Coevolution between Parasite Virulence and Host Life-History Traits

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Submitted January 2, 2001; Accepted February 8, 2002

ABSTRACT: Epidemiological models generally explore the evolution of parasite life-history traits, namely, virulence and transmission, against a background of constant host life-history traits. However, life-history models have predicted the evolution of host traits in response to parasitism. The coevolution of host and parasite life-history traits remains largely unexplored. We present an epidemiological model, based on resource allocation theory, that provides an analysis of the coevolution between host reproductive effort and parasite virulence. This model allows for hosts with either a fixed (i.e., genetic) or conditional (i.e., a phenotypically plastic) response to parasitism. It also considers superinfections. We show that parasitism always favors increased allocation to host reproduction, but because of epidemiological feedbacks, the evolutionarily stable host reproductive effort does not always increase with parasite virulence. Superinfection drives the evolution of parasite virulence and acts on the evolution of the host through parasite evolution, generally leading to higher host reproductive effort. Coevolution, as opposed to cases where only one of the antagonists evolves, may generate correlations between host and parasite life-history traits across environmental gradients affecting the fecundity or the survival of the host. Our results provide a theoretical framework against which experimental coevolution outcomes or field observations can be contrasted.

Keywords: reproductive effort, virulence, life history, evolution, coevolution, superinfection.

Evidence continues to accumulate in favor of the idea that hosts may alter their life-history traits in a way to compensate, at least partially, for the negative effects of parasitism (see Minchella 1985; Michalakis and Hochberg 1994; Koella et al. 1998; Richner 1998; Agnew et al. 2000 for reviews). Indeed, by affecting components of the host's current or future fecundity and/or probability of survival, parasites modify the ecological context in which host traits evolve. The host traits that have been shown to respond to parasitism vary from relationship to relationship and may depend on whether the host is simply exposed to parasitism or actually infected. These traits include early versus late fecundity (Reynolds 1970; Minchella and Lo-Verde 1981; Thornhill et al. 1986; Gérard and Théron 1997; Adamo 1999), reproductive effort (Sorci et al. 1996; Polak and Starmer 1998; Krist 2001), parental care (Christe et al. 1996; Richner and Trippet 1999), developmental time (Agnew et al. 1999), and body size (Lafferty 1993; Pontier et al. 1998; Arnott et al. 2000; we will not refer to the gigantism often preceding parasitic castration, whose interpretation remains controversial). In some cases, these modifications had a genetic determinism (e.g., body size at maturity; Lafferty 1993), while, in others, they were plastic, or conditional, responses (e.g., age of pupation; Agnew et al. 1999).

The type of host responses mentioned above are compatible with predictions from classical life history for any organism experiencing an environmental factor that reduces its probability of survival (Charnov and Shaffer 1973; Kisdi and Meszena 1995; Ronce and Olivieri 1997). However, the intrinsic dynamical nature of parasitism sets it apart from other abiotic components of the environment. Indeed, the selective pressures imposed by parasitism depend on the probability of becoming infected and on the cost of being infected (deleterious effect on the host). Both these factors may vary with host and parasite life histories. First, the rate at which susceptible hosts become infected (the force of infection) depends on parasite prevalence, which is a function of both host and parasite life-history traits. For example, all else being equal, a decrease in host life span and/or an increase in host mortality induced by parasitism reduce the duration of the infection and, therefore, yield low disease prevalence. Second, if parasite virulence (its deleterious effect on the host) is allowed to coevolve with the host, the cost of being infected may

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Am. Nat. 2002. Vol. 160, pp. 374–388.

also become an evolutionary variable. Both these epidemiological and coevolutionary processes may feed back on the evolution of host life-history traits. The impact of these feedbacks, however, has been overlooked in previous studies (Hochberg et al. 1992; Forbes 1993; Perrin et al. 1996; but see Koella et al. 1998 for a brief account and Koella 2000; Koella and Restif 2001; Restif et al. 2001). Perhaps because of the current lack of such a theoretical framework, experimental studies on the covariation of host and parasite life-history traits are also markedly absent.

In this article, we attempt to improve on this situation with the development of an epidemiological model allowing the evolution of host life history, exemplified here by its reproductive effort, and parasite life history, exemplified by virulence. Even though the latter could be viewed as a trait of the interaction or, indeed, even the host, we follow a long tradition of host-parasite theoretical models, assuming that variations in virulence are solely due to differences among parasite genotypes. First, we examine the evolution of the host trait; next, we examine the evolution of the parasite trait; and last, we explicitly address the issue of coevolution. This sequential examination is justified both heuristically and by the fact that coevolution does not necessarily occur between host and parasite traits. This could be the case for a number of reasons: one of the antagonists could lack genetic variation at the trait in question; the interaction under study could be essential for the fitness of one of the antagonists and negligible for the fitness of the other (e.g., host fitness is severely depressed by infection, while the parasite has many alternative hosts; the parasite is highly specific, while the host must face numerous parasites, predators, and competitors). Following Williams (1966), Forbes (1993), and Perrin et al. (1996), our model builds on resource allocation theory. In addition, we consider either conditional (i.e., phenotypically plastic) or fixed (i.e., genetic, host allocation patterns). Finally, our formalization allows for competition between parasites within infected hosts through superinfections (Nowak and May 1994; Gandon et al. 2001). The integration of these features enables us to explicitly study the coevolution of host and parasite life-history traits and make predictions on patterns relating them.

Host and Parasite Life Cycles

We consider a homogeneous host population where all individuals are equally susceptible to parasitic infection. Both infected and uninfected hosts can reproduce (we assume the parasite has no effect on host fecundity) and give birth to uninfected hosts (i.e., there is no vertical transmission). Infected hosts are unable to recover from the infection. As originally suggested by Williams (1966), we postulate that the host can allocate a fraction e, the reproductive effort, of its resources to reproduction and the remainder to maintenance and survival. For the sake of simplicity, we assume that the trade-off between reproduction and survival does not change during an individual's life. Host reproductive effort, however, may depend on the state of the host where e_x and e_y are the reproductive efforts of uninfected and infected hosts, respectively. The host may thus have different reproductive rates, $r_z = r[e_z]$ (with $z \equiv x$ or y), depending on whether it is infected or not. We further assume that the rate of host reproduction is reduced by a density-dependent factor $1 - \kappa(x + y)$, where κ measures the intensity of competition for resources and where x and y are the densities of uninfected and infected hosts, respectively. Death rates depend on the resources allocated to reproduction, $\delta_x = \delta[e_x]$ for uninfected hosts and $\delta_y = \delta[e_y]$ for infected hosts. The latter incur an additional mortality rate ν due to infection (i.e., parasite virulence). Note that density dependence is assumed to affect only host fecundity and not its survival rate.

Host exploitation by the parasite decreases the survival rate of infected individuals, and parasite virulence, ν, refers to this induced host mortality. The parasite is horizontally transmitted from one host to another with transmission rate β. Parasite transmission is assumed to depend on the host exploitation strategy and, consequently, to correlate with virulence, $\beta = \beta[\nu]$. The force of infection experienced by each host (i.e., the probability of being infected or reinfected) is $h = \beta y$. An infected host can be reinfected by another parasite strain with a rate σh, where σ measures the susceptibility to superinfection of already infected hosts. The process of replacing the previous strain is assumed to be instantaneous (superinfection) rather than slow (coinfection; May and Nowak 1995). Therefore, only

Table 1: Summary of main notations

Notation	Description
Host:	
e	Host reproductive effort
e_z	Conditional host reproductive strategy (with $z \equiv x$ or y)
r_m	Maximal rate of host reproduction
s_m	Maximal survival probability
r	Rate of host reproduction
δ	Natural host death rate
κ	Density-dependent factor
x	Density of uninfected hosts
Parasite:	
ν	Virulence (disease induced mortality)
β	Transmission rate
y	Density of infected hosts
$h \equiv \beta y$	Force of infection
σ	Susceptibility to superinfection

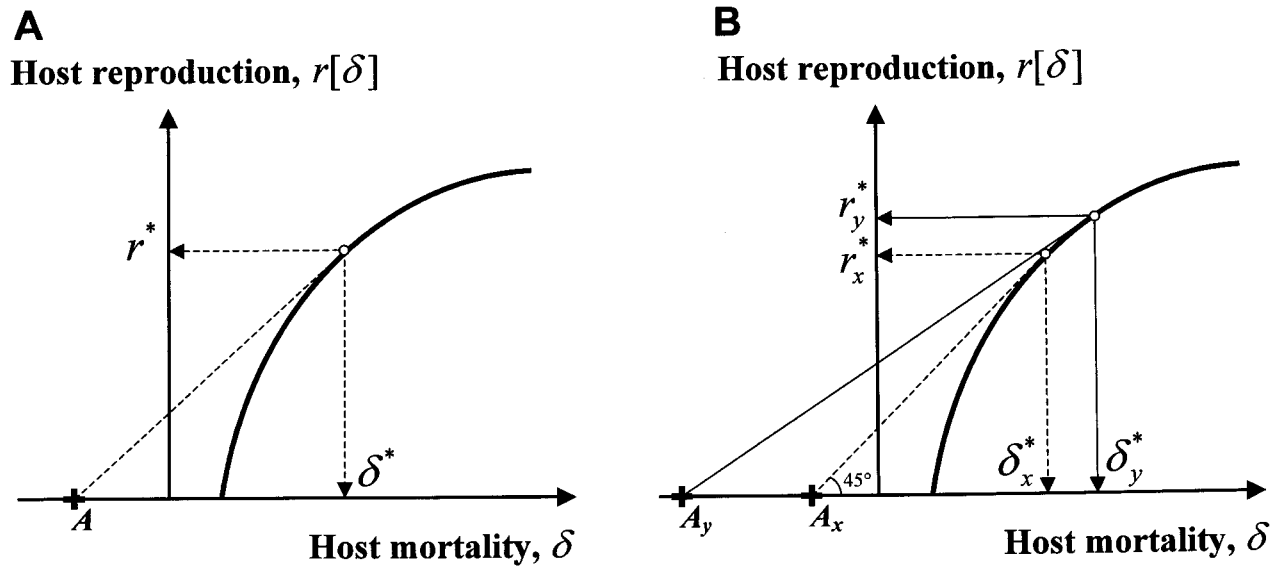

Figure 1: Graphical representation of the evolutionarily stable life-history traits of the host for (*A*) unconditional and (*B*) conditional strategies. In both cases, host rate of reproduction r is plotted (*bold line*) against host mortality rate δ. For unconditional hosts (*A*), the evolutionarily stable strategy (r^*, δ^*) is obtained by finding the tangent to the curve that passes through the point $A = \{-\nu h(2\delta + \nu + h)/[(\delta + \nu + h)^2 - \nu h], 0\}$. Higher virulence and higher force of infection always select for larger reproductive efforts (higher r^* and δ^*). For conditional hosts (*B*), the evolutionarily stable strategy of uninfected hosts (r_x^*, δ_x^*) is obtained by finding the tangent to the curve with a slope equal to 1. The evolutionarily stable strategy of infected hosts (r_y^*, δ_y^*) is obtained by finding the tangent of the curve that passes through the point $A_y = \{-\nu, 0\}$. The derivation of this graphical representation is detailed in the appendix B, "Conditional Hosts."

a single strain of parasite is present in a given infected host at anytime. The superinfection assumption provides a simple way to add another level of selection on the parasite (within-host selection), which avoids the complexity of a coinfection model (van Baalen and Sabelis 1995; Mosquera and Adler 1998).

The above life cycles can be described by the following set of differential equations (see table 1 for a summary of the main notations):

$$\dot{x} = (r_x x + r_y y)[1 - \kappa(x + y)] - (\delta_x + h)x,$$
$$\dot{y} = hx - (\delta_y + \nu)y, \tag{1}$$

where the dot notation indicates differentiation with respect to time.

There are two nontrivial population dynamical equilibria. First, there is the disease-free equilibrium, where $\hat{x} = K = \kappa^{-1}(1 - \delta_x/r_x)$ and $\hat{y} = 0$, with K as the carrying capacity of the host. Second, if the parasite can invade the host population, the equilibrium densities satisfy

$$\hat{x} = \frac{\delta_y + \nu}{\beta},$$
$$\hat{y} + \hat{x} = \frac{1}{\kappa}\left[1 - \frac{\delta_x \hat{x} + (\delta_y + \nu)\hat{y}}{r_x \hat{x} + r_y \hat{y}}\right]. \tag{2}$$

Note that there are threshold values for host and parasite life-history traits for the maintenance of the parasite population (see app. A for these different threshold values). In particular, if host mortality or parasite virulence are too high or if host reproduction is too low, the parasite population is driven to extinction.

Host Evolution

Following van Baalen (1998), it can be shown that the expected lifetime reproductive success of a mutant host (with reproductive effort strategies e_x^* and e_y^*) in a population dominated by a resident (with reproductive effort strategies e_x and e_y) is

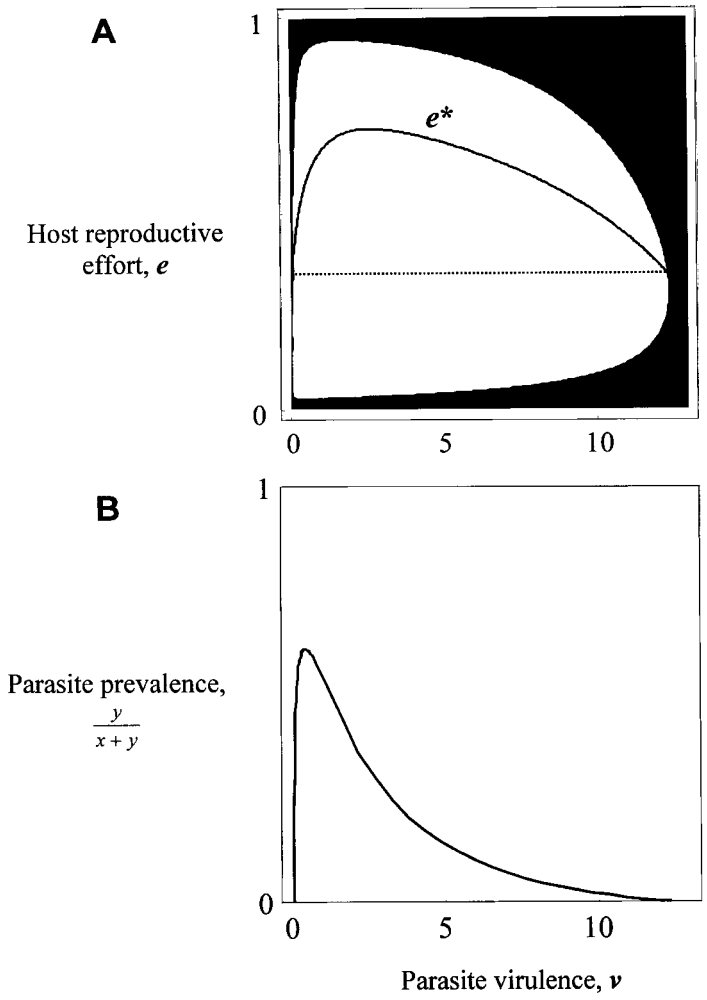

Figure 2: The effect of parasite virulence (*A*) on the evolutionarily stable (ES) unconditional reproductive effort, e^* (*solid line*), and (*B*) on parasite prevalence. The dotted line indicates the ES reproductive effort in the absence of parasites. In the black area, the parasite population becomes extinct. Parameter values: $q1 = 1$, $q2 = 1$, $r_m = 5$, $s_m = 0.9$.

$$W[e_x^*, e_y^*, e_x, e_y] = \frac{r[e_x^*]}{\delta[e_x^*] + h} + \frac{r[e_y^*]h}{(\delta[e_x^*] + h)(\delta[e_y^*] + \nu)}, \tag{3}$$

which is the sum over the different states of the host (uninfected or infected) of the product between host reproduction rate, $r_x^* \equiv r[e_x^*]$ or $r_y^* \equiv r[e_y^*]$, and the expected time spent in the uninfected or infected state.

Different cases can be considered depending on the ability of the host to adopt conditional strategies. We first consider the case where the host adopts an unconditional reproductive effort strategy (i.e., $e = e_x = e_y$ and $e^* = e_x^* = e_y^*$). We then analyze the case where host reproductive effort depends on the host's state (i.e., infected or not).

Unconditional Reproductive Effort Strategy

Mutation and selection in the host population will lead to an equilibrium state where the host population has evolved a resident strategy, e, that cannot be invaded by any mutant strategy, e^*. In other words, the evolutionarily stable (ES) reproductive effort must satisfy $dW[e^*, e]/de^* = 0$ at $e = e^*$. This yields the following condition for evolutionarily stability (app. B, "Unconditional Hosts"):

$$\frac{dr}{d\delta} = \frac{(\delta + \nu + h)^2 - \nu h}{(\delta + \nu)(\delta + h)(\delta + \nu + h)} r. \tag{4}$$

The above condition for evolutionarily stability has a simple graphical interpretation. When host reproduction is plotted against host mortality rate δ, the ES reproductive

effort can be obtained after finding the tangent to the curve that passes through the point A on the abscissa:

$$A = \left\{ -\frac{\nu h(2\delta + \nu + h)}{(\delta + \nu + h)^2 - \nu h}, 0 \right\}$$

(app. B, "Unconditional Hosts"; fig. 1*A*). This geometric view of the ES solution is very useful to get a qualitative intuition of the evolutionary outcome without having to specify the form of the trade-off between survival and reproduction. Note in particular that when either $\nu = 0$ or $h = 0$ the point A moves to the origin and, consequently, the ES reproductive effort decreases. In other words, the presence of virulent parasites induces a shift toward a higher allocation into reproductive effort.

The above qualitative analysis assumed that h was a fixed parameter. This is obviously not realistic since the force of infection depends on the density of infected hosts, which depends on various host and parasite life-history traits, including host reproductive effort and parasite virulence. The equilibrium solution of h is a complicated function of these traits, and we failed to find a simple analytic or graphic solution for the ES reproductive effort. Quantitative predictions can be obtained numerically, but this requires explicit expressions for the relationships between mortality, reproduction, and reproductive effort. It is convenient to assume the following trade-offs between reproduction and survival:

$$\begin{aligned} r[e] &= r_m e^{q1}, \\ s[e] &= s_m(1 - e)^{q2}, \end{aligned} \tag{5}$$

where $r \equiv r[e]$ is the reproductive rate of the host and r_m is the maximal rate of reproduction of the host if it allocates all its resources to reproduction and none to survival (i.e., $e = 1$). The probability of survival in a discrete time model is $s \equiv s[e]$, where s_m is the maximal survival probability if the host allocates all its energy to survival and does not reproduce at all (i.e., $e = 0$). Note that in our continuous time model this yields the following mortality rate: $\delta \equiv \delta[e] = -\log[s]$. Altering values of the parameters $q1$ and $q2$ allow us to easily modify the shape of the trade-off between survival and reproduction. Larger values of $q1$ select for higher reproductive effort, while larger values of $q2$ select for lower reproductive effort.

The numerical study of host evolution revealed some interesting results. In particular, figure 2*A* shows that ES reproductive effort is a humped function of virulence. For low virulence, the direct effect (fig. 1*A*) of parasite virulence prevails and selects for higher reproductive effort. However, an increase in virulence leads to a reduction in the density of infected hosts (fig. 2*B*). This epidemiological feedback can be strong enough that the ES reproductive

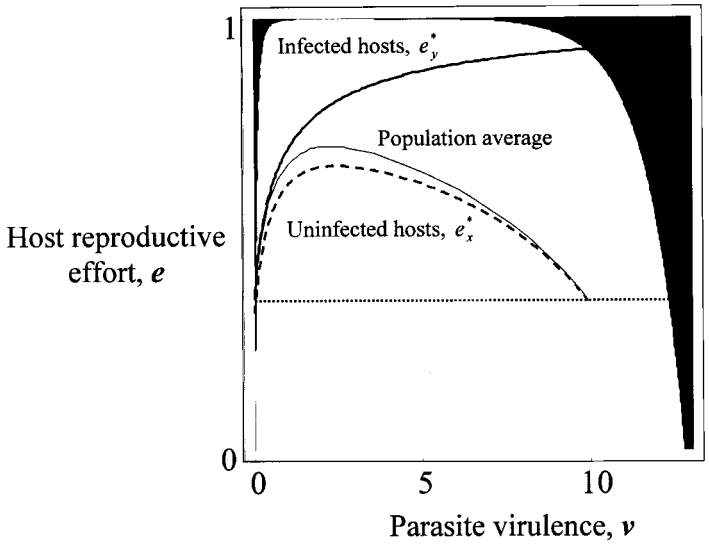

Figure 3: The effect of parasite virulence on the evolutionarily stable (ES) conditional reproductive effort strategies of infected hosts (*solid line*), uninfected hosts (*dashed line*), and the average of the host population (*narrow line*). The dotted line indicates the ES reproductive effort in the absence of parasites. The black area shows the values of virulence and reproductive effort of infected hosts for which parasites become extinct (here, the reproductive effort of uninfected hosts is fixed and equal to the ES reproductive effort in the absence of parasites). Parameter values: $q1 = 1$, $q2 = 1$, $r_m = 5$, $s_m = 0.9$, $\kappa = 0.05$.

effort decreases for higher values of virulence. Actually, for some parameter values, there is a threshold value of virulence above which the parasite population becomes extinct (app. A). Therefore, above this value the ES reproductive effort is equal to that obtained in the absence of parasites.

Interestingly, one can show that in the absence of density dependence ($\kappa = 0$) the evolution of host reproductive effort leads to a maximal force of infection. Here, we recover the "pessimization principle" (Mylius and Diekmann 1995), which states that only the strategy that can survive under the worst environment will remain since it cannot be invaded by any other strategy. Van Baalen (1998) obtained a similar result while studying the evolution of recovery ability. When some density dependence occurs in the host population, the ES reproductive effort is always slightly higher than the value that would maximize the force of infection. Further research is needed to show whether this difference arises because the pessimization principle does not hold whenever more than one factor defines the environment or, precisely, that the principle does hold but the "worst environment" is now defined not only with respect to parasitism but also relative to intraspecific competition.

Conditional Reproductive Effort Strategy

We now turn to the case where the host is able to evolve a conditional reproductive effort strategy depending on whether it is infected or not. We assume the same trade-off functions as in equation (5), and the ES reproductive effort strategies e_z (with $z \equiv x$ or y) must satisfy $dW[e_x^*, e_y^*, e_x, e_y]/de_x^* = 0$ and $dW[e_x^*, e_y^*, e_x, e_y]/de_y^* = 0$ at $e_x = e_x^*$ and $e_y = e_y^*$. After some algebra, this yields the following two conditions (app. B):

$$\frac{dr_x}{d\delta_x} = 1,$$

$$\frac{dr_y}{d\delta_y} = \frac{1}{\delta_y + \nu} r_y. \tag{6}$$

Again, these solutions have simple graphical interpretations. When host reproduction, r, is plotted against host mortality rate δ, the ES reproductive effort of uninfected hosts, e_x, can be obtained after finding the tangent to the curve that has a slope equal to one (fig. 1*B*; app. B, "Conditional Hosts"). This tangent cuts the abscissa axis at the point A_x. The ES reproductive effort of infected hosts is easily obtained after finding the point A_y on the abscissa, where $A_y = \{-\nu, 0\}$ (fig. 1*B*; app. B). Note that the point A_y is always on the left of A_x (app. B, "Proof That, at the ESS, A_y Lies on the Left of A_x") and that the point A_x is always on the left-hand side of the origin (app. B, "Proof That, at the ESS, A_x Is on the Left-Hand Side of the Origin"). Therefore, the above graphical solution proves that the ES reproductive effort of infected hosts is always higher than the ES reproductive effort of uninfected hosts.

Figure 3 presents the effect of parasite virulence on the evolution of conditional ES reproductive effort strategies. As illustrated, increases of virulence always favor a larger reproductive effort by infected hosts. The reproductive effort of uninfected hosts, however, depends on both virulence and the force of infection. Therefore, as in the case of unconditional strategies, the ES strategy of uninfected hosts is a humped function of virulence. When virulence is high, virulence and prevalence are negatively correlated and, consequently, the average reproductive effort of the population becomes increasingly dominated by that of uninfected individuals (fig. 3). Moreover, above some threshold values (app. A), the parasite population becomes extinct. It is interesting to note that the threshold reproductive effort value leading to parasite extinction is lower when host allocation is conditional than when it is unconditional. This is due to the higher reproductive effort of infected hosts and its effect in helping to decrease the prevalence of the disease.

Our model also predicts that the differences in reproductive effort between infected and uninfected individuals will be greatest when the host's maximal rate of reproduction, r_m, is low (not shown). Therefore, the detection

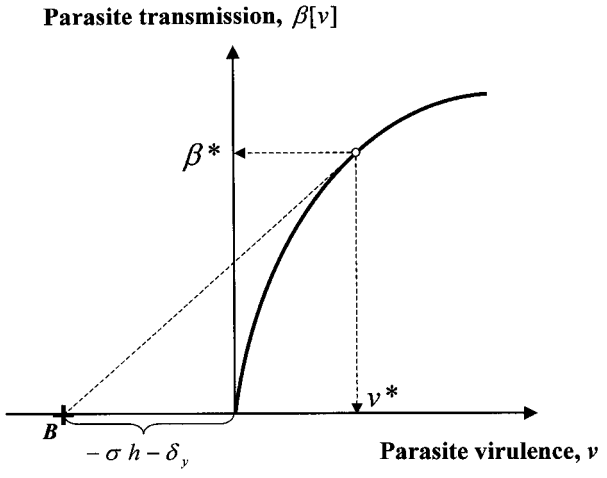

Figure 4: Graphical representation of the evolutionarily stable parasite virulence. Parasite transmission β is plotted (*solid line*) parasite virulence, ν. The evolutionarily stable parasite virulence, ν^*, is obtained by finding the tangent to the curve that passes through the point $B = \{-\sigma h - \delta_y, 0\}$. An increase of either σ, h, or δ_y favors higher parasite virulence.

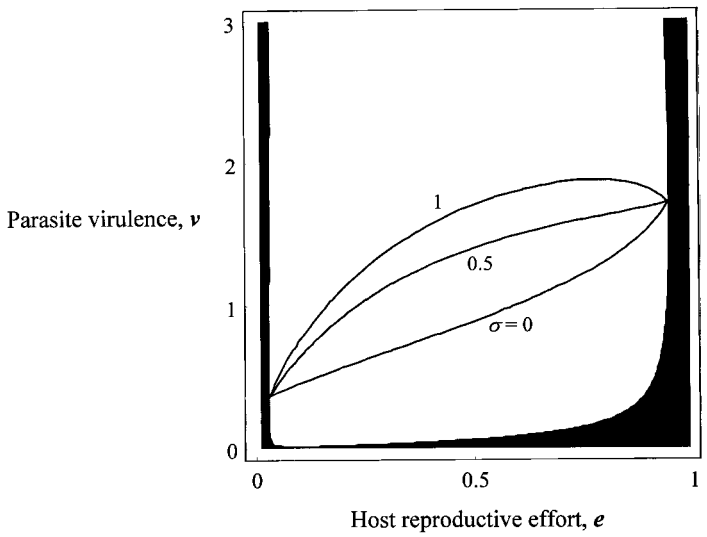

Figure 5: The effect of unconditional host reproductive effort on the evolutionarily stable parasite virulence, ν^*, for three levels of susceptibility to superinfection ($\sigma = 0, 0.5, 1$). In the black area, the parasite population becomes extinct. Parameter values: $q1 = 1$, $q2 = 1$, $r_m = 5$, $s_m = 0.9$, $\kappa = 0.05$.

of a conditional host response is likely to be harder in rich environments (high r_m) and when parasites are avirulent.

Parasite Evolution

We now analyze the case where parasite virulence can evolve as a function of host reproductive effort. This approach is equally applicable to situations where hosts respond conditionally or unconditionally to parasitism. The basic reproductive ratio of a mutant parasite (with virulence ν^*) in a population dominated by a resident (with virulence ν; van Baalen and Sabelis 1995; Gandon et al. 2001) is

$$R_0[\nu^*, \nu] = \frac{\beta[\nu^*]}{\delta_y + \nu^* + \sigma h}(\hat{x} + \sigma\hat{y}). \tag{7}$$

Only mutant strategies with $R_0[\nu^*, \nu] > 1$ can invade. Mutation and selection will lead to a situation where no mutant can increase its basic reproductive ratio above that of the resident. In other words, the evolutionarily stable virulence strategy must satisfy $dR_0[\nu^*, \nu]/d\nu^* = 0$ at $\nu = \nu^*$. After some algebra, this yields

$$\frac{d\beta}{d\nu} = \frac{\beta}{\delta_y + \nu + \sigma h}. \tag{8}$$

As we have previously established for the host, it is possible to obtain graphical solutions for the ES parasite strategy. Indeed, when transmission is plotted against parasite virulence, ν, the ES parasite strategy can be obtained after finding the tangent to the curve that passes through the point B, where $B = \{-\sigma h - \delta_y, 0\}$ (fig. 4). This graphical solution shows that higher mortality rates of infected hosts and higher rates of superinfection always select for higher virulence. However, the derivation of the ES parasite virulence needs to take into account epidemiological feedbacks through the effects of various parameters on h. In contrast to the qualitative results derived above, these quantitative predictions also depend on the specific relationship between virulence and transmission. Different functions have been used to formalize such a trade-off in previous models of parasite virulence, but here, for the sake of simplicity, we will assume the following function: $\beta[\nu] = \nu/(1 + \nu)$. This increasing but saturating function of parasite virulence qualitatively matches the observations on different host-parasite systems (reviewed by Mackinnon and Read 1999).

Figure 5 shows the effect of host reproductive effort on the ES parasite virulence. In the absence of superinfection ($\sigma = 0$), higher reproductive effort always increases the ES virulence strategy. This is due to the increase of the natural host death rate (a factor known to select for virulence; see Gandon et al. 2001 for a discussion of this effect). When superinfection occurs virulence increases. Indeed, for a parasite, superinfection is analogous to natural host mortality. They both limit the expected time the resource (the infected host) will be available and select for higher rates of host exploitation (virulence). Note, however, that when susceptibility to superinfection is high, the

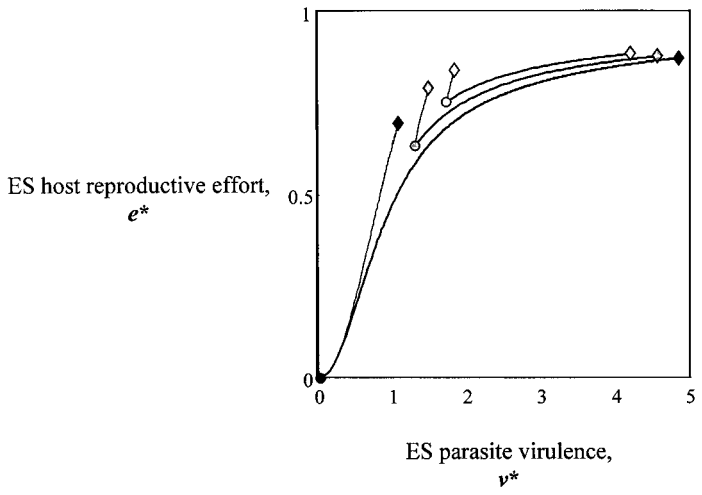

Figure 6: Relationship between host and parasite life-history traits at the coevolutionarily stable equilibrium. Here, the host is only allowed to adopt unconditional strategies. Each line (from a circle to a diamond) shows the relationship between host reproductive effort and parasite virulence for increasing values of r_m (from $r_m = r_T$ to 10, respectively), where the lowest value or $r_m(r_T)$ is the threshold value below which the parasite becomes extinct (app. A, "Unconditional Hosts"). Different lines are used for different levels of s_m: 0.2 (*open symbols*), 0.5 (*gray symbols*), and 1.0 (*filled symbols*). For each combination of parameter values, we present the coevolutionary results with or without superinfection: $\sigma = 1$ (*solid lines*), $\sigma = 0$ (*narrow lines*). Other parameter values: $q1 = 1$, $q2 = 1$, $\kappa = 0.01$.

ES parasite strategy may decrease with host reproductive effort. This is due to an epidemiological feedback. Strong reproductive effort increases host mortality and, consequently, decreases the force of infection. Such a reduction in the risk of superinfection decreases ES parasite virulence (see also Gandon et al. 2001 for a general discussion of the effect of various host life-history traits on the evolution of the parasite).

Finally, we would like to point out the fact that the gene that controls the reproductive effort acts just like a vertically transmitted parasite. A higher rate of vertical transmission (host reproduction) is traded off with parasite virulence (host mortality). Host and parasite share the same classical dilemma between reproduction and survival. Not surprisingly, our analysis reveals that the evolutionarily stable solution can be obtained in a similar way (see the analogy between figs. 1 and 4).

Host-Parasite Coevolution

In the previous section, we analyzed the situations where only one of the species involved in the host-parasite interaction could evolve (first, the host and then, the parasite). These situations will occur wherever evolution is prevented in one of the species because of a lack of sufficient genetic variation and/or because this evolution is governed by other forces. For example, the parasite may exploit other more abundant hosts. In this situation, a change in the life-history traits of the focal host is expected to have hardly any effect on parasite evolution. Reciprocally, if the focal host is infected by a variety of other parasites with more severe effects on its fitness, an evolution of the focal parasite will not be followed by a coevolutionary response of the host.

In other host-parasite systems, however, the fate of the two interacting partners may be tightly linked. For these situations, it is necessary to include coevolutionary feedbacks in the previous analysis. Ultimately, coevolution yields to a state (a coevolutionarily stable state) where both host and parasite traits lay at an evolutionarily stable equilibrium. Figure 6 presents such coevolutionary outcomes when the host adopts an unconditional strategy for a variety of abiotic environments (variable values of r_m and s_m). Increasing the host maximal rate of reproduction, r_m (follow each line from the circle to the diamond), always yields both higher host reproductive effort and higher parasite virulence. This leads to the prediction that if one samples hosts and parasites coevolving in populations with different r_m, say, across an environmental gradient, one could expect to find a general positive correlation between the traits of both species. This result contrasts with the situation where coevolution does not occur. Indeed, as shown above, parasite virulence does not have a monotonous effect on the ES reproductive effort of the host (fig. 2) and, reciprocally, host reproductive effort may also have a nonmonotonous effect on the ES parasite virulence when superinfection occurs (fig. 5).

Increasing the maximal host survival rate, s_m (fig. 6; for

a given symbol, s_m increases as the color of the symbol darkens), decreases both host and parasite evolutionarily stable strategies (ESSs) in the absence of superinfections ($\sigma = 0$). When superinfections occur ($\sigma = 1$), the relationship between host and parasite ESSs will further depend on the quality of the environment (perceived here through r_m; fig. 6, circles correspond to poor environments; diamonds correspond to rich environments). In poor environments, we have the same relationship as when superinfections are absent: increases in s_m decrease both host and parasite ESSs. In contrast, in rich environments, host and parasite traits become virtually independent. In other words, if one samples hosts and parasites coevolving in populations differing for s_m, the expectation regarding the link between the traits of the two species will depend on the occurrence of superinfections and the general quality of the environments in which the two species coevolve.

When the host adopts conditional strategies (not shown), we reach very similar conclusions. However, when only single infections occur ($\sigma = 0$), both the ES parasite virulence and the ES conditional strategy of infected hosts are independent of the maximal rate of reproduction, r_m.

Discussion

Host Evolution

Our results agree with previous empirical and theoretical studies in showing that parasitic infection can select for modifications of host life-history traits. More specifically, our analysis shows that infection can select for hosts with a higher allocation toward their reproductive effort. This results from the negative effect of infection on host survival and the trade-off linking survival with reproduction. Similarly, to any other factor decreasing survival, whether biotic or abiotic, infection leads to an increased allocation to host reproduction. Indeed, there is no need to allocate resources to survival if the individual is doomed to die soon.

The explicit incorporation of epidemiological dynamics revealed some interesting results. These results were complemented by the inclusion of conditional (phenotypically plastic) or unconditional (fixed or genetic) host responses to infection. In particular, increasing virulence provoked nonmonotonic responses in host reproductive effort for populations of "unconditional" hosts and for uninfected hosts in "conditional" host species (figs. 2, 3). The mechanism responsible for this behavior derives from the epidemiological feedback of parasite virulence on the force of infection. Relatively high levels of virulence, by killing infected hosts rapidly, induce reductions in the force of infection to a point where the evolution of host life-history traits is governed by what happens in the uninfected compartment of the host population (fig. 2*B*). This feedback can be substantial enough to outweigh the direct selective effects of virulence on the host's life-history traits. Similarly, Koella (2000) obtained a nonmonotonic response by the host when he studied the effect of parasite virulence on the evolution of host's age at reproduction. These results highlight the importance of taking into account epidemiological feedbacks when investigating the evolution of host-parasite relationships.

In contrast, the direct effect of the parasite's virulence acts in a monotonic fashion on the reproductive effort of infected hosts in "conditional" populations (fig. 3). These individuals are directly subjected to the costs of infection, and they will benefit from increasing their reproductive effort. Furthermore, the extent to which they should increase their reproductive effort is solely determined by the parasite's virulence (fig. 3). We note that the difference in reproductive effort of infected and uninfected individuals in a conditional population increases monotonically with virulence (fig. 1*B*) and that the virulence threshold at which the parasite becomes extinct is lower than for unconditional populations. This latter effect stems from the reduced survival of infected individuals in a conditional population due to their increased reproductive effort.

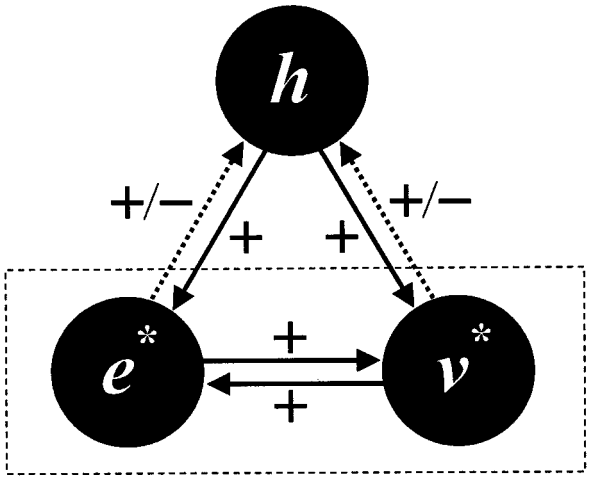

Figure 7: Graphical summary of (co)evolutionary (*solid arrows*) and epidemiological (*dotted arrows*) feedbacks between evolutionarily stable (ES) unconditional host reproductive effort, e^*, ES parasite virulence, v^*, and the force of infection, h. The dashed box focuses on the coevolutionary processes in the absence of epidemiological feedbacks (i.e., constant force of infection). The sign of each arrow shows the effect of the variable at the start of the arrow on the variable at the end of the arrow. Note that both higher host and parasite life-history traits may increase or decrease the force of infection. It is, however, the decrease in the force of infection that prevents a coevolutionary arms race between these two traits (see text for a discussion of this figure).

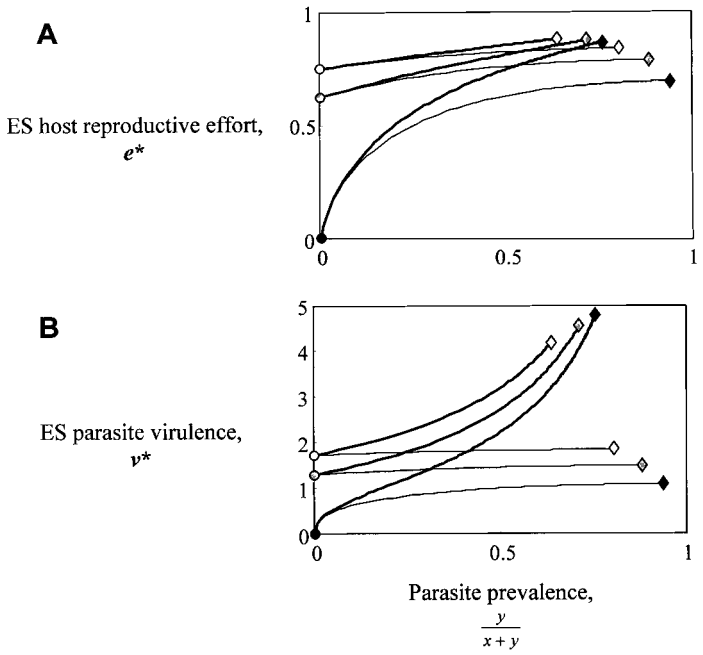

Figure 8: Relationship between parasite prevalence and both (*A*) host and (*B*) parasite life-history traits at the coevolutionarily stable equilibrium. Here, the host is only allowed to adopt unconditional strategies. As in figure 6, each line (from a circle to a diamond) shows the relationship between a trait (host reproductive effort in *A* and parasite virulence in *B*) and parasite prevalence for increasing values of r_m (from $r_m = r_T$ to 10, respectively; see app. B, "Unconditional Hosts" for a definition of r_T). Different lines are used for different levels of s_m: 0.2 (*open symbols*), 0.5 (*gray symbols*), and 1.0 (*filled symbols*). For each combination of parameter values, we present the coevolutionary results with or without superinfection: $\sigma = 1$ (*solid lines*), $\sigma = 0$ (*narrow lines*). Other parameter values: $q1 = 1$, $q2 = 1$, $\kappa = 0.01$.

Thus, by considering hosts capable of a conditional (or phenotypically plastic) response, we move closer to capturing how direct and indirect selection pressures act on the infected and uninfected components of a host population.

Parasite Evolution

The trade-off linking reproduction and survival for a host is markedly similar to that faced by a parasite for its transmission and virulence (cf. figs. 1*A* and 4). In our model, the parasite's optimal strategy was determined by the susceptibility to superinfection and the force of infection. If there is no superinfection, the parasite's strategy is only determined by the intrinsic death rate of infected hosts. The effects of superinfection act to reduce the parasite's probable tenure of its host and select for increased rates of host exploitation and virulence.

The rate of superinfection, σh, depends on the force of infection and, consequently, on both host and parasite life histories. As soon as superinfections occur ($\sigma > 0$), different host and parasite life-history traits may indirectly affect the evolution of parasite virulence through an epidemiological feedback. This was illustrated in figure 5, where we showed that increased host reproductive effort may either select for or against an increase in virulence depending on the susceptibility to superinfection. Here, higher host reproductive efforts, leading to higher host death rates, have direct and indirect effects on the evolution of virulence. The direct effect favors higher virulence, while the indirect effect (via the rate of superinfection) favors lower virulence. This highlights the importance of interactions between multiple infections and epidemiological parameters (Ebert and Mangin 1997; Gandon et al. 2001).

Coevolution

Figure 7 summarizes the network of epidemiological and evolutionary feedbacks involved in host-parasite coevolution and highlights the role that the force of infection has to play in this scenario. The explicit investigation of coevolution yields predictions regarding the expected relationship between host and parasite life-history traits. Unfortunately, we were enable to find any empirical data on this relationship.

Long-term experimental studies are likely to be the most profitable way of testing the validity of these predicted

relationships. For example, the experimental system studied by Ebert and Mangin (1997) may be suitable for such a long-term study. The authors followed the evolution of *Glugoides intestinalis*, a microsporidian parasite of the water flea *Daphnia magna*, for 14 months. In this experiment, the parasite's virulence was allowed to evolve in response to manipulations of its host's demography. The authors, however, only followed the evolution of the parasite and did not study the coevolutionary response of the host. They claim there was none because they used monoclonal host populations and the host populations were small (around 20 individuals). It should be possible to conduct a similar experiment under conditions enabling host evolution as well, that is, with larger host population sizes and starting with a mixture of different clones. Further, the parameters s_m and r_m could be manipulated as in figure 6 through the quality of the abiotic environment (e.g., amount of food available to hosts). Such an experimental setting would be ideal because it would allow epidemiology to feed back on the evolution of both the host and parasite. With other biological systems it would also be possible to remove this epidemiological feedback by controlling the force of infection, for example, through experimental transfer of the parasites. In this situation, one may expect a runaway process, where both the host and the parasite would evolve toward extreme strategies because of the synergistic interactions between host reproductive effort and parasite virulence. This situation is represented on figure 7 by the dashed box.

Experimental coevolution, however, is unrealistic in many, if not most, host-parasite systems. In such systems, it should still be possible to examine the covariation of host and parasite traits across sites, differing for the quality of their abiotic environment. In the cases where assessing environmental quality is unfeasible, a more pragmatic prediction would be to examine the relationship between parasite prevalence and both host reproductive effort and parasite virulence (fig. 8). For example, Krist (2001) recently observed a positive relationship between the prevalence of castrating trematodes and the reproductive output of a freshwater snail, *Elimia livescens*. This result is consistent with the predictions of our model (fig. 8*A*). It would be also interesting to study the covariation between prevalence and virulence since our model predicts a positive correlation in the presence of superinfections (fig. 8*B*).

Acknowledgments

We thank V. Jansen, J. Koella, and M. van Baalen for useful discussions. Two anonymous referees provided useful comments and suggestions. S.G. gratefully acknowledges support of the Wellcome Trust. This research was supported by a Centre National de la Recherche Scientifique Action Thématique Incitative sur Programme et Equipe grant to Y.M.

APPENDIX A

Epidemiological Analysis: Conditions for Host and Parasite Coexistence

Extreme values of host and parasite life-history traits may prevent the coexistence of the two species. We give below the threshold values of these traits for both unconditional and conditional host strategies.

Unconditional Hosts

The parasite population becomes extinct if

1. host mortality is above $\delta_T = r(\beta - \kappa v)/(\beta + \kappa r)$;
2. host reproduction is lower than $r_T = \beta\delta/[\beta - \kappa(\delta + v)]$;
3. parasite virulence is higher than $\nu_T = [\beta(r - \delta) - \kappa r\delta]/(\kappa r)$.

Conditional Hosts

The parasite population becomes extinct if

1. host mortality rate of uninfected hosts is above $\delta_{xT} = r_x[\beta - \kappa(\nu + \delta_y)]/\beta$;
2. host mortality rate of infected hosts is above $\delta_{yT} = \beta(r_x - \delta_x)/(\kappa r_x) - \nu$;
3. host reproduction rate of uninfected hosts is lower than $r_{xT} = \beta\delta_x/[\beta - \kappa(\delta_y + \nu)]$;
4. parasite virulence is higher than $\nu_T = \beta(r_x - \delta_x)/(\kappa r_x) - \delta_y$.

Note that, in this case, the condition for the viability of the parasite population does not depend on the fertility of infected hosts.

APPENDIX B

Evolutionary Analysis: Graphical Solutions for ES Host Reproductive Efforts

A classical way to represent the trade-off between host survival and host reproduction is to plot host's reproduction rate, r, versus host's mortality rate, δ. The ES host strategy will necessarily lay on the curve $r[\delta]$. In the following derivation, we show how we can find the exact position of the ESS through a geometrical construction in the r versus δ plane. The idea is to find the value of $dr/d\delta$ (the slope of the curve $r[\delta]$) at the ESS.

Unconditional Hosts

The evolutionarily stable host reproductive effort must satisfy

$$\left.\frac{dW[e^*, e]}{de^*}\right|_{e^*=e} = 0.$$

After some algebra, we obtain

$$\left.\frac{dW[e^*, e]}{de^*}\right|_{e^*=e} \propto \frac{dr}{d\delta}\frac{1}{r} - \frac{(\delta + \nu + h)^2 - \nu h}{(\delta + \nu)(\delta + h)(\delta + \nu + h)},$$

which yields equation (4). It is convenient to rewrite this ESS condition in the following way:

$$\frac{dr}{d\delta} = \frac{r}{\delta + \frac{h\nu(2\delta+h+\nu)}{(\delta+\nu+h)^2-\nu h}}.$$

This condition has a simple graphical representation. The slope given by the previous equation can be obtained through the construction of the line that is tangent to the curve $r[\delta]$ and passes through the point

$$A = \left\{-\frac{\nu h(2\delta + \nu + h)}{(\delta + \nu + h)^2 - \nu h}, 0\right\}.$$

Such a line touches the curve $r[\delta]$ at a point where the slope of the curve satisfies the ESS condition. In other words, this point gives the ES life-history strategy of the host (see fig. 1*A*). Note that the abscissa of A depends on δ, which is a function of host reproductive effort. However, the ESS can still be obtained graphically after recurrent iterations (where δ is a function of host reproductive effort obtained in the previous iteration). This graphical solution is general and, in particular, does not depend on the specific form of the trade-off between reproduction and survival.

Conditional Hosts

The evolutionarily stable host reproductive effort must satisfy

$$\left.\frac{dW[e_x^*, e_y^*, e_x, e_y]}{de_x^*}\right|_{e_x^*=e_x,\, e_y^*=e_y} = 0 \quad \text{and} \quad \left.\frac{dW[e_x^*, e_y^*, e_x, e_y]}{de_y^*}\right|_{e_x^*=e_x,\, e_y^*=e_y} = 0.$$

After some algebra, we obtain

$$\left.\frac{dW[e_x^*, e_y^*, e_x, e_y]}{de_x^*}\right|_{e_x^*=e_x,\, e_y^*=e_y} \propto \frac{dr_x}{d\delta_x}\frac{1}{r_x} - \frac{1}{r_x},$$

$$\left.\frac{dW[e_x^*, e_y^*, e_x, e_y]}{de_y^*}\right|_{e_x^*=e_x,\, e_y^*=e_y} \propto \frac{dr_y}{d\delta_y}\frac{1}{r_y} - \frac{1}{d_y + \nu}.$$

The above two equations yield equation (6). This ESS condition leads to a graphical construction explained in figure 1*B*. As for the unconditional case, this graphical representation of the ESS is independent of the shape of the trade-off function between host reproduction and host survival.

Proof That, at the ESS, A_y *Lies on the Left of* A_x

We start by finding the point A_x through the graphical method given in the main text (see also fig. 1*B*). This point yields the ESS of uninfected hosts (δ_x^*, r_x^*). Since we assume that the host-parasite system has reached a stable equilibrium, we can use $W[e_x^*, e_y^*, e_x, e_y^*] = 1$ to find the coordinates of the point A_x:

$$A_x = \left\{-h\left(1 - \frac{r_y}{\delta_y + \nu}\right), 0\right\}.$$

If A_y was on the right-hand side (RHS) of A_x, then (see fig. 1*B*) $r_y > \delta_y + \nu$. This would imply that the abscissa A_x would be positive (A_x would be on the RHS of the origin), and since A_y was originally assumed to be on the RHS of A_x, A_y would also be on the RHS of the origin. This is impossible since ν is assumed to be positive, and as a consequence, A_y can only be on the left-hand side (LHS) of the origin. Therefore, the initial assumption is wrong, and the point A_y is always on the LHS of A_x.

Note that when the force of infection decreases, the point A_x is moved to the right and, consequently, the difference between ESS of infected and uninfected individuals increases.

Proof That, at the ESS, A_x *Is on the Left-Hand Side of the Origin*

For some parameter values, the graphical solution may lead to placing the point A_x on the RHS of the origin. However, when we use $W[e_x, e_y, e_x, e_y] = 1$, we can show that, at the ESS,

$$h = \frac{(\delta_x - r_x)(\delta_y + \nu)}{r_y - \delta_y - \nu}.$$

We showed in the appendix section "Proof That, at the ESS, A_y Lies on the Left of A_x" that $r_y < \delta_y + \nu$ and, consequently, r_x has to be higher than δ_x for h to be positive. If the graphical solution places the point A_x on the RHS of the origin, it means that the parasite cannot coexist with the host whatever the virulence strategy. In other words, for the parasite to coexist with the host, the point A_x has to be located on the LHS of the origin.

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Editor: Joseph Travis
Associate Editor: Jim Bull