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PARASITE TRANSMISSION MODES AND THE EVOLUTION OF VIRULENCE

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Abstract.—A mathematical model is presented that explores the relationship between transmission patterns and the evolution of virulence for horizontally transmitted parasites when only a single parasite strain can infect each host. The model is constructed by decomposing parasite transmission into two processes, the rate of contact between hosts and the probability of transmission per contact. These transmission rate components, as well as the total parasite mortality rate, are allowed to vary over the course of an infection. A general evolutionarily stable condition is presented that partitions the effects of virulence on parasite fitness into three components: fecundity benefits, mortality costs, and morbidity costs. This extension of previous theory allows us to explore the evolutionary consequences of a variety of transmission patterns. I then focus attention on a special case in which the parasite density remains approximately constant during an infection, and I demonstrate two important ways in which transmission modes can affect virulence evolution: by imposing different morbidity costs on the parasite and by altering the scheduling of parasite reproduction during an infection. Both are illustrated with examples, including one that examines the hypothesis that vector-borne parasites should be more virulent than non-vector-borne parasites (Ewald 1994). The validity of this hypothesis depends upon the way in which these two effects interact, and it need not hold in general.

Key words.—Epidemiology, parasite, pathogen, transmission rate, virulence evolution.

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Recent years have witnessed a substantial increase in the application of evolutionary principles to medical issues (Williams and Nesse 1991; Stearns 1999; Trevathan et al. 1999). One area of research at the forefront of this endeavor is the study of the evolution of parasite virulence (Bull 1994; Read 1994; Ebert and Herre 1996; Frank 1996; Levin 1996). For years it was thought that most host-parasite relationships evolved to a state of relative mutualism (for discussion, see Levin and Svanborg Edén 1990; Levin 1996), but research over the last few decades has illustrated that this need not be so. High or low levels of virulence are expected to evolve depending upon the specifics of the host-parasite complex in question.

A number of evolutionary hypotheses have been put forward to explain different levels of virulence, but one that has received a great deal of attention focuses on evolutionary trade-offs between fitness components of the parasite and ignores evolutionary change in the host (Bull 1994; Frank 1996; Levin 1996; Ebert 1999). Much of this theoretical work is based on epidemiological models that describe aspects of the ecological dynamics of the host-parasite interaction. A well-known and frequently cited result that has emerged from these theoretical studies involves the so-called basic reproduction ratio, R_0 (Anderson and May 1982, 1991; Diekmann et al. 1990; Frank 1996). R_0 is the total number of new infections generated by a single infected individual in a wholly susceptible population over the duration of the infection. For horizontally transmitted parasites, and assuming that only a single parasite strain infects any given host, the strain with the largest R_0 is evolutionarily stable (i.e., the ESS; Frank 1996).

For a standard epidemiological model, R_0 is given explicitly as $R_0 = \beta S/(u + v + c)$, where S is the number of susceptible individuals, β is the transmission rate of the parasite from host to host, u is the natural host mortality rate, v is the additional host mortality rate caused by the infection (typically equated with virulence in such studies), and c is the rate of infection clearance through host defenses such as an immune response (Anderson and May 1982; Frank 1996; Levin 1996). The entire denominator can be viewed as the parasite's mortality rate because all three components are mortality from its perspective. The trade-off hypothesis is founded on the assumption that there are constraints among components of parasite fitness. In particular, it is often assumed that higher parasite virulence is an inevitable consequence of higher rates of reproduction within the host and that higher parasite reproduction is positively associated with higher rates of host-to-host transmission. Although these assumptions are probably not universally valid, growing empirical evidence suggests that these conditions might be quite common (Anderson and May 1982; Ebert 1994; Ebert and Mangin 1997; Lipsitch and Moxon 1997; Messenger et al. 1999; Mackinnon and Read 1999). Therefore, the evolution of virulence is expected to be governed, at least in part, by such fitness component trade-offs.

The above conceptual framework (and related ones) have been used to make several interesting predictions about how the optimal level of virulence should be affected by differences in the biology of the host and parasite. One question that has received considerable attention is how differences in transmission rates and patterns affect the evolution of virulence (Ewald 1983, 1991, 1994; Massad 1987, 1996; Herre 1993; Lipsitch and Nowak 1995; Lipsitch et al. 1995; van Baalen and Sabelis 1995b; Lipsitch 1997; Lipsitch and Moxon 1997; Frank 1996; Ebert 1998a; Hochberg 1998; Wallinga et al. 1999; Haraguchi and Sasaki 2000). Ewald is one of the main proponents of the importance of transmission patterns as determinants of virulence evolution. For example, he has hypothesized that vector-borne diseases should be more virulent than non-vector-borne diseases because vectors facilitate transmission of parasites between hosts, even if hosts are very adversely affected by the infection (Ewald 1983, 1994). Similarly, he has suggested that certain human-induced changes in transmission patterns might be used as an

effective means of causing parasites to evolve a lower virulence (Ewald 1994).

Some of these ideas have been the subject of theoretical work (Lipsitch and Nowak 1995; van Baalen and Sabelis 1995b; Massad 1996; Lipsitch 1997), but much of the current thought about how transmission patterns affect virulence evolution is still based on verbal arguments. This hampers a complete understanding of virulence evolution, because it is often unclear how such verbal models relate to previous theoretical work based on epidemiological models (Read et al. 1999). Moreover, parasite transmission patterns can differ in a number of ways, and verbal statements about differences in transmission patterns and rates are not as precise as is desirable to fully evaluate the hypotheses (e.g., see Ewald 1995; van Baalen and Sabelis 1995b). This difficulty is compounded by the fact that transmission rates (as well as parasite mortality rates) are likely to change over the course of an infection. This not only makes purely verbal arguments even more difficult to evaluate, but it makes arguments that are conceptually based on the above expression for R_0 difficult to evaluate as well, because that expression assumes all fitness components remain constant during an infection.

My intention here is to explore the relationship between transmission patterns and the evolution of virulence for horizontally transmitted parasites where only a single parasite strain can infect any given host, by using a mathematical model closely related to previous theory. I construct the model by decomposing the transmission rate, β, into two separate processes; the rate of contact between hosts and the probability of transmission per contact (for related ideas see Keeling and Grenfell 2000). I also allow the two transmission rate components as well as the total parasite mortality rate to vary over the course of the infection (Diekmann et al. 1990; Anderson and May 1991, ch. 11; Sasaki and Iwasa 1991; Antia et al. 1994; Levin et al. 1996). I then derive a general ESS condition that partitions the effects of virulence on parasite fitness into three components: fecundity benefits, mortality costs, and morbidity costs. Some general conclusions are drawn from this condition, and I then consider the special case in which the parasite density within hosts is roughly constant during an infection. In this setting, a series of examples are presented to draw out two important ways in which transmission modes can affect virulence evolution: by imposing different morbidity costs on the parasite and by altering the scheduling of parasite reproduction during an infection. The final example presented is a reasonably general model, and I illustrate its utility by using it to explore Ewald's (1983, 1994) hypothesis about vector-borne versus non-vector-borne parasites. Before proceeding to these issues, however, I first present the epidemiological model that underlies all of the evolutionary results contained in this article.

The Underlying Epidemiological Model

This section presents an epidemiological model of the SI/SIR variety (Hethcote 2000) that underlies the evolutionary results presented. It is not the most general model for which my conclusions are valid, but it strikes a balance between simplicity and generality. Similar models have been presented and analyzed previously (e.g., Dietz and Schenzle 1985; May and Anderson 1988; Diekmann et al. 1990; Anderson and May 1991, ch. 11; Diekmann and Heesterbeek 2000; Hethcote 2000), but I include this version here both for completeness and because many of these previous treatments were not framed in an evolutionary context.

Let $S(t)$ denote the number of susceptible individuals at time t and $I(a,t)$ the number of infected individuals at time t whose infection occurred a time units earlier (i.e., a denotes the ''infection age''; Anderson and May 1991; Levin et al. 1996). The reason for keeping track of infection age is to allow the parasite transmission rate, β, and the mortality rate, μ, to vary over the course of an infection. For simplicity, I assume that all individuals recovering from the infection are forever immune, and I do not explicitly keep track of them. Results are qualitatively similar if recovered individuals form a third class (making it an SIR model) that then become susceptible again at a constant rate.

Defining u as a constant natural host mortality rate, the temporal dynamics of S and I can be described by the differential equations

$$\frac{dS(t)}{dt} = \theta - uS(t) - S(t)\int_0^\infty \beta(a)I(a, t)\,da \quad \text{and} \quad (1)$$

$$\frac{\partial I(a, t)}{\partial t} = -\frac{\partial I(a, t)}{\partial a} - \mu(a)I(a, t), \quad (2)$$

with boundary condition

$$I(0, t) = S(t)\int_0^\infty \beta(a)I(a, t)\,da \quad (3)$$

(also see Anderson and May 1991, ch. 11). θ is a constant immigration rate that guarantees that the host population reaches a stable equilibrium in the absence of disease. More generally, θ might also involve the birth of new susceptibles, but results are often qualitatively similar in either case. These equations assume that the population is well mixed and that new infections occur at a rate proportional to the number of susceptible individuals. This is reflected by the last term of equation (1), and it should be kept in mind when considering the various forms of parasite transmission presented later. The term $-\partial I(a, t)/\partial a$ gives the net flow of infected individuals into infection age class a at time t, all of which come from individuals with younger infection ages that have survived. The boundary condition (3) illustrates the fact that all newly infected individuals initially belong to infection age class 0. I also remind the reader that the parasite mortality rate, $\mu(a)$, is composed of three components: the natural host mortality rate, u, the disease-induced mortality rate, $d(a)$, and the disease clearance rate $c(a)$, where both d and c are functions of infection age. We expect that d increases as within-host parasite density increases, whereas c increases as parasite density decreases (i.e., the likelihood of clearing the disease is higher if the parasite density is low).

To determine whether a given strain is evolutionarily stable, we suppose that it is at an equilibrium of the above model, and then ask whether a mutant strain can invade. This requires augmenting the above equations to allow for another parasite strain (eqs. A8 and A9, Appendix 1). After doing so, it can

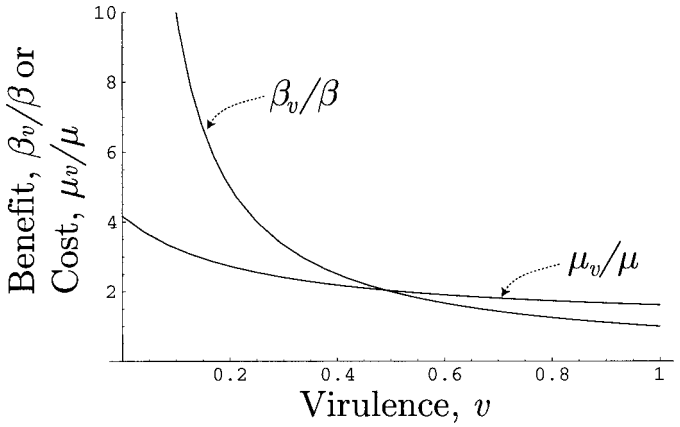

FIG. 1. A hypothetical example of the optimal level of virulence as determined by equation (5). The optimal level of virulence (i.e., the ESS) occurs where the curves intersect. Anything raising the cost of virulence will raise the μ_v/μ curve. This causes the curves to intersect at lower values of virulence, *v*.

be shown (Appendix 1) that the strain with the largest fitness, *R*, is evolutionarily stable, where

$$R = \int_0^\infty \beta(a) l(a)\, da \tag{4}$$

and $l(a) = \exp[-\int_0^a \mu(s)\, ds]$. This is a measure of the parasite's fitness because it is the expected number of new infections caused by a single infected individual, *per susceptible host*. Therefore, it represents the parasite's lifetime reproductive output in terms of new infections. An equivalent version of *R* has been presented previously (e.g., Anderson and May 1991, ch. 11) as have other versions (Dietz and Schenzle 1985; Diekmann et al. 1990). Also notice that equation (4) differs from the often-used definition of a parasite's reproduction ratio, R_0 (Diekmann et al. 1990) in that it does not include the factor *S*, which is the density of susceptible hosts; that is, $R_0 = SR$ (as in the use of R_0 in the introduction).

PARASITE TRANSMISSION AND THE EVOLUTION OF VIRULENCE

For the sake of comparison, I begin my consideration of virulence evolution by presenting the first-order ESS condition derived from the expression for R_0 presented in the introduction. Assuming β depends on virulence, *v* (as the trade-off hypothesis postulates), the ESS virulence is found by determining the value of *v* that maximizes $\beta S/\mu$ where $\mu = u + v + c$. Differentiating with respect to *v* gives the first-order ESS condition,

$$\frac{d\beta/dv}{\beta} = \frac{d\mu/dv}{\mu}. \tag{5}$$

The left side of the equation is the proportional change in transmission from an increase in virulence, and the right side is the proportional change in mortality rate. At the ESS, the two must balance (Bull 1994; Read 1994; Ebert and Herre 1996; Frank 1996; Levin 1996; Fig. 1). From equation (5) we can see that any change in the transmission rate, β, amounting to a multiplicative factor will not alter the ESS virulence (Frank 1996). This result is the basis for the conclusion that (assuming demographic equilibrium) a higher rate of contact does not affect the ESS virulence (e.g., Lipsitch and Nowak 1995; Lipsitch 1997). Importantly, however, this result assumes that the transmission rate remains constant over the course of the infection. One goal of the results presented here is to relax this assumption.

To work with the more general fitness expression (4), I first construct functions for the mortality rate, μ, and the transmission rate, β. I assume that each parasite strain is characterized by a single, evolutionarily labile trait, *v*. The notation *v* reflects the fact that this trait will be viewed as virulence. Most evolutionary models equate a strain's virulence with the additional mortality that it imposes on the host (Bull 1994; Ebert and Herre 1996; Frank 1996; Levin 1996), although some verbal discussions also include aspects of host morbidity (i.e., adverse effects of infection other than an increased mortality rate) in the term virulence (as do models with vertical transmission; Read 1994; Levin 1996). The use of *v* here is consistent with these earlier definitions in the sense that I will typically assume that larger *v* values indirectly result in higher host mortality and/or morbidity as described next. It should be stressed, however, that *v* is no longer to be viewed as the parasite-induced host mortality rate per se, as it was in condition (5).

To construct μ, I assume that a parasite with trait *v* has density within a host at infection age *a* given by $N(v, a)$ and that higher parasite densities lead to higher host mortality/morbidity. I also assume that larger values of *v* lead to larger values of *N* at any given time. More generally one could allow the temporal dynamics of *N* to fluctuate over the course of the infection in a way that was dependent upon *v* (and the dynamics of the host's defenses), and the framework employed here (along with the epidemiological model above) allows for any such dynamic (e.g., Antia et al. 1994).

Now let us consider β. The likelihood of transmission in a very small interval of time, Δa, is divided into two components: (1) the probability that a contact occurs between an infected individual and a susceptible individual; and (2) the probability of successful transmission when a contact occurs (Diekmann and Heesterbeek 2000; Keeling and Grenfell 2000). I assume Δa is small enough that the probability of more than one contact occurring during this interval is negligible (mathematically $o[\Delta a]$). A contact is any process that potentially takes parasites from an infected host to a susceptible host. This could be direct host-host contact but it could also be a vector (e.g., a mosquito) moving between hosts. Writing ϕ as the rate of contact occurrence and τ as the probability of successful transmission given a contact occurs, the expected transmission over this small time interval (i.e., $\beta\Delta a$) is $\phi\tau\Delta a$.

In general, both the rate of contact occurrence, ϕ, and the probability of successful transmission, τ, will change over the course of an infection. The rate of contact occurrence can change as a result of changes in host behavior (e.g., the host might become less active during the course of the infection or infected hosts might eventually be quarantined) as well as through disease-induced morbidity (e.g., some parasite strains might cause the host to become very ill, thereby reducing its rate of contact). Similarly, the probability of suc-

cessful transmission per contact can change as the density of parasites within the infected host changes. In general, the rate of contact occurrence will be a function of infection age as well as the density of parasites within the host, $N(v, a)$; that is, $\phi[a, N(v, a)]$, whereas I assume that the probability of successful transmission is a function of $N(v, a)$ only; that is, $\tau[N(v, a)]$. The function ϕ can be quite arbitrary, whereas τ is zero when $N = 0$, and it increases with N (and therefore with v), eventually plateauing at a value ≤ 1. Also note that ϕ itself is independent of host density. The main goal is to explore how different modes of transmission affect the evolution of virulence, and different transmission modes can be modeled by choosing different forms for τ and ϕ. Throughout, I will assume that the mode of transmission affects ϕ only, although I consider the consequences of allowing transmission mode to affect τ in the Discussion.

With these general definitions, we can now differentiate R_0 (i.e., eq. 4), with respect to v to obtain a general condition that must be satisfied at the ESS:

$$\int_0^\infty \beta l \left\{ \frac{\beta_v}{\beta} - \int_0^a \mu_v \, ds \right\} da = 0. \tag{6}$$

I use the subscript v to denote differentiation with respect to v to simplify notation while still allowing arbitrary functional forms for β and μ. For instance, if $\beta = \hat{\phi}\tau\,[N(v, a)]$, where $\hat{\phi}$ is a constant, then $\beta_v = \hat{\phi}(d\tau/dN)(\partial N/\partial v)$ and so on. β_v/β is the proportional change in transmission that comes from an increase in virulence, v, at infection age a, whereas μ_v is the increase in mortality rate at infection age a. A nice interpretation of condition (6) is obtained by dividing through by $\int_0^\infty \beta l \, da$. Condition (6) then becomes

$$\mathrm{E}\left[\frac{\beta_v}{\beta}\right] = \mathrm{E}\left[\int_0^a \mu_v \, da\right], \tag{7}$$

where $\mathrm{E}[\cdot]$ is the expectation over the probability density $\beta l / \int_0^\infty \beta l \, da$. At the ESS, the average proportional change in transmission over the entire infection must equal the average mortality cost over the entire infection, where each point in time is weighted by its contribution to total parasite reproduction. Thus, time periods during the infection with high reproductive output get large weightings, whereas those with low output get small weightings. Also notice that β_v/β is the proportional change in transmission at infection age a, whereas the mortality cost at that infection age, $\int_0^a \mu_v \, ds$, is the sum of time-specific changes in the mortality rate from the beginning of the infection until that time. This is because mortality costs are cumulative: The parasite has to survive all points in time up to a, and increasing v will change the mortality rate at all these times.

Using the fact that $\beta = \tau\phi$, condition (6) can be written more explicitly as

$$\mathrm{E}\left[\frac{\tau_v}{\tau}\right] = \mathrm{E}\left[\int_0^a \mu_v \, ds\right] - \mathrm{E}\left[\frac{\phi_v}{\phi}\right]. \tag{8}$$

This is the main result used in the remainder of this article, and it partitions the effect of an increase in virulence into three terms: (1) $\mathrm{E}[\tau_v/\tau]$ is the fecundity benefit (a greater likelihood of successful transmission per contact); (2) $\mathrm{E}[\int_0^a \mu_v \, ds]$ is the mortality cost (a smaller chance of survival); and (3) $\mathrm{E}[\phi_v/\phi]$ is what I will call the morbidity cost. ϕ_v/ϕ will typically be negative (or zero if ϕ is independent of v) because parasite strains with large v values have large densities, N. If this has any effect on the rate of contact occurrence, it will likely cause a reduction because hosts with such strains probably experience greater illness (morbidity), which reduces their activity level. It is possible, however, that increased host morbidity confers a fitness advantage on some parasites so that ϕ_v/ϕ might be positive (Ewald 1994). Again, notice that it is the expectation of these costs and benefits over the duration of the infection that appear in equation (8).

To better understand the implications of the above result, I will restrict attention to the case in which parasite density remains constant during the infection. Before doing so, however, there are two interesting conclusions that can immediately be drawn from equation (8). First, most previous models have not explicitly included a morbidity cost (Levin 1996; Read et al. 1999), although ideas related to morbidity costs play a central role in Ewald's (1994) hypotheses about virulence evolution. Condition (8) reveals how such costs can be incorporated into the commonly used mathematical framework for virulence evolution. It also reveals that, all else being equal, transmission modes that entail the largest morbidity cost will result in the lowest virulence, just a Ewald suggested. I hasten to point out, however, that all else need not be equal when comparing two modes of transmission. The other terms in condition (8) can differ as well, and the examples examined below serve to illustrate the consequences that this can have.

A second conclusion is that mortality costs are not necessary for there to be an intermediate ESS level of virulence. Although much of the previous theoretical work has focused attention on the need for a mortality cost to stabilize intermediate levels of virulence (Anderson and May 1982; Bull 1994; Ebert and Herre 1996; Frank 1996; Levin 1996; Read et al. 1999), condition (8) reveals that this is unnecessary. Intermediate virulence can be stable in the absence of mortality costs (i.e., when $\mu_v = 0$) provided that a morbidity cost exists. The ESS virulence strikes a balance between the fecundity benefits and the morbidity costs (with virulence defined in terms of morbidity). An example is presented below.

Constant Parasite Density during Infection

One of the most frequent simplifying assumptions in models of virulence evolution is that transmission and mortality rates are constant over the course of an infection (Frank 1996). In the present model this assumption would imply that parasite density within a host is constant during the infection, and therefore we can equate v with N. Now τ and μ no longer change with infection age, and condition (8) becomes

$$\frac{\tau_v}{\tau} = \mu_v \mathrm{E}[a] - \mathrm{E}\left[\frac{\phi_v}{\phi}\right]. \tag{9}$$

The mortality cost is now simply the product of μ_v with the expectation of a, which is the center of reproductive mass; if we consider that part of the parasite's lifetime reproductive output that occurs at infection age a for all such ages, $\mathrm{E}[a]$ is the center of mass of this distribution. Anything that tends to concentrate more of the output at earlier infection ages

TABLE 1. A summary of the major assumptions involved in each of the three main examples for the case in which parasite density within the host remains constant during an infection (i.e., subsections 1, 2, and 3 of the section Constant Parasite Density during Infection).

No.	Assumption
1	Rate of contact occurrence depends on the parasite's strategy, *v*, only. Different parasite strategies have different rates of contact occurrence, and the dependence of ϕ on *v* can differ for different transmission modes (e.g., ϕ will likely decrease with *v* much more strongly for directly transmitted than for vector-borne parasites).
2	Rate of contact occurrence depends on infection age, *a*, only. This affects a parasite's fitness by altering the timing of its reproductive output, and different transmission modes can differ in the timing of output, thereby selecting for different level of virulence.
3	Rate of contact occurrence depends on both *v* and *a*. This combines 1 and 2 into a single model.

will reduce E[*a*] and thereby reduce the mortality cost, selecting for higher virulence. In particular, because τ is independent of *a*, anything that increases the relative proportion of contact events early in the infection will select for higher virulence.

It is also worth noting that condition (9) is a generalization of condition (5). Neglecting the morbidity cost (i.e., $\phi_v = 0$) and assuming that ϕ does not change with infection age, condition (9) becomes

$$\frac{\tau_v}{\tau} = \frac{\mu_v}{\mu}, \tag{10}$$

which is equivalent to condition (5) because $\beta_v/\beta = \phi\tau_v/\phi\tau = \tau_v/\tau$. This illustrates that, even with constant parasite densities, there are two ways in which different transmission modes can affect the evolution of virulence and that are not apparent in condition (5). First, the rate of contact occurrence can change with infection age regardless of the properties of the parasite. This alters the temporal schedule of parasite reproduction, and thereby changes the probability density used in calculating the expectations in condition (9). Second, the rate of contact occurrence (at any infection age) can depend on the properties of the parasite. This dependence affects the morbidity cost of virulence by altering the magnitude of ϕ_v/ϕ in (9). I first explore each of these possibilities in isolation to understand their effects, and I give examples of each. I then combine them into a relatively general model to get a more complete understanding of how transmission patterns affect virulence evolution (see Table 1 for a summary of the assumptions in each of the three models).

1. Rate of contact occurrence depends on parasite properties only

In this case ϕ depends on *v* but not on *a*; that is, the contact rate does not change throughout the infection. Condition (9) becomes

$$\frac{\tau_v}{\tau} = \frac{\mu_v}{\mu} - \frac{\phi_v}{\phi}. \tag{11}$$

This condition differs from (10) only by including a morbidity cost, and again we see how morbidity costs fit into the general mathematical framework of virulence evolution. This is also one of the simplest scenarios that can be used to evaluate ideas about how transmission patterns affect the evolution of virulence. For example, Ewald has suggested that vector-borne parasites are expected to evolve greater virulence than non-vector-borne parasites because hosts need not be mobile for the transmission of vector-borne parasites (Ewald 1983, 1994). Thus, we might then expect ϕ to be independent of *v* for vector-borne parasites (or nearly so) because the rate of contact occurrence is largely unaffected by the parasite. But ϕ will decrease with *v* for parasites that require direct host-host contact for transmission. This makes the last term of condition (8) zero for vector-borne parasites (there is no morbidity cost), whereas it is positive for non-vector-borne parasites. In general this shifts the cost-benefit balance toward higher virulence for vector-borne parasites relative to non-vector-borne parasites, just as Ewald has hypothesized. More generally, condition (8) shows that any transmission mode that entails a morbidity cost will reduce the level of virulence regardless of its cause. An important assumption implicit in this reasoning, however, is that the contact rate does not change during an infection. The results presented below will demonstrate that the above conclusion is substantially altered once this assumption is relaxed.

Finally, we can also see from condition (11) that mortality costs are not necessary for an intermediate level of virulence. The following simple example illustrates this point.

Example a.—Suppose that $\tau(v) = \kappa(1 - \exp[-\gamma v]$ so that the probability of successful transmission per contact increases with virulence, gradually plateauing (at a rate determined by γ) to a maximum of κ. For simplicity, I assume the rate of contact occurrence decreases exponentially with rate α as virulence increases due to increased morbidity ($\phi[v] = \hat{\phi} \exp[-\alpha v]$), and that the parasite has no effect on host mortality. Using condition (11) (with $\mu_v = 0$), the ESS is

$$v^* = \ln\left[1 + \frac{\gamma}{\alpha}\right] \Big/ \gamma. \tag{12}$$

As the morbidity cost, α, increases, virulence decreases, just as Ewald (1994) argued. Also, as γ increases (so the $\tau - v$ relationship plateaus more quickly), v^* decreases as well because little is then gained from having high virulence (Fig. 2). Finally, note that equation (12) reveals the general prediction (seen from condition 11) that the ESS virulence in the absence of mortality costs is unaffected by the natural host mortality rate or the disease clearance rate. This contrasts sharply with models that rely on mortality costs to explain intermediate levels of virulence (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Williams and Day 2001).

2. Rate of contact occurrence depends on infection age only

In this case there is no morbidity cost and ϕ is a function of *a* only. Condition (9) becomes

$$\frac{\tau_v}{\tau} = \mu_v \mathrm{E}[a]. \tag{13}$$

Condition (13) makes the general prediction that anything placing a greater proportion of the potential contacts early

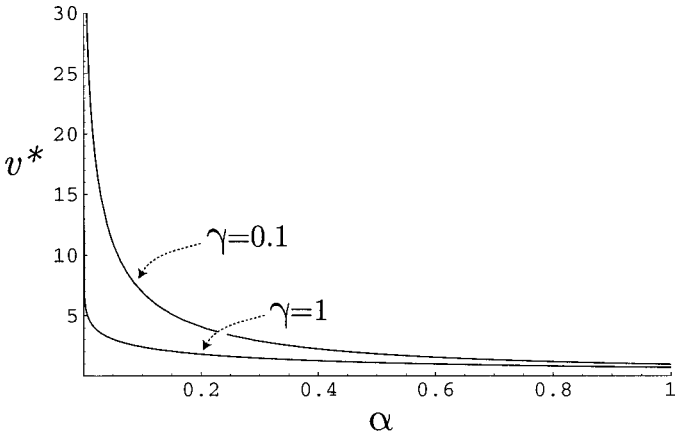

FIG. 2. The ESS virulence, v^*, as a function of the morbidity cost, α, and the rate at which the $\tau - N$ relationship plateaus, γ, in the absence of any mortality cost to virulence. Higher morbidity costs lead to lower virulence, as does an increase in the rate at which the probability of transmission plateaus.

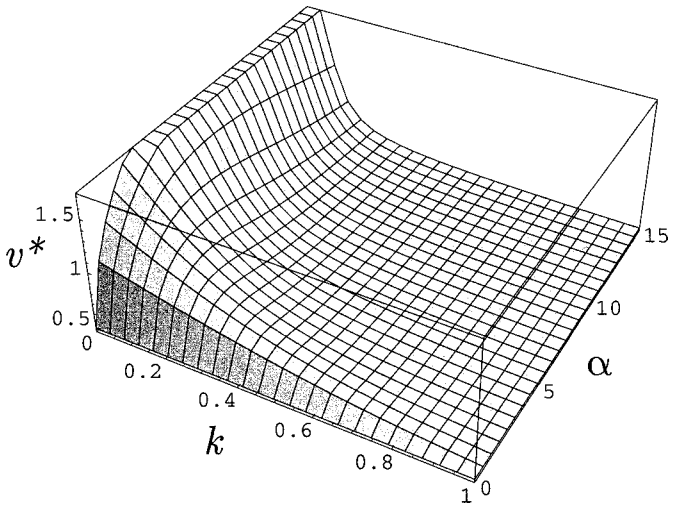

FIG. 3. A specific instance of the model considered in example b. The ESS virulence, v^*, is plotted against α and k. Notice that any positive α results in higher virulence compared to $\alpha = 0$. Virulence also increases as the drop in contact rate increases (i.e., as k decreases). Also notice, however, that for any fixed k the highest level of virulence occurs at an intermediate value of α. Results assume $\tau(v) = \kappa(1 - \exp[-\gamma v])$ and $\mu = u + v + c$, with parameter values $\gamma = 1$, $u = 0.02$, $c = 0.1$.

in the infection will decrease E[a], thereby reducing the mortality cost and selecting for higher virulence. A well-known example of this occurs when the host's natural mortality rate is increased (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Williams and Day 2001). This places a greater proportion of the total transmission events earlier in the infection, thereby reducing E[a] and selecting for higher virulence. An analogous phenomenon occurs if the rate of contact occurrence (and therefore transmission rate) changes during an infection. If different transmission modes cause different schedules of parasite transmission over the course of an infection, modes that result in a greater proportion of the total transmission events occurring early in an infection will reduce E[a] and select for higher virulence.

Example b.—Suppose that at some point after infection the rate of contact occurrence drops from a constant, $\hat{\phi}$, to a lower value, $k\hat{\phi}$, where $0 \leq k \leq 1$. This might occur if the host maintains its normal activity level until a point in time at which it becomes ill and its activity level is then reduced by a factor k. Alternatively, the same situation arises if infected hosts are eventually quarantined (the quarantine is partial if $k > 0$). Notice that I do not consider such drops in contact rates to be morbidity costs of virulence here because all strains are assumed to be affected equally by such drops, regardless of their virulence (Example c below relaxes this assumption). Now the time at which the contact rate drops will be random from host to host, and I model it as an exponentially distributed random variable with parameter α. Therefore, provided the host does not die or clear the infection before changing contact rate, the expected amount of time that it remains at its normal activity level is $1/\alpha$. Thus, different transmission modes in the present example are characterized by different values of k and α.

The probability that an infected host is still at its normal contact rate at infection age a is $e^{-\alpha a}$, and therefore,

$$\phi(a) = \hat{\phi}e^{-\alpha a} + k\hat{\phi}(1 - e^{-\alpha a}). \tag{14}$$

By evaluating the expectation of a in condition (13) over the probability density $\beta(a)l(a)/\int_0^\infty \beta(a)l(a)\,da$ (where $\beta[a] = \tau[v]$, $\phi[a]$, $\phi[a]$, is given by condition 14, and $l[a]\ e^{-\mu a}$) we get

$$\frac{\tau_v}{\tau} = \frac{\mu_v}{\mu}\frac{\mu^2 + k\alpha(\alpha + 2\mu)}{(\alpha + \mu)(k\alpha + \mu)}. \tag{15}$$

As expected, when $\alpha \to 0$ (i.e., the host remains at the high contact rate forever), condition (15) reduces to (10). For any positive α, however, the mortality cost in (15) is smaller than that of condition (10), which selects for higher virulence (Fig. 3). The cost of virulence (which is a reduced future reproductive output due to increased mortality) is diminished whenever an infection's lifespan is truncated, and a drop in host contact rate does this in much the same way as higher natural host mortality or infection clearance rates do (Anderson and May 1982; Sasaki and Iwasa 1991; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Williams and Day 2001). This illustrates that, although different transmission modes in the above model do not differentially affect the transmission of different parasite strains (because transmission rates are unaffected by virulence), these strains' *fitnesses* are differentially affected. This occurs because different transmission modes result in a different scheduling of the parasite's reproductive output during an infection. This phenomenon cannot be appreciated from previous theoretical results that assume $R = \beta/\mu$ (e.g., see Ewald 1995; van Baalen and Sabelis 1995b).

Finally, notice that provided $k \neq 0$, condition (15) again approaches (10) as $\alpha \to \infty$ (i.e., most hosts drop to the low contact rate very early in the infection). In this case, $\phi(a)$ is essentially constant at $k\hat{\phi}$ throughout the infection because infected hosts drop to the low contact rate immediately. In fact, for any level of virulence, the mortality cost in (15) reaches a minimum of $2\sqrt{k}/\mu(1 + \sqrt{k})$ when $\alpha = \mu/\sqrt{k}$ (Fig. 3).

3. Rate of contact occurrence depends on parasite properties and infection age

The two special cases above illustrate two different ways in which changes in transmission patterns can affect the evolution of virulence. Of course, in many situations both factors will be important, and often they will have opposing effects. For example, if a particular transmission mode entails a morbidity cost, so that higher virulence results in a general decrease in the rate of contact, this will select for reduced virulence. If, however, this transmission mode also causes a greater proportion of the parasites reproductive output to be realized earlier in an infection, this effectively truncates the infection's lifespan and selects for higher virulence. The following example is an extension of example b that incorporates both effects.

Example c.—I extend example b by allowing the mean amount of time that the host remains in a high activity level, $1/\alpha$, to depend upon the parasite strain in question. For example, we might expect α to be higher for strains with a larger v because such infections might make the host drop to a low activity level earlier in the infection. Alternatively, if α is the rate of quarantine, we might expect this to increase with v because such infections can be more readily recognized. Along similar lines, I allow k to change with v as well because we might expect parasite strains with a large v to induce a lower activity level in their hosts once the host can no longer maintain its normal level. The resulting model is quite general, and to explore different hypotheses about the effects of transmission modes on virulence evolution we simply need to choose functions $\alpha(v)$ and $k(v)$ to suit the transmission modes of interest.

For this general model, condition (9) evaluates to

$$\frac{\tau_v}{\tau} = \frac{\mu_v}{\mu}\frac{\mu^2 + 2k\mu\alpha + k\alpha^2}{\mu^2 + (1 + k)\mu\alpha + k\alpha^2} + \left[\frac{(1 - k)\mu\alpha_v}{(\mu + \alpha)(\mu + k\alpha)} - \frac{k_v\alpha}{\mu + k\alpha}\right]. \quad (16)$$

I have grouped the last two terms in brackets because both are components of the morbidity cost of virulence. Now consider two transmission modes, one in which $k \equiv 1$, so that the contact rate never changes during an infection, and another in which k is a decreasing function of v, so that more virulent strains eventually induce a lower contact rate. If $k \equiv 1$, then condition (16) reduces to condition (10), and therefore we simply need to compare the total cost of virulence in the above condition (i.e., the right side of condition 16) with that of condition (10) to determine how these transmission modes affect the evolution of virulence. The bracketed term in (16) is positive, and as mentioned in the consideration of condition (8), this will select for lower virulence *provided all else is equal.* The mortality cost term in (16) reveals, however, that all else need not be equal when comparing two modes of transmission. In particular, the factor multiplying μ_v/μ is always less than 1 provided that $k < 1$, and therefore the transmission mode that results in a greater morbidity cost of virulence also *reduces* the mortality cost virulence. The net effect will depend on the relative magnitude of each component (Fig. 4). Appendix 2 shows that

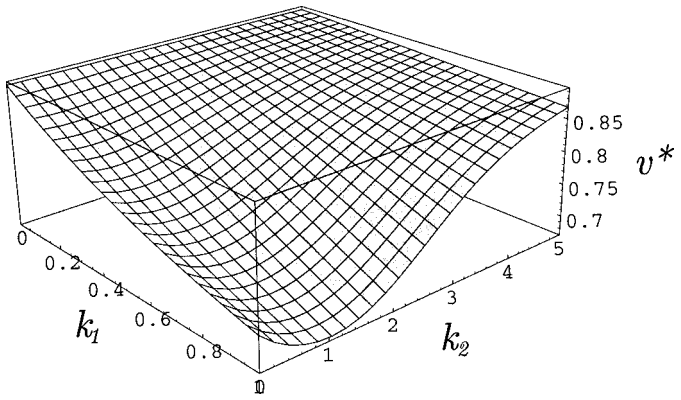

FIG. 4. A specific instance of the model considered in example c. Results assume $\tau(v) = \kappa(1 - \exp[-\gamma v])$, $\alpha(v) = \alpha_1 + \alpha_2 v$, $k(v) = k_1\exp[-k_2(v)]$, $\mu(v) = (u) + \exp[\mu_1(v)] + c$. The ESS virulence is plotted against k_1 and k_2. The ESS level of virulence determined by condition (10) occurs at $k_1 = 1$, $k_2 = 0$ (so that the contact rate never drops during an infection). The graph illustrates that the ESS virulence determined by condition (16) can easily be larger or smaller than this value. Thus, a transmission mode that entails a morbidity cost (e.g., non-vector-borne transmission) can result in higher or lower virulence than one that does not (e.g., vector-borne transmission) depending on the situation. Parameter values are $\mu_1 = 1$, $c = 0.1$, $u = 0.02$, $\alpha_1 = 1$, $\alpha_2 = 0.1$, $\gamma = 1$, $\kappa = 0.75$.

the ESS virulence predicted from condition (16) will be lower than that predicted from condition (10) provided that

$$\frac{d}{dv}\left[\frac{\alpha}{\mu + \alpha}(1 - k)\right] > 0. \quad (17)$$

Condition (17) has a useful interpretation. Consider the transmission mode that induces a morbidity cost. After infection, a host will either eventually drop to a low contact level due to morbidity, or the infection will end through clearance or death before this happens. The factor $\alpha/(\mu + \alpha)$ is the probability that the host does eventually drop to a low contact level prior to death or disease clearance, and $(1 - k)$ is the proportion of the reproduction that is given up if such a drop occurs. Thus, $(\alpha/\mu + \alpha)(1 - k)$ is the expected proportion of the parasite's total fitness that is lost because of morbidity (Appendix 2). What matters in condition (17) is how this expected loss changes with a change in virulence.

To illustrate this point, I now use the above analysis to explore Ewald's hypothesis about vector-borne versus non-vector-borne parasites more thoroughly (Ewald 1983, 1994). For vector-borne parasites we expect that changes in host behavior (due to illness) will have little effect on the rate of contact because vector transmission guarantees high rates regardless of the host's state. This means that k will be independent of v and close to one, and thus the ESS virulence for such parasites will satisfy condition (16) with $k \equiv 1$ (which, as mentioned, reduces it to condition 10). Conversely, non-vector-borne parasites are expected to have a virulence level satisfied by the general condition (16). Now we can imagine conducting an experiment in which we start with a vector-borne parasite at evolutionary equilibrium, and we artificially alter its mode of transmission to being non-vector-borne. This alters k from being identically one to being a decreasing function of v, and it reduces the current parasite

strain's total fitness because of the effects of morbidity. As explained above, the proportion of fitness lost through this morbidity to the current strain now that it is non-vector-borne is $(\alpha/\mu + \alpha)(1 - k)$. Because the system is no longer in evolutionary equilibrium, however, we expect evolutionary change to now occur. Strains with a reduced virulence will have a higher fitness than the current strain (and thus Ewald's hypothesis will be valid) provided that this fitness loss decreases with a decrease in virulence (i.e., condition 17 is satisfied). To paraphrase Ewald (1994), we require that highly virulent strains are most adversely affected by switching the mode of transmission to non-vector-borne.

The value of the above result over verbal arguments, however, is that it states precisely the conditions under which this will be true. In particular, the results reveal two different ways in which a change in transmission mode affects virulence evolution. First, as Ewald has argued, for some modes of transmission (e.g., non-vector-borne) highly virulent parasites pay a larger morbidity cost than avirulent parasites because they cause a general reduction in the rate of contact and thus the rate of parasite transmission. Second, and perhaps less well appreciated in verbal models of virulence evolution, different transmission modes can also have different effects on the schedule or timing of a parasite's reproductive output during the course of an infection, and this can also have important evolutionary consequences (Fig. 5). In the above example, non-vector-borne transmission not only entails a substantial morbidity cost to virulence, but it can also place a greater proportion of a parasite's total reproductive output earlier in an infection due to the temporal decline in the rate of contact that occurs as the host becomes ill. These two effects work in opposition, and for the specific model in example c, condition (17) reveals when the latter effect outweighs the former. In particular, it shows that non-vector-borne transmission can actually result in higher virulence than vector-borne transmission provided that highly virulent strains cause the host to die or clear the infection very quickly relative to the amount of time that the host maintains a normal activity level. The reason is that highly virulent strains are then less likely to suffer any morbidity cost because the host dies or clears the infection before any morbidity effects are felt. For the above model, this suggests that Ewald's hypothesis is most likely to fail when infections last a very short time compared with the time span over which infected hosts maintain a normal contact rate.

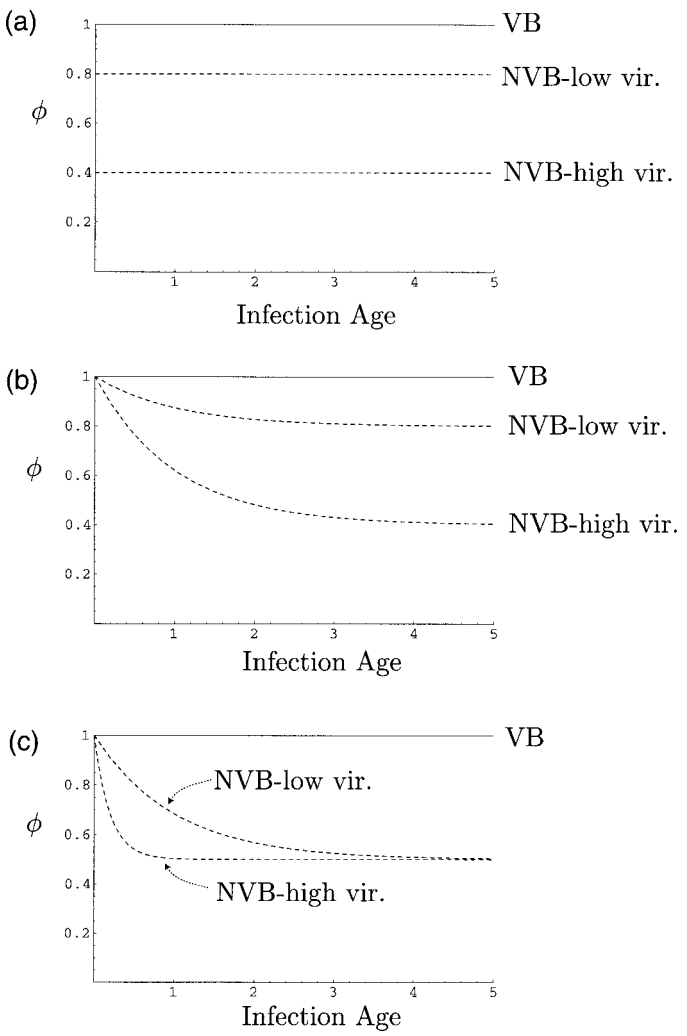

FIG. 5. Three qualitatively different ways in which two transmission modes such as vector-borne (VB) versus non-vector-borne (NVB) can affect the rate of contact occurrence, ϕ, and thus the evolution of virulence. (a) The case that most verbal arguments appear to rely on. NVB transmission reduces the contact rate from VB transmission, and the drop is assumed to increase as virulence increases. Notice that the contact rate is constant throughout the entire infection. (b) A more realistic assumption in which the rate of contact occurrence starts out the same for both transmission modes, but it decays to a lower level for NVB transmission as the host becomes ill (and the asymptote is lower for more virulent strains). (c) Another possibility in which the rate of contact starts out the same for both transmission modes, but it decays to a lower level for NVB transmission as the host becomes ill. Here, however, it is the *rate* of decay that increases for strains with higher virulence. A combination of both (b) and (c) are probably most realistic. Therefore, when comparing transmission modes, one needs to consider not only the reduction in contact rate that occurs from virulence (cases a and b) but also the rate at which this reduction occurs (cases b and c). It is very difficult to discern the evolutionary consequences of the combination of these two effects without an explicit quantitative model.

DISCUSSION

The effect of parasite transmission mode on the evolution of virulence has been a topic of considerable interest over the last few decades (Ewald 1983, 1991, 1994; Massad 1987, 1996; Lipsitch and Nowak 1995; Lipsitch et al. 1995; van Baalen and Sabelis 1995b; Frank 1996; Lipsitch 1997; Ebert 1998a; Hochberg 1998; Wallinga et al. 1999; Haraguchi and Sasaki 2000). Although there has been some quantitative modeling of various hypotheses, a great deal of the current thought about how transmission patterns affect virulence evolution has been based on verbal arguments (Read et al. 1999). The general model presented in this article extends current theory in a way that can be used to explore the evolutionary consequences of a variety of transmission patterns.

The main theoretical result presented is equation (8), which is a general condition that must be satisfied by the ESS level of virulence. Although it is necessary to restrict attention to

special cases to make precise predictions, it is still possible to draw some general qualitative conclusions from this expression. First, condition (8) reveals three effects of virulence on components of parasite fitness; fecundity benefits, mortality costs, and morbidity costs. At the ESS, the average benefits must equal the average costs over the entire duration of an infection, with each point in time weighted by its contribution to the total reproductive output of the parasite. Second, condition (8) demonstrates how morbidity costs (which have played a central role in many verbal models of virulence evolution; Ewald 1994), can be incorporated into the mathematical framework used to study virulence evolution. Lastly, although most previous theoretical work has focussed on the need for a mortality cost to stabilize intermediate levels of virulence, condition (8) reveals that this is unnecessary once morbidity costs are incorporated. An evolutionary equilibrium can be reached when the fecundity benefits of virulence are balanced by the morbidity costs and when the parasite in question has no effect on host mortality rate. The example of this presented above also demonstrates that, in the absence of such mortality costs, the host's natural mortality rate and the disease clearance rate have no effect on the ESS level of virulence. This is in contrast to previous results that rely on a mortality cost to stabilize intermediate levels of virulence (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Williams and Day 2001).

To generate further predictions I focussed on the special case in which parasite density is assumed to be relatively constant during an infection. This assumption is useful because the vast majority of previous theoretical work relies on it, and because it is probably a reasonable approximation for many host-parasite interactions. Even in this restricted setting, however, there are two important ways in which parasite transmission mode can affect the costs and benefits of virulence and that are not apparent in earlier theoretical work. First, different transmission modes can impose different morbidity costs in terms of the extent to which the contact rate is reduced by higher virulence (Fig. 5). Higher virulence will often cause a greater general reduction in host activity level as compared with low virulence, and different transmission modes translate this activity level into a contact rate in different ways. For example, vector-borne parasites might well be unaffected by reductions in host activity level, whereas non-vector-borne parasites will be greatly affected. In general we expect the ESS level of virulence to decrease when these morbidity costs are important (example a). This type of argument plays a central role in many of Ewald's (1994) hypotheses about virulence evolution

Second we can see from condition (9) that a change in transmission mode can alter the way in which virulence affects the mortality cost by changing the timing or schedule of reproductive output over the duration of an infection (Fig. 5). In particular, any change that tends to decrease the center of reproductive mass (defined earlier) by placing a greater proportion of the total reproductive output earlier in the infection will select for higher virulence. This second aspect is often not appreciated in verbal models of the effects of transmission mode on virulence evolution. Moreover, even with previous mathematical models that assume constant parasite transmission and mortality rates (van Baalen and Sabelis 1995b; Frank 1996), any change in the transmission rate of the parasite that is independent of strain (and therefore independent of virulence, v) will not affect the ESS level of virulence. Rather it simply alters a parasite's fitness by a multiplicative constant. If the transmission rate varies throughout an infection, however, different patterns of variation can affect the *fitness* of different parasite strains in different ways, even though they affect the strain's *transmission patterns* identically (Example b above).

These results all demonstrate the general principle that, when comparing two transmission modes to determine which will likely result in the evolution of the highest level of virulence, one needs to consider how the morbidity cost differs between them as well as how the timing of reproductive output will differ. This is illustrated well by example c, which compares a transmission mode that results in no morbidity cost (vector-borne transmission) with one that does entail a morbidity cost (non-vector-borne transmission). The fact that higher virulence eventually results in a decreased rate of contact occurrence for non-vector-borne parasites tends to select for reduced virulence in such cases. However, because non-vector-borne parasites can also have a greater proportion of their total reproductive output very early in an infection (because host contact rate diminishes throughout the infection) this selects for increased virulence. It is the relative strengths of these two effects that will determine how these two modes of transmission affect virulence evolution. Finally I note that, although example c partitions these effects neatly into two parameters (α and k; Fig. 5), a more general theory would allow more flexibility (e.g., any possible curve in Fig. 5). A future publication will explore this possibility using dynamic optimization.

Experimental Evolution of Parasites

As a final comment, it is worth considering another special case of condition (8) that is relevant to experimental studies of the evolution of virulence. All of the examples considered in this article have assumed that different transmission modes can be characterized by different choices for the rate of contact occurrence, ϕ. In laboratory settings, however, it is also likely that τ is altered by different experimental protocols relative to what is characteristic of transmission in the wild. For instance, in many studies parasites are serially transferred at certain times in the parasite's life cycle, and this will likely affect both ϕ and τ from what they are in a natural setting.

First, in many serial transfer experiments, the rate of contact occurrence, ϕ, is zero at all times except at the infection age, a^*, when the transfer takes place. Consequently, the general optimality condition (8) reduces to

$$\frac{\tau_v}{\tau} = \int_0^{a^*} \mu_v \, ds - \frac{\phi_v}{\phi}, \tag{18}$$

where all terms involving a are evaluated at $a = a^*$ (this formulation is not strictly valid for experiments in which several host generations occur between horizontal transmission events but is quantitatively valid; e.g., Messenger et al. 1999). The fecundity benefit and morbidity cost of virulence are dependent upon the functions τ and ϕ only at time a^*,

whereas the mortality cost depends on the function μ at all previous times. It is quite likely, however, that the forms of ϕ and τ as functions of parasite density, N, are also altered substantially by experimental manipulation.

For simplicity, first let us suppose that the functional forms of the costs and benefits are not altered from what they are in a natural setting. This might occur of the experiment was carried out in a seminatural setting but transmission was allowed only at infection age a^*. If parasite density within a host increases over time (perhaps to a carrying capacity), the fecundity benefit will decrease as a^* increases, whereas the mortality cost will increase. In the absence of a morbidity cost this demonstrates that the ESS level of virulence decreases as the transfer time, a^*, increases. The reason is that $\tau_v/\tau - \int_0^{a^*} \mu_v \, ds$ decreases with infection age. If morbidity costs are also present in the experiment, then more information about how this morbidity cost changes over the infection is required to make predictions.

We might also use information about the way in which $\tau_v/\tau - \int_0^{a^*} \mu_v \, ds$ decreases to make predictions about how the evolved level of virulence in such experiments should differ from that in the wild. For example, if a plot of this costs minus benefits is decreasing and concave up, then we would often expect the level of virulence observed in the wild to be higher than that evolved in an experiment. The reason for this is that most experiments probably have the time of transfer somewhere near the center of reproductive mass (defined earlier) because, from a practical standpoint, this would be easiest. In the wild, however, there is variation in the transfer time, with earlier times selecting for higher virulence and later times selecting for lower virulence. If the costs minus benefits plot is concave up, then the occasional early transfer event selects for higher virulence more strongly than the occasional late transfer event selects for lower virulence. This results in an overall net selection for higher virulence in the wild (mathematically, a consequence of Jensen's inequality). The most common experimental finding actually appears to be the opposite of this pattern (Ebert 1998b, 1999), and therefore, if the above argument is to explain this pattern then the costs minus benefits curve must be concave down. Unfortunately, from a theoretical standpoint, it is not possible to say which is most likely.

Another explanation for these results, however, stems from the fact that many experiments are not this close to a seminatural setting. Rather they often involve artificially transferring parasites between hosts. The result of this will be to alter the functional forms (and thus the cost and benefits) of the terms in condition (18). In fact, one explanation for the evolution of higher virulence in the laboratory is that the mortality cost is greatly reduced in experiments because the experimenter artificially transfers parasites (Ebert 1998b). Although this is undoubtedly true in some situations, artificial transmission will also likely reduce the first term (the fecundity benefits) in condition (18) because it ensures a high transmission probability even for relatively low parasite densities (Ebert 1999). Given that morbidity costs might also be greatly reduced (or completely eliminated) in the laboratory, this means that all virulence costs are likely reduced, and so are the benefits. Therefore, making predictions requires more information about how different experimental protocols affect the terms in condition (18). If the above type of model is to explain the observed experimental results, then for some reason the costs would have to be reduced more than the benefits most of the time. Of course, an alternative hypothesis is that within-host competition plays a more significant role in the laboratory than in natural populations and this selects for higher virulence (Bremermann and Pickering 1983; Knolle 1989; Sasaki and Iwasa 1991; Nowak and May 1994; van Baalen and Sabelis 1995a; Frank 1996). It would be useful to try and better distinguish the predictions of these two hypotheses.

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Appendix 1

Here I demonstrate that the strain with the largest value of R (i.e., condition 4) is evolutionarily stable. To do so, I first conduct a local stability analysis of system (1, 2, 3) to determine when a single parasite strain can persist in the host population. Then I augment the system to allow for a competing parasite strain and derive the desired condition about evolutionary stability.

The system (1, 2, 3) has two equilibria: (1) disease-absent, $\hat{I}(a) \equiv 0$, $\hat{S} = \theta/u$; and (2) disease-endemic, $\hat{I}(a) = \hat{I}(0)l(a)$, where $l(a) = \exp[-\int_0^a \mu(s)\,ds]$, $\hat{S} = 1/R$, where R is given by condition (4), and $\hat{I}(0) = \theta - u/R$. Define perturbations from equilibrium as $\epsilon(t) = S(t) - \hat{S}$ and $\delta(a, t) = I(a, t) - \hat{I}(a)$. We can then obtain a system of differential equations for these perturbation (to first order) as

$$\frac{d\epsilon(t)}{dt} = -u\epsilon(t) - \hat{S}\int_0^\infty \beta(a)\delta(a, t)\,da - \epsilon(t)\int_0^\infty \beta(a)\hat{I}(a)\,da \quad \text{and} \tag{A1}$$

$$\frac{\partial\delta(a, t)}{\partial t} = -\frac{\partial\delta(a, t)}{\partial a} - \mu(a)\delta(a, t) \tag{A2}$$

along with the boundary condition

$$\delta(0, t) = \epsilon(t)\int_0^\infty \beta(a)\hat{I}(a)\,da + \hat{S}\int_0^\infty \beta(a)\delta(a, t)\,da. \tag{A3}$$

Now consider the equilibrium where the disease is absent (to see when the disease can spread into the population). Because $\hat{I} \equiv 0$ at this equilibrium, we can see from (A2) and (A3) that the dynamics of δ are completely uncoupled from those of ϵ. Therefore, we can solve the partial differential equation for δ by itself. Trying a solution of the form $\delta(a, t) = A(a)T(t)$, and using the technique of separation of variables shows that

$$\delta(a, t) = T_0 e^{\lambda t} A_0 \exp\left[-\int_0^a \mu\,ds - \lambda a\right] \tag{A4}$$

for some constant, λ. Therefore, ignoring complex λ, $\delta \to 0$ (i.e., the disease will fail to invade) if and only if $\lambda < 0$. Noting that $l(a) = \exp[-\int_0^a \mu\,ds]$, and substituting (A4) into the boundary condition (A3) yields

$$1 = \hat{S}\int_0^\infty e^{-\lambda a}\beta(a)l(a)\,da. \tag{A5}$$

From this we can drawn the following conclusions:

$$R\hat{S} < 1 \Leftrightarrow \lambda < 0 \quad \text{and} \tag{A6}$$

$$R\hat{S} > 1 \Leftrightarrow \lambda > 0, \tag{A7}$$

where R is given by condition (4). In other words, the disease will invade if and only if $R\hat{S} > 1$ (Anderson and May 1991; Hethcote 2000).

To derive the evolutionary stability results, we augment system (1, 2, 3) to allow for a second, competing strain of parasite:

$$\frac{dS(t)}{dt} = \theta - S(t) - S(t)\int_0^\infty \beta_1(a)I_1(a, t)\,da - S(t)\int_0^\infty \beta_2(a)I_2(a, t)\,da, \quad \text{(A8a)}$$

$$\frac{\partial I_1(a, t)}{\partial t} = -\frac{\partial I_1(a, t)}{\partial a} - \mu_1(a)I_1(a, t), \quad \text{and} \quad \text{(A8b)}$$

$$\frac{\partial I_2(a, t)}{\partial t} = -\frac{\partial I_2(a, t)}{\partial a} - \mu_2(a)I_2(a, t), \quad \text{(A8c)}$$

with

$$I_1(0, t) = S(t)\int_0^\infty \beta_1(a)I_1(a, t)\,da \quad \text{(A9a)}$$

$$I_2(0, t) = S(t)\int_0^\infty \beta_2(a)I_2(a, t)\,da. \quad \text{(A9b)}$$

Now by defining perturbations analogous to those above, we can obtain a system of differential equations in these perturbations (to first order) near the equilibrium with strain 1 present and strain 2 absent:

$$\frac{d\epsilon(t)}{dt} = -u\epsilon(t) - \hat{S}\int_0^\infty \beta(a)\hat{I}_1(a)\,da - \hat{S}\int_0^\infty \beta(a)\delta_2(a, t)\,da, \quad \text{(A10)}$$

$$\frac{\partial \delta_1(a, t)}{\partial t} = -\frac{\partial \delta_1(a, t)}{\partial a} - \mu_1(a)\delta_1(a, t), \quad \text{(A11)}$$

$$\frac{\partial \delta_2(a, t)}{\partial t} = -\frac{\partial \delta_2(a, t)}{\partial a} - \mu_2(a)\delta_2(a, t), \quad \text{(A12)}$$

$$\delta_1(0, t) = \epsilon(t)\int_0^\infty \beta(a)\hat{I}_1(a)\,da + \hat{S}\int_0^\infty \beta(a)\delta_1(a, t)\,da, \quad \text{(A13)}$$

and

$$\delta_2(0, t) = \hat{S}\int_0^\infty \beta(a)\delta_2(a, t)\,da. \quad \text{(A14)}$$

Again we can see that the dynamics of strain 2 are completely uncoupled from those of the other variables. Consequently, the solution for δ_2 is the same as that obtained above. As a result, strain 2 will invade if and only if $R_2\hat{S} > 1$, where $\hat{S} = 1/R_1$. This implies that the evolutionarily stable strain is the one with the largest value of R.

Appendix 2

Here I derive condition (17). Subtracting the right side of equation (10) from that of equation (16) results in an expression that is proportional to

$$\frac{\alpha_v}{\alpha + \mu}\left(\frac{\mu}{\alpha}\right) - \frac{\mu_v}{\alpha + \mu} - \frac{k_v}{1 - k}. \quad \text{(A15)}$$

If this is positive then condition (16) has larger costs to virulence and hence it predicts a lower ESS. Now the above expression has the same sign as

$$\frac{d}{dv}\left[\frac{\alpha}{\mu + \alpha}(1 - k)\right], \quad \text{(A16)}$$

which gives condition (17).

To see that $(\alpha/\mu + \alpha)(1 - k)$ is the expected proportion of a parasite's fitness that is lost due to the introduction of a morbidity cost, first note that a parasite with no morbidity cost has total fitness $R_{nm} = \tau\hat{\phi}\int_0^\infty l(a)\,da$. A parasite with a morbidity cost, that is otherwise identical, has a total fitness $R_m = \tau\int_0^\infty \phi(a)l(a)\,da$, where $\phi(a)$ is given by condition (14). Thus, the expected proportion of a parasite's fitness that is lost due to the introduction of a morbidity cost is

$$\frac{R_{nm} - R_m}{R_{nm}} = \frac{\alpha}{\alpha + \mu}(1 - k), \quad \text{(A17)}$$

which is the quantity given in condition (17). The factor $\alpha/(\alpha + \mu)$ is the probability that a drop in contact rate occurs before the infection ends, and $(1 - k)$ is the proportion of fitness that is lost when this happens.