BRIEF COMMUNICATIONS

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HOST LIFE HISTORY AND THE EVOLUTION OF PARASITE VIRULENCE

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Abstract.—We present a general epidemiological model of host-parasite interactions that includes various forms of superinfection. We use this model to study the effects of different host life-history traits on the evolution of parasite virulence. In particular, we analyze the effects of natural host death rate on the evolutionarily stable parasite virulence. We show that, contrary to classical predictions, an increase in the natural host death rate may select for lower parasite virulence if some form of superinfection occurs. This result is in agreement with the experimental results and the verbal argument presented by Ebert and Mangin (1997). This experiment is discussed in the light of the present model. We also point out the importance of superinfections for the effect of nonspecific immunity on the evolution of virulence. In a broader perspective, this model demonstrates that the occurrence of multiple infections may qualitatively alter classical predictions concerning the effects of various host life-history traits on the evolution of parasite virulence.

Key words.—Epidemiology, life history, parasitism, superinfection, virulence.

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Parasite virulence (i.e., disease-induced host mortality) is often considered to be an unavoidable consequence of host exploitation. This implies a trade-off between within-host reproduction and between-host transmission. On the one hand, a minimal level of host exploitation is required for parasite reproduction, while, on the other hand, there is a cost associated with extreme exploitation of the host. Increased virulence reduces the host's life expectancy and consequently reduces the likelihood of parasite transmission from one host to another. The balance between the costs and the benefits of virulence yields the prediction that parasites should evolve toward optimal host exploitation strategies characterized by intermediate levels of virulence. Several theoretical models have been developed along this cost-benefit argument to analyze the effect of various host and parasite life-history traits on the evolution of parasite virulence (Fenner et al. 1956; Levin and Pimentel 1981; Anderson and May 1982; Ewald 1983; Levin 1983; Sasaki and Iwasa 1991; van Baalen and Sabelis 1995a,b; Ebert and Herre 1996). These models show that a higher intrinsic mortality rate of the host favors more virulent parasite strategies.

The above result can be explained by a classical life-history argument. Parasites should allocate more resources to reproduction (i.e., host exploitation and virulence) when the likelihood of survival and, therefore, the cost of virulence is low. At first sight this result seems to be extremely robust from one type of model to another, but convincing empirical evidence for such an effect is difficult to obtain. Host mortality is often correlated with other potentially confounding factors that should be carefully removed before performing any statistical test of this hypothesis. A more conclusive approach (although, often technically difficult) is to experimentally manipulate the intrinsic host mortality and to follow the evolutionary response of the parasite over several generations. According to the previous arguments, one would expect parasite virulence to increase with host mortality.

Ebert and Mangin (1997) carried out such an experimental test using monoclonal cultures of the water flea *Daphnia magna* and its horizontally transmitted microsporidian parasite *Glugoides intestinalis.* They allowed the parasite to evolve for 14 months under high and low host-mortality treatments. In the first treatment (high host mortality), they enhanced the natural host death rate by randomly removing between 70% and 80% of the hosts every week and, to keep host density constant, by replacing them with new uninfected hosts (from a stock culture). In the second treatment (low host mortality) they did not replace any hosts and, therefore, allowed them to have a longer life expectancy (approximately three times longer than in the previous treatment). Note that replacement is not completely equivalent to mortality because death removes hosts from the population. Classical predictions are not affected by such a distinction and a high frequency of replacement is expected to select for higher parasite virulence just as increased mortality. However, contrary to this prediction, parasites evolved lower virulence in the high replacement treatment.

Ebert and Mangin (1997) argued that their counterintuitive result could be explained by the occurrence of multiple infections and within-host competition. Indeed, the verbal life-history argument detailed above implicitly assumes that hosts are infected by only one strain of parasite. If multiple infections occur, different strains of parasite will compete within individual hosts. Within-host competition has two major consequences. First, it will select for faster exploitation strategies and, consequently, higher virulence (Levin and Pimentel 1981; Bremermann and Pickering 1983; Frank 1992, 1994, 1996; May and Nowak 1994, 1995; Nowak and May 1994; van Baalen and Sabelis 1995a,b; Gandon 1998; Mosquera

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TABLE 1. Summary of main notations.

The host	
r	host reproduction rate
δ	natural host death rate
γ	replacement rate
x	density of uninfected hosts
The parasite	
v	virulence (disease induced mortality)
β	transmission rate
y	density of infected hosts
h (= βy)	force of infection
σ	susceptibility to superinfection
σ'	dominance

and Adler 1998). Second, because the occurrence of multiple infection depends on the force of infection (i.e., the probability per unit of time to become infected), which itself depends on various parameters of both host and parasite life cycles, the evolution of parasite virulence depends on all parameters that affect the force of infection (van Baalen and Sabelis 1995a,b; Gandon 1998; Gandon and Michalakis 2000; S. Gandon, M. van Baalen, and V. A. A. Jansen, unpubl. ms.). For example, a higher host mortality decreases the force of infection through a reduction in the density of infected hosts and, thus, the risk of multiple infection. Ebert and Mangin (1997) pointed out that such epidemiological consequences of host replacement may well explain the results of their experimental evolution: Replacement decreases the risk of multiple infection that may select for lower parasite virulence.

In the present paper we use a general host-parasite model with superinfections to analyze the validity of the verbal argument proposed by Ebert and Mangin. We show that when superinfection occurs, both host mortality and replacement rate may favor lower parasite virulence strategies (although, the effect of replacement rate is less pronounced). The results obtained by Ebert and Mangin (1997) are discussed in the light of the present model. More generally, our analyses demonstrates the importance of multiple infection and ecogenetical feedbacks in the evolution of parasite virulence (Eshel 1977; van Baalen and Sabelis 1995a,b,c).

HOST AND PARASITE LIFE CYCLES

We consider a homogeneous host population where all individuals are equally susceptible to parasitic infections (Table 1). Both uninfected (x) and infected (y) hosts can reproduce, that is, parasites do not reduce the fecundity. However, we will assume that birth rate depends in some way on total host density $r = f(x + y)$. Uninfected hosts have a death rate δ, while infected hosts incur an extra mortality rate v (i.e., parasite virulence).

The parasite is horizontally transmitted from infected to uninfected hosts with transmission efficiency β. The parasite's transmission efficiency is assumed to depend on its host exploitation strategy and, consequently, to correlate with virulence. Several studies of different host-parasite systems indicate that parasite transmission is an increasing but saturating function of parasite virulence (reviewed by Mackinnon and Read 1999). To make our argument as general as possible, we will assume an arbitrary but saturating relationship between transmission efficiency and virulence, $\beta = \beta(v)$. The force of infection experienced by each host (i.e., the probability of being infected or reinfected) is $h = \beta y$. We assume that whenever an infected host is reinfected with another parasite, the new strain of parasite may replace the old strain with a rate σ (σ thus measures the efficiency of superinfection relative to first infections). Therefore, only a single strain of parasite is present in a given infected host. Such immediate replacement is called superinfection (as opposed to coinfection, where multiple strains share the same host). As a first step we will assume that the take-over rate σ is constant, later we will relax this assumption and allow it to depend on the contestants' virulences.

Note that infected hosts are unlikely to be as susceptible to (re)infection as uninfected hosts. Such differential susceptibilities can be caused by many different mechanisms, which can either be based on the host's or on the parasite's physiology. For example, the induced immune response following a first infection could lower susceptibility to subsequent superinfections. Some allorecognition mechanisms developed by the parasite could also be involved to prevent or, at least, decrease the risk of superinfection. The parameter σ may also depend on demographic stochasticity because a strain can take over an already infected host just by chance (this process operates in particular if within-host densities are low). All these processes reduce the relative susceptibility of infected hosts ($\sigma < 1$). However, the relative susceptibility of infected hosts might just as well be larger than one if, for example, the first infection has weakened the host and rendered its defenses less effective.

To describe Ebert and Mangin's (1997) experiment, we introduce a parameter, the replacement rate γ, that describes the action of replacing a fraction of the host population by new uninfected hosts. Because removing an uninfected host by a new healthy host does not change anything (from the point of view of the parasites), the replacement rate is equivalent to the classical recovery rate, which describes the effect of nonspecific immunity. Therefore, Ebert and Mangin's experiment could also be viewed as an experimental test of the effect of a cost-free immune system on the evolution of parasite virulence.

This life cycle leads to the following set of differential equations (when parasite population is monomorphic with virulence v):

$$\dot{x} = r(x + y) - (\delta + h)x + \gamma y \quad \text{and} \tag{1a}$$

$$\dot{y} = hx - (\delta + v + \gamma)y, \tag{1b}$$

where the dot notation indicates differentiation with respect to time.

Note that, when the parasite population is monomorphic, the dynamics of the parasite is independent of the occurrence of superinfection. Indeed, replacing one strain by an identical one will have no epidemiological consequences. This is particularly convenient because superinfection will not affect the epidemiological equilibrium of the above system.

MUTANT FITNESS

Superinfection has no direct epidemiological consequences, but it changes selection pressure on the parasites, as we will show now. To study selection pressure, we need to determine the fate of a rare mutant strategy, which we will denote v^*, in a monomorphic parasite population with the resident strategy, v. The dynamics of the rare mutant is given by the following (additional) differential equation:

$$\dot{y}^* = h^*(x + \sigma y) - (\delta + v^* + \gamma + h\sigma)y^*, \qquad (2)$$

where y^* is the density of hosts infected by the mutant parasites, h the force of infection of the resident, and $h^* = \beta^* y^*$ is the force of infection of mutant parasites, where $\beta^* = \beta(v^*)$. Note that superinfection occurs twice in the mutant's equation: It allows the mutant to take over hosts infected by the resident, but superinfection will also cause the mutant to lose hosts to the resident.

The basic reproduction ratio of the mutant parasite in a population dominated by a resident with densities $\hat{x}$ and $\hat{y}$ can then be derived directly from equation (2), and is equal to:

$$R_0(v^*, v) = \frac{\beta^*(\hat{x} + \sigma\hat{y})}{\delta + v^* + \gamma + h\sigma}. \qquad (3)$$

Note that this definition of R_0 is more general than the standard epidemiological definition: It tells us not only whether the mutant can invade a virgin host population (it suffices to set host density to its carrying capacity and set the density of infecteds to zero), but it also tells us whether the mutant can invade a population infected with a resident parasite.

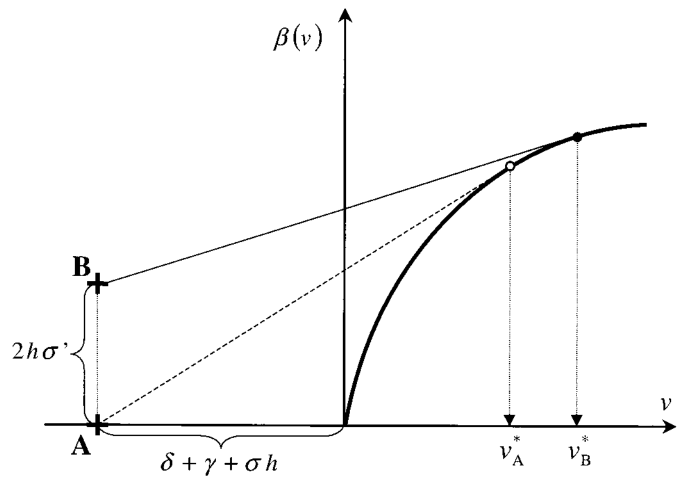

FIG. 1. Graphical solution of the optimum virulence strategy, given a constraint $\beta(v)$ and given the force of infection of the resident. When virulence does not affect competitive ability ($\sigma' = 0$) the optimum strategy (v^*_A) is given by the point on the curve where the tangent goes through the point A = $\{-\delta - \gamma - \sigma h, 0\}$. When virulence affects competitive ability ($\sigma' \neq 0$) the optimum strategy (v^*_B) is given by the point on the curve where the tangent goes through the point B = $\{-\delta - \gamma - \sigma_0 h, 2h\sigma'\}$. The evolutionarily stable strategy (optimum against itself) can be found iteratively by substituting h by the force of infection associated with the optimum strategy.

Optimum Virulence

From the mutant's reproduction ratio, the optimum virulence for the mutant (maximizing its invasion rate) can therefore be found by maximization of R_0 with respect to v^* (while keeping the resident's virulence constant). A little algebra shows that the mutant's optimum virulence should satisfy

$$\frac{d\beta(v^*)}{dv^*} = \frac{\beta(v^*)}{\delta + v^* + \gamma + \sigma h}. \qquad (4)$$

Note that this condition does not depend on the density of uninfected hosts, but it does depend on the force of infection of the resident (see also van Baalen and Sabelis 1995a,b). It has a simple graphical solution (van Baalen and Sabelis 1995a). When transmission efficiency is plotted against virulence, optimum virulence is given by that point on the curve where the slope goes through the point A = $\{-\delta - \gamma - \sigma h, 0\}$ (see Fig. 1). Thus, if either susceptibility to superinfection or the force of infection increases, the optimum virulence of the mutant goes up. This constitutes the most basic proof that within-host competition favors increased virulence.

The graphical solution indicates that optimum virulence increases with host mortality rate. This is in direct contrast with the observations of Ebert and Mangin (1997). However, this explanation is implicitly based on the assumption that nothing else changes, which is evidently not true if host mortality or replacement rates change on a populationwide basis. For example, it is easy to show that the density of infected hosts (and hence the force of infection) goes down if the replacement rate goes up. This implies that ultimately, recovery has both a direct effect (favoring increased virulence) and an indirect effect (through the force of infection, favoring decreased virulence). The net effect of a change in recovery rate therefore depends on which effect is the larger. To assess the relative importance of direct and indirect effects, the graphical method no longer suffices and we have to calculate evolutionarily stable strategies (ESSs) explicitly, taking into account all of the details of the host-parasite interaction.

Evolutionary Responses

After a successful mutant has invaded and replaced the resident strain, the force of infection will have changed. As a consequence, optimum virulence will shift and other mutants can invade. An ESS is eventually reached when the virulence of the resident is the optimum against itself. The ESS should thus satisfy equation (4) for $v = v^*$, noting that the force of infection is itself a function of v. This condition is too complex to solve analytically, but numerical solutions are readily found. We can use this method to find ESSs as a function of parameters like background mortality or recovery rate and deduce the relative importance of direct and indirect effects.

As it turns out, the balance between these two effects is strongly affected by the susceptibility to superinfection σ. For low values of σ, the direct effect prevails and evolutionarily stable virulence increases with these parameters. However, for large values of σ, the indirect effect will dominate and select for lower parasite virulence instead. Note that there is a subtle difference between the effects of host mortality and replacement rate. Many more superinfections are required to observe a decrease of evolutionarily stable parasite virulence with higher replacement rate as compared to a higher mortality rate (cf. Figs. 2B and 2C). This is due to a weaker indirect effect of replacement rate. Indeed, it can

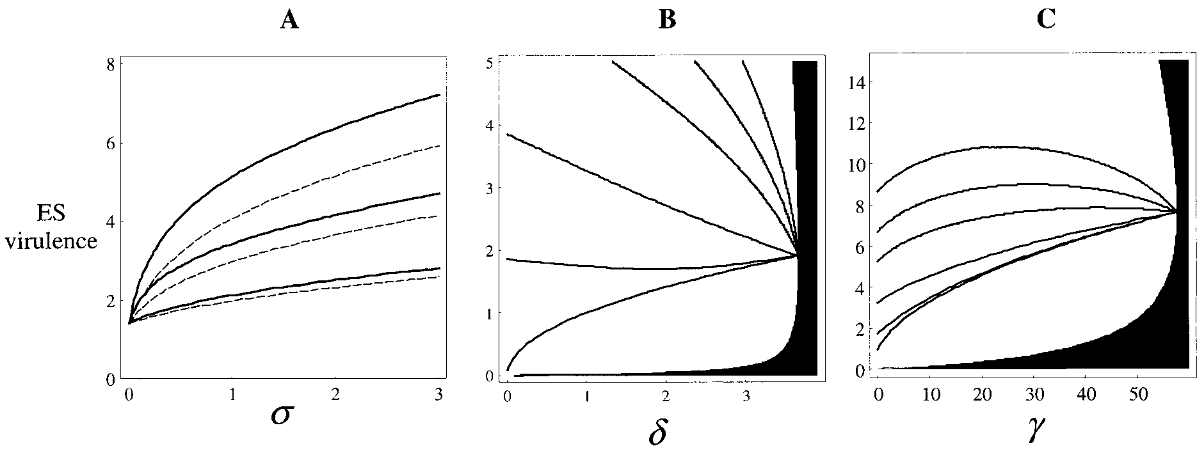

FIG. 2. Evolutionarily stable (ES) virulence as a function of (A) the susceptibility to superinfection (σ); (B) background host mortality (δ); and (C) replacement rate (γ). The results are obtained from a numerical analysis of the model presented in the main text, using a density-dependent rate of host reproduction $r \equiv r_m[1 - \kappa(x + y)]$ and a constraint $\beta(v) = v/(1 + v)$. In (A), ES virulence is plotted for different combinations of maximum growth ($r_m = 2, 4, 8$) and density dependence ($\kappa = 0.01$, solid curves, and $\kappa = 0.02$, dashed curves). In (B) and (C), ES virulence is plotted for different values of the susceptibility to superinfection ($\sigma = 0, 0.1, 1, 5, 10, 20$; upper curves are for higher superinfection rates); the black area indicates parameter values where the parasite goes extinct. (Default parameter values used in all panels: $r_m = 4$, $\kappa = 0.01$, $\delta = 1$, and $\gamma = 1$.)

be shown that the effect of replacement rate on the force of infection is much lower compared to the effect of host mortality. Finally, note that for intermediate values of the susceptibility to superinfection the effect of host mortality and of replacement rate need not be monotonic (Fig. 2).

VIRULENCE AND DOMINANCE

So far, we have assumed that a parasite's virulence has no relation with within-host competitiveness. However, it is likely that such relationships exist. For example, both virulence and competitiveness may be correlated with within-host growth rate (Ebert 1999). To allow for such a relationship, we have also analyzed the case where the susceptibility of superinfection depends on the difference in the contestant's virulences: $s[v_2 - v_1]$ (the indices refer to the order of arrival). If the mutant's virulence is identical to that of the resident, its take-over rate is a certain baseline take-over rate $\sigma = s[0]$, but by increasing its virulence it automatically increases its take-over rate, what Bonhoeffer and Nowak (1994) call the strain's ''dominance.'' We will use the symbol $\sigma' = \mathrm{d}s[v^* - v]/\mathrm{d}v^*|_{v=v^*}$ to describe the strength of the effect of virulence on competitiveness. Note that if σ' goes to infinity, the take-over rate function will approach a step function. This means that we recover Nowak and May's (1994) model where an infinitesimal increase in virulence allows a parasite to take over all infected hosts instead of just uninfected hosts. We will not present the analysis in full detail here (it goes basically along the lines as we have discussed), but we will point out the most salient differences and how it affects the end results.

The first important difference is in parasite fitness. The resident's dynamics remains the same but the mutant's dynamics is now given by

$$\dot{y}^* = h^*[x + s(v^* - v)y] - [\delta + v^* + \gamma + hs(v - v^*)]y^*, \quad (5)$$

and, consequently, its basic reproduction ratio becomes

$$R_0(v^*, v) = \frac{\beta^*[\hat{x} + s(v^* - v)\hat{y}]}{\delta + v^* + \gamma + hs(v - v^*)}. \quad (6)$$

Thus, the mutant optimizing its virulence should now also take into account the effect of virulence on s. Optimizing v^* (while keeping the resident constant) now leads to the condition

$$\frac{\mathrm{d}\beta(v^*)}{\mathrm{d}v^*} = \frac{\beta(v^*)(1 - 2h\sigma')}{\delta + v^* + \gamma + \sigma h}. \quad (7)$$

The direct effect of the relationship between virulence and within-host competitiveness is that it favors increased virulence, as shown in the graphical solution presented in Figure 1.

Note that if σ' is above a certain threshold value the strategy that satisfies equation (7) is not a local maximum of parasite fitness but a local minimum (i.e., $\mathrm{d}^2R_0(v^*, v)/\mathrm{d}v^{*2} > 0$). This means that parasites with either a lower or a higher virulence can invade; in other words, the parasite population will diverge (Jansen and Mulder 1999). This process leads to the coexistence of different parasite strategies and the emergence of virulence polymorphisms (for simulation results in the limiting case where $\sigma' \to \infty$, see Nowak and May 1994). In the following analysis we will only focus on the case where σ' is lower than the threshold value (see gray area in Fig. 3). The emergence of polymorphisms in our model will be analyzed elsewhere using the method outlined in Jansen and Mulder (1999).

Numerical solutions show that around $\sigma' = 0$, small variations in the dominance of the mutant have a strong effect on the evolution of virulence, but that the effect saturates rapidly (see Fig. 3A). Other parameters affect the evolution of parasite virulence through their effects on the force of infection. Figures 3B and 3C show that the effects of host mortality and replacement rate, respectively, are more sensitive to the effect on competitiveness than to the susceptibility to superinfection. In particular, a decrease in the evolutionarily stable virulence for higher replacement rate is eas-

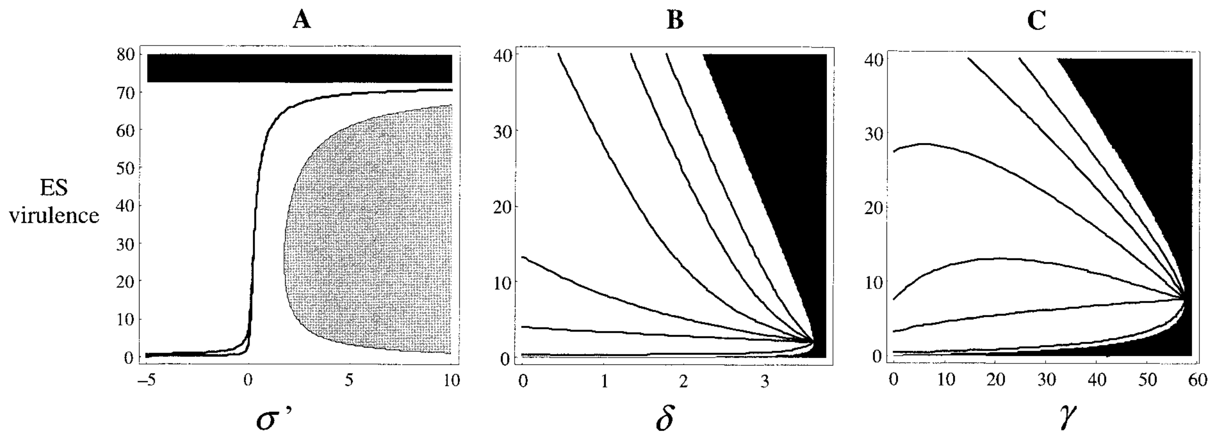

FIG. 3. Evolutionarily stable (ES) virulence as a function of (A) dominance (σ'); (B) background host mortality (δ); and (C) replacement rate (γ). The model is the same as analyzed in Figure 2, except for the superinfection, which now depends on the difference between the contestants' virulences. In (A), ES virulence is plotted for two values of the baseline level of the susceptibility to superinfection ($\sigma = 1$, lower curve; and $\sigma = 10$, upper curve) as well as the unfeasibility area (black) and the area where virulence would be unstable (gray). In (B) and (C), ESS virulence is plotted for different values of the dominance parameter ($\sigma' = -1$, 0, 0.1, 0.25, 0.5, 1; upper curves are for higher dominance values). Default parameter values as in Figure 2.

ier to obtain for larger values of dominance (cf. Figs. 2C and 3C).

Discussion

Host Life History and Parasite Virulence

As pointed out by Frank (1996, p. 54), when the host-parasite system has reached a demographic equilibrium, the evolution of the parasite does not depend on parasite birth rates (i.e., parameters that affect parasite transmission efficiency) such as host reproduction rate (r). Evolutionarily stable parasite virulence is only governed by parasite death rates (i.e., parameters that affect the probability of extinction of parasite populations) such as host death rate (δ) or replacement rate (γ). Both these parameters select for higher virulence strategies. When only single infections occur, we recover these classical results.

However, when superinfections occur, another level of selection emerges. Parasite virulence then evolves under the action of both between- and within-host selection pressures (Eshel 1977; Levin and Pimentel 1981; Bremermann and Pickering 1983; Frank 1992, 1994, 1996; Bonhoeffer and Nowak 1994a,b; May and Nowak 1994; Nowak and May 1994; van Baalen and Sabelis 1995a,b; Gandon 1998; Gandon and Michalakis 2000). The balance between the action of these two levels of selection is mediated by the risk for a given parasite to be outcompeted by another strain. This risk depends on the outcome of within-host interactions among parasites (in our model represented by the parameters σ and σ'), but also on the force of infection, h, which is itself a complicated function of both host and parasite life-history traits. As a consequence, life-history parameters that do not affect the parasite transmission efficiency, but do have an effect on the parasite density (e.g., the host growth rate) play a part in the evolution of virulence. More interestingly parasite death rates, such as δ and γ, may select for lower virulence through a complicated ecogenetical feedback. Indeed, host mortality and replacement rate act both directly (classical effect) and indirectly (via the force of infection) on the evolution of parasite virulence. These two effects act in different directions. When the susceptibility to superinfection and/or dominance are high, the direct effect becomes negligible compared to the indirect effect and the evolutionarily stable virulence becomes a decreasing function of parasite death rates. Interestingly, the latter result can also be obtained in very different models for the evolution of virulence (e.g., eq. 24 in Nowak and May 1994; eqs. E4 and E10 in van Baalen and Sabelis 1995a), but so far has gone unnoticed. The convergence of these results in models that vary considerably in their underlying assumptions (e.g., May and Nowak [1994] assume that potentially very different strategies can emerge by mutation, van Baalen and Sabelis [1995a,b] assume a coinfection process) indicates that this result does not depend sensitively on the specific assumptions of our model.

Ebert and Mangin's Experiment

Our results corroborate the hypothesis put forward by Ebert and Mangin (1997): High mortality can decrease the intensity of within-host competition to such an extent that it counteracts the direct effect favoring increased virulence. However, as Ebert and Mangin (1997) point out, there are alternative hypotheses to explain this phenomenon.

The argument would be more convincing if the intensity of within-host competition in the two treatments could be assessed, which is not an easy task. In terms of our model, this intensity depends on (1) the force of infection; (2) the susceptibility to superinfection (σ); and (3) the dominance (σ') of the parasite. The force of infection can, in principle, be assessed from epidemiological data. Assessing the susceptibility to superinfection is much more difficult: It would require strains differing in a neutral marker and then individual hosts should be tracked to see how often one strain replaces another. Insight into dominance effects requires a similar effort, but then with parasites that differ in virulence.

A more indirect test would be similar to Ebert and Mangin's (1997) experiment, but now the hosts should not be replaced by individuals from a disease-free stock but from a parallel stock infected with a strain of parasites that is distinguishable through a neutral marker. Then, the parasites in the experiment would still be subject to an increased mortality rate, but the effect of replacement on the force of infection (of both strains combined) would be much reduced. In other words, only the direct effect remains and thus the prediction is the evolving parasites will evolve toward increased virulence.

Multiple Infections and Virulence

Multiple infection often goes unnoticed in epidemiological and population dynamic studies. This is partly because if there is little or no variability in the parasite population, multiple infections will not affect the number of infected hosts. Thus, multiple infections have no direct consequences for population dynamics or epidemiology. Yet, as exemplified by our results, multiple infection can be instrumental in the evolution of life-history parameters (e.g., parasite virulence) that govern these dynamics. Unfortunately, evidence for the occurrence of multiple infection is difficult to obtain. It requires extensive screening of the infected host population and the ability to distinguish among different strains of parasites.

Our model indicates that the frequency of multiple infections is not sufficient to predict the direction of parasite virulence. Most models of parasite virulence assume a correlation between competitive ability within the host and parasite virulence (e.g., Frank 1992, 1994, 1996; Bonhoeffer and Nowak 1994a; May and Nowak 1994; Nowak and May 1994; Gandon 1998). Turner and Chao (1998, 1999) and Chao et al. (2000) present convincing empirical evidence for a negative correlation in the RNA bacteriophage $\phi 6$ and other parasitic species. Indeed, increased competitivity between different strains may incur a cost in terms of lower host exploitation and, consequently, lower parasite virulence. Our model allows such cases to be analyzed when we consider negative dominance. As expected, in such cases, the evolutionarily stable parasite virulence can be lower than single infection cases (see Fig. 1 for a graphical presentation of this result).

In the present model we assume fixed values for these superinfection parameters. These parameters are likely to be under strong selective pressures. On the one hand, the ability to superinfect an already infected host presents obvious advantages, while, on the other hand, resistance against superinfection could be selected for in the parasite population. The host population could also benefit from the latter behavior and one may expect host and their parasites to cooperate to prevent subsequent infections (van Baalen and Sabelis 1995a). Note also the indirect benefits of multiple infections that could be gained through sexual reproduction (e.g., avoid accumulation of deleterious mutations, allow adaptation to the coevolving host population). The balance between costs and benefits may lead to an optimal level of multiple infections for the parasite (Turner et al. 1999).

Nonspecific Immunity and the Evolution Virulence

We pointed out above the analogy between our replacement rate and the classical recovery rate, which expresses the action of a nonspecific immune system against parasites. Several authors demonstrated that the ability of a host to recover from an infection affects the evolution of the parasite (Frank 1992, 1996; van Baalen 1998; Gandon and Michalakis 2000). Indeed, a higher clearance rate implies that the parasite may have a shorter period of time to exploit its host. Host mortality also selects for more virulent strategies for the same reason (Frank 1992, 1996; van Baalen 1998; Gandon and Michalakis 2000). However, as for host mortality, the above models did not consider the indirect effects of clearance rate when multiple infections occur. Note, however, that Frank (1992, 1996) and Gandon and Michalakis (2000) assume multiple infections but do not relate the clearance rate (or quantitative resistance in Gandon and Michalakis 2000) to the risk of multiple infection (relatedness among parasites within infected hosts is a fixed parameter). Our models show that, contrary to the above predictions, when σ and σ' are sufficiently high, higher recovery rate can select for lower parasite virulence. This has implications for the evolution of host resistance. When multiple infections occur, this type of host resistance has a twofold advantage. First, it allows the individual host to get rid of the parasite. Second, in the long term and at a larger spatial scale, higher resistance drives the evolution of the parasite toward lower levels of virulence, which may benefit the whole host population.

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