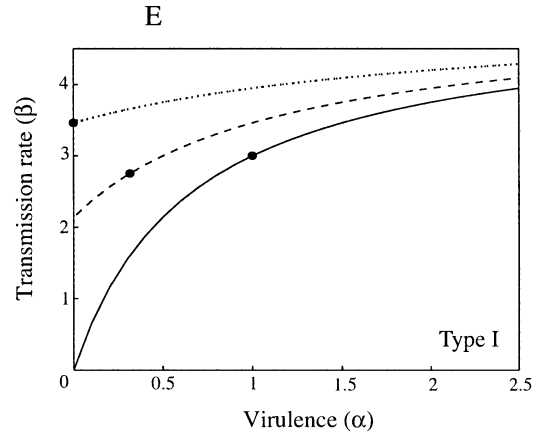
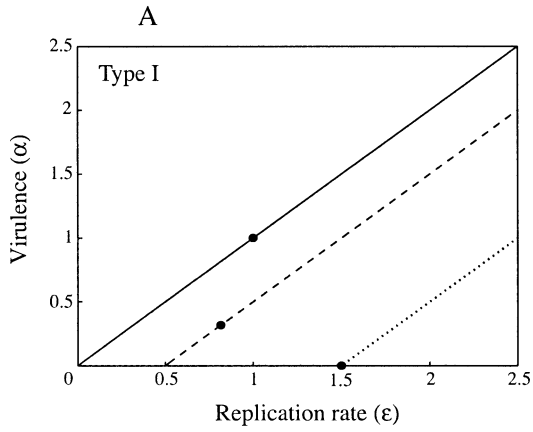
Type I (Complete) Tolerance

When the tolerance mechanism is complete (type I), the evolution of the parasite depends crucially on the extent to which the host can completely tolerate the parasite's growth rate. The optimal parasite strategy against the tolerant host ( $\varepsilon_T^*$ ) is given as (see eqs. A8–A11):

$$\varepsilon_T^* = \begin{cases} \sqrt{\eta(\gamma + b - \rho v_W)/v_W} & \text{if } \rho < \rho_c = \sqrt{\eta(\gamma + b)/v_W + \eta^2/4} - (\eta/2) \\ \rho & \text{if } \rho \geq \rho_c. \end{cases} \tag{6}$$

It can be shown that  $\rho_c < \varepsilon_W^*$  (see eq. A12). If the maximum growth rate the host can completely tolerate is significantly less than that of the ES wild-type parasite (such that  $\rho \leq \rho_c$ ), then tolerance selects for reduced parasite replication ( $\varepsilon_T^* < \varepsilon_W^*$ ), with positive but reduced rates of transmission and virulence (Figs. 1A, E). If  $\rho_c < \rho < \varepsilon_W^*$ , then a form of apparent

FIG. 1. Responses for different forms of the tolerance mechanism. The left panels plot virulence ( $\alpha$ ) as a function of the replication rate ( $\varepsilon$ ); the right panels give the corresponding transmission rate ( $\beta$ ) as a function of virulence. The solid lines give the trajectories when the host genotype is wild. Filled circles denote the evolutionarily stable replication rate, virulence, and transmission. Type I: (A, E) the tolerant host is characterized by  $\rho = 0.5$  (dashed line),  $\rho = 1.5$  (dotted line). Type II: (B, F) the tolerant host is characterized by  $v_T = 0.5$  (dashed line). Type III: (C, D, G, H) the tolerant host is characterized by  $a = 2.5$  (dashed line). In all cases  $\eta = 2/3$ , except in (D, H), where there is a higher rate of saturation,  $\eta = 5$ . Other parameters are:  $\gamma = 1$ ,  $b = 0.5$ ,  $K = 5$ ,  $v_W = 1$ , and  $m = 5$  (type III).



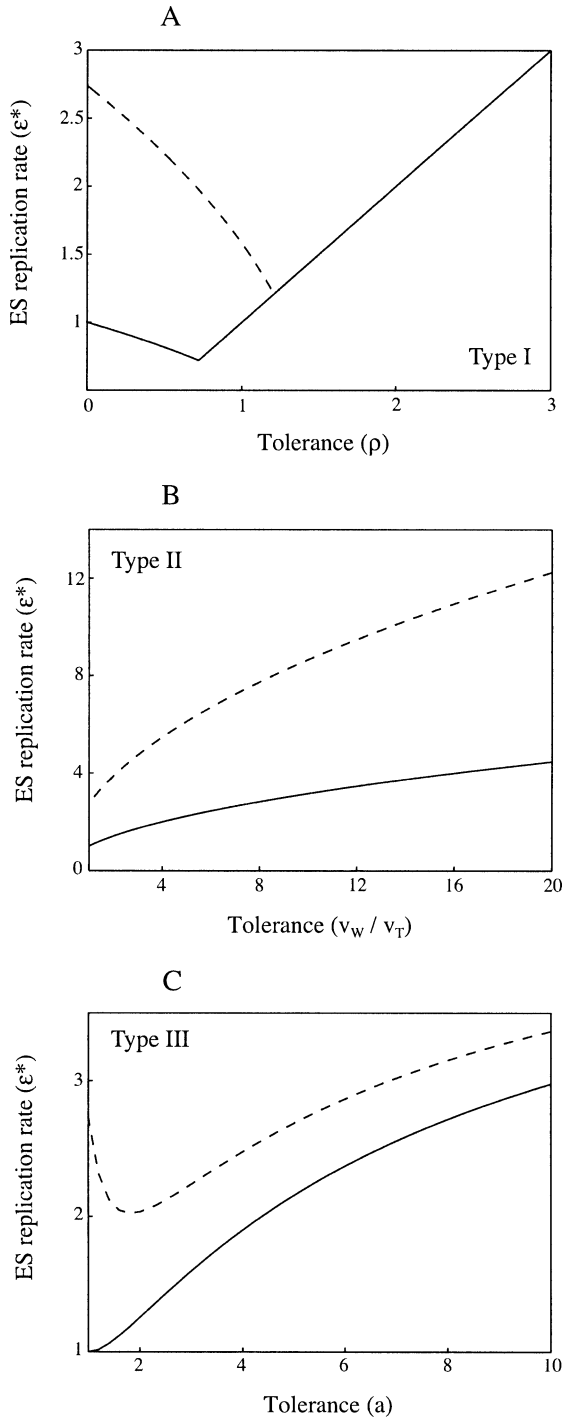


FIG. 2. Evolutionarily stable (ES) pathogen replication rate ( $\epsilon^*$ ) as a function of the level of tolerance. The rate at which transmission saturates is varied, such that  $\eta = 2/3$  (solid line),  $\eta = 5$  (dashed line). Other parameters are:  $\gamma = 1$ ,  $b = 0.5$ ,  $K = 5$ ,  $v_w = 1$ , and  $m = 5$  (type III).

commensalism evolves where the ES replication rate falls to the maximum value for which virulence is zero ( $\epsilon^* = \rho$ ). This also corresponds to a reduction in the parasite's transmission rate. If  $\rho > \epsilon_w^*$ , again the parasite evolves to the maximum replication rate for which virulence is zero ( $\epsilon^* =$

$\rho$ ), but this is now higher than that of the wild type (Fig. 1A). The transmission rate will also be correspondingly higher (Fig. 1E). The relationship between tolerance,  $\rho$ , and the ES replication rate,  $\epsilon^*$ , is illustrated in Figure 2A. The level of virulence,  $\alpha$ , experienced by infected hosts is always reduced when a tolerant genotype becomes fixed in the population (Figs. 3A, D).

The evolution of type I tolerance is likely to increase disease prevalence (Figs. 4A, D). This is due, in part, to the lower death rate of infected hosts, which also increases the opportunities for disease transmission (Roy and Kirchner 2000). The reduction in virulence associated with the evolution of tolerance may also reduce the number of hosts dying from infection  $\alpha Y^*$  (Fig. 5A). However, a reduction in virulence due to tolerance may sometimes result in greater total mortality, particularly if the level of tolerance is low (Fig. 5D). This counter-intuitive result can be explained by the following consideration. If the wild-type virulence (which is proportional to the parameter  $\eta$ ) is relatively low, then the initial prevalence of infection will tend to be high (Fig. 4A). The evolution of tolerance therefore generates a relatively small increase in prevalence compared to the reduction in virulence experienced by infected hosts. Thus, the number of infected mortalities is likely to decrease as tolerance increases (Fig. 5A). If, however, wild-type virulence is high, initial prevalence will be low and tolerance induces a relatively large increase in prevalence compared to the reduction in virulence (Fig. 4D). As a result, there often may be more infected mortalities in response to low tolerance. Mortality always decreases at high tolerance (Fig. 5D), where the reduction in virulence is sufficiently large to outweigh the increase in prevalence. If the parasite is selected, the described changes in the epidemiology occur at lower levels of tolerance, due to the evolutionary decrease in virulence. Prevalence increases more rapidly (Figs. 4A, D), and absolute mortality increases at lower levels of tolerance (Fig. 5D). When the host evolves complete (type I) tolerance, relative infected mortality is generally lower (Figs. 6A, D). If tolerance also selects the pathogen, there is a greater reduction in virulence (Figs. 3A, D) and in relative mortality. Even in cases where the absolute mortality increases in response to low tolerance (Fig. 5D), the relative mortality is still reduced (Fig. 6D).

*Type II (Constant) Tolerance*

Where tolerance manifests as a constant (type II) reduction in virulence, the optimal parasite replication rate and the corresponding virulence are given as (see eq. A13):

$$\epsilon_T^* = \sqrt{\eta(\gamma + b)/v_T} \quad \text{and} \quad (7)$$

$$\alpha_T^* = v_T \epsilon_T^* = \sqrt{v_T \eta(\gamma + b)}. \quad (8)$$

Fixation of the tolerant genotype increases the ES replication rate (because  $v_T < v_w$ ). Faced with a more robust host, the cost of a given level of replication in terms of virulence is reduced and this selects for higher parasite replication and transmission rates (Figs. 1B, 1F, 2B). The increase in replication rate (compared to  $\epsilon_w^*$ ) corresponds to an evolutionary increase in virulence and this reduces some of the benefit

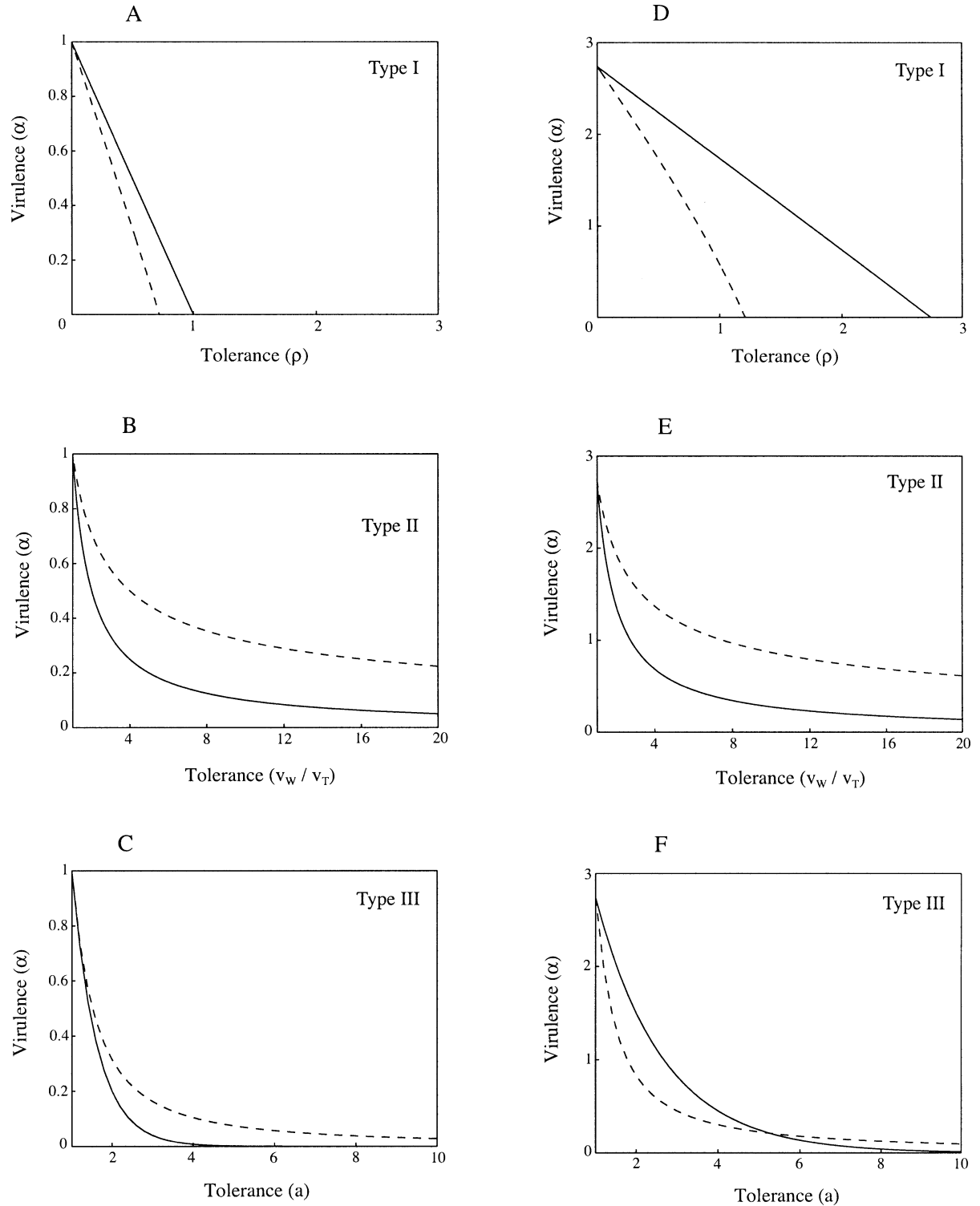


FIG. 3. Virulence ( $\alpha$ ) as a function of the level of tolerance. The solid line gives the virulence when the pathogen is wild type ( $\varepsilon = \varepsilon_W^*$ ); the dashed line gives the virulence when the pathogen is selected ( $\varepsilon = \varepsilon_S^*$ ). (A–C):  $\eta = 2/3$ ; (D–F):  $\eta = 5$ . Tolerance is costly in terms of a reduced intrinsic growth rate such that:  $r = 2 - 0.05\rho$  (type I),  $r = 2 - 0.05(v_W - v_T)/v_W$  (type II),  $r = 2 - 0.05(a - 1)$  (type III). Other parameters are:  $\gamma = 1$ ,  $q = 0.05$ ,  $b = 0.5$ ,  $K = 5$ ,  $v_W = 1$ , and  $m = 5$ (type III).

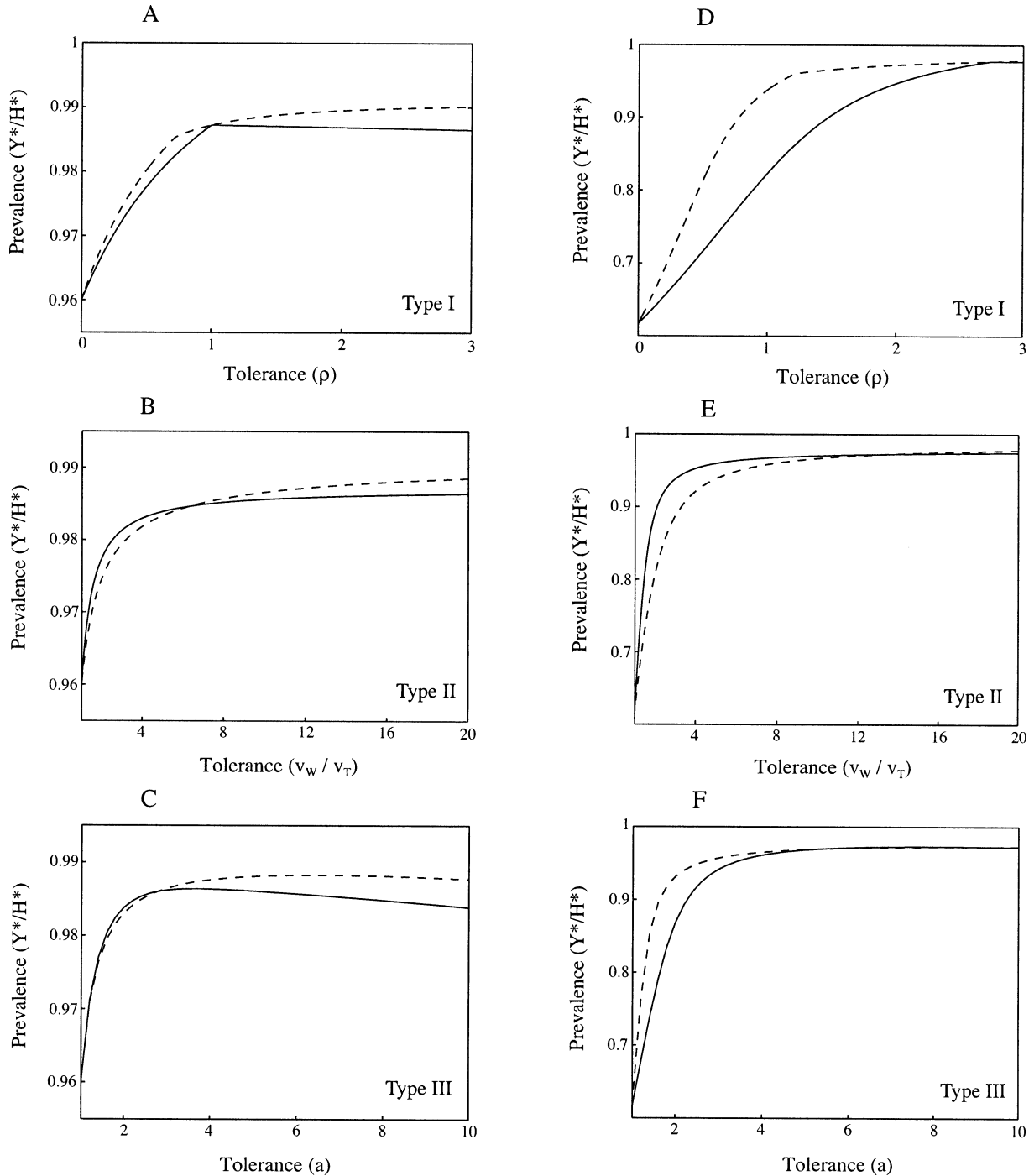


FIG. 4. Disease prevalence ( $Y^*/H^*$ ) as a function of the level of tolerance. The solid line gives the prevalence when the pathogen is wild type ( $\epsilon = \epsilon_w^*$ ); the dashed line gives the prevalence when the pathogen is selected ( $\epsilon = \epsilon_s^*$ ). (A–C):  $\eta = 2/3$ ; (D–F):  $\eta = 5$ . All other parameters are as in Figure 3.

conferred by the tolerance mechanism. However, the level of virulence experienced by the tolerant host is always less than that of the wild type (cf. eqs. 5 and 8; Figs. 3B, E).

Prevalence is likely to be higher in response to type II tolerance (Figs. 4B, E). If the parasite is selected, prevalence may increase less rapidly (Figs. 4B, E). This is not necessarily

the case at high tolerance, where pathogen evolution may increase prevalence still further (Fig. 4B). Fixation of a tolerant genotype will often reduce total mortality ( $\alpha Y^*$ ), particularly at low initial virulence (Fig. 5B). Alternatively, mortality may increase if the initial virulence is high. Indeed, if the pathogen evolves then mortality may be considerably

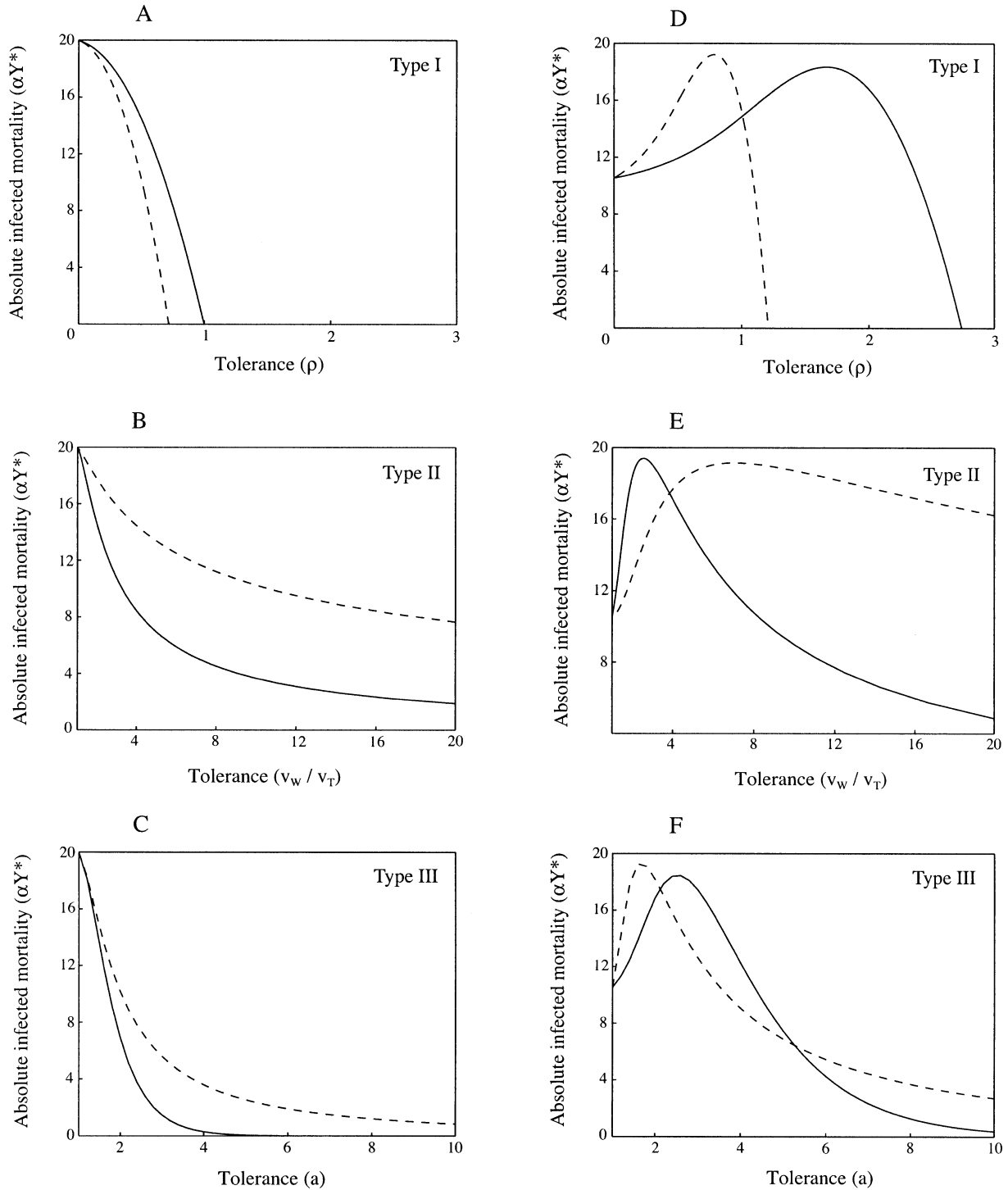


FIG. 5. Absolute infected mortality ( $\alpha Y^*$ ) as a function of the level of tolerance. The solid line gives mortality when the pathogen is wild type ( $\epsilon = \epsilon_{\text{w}}^*$ ); the dashed line gives mortality when the pathogen is selected ( $\epsilon = \epsilon_{\text{s}}^*$ ). (A–C):  $\eta = 2/3$ ; (D–F):  $\eta = 5$ . All other parameters are as in Figure 3.

higher, even at high tolerance (Fig. 5E). This result notwithstanding, tolerance is likely to reduce relative mortality ( $\alpha Y^*/H^*$ ). The decrease is always less when the pathogen is selected, due to the higher replication rate and virulence (Figs. 6B, E). Extensive computer simulations suggest that relative

mortality is generally reduced by type II tolerance, although it may increase if the parameter  $\eta$  is sufficiently large. For extremely large  $\eta$ , even a highly tolerant population may experience greater relative mortality when the pathogen is selected (results not shown).

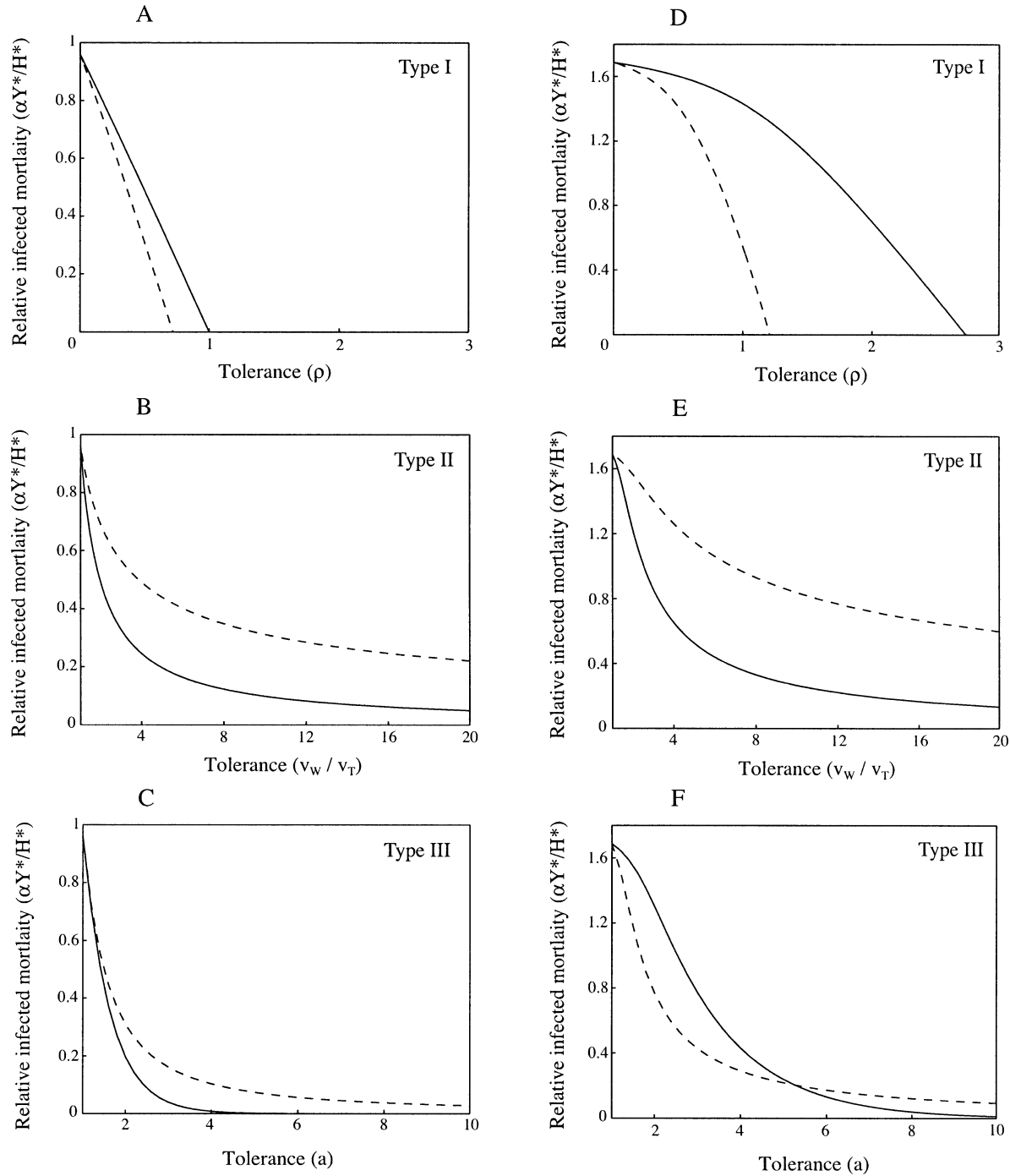


FIG. 6. Relative infected mortality ( $\alpha Y^*/H^*$ ) as a function of the level of tolerance. The solid line gives mortality when the pathogen is wild type ( $\varepsilon = \varepsilon_w^*$ ); the dashed line gives mortality when the pathogen is selected ( $\varepsilon = \varepsilon_s^*$ ). (A–C):  $\eta = 2/3$ ; (D–F):  $\eta = 5$ . All other parameters are as in Figure 3.

*Type III (Saturating) Tolerance*

The evolution of saturating tolerance may select for either higher or lower parasite replication rates, compared to a wild-type host. Here, the parameter  $\eta$  strongly influences the evolutionary outcome. When  $\eta$  is small, transmission saturates relatively quickly and tolerance generally selects for increased replication and transmission rates (Fig. 1C, 1G, 2C).

This eliminates some of the benefit of tolerance in terms of reduced virulence but never increases virulence above the level experienced by the wild-type host (Fig. 3C). At larger values of  $\eta$ , tolerance may select for either increased or decreased replication rates. Slower replicating pathogens are more likely to be selected if the tolerance mechanism is weak (Figs. 1D, 2C); this will lower the transmission rate (Fig.



TABLE 1. Evolutionarily stable pathogen replication rates for different forms of tolerance.

	Evolutionarily stable pathogen replication rate ( $\varepsilon = \varepsilon^*$ )
Wild-type host	$\sqrt{\eta(\gamma + b)/v_W}$
Type I (complete)	$\sqrt{\eta(\gamma + b - \rho v_W)/v_W}$ if $\rho < \rho_C = \sqrt{\eta(\gamma + b)/v_W + \eta^2/4} - (\eta/2)$ $\rho$ if $\rho \geq \rho_C$
Type II (constant)	$\sqrt{\eta(\gamma + b)/v_T}$
Type III (saturating)	The optimal strategy, $\varepsilon = \varepsilon^*$ , is given by solution of: $\varepsilon(\varepsilon + \eta)av_W(\varepsilon/m)^{a-1} - \eta v_W m(\varepsilon/m)^a = \eta(\gamma + b)$

1H) and further reduce virulence (Fig. 3F). High levels of tolerance are always likely to select for more exploitative pathogens (Fig. 2C). Computer simulations also suggest that when  $v_W$  is large, tolerance is more likely to select for faster replicating pathogens.

As with the previous two forms, saturating tolerance generally increases prevalence (Figs. 4C, F). If the pathogen evolves a lower replication rate, the increase in prevalence will be greater (Fig. 4F). When initial virulence is low, the evolution of tolerance generally reduces absolute infected mortality  $\alpha Y^*$  (Fig. 5C). At higher initial virulence, low levels of tolerance may result in greater absolute mortality (Fig. 5F). More efficient tolerance mechanisms are likely to reduce absolute mortality (Fig. 5F), where the reduction in virulence outweighs the increase in prevalence. These same results are obtained when the pathogen is selected, although the extent of the increase or decrease in mortality depends on whether the evolved replication rate ( $\varepsilon^*$ ) is higher or lower than the wild type ( $\varepsilon_W^*$ ) and on the balance between prevalence and virulence in terms of their effect on mortality (Fig. 5F). Saturating tolerance is likely to reduce the relative infected mortality ( $\alpha Y^*/H^*$ ), regardless of whether absolute mortality ( $\alpha Y^*$ ) increases or decreases (Figs. 6C, F). If the pathogen is selected to increase (decrease) its replication rate, then the reduction in mortality is less (more) pronounced (Fig. 6C).

### Conclusions

To summarize the epidemiological effects, the evolution of host tolerance generally increases disease prevalence (Fig. 4). Consequently, the number of pathogen-induced deaths ( $\alpha Y^*$ ) may actually increase, if the tolerance mechanism is weak and the initial virulence ( $\alpha_W^*$ ) is high (Figs. 5D–F). When the wild-type host experiences less severe virulence, tolerance is more likely to reduce absolute mortality (Figs. 5A–C). A high degree of tolerance always results in less absolute mortality, unless the mechanism is constant (type II) and the wild-type virulence ( $\alpha_W^*$ ) is high (Fig. 5E). The relative mortality due to infection ( $\alpha Y^*/H^*$ ) is generally lower in tolerant populations (Fig. 6). An exception to this may occur with constant (type II) tolerance: if transmission saturates particularly slowly, then pathogen evolution may result in greater relative mortality, even at high tolerance.

### DISCUSSION

We have shown how the evolution of tolerance in hosts may act as an important selective pressure on parasites. The evolutionary outcome is dependent on the nature of the tolerance mechanism. When tolerance reduces death rate by a constant factor (type II), it always selects for higher parasite replication rates. This is a somewhat intuitive result: the parasite responds to tolerance due to its ability to gain more transmission without paying as large a cost in terms of host death. However, the post-selection parasite-induced death rate never reaches the level prior to the evolution of the tolerance mechanism, implying some of the benefit of tolerance is lost, but not all of it. Because tolerance increases prevalence, there is also the possibility that it leads to greater total mortality in the population. Whether absolute mortality increases or decreases will depend not only on the degree of tolerance that evolves, but also the initial virulence of the pathogen in wild-type hosts. However, even if the number of deaths due to infection increases, the relative chance of any individual in the population dying of infection will probably be less.

When a tolerance mechanism evolves that is able to completely compensate for the damage the parasite causes at particular growth rates, there is the possibility of evolution from parasitism to commensalism. This is always the outcome if the natural, wild-type parasite growth rate can be completely tolerated. Furthermore, if parasite strains with a higher growth rate than that of the ES wild type can be completely tolerated, the parasite will evolve to this higher growth rate, leading not only to commensalism, but also a higher level of transmission. Less intuitively, commensalism can also evolve if the level of complete tolerance is less than but relatively close to the natural ES growth rate. The parasite evolves to reduce its growth rate to the level that can be completely tolerated. In this case, transmission rate is reduced, although prevalence still increases. Complete (type I) tolerance therefore potentially selects for a parasite strain that causes no virulence, although this is not always the outcome. If the parasite growth rate that can be completely tolerated is significantly below that of the wild parasite, commensalism will not evolve. It should be noted that when commensalism does evolve, the resulting commensal's growth rate within the host is still constrained by a transmission-virulence trade-off. The distinction between commensal and parasitic, in many groups of microorganisms in particular, is often far from clear-cut. Species considered commensal may therefore be on the edge of parasitism with some strains causing damage to their hosts. Furthermore, when commensalism evolves through tolerance mechanisms in the host, there is likely to be a cost for the host. Once established, this apparent commensalism shows no evidence of this evolutionary cost. It is interesting to speculate how many seemingly commensal interactions in nature have been bought at an evolutionary cost to the host. In such interactions, the removal of the commensal may lead to benefits for the host if evolution selects against the redundant tolerance mechanism.

Saturating (type III) tolerance is similar to complete tolerance in that the mechanism is particularly efficient at tolerating relatively low replication rates. Indeed, the evolu-

tionary dynamics are often similar. Low levels of tolerance may select for reduced parasite replication, although evolution to complete commensalism does not occur. That being said, interactions with parasite strains that cause very little virulence to their hosts may often evolve. Given the difficulty in measuring costs to parasites in the wild, such low levels of virulence may often not be detected. Saturating tolerance mechanisms may also therefore lead to the evolution of interactions that are thought to be commensal. Again these interactions will be characterised by high disease prevalence and as such they are likely to be relatively stable.

In relation, the evolution of host tolerance may be partly responsible for the ubiquity of parasites in nature. Roy and Kirchner (2000) noted that because tolerance leads to higher prevalence of the parasite, it more easily allows their persistence. Our work lends support to this idea because, although the parasite increases its growth rate and transmission in the face of tolerance, it never attains the level of virulence prior to the evolution of tolerance. Individual selection for the evolution of tolerance, its tendency to become fixed in populations, and the subsequent individual selection on the parasite may have had important effects on shaping communities in nature. Parasites are ubiquitous in nature, and tolerance in their hosts may therefore have contributed to this.

Tolerance is most often implicated in plant host–natural enemy interactions. The implications of tolerance to herbivores have received considerable theoretical and empirical attention (Fineblum and Rausher 1995; Mauricio et al. 1997; Strauss and Agrawal 1999; Tiffin and Rausher 1999; Tiffin 2000). Tolerance in plants to infectious organisms is also being increasingly considered in both crop (Zuckerman et al. 1997; Schurch and Roy 2004) and model systems (Simms and Triplett 1994; Kover and Schaal 2002). Although there is some debate regarding definitions, there is an increasing awareness that tolerance rather than other resistance mechanisms is most important in a number of host–parasite interactions. Schurch and Roy (2004) have suggested that tolerance may be nonlinear and more likely to operate at low virulence. They note that in such cases, there may be no clear relationship between pathogen growth and host damage, because the deleterious effects of less virulent pathogens are ameliorated, whereas virulent strains inflict significant fitness losses to the host. This resembles saturating (type III) tolerance in our definition. Given that pathogens may evolve lower replication rates in the face of such tolerance, this may be responsible for maintaining low virulence in these interactions.

The selective pressures caused by tolerance are different from those of resistance mechanisms that reduce the reproductive rate of the parasite. Understanding whether any response to infectious organisms is tolerance or other forms of resistance is therefore vital if the final outcome of evolution is to be predicted. Tolerance mechanisms have received relatively little attention in animal–parasite interactions. Various forms of resistance are generally implicated in both the innate and acquired immune systems (Rolff and Siva-Jothy 2003). Whether tolerance mechanisms in animals really are rare remains to be determined and due to the importance of selection on parasites, it is a priority area.

There is a growing interest in the use of parasite-tolerant crop plants as alternatives to chemical control. Our work emphasises that it is important to consider selection on the target parasites. Their evolution may lead to higher disease prevalence with lower, but still significant damage to the host. High levels of tolerance are more likely to be successful at reducing absolute mortality. Perfect or very high levels of tolerance should therefore ideally be achieved before the widespread use of tolerant crops to reduce the problems of selection on the parasites, although there may still be concerns if the tolerance mechanism is constant (type II). If pathogen damage is measured as the individual risk of dying from infection (relative infected mortality), problems appear less likely. However, if the tolerance mechanism is constant in response to a wide range of parasite growth rates, then pathogen evolution may result in greater prevalence and mortality even in highly tolerant populations.

Throughout our study, we have assumed only single infections. However, infected hosts may often harbor more than one parasite strain simultaneously. Models generally predict that multiple infection will select for higher virulence and the coexistence of multiple parasite strains (Bremermann and Pickering 1983; Frank 1992, 1994, 1996; May and Nowak 1994, 1995; Nowak and May 1994; van Baalen and Sabelis 1995; Mosquera and Adler 1998). There has been relatively little work on host–parasite coevolution with the assumption of multiple infections. However, Gandon et al. (2002b) have shown that reducing the force of transmission may select for lower virulence by reducing the level of competition between parasite strains. Indeed, any mechanism (of the host or otherwise) affecting the probability of multiple infections will indirectly influence the evolution of virulence (Gandon et al. 2002b). Because tolerance is likely to increase disease prevalence (Roy and Kirchner 2000), it may also increase the level of competition between parasite strains. Assuming within-host exploitation rates are positively correlated with competitiveness, this would select for increased virulence. This is perhaps particularly important in the case of type II (constant) tolerance, where virulence might be restored to (or exceed) its pretolerance level. If instead, within-host competition (and virulence) is negatively correlated with host exploitation (Chao et al. 2000), by increasing the level of infection in the population, tolerance may conceivably select for reduced virulence. In superinfecting parasites, where the more virulent strains are more likely to be transmitted (Nowak and May 1994; Mosquera and Adler 1998), the evolution of reduced exploitation rates (type I and III tolerance) may well be constrained, as less exploitative parasites are selected against. These conclusions are somewhat speculative, however, and future work on the evolution of parasites in response to tolerance should consider the role of multiple infections in detail.

We have shown how tolerance can select parasites to increase their replication rate within the host. Tolerance may only evolve in particular local populations of hosts. The implications for nontolerant hosts coming into contact with a parasite that has evolved in response to tolerance in another population may be severe. Type II (constant) tolerance always selects for more exploitative parasites. The levels of virulence experienced by intolerant hosts exposed to an evolved path-

ogen may therefore be significantly higher than those optimal for the pathogen, and intolerant populations may suffer catastrophic levels of mortality. There are also problems when tolerance results in apparent commensalism. As demonstrated, commensal strains may have evolved higher replication and transmission rates. Intolerant hosts coming into contact with an evolved parasite would again experience high levels of virulence and transmissibility. The emergence of disease from seemingly commensal organisms may therefore occur without changes in the parasite but due to a lack of tolerance mechanisms in new host populations.

We have emphasized how tolerance mechanisms can have important implications to the life histories of parasites and pathogens. Tolerance tends to be underresearched in animal-parasite interactions but may have been important in shaping their community structure. The form of the tolerance mechanism has been shown to determine the selective pressure acting on parasites. A mechanistic understanding of tolerance is vital if we are to understand its role in natural host-parasite and seemingly commensal interactions.

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#### APPENDIX

In the absence of any infection, the host population ( $X$ ) grows until it reaches its carrying capacity,  $C = r/q$ . This uninfected equi-

librium will be invaded by a parasite strain with replication rate  $\varepsilon$ , if and only if the parasite's reproductive ratio ( $R_0$ ) is greater than unity. The reproductive ratio is given as (Anderson and May 1981, 1982; van Baalen and Sabelis 1995; Frank 1996):

$$R_0 = \frac{\beta(\varepsilon)C}{\alpha(\varepsilon) + \gamma + b}. \tag{A1}$$

We assume that  $R_0 > 1$  for all parasite strains in this study. Assume the host-parasite interaction with replication rate  $\varepsilon_1$  (strain 1) attains a positive stable equilibrium ( $X_1^*, Y_1^*$ ), found by equating the right hand side of equations (1) and (2) to zero. In particular:

$$X_1^* = \frac{[\alpha(\varepsilon_1) + \gamma + b]}{\beta(\varepsilon_1)}. \tag{A2}$$

The evolutionary dynamics of the parasite are determined using invasion analysis. We examine whether a parasite strain with a different replication rate  $\varepsilon_2$  (strain 2) can invade the resident equilibrium set by strain 1. From equation (2) the parasite strain 2 can invade if and only if:

$$\beta(\varepsilon_2)X_1^* - [\alpha(\varepsilon_2) + \gamma + b] > 0. \tag{A3}$$

By direct substitution of  $X_1^*$  (using eq. A2) into equation (A3) we find that strain 2 can invade if and only if:

$$\frac{\beta(\varepsilon_2)}{\alpha(\varepsilon_2) + \gamma + b} > \frac{\beta(\varepsilon_1)}{\alpha(\varepsilon_1) + \gamma + b}. \tag{A4}$$

It is clear from equation (A4) that mutual invadability cannot occur and therefore any strain satisfying (A4) will replace the resident. If we define:

$$S(\varepsilon) = \frac{\beta(\varepsilon)}{\alpha(\varepsilon) + \gamma + b}, \tag{A5}$$

then the parasite evolves to maximize  $S(\varepsilon)$  and the unique global maximum of  $S(\varepsilon)$  is the ES parasite strategy  $\varepsilon^*$ . Substituting the functional form for  $\alpha(\varepsilon)$  and  $\beta(\varepsilon)$  for the wild-type host, that has not evolved any tolerance, into (A5) implies the following:

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon + \eta)(\varepsilon v_W + \gamma + b)}. \tag{A6}$$

Solving  $dS(\varepsilon)/d\varepsilon = 0$ , we obtain the ES parasite strategy:

$$\varepsilon_W^* = \sqrt{\eta(\gamma + b)/v_W}. \tag{A7}$$

*Type I (Complete) Tolerance*

Let us first consider the case  $\varepsilon \leq \rho$ , which implies that  $\alpha = 0$ . Here:

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon + \eta)(\gamma + b)} \Rightarrow \frac{dS(\varepsilon)}{d\varepsilon} = \frac{\eta K}{(\varepsilon + \eta)^2(\gamma + b)} > 0. \tag{A8}$$

Since  $dS(\varepsilon)/d\varepsilon$  is always positive, it implies that  $S(\varepsilon)$  is an increasing function and so is maximized when  $\varepsilon = \rho$ . Now consider  $\varepsilon > \rho$ . Here:

$$S(\varepsilon) = \frac{\varepsilon K}{(\varepsilon + \eta)[(\varepsilon - \rho)v_W + \gamma + b]}, \tag{A9}$$

which is maximized at  $\varepsilon_W^*$ , by solving  $dS(\varepsilon)/d\varepsilon = 0$ , where:

$$\varepsilon_T^* = \sqrt{\eta(\gamma + b - \rho v_W)/v_W}. \tag{A10}$$

Here the condition for the host to have positive density ( $X^* > 0$ ) ensures that  $\varepsilon_W^*$  is positive. The parasite will evolve to  $\varepsilon_W^*$  provided  $\rho < \varepsilon_W^*$ . This requires that:

$$\rho < \rho_C = \sqrt{\eta(\gamma + b)/v_W + \eta^2/4} - (\eta/2). \tag{A11}$$

Substituting for  $\varepsilon_W^*$  from (A7) into (A11), it is possible to show that:

$$(\rho_C + \eta/2)^2 = (\varepsilon_W^*)^2 + \eta^2/4 \Rightarrow (\rho_C)^2 + \eta\rho_C = (\varepsilon_W^*)^2. \tag{A12}$$

Since all parameters are positive, this implies  $\rho_C < \varepsilon_W^*$ .

*Type II (Constant) Tolerance*

Replacing  $v_W$  with  $v_T$  in equations (A6) and (A7) gives the optimal parasite strategy:

$$\varepsilon_T^* = \sqrt{\eta(\gamma + b)/v_T}. \tag{A13}$$

*Type III (Saturating) Tolerance*

Numerical simulations are used to determine the optimal parasite strategy. This is given by the value  $\varepsilon = \varepsilon_W^*$  satisfying:

$$\varepsilon(\varepsilon + \eta)av_W(\varepsilon/m)^{a-1} - \eta v_W m(\varepsilon/m)^a = \eta(\gamma + b). \tag{A14}$$