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THE EVOLUTION OF VIRULENCE IN PATHOGENS WITH VERTICAL AND HORIZONTAL TRANSMISSION

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Abstract.—The idea that vertical transmission of parasites selects for lower virulence is widely accepted. However, little theoretical work has considered the evolution of virulence for parasites with mixed horizontal plus vertical transmission. Many human, animal, and plant parasites are transmitted both vertically and horizontally, and some horizontal transmission is generally necessary to maintain parasites at all. We present a population-dynamical model for the evolution of virulence when both vertical and horizontal transmission are present. In the simplest such model, up to two infectious strains can coexist within one host population. Virulent, vertically transmitted pathogens can persist in a population when they provide protection against more virulent, horizontally transmitted strains. When virulence is maintained by a correlation with horizontal transmission rates, increased levels of vertical transmission always lower the evolutionarily stable (ESS) level of virulence. Contrary to existing theory, however, increases in opportunities for horizontal transmission also lower the ESS level of virulence. We explain these findings in light of earlier work and confirm them in simulations including imperfect vertical transmission. We describe further simulations, in which both vertical and horizontal transmission rates are allowed to evolve. The outcome of these simulations depends on whether high levels of vertical transmission are possible with low virulence. Finally, we argue against the notion of a virulence-avirulence continuum between horizontal and vertical transmission, and discuss our results in relation to empirical studies of transmission and virulence.

Key words.—Epidemiology, horizontal transmission, parasite, pathogen, pathogenicity, vertical transmission, virulence.

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It is widely accepted that vertical transmission of parasites exerts natural selection on the parasites to be less harmful to their hosts. Because the host's reproduction, and therefore its survival, contributes to the parasite's reproduction, parasites transmitted from hosts to their offspring will have higher fitness if they are less virulent, where virulence is defined as reduction in host lifetime reproductive success. Indeed, if vertical transmission is the only route of transmission, then natural selection against infected hosts will clear the parasite from the population if it lowers host fitness at all (Fine 1975), unless the parasite has some special feature such as biparental transmission (Fine 1975) or sex-ratio distortion (Hurst 1993), which increases its representation in subsequent generations enough to offset the effects of selection against infected hosts. The prediction that vertical transmission alone should select for decreased virulence, compared with horizontal transmission, has been confirmed experimentally in a bacterial host-symbiont system, using a hybrid bacteriophage-plasmid as a symbiont (Bull et al. 1991).

Although it is clear that vertical transmission alone selects for decreased virulence of symbionts/parasites (with the exceptions mentioned above), the case of most interest is that of mixed horizontal and vertical transmission. A number of plant and animal viruses (reviewed in Power 1992; Mims 1981) spread by a combination of vertical and horizontal transmission. Among the medically important viruses of humans with both transmission modes are HTLV-I (Mueller 1991); HIV (Khouri et al. 1995); human papilloma virus (Kaye et al. 1994); and hepatitis B and C viruses (Biswas et al. 1989; Moriya et al. 1992). Mixed vertical and horizontal transmission also occurs for bacterial infections and has been extensively documented in microsporidian parasites of arthropods (Mangin et al. 1995; Zchori-Fein et al. 1992; Ewald and Schubert 1989 and references therein).

Ewald (1987) has proposed that infections with mixed modes of transmission should fall along a continuum, with mostly horizontally transmitted parasites tending toward higher virulence, and mostly vertically transmitted agents tending toward lower virulence. Ewald and Schubert (1989) adduced support for this view from comparative studies of microsporidian parasites of mosquitoes. Perhaps the most

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convincing evidence in favor of the continuum hypothesis comes from Herre's (1993) observational studies of the nematode parasites of fig wasps, which showed that nematode virulence correlated very closely with degree of horizontal transmission relative to vertical transmission.

In this paper, we model the transmission dynamics of a vertically and horizontally transmitted pathogen. The models support the idea that vertical transmission is more effective when virulence is low and that high degrees of vertical transmission therefore select for pathogen strains with lowered virulence. Horizontal transmission, however, presents a more complicated picture. Increased opportunities for horizontal transmission—due to higher host population densities or contact rates, for example—increase the prevalence of the parasite, and under many circumstances, therefore, *decrease* the fraction of cases that are horizontally acquired at equilibrium (Lipsitch et al. 1995). This, in turn, selects for decreased virulence. Thus, the simple prediction of the continuum hypothesis—that increased opportunities for horizontal transmission (relative to vertical transmission) select for increased virulence—is not correct, when the system is considered at equilibrium.

In the first part of this paper, we use a formal model of vertical and horizontal transmission to consider the effects of different transmission rates and modes on the evolution of virulence. We give analytic results for a simplified version of the model and describe simulations of more complete models that confirm the analytic results. These models show that increasing vertical transmission selects for less virulent strains. However, we also find that increases in opportunities for horizontal transmission select for strains with lower virulence, as long as any single host can be infected only by one pathogen strain.

Next, we describe further simulations in which all epidemiological properties of a strain, including the vertical transmission rate itself, can evolve. Finally, we discuss the findings of the paper in relation to the evolution of virulence in general.

Mathematical Model for the Evolution of Virulence

We consider the evolution of virulence in a system with mixed vertical and horizontal transmission using a model with uninfected hosts plus hosts infected with either of two strains. Let X be the number of uninfected hosts, and Y_1 and Y_2 be the number of hosts infected with strains 1 and 2, respectively. Uninfected hosts give birth at a maximum rate of b_x per capita per unit time, and have a lifespan of $1/u_x$. Birth is density dependent according to a logistic term, and the birth rate reaches zero when the total number of hosts reaches K. Hosts infected with strain i (for $i = 1, 2$) give birth to uninfected offspring at a rate e_i per capita per unit time, and to offspring infected with strain i at the rate b_i; this term measures vertical transmission. Infected hosts die at the rate $u_i \geq u_x$, and horizontal transmission occurs at a rate proportional to the rate of contacts between hosts c and also proportional to the densities of infected and uninfected hosts, with horizontal transmission parameter β_i. Such a model is as follows:

$$\frac{dX}{dt} = (b_x X + e_1 Y_1 + e_2 Y_2)\left(1 - \frac{X + Y_1 + Y_2}{K}\right) - u_x X - c(\beta_1 Y_1 + \beta_2 Y_2)X \quad (1)$$

$$\frac{dY_1}{dt} = b_1 Y_1\left(1 - \frac{X + Y_1 + Y_2}{K}\right) - u_1 Y_1 + c\beta_1 X Y_1 \quad (2)$$

$$\frac{dY_2}{dt} = b_2 Y_2\left(1 - \frac{X + Y_1 + Y_2}{K}\right) - u_2 Y_2 + c\beta_2 X Y_2. \quad (3)$$

The model is a generalization of the single-strain model described by Lipsitch et al. (1995); for related models, see also Busenberg and Cooke (1993) and Stewart and Levin (1977).

For this model, the invasion and persistence condition for a single strain (strain i) is

$$R_0 = H_0 + V_0 > 1,$$

where $H_0 = c\beta_i/u_i\, K(1 - u_x/b_x)$ is the number of new horizontally acquired cases created by a single infected host in a population of uninfected hosts before the primary host dies, and $V_0 = b_i u_x/(b_x u_i)$ is the number of new vertically acquired cases created by the same host introduced into the uninfected population at equilibrium. Hence, the invasion condition is that the basic reproductive ratio of the parasite must exceed unity (Lipsitch et al. 1995; Busenberg and Cooke 1993), a straightforward generalization of the condition for a purely horizontally transmitted parasite (Anderson and May 1979).

Exact Solution of a Simplified Model

Even for a single strain, this model is unwieldy, involving quadratic terms in the equations determining its equilibria, and we have been unable to derive intuitively meaningful stability conditions for the full model. The difficulties are compounded with multiple strains. However, a simplified version of the model is analytically straightforward for two strains: this simplified version assumes that vertical transmission is 100% efficient. Biologically, this means that all offspring of infected hosts are infected; mathematically, $e_i = 0$ for $i = 1, 2$. We also, without loss of generality, set the parameter $K = 1$; this corresponds to choosing an appropriate unit of space in which to measure population densities. In this section, we derive analytic results for the simplified model, and in later sections we test the robustness of the results by computer simulation of the full model and elaborations of it.

The simplified version of the model is

$$\frac{dX}{dt} = X[b_x(1 - X - Y_1 - Y_2) - u_x - c(\beta_1 Y_1 + \beta_2 Y_2)] \quad (4)$$

$$\frac{dY_1}{dt} = Y_1[b_1(1 - X - Y_1 - Y_2) - u_1 + c\beta_1 X] \quad (5)$$

$$\frac{dY_2}{dt} = Y_2[b_2(1 - X - Y_1 - Y_2) - u_2 + c\beta_2 X]. \quad (6)$$

Strain 1 by itself will reach one of two equilibria, either infecting the entire population or, if transmission is slower, infecting some hosts while others remain uninfected (Lipsitch

et al. 1995). The first equilibrium lies on a boundary of the phase space (since $X = 0$), the second in the interior.

If the first strain establishes a boundary equilibrium, the invasion condition for strain 2 is

$$b_2/u_2 > b_1/u_1. \quad (7)$$

Using the definition of virulence given above as proportionate reduction in host fitness, virulence in this special case of the model is simply $1 - V_0 = 1 - (b_i u_x)/(b_x u_i)$. Therefore, a strain can invade a boundary equilibrium if and only if it is less virulent than the resident strain. Thus, it is impossible for two strains to be capable of invading one another if they both have boundary equilibria; the one of lower virulence will always competitively exclude the other.

If, on the other hand, the first strain establishes an interior equilibrium, a second strain can invade if

$$\frac{\beta_2 u_1}{\beta_1 u_2} > 1 + \left(\frac{b_1\beta_2 - b_2\beta_1}{u_2\beta_1}\right)\left(\frac{c\beta_1 + u_x - u_1}{c\beta_1 + b_x - b_1}\right). \quad (8)$$

Note that in the absence of vertical transmission, this is simply the condition for a horizontally transmitted parasite, which can invade only when its R_0 is greater than that of the resident strain: $\beta_2/u_2 > \beta_1/u_1$. However, when vertical transmission is present, it is possible for strain 1 and strain 2 to be able to invade each other's interior equilibria. In this case, the two strains will coexist at equilibrium, along with some uninfected hosts. Such coexistence occurs, roughly speaking, when one strain has higher rates of horizontal transmission, while the other has higher rates of vertical transmission. However, no more than two strains (plus susceptibles) can coexist in this model. Effectively, vertical and horizontal transmission create two separate "niches" or ways in which pathogens can exploit hosts.

Finally, if strain 1 cannot invade strain 2, then strain 2 can invade strain 1 and will exclude it. The upshot of these considerations is that the system has exactly one locally stable equilibrium, and this equilibrium is therefore globally stable.

The mathematical details of these arguments are given in the Appendix.

Biological Interpretation of the Model

Parasite strains with basic reproductive ratios greater than one can invade and persist in a host population, just as in models with purely horizontal transmission (Anderson and May 1979). However, in contrast to purely horizontally transmitted parasites, parasites with vertical and horizontal transmission do not obey a competitive exclusion principle in which the strain with the highest basic reproductive ratio wins (Anderson and May 1979; Nowak 1991). This is because the invasion conditions depend on V_0 only (boundary equilibrium) or on a complicated combination of parameters (interior equilibrium). As a result, strains with lower R_0 can coexist with or displace strains with higher R_0.

A virulent strain with exclusively vertical transmission, which would be eliminated by selection against infected hosts in an otherwise uninfected population, can survive in the presence of a sufficiently virulent, second strain circulating in the same population by horizontal (or horizontal and vertical) transmission. The reason is that infection with the strictly vertical strain can act as a kind of vaccine, thereby increasing the fitness of its carrier. If the strictly vertical strain can invade the population, it will coexist with the horizontally transmitted strain; it will not drive the horizontal strain out of the population, because it is selected only when uninfected hosts face a greater risk from acquiring the virulent strain horizontally than from harboring the less virulent strain, acquired vertically. As we discuss below, this phenomenon may explain the persistence of endogenous retroviruses in the genomes of animal hosts (Weiss 1993).

ESS Analysis of the Relationship between Virulence and Transmission

Using this model, we can examine the effect of horizontal and vertical transmission opportunities on the evolution of pathogen virulence. Let $b_y = b_1 = b_2$ be a fixed birth rate for infected mothers, where $b_y \leq b_x$, the uninfected birth rate. Then b_y is a measure of the vertical transmission rate. Furthermore, consider a constraint function $\beta_i = \beta(u_i)$, where β is an increasing function of u_i, such that strains causing higher mortality are also more transmissible horizontally (in the absence of such a constraint, selection would favor less virulent and more transmissible strains). In this case, it can be shown that the evolutionarily stable mortality rate is a decreasing function of the vertical transmission rate (b_y). The derivation of this result is given in the Appendix. This result confirms the theoretical expectation that vertical transmission favors the evolution of less virulent strains.

A more surprising result is that increased opportunities for horizontal transmission, achieved by increasing the host-host contact rate c, also decrease the evolutionarily stable level of virulence. The reason for this result is the effect described by Lipsitch et al. (1995): as horizontal transmission increases, the fraction of the population infected increases; thus, vertical transmission actually becomes more important. Thus, at these high levels of prevalence, selection for low virulence becomes stronger.

Figure 1 shows the evolutionarily stable mortality rate for a particular constraint function, for varying levels of vertical transmission (b_y) and horizontal transmission (c). Any increase in the vertical transmission rate b_y lowers the ESS level of virulence, and whenever there is some vertical transmission, any increase in c, which increases horizontal transmission, also lowers the level of equilibrium virulence.

Simulations of More Complex Models

The conclusions of the previous section depend on a highly simplified model in order to get analytic results. In particular, they require the assumption that vertical transmission is perfect—all offspring of infected mothers are infected. In this section, we describe models that incorporate imperfect vertical transmission. These simulations show that the conclusions described earlier are robust to more realistic assumptions.

Imperfect Vertical Transmission

First, we present simulations using the full version of the model, Equations (1) through (3), in which infected hosts have a mix of infected and uninfected offspring, to test the

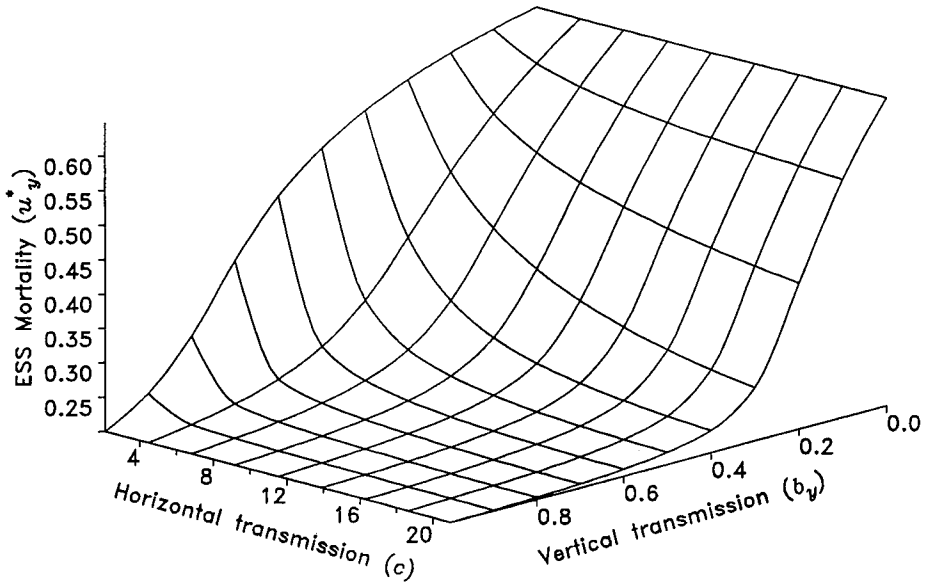

FIG. 1. The evolutionarily stable (ESS) mortality rate (u_y) for different values of c, which measures horizontal transmission opportunities, and b_y, which measures vertical transmission rates. The ESS mortality decreases with both c and b_y. We assume a constraint relating mortality and horizontal transmission: $\beta(u_y) = 3(u_y - u_x)/(u_y - u_x + 1)$. This is perhaps the simplest constraint that satisfies $\beta(u_x) = 0$, $d\beta/du_y > 0$, and $d^2\beta/du_y^2 < 0$. See Appendix for further discussion of these assumptions. Other parameters: $b_x = 1$, $u_x = 0.2$.

generality of the conclusions about the effect of vertical transmission and horizontal transmission rates on the evolution of virulence.

In these simulations we hold the host contact rate (c) and the vertical transmission rate (b_y) constant, and we also set a constant birthrate for uninfected offspring from infected mothers (e_y). We allow strains of different horizontal transmission rates and different disease-induced mortality rates to compete, spreading in a host population, with the assumption that horizontal transmission increases with disease-induced mortality, ($d\beta(u)/du > 0$), such that more horizontally transmissible strains also kill the host faster. In each simulation, we create 1000 strains with randomly chosen mortality rates and assign them horizontal transmission rates according to the same constraint used in Figure 1. We then introduce the strains, one at a time, every 1000 host generations, and keep track of the density of hosts infected with each strain until that number drops below half the starting density.

Figure 2 shows the evolutionary trajectories for two different levels of vertical transmission, $b_y = 0.1$ and $b_y = 1.0$. To reduce variation due to chance, the same strains are introduced in each simulation. However, different ones persist because the process of competitive exclusion and coexistence occurs differently as the level of vertical transmission changes. As predicted analytically, R_0 does not always increase in the course of evolution; in both cases, the average R_0 both increases and decreases (although the differences are too small to appear on the graph for $b_y = 0.1$). In the case of $b_y = 1.0$, transmission is strong enough for many strains to eliminate susceptibles altogether (reach a boundary equilibrium); as long as this is true, only less virulent strains can invade, and evolution moves towards avirulence. This can be seen by the fact that the average infected death rate approaches 0.2, which is the death rate in the absence of infection. For the lower rate of vertical transmission, R_0 remains higher in the course of evolution, reflecting the greater importance of horizontal transmission and the fact that the population is not saturated with infecteds.

Table 1 shows the evolutionary "end points" of these simulations after 5000 strains have been introduced. These data confirm the analytical results derived above. Increases in the vertical transmission rate b_y select for strains of lower mortality and lower horizontal transmission rates; hence, in these simulations, too, vertical transmission selects for lower virulence. The simulations also confirm that greater opportunities for horizontal transmission select for less deadly strains. As c increases, the evolved mortality rate declines.

Evolution of Vertical and Horizontal Transmission, and Virulence

Thus far, we have considered only the case in which the vertical transmission rates are externally specified, rather than allowing strains with different vertical transmission rate to compete. In this section, we permit total virulence, rate of vertical transmission, and infectiousness of horizontal transmission to vary as characteristics of parasite strains—each strain has its own values of b_i, the number of infected offspring from an infected host; e_i, the number of uninfected offspring from an infected host; u_i, the death rate of infected hosts, and β_i, the horizontal transmission rate. The host population parameters c and b_x are held constant in each simulation.

As before, we create strains at random and introduce them sequentially into a host population, following the number of hosts infected with each strain until it dips below a set extinction threshold, set at half the starting value.

For this simulation, we must choose more parameters than in the previous section: horizontal transmissibility (β), mortality rate (u_i), and birth rates of infected hosts (b_i and e_i). We use a constraint function that enforces a trade-off among

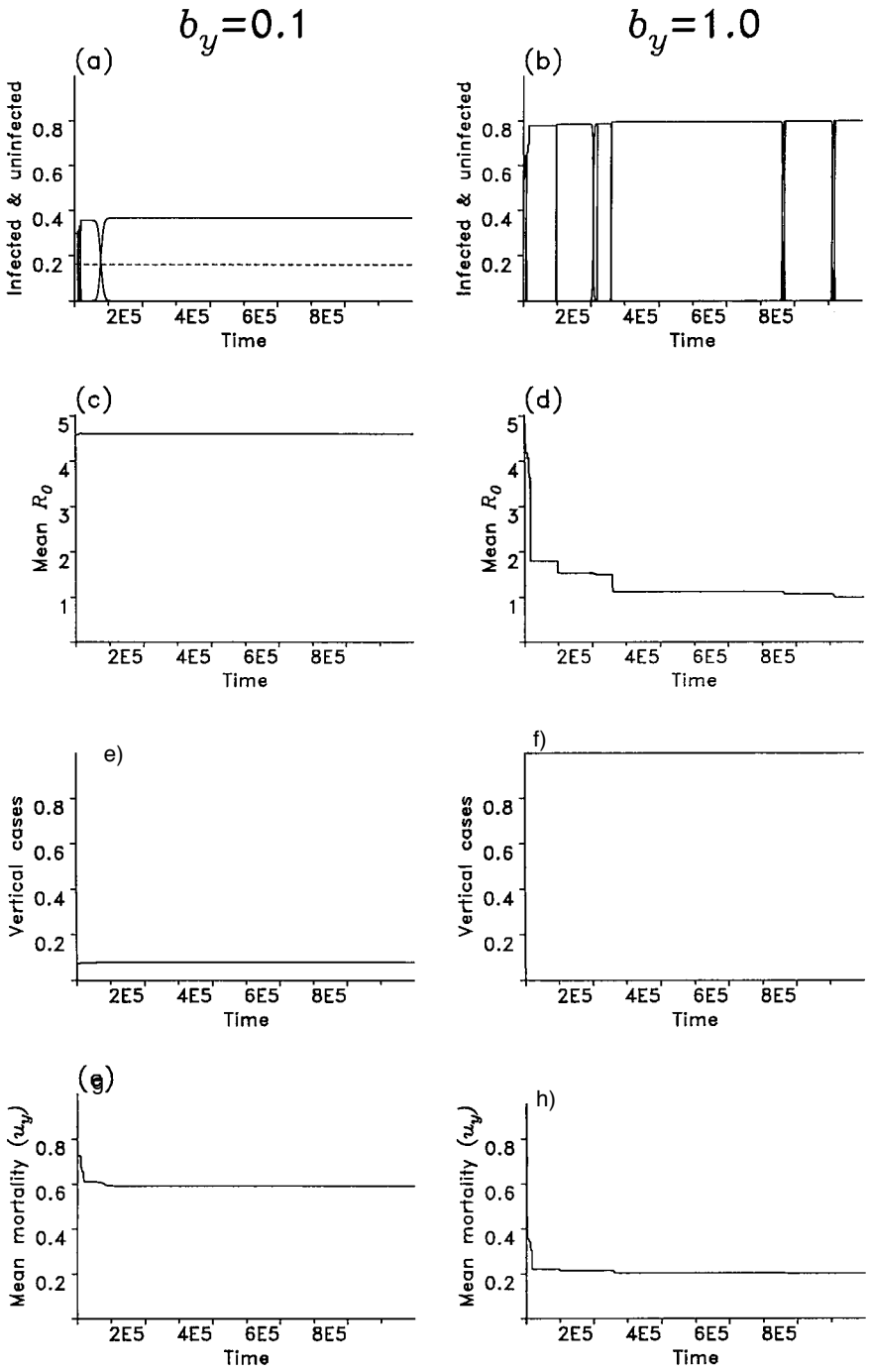

FIG. 2. Evolutionary trajectories for two values of vertical transmission, b_y = 0.1 (a,c,e,g), and b_y = 1.0, (b,d,f,h). Shown are the number of uninfected hosts (dashed line) and hosts infected with each extant strain (solid lines) (a,b); average R_0 in the population (c,d); fraction of all new cases acquired vertically (as opposed to horizontally) (e,f); and average u_y in the population (g,h). Higher vertical transmission selects for lower mortality and horizontal transmission, and lower R_0. Parameters: as above, plus c = 4.0, $e_y = b_x - b_y$ for all strains. The latter condition gives imperfect vertical transmission and ensures that there is no net fecundity loss due to infection; all virulence is due to mortality in this simulation. Simulations represent 1000 strains introduced every 1000 generations. Similar patterns were observed for up to 5000 generations (data not shown).

the properties that contribute to the fitness of the parasite: β_i, u_i, and b_i. The constraint also takes into account total virulence, and therefore e_i; hence, the four parasite parameters have three degrees of freedom, supplied by three random numbers generated for each strain.

We present two sets of simulations, each using a different constraint. In the first, it is possible for a strain to have very low virulence and a very high vertical transmission rate. This condition is favorable for the evolution of avirulence, because high levels of vertical transmission can be epidemiologically

TABLE 1. Mortality evolves to lower levels as vertical and horizontal transmission opportunities increase. Table gives average disease-induced mortality rates ($u_i - u_x$) in the population after 5000 strains have been introduced into competition. Disease-induced mortality rates are related to horizontal transmissibility by the constraint $\beta_i(u_i) = 3\,(u_i - u_x)/(u_i - u_x + 1)$. b_y measures vertical transmission from infected hosts, whereas c measures opportunities for horizontal transmission (i.e., the rate of potentially infectious contact between hosts). Other parameters: $u_x = 0.2$, $b_x = 1$, $e_i = b_x - b_y$.

b_y	$c = 1$	$c = 4$	$c = 10$
0	0.447	0.447	0.447
0.01	0.445	0.440	0.440
0.1	0.418	0.391	0.385
0.5	0.252	0.172	0.159
1.0	0.000	0.000	0.000

important only if virulence is very low; otherwise, the high likelihood of being transmitted vertically becomes insignificant because infected hosts do not have many offspring. This situation probably held for the evolution of obligate symbionts and is known for some viruses (L'Héritier 1970) and microsporidians (Ewald and Schubert 1989), among others.

In the second set of simulations, we assume that high levels of vertical transmission are possible only with high levels of virulence. This is known to be the case for some plant viruses (Power 1992); more generally, the vertical transmission rate of many organisms depends on sufficient replication within the host, which is in turn implicated in harming the host (Kaye et al. 1994; Moriya et al. 1992; Khouri et al. 1995; Mueller 1991; Biswas et al. 1989; Timian 1974).

Evolution when high vertical transmission is compatible with low virulence.—In the first simulation, parameters of each strain are set up as follows: a random number r_1 between zero and one is selected as the total virulence of the strain. Because we have defined virulence as the proportional fitness loss of an infected host, we have $r_1 = 1 - (b_i + e_i)u_x/(b_x u_i)$. A second random number, r_2, also uniformly distributed between zero and one, represents the fraction of virulence attributable to fecundity loss, according to the formula $1 - (b_i + e_i)/b_x = r_1 r_2$. Finally, a third random number, r_3, determines the fraction of the offspring of infected hosts which are themselves infected. Thus, $e_i = b_x(1 - r_3)(1 - r_1 r_2)$ and $b_i = b_x r_3(1 - r_1 r_2)$. The constraint acts as follows: each strain has a set number of infectious propagules proportional to its total virulence. The horizontal transmission rate is determined as proportional to this number of propagules minus a deduction for vertically transmitted infections: mathematically, $\beta_i = r_1 - \alpha b_i/b_x$, unless this quantity is negative, in which case we set $\beta_i = 0$. The parameter α represents the "cost" of vertical transmission, relative to horizontal transmission. Note that this constraint actually limits only horizontal transmission; it puts no direct limit on the degree of vertical transmission (which may be 100% if $r_3 = 1$).

This constraint, although arbitrary, accomplishes the goal of enforcing a trade-off among parasite fitness components. We have also performed simulations with a variety of other constraints (data not shown), and the qualitative behavior is similar to that described below.

Figure 3 shows evolutionary trajectories for two representative cases. In the two simulations, all parameters are the same, except that in Figure 3(a,c,e,g), $c = 0.5$, whereas in Figure 3(b,d,f,h), $c = 4.0$. As predicted in the previous section, increases in the intensity of horizontal transmission generated by increased host density consistently select for lower rates of horizontal transmission and total virulence. Once again, this result goes against the naive expectation that increased horizontal transmission increases the selected level of virulence. The reason is the same as in the previous section; for a given strain, the number of susceptibles falls as horizontal transmission intensifies; thus, horizontal transmission becomes less effective. As shown in Figure 3(e,f), the fraction of cases acquired vertically is higher at equilibrium when horizontal transmission opportunities are greater, as a result of this feedback. Interestingly, in these simulations, the long-term equilibrium level of susceptibles is approximately equal; however, this reflects the evolutionary success of different strains in different simulations. This was verified by checking the prevalence reached by the strain that won for $c = 0.5$, if c changes to $c = 4$. The equilibrium number of susceptibles for that strain is much lower for $c = 4$ than for $c = 0.5$; the roughly equal levels observed, therefore, are a result of the invasion of less virulent, less horizontally transmissible strains. Finally, it is interesting to note that the average R_0 in the $c = 4$ population settles down to nearly 1, despite the existence of strains with $R_0 > 3$ in Figure 3(b,d,f,h). The winning strains have very low virulence and horizontal transmission, such that $V_0 \approx 1$ and $H_0 \approx 0$. Thus, when the constraint is set up so that strains of very low virulence and high vertical transmission compete against strains of high virulence and horizontal transmission, the vertically transmitted, low-virulence strains win.

Evolution when high vertical transmission requires high virulence.—In the second set of simulations, we exclude the most successful strains in the previous simulation—those of low virulence and high vertical transmission. Mathematically, we choose strain parameters exactly as before, except that we choose r_3 from a uniform distribution over $(0,r_1)$. Thus, vertical transmission (r_3) is limited by total virulence (r_1).

Figure 4 shows the outcome of these simulations. In these cases, selection favors strains of much higher virulence and horizontal transmission. Under the constraint in these simulations, the vertical basic reproductive ratio of even the most vertically transmitted strain is only $V_0 = 0.25$. Given this limitation, it is not surprising that vertical transmission cannot play a major role in fitness. Interestingly, with this constraint, selection no longer favors high vertical transmission rates; the high values of R_0 for the selected strains show that high levels of horizontal transmission are maintained, which is possible only when vertical transmission is far from 100% efficient. This makes sense, because even if most of an infected host's offspring are infected, the high virulence required would make them poor transmitters of the disease. Once again, the same relation between horizontal transmission opportunities (contacts), equilibrium transmission modes, and virulence holds.

DISCUSSION

Using a model incorporating the epidemiology of vertical and horizontal transmission and host demography, we have

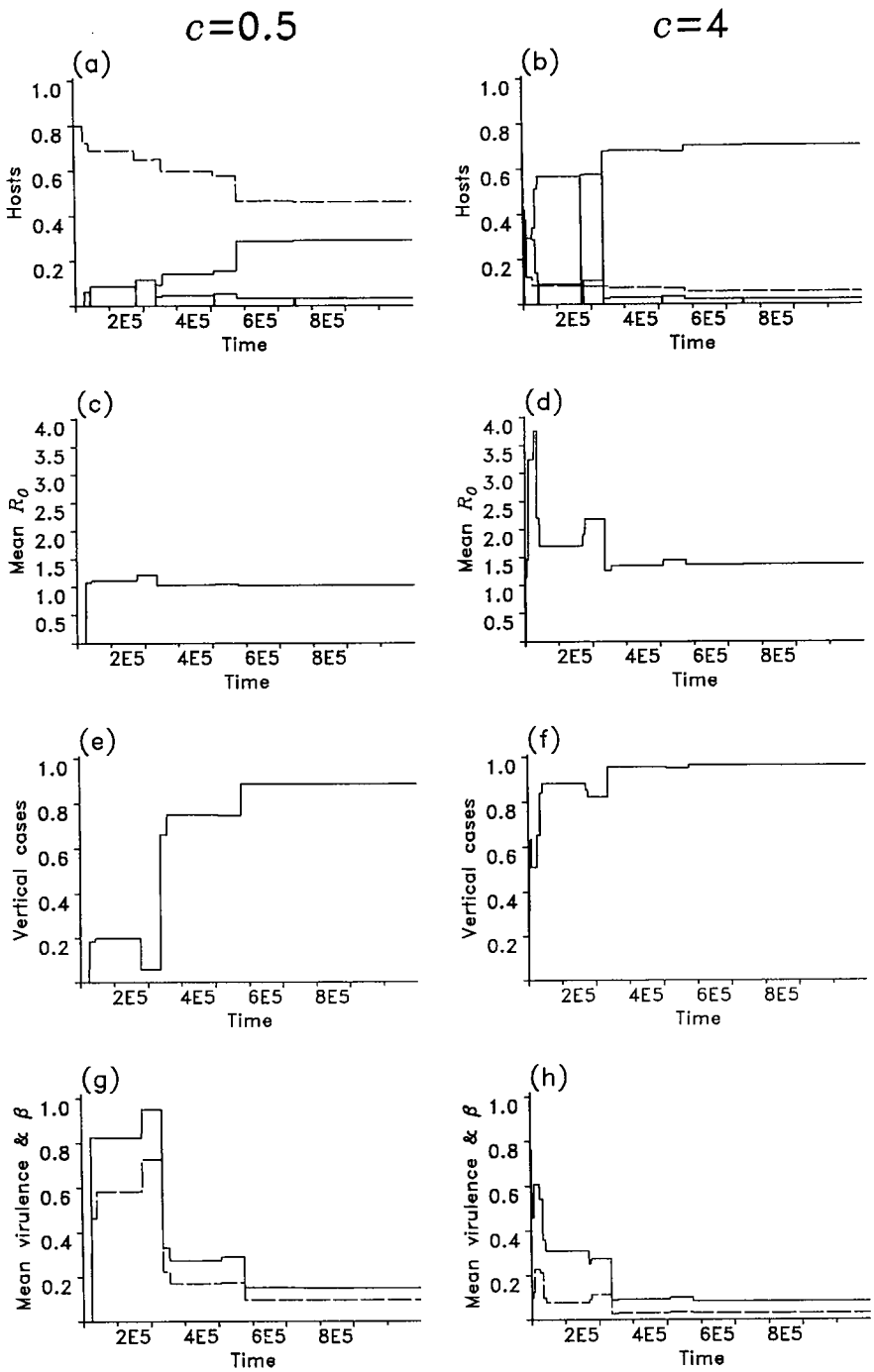

FIG. 3. Evolutionary trajectories when vertical and horizontal transmission parameters are allowed to vary, with a constraint. Here, strains of high vertical transmission and low virulence are permitted, and they are successful. Increasing horizontal transmission opportunities (c) favors less virulent strains that are good at vertical transmission. Shown are the number of uninfected hosts (dotted line) and hosts infected with each extant strain (solid lines) (a,b); average R_0 in the population (c,d); fraction of all new cases acquired vertically (E,F); and average virulence ($1 - (b_i + e_i)u_x/(b_x u_i)$; solid line) and horizontal transmissibility (β, dashed line) (g,h). Constraint described in the text; all parameters as in Figure 2, except that $c = 0.5$ (a,c,e,g) and $c = 4.0$ (b,d,f,h).

confirmed the idea that increasing levels of vertical transmission favor the evolution of lower virulence in pathogens. The model also predicts, however, that increased opportunities for horizontal transmission should lower equilibrium virulence. This effect stems from an epidemiological feedback, in which higher transmission opportunities raise equilibrium prevalence and decrease the efficacy of rapid horizontal transmission at equilibrium (Lipsitch et al. 1995). Because of such feedbacks, strains with high basic reproductive ratios may lose in competition to strains with much lower ones.

In simulations that permit the rate of vertical transmission

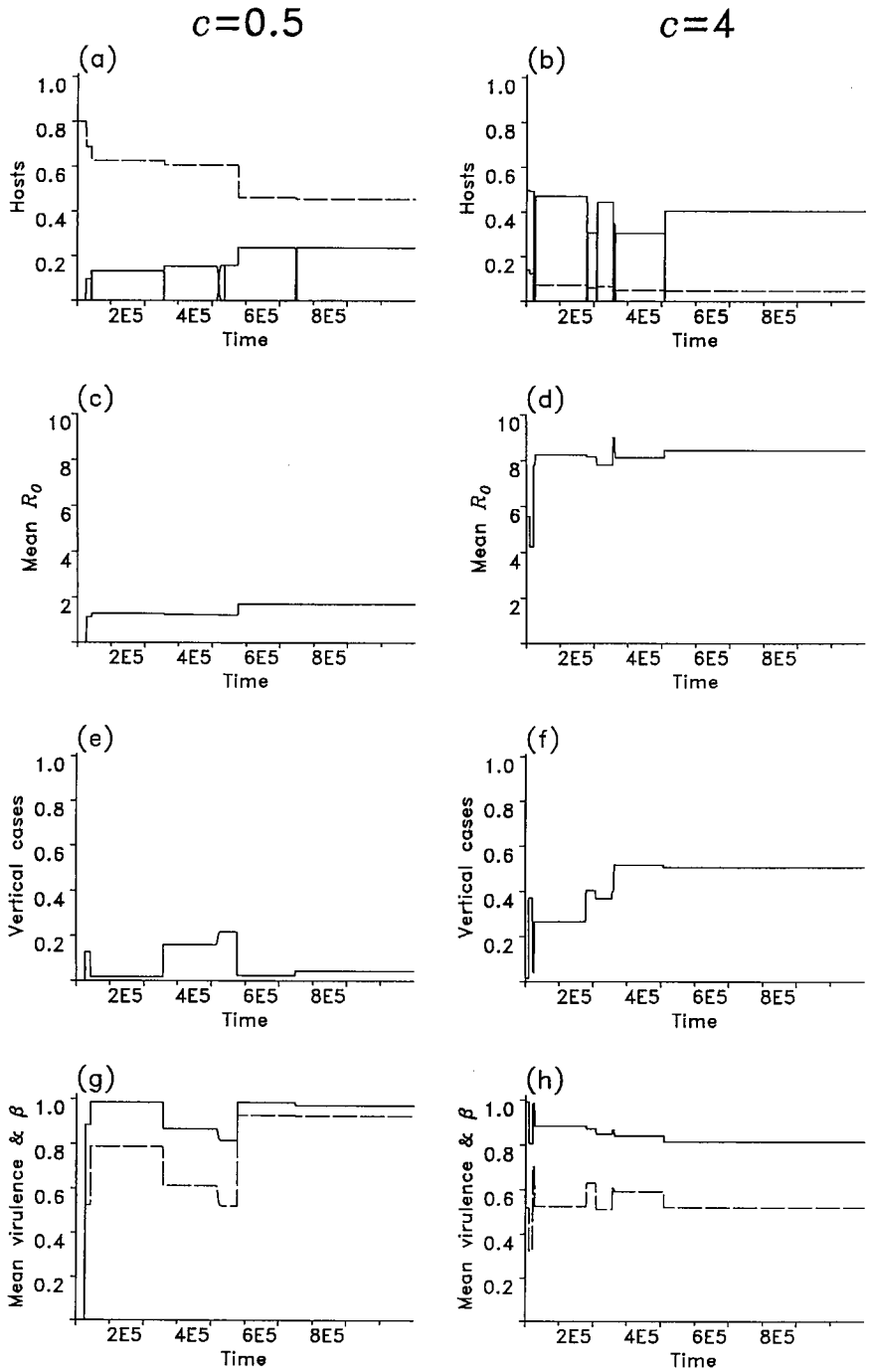

FIG. 4. Evolutionary trajectories when vertical and horizontal transmission parameters are allowed to vary, with a constraint, but vertical transmission requires high virulence. Here, vertical transmission gives little fitness benefit, and higher levels of virulence evolve than in Figure 3. Again, increased c lowers equilibrium virulence. All parameters as in Figure 4, except that here $r_3 \in (0, r_1)$ (see text).

itself to evolve, the outcome depends on the constraints assumed on vertical transmission and virulence. When strains of high vertical transmission and low virulence are permitted, these strains generally outcompete other strains. The parasites surviving after competition involving 1000 different strains have R_0s of approximately 1, with very low virulence, mostly vertical transmission, and just enough horizontal transmission to maintain them in the population. In sum, vertical transmission outcompetes horizontal transmission. When such strains are not permitted, however, vertical transmission becomes relatively unimportant evolutionarily, and strains of much higher virulence and horizontal transmission rates prevail.

These findings are consistent with the limited data available from viral infections. When vertical transmission of plant viruses is possible with extremely low virulence, such

strains predominate; when vertical transmission depends on high levels of virulence, strains of intermediate virulence predominate but must have some horizontal transmission as well to survive (Power 1992). Similarly, in HIV-1 infection, vertically infected newborns generally die before they are old enough to transmit the virus; vertical transmission is an epidemiological, and therefore evolutionary, dead end for the virus. Furthermore, vertical transmission is most efficient when the virus has reached high titres (Khouri et al. 1995), which are generally associated with disease. It thus appears unlikely that the potential for increased vertical transmission could be much of a selective force on HIV. In HTLV-I, by contrast, symptoms appear late enough in life to permit substantial host reproduction; the existence of vertical transmission may have had an effect in selecting for strains of relatively low virulence.

We are aware of only one experiment that tests the predictions of our model, and its results are in close agreement with the predictions. In an experimental study of the epidemiology of lymphocytic choriomeningitis virus (LCMV) in laboratory mice, Traub (1936, 1939) followed changes in the prevalence and pathogenicity of the virus over 4 yrs. LCMV is transmitted both vertically from infected mothers and horizontally by contact between mice. Once infected, mice remain infectious for a long period, and infection with one strain confers immunity to further infection by another strain (Traub 1938). During the course of experiments in which infected animals were placed in cages with initially uninfected ones, the prevalence of the infection reached 100%, at which point all transmission was vertical (Traub 1939). Concurrently, the virulence characteristics of the virus changed, such that infections acquired vertically, which had caused 100% morbidity and 0% to 60% mortality at the beginning of the experiment (Traub 1936), were subclinical by the end (Traub 1939). This evolutionary change is exactly in accordance with the predictions of our model: increased horizontal transmission opportunities (due to placement of susceptibles together with infectives in relatively small cages) led to increased prevalence and a shift toward vertical transmission; this was followed by a decline in the pathogenicity of the virus. Traub did not, of course prove that the epidemiological events caused the evolutionary ones, though he suspected a connection (Traub 1939). A further caveat in interpreting these results is that it is not possible to separate host adaptation from pathogen adaptation in Traub's papers; because pathogenesis in LCMV infection results from the immune response rather than from virus replication per se, there is good reason to expect host factors to be important.

Another interesting prediction of the model is that a virulent, strictly vertically transmitted strain that would ordinarily be unable to persist in the population can do so if a second, more virulent strain is already circulating by horizontal transmission. Such a phenomenon may exist in the case of endogenous retroviruses—defective fragments of retroviral genomes integrated into host genomes and transmitted like ordinary genes. Recent work has shown that the dominant *R* allele at the *Fv-4* locus in *Mus musculus domesticus* provides protection against infection by a virulent variant of the same retrovirus currently transmitted horizontally and vertically in the population (Gardner et al. 1991; Gardner 1993). Despite its apparently strong selective advantage in the presence of the virulent strain, it is possible that the endogenous retrovirus in $Fv\text{-}4^R$ is deleterious in the absence of the virulent, contagious strain; endogenous retroviruses are known to have a variety of detrimental effects on their hosts, including mutagenesis and carcinogenesis (Wilkinson et al. 1994). If so, the the $Fv\text{-}4^R$ gene is an example of a virulent, vertically transmitted agent maintaining coexistence with a more virulent, vertically and horizontally transmitted one against which it provides protection.

The results of our model raise questions about the validity of the notion that there is a continuum between vertical and horizontal transmission that corresponds to a continuum between low virulence (or even mutualism) and high virulence (Ewald 1987, 1994a). Our results agree with previous studies that vertical transmission places selective pressure on pathogens for low virulence (Fine 1975; Yamamura 1993), whereas horizontal transmission may select for strains of higher virulence (Anderson and May 1991). However, because of the epidemiological feedbacks described, changes in horizontal transmission opportunities (e.g., changes in the number of potentially infectious contacts between hosts) do not have the effects predicted by the continuum hypothesis. Furthermore, because evolutionary trajectories depend on the constraints linking transmission rates and virulence, generalizations across taxa about the relationship between transmission modes and virulence are difficult.

Applying the continuum hypothesis to a human retrovirus, Ewald (1994a,b) has argued that HTLV-I is more virulent in Jamaica than in Japan, and that the reason for this difference is that horizontal transmission is more intense in Jamaica, selecting for more virulent, more transmissible strains. A number of studies have been unable to find genetic or geographic correlates of pathogenicity in HTLV-1 (Komurian et al. 1991; Major et al. 1993; Bangham 1993; Parker 1994). Moreover, the model presented here suggests that the theoretical premise of this argument, that additional horizontal transmission selects for higher virulence in the presence of vertical transmission, is not correct.

Drawing surprising public health conclusions from these premises, Ewald (1994a, p. 201) has written that "efforts to reduce mother-to-offspring transmission [of HTLV-I] [references omitted] could backfire" by selecting for mutants of increased virulence. As discussed above, it is possible that vertical transmission has placed a selection pressure on HTLV to evolve its current rather low level of virulence. Very few carriers become ill in the early decades of their lives; therefore, the vertical chain of transmission may continue for multiple generations. However, given the lack of evidence for genetic variation in pathogenicity in HTLV-I and the speculative nature of the evolutionary scenario, Ewald's evolutionary caveat against reducing vertical transmission seems premature. In light of the rather low horizontal transmission rates in Japan (Mueller 1991), reductions in vertical transmission might indeed be sufficient to eliminate HTLV-1 by bringing its basic reproductive ratio below 1.

In comparisons across multiple parasite-host associations, one may find that vertical transmission actually increases the number of virulent parasites persisting in nature. This can occur in at least two ways. First, because vertical transmission

TABLE 2. Modes of transmission and types of symbiosis.

	Virulent	Commensal or Mutualistic
Horizontal	Many human and animal pathogens	Many lichens (Hawksworth 1988) Many mycorrhizae (Maynard Smith 1989) Symbiotic bacteria in fish and worms (McFall-Ngai 1991; Vetter 1991)
Horizontal + vertical	Microsporidians, plant viruses (cited in text)	?
Vertical	Sex-ratio distorters (Hurst 1993)	Organelles *Drosophila* sigma viruses (Fleuriet 1988; L'Héritier 1970)

does not depend on a certain density of susceptible hosts as horizontal transmission does, vertical transmission can be an essential link in the chain of transmission during periods of low host density due to seasonal factors, or can provide an important mechanism of parasite transmission between generations. This occurs in seed-transmitted plant viruses (Mandahar 1981) and in microsporidian parasites of arthropods (Bauer and Nordin 1989); it may also be important in HTLV-I (Morofuji-Hirata et al. 1993; Mueller 1991). Second, vertical transmission can substantially increase the equilibrium prevalence of a parasite over that which could be maintained by horizontal transmission alone, because vertical transmission remains effective even at high levels of prevalence (Lipsitch et al. 1995). A large number of microsporidian parasites are known with high degrees of virulence and high levels of vertical transmission: (Thompson 1958a,b; Andreadis and Hall 1979; Zchori-Fein et al. 1992; Mangin et al. 1995; Raina et al. 1995). In each of these cases, some level of horizontal transmission is known or hypothesized to maintain the parasite in the face of strong selection against infected hosts. In one other case, a microsporidian that infects the shrimp *Gammarus duebeni,* sex ratio distortion, rather than horizontal transmission, is thought to be responsible for the maintenance of the parasite (Dunn et al. 1993). It has been shown theoretically that non-Mendelian genetic elements and parasitic organisms that bias the sex ratio toward the sex that transmits them can be maintained by pure vertical transmission despite selection against infected hosts (Hurst 1993).

These considerations suggest that no single, simple theory is likely to account for the relationship between horizontal and vertical transmission and the virulence or benevolence of symbionts. As shown in Table 2, nearly all combinations of transmission modes and parasitism/commensalism/mutualism are known. Rather than dismissing some of these as aberrations, our results suggest that a complex mix of selection pressures may produce many, if not all such combinations as potential evolutionary outcomes. Further studies will be necessary to elucidate particular mechanisms that favor parasitic or mutualistic associations; however, broad generalizations may well turn out to be impossible.

Yamamura (1993) has used an ESS model to consider the effects of changing vertical transmission rates on the evolution of parasitism and mutualism. He also found that increased rates of vertical transmission select for less virulent strains, on the assumption that virulence is positively related to horizontal and vertical transmission. This study differs from his in design: we use a more conventional epidemiological model, assume overlapping generations, use a wider variety of functions relating transmission and virulence, and consider changes in host demography.

Our conclusions about the effects of horizontal transmission opportunities on virulence depend on two assumptions made in constructing the model. The first is that a host, once infected, is not susceptible to further infection by another strain. Such protection seems to exist in some natural systems (Traub 1938; Gardner et al. 1991) but full protection is lacking in others (Robertson et al. 1995). A number of studies (Levin and Pimentel 1981; Bremermann and Pickering 1983; Frank 1992, 1996; Nowak and May 1994; May and Nowak 1995; van Baalen and Sabelis 1995; Lipsitch and Nowak, ms.) have shown role that multiple infection can select for strains of increased virulence. The possibility that a different strain will displace the resident strain lowers the relative fitness of strains that persist for long periods in the host, because such strains are more exposed to the possibility of being displaced. Rapid transmission and higher virulence, therefore, become more successful strategies. In such models, increases in horizontal transmission intensities increase the selected level of virulence because multiple infection becomes more common (Nowak and May 1994; van Baalen and Sabelis 1995; Lipsitch and Nowak, ms.). Preliminary results using the models described here, modified to include superinfection, suggest that the effect of multiple infections can be much greater than the effect highlighted in this paper, such that in the presence of substantial levels of both vertical transmission and multiple infection, increased horizontal transmission can select for more virulent strains.

A second key assumption of the model is that variations in the prevalence of infection in the host population can modify the relative importance of horizontal and vertical transmission modes. An earlier study (Lipsitch et al. 1995) showed that increases in horizontal transmission opportunities (due to an increase in contagiousness or in the rate of infectious contact between hosts) are offset by the increased prevalence that results at equilibrium. In many circumstances, the net effect is to *lower* the fraction of new cases resulting from horizontal, as opposed to vertical transmission. This phenomenon is crucial to the results in this paper about horizontal transmission. In particular, it accounts for the discrepancies between our predictions about horizontal transmission and the results of Bull et al. (1991) and Herre (1993). The systems in both of these studies differed in several important respects from the assumptions of our model, notably in the fact that increases in prevalence either were not possible (Bull et al. 1991) or did not have the effect modeled here on the rates of transmission.

In summary, we have analyzed a model of a vertically and horizontally transmitted pathogen spreading in a host population. The analysis shows that up to two strains can coexist in the host population, apparently because vertical and horizontal transmission provide different "niches" for the two strains, which infect a single host population. We have derived ESS conditions for a simple version of the model and shown that as vertical or horizontal transmission opportunities increase, the ESS level of virulence declines. Simulations of the full model confirm these findings. When a strain's rates of vertical and horizontal transmission are allowed to evolve independently, the outcome depends on whether high vertical transmission rates are compatible with low virulence. If they are, the winning strains have low virulence, high vertical transmission levels, and very low horizontal transmission levels. If high vertical transmission rates require high virulence, then horizontally transmitted strains outcompete vertically transmitted ones.

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MATHEMATICAL APPENDIX

There are two possible equilibria for equations (4) and (5), with only strain 1. If

$$b_1(u_x + c\beta_1) > u_1(b_x + c\beta_1), \tag{9}$$

then all hosts are infected at equilibrium, and the number of infected hosts is $\hat{Y}_{1\text{-only}} = (1 - u_1/b_1)$. We call this the boundary equilibrium (Hofbauer and Sigmund 1988). When inequality (9) is not true, the system reaches an interior equilibrium, where susceptible and infected hosts coexist, with

$$\hat{X}_{1\text{-only}} = [b_x u_1 - b_1 u_x - c\beta_1(b_1 - u_1)]/[c\beta_1(c\beta_1 + b_x - b_1)],$$

and

$$\hat{Y}_{1\text{-only}} = [b_1 u_x - b_x u_1 + c\beta_1(b_x - u_x)]/[c\beta_1(c\beta_1 + b_x - b_1)].$$

Invasion Conditions

A second strain ("strain 2") can invade a resident strain ("strain 1") when $dY_2/dt > 0$ at the $X - Y_1$ equilibrium. This condition is inequality (8) for an interior equilibrium and inequality (7) for the boundary equilibrium. When two strains can both invade one another's equilibria, they will coexist, along with some susceptibles. Table 3 summarizes the conditions for coexistence between strains. When coexistence is possible, the equilibrium is

$$\hat{X} = \frac{b_2u_1 - b_1u_2}{c(\beta_1b_2 - \beta_2b_1)}, \tag{10}$$

$$\begin{aligned}\hat{Y}_1 = {} & [(\beta_1u_2 - \beta_2u_1)(c\beta_2 + b_x - b_2) \\ & - (\beta_1b_2 - \beta_2b_1)(c\beta_2 + u_x - u_2)] \\ & \div [c(\beta_1 - \beta_2)(\beta_1b_2 - \beta_2b_1)],\end{aligned} \tag{11}$$

$$\begin{aligned}\hat{Y}_2 = {} & [(\beta_1b_2 - \beta_2b_1)(c\beta_1 + u_x - u_1) \\ & - (\beta_1u_2 - \beta_2u_1)(c\beta_1 + b_x - b_1)] \\ & \div [c(\beta_1 - \beta_2)(\beta_1b_2 - \beta_2b_1)].\end{aligned} \tag{12}$$

If strain 2 cannot invade strain 1's equilibrium, then strain 1 can invade strain 2's equilibrium. This can be shown as follows. Assume strain 1 and 2 are both uninvadable by one another at their equilibria. Then both strain 1 and strain 2 have saturated equilibria (Hofbauer and Sigmund 1988) on the boundaries of the (X^+, Y_1^+, Y_2^+) orthant. Therefore, there must be an additional fixed point of the $X - Y_1 - Y_2$ system in the interior of the positive orthant (Hofbauer and Sigmund 1988, p. 167). Equations (10) through (12) give the coordinates of an interior fixed point. However, the stability condition for the $X - Y_1$ equilibrium makes Y_2 in equation (12) negative, whereas the stability condition for the $X - Y_2$ equilibrium makes Y_1 in equation (11) negative. Thus, the only interior fixed point of (10–12) is not in the (+, +, +) orthant. By contradiction, there cannot be two saturated equilibria on the boundary; thus, either strain 1 or strain 2 must be able to invade the other.

Finally, at most two strains can coexist at equilibrium, along with susceptibles. This can be shown by evaluating the matrix of coefficients in the three-strain plus susceptibles model. The determinant of the matrix is zero.

Evolutionarily Stable Strategy (ESS) Level of Virulence

Given some function $\beta = \beta(u_y)$ that acts as a constraint on the relationship between disease-induced mortality (u_y) and transmissibility (β), define the evolutionarily stable virulence u^* as the virulence of a strain that cannot be invaded by any other strain with $u_y \neq u^*$ (following Maynard Smith [1982]). Here we show that the ESS mortality rate declines as b_y and K increase, where we assume b_y is the same for both strains. We begin by considering only interior equilibria.

The condition for strain 2 to invade strain 1's interior equilibrium is given in inequality (8). When b_y is fixed for all strains, the condition for strain 1 to be uninvadable (the inverse condition) is

$$\beta_2u_1 - \beta_1u_2 - b_y(\beta_2 - \beta_1)\left(\frac{c\beta_1 + u_x - u_1}{c\beta_1 + b_x - b_y}\right) < 0. \tag{13}$$

If $\beta = \beta(u_y)$ is an increasing function (or is increasing for some values of u_y), then strains face a trade-off between host survival and horizontal transmission rate (if it is not increasing, then the strain with the highest β and lowest u_y will outcompete the others). We also assume that the constraint is convex; thus, $d^2\beta/du^2 < 0$. This assumption is reasonable; the probability of horizontal transmission to any individual contact is limited to one; thus, the total number of transmissions per unit time (β) is limited by the infectious contact rate of the population. No matter how high u goes, β cannot increase beyond some limit; thus, at least at the higher levels of transmission, $\beta(u_y)$ must be convex.

TABLE 3. Coexistence conditions for two strains with vertical and horizontal transmission.

Assumptions	Coexistence?
I. All parameters different	Yes, when strains 1 and 2 can both invade each other's equilibrium. Equivalently, assuming (without loss of generality) that $\beta_1 > \beta_2$: $b_1/b_2 < \beta_1/\beta_2$, $b_1/b_2 < u_1/u_2$, $\hat{Y}_1 > 0$ and $\hat{Y}_2 > 0$
II. Two parameters different	
(a) $b_1 = b_2 = b_y$	Yes, when $\frac{\beta_2 u_1}{\beta_1 u_2} > 1 + b_y \frac{\beta_2 - \beta_1}{u_2 \beta_1}\left(\frac{c\beta_1 + u_x - u_1}{c\beta_1 + b_x - b_y}\right)$ and $\frac{\beta_1 u_2}{\beta_2 u_1} > 1 + b_y \frac{\beta_1 - \beta_2}{u_1 \beta_2}\left(\frac{c\beta_2 + u_x - u_2}{c\beta_2 + b_x - b_y}\right)$
(b) $\beta_1 = \beta_2 = \beta$	No, strain 1 wins when $c\beta(b_2 - b_1 + u_1 - u_2) < b_x(u_2 - u_1) - u_x(b_2 - b_1) + b_1 u_2 - b_2 u_1$; strain 2 wins otherwise.
(c) $u_1 = u_2 = u_y$	Yes, when $\frac{\beta_2}{\beta_1} > 1 + \frac{b_1\beta_2 - b_2\beta_1}{u_y \beta_1}\left(\frac{c\beta_1 + u_x - u_y}{c\beta_1 + b_x - b_1}\right)$ and $\frac{\beta_1}{\beta_2} > 1 + \frac{b_2\beta_1 - b_1\beta_2}{u_y \beta_2}\left(\frac{c\beta_2 + u_x - u_y}{c\beta_2 + b_x - b_2}\right)$
III. One parameter different	
(a) $b_1 = b_2$, $\beta_1 = \beta_2$	No—strain 1 wins when $u_1 < u_2$; 2 wins otherwise.
(b) $b_1 = b_2$, $u_1 = u_2$	No—strain 1 wins when $\beta_1 > \beta_2$; 2 wins otherwise.
(c) $u_1 = u_2$, $\beta_1 = \beta_2$	No—strain 1 wins when $b_1 > b_2$; 2 wins otherwise.

Locally Evolutionarily Stable Strategy (local ESS)

We define a local ESS u^* as the virulence of a strain that cannot be invaded by any strain that is slightly more or less virulent—formally, u^* is a point for which there exists $\epsilon > 0$ such that for all u_i such that $|u_i - u^*| < \epsilon$, strains with parameters $(u_i, \beta(u_i))$ cannot invade. This occurs when a first order approximation of (13), evaluated at $u_1 = u_2 = u^*$, gives equality, and a second order approximation with the same conditions makes (13) true.

For clarity, rewrite (13) as

$$F < 0,$$

where

$$F := \beta_2 u_1 - \beta_1 u_2 - b_y(\beta_2 - \beta_1)\left(\frac{c\beta_1 + u_x + b_y}{c\beta_1 + bx - by}\right).$$

The first-order expression is

$$\left.\frac{dF}{du_2}\right|_{u_1 = u_2 = u^*} = 0.$$

This reduces to

$$\left\{\beta'(u_2)\left[u_1 - b_y\left(\frac{c\beta(u_1) + u_x - u_1}{c\beta(u_1) + b_x - b_y}\right)\right] - \beta(u_1)\right\}\Bigg|_{u_1 = u_2 = u^*} = 0. \tag{14}$$

The second-order condition,

$$\left.\frac{d^2F}{du_2^2}\right|_{u_2 = u_1} = 0,$$

substituting from (14), reduces to

$$\beta''(u_2)\left.\frac{\beta(u_1)}{\beta'(u_2)}\right|_{u_1 = u_2} < 0, \tag{15}$$

which is true by assumption. Thus, the local ESS u^* is given implicitly by

$$\beta'(u^*)\left[u^* - b_y\left(\frac{c\beta^* + u_x - u^*}{c\beta^* + b_x - b_y}\right)\right] - \beta^* = 0. \tag{16}$$

Local ESS is Globally Uninvadable

Next, we show that if u^* is a local ESS, then it is a global ESS; that is, it is uninvadable by any other strain. Consider a strain with parameters $\{u_2, \beta(u_2)\}$, where $u_2 = u^* + c$. The condition for strain u_2 to invade the local ESS u^* is

$$F > 0,$$

using $u_1 = u^*$. This is equivalent to

$$\int_{u^*}^{u^*+c}\left[\frac{dF}{du_2}\right] du_2 > 0.$$

Using (16), this becomes

$$\int_{u^*}^{u^*+c} \beta'(u^*)\left(\frac{\beta'(u_2)}{\beta'(u^*)} - 1\right) du_2 > 0. \tag{17}$$

When $c > 0$, the integrand is always negative, because $\beta'(u_2) < \beta'(u^*)$ for $u_2 > u^*$. Thus, (17) cannot be true. When $c < 0$, the integrand is positive, but the integral is from right to left; thus, the integral is again negative and (17) cannot be true. Hence, u^* is a global ESS.

Because it is impossible for two strains to be unable to invade one anothers' equilibria, the ESS strain can invade all other strains. Therefore, the ESS is unique.

Effect of Changes in c and b_y on the ESS

Here we show that as c and b_y increase, the ESS, if it exists, moves down (to a lower value of virulence/transmissibility). For the ESS, equation (16) holds, but the LHS of (16) is decreasing in b_y and c at the ESS; thus, any increase in these parameters makes the LHS smaller than 0. Therefore, as b_y and c increase, the old ESS becomes invadable from below and cannot be the new ESS.

Furthermore, the new ESS cannot be at a higher virulence than the old ESS. Let u^* be the ESS for a given (c, b_y): the "old" ESS. We are interested in the new ESS u^{**} when we increase c and/or b_y. Because u^* is the ESS, we know that for all $u_2 \neq u^*$,

$$\beta_2 u^* - \beta^* u_2 - b_y(\beta_2 - \beta^*)\left(\frac{c\beta^* + u_x - u^*}{c\beta^* + b_x - b_y}\right) < 0. \tag{18}$$

Consider strains of higher virulence than the ESS strain: $u_2 > u^*$. For such strains, the LHS of (18) is decreasing in b_y and c. Thus, if b_y or c goes up, inequality (18) will still be true, and strain u^* will still be uninvadable by strains of higher virulence. As noted earlier, two strains cannot be mutually unable to invade. Therefore, u^* can invade all strains $u_2 > u^*$ as b_y and c increase. Therefore, no such strain can be the new ESS; if there is one, it will be some $u^{**} < u^*$. QED.