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A UNIFIED MODEL FOR THE COEVOLUTION OF RESISTANCE, TOLERANCE, AND VIRULENCE

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We present a general host–parasite model that unifies previous theory by investigating the coevolution of virulence, resistance, and tolerance, with respect to multiple physiological, epidemiological, and environmental parameters. Four sets of new predictions emerge. First, compared to virulence coevolving with resistance or tolerance, three-trait coevolution promotes more virulence and less tolerance, and broadens conditions under which pure defenses evolve. Second, the cost and efficiency of virulence and the epidemiological rates are the key factors of virulence coevolving with resistance and tolerance. Maximum virulence evolves for intermediate infection rate, at which coevolved levels of resistance and tolerance are both high. The influence of host and parasite background mortalities is strong on the evolution of defenses and weak on the coevolution of virulence. Third, evolutionary correlations between defenses can switch sign along single-parameter gradients. The evolutionary trade-off between resistance and tolerance may coevolve with virulence that either increases or decreases monotonically, depending on the underlying parameter gradient. Fourth, despite global attractiveness and stability of coevolutionary equilibria, not-so-rare and not-so-small mutations can beget large variation in virulence and defenses around equilibrium, in the form of transient "evolutionary spikes." Implications for evolutionary management of infections are discussed and directions for future research are outlined.

KEY WORDS: **Adaptive dynamics, host defense, infection, parasitism, pathogen, trade-offs.**

Host–parasite interactions pervade living systems, and understanding how parasite virulence and host defense evolve is a matter of major fundamental and applied interest across biological, agricultural, and health sciences (Woolhouse et al. 2002). This had led the development of a large body of mathematical theory, yet thus far most of the theory has focused on the evolution of a single species, and models that examine parasite virulence and host defense as continuous characters that coevolve remain relatively few (e.g., Hochberg and van Baalen 1998; van Baalen 1998; Gandon et al. 2002; Koella and Boete 2003; Restif and Koella 2004; Bonds 2006; Best et al. 2009; see also Dieckmann et al. 2002 for an overview).

In long-lasting, often specialized and in some cases obligate pairwise interactions, it is expected, however, that as one species evolves, selective pressures on the other change (e.g., Thompson 1994). Selection on parasite virulence involves a trade-off between within-host reproduction (replication resulting from exploitation of the host) and within-host survival (as affected by exploitation-induced host mortality) mediated at between-host level by transmission success (Anderson and May 1979; Frank 1996; Alizon et al. 2009). In response, there are basically two ways for the host to defend itself: with resistance, the host fights the parasite to prevent or limit exploitation; with tolerance, the host fights the "disease" to prevent or limit the adverse effect of

exploitation. Resistance implies that the host invests resources into mechanisms (avoidance, control, recovery) that cause a reduction in the fitness of the parasite; tolerance implies that the host invests resources to limit its own fitness reduction by reducing the damage that the parasite causes (Clarke 1986; Barker 1993; Boots 2008). The significance of tolerance as a plant defense against herbivory is well known, and recent empirical research suggests that tolerance is a widespread host response to parasitic infection, not only in plants but also in animals (Simms and Triplett 1994; Kover and Schaal 2002; Carr et al. 2006; Raberg et al. 2007; Boots 2008; Raberg et al. 2009). Genetic variation in tolerance has been evidenced in experimental systems (Rausher 2001; Kover and Schaal 2002), and genetic data are now unraveling molecular mechanisms of coevolution with virulence (Ayres and Schneider 2008).

In the coevolutionary perspective, the distinction between resistance and tolerance is a fundamental one, because resistance and tolerance have radically different ecological and epidemiological consequences and therefore generate very different evolutionary feedbacks on virulence (Roy and Kirchner 2000; Boots 2008). Resistance has a negative effect on parasites, whereas tolerance does not. As they live longer when infected, tolerant hosts increase the infectious period of the parasite. This means that selection for tolerance will tend to increase the prevalence of the disease. In contrast, the evolution of resistance, by definition, decreases parasite fitness and reduces the infection prevalence. Emerging theory has begun to shed light on the evolutionary implications of this fundamental ecological difference. Tolerance alleles are likely to be promoted by positive frequency-dependent selection (Roy and Kirchner 2000) and quantitative models have been developed to compare the cost for the host to evolve either resistance or tolerance against a nonevolving parasite (Miller et al. 2005). When tolerance evolves, the evolutionary feedback on the parasite can drive the evolution of high virulence (Restif and Koella 2003; Miller et al. 2006). Data and models show that selection can favor mixed defenses, combining resistance and tolerance (Mauricio et al. 1997; Fornoni et al. 2004; Restif and Koella 2004). This begs the question of how the evolution of high virulence promoted by tolerance feeds back on the evolution of both defenses, and ultimately how the concurrent evolution of resistance and tolerance shapes coevolution with virulence. Addressing these questions requires that previous theory be extended and unified in a model in which all three traits—resistance, tolerance, and virulence—can coevolve.

The model presented here combines the ecological process of host–parasite interaction with the evolutionary process fueled by heritable variation in virulence and defenses. Evolution of a trait changes the ecological state of the system and the epidemiology of infection, which feeds back on selection on all traits and thus entangles the evolutionary dynamics of the two species (Fig. 1A). The ecological model was designed to integrate several key physiological, environmental, and epidemiological factors of host and parasite population dynamics (Fig. 1B, C). At the physiological level, the resources allocated to the traits (virulence in the parasite, defenses in the host) are diverted from reproductive potential, and the corresponding reproductive cost functions can be accelerating as well as decelerating (Miller et al. 2005, Best et al. 2009). With respect to environmental and epidemiological factors, the model accounts for a free-living stage in the parasite population: infected hosts release parasite propagules. The propagules' longevity is determined in part by their "background mortality" that thus becomes an environmental factor of the coevolutionary process (Bonhoeffer et al. 1996; Day 2001). Infection occurs upon contact between a susceptible host and a propagule. Transmission depends upon a propagation factor—the rate at which an internalized parasite uses resources exploited from the host to produce infectious propagules; and the infection rate—the frequency of encounters between susceptible hosts and free-living parasites. The host population is regulated by density dependence of the birth rate, while the parasite population is kept from growing unbounded by the obligate nature of the interaction.

We organize the model analysis around three general questions: (1) How do physiological, environmental, and epidemiological parameters affect resistance–tolerance coevolution? (2) How does the nature of host defense—resistance versus tolerance—affect virulence evolution? (3) How does the concurrent evolution of all three traits alter the patterns of resistance–tolerance covariation predicted under fixed virulence and the response of virulence to variation in physiological, environmental, and epidemiological parameters? We answer these questions by examining two-trait (resistance–tolerance, virulence–resistance, virulence–tolerance) and three-trait (virulence–resistance–tolerance) evolutionary equilibria. Evolutionary convergence and stability of the equilibria is studied under the assumption of small, rare, and independent genetic variation in the traits. Finally, an invasion analysis is performed to examine the consequences of not-so-small and not-so-rare mutations for the maintenance of variation in virulence, resistance, and tolerance.

Model Construction and Analysis

We consider the coevolution of resistance, tolerance, and virulence between a host and an obligate endoparasite (Fig. 1). The parasite has a free-living, infectious stage. Transmission is purely horizontal (the consequences of vertical transmission have also been studied and will be presented elsewhere). Infection happens upon contact and there is no multiple infection. The endoparasite exploits its host's resources to produce infectious propagules in the free-living stage. Virulence is expressed in terms of endoparasite reproductive success at the expense of host survival.

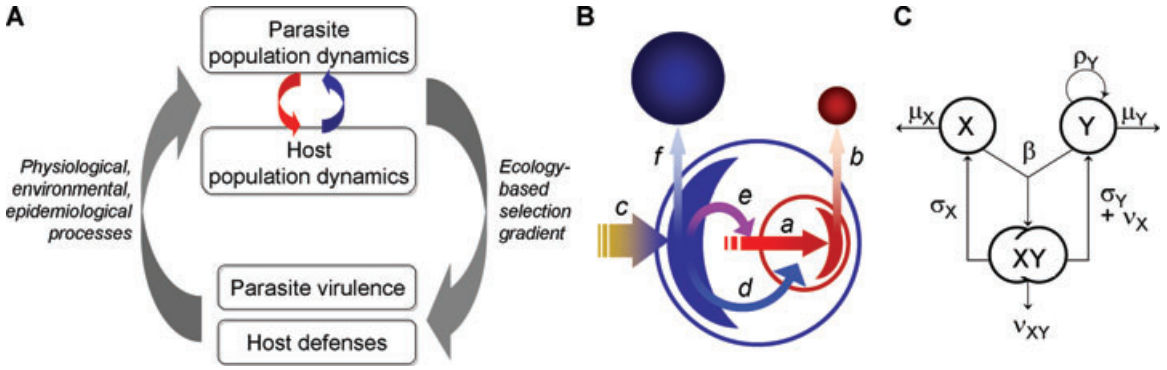

Figure 1. **Theoretical principles and model structure. (A) Host–parasite coevolutionary dynamics driven by ecogenetic feedback. Resident trait values set the ecological state of the system, given physiological, environmental, and epidemiological parameters (assumed to be constant). The ecological state generates selective pressures on the genetic variation that arise from mutation in the resident populations. Thus, heritable variation in the individual traits changes the system's ecology, and variation in the ecology feeds back, via selection, on trait variation. Iteration of this ecogenetic feedback loop determines the long-term evolutionary dynamics of the adaptive traits. Note that variation in the trait(s) of one species will change the ecology of the whole system and therefore the selective pressures acting on genetic variation in this species and the other as well, thus entangling both species in a coevolutionary process. Similarly, physiological, environmental, and epidemiological parameters pertaining to one species may affect the whole ecology and thus the selective pressures experienced by both species. (B) Physiological model of virulence, resistance, and tolerance. A parasite (small red circle) is shown as internalized in its host (large blue circle). Metabolized resources that are potentially available for parasite and host reproduction are indicated by the small red and large blue crescents, respectively. Virulence is defined as the fraction of somatic (nonreproductive) energy that the host loses to the parasite (*a*). This energy discounted by the cost of virulence is available for production (*b*) of free-living parasites (small red sphere). The host acquires resources from the external environment (*c*). Metabolized resources can be invested in resistance (*d*) which decreases parasite survival; in tolerance (*e*) which reduces the negative impact of virulence on host survival. Metabolized resources discounted by the cost of investments in resistance and tolerance are available for production (*f*) of new susceptible hosts (large blue sphere). (C) Ecological model of host and parasite population dynamics. Susceptible hosts reproduce at (density-dependent) rate ρ_Y and die at rate μ_Y. Free-living parasites die at rate μ_X and infect hosts at rate β. Infected hosts die at rate ν_{XY}, produce free-living parasites at rate σ_X and susceptible hosts either by host reproduction (no vertical transmission) at rate σ_Y or by clearance and recovery (death of infecting parasite) at rate ν_X. We use a modified version of the original Kostitzin model in which the linear density dependence of birth that regulates the host population is replaced with a more realistic nonlinear (saturating) function of density (see van Baalen and Jansen 2001 for a similar adjustment).**

Resistance increases the endoparasite's within-host mortality rate whereas tolerance reduces the host mortality risk caused by the parasite. The cost of a trait is paid in terms of reduced reproductive potential.

For given virulence, resistance and tolerance trait values, we construct the epidemiological model of the system; the model governs the ecological dynamics of the parasite and host populations. Next we allow for genetic variation in the traits. Deterministic equations for the coevolutionary dynamics of the traits are obtained under the assumption of small and rare mutations. The analysis of the selection gradient yields insights into the consequences of larger and more frequent mutations on the traits dynamics around evolutionary equilibrium.

ECOLOGICAL MODEL

The biological assumptions are translated mathematically by using an epidemiological SIS model that includes a free-living stage for the parasite (Bonhoeffer et al. 1996; Day 2001), and negative density dependence of the birth rate of susceptible and infected hosts (Kostitzin 1934; Wolin 1985); see Figure 1. The parasite species is denoted by X (population density X) Susceptible hosts have density Y and infected hosts have density Z. Parasitism is obligate in the sense that parasites cannot reproduce in their free-living stage. From the infected stage Z, hosts can give birth to susceptible individuals Y, and internalized parasites can give birth to free-living propagules X. The assumption of no vertical transmission implies that Z individuals cannot give birth to new Z individuals. Death of an infected host implies the death of the associated parasite X. Death of an infecting parasite can be caused by intrinsic mortality or by host resistance, and returns a recovered, susceptible host Y.

The model parameters are defined as follows. Free-living parasites X die at a per capita rate $\mu_X = \mu_{0X} + \mu_{1X}$, where μ_{0X} denotes the intrinsic mortality rate of X and μ_{1X} is the background mortality rate of X due to environmental hazards. Free-living parasites infect susceptible hosts at rate β according to the law of mass action on densities X and Y. Finally, new free-living parasites are produced from infected hosts at rate σ_X. The rate of change of

free-living parasite density X is therefore given by

$$dX/\mathrm{d}t = -\mu_X X - \beta XY + \sigma_X Z. \quad (1A)$$

Susceptible hosts reproduce at per-capita rate ρ_Y and die at per-capita rate $\mu_Y = \mu_{0Y} + \mu_{1Y}$, where μ_{0Y} is the host per-capita intrinsic mortality rate and μ_{1X} is the host background mortality rate due to environmental hazards. Infection removes hosts from the susceptible population at rate β. New susceptible hosts are produced from infected hosts at per-capita rate $(\sigma_Y + \nu_X)$ where σ_Y measures the rate of reproduction of infected hosts (there is no vertical transmission) and ν_X denotes the rate of mortality of an internalized parasite, which in effect clears the infection and returns a susceptible host. Hence the rate of change of susceptible host density Y is:

$$\mathrm{d}Y/\mathrm{d}t = (\rho_Y - \mu_Y)Y - \beta XY + (\sigma_Y + \nu_X)Z. \quad (1B)$$

Finally, the density of infected hosts changes due to contact between X and Y (rate β), death of infecting parasite at per-capita rate ν_X, and death of infected hosts at per-capita rate ν_{XY}:

$$\mathrm{d}Z/\mathrm{d}t = \beta XY - (\nu_X + \nu_{XY})Z. \quad (1C)$$

Equations (1A–C) thus determine the epidemiological dynamics of the system. The birth and death rates involved are potentially affected by parasite virulence and host defenses. Virulence, resistance, and tolerance are modeled as continuous traits, denoted by x_1, y_1, and y_2, respectively.

Virulence is defined as the process whereby the parasite exploits the host to produce free-living propagules from the infected stage. Mathematically, we use the intrinsic expected lifetime of the host, $1/\mu_{0Y}$, as a measure of the host "somatic energy" that the parasite may exploit; and we define parasite virulence as the fraction, x_1, of host somatic energy that the parasite actually exploits to produce propagules. Host somatic energy is converted into parasite production with a conversion coefficient, γ, that we call propagation factor, and the efficiency of the conversion is discounted by the physiological cost of virulence. By setting $\phi = \gamma/\mu_{0Y}$, and parameterizing the cost function of virulence by θ_{x1}, the parasite production rate can be written as

$$\sigma_X = \phi x_1 (1 - x_1)^{\theta_{x1}}. \quad (2)$$

Inside the host, the parasite is exposed to host resistance, the effect of which is modeled as a mortality factor that adds to the parasite's intrinsic mortality rate. Thus, for a given degree y_1 of host resistance, the mortality rate of the parasite in the complex stage is

$$\nu_X = \mu_{0X} + \omega_{y1} y_1, \quad (3)$$

where ω_{y1} measures the efficiency of resistance.

The effect of virulence on the host is to increase mortality in the complex stage—an increase that the host can mitigate by investing resources into tolerance. The mortality increase is proportional to x_1; the proportionality factor, ω_{x1}, is called virulence efficiency. The host tolerance, as measured by the continuous trait y_2, limits the mortality increase with an efficiency factor denoted by ω_{y2}. Hence, the mortality rate of the complex as a function of virulence x_1 and tolerance y_2 is:

$$\nu_{XY} = \mu_{0Y} + \mu_{1Y} + \omega_{x1} x_1/(1 + \omega_{y2} y_2). \quad (4)$$

The host pays the physiological cost of resistance and tolerance in terms of reduced reproduction. Thus, the per-capita birth rate ρ_Y of free-living hosts equals the intrinsic birth rate ρ_{0Y} discounted by a density-dependent regulatory factor, and by the multiplicative costs of resistance y_1 and tolerance y_2. The shape of resistance and tolerance cost functions is fixed by parameters θ_{y1} and θ_{y2}. Hence

$$\rho_Y = \rho_{0Y}(1 - y_1)^{\theta_{y1}}(1 - y_2)^{\theta_{y2}}/(1 + \kappa(Y + Z)), \quad (5)$$

where the Beverton–Holt density-dependent regulatory factor $1/(1 + \kappa(Y + Z))$ reflects competition within and between free-living host and complex stages with equal intensity κ. In the absence of vertical transmission, the birth rates of the host susceptible and infected stages are assumed to be equal:

$$\sigma_Y = \rho_Y. \quad (6)$$

The actual shape of costs in natural systems remains poorly known. General life-history theory (e.g., Rueffler et al. 2006), and models of host defense evolution in particular, have emphasized the critical influence of the accelerating versus decelerating profile of the cost function on the evolution of the corresponding character. This influence was demonstrated by Miller et al. (2005) for the evolution of tolerance, by Best et al. (2009) for the evolution of avoidance coevolving with virulence, and by Restif and Koella (2004) for the evolution of mixed, resistance/tolerance defenses. Our choice of power functions for the direct costs of virulence and defenses (eqs. 2 and 5) is grounded in previous models (e.g., Sasaki 2000, Restif and Koella 2004) and the simplest mathematically to explore the effect of the cost profile by tuning a single parameter (θ).

EVOLUTIONARY DYNAMICS

We use the adaptive dynamics framework (Metz et al. 1992; Dieckmann and Law 1996; Champagnat et al. 2006) to model the coevolution of virulence, x_1, resistance, y_1, and tolerance, y_2, and investigate the effect on the traits' coevolution of three classes of parameters: physiological, environmental, and epidemiological (Table 1). Physiological factors include the costs of traits (θ_{x1}, θ_{y1}, θ_{y2}) and traits' efficiencies (ω_{x1}, ω_{y1}, ω_{y2}). Environmental

Table 1. Model parameters and default values. All rates are measured with respect to the time unit of the ecological model, eq. (1A–C).

	Symbol	Parameter	Default value
Parasite	x_1	Investment in virulence	0.75
	ω_{x1}	Virulence efficiency	5
	μ_{0X}	Intrinsic mortality rate	1
	μ_{1X}	Background mortality rate	0
	γ	Propagation factor	50
	θ_{x1}	Exponent of the cost function of virulence	0.25
Host	y_1	Investment in resistance	0
	y_2	Investment in tolerance	0
	ρ_{0Y}	Intrinsic birth rate	10
	κ	Competition coefficient	5.10^{-5}
	μ_{0Y}	Intrinsic mortality rate	1
	μ_{1Y}	Background mortality rate	0
	ω_{y1}	Resistance efficiency	5
	ω_{y2}	Tolerance efficiency	2.5
	θ_{y1}	Exponent of the cost function of resistance	0.1
	θ_{y2}	Exponent of the cost function of tolerance	0.25
Other	β	Infection rate	1.10^{-5}
	k	Trait evolutionary rate	1.10^{-7}

factors include background mortalities (μ_{1X}, μ_{1Y}). Epidemiological factors include infection rate (β) and propagation factor (γ).

The coevolutionary process is described by a sequence of mutation–selection steps in phenotypic trait space (Metz et al. 1996; Champagnat et al. 2006). Each selection step is determined by the invasion fitness of a mutant host or parasite phenotype interacting with the resident host–parasite system in stationary ecological (epidemiological) state (Metz et al. 1992). Successful invasion by a mutant changes the ecological state of the system, which entails that subsequent host or parasite mutants will experience a different selection gradient. This feedback between heritable variation in any one trait and the ecology-based selection gradient of all traits entangles the evolutionary dynamics of the two interacting species (Fig. 1A).

Combinations of traits where the selection gradient equals zero are called (co)evolutionary equilibria and represent potential rest points for the coevolutionary process. Whether evolutionary equilibria predict adaptations that can be expected in real systems critically depends on their attractivity, that is, whether they can be reached by the mutation–selection process from some ancestral conditions. If mutations are rare and have small effects, and if the resident system is always at ecological equilibrium, then the attractivity of evolutionary equilibria can be analyzed by using the so-called canonical equations of the adaptive traits dynamics (Dieckmann and Law 1996). This is the approach followed here (see Appendix).

First, the ecological model is analyzed. We use a combination of analytical and numerical tools to check that the host–parasite system is at ecological equilibrium (provided it is ecologically viable) across the entire phenotypic trait space for all parameter intervals considered in this study (see Fig. S1 for representative numerical results). Then we numerically solve the canonical equations of adaptive dynamics for a range of initial conditions (i.e., ancestral trait values) that sample the whole phenotypic trait space. This yields the (unique) evolutionary equilibrium and establishes its global attractivity for at least some range of host and parasite evolutionary rates that includes their default values (Table 1). Finally, we test the invasion stability of the evolutionary equilibrium by relaxing the small-and-rare mutation assumption of the canonical equations.

This computational routine can be used to study the system's coevolutionary dynamics with respect to any set of parameter values. For each parameter there is a default value (Table 1), and all physiological, environmental, and epidemiological parameters that are relevant to our biological questions are varied across intervals that contain their default value. The model analysis aims at determining how the evolutionary equilibria vary and covary in response to variation in each relevant parameter. Answers to our focal questions are obtained by doing this for the full model in which virulence, resistance, and tolerance coevolve (VRT model), and for three submodels: the RT model, in which resistance and tolerance coevolve while virulence is fixed; the VR and VT models, in which virulence coevolves either with resistance or with tolerance.

Results

COEVOLVING RESISTANCE AND TOLERANCE: EMERGING PATTERNS OF VARIATION AND COVARIATION

We identify conditions that favor resistance or tolerance by investigating numerically how the RT model responds to changes in parameter values (Fig. 2). When comparing evolved traits among populations that differ by one parameter, we say that evolution promotes "supplementary defenses" if defenses show positively correlated responses to selection: a change in the parameter causes both defenses to increase (or decrease) evolutionarily. This is actually the case with virulence: increasing virulence generally selects resistance and tolerance in the same direction (Fig. 2A). We say that evolution promotes "complementary defenses" if the response of tolerance and resistance to selection are negatively correlated: evolution trades off one defense for the other.

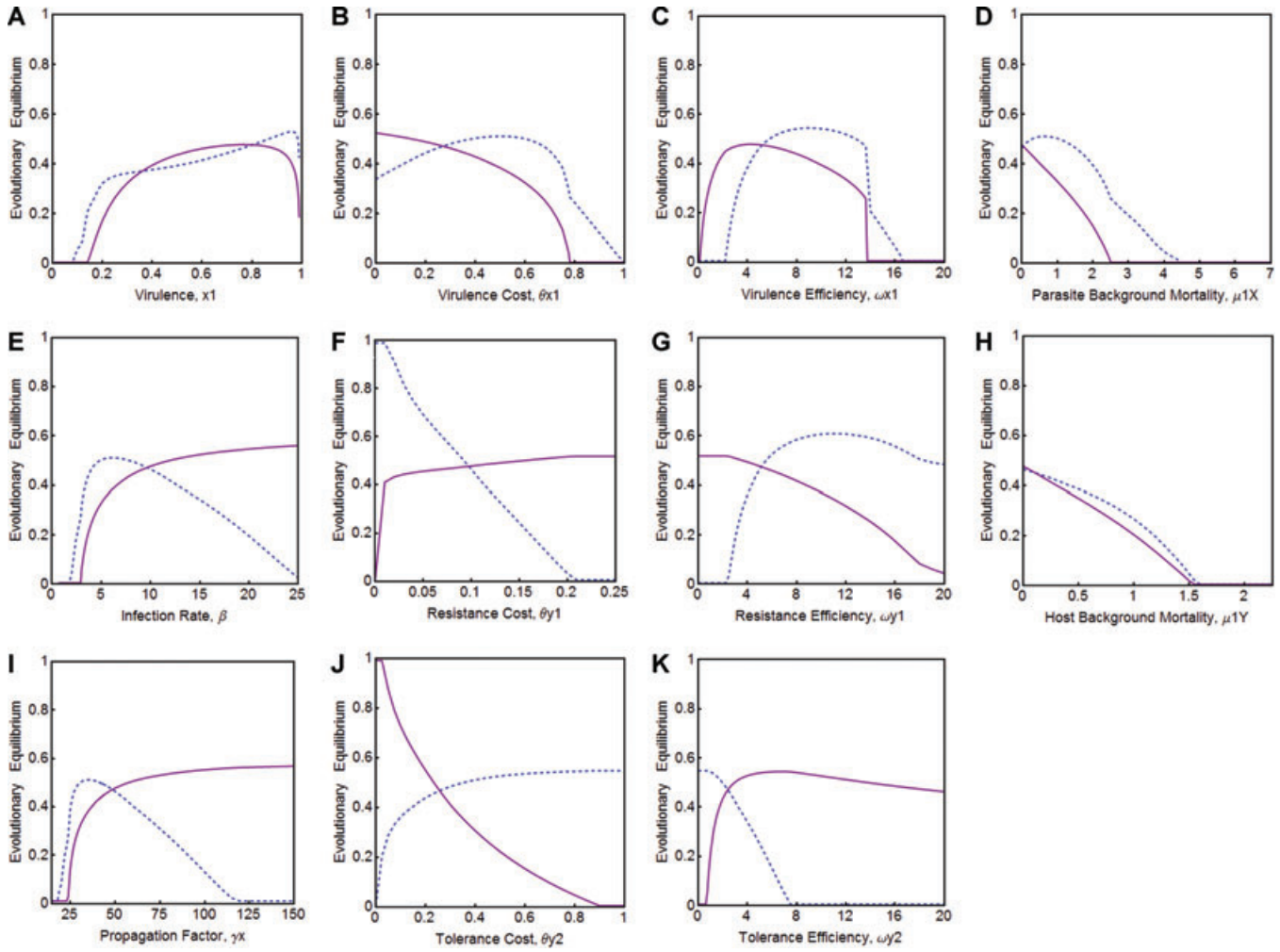

Figure 2. Coevolved resistance and tolerance with respect to physiological, epidemiological, and environmental parameters (RT model). Dashed blue line: resistance. Solid purple line: tolerance. In each panel, all nonvarying parameters are fixed to default values (Table 1). The infection rate is scaled by 10^6. See Figures S2–S4 for a sensitivity analysis of patterns C, D and E with respect to virulence efficiency, parasite background mortality, and infection rate, respectively.

The distinction between supplementary and complementary defenses leads to recognize two evolutionary routes toward pure strategies. One route involves selection for low defense altogether when defenses are supplementary: both defenses decrease, and a pure strategy is established after one defense trait has reached zero. The other route involves "all-or-nothing" selection when defenses are complementary: one defense trait increases whereas the other decreases, and a pure strategy is established once the latter has reached zero. To analyze the occurrence of evolutionary complementarity versus supplementarity, and conditions under which pure versus mixed strategies evolve, we fixed virulence to a high value ($x_1 = 0.75$) at which a mixed strategy of strong resistance and strong tolerance evolves for parameters set to their default values (Fig. 2A). Then we examined the consequences of varying physiological, environmental, and epidemiological parameters (Fig. 2B–K), one at a time. After having identified the key parameters to which the evolution of resistance and tolerance was most sensitive, we tested the generality and robustness of all univariate responses (Fig. 2) by simultaneously varying all key parameters (Figs. S2–S4).

Except for high values of resistance efficiency (Fig. 2G), variation in the cost or efficiency of defenses results in evolutionary complementarity. Pure resistance evolves when the efficiency of resistance or the cost of tolerance is high (Fig. 2G, J). Pure tolerance evolves when the efficiency of tolerance or the cost of resistance is high (Fig. 2F, K). Pure tolerance also evolves by complementarity under high infection rate (Fig. 2E) or high propagation factor (Fig. 2I). These epidemiological conditions put the host at high risk of infection, which disfavors investment in resistance while promoting tolerance.

All other instances of pure defense involve resistance evolving by supplementarity. Pure resistance thus evolves under low

virulence (Fig. 2A), high virulence cost (Fig. 2B), or high virulence efficiency (Fig. 2C). When virulence is low or the cost of virulence is high, selection for defense is weak, and investment in tolerating a parasite that causes little harm is disfavored, hence pure resistance. When virulence efficiency increases, resistance becomes selectively advantageous over tolerance, hence a pattern of complementarity, up to a threshold beyond which the total fitness benefit of defense declines—the host "gives up" evolutionarily, hence a supplementary pattern in which tolerance falls faster, leading to pure resistance.

Pure resistance also evolves under low infection rate (Fig. 2E) or low propagation factor (Fig. 2I). These conditions reduce the risk for a free host to be infected. Selection for defense weakens as a consequence, hence a fitness advantage to shorten the association by expressing resistance and no tolerance. Finally, pure resistance evolves under high parasite or host background mortality rates (Fig. 2D, H). Under low infection rate or low propagation factor, increasing background mortality in hosts or parasites relaxes selection on defenses and promotes evolutionary supplementarity. High background mortality in the host makes tolerance—that is, an increase in host survival—of little selective value, hence the evolution of pure resistance. High background mortality in the parasite selects against that host strategy—tolerance—which would "protect" the parasite from background mortality factors.

When mixed strategies evolve, the RT model can be used to explore patterns of evolutionary covariation of resistance and tolerance among populations that differ in physiological, epidemiological, or environmental conditions (Fig. 3). In general, evolutionary covariation arises from shared selection pressures (i.e., the same selective pressure applies on both traits) and selective interactions (one trait influences selective pressures on the other) (e.g., Le Galliard et al. 2005). Evolutionary supplementarity implies a positive correlation between resistance and tolerance, whereas evolutionary complementarity means a trade-off between resistance and tolerance.

For fixed virulence, variation in host or parasite background mortality rates drives essentially positive correlations between resistance and tolerance (Fig. 3F for variation with respect to parasite background mortality rate; the response curves to host background mortality rate are very similar and not shown), that is, evolutionary supplementarity. The background mortality rates basically scale up or down the selective pressures on both traits and hence on their values at coevolutionary equilibrium.

In contrast, both complementarity and supplementarity can evolve in response to variation in a single physiological or epidemiological parameter, provided that variation occurs across wide enough a range. Sign reversals are therefore expected in the evolutionary correlations obtained by comparing populations that have adapted to conditions differing in one of these parameters:

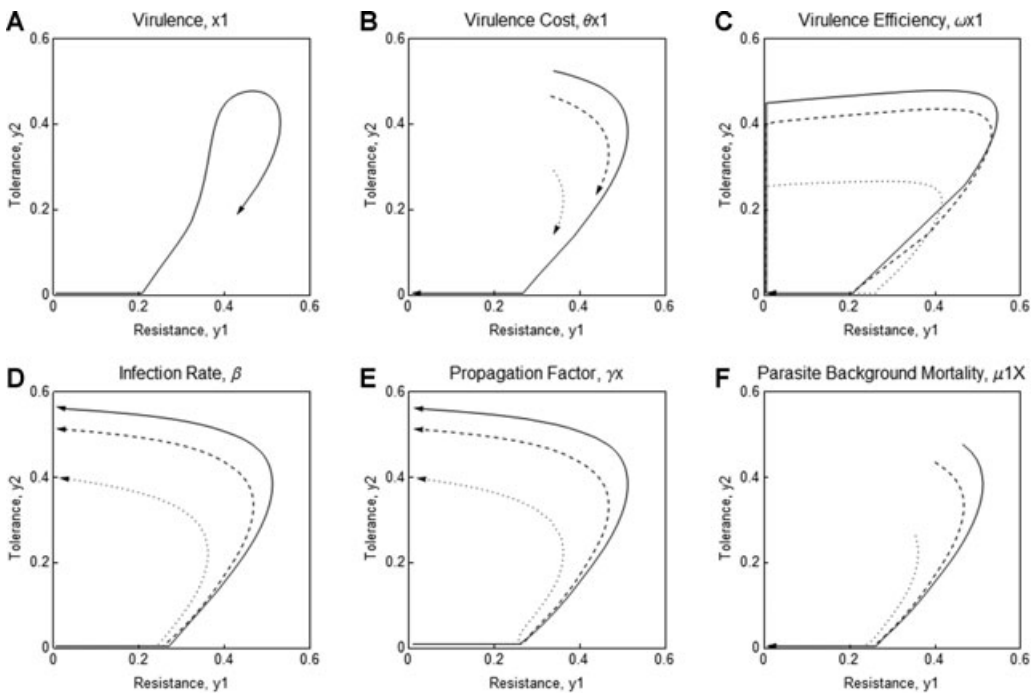

Figure 3. **Resistance–tolerance evolutionary correlations in response to variation in virulence and associated physiological parameters (A–C), epidemiological parameters (D, E) and environmental parameters (F). Each curve shows the value of resistance (y_1) and tolerance (y_2) at evolutionary equilibrium in the RT model. In B–F, curves are plotted for different parasite virulence : 0.25 (dotted), 0.5 (dashed), and 0.75 (plain). In each panel, all nonvarying parameters are fixed to default values (Table 1).**

virulence cost, virulence efficiency, infection rate, and propagation factor (Fig. 3B–E). These parameters are direct (the latter two) or indirect (the former two) influences of parasite prevalence, and prevalence indeed plays a key role in driving the correlation reversals. Below some threshold on prevalence, both resistance and tolerance are selected for, and their responses correlate positively as long as variation in the underlying parameter keeps prevalence below that threshold. Above the threshold, the risk of reinfection becomes so high that resistance is selected against; as long as the risk of parasite-induced mortality is not too high, selection remains positive on tolerance, hence a trade-off between resistance and tolerance.

These results altogether show, first, that the evolution of resistance and tolerance responds in intuitive and expected ways to the traits' physiological parameters (costs and efficiencies) (Fig. 2F, G, J, and K); in contrast, the cost and the efficiency of virulence have strong impact on the parasite population dynamics that feed back and drive highly nonlinear patterns of variation in host defenses (Figs. 2B,C and 3B,C). Second, both epidemiological parameters (infection rate and propagation factors) have very similar influences on resistance and tolerance (Figs. 2E,I and 3D,E). Third, deterioration of environmental conditions that result in increasing host or parasite background mortality will beget similar decline in resistance and tolerance (Fig. 2D, H), with the exception of an increase of resistance when parasite background mortality increases across low values (Figs. 2D and 3F). In conclusion, most variation in resistance and tolerance that is not explained by the traits' cost and efficiency is accounted for by three key parameters: virulence efficiency, infection rate, and parasite background mortality. The robustness of univariate patterns of resistance and tolerance (Fig. 2) thus depends on the strength of the interaction effects between the key parameters. These interaction effects turn out to be weak (Figs. S2–S4): the univariate response of resistance and tolerance to each key parameter is affected essentially linearly by simultaneously varying the other two key parameters. Thus, the evolutionary patterns shown in Figure 2 and our conclusions for the evolution of pure and mixed defenses hold in general.

HOW IS VIRULENCE AFFECTED BY COEVOLUTION WITH RESISTANCE VERSUS TOLERANCE?

When host and parasite coevolve, the evolutionary equilibrium virulence is influenced by the trait's physiological parameters as expected: virulence decreases as virulence cost or virulence efficiency increases (results not shown). Because no correlation is assumed between virulence and transmission, variation in the infection rate or propagation factor has no effect on virulence when virulence evolves alone (results not shown). Yet the infection rate and propagation factor do influence virulence when parasites and hosts coevolve. Increasing the contact rate (or propagation factor) across low values favors a rapid increase in virulence along with a sharp increase of host defense, either resistance (Fig. 4A) or tolerance (Fig. 4B). The increase of virulence and tolerance saturates at high infection rates (Fig. 4B) whereas coevolved virulence and resistance reach a peak and then decline (Fig. 4A). Interestingly, the same variation in resistance can correlate with a wide change in virulence across low infection rates, or a narrow change in virulence across high infection rates.

With higher infection rate or propagation factor, the infection probability is larger and selection favors parasites that invest less in virulence, for two reasons: they pay a lower cost of virulence, and the lesser damage they cause to their host results in a longer infection time, hence a larger production of propagules. The coevolving resistance then also decreases with increasing the infection rate or propagation factor (Fig. 4A). In contrast, within a range of low infection rate (Fig. 4A), more contact will select for more virulence and more resistance. With infrequent contact, the probability for a host, once recovered, to be reinfected is low, which favors investment in resistance, hence stronger selection for virulence. Because the proportion of susceptible hosts

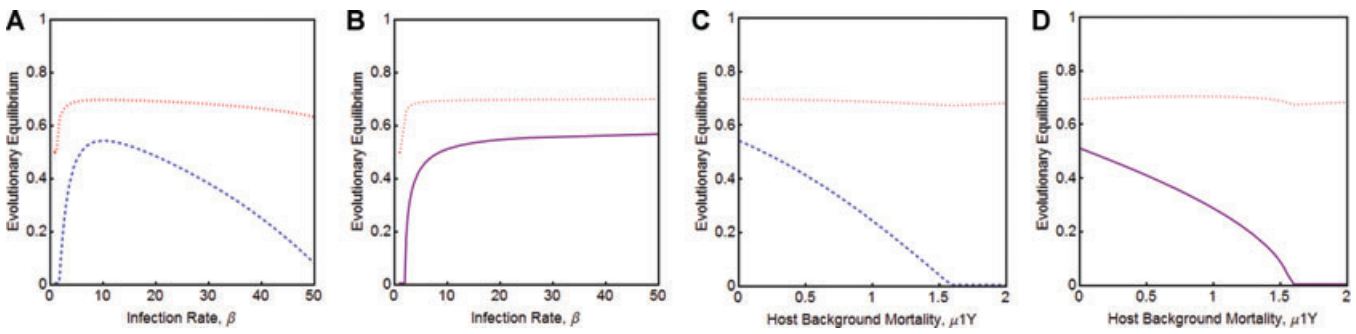

Figure 4. **Virulence coevolving with resistance (A and C, VR model) or tolerance (B and D, VT model), with respect to infection rate and host background mortality. Dotted red line: virulence. Dashed blue line: resistance. Solid purple line: tolerance. All nonvarying parameters are fixed to default values (Table 1). The infection rate is scaled by 10^6. See Figures S5–S8 for a sensitivity analysis of these patterns with respect to virulence efficiency, parasite background mortality, and infection rate.**

remains high (because of infrequent contact and likely recovery), the increase in virulence is not counter-selected.

An increase in the host's background mortality selects for higher virulence when virulence evolves alone (results not shown). When virulence and defense coevolve, the effect of host background mortality on virulence is often minor, whereas the coevolving defense, either resistance or tolerance, decreases dramatically as mortality increases (Fig. 4C, D). According to the nonlinear response of virulence and defense to infection rate (Fig. 4A, B), we expected a more pronounced correlated response of virulence and defense to mortality at low infection rate and this is indeed the case (Figs. S5–S8), but only when virulence coevolves resistance (Figs. S5 and S7), and the pattern is further influenced by virulence efficiency (Figs. S6A–C and S7A–C). Thus, the prediction of virulence increasing with host background mortality only holds when virulence coevolves with resistance, and under the condition of low infection rate and low virulence efficiency.

THREE-WAY COEVOLUTION OF RESISTANCE, TOLERANCE, AND VIRULENCE

Three-way coevolution preserves all qualitative predictions of evolutionary supplementarity and complementarity and the resistance–tolerance trade-off (Fig. 5), but causes several important quantitative changes (Figs. 5 and 6). Three-way coevolution generally selects for more virulence (Fig. 6A–E) and less tolerance (Fig. 6K–O). Compared to two-way tolerance–virulence coevolution, tolerance decreases faster in response to increasing host or parasite background mortality (Fig. 6N, O), leaving resistance as a pure defense at levels of background mortality lower than in two-way coevolutionary scenarios (Fig. 6I, J). Compared to two-way resistance–virulence coevolution, resistance is affected chiefly in its response to variation in epidemiological parameters. Thus, as the infection rate or propagation factor increases, resistance becomes strongly counter-selected and tolerance is favored as pure defense (Fig. 6G, H, L, and M).

Relative to the infection rate (or propagation factor), virulence is maximized at a contact rate where the total investment in defense also peaks (involving significant resistance and close-to-maximum tolerance, Fig. 5A, B), but in general there is no tendency for three-way coevolution to maximize parasite virulence and host defenses concurrently. With respect to virulence efficiency, virulence increases as virulence efficiency decreases while both defenses coevolve to zero (Fig. 5D). With respect to host or parasite background mortality, virulence remains high and shows little variation while defenses coevolve from high to null as background mortalities increase from zero (Fig. 5E, J).

In fact, all patterns of coevolutionary variation are possible. Virulence is predicted to increase correlatively with resistance increasing and tolerance decreasing when the cost of resistance decreases (Fig. 5F) or resistance efficiency increases (Fig. 5G). Virulence increasing in correlation with resistance decreasing and tolerance increasing is expected in response to variation in the cost of tolerance (Fig. 5H), or across low tolerance efficiency (Fig. 5I), or across intermediate virulence efficiency (Fig. 5D). A positive correlation of virulence, resistance, and tolerance is predicted in response to variation in virulence cost (Fig. 5C), or low infection

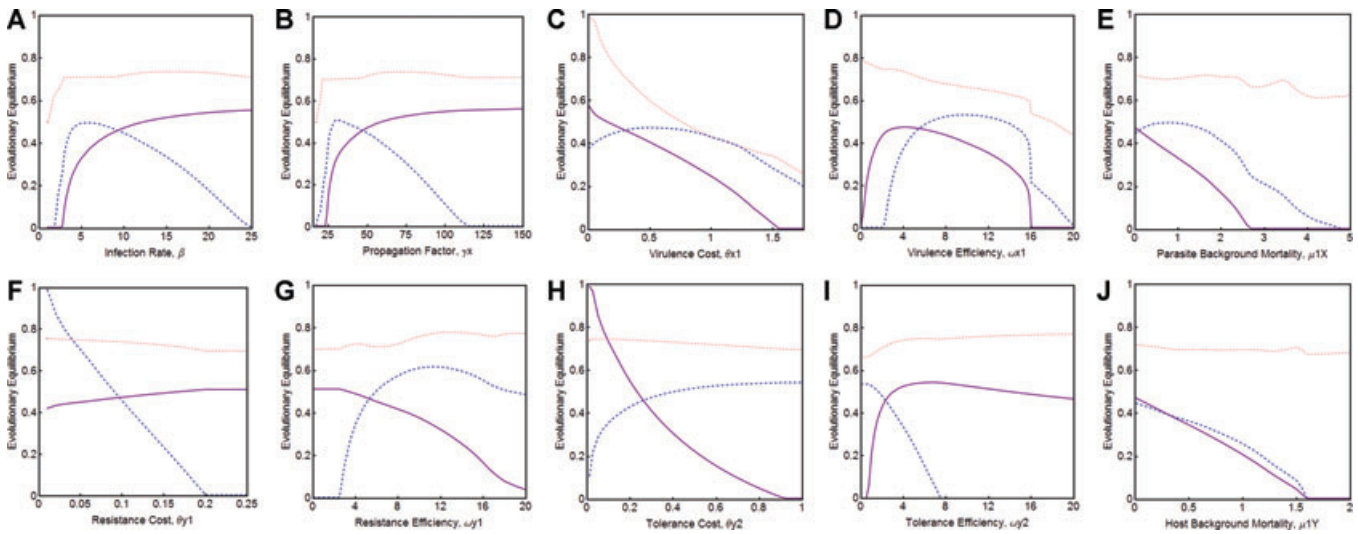

Figure 5. Coevolved virulence, resistance, and tolerance (VRT model) with respect to epidemiological, physiological, and environmental parameters. Dotted red line: virulence. Dashed blue line: resistance. Solid purple line: tolerance. No vertical transmission ($x_3 = y_3 = 0$). All nonvarying parameters are fixed to default values (Table 1). The infection rate is scaled by 10^6. See Figures S9 and S10 for a sensitivity analysis of VRT model with respect to virulence efficiency and infection rate.

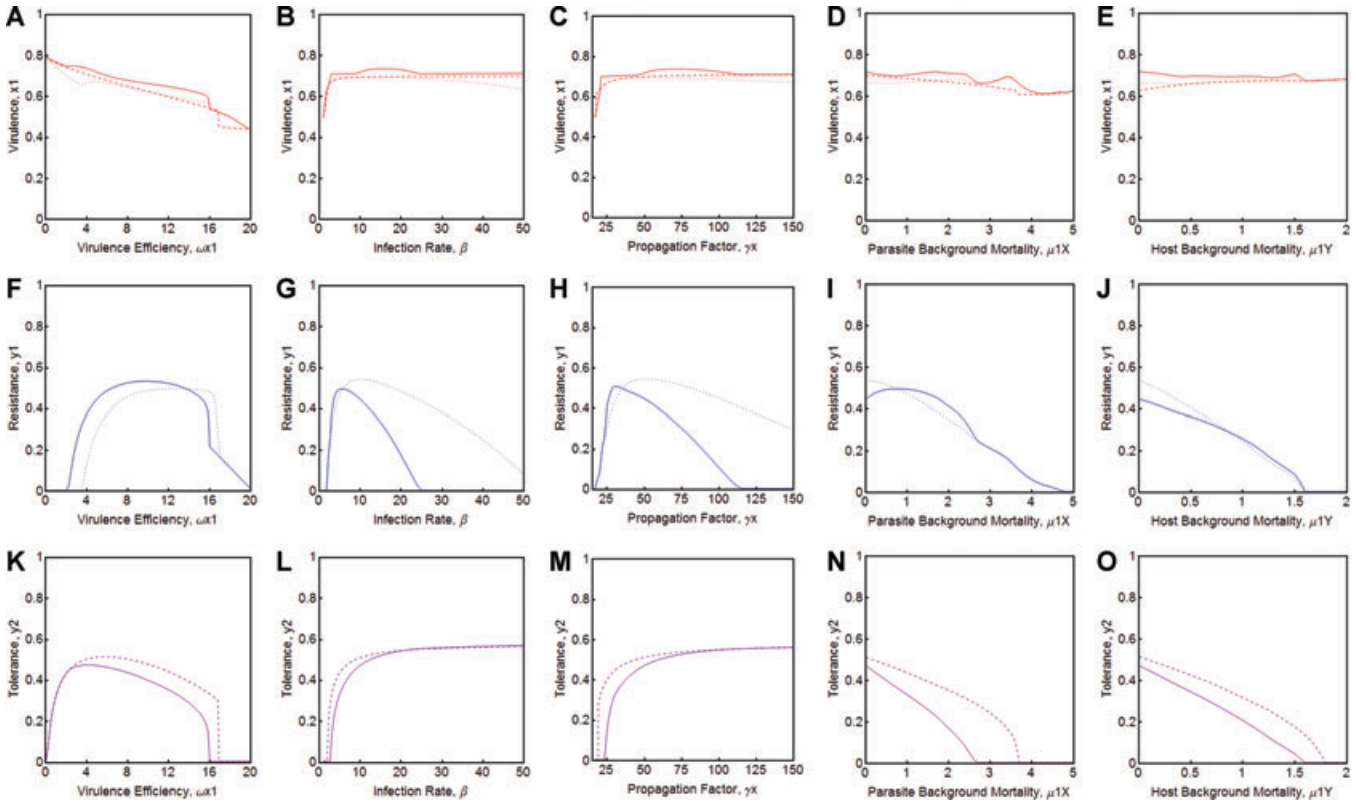

Figure 6. Coevolved virulence, resistance, and tolerance in the two-trait and three-trait models. Coevolved virulence–resistance (dotted curves, VR model), virulence–tolerance (dashed, VT model), and virulence–resistance–tolerance (solid, VRT model) are shown with respect to five underlying parameters: virulence efficiency, infection rate, propagation factor, parasite background mortality, and host background mortality. (A–E), Comparing evolved virulence between VR, VT, and VRT models. (F–J), Comparing evolved resistance between VR and VRT models. (K–O), Comparing evolved tolerance between VT and VRT models. All nonvarying parameters are fixed to default values (Table 1). The infection rate is scaled by 10^6.

rate or propagation factor (Fig. 5A, B), or high virulence efficiency (Fig. 5D).

Quantitatively, the key factors of virulence evolution are the cost of virulence, the efficiency of virulence, and both epidemiological parameters at low values (infection rate and propagation factors) (Figs. 5A–D and 6A–C; Figs. S9 and S10). The indirect effect of the host's physiological parameters, mediated by eco–evolutionary feedbacks, is always relatively small (Figs. 5F–J and 6E). In contrast, the physiological parameters of the parasite have strong quantitative effects on the evolution of host defenses (Figs. 5A–E and 6F, I, K, N; Fig. S10). Comparing resistance–tolerance coevolution (Fig. 2) and three-trait coevolution (Fig. 5) shows that eco–evolutionary feedbacks work synergistically to reinforce two-trait evolutionary patterns: The resistance–virulence pattern in response to decreasing virulence cost for fixed virulence (Fig. 2B) mirrors the pattern predicted for increasing virulence under fixed cost (Fig. 2A); when all three traits coevolve, decreasing the cost of virulence does promote an increase in virulence, and resistance and tolerance responds as predicted by combining the selective responses seen in Figure 2A and B.

EFFECT OF NOT-SO-SMALL AND NOT-SO-RARE MUTATION

Evolutionary equilibria in all four models (RT, VR, VT, VRT) are globally attractive and globally stable over all ranges of parameters that we investigated (Fig. 7, Figs. S12–S20). Global attractivity means that evolutionary equilibria can be reached by small and rare mutational steps from any combination of ancestral trait values (provided that the system is ecologically viable for these ancestral traits), including the "mellowest" ancestral stage of interaction, in which the parasite exploits its host with the minimum virulence that ensures ecological viability, and the host expresses no defense. Global stability means that no mutation in a single trait can invade the system once at evolutionary equilibrium.

More frequent and/or larger mutations may have dramatic effects on evolutionary dynamics (see Champagnat et al. 2006 for general theory, and e.g., Pugliese 2002 and Best et al. 2009 for examples pertaining to host–parasite systems). Here, we took a first step in studying these effects by examining the invasion structure of the trait space when the host and the parasite are at their expected coevolutionary equilibrium (models VR, VT, and

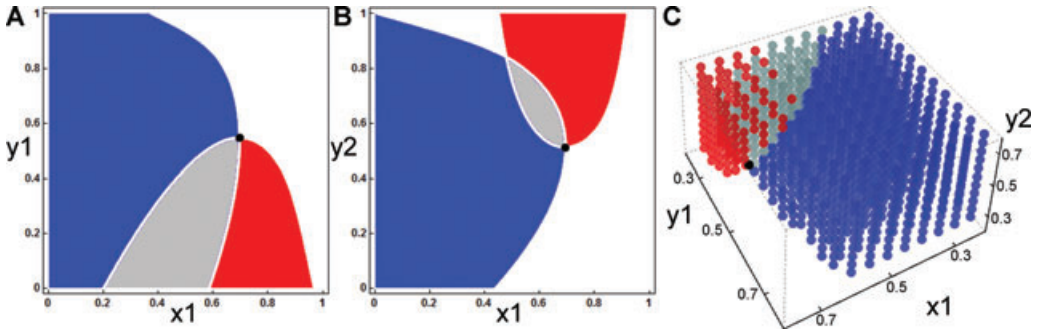

Figure 7. **Invasibility of the evolutionary equilibrium (black circle) by mutant traits. Colored regions indicate combinations of trait values for which at least one mutant can invade. When a mutant parasite and a mutant host simultaneously arise in the red region: the mutant parasite invades whereas the mutant host goes extinct; in the blue region: the mutant host invades whereas the mutant parasite goes extinct; in the gray region: both mutant parasite and mutant host invade; in the white region: neither one can invade. The convexity of the regions of mutant parasite invasion (red and gray) and mutant host invasion (blue and gray) and their, respectively, horizontal and vertical tangent spaces (line or plane) at evolutionary equilibrium indicate that the evolutionary equilibrium is always a global ESS in the classical game-theoretical sense. (A) Virulence–resistance coevolution (VR model). (B) Virulence–tolerance coevolution (VT model). (C) Virulence–resistance–tolerance coevolution (VRT model). All parameters are set at their default values (Table 1). Figures S15–S20 provide a sensitivity analysis of (A), (B), and (C) with respect to virulence efficiency, parasite background mortality, and infection rate.**

VRT). Although the coevolutionary equilibrium is globally stable against any mutant (small or large) expressed in any single trait, a rather different picture emerges when a mutant parasite and a mutant host assume a nonnegligible probability of arising in the same short interval of evolutionary time—that is, when we relax the rare mutation assumption of adaptive dynamics theory. Then one of four events happens: (1) both mutants go extinct; (2) the mutant parasite invades and replaces the resident parasite while the mutant host goes extinct; (3) the mutant host invades and replaces the resident host while the mutant parasite goes extinct; (4) both mutant parasite and mutant host invade and displace both resident populations. Thus, in cases (2)–(4) the coevolutionary equilibrium appears vulnerable to invasion provided that the probability of mutations co-occurring in the parasite and the host is nonzero. This is likely to be the case if the parasite has a much higher mutation probability than the host, which is commonly observed in natural host–parasite interactions; then probability that the parasite mutates whenever the host population does is high.

Cases (2) and (3) are remarkable instances of "evolutionary catalysis" (Nowak and Sigmund 1992): one mutant goes to fixation whereas the other goes extinct, but the former would have failed to invade without the presence of the latter. The unsuccessful mutant is "catalytic" in the sense that it is initially rare, it gives a foothold to the other mutant and thereby begets a potentially large evolutionary change in the other species, but eventually it leaves no trace in the system. This mutation catalysis phenomenon is significant because it entails that "evolutionary spikes" can be expected in the trait dynamics of one species without any noticeable change in the trait of the other species. Indeed on the evolutionary timescale, mutation catalysis will result in potentially large changes in the defense of the host while the parasite virulence remains at evolutionary equilibrium, and large changes in the parasite virulence while the host defenses remain at evolutionary equilibrium. Because the coevolutionary equilibrium is globally attractive, from the peak of a spike the small mutation–selection process will drive the trait of the spiking species back to its evolutionary equilibrium. If mutation are not so small and not so rare, in particular if mutation steps are frequent enough in the parasite and mutation variance is large enough in the host, then highly variable virulence and defenses may evolve.

More quantitative insights can be gained from the numerical analysis of the models (Fig. 7, Figs. S15–S20). The invasion structure of the trait space, that is, the distribution of cases (1)–(4), changes little in response to varying parameters to which evolutionary equilibria are most sensitive (virulence efficiency, infection rate, background mortalities). When virulence coevolves with resistance (VR model, Figs. 7A, S15, and S16), mutant parasites that are slightly less virulent than the evolutionary equilibrium will catalyze invasion by a wide range of host mutants, including mutants with low or even zero resistance (blue and gray areas in Figs. 7A, S15, and S16). Likewise, the invasion of parasite mutants can be catalyzed by host mutants that are less resistant than the evolutionary equilibrium, but the range of virulence that may be reached (both lower and higher than evolutionary equilibrium virulence) is comparatively narrower than it is for resistance (red and gray areas in Figs. 7A, S15, and S16). Evolutionary spikes of higher resistance (blue area in Figs. 7A, S15, and S16) or higher virulence (red area in Figs. 7A, S15, and S16) are predicted, the magnitude of which is sensitive primarily to parasite background mortality (Figs. S15 and S16). Invasion by co-occurring mutants

that are more virulent and more resistant may not happen (in Figs. 7A, S15, and S16 the north-east quadrant from coevolutionary equilibrium is always blank).

A horizontally mirrored image obtains for virulence–tolerance evolution (VT model, Figs. 7B, S17, and S18). Less-virulent mutant parasites will catalyze invasion by a wide range of host tolerance (blue and gray areas in Figs. 7B, S17, and S18); evolutionary spikes of reduced tolerance are expected around coevolutionary equilibrium (blue area in Figs. 7B, S17, and S18). Likewise, more tolerant mutant hosts will catalyze invasion by a wide range of parasite virulence (red and gray areas in Figs. 7B, S17, and S18); evolutionary spikes of increased virulence are expected around evolutionary equilibrium (red area in Figs. 7B, S17, and S18), the magnitude of which increases with higher virulence efficiency (Figs. S17 and S18), higher parasite background mortality (Fig. S17), or lower infection rate (Fig. S18). Invasion by co-occurring mutants that are more virulent and less tolerant may not happen (in Figs. 7B, S17, and S18 the south-east quadrant from coevolutionary equilibrium is always blank).

The results for two-trait coevolution are entirely preserved in the three-trait (VRT) model (Figs. 7C, S19, and S20), and there are several new phenomena rooted in the three-dimensionality of the trait space. Mutant catalysis is now possible between a mutant parasite that is more virulent than at coevolutionary equilibrium and a mutant host that is both more resistant and more tolerant, or less resistant and less tolerant (Fig. 7C). Thus, three-trait coevolution makes even more likely the occurrence of evolutionary spikes in virulence. The likelihood and magnitude of evolutionary spikes in virulence are complex functions of virulence efficiency, infection rate, and parasite background mortality (Figs. S19 and S20): they increase with virulence efficiency, all the more as the parasite background mortality is higher (Fig. S19); they decrease with increasing the infection rate when parasite background moratlity is low (Fig. S20A–C), but peak at intermediate infection rate when parasite background mortality is higher (Fig. S20D–F).

Discussion

We presented a simple yet general eco–evolutionary model of host–parasite interaction that unifies and extends previous theory of parasite virulence and host defense. On the ecological timescale, physiological, environmental, and epidemiological processes determine the dynamics of populations of parasites and hosts with constant traits values. On the evolutionary timescale, long-term trait dynamics result from genetic variation in the traits (due to mutation) and selection pressures generated by the ecological state of the system.

The model was analyzed with the aim of better understanding (1) adaptive patterns of resistance and tolerance in hosts, (2) the evolution of virulence depending on the nature of the coevolving defense in the host, and (3) how the coevolution of virulence and both defenses differ from virulence–resistance and virulence–tolerance coevolution.

Our analysis of the ecological model shows that across the entire trait and parameter space the host–parasite interaction either drives the species to a stable equilibrium of coexistence, or causes extinction of the parasite or both species. Our evolutionary analysis identifies the efficiency of virulence, the infection rate, and the parasite background mortality as key factors of the evolutionary process that generally have strong, nonlinear effects on virulence and defenses. A detailed numerical study with respect to these key parameters indicates that the evolutionary process generally has a single equilibrium in the (two- or three-dimensional) trait space; that the equilibrium is always globally attractive through small and rare mutational steps for at least some range of host and parasite evolutionary rates around their default values; and that the equilibrium is globally stable against invasion by single-trait mutation, that is, an "ESS" (Evolutionarily Stable State) in the classical game-theoretical sense (Hofbauer and Sigmund 1998).

Thus, we could analyze evolutionary patterns of variation and covariation in virulence, resistance, and tolerance by examining the response of evolutionary equilibria to univariate changes of a large number of underlying physiological, epidemiological, and environmental parameters, and then testing the sensitivity of the results to concurrent changes of the three key parameters. Our predictions on the coevolution of virulence, resistance, and tolerance can therefore be taken as robust and general, relative to our physiological, ecological, and evolutionary assumptions.

EMPIRICAL SCOPE OF THE MODEL

The structure of the model is general and may apply, straightforwardly or by bringing in additional details, to a wide range of host–parasite/pathogen systems. In the context of theoretical evolutionary epidemiology at large, our model is closely related to earlier theory for spore-producing pathogens (e.g., Bonhoeffer et al. 1996; Day 2002). Transmission via the release of infectious propagules in the environment (rather than direct host–host contact) is found in many pathogens, with a great diversity in virulence and survival. Bonhoeffer et al. (1996) listed parasitic plants of the genus *Striga*, plant-parasitic nematode, several spore-forming bacteria, and viruses of the nuclera-polyhedrosis and granulosis families, as examples of highly virulent parasites with long-lived free-living propagules; microsporidian parasites typically produce long-living spores and range from high to low virulence; there are virulent pathogens whose transmission stages are very short-lived, for example, the measles virus, the endospores of the honey bee pathogenic bacteria *Bacillus larvae*, or the conidia of the caterpillar-infecting fungus *Nomurae rileyi*; in protozoans such as *Trichomonadida*, only the nonpathogenic species possess long-lived transmission stages. Thus, there is considerable

diversity in virulence and propagule survival in nature, hence a fertile terrain for theory and the search of causal patterns.

Rather than trying to match any particular system, the model structure was chosen for its relevance to our questions—in particular, the evolution of virulence when parasite-induced mortality can be mediated by host tolerance. Having a parasite free-living stage and direct costs of both tolerance and virulence allows to analyze the coevolution of virulence and defenses while taking into account selection pressures on the parasite and the host that are independent (direct costs of virulence, resistance and tolerance) or interactive (mortality cost for the parasite, mitigated by the host's investment in tolerance). Having a free-living stage sets a "worst-case scenario" for the evolution of host defenses (other than avoidance) because the host has no direct control over the survival or the effect of parasites when they are free-living. The free-living stage also avoids limiting the model to host-to-host transmission, and instead parameterize (with the infection rate and parasite background mortality) a continuum of transmission routes from "quasi host-to-host" (high infection rate and short-lived parasite free stage), to rare host exposure to long-lived propagules (low infection rate, low parasite background mortality).

What the model's current structure does not include is explicit within-host dynamics. This does not imply, however, that systems with parasites that proliferate inside their host are excluded from the scope of the model. Rather, the parasite's within-host birth-and-death process is treated as a "blackbox," the outcome of which is encapsulated in two parameters, the propagation factor (γ) and recovery rate (ν_X). This "blackbox treatment" is sufficient, in fact, to answer many evolutionary questions that have been addressed using epidemiological models with "nested" within-host dynamics (Mideo et al. 2008). The reason is that for these questions and models the nesting was "inessential": The within-host dynamical model provides a mechanistic description of virulence, recovery and transmission processes and these feed into the epidemiological model at the level of the host population; but no reciprocal feedback operates from the between-host dynamics down to the within-host level in these studies.

As emphasized by Mideo et al. (2008), host–parasite evolutionary theory in which within-host dynamics are truly "essential" awaits further development. To this end, models like ours that account for a free-living stage appear to be well suited. For example, the density of free-living propagules may alter inoculum size; if inoculum size influences the progression of disease within a host, this would then lead to a feedback from between-host to within-host dynamics (Schmid-Hempel and Frank 2007). With virulence modeled mechanistically as exploitation of host resources, and free-living parasite population dynamics modeled explicitly, our framework sets the stage for advancing theory in which the processes of within-host resource dynamics, multiple infection, and competition among parasitic strains interact and make nesting essential.

EVOLUTION OF PURE DEFENSES

As emphasized by Roy and Kirchner (2000), even though resistance and tolerance may have equivalent short-term benefits for individual hosts, the traits feed back on and reshape selection pressures in opposite ways. There is a negative feedback between the prevalence of resistant hosts and their fitness advantage, which may limit the evolution of resistance; there is a positive feedback between the prevalence of tolerant hosts and their fitness advantage, which may promote the evolution of tolerance. Thus, one expects the evolution of resistance and tolerance to be critically influenced by the system's epidemiology—the abundance and survival of hosts, the prevalence of infection, and the dynamics of transmission. These factors depend in turn on the phenotype of the parasite itself: virulence is known to shape the evolution of costly resistance (Anderson and May 1982) and tolerance as well (Restif and Koella 2003; Miller et al. 2005).

As expected, the physiological costs and benefits of resistance and tolerance are key determinants of the evolution of pure defenses. Resistance or tolerance evolves as a pure defense by supplementarity when the efficiency of that trait is high, and by complementarity when the cost of the other trait is high. Pure tolerance is also expected to evolve by complementarity under high risk of transmission due to a large infection rate or propagation factor. Pure resistance is expected to evolve by supplementarity under low infection rate or propagation factor, and under high host or parasite background mortality. Three-way coevolution of resistance and tolerance with virulence tends to broaden the range of parameters over which evolution promotes pure defenses.

The evolution of pure defenses thus appears not to be restricted to the special cost functions (constant or linear and additive) that have been considered in previous studies of resistance–tolerance coevolution (Mauricio et al. 1997; Roy and Kirchner 2000; Tiffin 2000; Restif and Koella 2004). The prediction that very low infection rate or propagation selects completely against tolerance matches Restif and Koella's (2003) results based on a tolerance–virulence coevolutionary model. But in contrast with their analysis, our two-trait and three-trait coevolutionary models consistently predict the evolution of high levels of tolerance as a pure defense under high infection rate or high propagation factor.

EVOLUTIONARY CORRELATION BETWEEN RESISTANCE AND TOLERANCE

Plant defense combining resistance and tolerance has received growing attention since the study of inbred lines of *Ipomoea purpurea* by Fineblum and Rausher (1995) revealed a negative correlation between resistance against and tolerance of herbivory. Yet no general pattern of covariation seems to hold, even within

species. In contrast to Fineblum and Rausher (1995) and Baucom and Mauricio (2008), other populations of *I. purpurea* showed no trade-off between defense strategies against herbivory (Tiffin and Rausher 1999) or pathogens (Simms and Triplett 1994). Likewise, tolerance and resistance were uncorrelated among inbred lines of *Arabidopsis thaliana* (Mauricio et al. 1997; Weinig et al. 2003). Further studies found negative correlations in plant–pathogen (e.g., Kover and Schaal 2002) and recently in animal–pathogen (Raberg et al. 2007) systems, whereas Carr et al. (2006) found no evidence for a trade-off between resistance and tolerance to Cucumber mosaic virus in *Mimulus guttatus*. Interestingly, Fornoni et al. (2003) observed an environment-dependent correlation between resistance and tolerance against herbivory in two natural populations of *Datura stramonium*. Our comparison of evolutionary patterns across physiological, environmental, and epidemiological conditions shows that resistance and tolerance can vary in similar or opposite directions and that the direction of covariation can revert in response to even a single physiological, environmental, or epidemiological factor—a conclusion that backs up and extends Restif and Koella's (2004) model.

Specifically, the evolution of complementary defenses, hence a resistance–tolerance trade-off, is predicted as a general and consistent response to variation in the cost of either trait. Variation of resistance or tolerance efficiency up to a threshold also drives the evolution of complementary defenses, hence the trade-off; above the threshold on either efficiency, evolution favors supplementary defenses, hence a positive correlation between resistance and tolerance. Such a sign reversal in the resistance–tolerance evolutionary correlation is found also in response to variation in the infection parameters (infection rate and propagation factor), in line with Restif and Koella's (2004) previous results.

Variation in the cost of virulence also begets sign reversal of the resistance–tolerance correlation. In contrast, as virulence efficiency varies, the correlation is essentially "piecewise positive:" positive but relatively flat for low virulence efficiency; positive and steep across higher virulence efficiency. Finally, variation in host or parasite background mortality drives the evolution of supplementary defenses, hence a positive, strong correlation between resistance and tolerance.

EVOLUTION OF VIRULENCE

Evolutionary theory traditionally defines virulence as induced host mortality. However, a more mechanistic definition of virulence can help incorporate finer details about the interaction between an individual parasite and its individual host and among multiple strains within the host (e.g., André et al. 2003; Alizon and van Baalen 2005, 2008; Mideo et al. 2008). We took such a mechanistic stance on virulence and defined it as the degree of exploitation of host resources (see Day 2002 for a similar approach). Exploitation mechanistically increases host mortality (because the host is deprived from somatic resources), and we defined "virulence efficiency" to measure the intensity of this impact.

In addition to the indirect cost of virulence generated by disease-induced mortality, the model accounts for the direct cost that the parasite may pay for greater exploitation of the host's resources. A direct cost of virulence is assumed in the population genetic theory of virulence (gene-for-gene models of virulence–resistance coevolution), where the benefit of a virulence allele for the parasite is discounted by the direct cost of carrying and expressing the allele. Sasaki's model (2000) provides a good example, and his fitness cost function ($\exp(-n.c)$ wheren n is the number of virulence alleles and c is the cost per allele), is mathematically very similar to our power function (eq. 2). Empirical evidence for such costs is conclusive although scant (e.g., Vera Cruz et al. 2000).

In contrast, quantitative evolutionary theory has largely ignored the direct cost, probably because of the use of a phenomenological, rather than mechanistic, definition of virulence. The basis for such costs, however, has been recognized. Direct costs may be generated physiologically by a more energy-demanding molecular or cellular machinery to acquire and process a larger amount of resources from the host (a classical assumption of life-history theory of resource acquisition/resource allocation evolution). This was addressed in some detail by Gilchrist et al. (2004) in their analysis of within-host viral fitness. In viruses, higher protein translation rates associated with higher propagule production may go with an increased probability of misfolding proteins. Misfolded proteins involved in reverse transcription may have lower enzymatic activities and shorter intracellular half-lives, and misfolded envelope proteins may have a lower target cell binding rate. Either effect may cause the production of infectious propagules to decline if translation occurs faster. Propagule production would thus peak at an intermediate rate of exploitation, which is what the cost function (eq. 2) describes. Another possible underlying mechanism is toxin production (Day 2002): greater exploitation of the host may be achieved by the production of molecular compounds that compromise the host immune system and increase host mortality as a side effect; there must be a cost, however, to the production of toxins, and the net benefit for the parasite may thus again reach its maximum at an intermediate level of toxin production.

The physiological cost of virulence may also follow indirectly from the increased morbidity of the host: as the host suffers greater exploitation, its very ability to acquire resources may be impaired, hence a reduced net income for the parasite. Morbidity costs were taken into account phenomenologically by Day (2001) by linking them to the contact rate; our approach is slightly more mechanistic, in the sense that morbidity costs would impact the parasite production rate, which might then alter the pattern of

contacts (depending on the emerging host and parasite population dynamics). One of Day's (2001) important conclusions was that morbidity costs can drive the evolution of intermediate virulence even in the absence of a mortality cost. In general, virulence evolution will be influenced by the combined effects of mortality costs and direct costs. This distinction was important to us because it makes it possible to study the relative effects of two selective pressures on virulence, one that actually depends on the host's coevolving defense—tolerance—and one that is independent of host defense (direct cost).

The model reveals nonmonotonic patterns of virulence coevolving with resistance and tolerance. As larger infection rate or propagation factor drives progressively higher risk of transmission, virulence increases sharply under the synergistic effect of coevolution with (rising) resistance, and tolerance; then virulence increases slowly in a coevolutionary pattern dominated by a selective interaction with tolerance; past some threshold on infection rate or propagation factor, the selective balance shifts and favors the influence of (falling) resistance, causing virulence to decrease, until resistance is completely counter-selected and tolerance is left as pure defense—then both virulence and tolerance essentially plateau.

Earlier models predicted the evolution of more virulent parasites in response to increasing host background mortality (Anderson and May 1979; Lenski and May 1994; van Baalen and Sabelis 1995; Ebert and Weisser 1997; Gandon et al. 2001). We found host physiological and environmental parameters in general, and host background mortality in particular, to have little effect on virulence, relative to the dominant influence of the physiological parameters of virulence (cost and efficiency) and the epidemiological parameters at low level of transmission (low infection rate or propagation factor). The relatively small sensitivity of evolved virulence to host parameters results primarily from the coevolutionary response of host defenses, which mitigates the effect of host parameters on virulence selection gradient (see Appendix S1 and Figs. S21–S28 therein). In particular, the quantitative response of virulence to increasing host background mortality suggests a complex interplay of selective forces acting on virulence and defenses, with net selection on virulence possibly changing sign depending on whether each defense is high, low, or zero. We also note that the related prediction of less virulence when parasite background mortality increases (Ewald 1993, 1994; Hochberg et al. 2000) was not systematically upheld. As parasite background mortality increases to high values, defenses are completely counterselected, which can select for more virulence.

According to previous theory, more virulence was expected to evolve when host resistance coevolves (e.g., Gandon et al. 2002). This model shows that in general, at evolutionary equilibirum, virulence coevolving with tolerance is lower than virulence coevolving with resistance, which is itself lower than virulence coevolving with both tolerance and resistance. Evolutionary patterns of virulence and defenses are generally complex, even under two-way coevolution (Restif and Koella 2003). Under three-way coevolution, there is a general tendency for systems that evolve more resistance and more tolerance also to evolve more virulence. However, more virulence in the parasite does not always coevolve with more defense in the host. More virulence can evolve correlatively with more resistance and less tolerance (when the cost of resistance decreases or resistance efficiency increases), or with less resistance and more tolerance (with the cost of tolerance, across low tolerance efficiency, or across intermediate virulence efficiency). Thus, groups of populations or species that experience different physiological factors may evolve the same evolutionary trade-off between defenses and yet opposite patterns of virulence covariation.

MUTATION DYNAMICS AND NONEQUILIBRIUM EVOLUTION

In this model, the adaptive dynamics always admitted a single, globally attracting point equilibrium. For given physiological, epidemiological, and environmental parameters, the evolutionary equilibrium was computed by numerical integration of the canonical equations of the adaptive traits dynamics (see Appendix), with an array of initial conditions (i.e., the traits ancestral values) that spanned the whole ecologically viable region of the trait space (see Fig. S1 for examples) and with evolutionary rates scaled to 1 for both species. Evolutionary rates compound (1) the probability that an offspring carries a mutation that alters the adaptive trait, and (2) the variance of the distribution of mutational effects on the trait. In real systems, the parasite or pathogen may have a higher mutation probability (1) and a smaller range of mutational effects (2) relatively to the host; as a consequence, there is no obvious assumption to make about the host's and parasite's evolutionary rates as defined and used in adaptive dynamics models. Moreover, the canonical equations of adaptive dynamics (see Appendix, eqs. A.1 and A.2) account for faster evolutionary change when generation time is shorter or reproductive population size is larger, both factors that are function of the ecological and evolutionary state of the system, and thus dynamical.

However, the evolutionary rates of adaptive dynamics are relative to the slow timescale of the model, that is, the evolutionary timescale as opposed to the ecological timescale. In host–parasite systems, this timescale separation may break down when mutation dynamics and ecological dynamics overlap (Day and Gandon 2007). We have taken a first step to understanding the consequences of not-so-rare (and not-so-small) mutations by examining the consequences of multiple mutants arising around evolutionary equilibrium. It turns out that invasion of a mutant catalyzed by the presence of another, eventually unsuccessful

mutant, is a common outcome. "Evolutionary spikes" of virulence or defense may often result, whereby a large mutant in one trait invades whereas the other traits essentially remain at evolutionary equilibrium. The model predicts evolutionary spikes to be significant source of variation in virulence in populations in which the infection rate is low, virulence efficiency is high, and parasite background mortality is high. A related phenomenon has been described by Best et al. (2009) in a model of virulence coevolving with avoidance. When the parasite has a higher mutation rate than the host, virulence was found to vary considerably on its way to the system's evolutionary equilibrium. Thus, Best et al.'s (2009) model and ours predict substantial transients in virulence of parasites with rapid mutation, and this may explain some of the bursting variation in parasite virulence that we see in nature. This may have practical implications for the control of disease emergence and the management of virulence (Dieckmann et al. 2002; Ebert and Bull 2003).

IMPLICATIONS FOR THE EVOLUTIONARY MANAGEMENT OF INFECTIONS

Evolutionary management of an infection seeks to interfere with or even redirect the evolution of host–parasite systems to achieve some desired practical goals—such as low virulence in the pathogens or pests, and high resistance or high tolerance in their hosts (Dieckmann et al. 2002). In agriculture for example, there is a growing interest in the use of parasite-tolerant crop plants as alternatives to chemical control. In this model, there are at least six parameters that may be amenable to management. On the one hand, epidemiological measures can alter the rate of contact, propagation factor, and background mortality rate of the parasite, thus modifying the pattern of transmission. On the other hand, virulence efficiency, resistance efficiency, and tolerance efficiency may be targeted by drug treatments.

Miller et al. (2006) cautioned that parasite evolution in response to host tolerance may lead to higher prevalence with lower, but still significant damage to the host. The results of the three-trait coevolutionary model further illuminates such conflicting effects and potential pitfalls of the evolutionary management of infections. Designing and using drugs that reduce virulence efficiency will select for more resistance and more tolerance provided that virulence efficiency is not knocked down too low; but in general reducing virulence efficiency will select parasites that are more virulent (Figs. 5D and 6A,F,K). Increasing resistance efficiency seems also problematic, as this would select strongly against tolerance, favor more virulent parasites, and could even lead to decreased resistance (Fig. 5G); similar consequences would follow from increasing tolerance efficiency (Fig. 5I). On the epidemiological side, management action would have to be strong enough to reduce the infection rate or propagation factor drastically to beget an evolutionary fall of virulence; but this would happen at the cost of a dramatic loss of resistance and tolerance occurring first (Figs. 6B, C, G, H, L, and M). Increasing the rate of mortality of free-living parasites may yield only a slim reduction in virulence while selecting strongly against both resistance and virulence (Figs. 5E and 6D, I, N).

Thus, coevolution of virulence and both defenses is unfavorable to evolutionary management compared to predictions from two-trait models, by promoting more virulence in general, and by accelerating the loss of defenses in response to management action on epidemiological, physiological, or environmental parameters. Evolutionary transients due to mutant catalysis and evolutionary spikes add to the "moving target" challenge raised by virulence evolution (Best et al. 2009). Put in a spatially heterogeneous context, these effects may prove disastrous if more virulent strains and less-defended hosts end up encountering in areas that are not covered by the management plan. To be effective, evolutionary management programs would have to combine actions on several parameters simultaneously, and optimize their implementation in time and space.

Conclusions and Perspectives

Our model provides a unified framework to study the concurrent evolution of resistance, tolerance, and virulence. The results are consistent with previous findings that provided partial insights into the coevolutionary process: greater tolerance evolved as a single trait (Miller et al. 2005) or coevolved with resistance (Restif and Koella 2004) in response to increasing transmission risk; resistance (coevolved with tolerance) maximized at intermediate transmission risk (Restif and Koella 2004); greater defense (resistance or tolerance) evolving as a single trait (Miller et al. 2005) or coevolving with virulence (Restif and Koella 2003) in response to decreasing host background mortality; negative correlation evolving between resistance and tolerance without assuming any physiological trade-off between the traits at the individual level (Restif and Koella 2004). Echoing the conclusions drawn from earlier models, our results emphasize the strong evolutionary effects of physiological costs of virulence and defenses, and thus reiterate the need to devote more experimental work to measuring these costs (Boots and Begon 1993; Antonovics and Thrall 1994; Bowers et al. 1994; Restif and Koella 2004).

The model yields several novel predictions that contrast with previous theory. This is because the model analysis addressed the concurrent evolution of all three traits, and studied their response to variation in a broad set of physiological, epidemiological, and environmental parameters. These predictions include: (1) Compared to two-way coevolutionary scenarios (virulence coevolving with resistance or tolerance), three-trait coevolution generally favors more virulence and less tolerance, and enlarges the range of parameters over which pure defenses evolve. (2) The key factors of

adaptive variation in virulence are physiological virulence parameters (cost, efficiency) and epidemiological parameters (infection rate, propagation factor). The host's physiological and environmental parameters have relatively little influence on virulence evolution. In particular, the expectation that decreasing host background mortality selects against virulence is matched only when virulence efficiency and transmission risk are low. (3) Maximum virulence evolves at intermediate transmission risk, at which both coevolving resistance and tolerance reach high levels. (4) More virulence may evolve in response to increasing host background mortality, but only when virulence efficiency and transmission risk are low. (5) Evolutionary correlations between defenses (resistance and tolerance) can switch sign in response to variation in single physiological or epidemiological parameters. (6) The same negative correlation between resistance and tolerance (evolutionary trade-off) may coevolve with monotonically increasing or monotonically decreasing virulence, depending of the underlying factor of variation. (7) In spite of the global attractivity and stability of coevolutionary equilibria, mutant-catalyzed invasion and large "evolutionary spikes" of virulence and defenses are expected around equilibrium.

The results illustrate the complexity of interactions between selective pressures acting on multiple traits, and feedbacks between epidemiological and evolutionary dynamics. In particular, physiological parameters involved in the cost or benefit of one trait can have selective effects that propagate to the evolutionary dynamics of the other traits. These indirect effects may dominate in magnitude over direct effects: variation in resistance or tolerance efficiency parameters have much less direct effects on selected resistance or tolerance, respectively, as they have on the other defense trait and on virulence. Moreover, the counterselection of one defense may have abrupt and unexpected consequences for the coevolution of the other defense and virulence. Implications for the evolutionary management of infections are potentially severe.

Our model analysis and conclusions point to three directions for future research. First, our analysis has confirmed the importance of the feedbacks between adaptive change in tolerance and epidemiological change in prevalence (Roy and Kirchner 2000). This suggests that acquired immunity by the host is a factor—not considered in this model—that could have profound consequences for the evolution of tolerance, and therefore resistance and virulence. Immunity could be modeled first as an additional parameter in the model, and then as an adaptive trait that would be expressed at an additional cost to the host (e.g., Gilchrist and Sasaki 2002, André and Gandon 2006).

Second, our analysis focused on evolutionary outcomes as predicted by evolutionarily attractive and stable equilibria. When mutation occurs on a fast enough timescale (in one or both species), mutant catalysis can trigger evolutionary spikes that keep the system away from evolutionary equilibrium. Whether different ecological or epidemiological assumptions might lead to the persistent coexistence of multiple phenotypes, hence the evolution of polymorphism, warrants further investigation. For example, in their model of virulence-clearance coevolution, Best et al. (2009) found that density dependence acting on the host birth rate may oppose evolutionary branching in virulence, whereas density dependence acting on host death rate is conducive to virulence branching. A role for evolutionary branching to explain highly polymorphic virulence was advocated also by Svennungsen and Kisdi (2009). Evolutionary branching may also explain the coexistence of different strains of resistance in the host (Miller et al. 2005). Host and parasite mutation rates play an important role in determining the actual occurrence of evolutionary branching once the ecological conditions permit branching (Kisdi 1999; Best et al. 2009). Variation in the mutation rates may also affect the attractiveness of the evolutionary equilibrium, by turning the equilibrium into an evolutionary cycle (Dieckmann and Law 1996; Khibnik and Kondrashov 1997; Dercole et al. 2006a) or a more complex evolutionary attractor (Dercole et al. 2006b; Dercole and Rinaldi 2008). Investigating such a possibility would shed light on the consequences of tolerance for the Red Queen cycle of adaptation and counter-adaptation that is known to evolve under certain conditions between virulence and resistance (Khibnik and Kondrashov 1997; Dercole et al. 2006b).

In a related vein, our analysis assumed genetic independence of variation in the host defenses. This approach is appropriate to predict the patterns of trait covariation resulting purely from adaptive responses to physiological, environmental, or epidemiological factors, and thus to tease these patterns apart from potential effects of genetic constrains. Furthermore, genetic covariance, although not changing the evolutionary equilibria, may alter their long-term stability properties (Dieckmann and Law 1996; Dercole and Rinaldi 2008). There is empirical evidence that resistance and tolerance can be genetically linked (Stowe 1998; Ayres and Schneider 2008) or vary pleiotropically, for example, when a single trait combines tolerance and resistance, such as slow rusting in cereal crops (Vanderplank 1984). Quantitative analysis of such genetic covariance is still lacking. The tools of ecological genomics will help tackle this challenge, but even in plants, where tolerance has long been studied, genes conferring disease tolerance have yet to be identified at the molecular level (Rausher 2001; Raberg et al. 2009). Theoretical analyses, by identifying the characteristics of systems in which genetic covariation should have strong coevolutionary consequences, will help and guide this empirical endeavor.

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LITERATURE CITED

Alizon, S., and M. van Baalen. 2005. Emergence of a convex trade-off between transmission and virulence. Am. Nat. 165:E155–E167.

———. 2008. Multiple infections, immune dynamics, and the evolution of virulence. Am. Nat. 172:E150–E168.

Alizon, S., A. Hurford, N. Mideo, and M. van Baalen. 2009. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. J. Evol. Biol. 22:245–259.

Anderson, R. M., and R. M. May. 1979. Population biology of infectious diseases: part I. Nature 280:361–367.

Anderson, R. M., and R. M. May. 1982. Coevolution of hosts and parasites. Parasitology 85:411–426.

André, J. B., and S. Gandon. 2006. Vaccination, within-host dynamics, and virulence evolution. Evolution 60:13–23.

André, J. B., J. B. Ferdy, and B. Godelle. 2003. Within-host parasite dynamics, emerging trade-off, and the evolution of virulence with immune system. Evolution 57:1489–1497.

Antonovics, J., and P. H. Thrall. 1994. The cost of resistance and the maintenance of genetic polymorphism in host-pathogen systems. Proc. R. Soc. Lond. B 247:105–110.

Athreya, K. B. 1993. Rates of decay for the survival probability of a mutant gene. II. The multitype case. J. Math. Biol. 32:45–53.

Athreya, K. B., and P. E. Ney. 1972. Branching processes. Springer-Verlag, New York.

Ayres, J. S., and D. S. Schneider. 2008. A signaling protease required for melanization in *Drosophila* affects resistance and tolerance of infections. PLoS Biol. 6:2764–2773.

Barker, K. R. 1993. Resistance/tolerance and related concepts/terminology in plant nematology. Plant Disease 77:111–113.

Baucom, R. S., and R. Mauricio. 2008. Constraints on the evolution of tolerance to herbicide in the common morning glory: resistance and tolerance are mutually exclusive. Evolution 62:2842–2854.

Best, A., A. White, and M. Boots. 2009. The implications of coevolutionary dynamics to host-parasite interactions. Am. Nat. 173:779–791.

Bonds, M. H. 2006. Host life-history strategy explains pathogen-induced sterility. Am. Nat. 168:281–293.

Bonhoeffer, S., R. E. Lenski, and D. Ebert. 1996. The curse of the pharaoh: the evolution of virulence in pathogens with long living propagules. Proc. R. Soc. London B. 263:715–721.

Boots, M. 2008. Fight or learn to live with the consequences? Trends Ecol. Evol. 23:248–250.

Boots, M., and M. Begon. 1993. Trade-off with resistance to a granulosis virus in the Indian meal moth, examined by a laboratory evolution experiment. Funct. Ecol. 7:528–534.

Bowers, R. G., M. Boots, and M. Begon. 1994. Life-history trade-offs and the evolution of pathogen resistance: competition between host strains. Proc. R. Soc. Lond. B 257:247–253.

Carr, D. E., J. F. Murphy, and M. D. Eubanks. 2006. Genetic variation and covariation for resistance and tolerance to Cucumber mosaic virus in *Mimulus guttatus* Phrymaceae: a test for costs and constraints. Heredity 96:29–38.

Champagnat, N., R. Ferriere, and S. Meleard. 2006. Unifying evolutionary dynamics: from individual stochastic processes to macroscopic models. Theor. Popul. Biol. 69:297–321.

Clarke, D. D. 1986. Tolerance of parasites and disease in plants and its significance in host-parasite interactions. Adv. Plant Pathol. 5:161–197.

Day, T. 2001. Parasite transmission modes and the evolution of virulence. Evolution 55:2389–2400.

———. 2002. Virulence evolution via host exploitation and toxin production in spore-producing pathogens. Ecol. Lett. 5:471–476.

Day, T., and S. Gandon. 2007. Applying population-genetic models in theoretical evolutionary epidemiology. Ecol. Lett. 10:876–888.

Dercole, F., J. O. Irisson, and S. Rinaldi. 2006a. Bifurcation analysis of a predator-prey coevolution model. SIAM J. Appl. Math. 63:1378–1391.

Dercole, F., R. Ferriere, A. Gragnani, and S. Rinaldi. 2006b. Coevolution of slow-fast populations: evolutionary sliding, evolutionary pseudo-equilibria and complex Red Queen dynamics. Proc. Biol. Sci. 273:983–990.

Dercole, F., and S. Rinaldi. 2008. Analysis of evolutionary processes. Princeton Univ. Press, Princeton, NJ.

Dieckmann, U., and R. Law. 1996. The dynamical theory of coevolution: a derivation from stochastic ecological processes. J. Math. Biol. 34:579–612.

Dieckmann, U., J. A. J. Metz, M. W. Sabelis, and K. Sigmund. 2002. Adaptative dynamics of infectious diseases. Cambridge Univ. Press, Cambridge.

Ebert, D., and J. J. Bull. 2003. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? Trends Microbiol. 11:15–20.

Ebert, D., and W. W. Weisser. 1997. Optimal killing for obligate killers: the evolution of life histories and virulence of semelparous parasites. Proc. Biol. Sci. 264:985–991.

Ewald, P. W. 1993. Evolution of virulence. Sci. Am. 268:86–93.

———. 1994. The evolution of infectious diseases. Oxford Univ. Press, Oxford.

Fineblum, W. L., and M. D. Rausher. 1995. Trade-off between resistance and tolerance to herbivore damage in a morning glory. Nature 377:517–520.

Fornoni, J., P. L. Valverde, and J. Nunez-Farfan. 2003. Quantitative genetics of plant tolerance and resistance against natural enemies of two natural populations of *Datura stramonium*. Evol. Ecol. Res. 5:1049–1065.

Fornoni, J., J. Nunez-Farfan, P. L. Valverde, and M. D. Rausher. 2004. Evolution of mixed plant defense allocation against natural enemies. Evolution 58:1685–1695.

Frank, S. A. 1996. Models of parasite virulence. Q. Rev. Biol. 71:37–78.

Gandon, S., V. A. Jansen, and M. van Baalen. 2001. Host life history and the evolution of parasite virulence. Evolution 55:1056–1062.

Gandon, S., M. van Baalen, and V. A. Jansen. 2002. The evolution of parasite virulence, superinfection, and host resistance. Am. Nat. 159:658–669.

Gilchrist, M. A., and A. Sasaki. 2002. Modeling host-parasite coevolution: a nested approach based on mechanistic models. J. Theor. Biol. 218:289–308.

Gilchrist, M. A., D. Coombs, and A. S. Perelson. 2004. Optimizing within-host viral fitness: infected cell lifespan and virion production rate. J. Theor. Biol. 229:281–288.

Hochberg, M. E., and M. van Baalen. 1998. Antagonistic coevolution over productivity gradients. Am. Nat. 152:620–634.

Hochberg, M. E., R. Gomulkiewicz, R. D. Holt, and J. N. Thompson. 2000. Weak sinks could cradle mutualistic symbioses: strong sources should harbour parasitic symbioses. J. Evol. Biol. 13:213–222.

Hofbauer, J., and K. Sigmund. 1998. Evolutionary games and population dynamics. Cambridge Univ. Press, Cambridge.

Khibnik, A. I., and A. S. Kondrashov. 1997. Three mechanisms of Red Queen dynamics. Proc. R. Soc. Lond. B 264:1049–1056.

Kisdi, E. 1999. Evolutionary branching under asymmetric competition. J. Theor. Biol. 197:149–162.

Koella, J., and C. Boete. 2003. A model for the coevolution of immunity and immune evasion in vector-borne diseases with implications for the epidemiology of malaria. Am. Nat. 161:698–707.

Kostitzin, V. A. 1934. Symbiose, parasitisme et évolution (étude mathématique). Actualités Scientifiques et Industrielles 96:337–381.

Kover, P. X., and B. A. Schaal. 2002. Genetic variation for disease resistance and tolerance among *Arabidopsis thaliana* accessions. Proc. Natl. Acad. Sci. USA 99:11270–11274.

Law, R., and U. Dieckmann. 1998. Symbiosis through exploitation and the merger of lineages in evolution. Proc. R. Soc. Lond. B. 265:1245–1253.

Le Galliard, J. F., R. Ferriere, and U. Dieckmann. 2005. Adaptive evolution of social traits: origin, trajectories, and correlations of altruism and mobility. Am. Nat. 165:206–224.

Lenski, R. E., and R. M. May. 1994. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. J. Theor. Biol. 169:253–265.

Mauricio, R., M. D. Rausher, and D. S. Burdick. 1997. Variation in the defense strategies of plants: are resistance and tolerance mutually exclusive? Ecology 78:1301–1310.

Metz, J. A. J., R. M. Nisbet, and S. A. H. Geritz. 1992. How should we define 'fitness' for general ecological scenarios? Trends. Ecol. Evol. 7:198–202.

Metz, J. A. J., S. A. H. Geritz, G. Meszena, F. J. A. Jacobs, and J. S. van Heerwaarden. 1996. Adaptive dynamics, a geometrical study of the consequences of nearly faithful reproduction. Pp. 183–231 *in* S. J. van Strien and S. M. Verduyn Lunel, eds. Stochastic and spatial structures of dynamical systems. North Holland, Amsterdam.

Mideo, N., S. Alizon, and T. Day. 2008. Linking within- and between-hot dynamics in the evolutionary epidemiology of infectious diseases. Trends. Ecol. Evol. 23:511–517.

Miller, M. R., A. White, and M. Boots. 2005. The evolution of host resistance: tolerance and control as distinct strategies. J. Theor. Biol. 236:198–207.

———. 2006. The evolution of parasites in response to tolerance in their hosts: the good, the bad, and apparent commensalism. Evolution 60:945–956.

Nowak, M. A., and K. Sigmund. 1992. Tif-For-Tat in heterogeneous populations. Nature 355:250–253.

Pugliese, A. 2002. On the evolutionary coexistence of parasite strains. Math Biosci. 177:355–375.

Raberg, L., D. Sim, and A. F. Read. 2007. Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. Science 318:812–814.

Raberg, L., A. L. Graham, and A. F. Read. 2009. Decomposing health: tolerance and resistance to parasites and animals. Philos. Trans. R. Soc. Biol. Sci. 364:37–49.

Rausher, M. D. 2001. Co-evolution and plant resistance to natural enemies. Nature 411:857–864.

Restif, O., and J. C. Koella. 2003. Shared control of epidemiological traits in a coevolutionary model of host-parasite interactions. Am. Nat. 161:827–836.

———. 2004. Concurrent evolution of resistance and tolerance to pathogens. Am. Nat. 164:E90–E102.

Roy, B. A., and J. W. Kirchner. 2000. Evolutionary dynamics of pathogen resistance and tolerance. Evolution 54:51–63.

Rueffler, C., M. Egas, and J. A. J. Metz. 2006. Evolutionary predictions should be based on individual-level traits. Am. Nat. 168:E148–E162.

Sasaki, A. 2000. Host-parasite coevolution in a multilocus gene-for-gene system. Proc. Biol. Sci. 267:2183–2188.

Schmid-Hempel, P., and S. A. Frank. 2007. Pathogenesis, virulence, and infective dose. PLoS Pathog. 3:1372–1373.

Simms, E. L., and J. Triplett. 1994. Costs and benefits of plant responses to disease: resistance and tolerance. Evolution 48:1973–1985.

Stowe, K. A. 1998. Experimental evolution of resistance in *Brassica rapa*: correlated response in lines selected for glucosinolate content. Evolution 52:703–712.

Svennungsen, T. O., and E. Kisdi. 2009. Evolutionary branching of virulence in a single-infection model. J. Theor. Biol. 257:408–418.

Thompson, J. N. 1994. The coevolution process. Univ. of Chicago Press, Chicago.

Tiffin, P. 2000. Are tolerance, avoidance, and antibiosis evolutionarily and ecologically equivalent responses of plants to herbivores? Am. Nat. 155:128–138.

Tiffin, P., and M. D. Rausher. 1999. Genetic constraints and selection acting on tolerance to herbivory in the common morning glory *Ipomoea purpurea*. Am. Nat. 154:700–716.

van Baalen, M. 1998. Coevolution of recovery ability and virulence. Proc. R. Soc. Lond. B 265:317–325.

van Baalen, M., and V. A. A. Jansen. 2001. Dangerous liaisons: the ecology of private interest and common good. Oikos 95:211–224.

van Baalen, M., and M. W. Sabelis. 1995. The dynamics of multiple infection and the evolution of virulence. Am. Nat. 146:881–910.

Vanderplank, J. E., Ed. 1984. Disease resistance in plants. Academic Press, Orlando.

Vera Cruz, C. M., J. F. Bai, I. Ona, H. Leung, R. J. Nelson, T. W. Mew, and J. E. Leach. 2000. Predicting durability of a disease resistance gene based on an assessment of the fitness loss and epidemiological consequences of avirulence gene mutation. Proc. Natl. Acad. Sci. USA 97:13500–13505.

Weinig, C., L. A. Dorn, N. C. Kane, Z. M. German, S. S. Halldorsdottir, M. C. Ungerer, Y. Toyonaga, T. F. C. Mackay, M. D. Purugganan, and J. Schmitt. 2003. Heterogeneous selection at specific loci in natural environments in *Arabidopsis thaliana*. Genetics 165:321–329.

Wolin, C. 1985. The population dynamics of mutualistic systems. Pp. 248–269 *in* D. H. Boucher, ed. The biology of mutualism. Oxford University Press, New York.

Woolhouse, M. E. J., J. P. Webster, E. Domingo, B. Charlesworth, and B. R. Levin. 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. Nat. Genet. 32:569–577.

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Appendix: Ecological and Evolutionary Analysis

ECOLOGICAL DYNAMICS

The ecological model is an SIS model with a free-living parasite stage and no direct host-to-host parasite transmission. The equations are adapted from Kostitzin's model (Kostitzin 1934) in which the linear density dependence of birth that regulates the host population is replaced with a more realistic nonlinear (saturating) function of density (see van Baalen and Jansen 2001 for a similar adjustment). Writing densities explicitly in the right-hand side of equations (1A–C) we have

$$\frac{dX}{dt} = -\mu_X X - \beta XY + \sigma_X Z$$
$$\frac{dY}{dt} = \left(\frac{\hat{\rho}_Y}{1+\kappa(Y+Z)} - \mu_Y\right) X - \beta XY + \left(\frac{\hat{\rho}_Y}{1+\kappa(Y+Z)} + \nu_X\right) Z$$
$$\frac{dZ}{dt} = \beta XY - (\nu_X + \nu_{XY})Z,$$

where $\hat{\rho}_Y$ is a function of host traits given by eq. (5). Straightforward algebra on this system of equations shows that there are at least two and at most four ecological equilibria (i.e., equilibria with nonnegative X, Y, and Z values):

- If the parasite population is in demographic deficit, that is, $\sigma_X < \nu_X + \nu_{XY}$, then there are exactly two ecological equilibria: (0, 0, 0) that is, extinction of the whole system, and the host-only equilibrium $(0,\ (\hat{\rho}_Y/\mu_Y - 1)/\kappa,\ 0)$.
- If $\sigma_X > \nu_X + \nu_{XY}$, nonzero X at equilibrium can take on one or two values $\bar{X}$. Then $\bar{Y}$ and $\bar{Z}$ are uniquely determined by $\bar{Y} = ((\nu_X + \nu_{XY})/\beta)\ (\mu_X/(\sigma_X - \nu_X - \nu_{XY}))$ and $\bar{Z} = \beta\bar{X}\bar{Y}/(\nu_X + \nu_{XY})$.

When $\sigma_X > \nu_X + \nu_{XY}$, ecological equilibrium $\bar{X}$ assumes one or two values depending on whether the discriminant of a polynomial equation of degree 2 is null or positive. The polynomial, the zeros of which return the $\bar{X}$ values, is

$$P(X) = \hat{\rho}_Y(1+\zeta X) - (\mu_Y + \zeta\nu_{XY}X)[1 + (\kappa\mu_X/(\zeta\sigma_X - \beta))(1+\zeta X)].$$

Local stability analysis of each ecological equilibrium involves the Jacobian matrix of the system, $\mathbf{J} = [J_{ik}]$ with $1 \le i, k \le 3$. We have

$$J_{11} = -\mu_X - \beta Y, \quad J_{12} = -\beta X, \quad J_{13} = \sigma_X,$$
$$J_{21} = -\beta Y, \quad J_{22} = -\mu_Y - \beta X + \hat{\rho}_Y/[1+\kappa(Y+Z)]^2,$$
$$J_{23} = \beta + \hat{\rho}_Y/[1+\kappa(Y+Z)]^2,$$
$$J_{31} = \beta Y, \quad J_{32} = \beta X, \quad J_{33} = -(\nu_X + \nu_{XY}).$$

At ecological equilibrium (0, 0, 0), the Jacobian eigenvalues are $-\mu_X, -(\nu_X + \nu_{XY}), \hat{\rho}_Y - \mu_Y$. Hence the condition for local stability of (0, 0, 0): $\hat{\rho}_Y < \mu_Y$, that is, deficit in the host's demographic potential. At the host-only ecological equilibrium, some straightforward algebra shows that one eigenvalue is always real negative, and the other two are the roots of the degree 2 polynomial with positive discriminant, with at least one of the two (real) roots that is negative. The condition for local stability of the host-only equilibrium follows:

$$(\nu_X + \nu_{XY})\mu_X/\beta \ < \ (\sigma_X - \nu_X - \nu_{XY})(\hat{\rho}_Y/\mu_Y - 1)/\kappa.$$

To check the existence of one or two internal equilibria of host–parasite ecological coexistence and establish their local stability, systematic numerical analysis can be performed throughout the entire trait space $0 \le x_1, y_1, y_2 \le 1$, for any given set of physiological, environmental, and epidemiological parameter values. Exact expressions for the equilibrium or equilibria and for the corresponding Jacobian eigenvalues were obtained by symbolic computation using *Mathematica*®6 software (Wolfram Research Inc.). Numerical testing was then performed for a broad range of parameter values, with six theoretically possible outcomes: there are two internal equilibria and both, only one, or none are (is) locally stable; there is only one internal equilibria and it is locally stable, or not; or there is no internal equilibrium, that is, no host–parasite coexistence (in which case possible equilibria are host-only and extinction). Extensive simulations showed that only two outcomes are realized: one locally stable internal equilibrium, or no coexistence. A sample of numerical examples are provided in Figure S1, where parameters that turn out to have the greatest evolutionary influence are investigated.

EVOLUTIONARY DYNAMICS

Evolutionary dynamics of the adaptive traits are driven by the traits' selection gradient, which obtains from calculating the population growth rate of a mutant host or parasite in a resident host–parasite system at ecological equilibrium. The population dynamics of a mutant parasite with density $\tilde{X}$ interacting with a resident population of susceptible hosts (density Y) are governed by

$$\frac{d\tilde{X}}{dt} = -\mu_X\tilde{X} - \beta\tilde{X}Y + \sigma_{\tilde{X}}\tilde{Z}$$
$$\frac{d\tilde{Z}}{dt} = \beta\tilde{X}Y - (\nu_{\tilde{X}} + \nu_{\tilde{X}Y})\tilde{Z},$$

where $\tilde{Z}$ denotes the density of hosts infected by mutant $\tilde{X}$. Likewise the dynamics of a susceptible population of mutant host with density $\tilde{Y}$ interacting with a resident parasite population (density X) are governed by

$$\frac{d\tilde{Y}}{dt} = (\rho_{\tilde{Y}} - \mu_Y)\tilde{Y} - \beta X\tilde{Y} + (\sigma_{\tilde{Y}} + \nu_{\tilde{Y}})\tilde{Z}$$
$$\frac{d\tilde{Z}}{dt} = \beta X\tilde{Y} - (\nu_X + \nu_{X\tilde{Y}})\tilde{Z},$$

where we (slightly abusively) denote again by $\tilde{Z}$ the density of mutant hosts that are infected by resident parasite X.

Mutant populations are initially small and their impact on the resident populations at ecological equilibrium is negligible. Linearization of the resident-mutant dynamical system around the resident ecological equilibrium, $(\bar{X}, \bar{Y}, \bar{Z})$, yields the following equations for mutant population growth from small density:

$$\frac{d}{dt}\begin{pmatrix}\tilde{X}\\ \tilde{Z}\end{pmatrix} = \mathbf{L}_{\tilde{X}}\begin{pmatrix}\tilde{X}\\ \tilde{Z}\end{pmatrix}$$

where

$$\mathbf{L}_{\tilde{X}} = \begin{pmatrix} -\mu_X - \beta\bar{Y} & \sigma_{\tilde{X}} \\ \beta\bar{Y} & -(\nu_{\tilde{X}} + \nu_{\tilde{X}Y}) \end{pmatrix}$$

and

$$\frac{d}{dt}\begin{pmatrix} \tilde{Y} \\ \tilde{Z} \end{pmatrix} = \mathbf{L}_{\tilde{Y}} \begin{pmatrix} \tilde{Y} \\ \tilde{Z} \end{pmatrix}$$

where

$$\mathbf{L}_{\tilde{Y}} = \begin{pmatrix} (\rho_{\tilde{Y}} - \mu_Y) - \beta\bar{X} & \sigma_{\tilde{Y}} + \nu_X \\ \beta\bar{X} & -(\nu_X + \nu_{X\tilde{Y}}) \end{pmatrix}.$$

A first-order approximation of the invasion fitness $\lambda_{\tilde{X}}$ of mutant $\tilde{X}$ is given by

$$\lambda_{\tilde{X}} = \frac{-(\nu_{\tilde{X}} + \nu_{\tilde{X}Y})}{\mathrm{Tr}_{\tilde{X}}}\left[-\mu_X + \beta\bar{Y}\left(\frac{\sigma_{\tilde{X}}}{\nu_{\tilde{X}} + \nu_{\tilde{X}Y}} - 1\right)\right]$$

where $\mathrm{Tr}_{\tilde{X}}$ is the trace of the matrix $\mathbf{L}_{\tilde{X}}$. Likewise, invasion fitness $\lambda_{\tilde{Y}}$ of mutant $\tilde{Y}$ is

$$\lambda_{\tilde{Y}} = \frac{-(\nu_X + \nu_{X\tilde{Y}})}{\mathrm{Tr}_{\tilde{Y}}}\left[(\rho_{\tilde{Y}} - \mu_Y) + \beta\bar{X}\left(\frac{\sigma_{\tilde{Y}}}{\nu_X + \nu_{X\tilde{Y}}} - 1\right)\right],$$

where $\mathrm{Tr}_{\tilde{Y}}$ is the trace of the matrix $\mathbf{L}_{\tilde{Y}}$.

Let the right and left eigenvectors of matrix $\mathbf{L}_{\tilde{X}}$ be denoted by $\mathbf{U}_{\tilde{X}} = (U_{1\tilde{X}}\ ,\ U_{2\tilde{X}})$ and $\mathbf{V}_{\tilde{X}} = (V_{1\tilde{X}}\ ,\ V_{2\tilde{X}})$, with the normalizations $U_{1\tilde{X}} + U_{2\tilde{X}} = 1$ and $U_{1\tilde{X}}V_{1\tilde{X}} + U_{2\tilde{X}}V_{2\tilde{X}} = 1$. We use corresponding notations for the host. Then, the probabilities of nonextinction of the mutant parasite and mutant host are, respectively,

$$\mathrm{P}_{\tilde{X}} = \frac{\lambda_{\tilde{X}}}{\sigma_{\tilde{X}}U_{2\tilde{X}}V_{2\tilde{X}}}$$

$$\mathrm{P}_{\tilde{Y}} = \frac{\lambda_{\tilde{Y}}}{\sigma_{\tilde{Y}}U_{2\tilde{Y}}V_{2\tilde{Y}}}$$

(Athreya and Ney 1972; see also Theorem 1 in Athreya 1993, and Law and Dieckmann 1998).

The canonical equations for the adaptive dynamics of the parasite's trait x_1 and the host's trait y_i ($i = 1$ or 2) follow:

$$\frac{dx_1}{dt} = k_{x_1}\,\sigma_X\bar{Z}\,\frac{\partial P_{\tilde{X}}}{\partial\tilde{x}_1} \tag{A.1}$$

$$\frac{dy_i}{dt} = k_{y_i}\,(\rho_Y\bar{Y} + \sigma_Y\bar{Z})\,\frac{\partial P_{\tilde{Y}}}{\partial\tilde{y}_i}, \tag{A.2}$$

where partial derivatives with respect to mutant traits $(\tilde{x}_1, \tilde{y}_i)$ are evaluated at the resident trait values. In each equation, the k coefficient is the trait's evolutionary rate, which compounds mutation probability per birth, and mutation step variance. The effective speed of evolutionary change is determined by the evolutionary rate times the total reproductive rate ($\sigma_X\bar{Z}$ in eq. A.1 and $(\rho_Y\bar{Y} + \sigma_Y\bar{Z})$ in eq. A.2).

Numerically, for any given set of parameter values, we implemented a sampling scheme (grid) that spanned the entire trait space, and for each point on the grid, that is, each combination of resident trait values, the ecological equilibrium was computed (see previous section), and the selective pressures were then evaluated. The results of these evaluations over the grid were interpolated to recover a continuous (polynomial) selection gradient. The interpolation was then used for the numerical integration of the canonical equations (by means of standard Runge–Kutta method). Finally, the convergence of the solutions to a single equilibrium was tested by varying the initial conditions across the grid.

Supporting Information

The following supporting information is available for this article:

Figure S1. Ecological equilibria across virulence–resistance–tolerance trait space. Effect of virulence efficiency (ω_{x1}), infection rate (β), and parasite background mortality (μ_{1X}).

Figures S2–S10. Univariate evolutionary patterns of resistance, tolerance, and virulence as predicted by RT, VR, VT, and VRT models: Sensitivity analysis with respect to virulence efficiency, infection rate, and host or parasite background mortality.

Figure S11. Resistance–tolerance correlation evolving in response to variation in parasite parameters under three-way coevolution (VRT model).

Figures S12–S14. Invasibility of the resistance–tolerance evolutionary equilibrium by mutant traits (RT model): Sensitivity analysis with respect to virulence efficiency, infection rate, and parasite background mortality.

Figures S15–S20. Invasibility of virulence–resistance (VR model), virulence–tolerance (VT model), and virulence–resistance–tolerance (VRT model) evolutionary equilibria by mutant traits: Sensitivity analysis with respect to virulence efficiency, infection rate, and parasite background mortality.

Appendix S1. On the sensitivity of virulence to host parameters. Includes:

Figure S21: Effect of host background mortality on virulence evolved in the absence of host coevolution compared to virulence coevolved with host defenses.

Figures S22, S23: Coevolved virulence and host defenses with respect to direct and indirect costs of virulence.

Figure S24: Effect of relative strength of direct and indirect costs of virulence on coevolved virulence and host defenses with respect to infection rate and host background mortality.

Figures S25, S26: Effect of direct cost of virulence and virulence–transmission conventional trade-off on coevolved virulence and host defenses with respect to infection rate and host background mortality.

Figures S27, S28: Effect of direct cost of virulence and nonlinearity in the indirect cost on coevolved virulence and host defenses with respect to infection rate and host background mortality.

Supporting Information may be found in the online version of this article.

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