

A General Theory for the Evolutionary Dynamics of Virulence

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ABSTRACT: Most theory on the evolution of virulence is based on a game-theoretic approach. One potential shortcoming of this approach is that it does not allow the prediction of the evolutionary dynamics of virulence. Such dynamics are of interest for several reasons: for experimental tests of theory, for the development of useful virulence management protocols, and for understanding virulence evolution in situations where the epidemiological dynamics never reach equilibrium and/or when evolutionary change occurs on a timescale comparable to that of the epidemiological dynamics. Here we present a general theory similar to that of quantitative genetics in evolutionary biology that allows for the easy construction of models that include both within-host mutation as well as superinfection and that is capable of predicting both the short- and long-term evolution of virulence. We illustrate the generality and intuitive appeal of the theory through a series of examples showing how it can lead to transparent interpretations of the selective forces governing virulence evolution. It also leads to novel predictions that are not possible using the game-theoretic approach. The general theory can be used to model the evolution of other pathogen traits as well.

Keywords: pathogen, disease, quantitative genetics, superinfection, mutation, parasite.

The trade-off hypothesis for virulence evolution postulates that a trade-off exists among parasite life-history characters such that those parasites with a high rate of host-to-host transmission necessarily also induce a high rate of mortality in their hosts (Bull 1994; Read 1994; Ebert and Herre 1996; Frank 1996; Levin 1996; Galvani 2003). It is this additional host mortality rate caused by infection that is typically taken as the definition of virulence in the theoretical literature (Bull 1994; Day 2002*a*), and although it

is undoubtedly affected by both host and parasite characteristics, most theory assumes that virulence evolution is governed solely by evolutionary change in the parasite population (but see van Baalen 1998; Gandon et al. 2002; Day and Burns 2003; Restif and Koella 2003). Mechanistically, such trade-offs are believed to occur because high rates of transmission are obtained only by having a high rate of host exploitation, and this also causes high host mortality (Galvani 2003). Thus the level of virulence expected to evolve depends on the relative magnitude of these costs and benefits of host exploitation. The utility of this theory is still unresolved (Ebert and Bull 2003), but there are a growing number of empirical studies aimed at testing several of its assumptions and predictions (Anderson and May 1982; Massad 1987; Bull et al. 1991; Ewald 1991; Ebert 1994, 1998; Jaenike 1996; Ebert and Mangin 1997; Kover et al. 1997; Lipsitch and Moxon 1997; Kover and Clay 1998; Taylor et al. 1998; Mackinnon and Read 1999; Messenger et al. 1999; Davies et al. 2001; Elena 2001; Cooper et al. 2002; Perlman and Jaenike 2003).

The majority of theory on virulence evolution is grounded in mathematical epidemiology (Diekmann and Heesterbeek 2000). This theory views the host population as a series of compartments between which hosts can move (i.e., the susceptible-infected-recovered models and variants thereof; Anderson and May 1979; May and Anderson 1979; Hethcote 2000) and was originally designed to model the epidemiological dynamics of host-parasite systems. These models have been extended to make predictions about parasite evolution (particularly virulence evolution) through the use of game-theoretic techniques (Frank 1996). This approach begins by assuming that there is a single parasite strain present and then supposes that the epidemiological dynamics reach equilibrium (nearly without exception, this theory considers only stable equilibria). Then it asks whether a mutant strain with different characteristics can invade the host-parasite system. The assumption is that over a series of such invasions and replacements (with the epidemiological dynamics reaching an equilibrium between successive invasions), the system will often end up with a single parasite strain that cannot be invaded by any other mutant. This is the evolutionarily stable strain (Frank 1996).

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The first models of this sort to appear in the literature demonstrated that the evolutionarily stable strain is the one that generates the largest number of new infections in an otherwise entirely susceptible population of hosts (per infected host; Anderson and May 1982; Bremermann and Thieme 1989). This quantity is analogous to lifetime reproductive output from life-history theory (Roff 1992; Stearns 1992) and has become known as R_0 (Diekmann et al. 1990; Frank 1996). This result is extremely useful because one can then derive an expression for R_0 , incorporate the assumptions of the trade-off hypothesis by specifying constraints among the various parameters that make up R_0 , and then calculate the level of virulence that maximizes this quantity.

The number of studies using this game-theoretic approach has grown rapidly over the past 10–20 yr, in part because it is relatively simple and intuitive and also because it has a clear connection with the threshold results for the occurrence of epidemics (e.g., a disease can spread into a host population only if $R_0 > 1$; Hethcote 2000). Indeed, this approach has become a mainstay of the theoretical literature on virulence evolution to the extent that it is now routine for authors to specify an epidemiological setting of interest and then to derive an expression for R_0 to understand and make predictions about virulence evolution (the “maximize R_0 ” technique).

We step back from this approach for a moment and ask the question, Are there other techniques for understanding (and making testable predictions about) virulence evolution that might offer some advantages? We suggest that the answer is yes. In particular, an approach analogous to that of quantitative genetics (QG; Lande 1976, 1979; Lande and Arnold 1983) can often have advantages in terms of its generality, intuitive appeal, and utility for making predictions that are closely tied to empirical tests of theory. As such, we will refer to the theory developed below as a QG approach although we note that the results presented here involve models with a single quantitative trait with a continuum of alleles rather than the more common situation of multiple quantitative traits in standard theory of quantitative genetics. Extensions for multiple traits will be published elsewhere, and therefore we retain the label QG here for consistency.

Our motivation for developing a QG theory stems from several sources. To begin, the assumption of game-theoretic models that an epidemiological equilibrium is reached between successive invasions by different parasite strains is unsatisfying for many reasons. First, this assumption implies that evolutionary change is very slow relative to epidemiological change. The production of substantial genetic variation and the occurrence of evolutionary change in the genetic composition of parasite populations can occur, even within a single host (Levin et al.

1991), and it therefore seems worthwhile to develop a theoretical approach capable of reflecting this fact. Second, many host-parasite complexes do not display equilibrium dynamics, highlighting the need for a dynamic theory of virulence evolution. Third, because of the equilibrium assumption, nearly all game-theoretic models of virulence evolution predict only the long-term equilibrium level of virulence. In fact, because there is no explicit evolutionary dynamic inherent in this approach, game-theoretic models have a very limited capacity to make predictions about the short-term evolutionary dynamics. We feel that this is a significant omission because many empirical measurements aimed at testing theory are made over the short term (i.e., after experimental perturbations have occurred). Moreover, understanding and being able to predict short-term evolutionary dynamics will probably be an essential component of any theory for making virulence management suggestions (Williams and Nesse 1991; Stearns 1999; Trevathan et al. 1999; Stearns and Ebert 2001; Dieckman et al. 2002; Ebert and Bull 2003).

Of course, the development of a suitably general dynamic framework would be of less interest if it were too cumbersome and difficult to use or if its results were too complex to interpret. Fortunately that is not the case. As we will show, a QG approach is at least as easy (and probably easier) to use than the game-theoretic approach. It also allows for any relative timescale of the epidemiological and evolutionary processes, and thus it provides a way to unify and generalize the common dichotomy between epidemic and endemic diseases (Frank 1996). It provides a route toward building relatively simple analytical and simulation models of virulence evolution in more realistic ecological settings that place the host within an explicit food web. It also provides a natural point of departure for developing theory where natural selection on virulence varies spatially throughout the host’s habitat.

We also suggest that the QG approach is well suited to experimental tests of virulence evolution because it clearly separates epidemiological and evolutionary processes (these are somewhat confounded in the single quantity R_0 in the game-theoretic approach). Specifically, most game-theoretic models assume that the parasite regulates the density of susceptible and infected hosts, and this generates evolutionary-epidemiological feedbacks. Importantly, in many experiments this feedback might not occur because the experimenter often controls the host density either purposefully or inadvertently. Therefore, it seems desirable to have a theoretical framework that can easily include or exclude these types of feedback, and the QG approach does so in a very natural way.

Theoretical Development

We begin with a particular epidemiological model of the continuous-time, susceptible-infected-susceptible variety (Anderson and May 1979; May and Anderson 1979; Hethcote 2000) that incorporates all of the relevant transmission dynamics as well as the host-specific ecological interactions that are of interest. To aid intuition we use a simple running example and comment on how the results apply more generally in appendix B. For example, although our focus here is on virulence evolution, the results in appendix B can be used to model any other pathogen trait as well (e.g., transmission rate).

The running example considers a host population consisting of a susceptible and an infected class of individuals whose densities are denoted by S and I (fig. 1):

$$\frac{dS}{dt} = \theta + b_s S + b_i I - dS - \phi_s \phi_i \tau u_s SI + cI, \quad (1)$$

$$\frac{dI}{dt} = \phi_s \phi_i \tau u_s SI - (d + c + \nu)I \quad (2)$$

(see table 1 for notation). Equation (1) represents the dynamics of the susceptible class. In the absence of an infection, the number of individuals will increase through immigration (θ) and birth (b_s) but decrease through mortality (d). In the presence of the parasite, the number of susceptible individuals can increase because infected individuals give birth to susceptible offspring (b_i) or because infected individuals successfully clear the infection (c). Susceptible individuals can become infected with a rate that depends on the probability that they come in contact with infected individuals ($\phi_s S \times \phi_i I$) and the probability

of transmission per interaction (τu_s). The probability that a susceptible individual interacts with an infected individual takes into account the possibility that infected individuals have altered behavior. Similar to Day (2001), ϕ_s and ϕ_i represent the activity level of susceptible and infected hosts, and ϕ_i might depend on virulence in such a way that $\phi_i(0) = \phi_s$ (i.e., the activity level of a host infected with a completely benign parasite is the same as that of an uninfected host; Day 2001). The components ϕ_s and ϕ_i can be viewed as factors that convert the density of susceptible and infected hosts into “effective densities” that account for their activity levels (which might change as a result of infection). As such, we will usually take $\phi_s = 1$ without loss of generality. The τ is the probability that the parasite is transmitted between hosts, and u_s is the probability that, given the parasite is transmitted to a susceptible host, it successfully causes infection. Note that u_s is typically set equal to 1 or subsumed in τ in many models, but it is useful to keep it separate here. The dynamics of infected individuals mirrors that of the susceptible class. More infected individuals are created when a susceptible individual becomes infected, while infected individuals are lost to normal mortality (d), virulence-related mortality (ν), and clearance of the infection (c). We define virulence (ν) as the additional per capita mortality rate caused by infection (Bull 1994; Frank 1996; Day 2002a).

Before proceeding, we also note that all parameters in model 1-2 (eqq. [1], [2]) might depend on the density of susceptible hosts as well as the total density of infected hosts. Thus model 1-2 (eqq. [1], [2]) is quite general, allowing for arbitrary forms of density dependence in the host population as well as nonlinear transmission dynam-

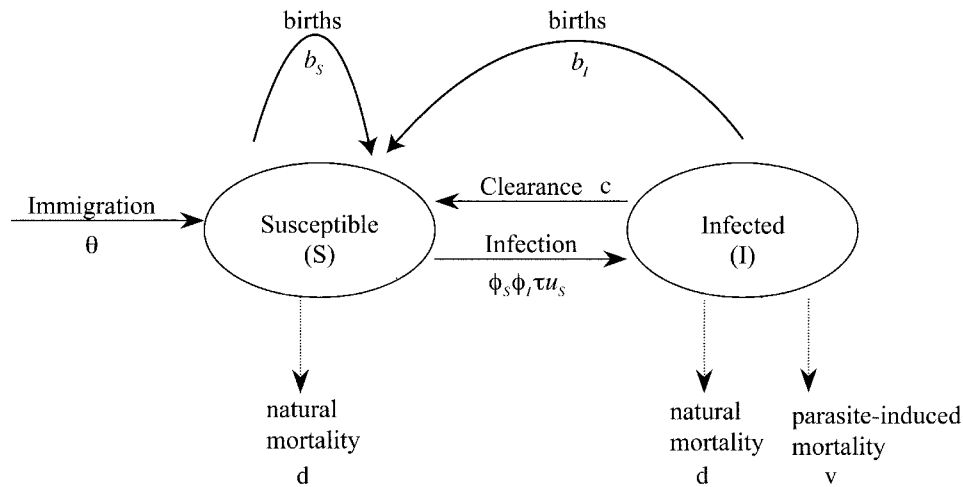


Figure 1: Flow diagram of the epidemiological model 1-2 (eqq. [1], [2])

Table 1: Notation

Term	Definition
b_s, b_i	Birth rates by susceptible and infected hosts
c	Instantaneous rate of infection clearance through host defense mechanisms
d	Natural instantaneous mortality rate of hosts
$\bar{\delta}(\nu)$	Mean displacement (i.e., mutational bias) of strains arising in a host infected with a strain of virulence ν
$\phi_i(\nu), \phi_s$	Activity levels of infection and susceptible hosts, respectively; $\phi_i(0) = \phi_s$
$\eta_m(\nu), \eta_s(\nu)$	Evolutionary effects of the mean level of virulence arising from within host mutation and secondary infection, respectively
$I(\nu)$	Density of infected hosts (with strain ν)
I_T	Total density of all infected hosts
κ	Scaling factor that allows $\tilde{u}_i(\delta)$ to be less than $u_i(\delta)$; $\kappa \leq 1$
ω	Genetic variance in strain type among infected hosts
θ	Net immigration rate of susceptible hosts
r	Instantaneous rate of increase of infected hosts
$\tau(\nu)$	Probability of transmission of a strain of virulence ν between hosts, given that a contact occurs
ρ_m	Rate of mutation per unit time
S	Density of susceptible hosts
σ	Second moment of the mutational distribution
$\tau(\nu)$	Probability of transmission of a strain of virulence ν between hosts, given that a contact occurs
u_s	Probability that a susceptible that is inoculated actually becomes infected
$u_i(\delta)$	Probability that a mutant parasite strain with its virulence displaced by an amount δ from that of the strain infecting the host in which it arises actually takes over the host; the function $u_i(\delta) = \gamma_0 + \gamma_1 \delta$ is usually used
$\tilde{u}_i(\delta)$	Probability that a secondary invading parasite strain, with its virulence displaced by an amount δ from that of the strain currently infecting the host, actually causes secondary infection and takes over the host; we use $\tilde{u}_i = \kappa u_i(\delta)$
ν	Virulence (instantaneous parasite-induced host mortality rate)
$\bar{\nu}$	Mean level of virulence across all infected hosts
ξ	Fraction of offspring of infected hosts that are infected in ‘‘Example 3’’
ζ	Variance in displacement of infection type among hosts

ics (as opposed to simple mass action transmission; McCallum et al. 2001). For example, ϕ_s and ϕ_i might be decreasing functions of the total host density such that the total transmission rate of the parasite, $\phi_s \phi_i \tau u_s S I$, increases less than linearly with S and/or I (McCallum et al. 2001). Finally, to simplify notation, we define $r \equiv \phi_s \phi_i \tau u_s S - (d + c + \nu)$, which represents the per capita rate of change of infected hosts (i.e., $dI/dt = rI$).

Our goal is to derive a model that tracks the evolutionary dynamics of virulence as well as the epidemiological dynamics, allowing for both within-host and between-host selection (Levin and Pimentel 1981; Bremermann and Pickering 1983; Frank 1992; Bonhoeffer and Nowak 1994; Nowak and May 1994; May and Nowak 1995; van Baalen and Sabelis 1995a; Frank 1996; Mosquera and Adler 1998; Gandon et al. 2001a). To do so, we suppose there is a continuum of variation in virulence among infected hosts and that all parasite strains are characterized by the level of virulence, ν , that they induce. We consider only the case of superinfection (Nowak and May 1994; Mosquera and Adler 1998; Gandon et al. 2001a), in which any given host

can be infected by at most one strain of parasite at a time, and we suppose that new strains continually arise through within-host mutation (Bonhoeffer and Nowak 1994). These new strains either immediately displace the prior resident strain or they die out. Additionally, infected hosts might acquire secondary infections, at which point either the original strain immediately excludes the secondary invader or vice versa. Under these assumptions, the epidemiological model (eqq. [1], [2]) can be extended to include evolutionary dynamics of the mean level of virulence, $\bar{\nu}$, as follows (app. A):

$$\frac{dS}{dt} = (\theta + b_s S - dS) + (b_i I_T + c I_T - \phi_s \phi_i \tau u_s S I_T), \quad (3)$$

$$\frac{dI_T}{dt} = I_T r, \quad (4)$$

$$\frac{d\bar{\nu}}{dt} = \omega \frac{\partial r}{\partial \nu} + \eta_m(\bar{\nu}) + \eta_s(\bar{\nu}), \quad (5)$$

where

$$\eta_m(\bar{\nu}) = \rho_m[\gamma_0\bar{\delta}(\bar{\nu}) + \gamma_1\sigma], \tag{6}$$

$$\eta_s(\bar{\nu}) = I_T\phi_1(\bar{\nu})^2\kappa\omega\left(\gamma_0\frac{d\tau}{d\nu} + \gamma_12\tau\right)_{\nu=\bar{\nu}}. \tag{7}$$

In the above equations, all quantities depending on virulence are evaluated at $\nu = \bar{\nu}$. The I_T is the total density of infected hosts, ρ_m is the rate of mutation, ω is the genetic variance in strain type among infected hosts, and $u_1(\delta) = \gamma_0 + \gamma_1\delta$ is the probability that a mutant strain with a virulence level displaced by an amount δ from that of the strain from which it arose succeeds in taking over the host (i.e., the host becomes an infected host of type $\nu + \delta$). The constant γ_0 represents the baseline probability of such an event, and γ_1 represents the extent to which virulence is associated with within-host competitive ability (i.e., $\gamma_1 > 0$ if higher virulence confers greater within-host competitive ability). Also, $\bar{\delta}(\nu)$ is the mean displacement in virulence of newly arising mutations within a host infected by strain ν (i.e., it is the mean value of δ for mutations arising within the host), and σ is the second moment of the mutational distribution (i.e., the expected value of the squared deviation of a mutant's virulence). We allow for the possibility of mutational bias within hosts because we might expect most new mutations to decrease virulence in hosts already infected with extremely virulent strains and vice versa. Alternatively, there might be a consistent directionality to mutation for some pathogens (see Bergstrom et al. 1999 for related suggestions). Finally, we define $\tilde{u}_1 \equiv \kappa u_1$ with $\kappa \leq 1$ as the corresponding probability of taking over a host for the case where the mutant strain arises from secondary infection. This allows for the possibility that this process is less effective than within-host mutation in causing within-host evolution (e.g., because strains arising from secondary infection have to pass more levels of host defense mechanisms than those arising from mutation before they compete with the strain currently infecting the host). The primary assumption involved in the derivation of these equations is that the distribution of parasite strains that infect hosts is Gaussian and has a small variance (see Abrams 2001). Results where the genetic variance, ω , is not necessarily small are found in appendix D (and "Example 4" below).

Several features of model 3–7 (eqq. [3]–[7]) hold more generally for models of virulence evolution involving ecological and epidemiological dynamics (app. B). First, the epidemiological equations (3) and (4) are identical to the original model (eqq. [1], [2]), except that I is replaced with the total density of infected hosts of all strain types. Second, any parameter that depends on the level of vir-

ulence, ν , is evaluated at the population average, $\bar{\nu}$. Third, equation (5), which gives the coupled evolutionary dynamics of the joint evo-epidemiological system, contains three terms representing the three ways in which selection affects virulence evolution as described below.

Between-Host Selection ($\omega\partial r/\partial\nu$). The first term represents the effect of selection on virulence as a result of between-host selection. This is the classic trade-off model introduced by Anderson and May (1982) and accounts for increases in infection rate and decreases in host survival with virulence. It is simply the genetic variance in strain type among hosts, ω , multiplied by the selection gradient (i.e., the derivative specifies the way in which a unit increase in virulence affects the parasite's ability to spread through the host population). For instance, in our running example, we have $r = \phi_s\phi_1\tau u_s S - (d + c + \nu)$. Using $\phi_s = 1$ and supposing that both ϕ_1 and τ are functions of ν , this term becomes

$$\omega\left(\frac{d\phi_1\tau}{d\nu} u_s S - 1\right). \tag{8}$$

Equation (8) reveals the intuitive fact that between-host selection arises as a result of the benefit of virulence for transmission to susceptible hosts (the first term) and the cost of virulence in terms of mortality of infected hosts (the second term). The benefit of virulence is proportional to the density of susceptible hosts, whereas the mortality cost of virulence is a constant (scaled to -1) by the definition of virulence (Frank 1996). Also notice that the speed of evolution as a result of between-host selection depends on the amount of genetic variation in strain type among hosts, ω .

Within-Host Mutation ($\eta_m[\bar{\nu}]$). The second term in equation (5), $\eta_m(\bar{\nu})$, represents the effect of within-host mutation and is specified more explicitly in equation (6). There are two ways in which within-host mutation can impart a directional force in virulence evolution. First, the displacement of the mutations that arise can be biased ($\bar{\delta} \neq 0$). For example, if mutations that cause an increase in virulence are more common than those that cause a decrease in virulence, then this will cause levels of virulence to rise. This effect is represented by the first term in equation (6), where $\bar{\delta}$ is weighted by the baseline probability that new mutants take over the host. Second, even if the displacement of newly arising mutations is unbiased (i.e., $\bar{\delta} = 0$), within-host mutation can still lead to a directional force in virulence evolution if there is a relationship between a strain's displacement and its within-host competitive ability. For example, if higher virulence is associated with a within-host competitive advantage, then $du_1/d\delta = \gamma_1 > 0$, imparting an evolutionary force toward

higher levels of virulence (Bonhoeffer and Nowak 1994). This effect is weighted by the second moment of the distribution of new mutations that arise, σ , and it drops out if virulence is unrelated to within-host competitive ability (i.e., if $du_1/d\delta = \gamma_1 = 0$).

Secondary Infection ($\eta_s[\bar{\nu}]$). The third term in equation (5), $\eta_s(\bar{\nu})$, represents the effect of secondary infection and is specified more explicitly in equation (7). Secondary infection requires that the infected host contact another infected host. Assuming that the distribution of infection types in the host population is narrow, this will occur at a rate $I_T \phi_1(\bar{\nu})^2$. Given such a contact occurs, this can impart a directional force on virulence evolution for two reasons. First, if strains with higher virulence are more likely to be transmitted (as is commonly assumed; i.e., if $d\tau/d\nu > 0$), then secondary inoculations will tend to be biased toward higher virulence. This is analogous to mutational bias in within-host mutation and is represented by the first term in equation (7). Second, if there is a relationship between a strain's virulence and its within-host competitive ability (e.g., if higher virulence is associated with a within-host competitive advantage: $d\tilde{u}_1/d\delta = \kappa\gamma_1 > 0$), this too will impart an evolutionary force toward higher levels of virulence (Gandon et al. 2001a). This is the second term in equation (7). Both of these effects are weighted by ω , meaning that the evolutionary effect of selection arising from secondary infection is greater if there is more genetic variation in strain type circulating in the population. Additionally, both terms are weighted by $\kappa \leq 1$ to allow for differences in the effectiveness of within-host mutation versus secondary infection in causing within-host evolution.

Equation (5) reveals that within-host evolution arising from either mutation or from secondary infection both result in a component of directional selection on virulence in addition to the effect of selection arising from between-host selection. Indeed, both forms of within-host evolution can be viewed as a process whereby a new strain is introduced into an already infected host (either by mutation or secondary infection), and this new strain then either reaches fixation in the host or dies out. Despite their superficial similarity, however, the QG approach also reveals fundamental differences between these two sources of within-host evolution. First, within-host evolution through secondary infection depends on the prevalence of the disease in the population, I_T , whereas within-host evolution through mutation does not. Second, equations (6) and (7) reveal that the importance of secondary infections also depends on the way in which virulence affects the activity level of infected hosts, ϕ_1 , as well as the genetic variance in strain type among hosts, ω . Third, secondary infection can result in the evolution of higher virulence, even in the absence of a relationship between virulence and within-host competitive

ability, if more virulent strains have a greater transmission rate. This is not true of mutation unless there is also mutational bias. Therefore it is of interest to know whether within-host genetic variation in natural pathogen populations is primarily a result of within-host mutation or secondary infection.

Example 1: A Standard SIS Model

As a simple example, suppose that the host population is maintained by immigration; we have

$$\frac{dS}{dt} = \theta - dS - \phi_1 \tau u_s SI + cI, \quad (9)$$

$$\frac{dI}{dt} = Ir, \quad (10)$$

where $r = \phi_1 \tau u_s S - (d + \nu + c)$, and all parameters are as defined earlier (see table 1). We assume that τ is increasing, with virulence and concave down, and that ϕ_1 is either a constant or it is either strictly increasing or strictly decreasing, with virulence and concave down. Together this implies that the transmission rate from infected to susceptible hosts is either increasing with diminishing returns or else is hump shaped and, therefore, that $d^2 \phi_1 \tau / d\nu^2 < 0$. This assumption is characteristic of nearly all game-theoretic models of virulence evolution (Frank 1996; Ebert and Bull 2003).

Following the general recipe of appendix B, the evolutionary dynamics of virulence for this model are

$$\frac{d\bar{\nu}}{dt} = \omega \frac{\partial r}{\partial \nu} + \eta_m(\bar{\nu}) + \eta_s(\bar{\nu}) \quad (11)$$

or

$$\begin{aligned} \frac{d\bar{\nu}}{dt} = & \omega \left(\frac{d\phi_1 \tau}{d\nu} u_s S - 1 \right) + \rho_m(\gamma_0 \bar{\delta} + \gamma_1 \sigma) \\ & + I \phi_1^2 \kappa \omega \left(\gamma_0 \frac{d\tau}{d\nu} + \gamma_1 2\tau \right), \end{aligned} \quad (12)$$

where for notational simplicity we have used I to represent the total density of infected hosts of all strain types, and all terms in equations (9), (10), and (12) are evaluated at $\nu = \bar{\nu}$.

Secondary Infection Absent

For simplicity, here we assume there is no mutational bias (i.e., $\bar{\delta} = 0$) and no relationship between virulence and within-host competitive ability (i.e., $\gamma_1 = 0$). As a result,

within-host mutation has no directional effect on virulence evolution (i.e., $\eta_m = 0$). For the moment, we also assume that secondary infection does not occur (i.e., $\kappa = 0$). As a result, equation (12) becomes

$$\frac{d\bar{v}}{dt} = \omega \left(\frac{d\phi_1\tau}{d\nu} u_s S - 1 \right). \tag{13}$$

An interpretation of each of the terms in equation (13) provides some clear insights into virulence evolution. The first term in parentheses (i.e., $[d\phi_1\tau/d\nu]u_sS$) represents the selective benefit obtained by strains with higher virulence; they have a higher transmission potential, $\tau\phi_1$, and the evolutionary advantage of this heightened potential is larger whenever there are abundant hosts available for infection (i.e., whenever S is large). The second term in parenthesis (i.e., -1) is the selective cost paid by strains with higher virulence; they kill their hosts more quickly, which, from how we have defined virulence, imposes a constant cost of -1 .

These considerations also suggest that a higher density of susceptible hosts selects for higher virulence because it enhances the benefit of virulence. Over the course of an epidemic, however, the density of susceptible hosts will decline as more infections occur, thereby eventually reducing this advantage. This suggests that we should observe an evolutionary escalation in virulence at the beginning of an epidemic, followed by an evolutionary reduction in virulence as the disease spreads and the density of susceptible hosts declines. This has been predicted previously (Lenski and May 1994), and the QG approach illustrates this effect (and why it occurs) very clearly. It also reveals the way in which the magnitude of the initial increase in virulence depends on the speed of the epidemiological dynamics relative to the amount of genetic variance in strain type among hosts (fig. 2).

Comparison with Previous Results. It is useful to contrast this QG approach with that of previous theory. To use the game-theoretic approach, we need to calculate R_0 . For the present model we have

$$R_0 = \frac{\phi_1\tau u_s N}{d + \nu + c}, \tag{14}$$

where N is the density of susceptible hosts in the absence of the infection. The first derivative condition that must be satisfied by the ESS virulence is therefore

$$\frac{d\phi_1\tau/d\nu}{\phi_1\tau} = \frac{1}{d + \nu + c}. \tag{15}$$

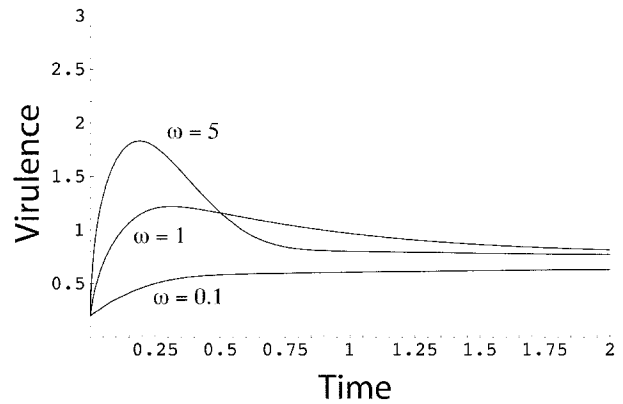


Figure 2: Effect of genetic variation in strain type ω ; evolutionary dynamics of virulence using the function $\tau(\nu) = \tau_1\nu/(\tau_2 + \nu)$ and the arbitrary parameter values $\theta = 10$, $d = 0.1$, $c = 1$, $\tau_1 = 2$, $\tau_2 = 0.5$, $S(0) = 10$, $I(0) = 1$, $\bar{v}(0) = 0.2$, and different levels of genetic variance in virulence ω .

Notice that N has dropped out of equation (15) because it is a multiplicative constant in equation (14) and therefore does not affect the optimal level of virulence. Equation (15) can be interpreted as stating that the proportional increase in transmission that comes from an increase in virulence (i.e., the fitness benefit) must equal the proportional increase in the total loss rate of infected hosts that comes from this increase in virulence (i.e., the fitness cost). In other words, at the ESS, the transmission benefits of a further increase in virulence must be balanced by the mortality costs.

It is worth noting that equation (15) can be derived from the QG approach as well. Assuming that the epidemiological equilibrium has been reached, we can solve equation (10) for S to get $S = (d + \nu + c)/\phi_1\tau u_s$. This can then be substituted into equation (13), giving the evolutionary dynamics of virulence under the assumption that evolution is very slow relative to epidemiology (i.e., the genetic variance, ω , is vanishingly small). At evolutionary equilibrium, equation (13) will also equal 0, and this can then be rearranged to obtain equation (15).

Much has been learned from theory based on R_0 . First, equation (15) has been used to demonstrate that an increase in natural mortality rate of the host, d , results in the evolution of higher virulence because it decreases the mortality cost of virulence (Anderson and May 1982; Sasaki and Iwasa 1991; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Day 2001, 2002a; Williams and Day 2001). A consideration of equation (13), however, suggests that the increase in mortality should first select for a decrease in virulence because it will initially decrease the density of susceptible hosts. This

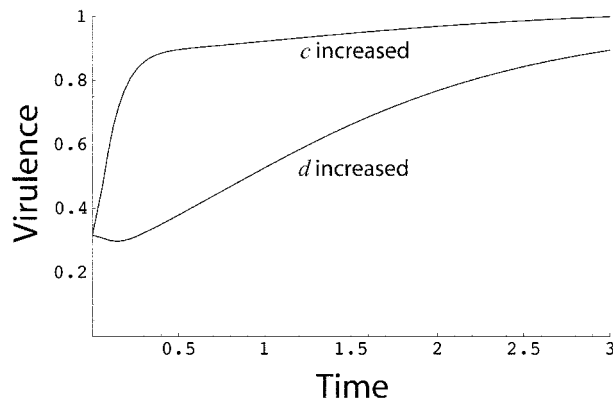


Figure 3: Effect of natural mortality, d , and clearance rate, c . Evolutionary dynamics of virulence using the function $\tau(\nu) = \tau_1\nu/(\tau_2 + \nu)$ and the arbitrary parameter values $\theta = 10$, $\tau_1 = 1$, $\tau_2 = 0.5$, and $\omega = 5$. The curves represent two different scenarios: in *c increased*, $d = 0.1$, and c increases from 0.1 to 2; in *d increased*, $c = 0.1$, and d increases from 0.1 to 2. Initial conditions were set to $S(0) = 1.33$, $I(0) = 23.7$, and $\bar{\nu}(0) = 0.32$, which are the equilibrium values corresponding to the above-mentioned parameter values before the change in either d or c .

also causes a reduction in the density of infected hosts, however, and over time this will counteract the decline in susceptible hosts because the force of infection will decline. Indeed, at equilibrium it can be shown that the density of susceptible hosts in this model is actually higher when the natural host mortality rate, d , is higher (fig. 3). Thus, the evolutionary predictions obtained from the game-theoretic approach miss an underlying level of complexity related to the evolutionary dynamics that can be understood only through the use of a dynamic model.

Previous results based on equation (15) have also suggested that an increase in the clearance rate of infection, c , has an identical effect on virulence evolution as an increase in the natural mortality rate, d , because both enter equation (15) in an identical way (in the denominator of the right-hand side; Frank 1996). The QG approach, however, demonstrates that there are important differences between these two cases that are masked by the game-theoretic approach. Increasing the clearance rate, c , will immediately increase the density of susceptible hosts, S , and decrease the density of infected hosts, I . Therefore, we expect an immediate evolutionary increase in virulence when c is increased (fig. 3).

Previous theory based on equation (15) has also predicted that changing the transmission rate by a multiplicative constant will have no effect on virulence evolution. This led some to question verbal theories of virulence management that are based on such manipulations (Ewald 1994, 1995; van Baalen and Sabelis 1995b). The QG approach demonstrates that there again is a hidden layer of

complexity that is ignored by these previous results. According to equation (13), increasing τ by a multiplicative constant will increase the transmission rate and therefore immediately select for an evolutionary increase in virulence. This will eventually result in a reduction in the density of susceptible hosts, however, which will counteract the initial increase in such a way that the equilibrium level of virulence remains unchanged (fig. 4). The magnitude of this initial increase in virulence will depend on the level of genetic variance in virulence relative to the timescale of the epidemiological dynamics.

Secondary Infection Present

We now incorporate secondary infection into the above model. We assume that activity level of infected hosts is unaffected by virulence (i.e., $\phi_1 \equiv 1$). In this case, again supposing that there is no mutational bias (i.e., $\delta = 0$) and that there is no relationship between virulence and within-host competitive ability (i.e., $\gamma_1 = 0$), equation (12) simplifies to

$$\frac{d\bar{\nu}}{dt} = \omega \left[\frac{d\tau}{d\nu} (u_s S + \tilde{u}_1 I) - 1 \right]. \quad (16)$$

Equations (9), (10), and (16) now give the coupled evolutionary-epidemiological dynamics.

A comparison of equations (16) and (13) reveals that secondary infection affects virulence evolution simply by changing $u_s S$ in the first term to $u_s S + \tilde{u}_1 I$ (note that ϕ_1 drops out of equation [13] when $\phi_1 \equiv 1$). Secondary in-

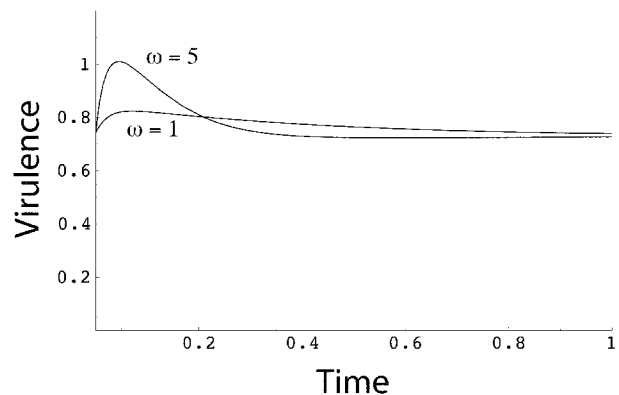


Figure 4: Effect of infected activity level ϕ_1 . Evolutionary dynamics of virulence using the function $\tau(\nu) = \tau_1\nu/(\tau_2 + \nu)$ and the arbitrary parameter values $\theta = 10$, $d = 0.1$, $c = 1$, $\tau_1 = 5$, $\tau_2 = 0.5$, and $\phi_1 = 1$. System was allowed to reach the equilibrium values of $S(0) = 3.1$, $I(0) = 11.5$, and $\bar{\nu}(0) = 0.74$, and the plot then begins after ϕ_1 is increased to 5. The plot shows results for two different values for the genetic variance.

fection therefore has a directional effect on virulence evolution, even though there is no relationship between within-host competitive ability and virulence, because strains that cause secondary infections tend to have higher than average virulence (because $d\tau/d\nu > 0$).

Comparison with Previous Results. Previous theory has demonstrated that secondary infection can result in the evolution of higher virulence in the absence of a relationship between virulence and within-host competitive ability (Gandon et al. 2001a). Interestingly, different interpretations of the biological reason behind this can emerge in the game-theoretic versus the QG approach. Gandon et al. (2001a) have shown that, in a model analogous to that above, the evolutionarily stable level of virulence, ν^* , satisfies an equation identical to equation (15) (with $\phi_1 \equiv 1$) except with an additional term, $\tilde{u}_1\tau I$, in the denominator of the right-hand side (Gandon et al. 2001a, eq. [4]). A cursory reading of this result would suggest that secondary infection selects for higher virulence by increasing the loss rate of infected hosts (through their being secondarily infected) in much the same way that an increase in host mortality rate, d , can select for higher virulence (Frank 1996). On the other hand, the QG approach (eq. [16]) suggests that higher virulence evolves because secondary infections are caused by parasite strains with a higher than average virulence (because the transmission probability, τ , is higher for more virulent strains). In this way, the effect is analogous to that of biased within-host mutation (see discussion after eq. [8]).

This discrepancy in interpretation can be resolved by conducting a thought experiment. Suppose we could eliminate the relationship between virulence and transmission probability for secondary infections only (i.e., τ is an increasing function of ν for interactions between susceptible and infected hosts but not for interactions between two infected hosts). In this way, we can maintain the heightened loss rate of infected hosts, but now these secondary infections are caused by strains with a random level of virulence. The QG approach then clearly predicts that secondary infection should have no effect on virulence evolution because equation (16) becomes $d\bar{\nu}/dt = \omega [(d\tau/d\nu)u_s S - 1]$, which is identical to the case of no secondary infection (i.e., eq. [13]). Importantly, the derivation of Gandon et al. (2001a) can be followed through in this case to give the exact same prediction; it is not the heightened loss rate per se that causes the evolution of higher virulence, but rather it is the fact that secondary infections are caused by strains with higher-than-average virulence. Thus, although the predictions of the game-theoretic approach are certainly correct, the correct biological interpretation of these predictions is immediately

apparent in the QG approach, whereas it is somewhat obscured in the game-theoretic approach.

Previous theoretical results have also demonstrated that changes in the host mortality rate, d , and the infection clearance rate, c , can have different effects once secondary infection is allowed (Gandon et al. 2001a). The QG approach provides further insights into why this occurs. Equation (16) reveals that it is the total “effective” host density, $u_s S + \tilde{u}_1 I$, that determines the level of virulence that evolves because this controls the selective advantage of virulence. It can be shown that when the mortality rate d is increased in the model used here, this quantity changes in a direction given by the sign of

$$(1 - \mathfrak{R})(\nu + d)^2 - \mathfrak{R}(u_s \tau \theta + c\nu), \quad (17)$$

where $\mathfrak{R} = \tilde{u}_1/u_s$. Thus virulence changes in a direction given by the sign of equation (17). In the absence of secondary infection, $\mathfrak{R} = 0$, and we can see that virulence always evolves to be larger (as seen earlier). The reason is that the density of susceptible hosts at equilibrium will be higher in this case (as detailed earlier). With secondary infection, however, $\mathfrak{R} > 0$, and if \mathfrak{R} is big enough, then virulence will evolve to be lower under higher host mortality. The reason is that although the density of susceptible hosts at equilibrium will be higher, the density of infected hosts will be lower. Depending on the relative importance of these two host types in the spread of infection (i.e., depending on the relative sizes of u_s and \tilde{u}_1), the total effective host density $u_s S + \tilde{u}_1 I$ can either increase or decrease, and this either increases or decreases the selective advantage of virulence.

It can also be shown that if the clearance rate, c , is increased, the total effective host density, $u_s S + \tilde{u}_1 I$, and thus virulence, changes in a direction given by the sign of

$$(1 - \mathfrak{R})d + \nu. \quad (18)$$

Notice that, as with mortality, in the absence of secondary infection, the equilibrium level of virulence always increases. Unlike with mortality, however, an increase in c can result in a decrease in the equilibrium level of virulence only if infected hosts are more important in the spread of the disease than susceptible hosts (i.e., if $\tilde{u}_1 > u_s$).

The QG approach also provides some clear insights into potential explanations for the results of selection experiments. For example, using a *Daphnia*-microsporidium system, Ebert and Mangin (1997) experimentally increased clearance rate by periodically replacing infected *Daphnia* with uninfected ones in such a way that the total host density remained largely constant. Thus, the treatment increased S and decreased I in such a way that $S + I$ remained constant. In the absence of secondary infection, equation

(13) predicts an evolutionary increase in virulence because the transmission benefits are higher (the anticipated response; Ebert and Mangin 1997). Interestingly, the opposite actually occurred, and Ebert and Mangin (1997) suggested that this was because of secondary infection, a possibility that has been given theoretical support by Gandon et al. (2001a).

Using the QG approach, we can clearly see the conditions under which this explanation is valid. Equation (16) reveals that virulence should decrease provided that $u_s S + \tilde{u}_1 I$ decreases. Recalling that the treatment effectively changed some of the I hosts into S hosts, we can immediately see that this will select for a decrease in virulence only if (as already mentioned) $u_s < \tilde{u}_1$, that is, if the probability that the parasite causes infection (given that it is transmitted) is larger for secondary infections than for primary infections (as might occur if infected hosts are less able to defend themselves against further infection). If this is not the case, then further conditions are required for secondary infection to explain the experimental findings. In particular, if there is a relationship between virulence and within-host competitive ability, then equation (16) extends to

$$\frac{d\bar{v}}{dt} = \omega \left[\frac{d\tau}{d\nu} (u_s S + \kappa\gamma_0 I) + 2\kappa\gamma_1 \tau I - 1 \right], \quad (19)$$

where we have used the fact that $\tilde{u}_1 = \kappa u_1$ and $u_1 = \gamma_0 + \gamma_1 \delta$. The third term clearly reveals that a decrease in I (as a result of replacement with susceptible hosts) will then weaken selection for virulence. If this effect is larger than the increase in the first term (assuming here that $u_s > \kappa\gamma_0$), then it might explain the empirical results.

Finally, we note that Gandon et al. (2001a) have remarked how introducing a relationship between virulence and within-host competitive ability can result in the evolutionary diversification of parasites with differing levels of virulence (provided this relationship is strong enough). Analogous findings are obtained with the QG approach. In particular, appendix C shows that the evolutionary dynamics of the variance in parasite strains need not reach an equilibrium if equation (C6) is positive. It can be seen that in the present model, this can be the case if γ_1 (which represents the strength of the relationship between virulence and within-host competitive ability) is large enough. More generally, the relationship between the present approach and the game-theoretic approach is detailed in appendix E.

Example 2: Horizontal versus Vertical Transmission

There has been considerable interest in determining the effects of vertical versus horizontal parasite transmission

on virulence evolution (Bull et al. 1991; Sasaki and Iwasa 1991; Ewald 1994; Lipsitch et al. 1995, 1996; Frank 1996; Kover et al. 1997; Kover and Clay 1998; Messenger et al. 1999). We illustrate how the QG approach can be used to gain insight into this question as well. Consider a simple epidemiological model of the form

$$\begin{aligned} \frac{dS}{dt} = & b_s S \left(1 - \frac{N}{K}\right) + b_1 I \left(1 - \frac{N}{K}\right) \\ & \times (1 - \xi) - dS - \tau u_s \phi_1 SI, \end{aligned} \quad (20)$$

$$\frac{dI}{dt} = \tau u_s \phi_1 SI - (v + d)I + b_1 I \left(1 - \frac{N}{K}\right) \xi. \quad (21)$$

Here b_s and b_1 are the (constant) per capita birth rates by susceptible and infected hosts when the total host population density, $N = S + I$, is low, and we allow for b_1 to be a function of virulence, v . Notice that, overall, the birth rates are density dependent, and K is the host density at which the birth rates equal 0. Finally, ξ is the fraction of offspring produced by infected hosts that are themselves infected. When $\xi = 0$, there is no vertical transmission, and when $\xi = 1$, there is perfect vertical transmission (i.e., all offspring of infected hosts are infected).

For this example, we will suppose that there is no secondary infection ($\eta_s = 0$) and no directional force to virulence evolution arising through within-host mutation ($\eta_m = 0$). Therefore, following appendix B, the evolutionary dynamics of virulence are

$$\frac{d\bar{v}}{dt} = \omega \left[\frac{d\tau}{d\nu} u_s \phi_1 S - 1 + \frac{db_1}{d\nu} \left(1 - \frac{N}{K}\right) \xi \right], \quad (22)$$

where we have assumed that ϕ_1 is independent of v . Equations (20)–(22) give the coupled evolutionary-epidemiological dynamics of this system.

Several clear predictions can be drawn from equation (22). First, in the absence of horizontal transmission (i.e., with purely vertical transmission; $\tau \equiv 0$), the first term disappears. Therefore, under the assumption that virulence either decreases the reproductive output of infected hosts or leaves it unchanged, equation (22) makes the well-known prediction that, under purely vertical transmission, the parasite will evolve toward avirulence (Lipsitch et al. 1995, 1996). Second, if we instead assume that the parasite has no effect on the reproductive rate of infected hosts, then the third term in equation (22) disappears. Therefore we are left with the same evolutionary dynamic as we had in equation (13) of example 1. Under such conditions, vertical transmission affects virulence evolution only through its effects on the density of susceptible hosts.

From these simple observations, if virulence does not affect fecundity, then we can also easily derive the prediction that the presence of vertical transmission reduces the equilibrium level of virulence by showing that vertical transmission reduces the density of susceptible hosts (and thus, from eq. [22], decreases the selective advantage of virulence). To do so, we simply solve equation (21) for S to obtain

$$S = \frac{d + \nu - b_1[1 - (N/K)]\xi}{\tau u_s \phi_1}. \quad (23)$$

We know that at equilibrium we must have $N < K$ because otherwise the birth rates would be negative and the population would go extinct. Therefore, we know that the third term in the numerator of equation (23) is positive, provided that vertical transmission occurs (i.e., when $\xi \neq 0$). Thus, the equilibrium density of susceptible hosts must be lower when vertical transmission occurs, and this leads to the evolution of lower virulence (at equilibrium).

It has also been noted that an increase in the propensity for horizontal transmission that comes about from an increase in the contact rate, ϕ_1 , actually leads to the evolution of lower virulence in this model (Lipsitch et al. 1996). This at first is counterintuitive because we might expect increased horizontal transmission to lead to higher virulence because it should make the importance of vertical transmission in the reproduction of the parasite relatively less important. Some insight into the reason for this prediction can be gained by recalling what happened in example 1 when the contact rate was increased. If virulence does not affect fecundity (i.e., $db_1/d\nu = 0$), we have

$$\frac{d\bar{\nu}}{dt} = \omega \left(\frac{d\tau}{d\nu} u_s \phi_1 S - 1 \right). \quad (24)$$

As in example 1, an increase in the contact rate, ϕ_1 , immediately increases the selective advantage of virulence. Initially, provided there is ample genetic variance in virulence, this leads to the evolution of higher virulence. Over time, however, the density of susceptible hosts declines to compensate for the change in contact rate. In the case of example 1, this compensatory decrease was equal to the increase in contact rate, and this left the mean level of virulence unchanged at equilibrium. In the present case, the decline in the density of susceptible hosts more than compensates, and at equilibrium the mean level of virulence is actually lower. Such overcompensation occurs here because the presence of vertical transmission essentially provides another route through which the density of infected hosts can increase at the expense of susceptible hosts.

Experiments have been conducted to test theory about how the extent of horizontal versus vertical transmission affects virulence evolution (Bull et al. 1991; Messenger et al. 1999). The results have been interpreted using theory based on the game-theoretic approach of maximizing R_0 , and this assumes that epidemiological equilibrium is reached. In experimental manipulations, however, this is probably often not the case, and the QG approach provides a clear conceptual route for making predictions for these sorts of experiments. For example, equation (24) reveals that if one experimentally manipulates the extent of vertical transmission by altering the proportion of offspring produced from infected hosts that are themselves infected (i.e., ξ), then we expect no evolutionary response in virulence unless this alteration is allowed to feed back on the density of susceptible hosts. Otherwise, the manipulation does not alter anything in equation (24). This sort of epidemiological feedback is probably often precluded in many experiments, and thus no evolutionary response is expected.

Interestingly, the experiments that have demonstrated the evolutionary consequences of these two transmission routes have tended to use a different manipulation. For example, horizontal transmission is largely prevented in one treatment (making $d\tau/d\nu = 0$) or largely enforced in another treatment (e.g., Bull et al. 1991). Equation (24) predicts an immediate selection for reduced virulence in the former case relative to the latter. Other protocols have enforced periods of solely vertical transmission followed by periods of solely horizontal transmission but have manipulated the amount of the life cycle that is made up of each of these types of transmission (e.g., Messenger et al. 1999). Results have shown that lower virulence evolves in treatments that spend a greater proportion of time under enforced vertical transmission. This is also expected from equation (24). Indeed, the QG approach can be used independent of any feedback in the epidemiological dynamics. One simply needs to specify the relevant quantities in the equation for the evolutionary dynamics of virulence. For example, the present situation might be modeled by assuming that S is constant (disallowing any epidemiological feedback) but where $d\tau/d\nu$ fluctuates between 0 and some positive value over time. Predictions obtained are in qualitative agreement with experimental results (fig. 5).

Example 3: Mutation and Virulence Evolution

Interest has also focused on determining how within-host mutation affects virulence evolution (Bonhoeffer and Nowak 1994). As a simple example, consider the epidemiological model 9–10 (eqq. [9], [10]) but ignore secondary infection. In this case, the coupled evolutionary-

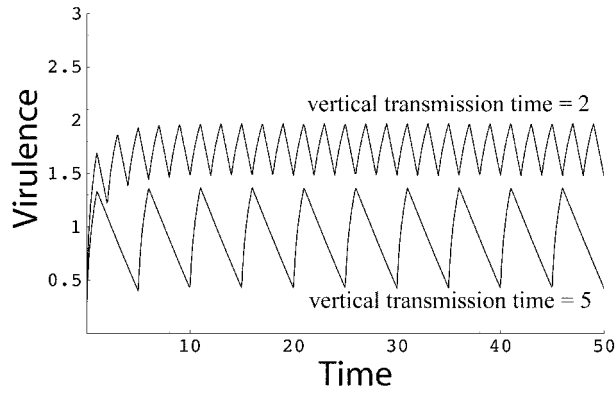


Figure 5: Evolutionary dynamics under the proposed experimental manipulation involving horizontal and vertical transmission. We used $\tau(\nu) = \tau_1\nu/(\tau_2 + \nu)$ and the arbitrary parameter values $\tau_1 = 2$, $\tau_2 = 0.5$, $\omega = 0.25$, and $S = 10$. We assumed that the system spends one unit of time with enforced horizontal transmission followed by a period of length vertical transmission time with enforced vertical transmission.

epidemiological dynamics are given by equations (9) and (10), along with

$$\frac{d\bar{\nu}}{dt} = \omega \left(\frac{d\phi_1\tau}{d\nu} u_s S - 1 \right) + \rho_m(\gamma_0\bar{\delta} + \gamma_1\sigma). \quad (25)$$

Equation (25) reveals that virulence evolution is governed by a compromise between within-host selection (the second term) and between-host selection (the first term). For simplicity, we will assume that the genetic variance in strain type is always at its equilibrium value, which, from equation (C6) of appendix C, is

$$\omega = \sqrt{\frac{\rho_m \zeta}{(-\partial^2 r / \partial \nu^2)_{\nu=\bar{\nu}}}}. \quad (26)$$

Substituting this into equation (25) then yields

$$\begin{aligned} \frac{d\bar{\nu}}{dt} = & \sqrt{\rho_m} \left[\frac{\sqrt{\zeta}}{\sqrt{-\partial^2 r / \partial \nu^2}} \left(\frac{d\phi_1\tau}{d\nu} u_s S - 1 \right) \right. \\ & \left. + \sqrt{\rho_m}(\gamma_0\bar{\delta} + \gamma_1\sigma) \right] \end{aligned} \quad (27)$$

for the evolutionary dynamics. Several interesting predictions can be obtained from equation (27). First, if there is no relationship between within-host competitive ability and virulence ($\gamma_1 = 0$) and no bias in the mutations that arise ($\bar{\delta} = 0$), then mutation has no directional effect on virulence evolution. Assuming that virulence is positively re-

lated to within-host competitive ability, however, then the equilibrium level of virulence will be higher than that predicted from a consideration of between-host selection alone. The reason is that the second term in equation (27) is then positive, pulling the mean level of virulence upward. Also notice from equation (27) that, as the mutation rate gets small ($\rho_m \rightarrow 0$), the effect of within-host selection gets weak relative to the effect of between-host selection, and the predicted equilibrium level of virulence then approaches that which occurs in the absence of mutation (the second term in eq. [27] goes to 0). Of course the rate of evolution also then gets very small, so that this equilibrium will be reached only after a very long period of time. Interestingly, this suggests that, from a biological standpoint, it is inconsistent to explore the effects of such within-host mutation on virulence evolution without also then explicitly considering the evolutionary dynamics of virulence evolution. In other words, if we want to assume that mutation rates are large enough to have a substantial effect on the predicted level of virulence, then this will also mean that there is substantial variation in virulence between hosts, which implies that we cannot assume that evolutionary change is slow relative to the epidemiological dynamics.

Finally, as pointed out in Bonhoeffer and Nowak (1994), within-host mutation can result in there being an intermediate level of virulence at equilibrium, even in the absence of a relationship between transmission and virulence. To see this, suppose that the probability of transmission is no longer a function of virulence. The evolutionary dynamics in equation (27) then become

$$\frac{d\bar{\nu}}{dt} = \sqrt{\rho_m} \left[\frac{-\sqrt{\zeta}}{\sqrt{-\partial^2 r / \partial \nu^2}} + \sqrt{\rho_m}(\gamma_0\bar{\delta} + \gamma_1\sigma) \right]. \quad (28)$$

At equilibrium, $d\bar{\nu}/dt = 0$, and therefore

$$\frac{\sqrt{\zeta}}{\sqrt{-\partial^2 r / \partial \nu^2}} = \sqrt{\rho_m}(\gamma_0\bar{\delta} + \gamma_1\sigma), \quad (29)$$

which can be satisfied for an intermediate level of virulence depending on the function r as well as how the mutational bias is a function of the mean level of virulence. In such cases, between-host selection always favors reduced virulence, but this is countered by selection for increased virulence within hosts.

Example 4: An Exact Model with Mutation and Secondary Infection

It is also possible to obtain exact equations for the joint evolutionary-epidemiological dynamics for certain choices of the functions τ and ϕ under the assumption that the parasite distribution remains Gaussian (app. D). In this case, the dynamics of the mean and variance of virulence are sufficient for modeling the dynamics of the entire distribution.

Using the results of appendix D, suppose that the host population is maintained by immigration, that $\tau(\nu) = \tau_1(1 - e^{-\tau_2\nu})$, $\phi_1 \equiv \phi_s = 1$, $u_s = 1$, $\kappa = 1$, and that there is no relationship between virulence and within-host competitive ability ($\gamma_1 = 0$) as well as no mutational bias ($\hat{\delta} = 0$). In this case, the evolution of virulence is governed by both between-host selection and within-host selection arising from secondary infection. The equations of appendix D reduce to

$$\frac{dS}{dt} = \theta - dS - \tau SI + cI, \tag{30}$$

$$\frac{dI_T}{dt} = \tau SI - (d + \bar{\nu} + c)I, \tag{31}$$

$$\frac{d\bar{\nu}}{dt} = \omega \left[\frac{d\tau}{d\nu} (S + \gamma_0 I) - 1 \right], \tag{32}$$

$$\frac{d\omega}{dt} = \omega^2 \frac{d^2\tau}{d\nu^2} (S + \gamma_0 I) + \rho_m \zeta, \tag{33}$$

where all instances of ν appearing in the function τ (or any of its derivatives) are evaluated at $\nu = \bar{\nu} - (\tau_2/2)\omega$. System 30–33 (eqq. [30]–[33]) gives the exact epidemiological dynamics along with the exact evolutionary dynamics of the entire parasite distribution.

Figure 6 gives an example of the dynamics of the system. It can also be shown that for the case where $\kappa = 0$ (i.e., no secondary infection), the equilibrium mean level of virulence in this situation increases with mutational input, $\rho_m \zeta$. In particular, from equation (33) we can see that the equilibrium level of variance increases with mutational input, $\rho_m \zeta$. Using equations (31) and (32), one can also show that the equilibrium mean level of virulence must satisfy

$$\left. \frac{d\tau/d\nu}{\tau} \right|_{\nu=\bar{\nu}-\tau_2\omega/2} = \frac{1}{d + \bar{\nu} + c}. \tag{34}$$

A simple graphical argument for the values of $\bar{\nu}$ satisfied by equation (34) reveals that $\bar{\nu}$ is an increasing function of ω (fig. 7). Notice, however, that if ω is small (as was

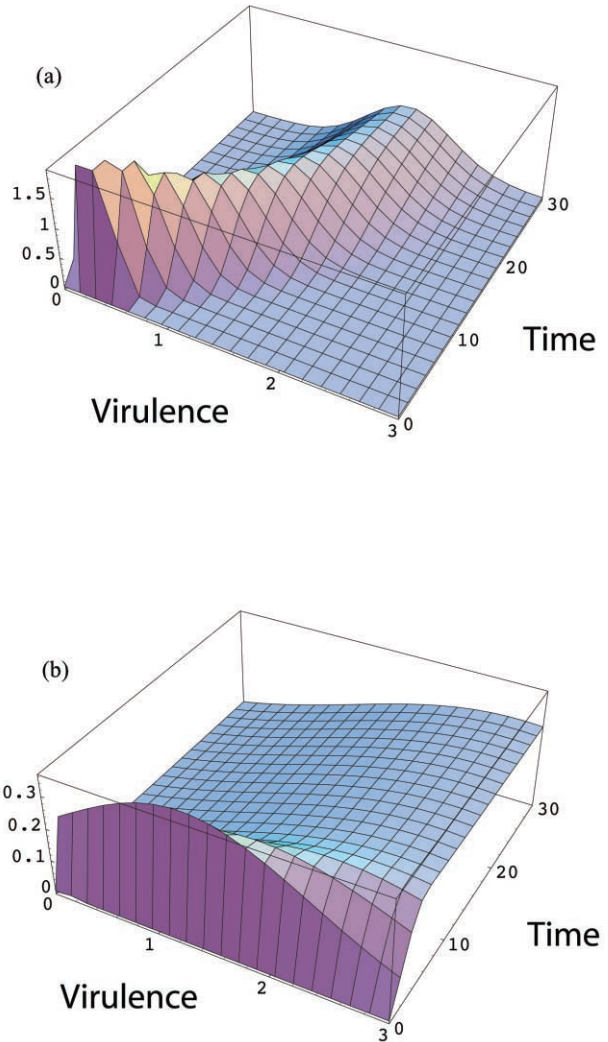


Figure 6: Evolutionary dynamics of the entire distribution of parasite virulence (assuming it remains Gaussian). Parameter values and functions are $\tau(\nu) = \tau_1\nu/(\tau_2 + \nu)$ and $\theta = 10$, $\zeta = 1$, $d = 0.1$, $c = 1$, $\tau_1 = 2$, $\tau_2 = 0.5$, $S(0) = 100$, $I(0) = 1$, $\bar{\nu}(0) = 0.2$. *a*, a low mutation rate, $\rho_m = 0.01$. *b*, a high mutation rate, $\rho_m = 1$.

assumed in example 3), then this effect of variance in strain type is negligible.

Conclusions and Future Prospects

We have attempted to illustrate how a QG approach to modeling virulence evolution can sometimes be both more general and more transparent than previous game-theoretic approaches. We suggest that the benefits of this QG approach lie in four main areas. (1) It allows prediction of the short-term evolutionary dynamics of virulence. This is significant because the short-term evolution of vir-

ulence is often in a direction opposite to that of its long-term evolution. (2) It explicitly separates evolutionary change from any epidemiological feedback. This tends to make the causes of virulence evolution more transparent because it illustrates how the epidemiological and ecological circumstances at any given time (regardless of their dynamics) give rise to the selective regime that governs virulence evolution. This yields considerable generality, and it also makes this approach readily applicable to many experimental techniques for testing theory. (3) It allows the construction of models in which evolutionary and epidemiological processes occur on any relative timescale, and it also allows for any form of nonequilibrium dynamics. (4) It is at least as easy (and usually easier) to apply than previous game-theoretic techniques.

The set of examples presented here was chosen to illustrate the breadth of applicability of the approach and the ease with which predictions can often be obtained. No doubt there are many other questions of interest that can be addressed using the results derived here, but there are also a number of important extensions of this framework that are required before it will be a completely satisfying theory.

First, the theory presented here is applicable only to situations in which there is a single type of host that can become infected. More realistically, we would want to allow for various types of host heterogeneity (Regoes et al. 2000; Gandon et al. 2001*b*; Ganusov et al. 2002; Pfennig 2001), including different host species or environments. Additionally, we have assumed that random environmental variation in virulence is negligible in the present results. In many cases this assumption is probably not reasonable, and it is relatively easy to extend the QG approach outlined here to incorporate both of the above effects (T. Day, unpublished manuscript). Additionally, we have assumed that there is a single parasite trait of interest, but it is clearly desirable to have a comparable theory that incorporates the simultaneous evolution of multiple parasite traits (e.g., that treats virulence and transmission as two separate traits that are potentially genetically correlated). Due to space limitations, we have reserved these results for a future publication as well.

Aside from the above extensions, there are two other areas to which this approach might be well suited. First, many host-parasite systems experience considerable spatial variation in the selective pressures on virulence as a result of abiotic environmental variation as well as endogenously generated spatial variation in biotic conditions (as a result of local ecological and epidemiological dynamics coupled with dispersal). For example, avian malaria in the Hawaiian Islands displays strong epidemiological variation across altitudinal gradients as a result of temperature changes (van Riper et al. 1986; Benning et al. 2002). Little theory has been developed to model virulence evolution

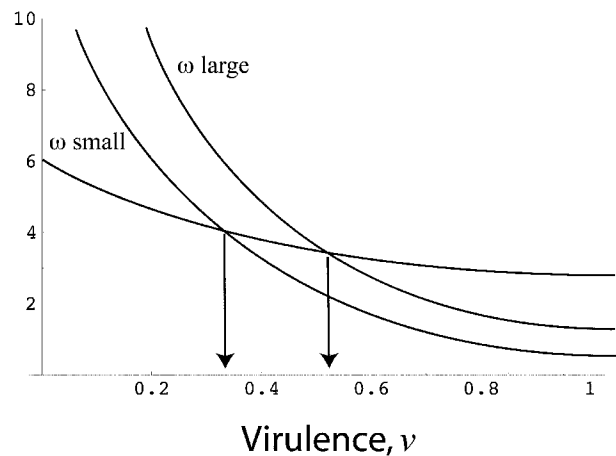


Figure 7: Graphical depiction of the prediction that the mean level of virulence is expected to be higher when there is higher variation in virulence among strains. The curve representing the left-hand side of equation (15) (i.e., the transmission benefit) is simply shifted to the right as the level of genetic variance ω increases. Therefore, the equilibrium level of virulence (i.e., where this curve crosses the curve representing the cost of virulence; the right-hand side of eq. [15]) increases.

in such situations, and the QG approach presented here is perhaps one way in which such spatial variation could be incorporated. There is already a considerable body of quantitative genetic theory similar to that used here for the evolution of traits in continuous spatial domains (Nagylaki 1975; Pease et al. 1989; Garcia-Ramos and Kirkpatrick 1997; Kirkpatrick and Barton 1997; Day 2000; app. A). It should be relatively straightforward to use a similar approach for evolutionary-epidemiological models as well.

Second, an increasing body of theory is directed toward linking within-host dynamics of parasite replication with between-host epidemiological and evolutionary dynamics (Diekmann et al. 1990; Anderson and May 1991, chap. 11; Sasaki and Iwasa 1991; Antia et al. 1994; Smith and Holt 1996; Ganusov et al. 2002; Day 2001, 2002*b*, 2003). There are also previous quantitative genetic techniques that have been developed to model the evolution of “infinite-dimensional” characters such as reaction norms (Gomulkiewicz and Kirkpatrick 1992), and these techniques can probably be used to extend the results presented here to allow for temporal changes in virulence (and possibly other parameters) over the course of an infection as well (see Day 2003).

Acknowledgments

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APPENDIX A

Derivation of Equations (3)–(7)

We allow a continuum of parasite strains (indexed by ν) and suppose that new strains continually arise through within-host mutation. A new strain either immediately displaces the prior resident strain or else dies out. Additionally, we allow infected hosts to acquire secondary infections from other infected hosts, at which point either the original strain immediately excludes the secondary invader or vice versa. Letting $I(\nu, t)$ denote the density of infected hosts of strain ν at time t , equation (1) generalizes to

$$\begin{aligned} \frac{dS}{dt} &= \theta + b_s S \\ &+ \int_{-\infty}^{\infty} b_1 q(\nu) d\nu I_T - dS - \phi_s u_s \int_{-\infty}^{\infty} \phi_1 \tau q(\nu) d\nu S I_T \quad (A1) \\ &+ \int_{-\infty}^{\infty} c q(\nu) d\nu I_T, \end{aligned}$$

where $I_T = \int_{-\infty}^{\infty} I(\nu) d\nu$ is the total density of infected hosts and $q(\nu)$ is the probability density $q(\nu) = I(\nu)/I_T$ (i.e., the proportion of hosts infected with strain ν).

To generalize equation (2), more specific assumptions are required regarding the dynamics of the distribution of infection types, $I(\nu)$. We suppose that this distribution changes through time because of three processes. First, the generation of new infections from previously susceptible hosts changes the total number of infected hosts, I_T , as well as the way in which these are distributed among different parasite strains. Second, within-host mutation and secondary infection redistribute the strain types in some way, potentially imposing some form of directionality on virulence evolution (although this does not affect the total number of infected hosts). Third, we suppose there is a purely random, unbiased component of mutation within hosts that allows for the continued maintenance of variation in parasite strains. These three effects are modeled using a reaction-advection-diffusion process whose dynamics are described by the Fokker-Planck equation (or, equivalently, the forward Kolmogorov equation) with a reaction term (Okubo and Levin 2001):

$$\frac{\partial I}{\partial t} = rI - \frac{\partial}{\partial \nu} (MI) + \rho_m \frac{\zeta}{2} \frac{\partial^2 I}{\partial \nu^2}. \quad (A2)$$

The first term in equation (A2) is the reaction term, and it represents the generation of new infections of type ν from

previously susceptible hosts. The second term is the advection term, and it represents the mean flow of one infection type to another as a result of within-host mutation and secondary infection. This is the redistribution process mentioned above. The third term is the diffusion term, and it represents random changes in infection type as a result of random within-host mutation and serves to maintain genetic variation in virulence. Mathematically, $M(\nu)$ (which depends on strain type, ν) represents the infinitesimal mean of the diffusion process (essentially the average change in strain type for hosts infected with strain ν in a small interval of time through within-host mutation and secondary infection), and ζ (which, for simplicity, we assume is a constant) represents the infinitesimal variance of the diffusion process (essentially the second moment of the change in strain type in a small interval of time). The parameter ρ_m is the rate of mutation.

To further specify the model, we need to derive an expression for M . The mean change in strain type in a small interval of time, Δt , is given by

$$\begin{aligned} M(\nu)\Delta t &= \mu_m(\nu)\rho_m\Delta t + \mu_s(\nu)\rho_s\Delta t \\ &+ (1 - \rho_m\Delta t - \rho_s\Delta t) \cdot 0 \quad (A3) \\ &= \mu_m(\nu)\rho_m\Delta t + \mu_s(\nu)\rho_s\Delta t, \end{aligned}$$

where $\mu_m(\nu)$ and $\mu_s(\nu)$ represent the mean change through mutation and secondary infection, respectively (given such events occur), and ρ_m and ρ_s are the rates of occurrence of these events (e.g., $\rho_m\Delta t$ is the probability that a mutation occurs in time interval Δt). We derive expressions for each of $\mu_m(\nu)$ and $\mu_s(\nu)$ in turn.

Mutation. Let J be a random variable denoting the jump size in strain type and Ψ be a random variable denoting the virulence displacement (from ν) of the new strain arising by mutation. Then,

$$\mu_m(\nu) = \int_{-\infty}^{\infty} E(J|\Psi = \delta) P_\nu(\Psi = \delta) d\delta, \quad (A4)$$

where the probability density of mutations, $P_\nu(\Psi = \delta)$, might depend on the strain of the host in question, ν . Using $u_1(\delta)$ to denote the probability that a strain with virulence displacement δ takes over the host infected with strain ν , we have $E(J|\Psi = \delta) = u_1(\delta) \cdot \delta + [1 - u_1(\delta)] \cdot 0 = u_1(\delta)\delta$. Therefore,

$$\mu_m(\nu) = \int_{-\infty}^{\infty} u_1(\delta)\delta P_\nu(\Psi = \delta) d\delta. \quad (A5)$$

For mathematical simplicity we use the specific function $u_1(\delta) = \gamma_0 + \gamma_1\delta$. Note that this represents a probability, and under the assumption that δ is not too large (i.e., mutations are of small effect), this will lie between 0 and 1. The parameter γ_0 is the baseline probability that any strain will take over an already infected host, and the parameter γ_1 denotes the extent to which virulence is associated with within-host competitive ability; for example, $\gamma_1 > 0$ means that strains with higher virulence have a within-host competitive advantage, whereas $\gamma_1 = 0$ means that there is no relationship between virulence and within-host competitive ability. We will assume that P_ν has a mean $\bar{\delta}$ and second moment, σ , and therefore equation (A5) simplifies to

$$\mu_m(\nu) = \gamma_0\bar{\delta}(\nu) + \gamma_1\sigma. \quad (\text{A6})$$

We assume that the rate of mutation, ρ_m , and the second moment, σ , are constant, and therefore we have

$$\mu_m(\nu)\rho_m = \rho_m[\gamma_0\bar{\delta}(\nu) + \gamma_1\sigma]. \quad (\text{A7})$$

Secondary Infection. The treatment of secondary infection is more complicated because, given that a host infected with strain ν contacts an infected host with strain $\hat{\nu}$, two events can happen. The host with strain type ν can become a host with strain type $\hat{\nu}$ and vice versa. We need to derive an expression for the mean change in strain type for hosts of type ν as a result of these two possibilities. Let J again be a random variable denoting the jump size in strain type at ν , and let C be a random variable denoting the type of infected host that is contacted. Then,

$$\mu_s(\nu) = \int_{-\infty}^{\infty} E(J|C = \hat{\nu})P(C = \hat{\nu})d\hat{\nu}. \quad (\text{A8})$$

We obtain an expression for $E(J|C = \hat{\nu})$ by further conditioning on whether strain type $\hat{\nu}$ gets transferred to the host with strain type ν and vice versa. There are four possible events: (1) $\hat{\nu} \rightarrow \nu$, $\nu \rightarrow \hat{\nu}$ (with probability $\tau[\hat{\nu}]\tau[\nu]$); (2) $\hat{\nu} \rightarrow \nu$ (with probability $\tau(\hat{\nu})[1 - \tau(\nu)]$); (3) $\nu \rightarrow \hat{\nu}$ (with probability $[1 - \tau(\hat{\nu})]\tau(\nu)$); and (4) no transfer occurs (with probability $[1 - \tau(\hat{\nu})][1 - \tau(\nu)]$). We use $\tilde{u}_1(\hat{\nu} - \nu)$ to denote the probability that a strain of type $\hat{\nu}$ supplants a strain of type ν (once secondary infection has occurred), and we define this as $\tilde{u}_1(\hat{\nu} - \nu) = \kappa u_1(\hat{\nu} - \nu)$. Here, $\kappa \leq 1$ is a factor that allows for the possibility that secondary infections are less likely to succeed in colonizing an infected host than are new mutations. Therefore the expected jump size for each of the above four events is:

$$\begin{aligned} & \tilde{u}_1(\hat{\nu} - \nu)[1 - \tilde{u}_1(\nu - \hat{\nu})][\hat{\nu} - \nu]/2 \\ & + \tilde{u}_1(\hat{\nu} - \nu)\tilde{u}_1(\nu - \hat{\nu})[(\hat{\nu} - \nu)/(2 + (\nu - \hat{\nu})/2) \\ & + [1 - \tilde{u}_1(\hat{\nu} - \nu)][1 - \tilde{u}_1(\nu - \hat{\nu})]0 \\ & + [1 - \tilde{u}_1(\hat{\nu} - \nu)]\tilde{u}_1(\nu - \hat{\nu})[\nu - \hat{\nu}]/2 \\ & = [\tilde{u}_1(\hat{\nu} - \nu) - \tilde{u}_1(\nu - \hat{\nu})] \times [\hat{\nu} - \nu]/2; \end{aligned} \quad (1)$$

(2)

$$\tilde{u}_1(\hat{\nu} - \nu)[\hat{\nu} - \nu]/2;$$

(3)

$$\tilde{u}_1(\nu - \hat{\nu})[\hat{\nu} - \nu]/2;$$

(4) 0.

Therefore we obtain

$$\begin{aligned} & E(J|C = \hat{\nu}) \\ & = \tau(\hat{\nu})\tau(\nu)^*[\tilde{u}_1(\hat{\nu} - \nu) - \tilde{u}_1(\nu - \hat{\nu})] \cdot (\hat{\nu} - \nu)/2 \\ & + \tau(\hat{\nu})[1 - \tau(\nu)]^* \tilde{u}_1(\hat{\nu} - \nu)[\hat{\nu} - \nu]/2 \\ & + [1 - \tau(\hat{\nu})]\tau(\nu)^* \tilde{u}_1(\nu - \hat{\nu})[\hat{\nu} - \nu]/2 \\ & = [\tau(\hat{\nu})\tilde{u}_1(\hat{\nu} - \nu) - \tau(\nu)\tilde{u}_1(\nu - \hat{\nu})](\hat{\nu} - \nu)/2. \end{aligned}$$

We also have $P(C = \hat{\nu}) = q(\hat{\nu})\phi(\hat{\nu})/\bar{\phi}$, where $\bar{\phi} = \int q\phi d\nu$. Therefore, equation (A8) can be simplified as

$$\begin{aligned} \mu_s(\nu) & = \int_{-\infty}^{\infty} \frac{q(\hat{\nu})\phi(\hat{\nu})}{2\bar{\phi}} [\tau(\hat{\nu})\tilde{u}_1(\hat{\nu} - \nu) \\ & - \tau(\nu)\tilde{u}_1(\nu - \hat{\nu})](\hat{\nu} - \nu)d\hat{\nu} \\ & = \frac{\kappa\gamma_0}{2\bar{\phi}} \int_{-\infty}^{\infty} q(\hat{\nu})\phi(\hat{\nu})[\tau(\hat{\nu}) - \tau(\nu)](\hat{\nu} - \nu)d\hat{\nu} \quad (\text{A9a}) \end{aligned}$$

$$+ \frac{\kappa\gamma_1}{2\bar{\phi}} \int_{-\infty}^{\infty} q(\hat{\nu})\phi(\hat{\nu})[\tau(\hat{\nu}) + \tau(\nu)](\hat{\nu} - \nu)^2 d\hat{\nu}. \quad (\text{A9b})$$

The rate of secondary contact is given by $\rho_s = \phi(\nu)\int \phi I d\nu = \phi(\nu)\bar{\phi}I_\tau$, and therefore we have

$$\begin{aligned} \mu_s(\nu)\rho_s = & \frac{\phi(\nu)I_T\kappa}{2} \left\{ \gamma_0 \int_{-\infty}^{\infty} q(\hat{\nu})\phi(\hat{\nu})[\tau(\hat{\nu}) - \tau(\nu)](\hat{\nu} - \nu)d\hat{\nu} \right. \\ & \left. + \gamma_1 \int_{-\infty}^{\infty} q(\hat{\nu})\phi(\hat{\nu})[\tau(\hat{\nu}) + \tau(\nu)](\hat{\nu} - \nu)^2d\hat{\nu} \right\}. \end{aligned} \tag{A10}$$

$M(\nu)$ is given by the sum of equations (A7) and (A10). System A1-A2 (eqq. A1, A2; with appropriate boundary and initial conditions) completely determines the evolutionary and epidemiological dynamics of interest. One might analyze this system to get a complete understanding of virulence evolution, but here we make some simplifying assumptions to derive a more manageable model. We assume that the distribution of strain types in the population is Gaussian and has a small variance, and therefore we will simply track the mean level of virulence (and assume that the distribution remains Gaussian with a small variance). We derive the conditions under which the variance will be small in appendix C and derive results for arbitrary levels of variance in appendix D.

To track the evolutionary dynamics of the mean level of virulence, we first derive an equation for the dynamics of q from equation (A2):

$$\frac{\partial q}{\partial t} = \frac{\partial I/\partial t}{I_T} - q \frac{dI_T/dt}{I_T} \tag{A11a}$$

$$\begin{aligned} = & - \frac{\partial(Mq)}{\partial \nu} + \rho_m \frac{\xi}{2} \frac{\partial^2 q}{\partial \nu^2} + rq \\ & - q \int_{-\infty}^{\infty} \left[- \frac{\partial(Mq)}{\partial \nu} + \rho_m \frac{\xi}{2} \frac{\partial^2 q}{\partial \nu^2} + rq \right] d\nu \end{aligned} \tag{A11b}$$

$$= q(r - \bar{r}) - \frac{\partial}{\partial \nu}(Mq) + \rho_m \frac{\xi}{2} \frac{\partial^2 q}{\partial \nu^2}, \tag{A11c}$$

where $\bar{r} = \int rq d\nu$. The mean level of virulence at time t is $\bar{\nu} = \int q\nu d\nu$, and therefore the dynamics of the mean level of virulence are

$$\frac{d\bar{\nu}}{dt} = \int_{-\infty}^{\infty} \nu \frac{\partial q}{\partial t} d\nu \tag{A12a}$$

$$= \int_{-\infty}^{\infty} \nu \left[q(r - \bar{r}) - \frac{\partial}{\partial \nu}(Mq) + \rho_m \frac{\xi}{2} \frac{\partial^2 q}{\partial \nu^2} \right] d\nu \tag{A12b}$$

$$\begin{aligned} = & \int_{-\infty}^{\infty} \nu q(r - \bar{r}) d\nu - \left(\nu Mq \Big|_{-\infty}^{\infty} - \int_{-\infty}^{\infty} Mq d\nu \right) \\ & + \rho_m \frac{\xi}{2} \left(\nu \frac{\partial q}{\partial \nu} \Big|_{-\infty}^{\infty} - \int_{-\infty}^{\infty} \frac{\partial q}{\partial \nu} d\nu \right) \end{aligned} \tag{A12c}$$

$$= \int_{-\infty}^{\infty} rq(\nu - \bar{\nu}) d\nu + \int_{-\infty}^{\infty} Mq d\nu. \tag{A12d}$$

Finally, under the assumption that q is Gaussian, equation (A12d) can be simplified (Taylor and Day 1997; eqq. [A1]–[A3]) to

$$\frac{d\bar{\nu}}{dt} = \omega E\left(\frac{\partial r}{\partial \nu}\right) + E[M(\nu)], \tag{A13}$$

where $E()$ is the expectation over the distribution q .

Equation (A13) gives the evolution of the mean level of virulence. We can evaluate the expectations in (A13) more explicitly using equations (A7) and (A10) for $M(\nu)$. Doing so results (after considerable calculation) in the expression

$$\begin{aligned} \frac{d\bar{\nu}}{dt} = & \omega \overline{\frac{\partial r}{\partial \nu}} + \rho_m (\gamma_0 \bar{\delta} + \gamma_1 \sigma) \\ & + I_T \omega \kappa \overline{\phi} \left(\gamma_0 \overline{\frac{d\tau}{d\nu}} + \gamma_1 2\overline{\phi\tau} \right) + o(\omega), \end{aligned} \tag{A14}$$

where overbars denote expectations over the distribution, q , and $o(\omega)$ represents a quantity such that $\lim_{\omega \rightarrow 0} o(\omega)/\omega = 0$. Therefore, if we assume that the variance in the strain distribution, ω , is relatively small, we obtain the approximation

$$\begin{aligned} \frac{d\bar{\nu}}{dt} \approx & \omega \left. \frac{\partial r}{\partial \nu} \right|_{\nu=\bar{\nu}} + \rho_m \left\{ \gamma_0 \left[\bar{\delta}(\bar{\nu}) + \omega \frac{d^2 \bar{\delta}}{d\nu^2} \right] + \gamma_1 \sigma \right\} \\ & + I_T \omega \kappa \phi^2(\bar{\nu}) \left(\gamma_0 \frac{d\tau}{d\nu} + \gamma_1 2\tau \right) \Big|_{\nu=\bar{\nu}}, \end{aligned} \quad (\text{A15a})$$

or

$$\begin{aligned} \frac{d\bar{\nu}}{dt} \approx & \omega \left. \frac{\partial r}{\partial \nu} \right|_{\nu=\bar{\nu}} + \rho_m [\gamma_0 \bar{\delta}(\bar{\nu}) + \gamma_1 \sigma] \\ & + I_T \omega \kappa \phi^2(\bar{\nu}) \left(\gamma_0 \frac{d\tau}{d\nu} + \gamma_1 2\tau \right) \Big|_{\nu=\bar{\nu}}, \end{aligned} \quad (\text{A15b})$$

where, in (A15b), we have assumed that the mutational bias, $\bar{\delta}(\nu)$, is a linear function of ν (i.e., $d^2 \bar{\delta}/d\nu^2 = 0$). This is equation (5) of the text. Of course the variance, ω , is itself a dynamic variable, but appendix C provides conditions under which this will be small. Additionally, for a particular (but still quite general) choice of the functions τ and ϕ , one can obtain the exact equations for the dynamics of the mean and variance (app. D).

To complete the model, we need a closed system of equations for the joint evolutionary and epidemiological dynamics of the model. This can be obtained by noting

$$\begin{aligned} \frac{dI_T}{dt} &= I_T E(r) \\ &\approx I_T r \Big|_{\nu=\bar{\nu}}, \end{aligned} \quad (\text{A16})$$

which gives equation (4) of the text. Assuming that the variance in strain type is small, equation (A1) can then be approximated by equation (3) of the text (where all parameters involving ν are evaluated at $\nu = \bar{\nu}$).

APPENDIX B

General Recipe for QG Approach

Our results are applicable to any model in which there is a single category of infected hosts (although there is a continuum of strain types that might infect hosts of this category) and a single phenotype of the parasite of interest (which in the text we have taken to be virulence: the parasite-induced instantaneous mortality rate). We extend this approach for questions involving multiple host species or other types of host heterogeneity as well

as multivariate parasite phenotypes in a future publication.

The first step in applying the QG approach is to formulate the epidemiological model of interest under the assumption that there is a single parasite strain. We suppose that the model of interest can be written as

$$\frac{dI}{dt} = r[\mathbf{x}; \mathbf{p}(\nu)]I, \quad (\text{B1})$$

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}[\mathbf{x}, I; \mathbf{p}(\nu)], \quad (\text{B2})$$

where I is the density of infected hosts, \mathbf{x} is a vector of the remaining state variables of the model (i.e., the variables whose epidemiological and ecological dynamics are also of interest, e.g., susceptible host density, predator density, competitor density, resource density, etc.). Here, ν denotes any phenotype of the parasite that is of interest. We have assumed that ν denotes the parasite-induced mortality rate, that is, virulence, in the simple model of the text, but this need not be the case. For example, it might represent the level of host exploitation by the parasite. The \mathbf{p} is a vector of all the parameters in the model (which might themselves be functions of the phenotype, ν). Finally, \mathbf{f} is the vector whose elements are the expressions for the dynamics of all of the state variables in the vector \mathbf{x} .

Given model B1–B2 (eqq. [B1], [B2]), the approach derived in appendix A shows that the coupled evolutionary-ecological-epidemiological dynamics are given by the exact same system ([B1], [B2]), except where I is replaced with I_T , the total density of infected hosts (of all strain types), where all instances of ν are evaluated at $\bar{\nu}$ and where the evolutionary dynamics of the mean level of virulence are given by

$$\frac{d\bar{\nu}}{dt} = \omega \left. \frac{\partial r}{\partial \nu} \right|_{\nu=\bar{\nu}} + \eta_m(\bar{\nu}) + \eta_s(\bar{\nu}), \quad (\text{B3})$$

where ω is the variance in strain type among hosts and η_m and η_s are the evolutionary effects of within-host mutation and secondary infection, respectively (and are specified explicitly by eqq. [6] and [7] of the text). The coupled system (eqq. [B1]–[B3]) is based on an assumption that the variance, ω , is small, which will be reasonable provided that selection does not favor an evolutionary diversification of parasite strains (see app. C) and that the rate of mutation, ρ_m , is small.

APPENDIX C

Evolutionary Dynamics of the Variance

Here we derive an equation governing the evolutionary dynamics of the variance in strain type. This allows us to determine the conditions under which we expect our assumption of small variance among hosts to be valid. The evolutionary dynamics of the genetic variance in strain types between hosts is

$$\begin{aligned} \frac{d\omega}{dt} &= \frac{d}{dt} \int_{-\infty}^{\infty} (\nu - \bar{\nu})^2 q d\nu \\ &= -2 \frac{d\bar{\nu}}{dt} \int_{-\infty}^{\infty} (\nu - \bar{\nu}) q d\nu + \int_{-\infty}^{\infty} (\nu - \bar{\nu})^2 \frac{\partial q}{\partial t} d\nu. \end{aligned} \quad (C1)$$

The first term of (C1) is 0, and the second term evaluates as follows:

$$\int_{-\infty}^{\infty} (\nu - \bar{\nu})^2 \frac{\partial q}{\partial t} d\nu = \int_{-\infty}^{\infty} (\nu - \bar{\nu})^2 \left[q(r - \bar{r}) - \frac{\partial}{\partial \nu} (Mq) + \rho_m \zeta \frac{\partial^2 q}{\partial \nu^2} \right] d\nu \quad (C2a)$$

$$\begin{aligned} &= \int_{-\infty}^{\infty} (\nu - \bar{\nu})^2 q(r - \bar{r}) d\nu \\ &\quad - \left[(\nu - \bar{\nu})^2 Mq \right]_{-\infty}^{\infty} - 2 \int_{-\infty}^{\infty} (\nu - \bar{\nu}) Mq d\nu \end{aligned} \quad (C2b)$$

$$\begin{aligned} &+ \frac{\rho_m \zeta}{2} \left[(\nu - \bar{\nu})^2 \frac{\partial q}{\partial \nu} \right]_{-\infty}^{\infty} - 2 \int_{-\infty}^{\infty} (\nu - \bar{\nu}) \frac{\partial q}{\partial \nu} d\nu \\ &= \omega^2 \int_{-\infty}^{\infty} q \frac{\partial^2 r}{\partial \nu^2} d\nu + 2\omega \int_{-\infty}^{\infty} q \frac{dM}{d\nu} d\nu \\ &\quad - \rho_m \zeta \left[(\nu - \bar{\nu}) q \right]_{-\infty}^{\infty} - \int_{-\infty}^{\infty} q d\nu, \end{aligned} \quad (C2c)$$

and therefore

$$\frac{d\omega}{dt} = \omega^2 E \left(\frac{\partial^2 r}{\partial \nu^2} \right) + 2\omega E \left(\frac{dM}{d\nu} \right) + \rho_m \zeta, \quad (C3)$$

where the first two terms in equation (C2c) follow from the assumption that q is Gaussian with mean $\bar{\nu}$ and variance ω (Taylor and Day 1997, appendixes), and $E()$ is the expectation over the distribution, q . This equation, along with equation (A14) of appendix A can, for some cases, be used as an exact model of the evolutionary dynamics

of the entire distribution of parasite strains under the assumption that it is Gaussian (see app. D). Using the expression for $M(\nu)$ derived in appendix A, we can evaluate (C3) more explicitly to obtain

$$\begin{aligned} \frac{d\omega}{dt} &= \omega^2 \frac{\overline{d^2 r}}{d\nu^2} + 2\omega \rho_m \gamma_0 \frac{\overline{d\delta}}{d\nu} \\ &\quad + I_T \omega^2 \kappa \gamma_0 \left(2 \frac{\overline{d\phi}}{d\nu} \frac{\overline{d\tau}}{d\nu} \bar{\phi} + \frac{\overline{d^2 \tau}}{d\nu^2} \phi \bar{\phi} \right) \\ &\quad + 2I_T \omega^2 \kappa \gamma_1 \left(\frac{\overline{d\phi}}{d\nu} \bar{\phi} \tau + \frac{\overline{d\phi}}{d\nu} \tau \bar{\phi} + \frac{\overline{d\tau}}{d\nu} \phi \bar{\phi} \right) \\ &\quad + \rho_m \zeta + o(\omega^2). \end{aligned} \quad (C4)$$

Therefore, we obtain the approximation

$$\begin{aligned} \frac{d\omega}{dt} &= \omega^2 \frac{d^2 r}{d\nu^2} + 2\omega \rho_m \gamma_0 \frac{d\bar{\delta}}{d\nu} \\ &\quad + I_T \omega^2 \kappa \gamma_0 \phi \left(2 \frac{d\phi}{d\nu} \frac{d\tau}{d\nu} + \phi \frac{d^2 \tau}{d\nu^2} \right) \\ &\quad + 2I_T \omega^2 \kappa \gamma_1 \phi \left(2 \frac{d\phi}{d\nu} \tau + \phi \frac{d\tau}{d\nu} \right) + \rho_m \zeta, \end{aligned} \quad (C5)$$

where all terms are evaluated at $\nu = \bar{\nu}$.

The approximations used in appendix A for the general QG approach assume that the genetic variance remains approximately constant and small during evolutionary change in the mean phenotype. We can set equation (C5) equal to 0 to obtain an expression for the equilibrium level of variance, and from this we may determine the conditions on the parameters under which this small variance assumption is valid. One can use the quadratic formula with equation (C5) to do so, but here we concern ourselves only with case where the bias in mutations that arises within an infected host is independent of the strain infecting the host (i.e., $d\delta/d\nu = 0$). In this case, the second term in equation (C5) drops out, and the equilibrium variance is given simply by

$$\omega = \sqrt{-\rho_m \zeta / D}, \quad (C6)$$

where

$$\begin{aligned} D &= r'' + \phi I_T \kappa [\gamma_0 (2\phi' \tau' + \phi \tau'')] \\ &\quad + \gamma_1 (4\phi' \tau + 2\phi \tau') \Big|_{\nu=\bar{\nu}}, \end{aligned} \quad (C7)$$

and we have simplified notation by using primes for differentiation with respect to ν . From equations (C6) and

(C7), we can see that an equilibrium level of variance occurs if and only if $D < 0$. Moreover, in this case, the equilibrium level of virulence will tend to be small, provided that the rate of mutational input, $\rho_m \zeta$, is small (assuming, of course, that D is bounded away from 0).

APPENDIX D

Exact Results for a Special Case

Here we illustrate how the QG approach can also be used to obtain a relatively simple, exact model for the joint epidemiological-evolutionary dynamics of the entire distribution of parasite strains if we assume that this distribution remains Gaussian and if we use some specific (but still quite general) functions for τ and ϕ . There are undoubtedly other scenarios for which a similar derivation can be carried out, and the calculations presented here can be used as a template for doing so.

Under the assumption that the distribution of parasite strains remains Gaussian, we can model the dynamics of this entire distribution by simply modeling the dynamics of its mean and variance. The assumptions used here allow for both within-host mutation as well as secondary infection as before, but we now use the specific functional forms $\tau(\nu) = \tau_1(1 - e^{-\tau_2\nu})$, $\phi(\nu) = e^{-\phi_1\nu}$, and $u_1(\delta) = \gamma_0 + \gamma_1\delta$, where τ_1 , τ_2 , and ϕ_1 are constant parameters (note that $\phi(0) = \phi_s$ in the earlier notation, reflecting the assumption that hosts infected with an avirulent strain have a contact rate equal to that of susceptible hosts). The exact evolutionary-epidemiological model for the entire distribution of strains is given by

$$\frac{dS}{dt} = \theta + b_s S + b_I I_T - dS - \int_{-\infty}^{\infty} \phi_s \phi_1 \tau u_s q(\nu) d\nu S I_T + c I_T, \quad (\text{D1a})$$

$$\frac{dI_T}{dt} = \int_{-\infty}^{\infty} [\phi_s \phi_1 \tau u_s S - (d + \bar{\nu} + c)] q(\nu) d\nu I_T, \quad (\text{D1b})$$

$$\frac{d\bar{\nu}}{dt} = \omega \int_{-\infty}^{\infty} \frac{\partial r}{\partial \nu} q(\nu) d\nu + \int_{-\infty}^{\infty} M(\nu) q(\nu) d\nu, \quad (\text{D1c})$$

$$\frac{d\omega}{dt} = \omega^2 \int_{-\infty}^{\infty} \frac{\partial^2 r}{\partial \nu^2} q(\nu) d\nu + 2\omega \int_{-\infty}^{\infty} \frac{dM}{d\nu} q(\nu) d\nu + \rho_m \sigma. \quad (\text{D1d})$$

Under the above assumptions, the integral terms can be solved explicitly. These calculations are tedious, but are easily conducted using software such as Mathematica (Wolfram Research 2003). One obtains

$$\frac{dS}{dt} = \theta + b_s S + b_I I_T - dS - \phi_1 \tau u_s S I_T + c I_T, \quad (\text{D2a})$$

$$\frac{dI_T}{dt} = \phi_1 \tau u_s S I_T - (d + \bar{\nu} + c) I_T, \quad (\text{D2b})$$

$$\begin{aligned} \frac{d\bar{\nu}}{dt} = & \omega [(\phi\tau)'S - 1] + \rho_m (\gamma_0 \bar{\delta} + \gamma_1 \sigma) \\ & + \omega \kappa \phi^2 I_T (\gamma_0 \tau' + \gamma_1 2\tau) \\ & - \omega^2 \kappa \phi^2 I_T (\gamma_1 \tau_2 \tau'), \end{aligned} \quad (\text{D2c})$$

$$\begin{aligned} \frac{d\omega}{dt} = & \omega^2 r'' + 2\omega \gamma_0 \rho_m \frac{d\bar{\delta}}{d\nu} \\ & + \omega^2 \kappa I_T \gamma_0 \phi (2\phi' \tau' + \phi \tau'') \\ & + \omega^2 \kappa I_T \gamma_1 \phi (4\phi' \tau + 2\phi \tau') \\ & + \omega^3 \kappa I_T \phi \gamma_1 [\tau' \tau_2 (\tau_2 + 2\phi_1)] + \rho_m \zeta, \end{aligned} \quad (\text{D2d})$$

where primes denote differentiation with respect to ν , and in all of the above expressions, all instances of ν appearing in the function τ (or any of its derivatives) are evaluated at

$$\nu = \bar{\nu} - \left(\frac{\tau_2}{2} + \phi_1 \right) \omega, \quad (\text{D3})$$

and all instances of ν appearing in the function ϕ (or any of its derivatives) are evaluated at

$$\nu = \bar{\nu} - \frac{\phi_1}{2} \omega. \quad (\text{D4})$$

“Example 4” of the text illustrates an application of these exact dynamics.

APPENDIX E

Comparison with Game-Theoretic Models

Here we illustrate how the condition for the existence of an equilibrium level of variance in the QG approach is related to the condition for there being a single evolutionarily stable (ESS) parasite strain under the game-theoretic approach. In game-theoretic models, a single ESS strain will exist if the intrinsic growth rate of any mutant is negative when attempting to invade (Maynard Smith

1982). Using $\lambda(\nu, \hat{\nu})$ to denote the intrinsic growth rate of a mutant with virulence ν in a population where the resident strain has virulence $\hat{\nu}$, we have

$$\begin{aligned} \lambda(\nu, \hat{\nu}) = & \phi_1(\nu)\tau u_s S(\hat{\nu}) - (d + \nu + c) \\ & + \phi_1(\nu)\phi_1(\hat{\nu})I(\hat{\nu})\tilde{u}_1(\nu - \hat{\nu})\tau(\nu) \\ & - \phi_1(\nu)\phi_1(\hat{\nu})I(\hat{\nu})\tilde{u}_1(\hat{\nu} - \nu)\tau(\hat{\nu}) \end{aligned} \quad (\text{E1})$$

(Gandon et al. 2001a). The first two terms of equation (E1) represent the production of new mutant infections in susceptible hosts and the loss of mutant infections through mortality and disease clearance mechanisms of the host. The last two terms represent the production of new mutant infections through the secondary infection of hosts infected with the resident strain and the loss of mutant infections through the secondary infection of them by the resident strain. Note that the notation $S(\hat{\nu})$, $I(\hat{\nu})$ reflects the assumption of such game-theoretic models that the epidemiological dynamics are always at equilibrium, and hence the density of susceptible and infected hosts can be expressed as functions of the resident level of virulence, $\hat{\nu}$. An ESS level of virulence, ν^* , must then maximize equation (E1) in ν at $\nu = \nu^*$ (when $\hat{\nu} = \nu^*$). The first and second order conditions for this are

$$\begin{aligned} \left. \frac{d\lambda}{d\nu} \right|_{\nu=\hat{\nu}=\nu^*} = & \left[\frac{\partial}{\partial \nu} (\phi\tau) S - 1 \right. \\ & \left. + \phi^2 I \left(\gamma_0 \frac{d\tau}{d\nu} + \gamma_1 2\tau \right) \kappa \right]_{\nu=\hat{\nu}=\nu^*} = 0 \end{aligned} \quad (\text{E2})$$

and

$$\begin{aligned} \left. \frac{d^2\lambda}{d\nu^2} \right|_{\nu=\hat{\nu}=\nu^*} = & \left[\frac{\partial^2}{\partial \nu^2} (\phi\tau) S + \kappa\gamma_0\phi I \left(2 \frac{d\phi}{d\nu} \frac{d\tau}{d\nu} + \phi \frac{d^2\tau}{d\nu^2} \right) \right. \\ & \left. + \kappa\gamma_1\phi I \left(4 \frac{d\phi}{d\nu} \tau + 2\phi \frac{d\tau}{d\nu} \right) \right]_{\nu=\hat{\nu}=\nu^*} < 0. \end{aligned} \quad (\text{E3})$$

Notice that in the absence of mutational bias ($\bar{\delta} \equiv 0$), equation (E2) is nearly identical to the equilibrium condition from the approximation to the evolutionary dynamics of virulence derived in appendix A, equation (A16). There are two differences. First, when there is a relationship between a parasite's virulence and its within-host competitive ability (i.e., $\gamma_1 \neq 0$), equation (A16) reveals that there is then an implicit form of mutational bias

that is absent from the game-theoretic equation (E2) (i.e., the term $\rho_m\gamma_1\sigma$ in eq. [A16]). Although mutations are not biased when they arise, the fact that higher levels of virulence are associated with greater within-host competitive ability means that unbiased mutation alone will nevertheless impart a directional force on virulence evolution because it then tends to be those strains with higher virulence that are most successful in taking over an already infected host. The QG model incorporates this effect, whereas the game-theoretic model does not. Second, the QG approach has a parameter reflecting the genetic variance in strain type ω , whereas the game-theoretic approach does not. Finally, notice that both the game-theoretic and the QG approximation differ from the exact QG model derived under the assumptions of appendix D, equation (D2c), in that the latter is evaluated using equations (D3) and (D4), and there is a fourth term appearing in equation (D2c).

Comparing the second-order condition (E3) with the results for the evolutionary dynamics of the variance in appendix C (neglecting any mutation bias) reveals that (E2) is equivalent to condition $D < 0$ where D is defined in (C7). This is simply the condition that there be an equilibrium level of genetic variance. Conditions under which this is not true are the same conditions under which we expect some sort of evolutionary diversification in game-theoretic models (e.g., Gandon et al. 2001a).

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