J. theor. Biol. (1995) **174,** 427–440

The Evolution of Virulence in Sexually Transmitted HIV/AIDS

MARC LIPSITCH AND MARTIN A. NOWAK

Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, U.K.

(*Received on* 19 *May* 1994, *Accepted in revised form on* 19 *September* 1994)

A mathematical model is used to examine the effects of host population demography and transmission behavior on the evolution of virulence of a sexually transmitted pathogen such as HIV. The effect of the rate at which hosts acquire new partners is shown to depend critically on the details of the host population's growth pattern, sexual contact rate, and level of infection. At density-limited equilibrium, new partner acquisition rates have no effect on virulence. In an exponentially growing host population, higher partner acquisition rates favor the less virulent strain, as do lower rates of host population growth. In contrast, in uninfected populations, faster new partner acquisition rates encourage epidemics of the more virulent strain. Two extensions of the model—one including vertical transmission and another including within-host evolution—confirm the robustness of the predictions.

1. Introduction

A variety of recent theoretical, experimental and field studies have challenged the old wisdom that parasites evolve to become harmless to their hosts. Longevity within the host often comes at the expense of other characteristics of evolutionary value to parasites: speed of replication, transmissibility, and resistance to the host's immune response.

A number of mathematical and other models have made theoretical predictions about the evolution of parasite virulence (Anderson & May, 1979, 1981, 1982; Levin & Pimentel, 1981; Bremermann & Pickering, 1983; May & Anderson, 1983; Ewald, 1983, 1991; Bremermann & Thieme, 1989; Knolle, 1989; Nowak, 1991; Frank, 1992; Lenski & May, 1994; Antia *et al*., 1994; Nowak & May, 1994). The simplest models predict that the most successful parasite strain is that with the highest basic reproductive number R_0, defined as the number of secondary infections created by a single infection in an uninfected population at equilibrium. Bremermann & Thieme (1989) have derived a "competitive exclusion principle" to show that under fairly general assumptions, the strain with the highest R_0 will outcompete all other strains. Depending on the functional relationship between virulence and transmissibility, however, R_0 may be maximized by either high, low, or moderate levels of virulence.

Models that include further complications, such as superinfection (Levin & Pimentel, 1981; Frank, 1992; Nowak & May, 1994) and vertical transmission (Anderson & May, 1981; Stewart & Levin, 1984; Nowak, 1991; Lipsitch *et al*., 1995) also assume that evolution is driven by a tradeoff between the benefits of high transmission rates and success within a host on the one hand, and the accompanying costs of killing the host on the other. These studies, too, predict that the evolutionarily optimal level of virulence may be high, low or intermediate, depending on the parameters of the parasite and the epidemiological characteristics of the hosts. However, when complications such as vertical transmission and superinfection are added, the simple prediction that evolution will maximize R_0 no longer holds.

Several theoretical and empirical studies have concentrated on the effects of transmission characteristics on the evolution of pathogen virulence. One of the best documented theoretical predictions in this area is that parasites that are frequently transmitted

0022–5193/95/120427+14 $08.00/0

vertically (between a mother and her offspring) should evolve low virulence, since such a parasite's reproductive success depends closely on that of its host. Parasites with frequent opportunities for horizontal transmission are less constrained by the need to keep their hosts alive and healthy until reproduction and will therefore be likely to evolve higher levels of virulence. Studies have confirmed this prediction for bacteria–phage (Bull *et al*., 1991), fig-wasp–nematode (Herre, 1993) and bird–ectoparasite (Clayton & Tompkins, 1994) systems. We recently argued (Lipsitch *et al*., 1994) that repeated transmission opportunities between the same host individuals should promote lower levels of pathogen virulence.

Evolutionary studies of human immunodeficiency virus (HIV), the retrovirus that causes AIDS, are of particular interest no only because of the size and severity of the epidemic, but also because of HIV's particularly high rate of mutation (Preston *et al*., 1988, Roberts *et al*., 1988, Nowak, 1990). HIV's process of reverse transcription, by which it copies its RNA genome into DNA, is highly error-prone. Even within single infected individuals, multiple strains of the virus have been found (Hahn *et al*., 1986; Phillips *et al*., 1991; Holmes *et al*., 1992). Evolution within a single host causes the acquisition of resistance to zidovudine (AZT) and other anti-retroviral drugs (Fischl *et al*., 1987; St. Clair *et al*., 1991; Kellam *et al*., 1992; McLean & Nowak, 1992) and may be an important factor in the pathogenesis of AIDS (Nowak *et al*., 1991; Nowak & May, 1993).

The selective forces on HIV include, on the one hand, the within-host pressures of the immune system, anti-HIV drugs, and perhaps between-strain competition, and on the other hand the pressures of between-host transmission dynamics. HIV and other rapidly mutating pathogens probably evolve in response to some balance of these forces (Bonhoeffer & Nowak, 1994).

Levin and Bull (1994) have argued that the virulence of HIV, among other pathogens, is probably attributable to "short-sighted" evolution of the virus. By this they mean that pathogenesis results from the advent of genetically distinct variants of the virus, which arise during the course of infection and gain local advantages in replicating within the host. They suggest that the short-term success of these variants is not connected to any epidemiological advantage, and that the pathogenic variants may represent "evolutionary dead-ends", which will die out with the death of the present host. Levin and Bull's argument turns on a conflict—or at least a lack of positive correlation—between the immediate evolutionary pressures on the virus and the long-term success of the virus in spreading between hosts. There is good reason to think that Levin and Bull's explanation of HIV's virulence is at least partially correct. The substantial genotypic and phenotypic variation observed within a single infection, and the rapid evolution of drug resistance in treated individuals, demonstrates HIV's ability to evolve rapidly and effectively during an infection, and in response to changes within a host.

Despite the potential for evolution within the host and the likely differences between the selection pressures operating on this level and on the epidemiological level, recent evidence suggests that there is genetic variation in HIV for virulence, measured inversely as the time from infection to AIDS, and that this variation is passed from host to host (Ashton *et al*., 1994). Further evidence for genetically determined transmission and virulence characteristics comes from the comparison between HIV-1 and HIV-2. HIV-1 is more virulent and also apparently more transmissible than HIV-2 (DeCock *et al*., 1993), and these characteristics are preserved from infection to infection. Such conserved virulence properties are unsurprising, for two reasons. First, there are a number of phenotypic properties that are not easily changed by intra-host (short-sighted) evolution. The HIV genome has certain "hypervariable" regions, concentrated on the envelope protein gene, in which mutations arise and are fixed rapidly, but is also has relatively conserved regions (Hahn *et al*., 1986, Li *et al*., 1988), which have important functional constraints and change only on a very slow time scale (Eigen & Nieselt-Struwe, 1990). Second, even if virulence is a characteristic of a particular variant or set of variants of HIV that arise during the course of infection, it is nonetheless also a characteristic of HIV itself, since pathogenesis is a regular feature of HIV infection. Thus, characteristics of HIV that permit such variants to arise in the time they do (the high mutation rate, the organization of the genome, the range of cell tropisms, etc.) can accurately be described as virulent phenotypes, although these are not the proximate cause of pathogenesis. These more conserved features of HIV are still in need of explanation, particularly if they inevitably permit the rise of variants that bring the infection to an end by killing the host.

Thus, in this paper, we look for an adaptive, epidemiological explanation of HIV virulence, while keeping in mind that this will provide only part of the story. Specifically, we assume that higher host mortality is correlated with a higher probability of transmission per contact between an infected and a susceptible partner. Under this assumption, we derive conditions under which more and less virulent forms of the virus are likely to succeed at the epidemiological level.

The evidence for this connection between transmissibility and pathogenicity in the literature on HIV is equivocal but there is some evidence that both transmissibility (European Collaborative Study, 1992) and the development of symptoms (Gupta *et al*., 1993) are correlated with virus load. In cases where this tradeoff does not exist, evolution will clearly favor longer lifespans (decreased pathogenicity) and increased transmissibility, unless there is some third, confounding factor that trades off with one of these two properties. This tradeoff thus presents important questions about the evolution of pathogenicity.

Despite a common assumption that more virulent strains are also more transmissible, theoretical workers have come to different conclusions about the effects of host behaviour—and particularly the effect of the rate at which infected hosts acquire new sexual partners—on the evolution of virulence. A direct corollary of Bremermann and Thieme's (1989) "competitive exclusion principle" is that the hosts' rate of new partner acquisition has no effect on the long-term success of pathogens. Ewald (1991) has argued, on the contrary, that increased "sexual contact diversity" should increase the evolutionary pressure for pathogens to be virulent. Although Ewald's terms are not precisely defined, he has argued (Ewald, 1992) that HIV has become more virulent because it has been introduced into uninfected and more promiscuous populations.

This paper attempts to give a systematic treatment of the effects of the rate of new partner acquisition in the host population on the evolution of virulence of a deadly, sexually transmitted pathogen such as HIV. By making explicit assumptions about the nature of host population growth and pathogen transmission dynamics, we show the conditions under which increased rates of new partner acquisition by hosts will (i) increase pathogen virulence, (ii) decrease pathogen virulence, or (iii) have no effect on pathogen virulence. By splitting the population and transmission dynamics into three time scales, we show that each of these scenarios is possible under certain demographic and epidemiological assumptions.

Section 2 outlines a simple model of the epidemiological dynamics of infection by two competing strains of different virulence and transmissibility. The long-term behavior of a system in which host population growth is limited, and the densities of infected individuals have reached equilibrium, are described in Section 3. Section 4 describes the medium-term behaviour, in which population growth is exponential, and frequencies, but not densities, of infecteds have reached equilibrium. Section 5 describes the short-term behavior of the system, in which pathogens invade an uninfected population of hosts. Each of these time scales shows a different effect of host partner acquisition rates on virulence. The final section discusses the implications of the findings here as they relate to the evolution of virulence of HIV and other pathogens.

2. Model

We present a model to show how the rates at which hosts change partners and reproduce affect the evolution of virulence of a sexually transmitted pathogen. The model, which closely follows those of May & Anderson (1987) and May *et al*. (1988), is constructed to be as simple as possible while remaining tied particularly to HIV. We look at the competition between two different strains: strain 1, which we will call the "more virulent" strain, is more pathogenic to its host and more transmissible during the course of a single partnership. Strain 2, which we will call the "less virulent" strain for its ability to remain longer in the host, is less pathogenic but also less transmissible. The rate of new partner acquisition is assumed to be independent of total population density or size; hence, the "force of infection" (λ) as defined below is proportional to the frequency of infecteds in the population, not (as with airborne diseases, for example) to their absolute number or density (Getz & Pickering, 1983). We assume that the rate of new partner acquisition is the same for hosts infected with both strains of the virus.

The spread of the two strains can be modeled with the following system of differential equations:

$$\dot{X}=\frac{\mathrm{d}X}{\mathrm{d}t}=f(N)-X(\lambda_1+\lambda_2+\mu) \tag{1}$$

$$\dot{Y}_1=\frac{\mathrm{d}Y}{\mathrm{d}t}=\lambda_1 X-v_1 Y_1-\mu Y_1 \tag{2}$$

$$\dot{Y}_2=\frac{\mathrm{d}Y_2}{\mathrm{d}t}=\lambda_2 X-v_2 Y_2-\mu Y_2. \tag{3}$$

X is the number of susceptibles in the population; Y_1 and Y_2 represent the number of hosts infected with strains 1 and 2, respectively. $N=X+Y_1+Y_2$ is the total population size. New susceptibles are born to all members of the population at a rate given by a function $f(N)$. λ_i is the so-called "force of infection" for strain i, which measures the rate at which a susceptible host will acquire an infection with strain i. We assume that

$$\lambda_i=\frac{c\beta_i Y_i}{N},$$

where c is the rate of new partner acquisition, and β_i is the probability that a host infected with strain i will infect a single, susceptible partner. The chance that a particular susceptible partner is infected with strain i is assumed to be equal to the fraction of hosts in the

population who are infected with strain i: Y_i/N. Hence, λ_i measures the probability per unit time that a susceptible host will acquire an infection with strain i.

v_1 and v_2 are the disease-induced host death rates from strains 1 and 2, respectively. Finally, as we have designated strain 1 as the more virulent, more transmissible strain, and strain 2 as the less virulent, less transmissible strain, we have $\beta_1 > \beta_2$ and $v_1 > v_2$. We assume that superinfection does not occur: once infected with either strain, a host stays infected with that strain until death.

Substituting the definition of λ_i above, we can rewrite the system as follows:

$$\dot{X} = \mathrm{d}X/\mathrm{d}t = f(N) - X\left[\frac{c(\beta_1 Y_1 + \beta_2 Y_2)}{N} + \mu\right] \quad (4)$$

$$\dot{Y} = \mathrm{d}Y_1/\mathrm{d}t = Y_1\left(\frac{c\beta_1}{N}X - v_1 - \mu\right) \quad (5)$$

$$\dot{Y}_2 = \mathrm{d}Y_2/\mathrm{d}t = Y_2\left(\frac{c\beta_2}{N}X - v_2 - \mu\right). \quad (6)$$

3. Evolution in a Population with a Constant Supply of New Susceptibles: Density Equilibria

No population of hosts can grow exponentially for an indefinite period. Bremermann & Thieme (1989) suggest that density-dependent limits on the number of susceptibles should be modeled by a decreasing per-capita birth rate that falls below the per-capita death rate when the population gets sufficiently large. The simplest such scenario assumes that the per-capita birth rate varies in inverse proportion to the population size; this amounts to a constant total birth rate of new susceptibles. A constant supply of new susceptibles would also be justified if we assumed that HIV is spreading in a population whose new members arrive mostly by immigration, rather than by birth to members of the population; such an assumption might fit a population of homosexuals. In the model given in the previous section, this assumption would be reflected by setting $f(N) = \Lambda$, a constant.

If the new susceptibles term is a constant, or if there is some other, more complex form of density-dependent regulation of birthrates in the population, then one of the pathogen strains will drive the other to extinction, and the winning strain will be the strain with the greatest basic reproductive number R_0 (Anderson & May, 1982). For strain i,

$$R_i = \frac{c\beta_i}{v_i + \mu}$$

(we drop the subscript 0 to avoid double indices). Changing the rate of new partner acquisition c scales R_i equally for all strains; thus, the same strain should be expected to "win", regardless of the value of c. The simplest mathematical model suggests, then, that in the long run, partner acquisition rates should have no effect on the evolution of pathogen virulence.

4. Parasite Evolution in Exponentially Growing Host Populations: Prevalence Equilibria

If the host population has not yet reached density-dependent limits, its growth can be approximated as exponential: in the model, we set the birth term $f(N) = kN$, where k is a constant per-capita birth rate. Now, the birth, death, and infection terms in this system are all strictly exponential; as a result, the system has only two states: exponential growth and exponential decay. Hence, equilibria are in general impossible in the $X - Y_1 - Y_2$ system. However, the system can be rewritten in terms of N, y_1, and y_2, where N is the total population size and y_1 and y_2 are the fraction of the population infected with strains 1 and 2, respectively: $y_1 = Y_1/N$ and $y_2 = Y_2/N$. The equations are:

$$\dot{N} = \mathrm{d}N/\mathrm{d}t = N(k - \mu - v_1 y_1 - v_2 y_2) \quad (7)$$

$$\dot{y}_1 = \mathrm{d}y_1/\mathrm{d}t = y_1[r_1 - k - r_1 y_1 + (v_2 - c\beta_1)y_2] \quad (8)$$

$$\dot{y}_2 = \mathrm{d}y_2/\mathrm{d}t = y_2[r_2 - k - r_2 y_2 + (v_1 - c\beta_2)y_1], \quad (9)$$

where $r_i = c\beta_i - v_i$ for $i = 1, 2$. The $y_1 - y_2$ subsystem is a Lotka–Volterra equation and has four equilibria:

Coexistence:

$$\left(\hat{y}_1 = \frac{kc(\beta_1 - \beta_2) - r_2(v_1 - v_2)}{c(\beta_1 - \beta_2)(v_1 - v_2)},\right.$$

$$\left.\hat{y}_2 = \frac{r_1(v_1 - v_2) - kc(\beta_1 - \beta_2)}{c(\beta_1 - \beta_2)(v_1 - v_2)}\right);$$

More-virulent only:

$$(\hat{y}_1 = 1 - k/r_1,\ \hat{y}_2 = 0);$$

Less-virulent only:

$$(\hat{y}_1 = 0,\ \hat{y}_2 = 1 - k/r_2);$$

Zero:

$$(\hat{y}_1 = \hat{y}_2 = 0).$$

Since infection and killing are both proportional to the frequency of infecteds, the total number of hosts in the system, N, either increases or decreases exponentially when the frequencies y_1 and y_2 have reached equilibrium. We can easily calculate these conditions

and show that the host population grows at equilibrium when:

$$k > r_1(\mu + v_1)/(c\beta_1) \text{(more-virulent only)}$$

$$\mu < \frac{v_1\beta_2 - v_2\beta_1}{(\beta_1 - \beta_2)} \text{ (coexistence)}$$

$$k > r_2(\mu + v_2)/(c\beta_2) \text{(less-virulent only).}$$

Note that the host reproduction rate k drops out of the condition for the coexistence equilibrium.

Assuming both strains are viable in an uninfected population (i.e. have a basic reproductive number larger than one, or equivalently, $r_i > 0$), exactly one of these equilibria is globally stable for each combination of parameters. Thus the necessary and sufficient conditions for convergence to each equilibrium are:

Zero:

$$k > \max\{r_1, r_2\}$$

More-virulent only:

$$r_1 > k > Ar_1$$

Coexistence:

$$Ar_1 > k > Ar_2$$

Less-virulent only:

$$k < \min\{r_2, Ar_2\},$$

where

$$A := \frac{v_1 - v_2}{c(\beta_1 - \beta_2)}.$$

The effect of changing k on the equilibrium reached can be seen in Fig. 1, where k is shown on the x-axis; these conditions are shown for a given c by a horizontal slice through Fig. 1. These conditions are mutually exclusive and cover all cases; their derivation is a special case of the proof given in the Appendix (setting $\delta_1 = \delta_2 = 0$).

This analysis shows that when the contact rate c is held constant, very high k allows host population growth to outrun the epidemic, yielding a zero asymptotic prevalence of both strains. This parameter range, however, is likely to be unrealistic for most host–pathogen systems. Very low host population growth favors the less virulent strain. Raising

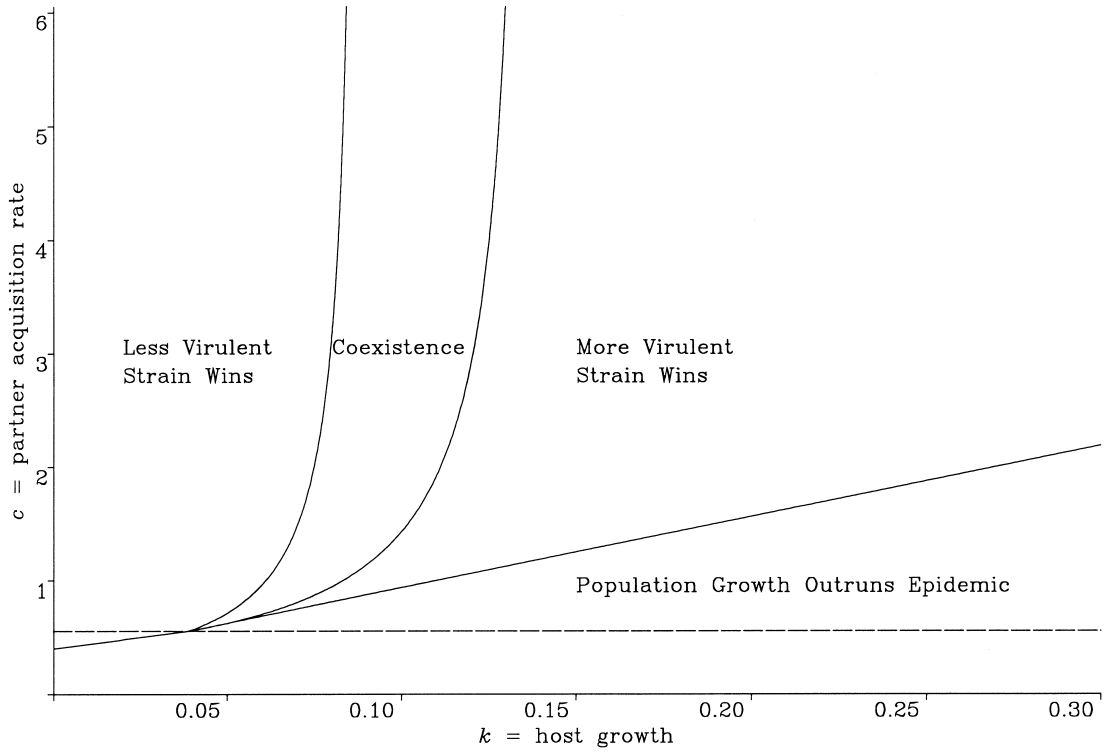

FIG. 1. In an exponentially growing population at frequency equilibrium, higher host partner acquisition rates and slower population growth rates favor the less virulent strain. Frequency equilibria reached for different values of host partner acquisition rate c (vertical axis) and population growth rate k (horizontal axis) are shown for competition between two strains, more-virulent and less-virulent. The horizontal, dashed line shows the boundary $c > (v_1 - v_2)/(\beta_1 - \beta_2)$; above this line, the virulent strain is at an initial advantage in an uninfected population, as discussed in section 5. Parameters: more-virulent strain: $v_1 = 0.1$/yr, $\beta_1 = 0.25$/partner; less-virulent strain: $v_2 = 0.05$/yr, $\beta_2 = 0.16$/partner.

population growth rates increasingly favors the more virulent strain, moving from the less-virulent only equilibrium, to coexistence, to the more-virulent only equilibrium.

From the above analysis we can rewrite the conditions for the existence and stability of each equilibrium, in terms of parameter regions for growth rate k and the new partner acquisition rate c. If host growth is sufficiently fast, then only the more virulent strain can persist an an equilibrium frequency, because the constant supply of new susceptibles magnifies its transmission advantage over its competitor. At lower levels of host growth, coexistence and competitive exclusion by the less virulent strain become possible.

Mathematically, for any given combination of parameters, exactly one equilibrium is globally stable. The host population growth rate k falls into three parameter regions, defined as follows:

Fast growth:

$$k > \frac{\beta_1(v_1 - v_2)}{\beta_1 - \beta_2}$$

Moderate growth:

$$\frac{\beta_1(v_1 - v_2)}{\beta_1 - \beta_2} > k > \frac{\beta_2(v_1 - v_2)}{\beta_1 - \beta_2}$$

Slow growth:

$$k < \frac{\beta_2(v_1 - v_2)}{\beta_1 - \beta_2}.$$

If we define the following quantities:

$$S_1 = \frac{v_1(v_1 - v_2)}{\beta_1(v_1 - v_2) - k(\beta_1 - \beta_2)}$$

and

$$S_2 = \frac{v_2(v_1 - v_2)}{\beta_2(v_1 - v_2) - k(\beta_1 - \beta_2)},$$

then the conditions listed above for convergence to equilibria can be rewritten as follows:

For fast host growth:

More-virulent only:

$$c > \frac{k + v_1}{\beta_1}$$

Zero:

$$c < \frac{k + v_1}{\beta_1}$$

For moderate host growth:

Coexistence:

$$c > S_1$$

More-virulent only:

$$\frac{k + v_1}{\beta_1} < c < S_1$$

Zero:

$$c < \frac{k + v_1}{\beta_1}$$

For slow host growth:

Less-virulent only:

$$c > S_2 \quad \text{and} \quad c > \frac{k + v_2}{\beta_2}$$

Coexistence:

$$S_1 < c < S_2$$

More-virulent only:

$$\frac{k + v_1}{\beta_1} < c < S_1$$

Zero:

$$c < \frac{k + v_1}{\beta_1} \quad \text{and} \quad c < \frac{k + v_2}{\beta_2}.$$

Figure 1 shows the parameter regions for c and k that produce each equilibrium outcome, given realistic parameters for the virulence and transmissibility of two strains. There are two important features of this diagram. First, for any given level of host population growth, increasing rates of partner acquisition (c) favor the less virulent strain. Second, for a given rate of new partner acquisition, increases in the host population growth rate favor the more virulent strain. Figure 2 plots the frequencies of the two strains under three assumptions for c and k, corresponding to the three possible equilibria.

5. Short Term: Dynamics of a Newly Infected Population

5.1. EFFECT OF CONTACT RATE ON VIRULENCE

The dynamics of an infection newly introduced into an uninfected population are different in a number of ways from those near equilibrium. One of these is in the effect of new partner acquisition rates on the competition between pathogen strains of different virulence. So far, we have shown conditions under which faster acquisition of new partners (i) has no effect on the evolution of virulence (Section 3) and (ii) favors the less virulent strain (Section 4). Here, we show that in a non-equilibrium system, increased partner acquisition rates can help the more virulent strain.

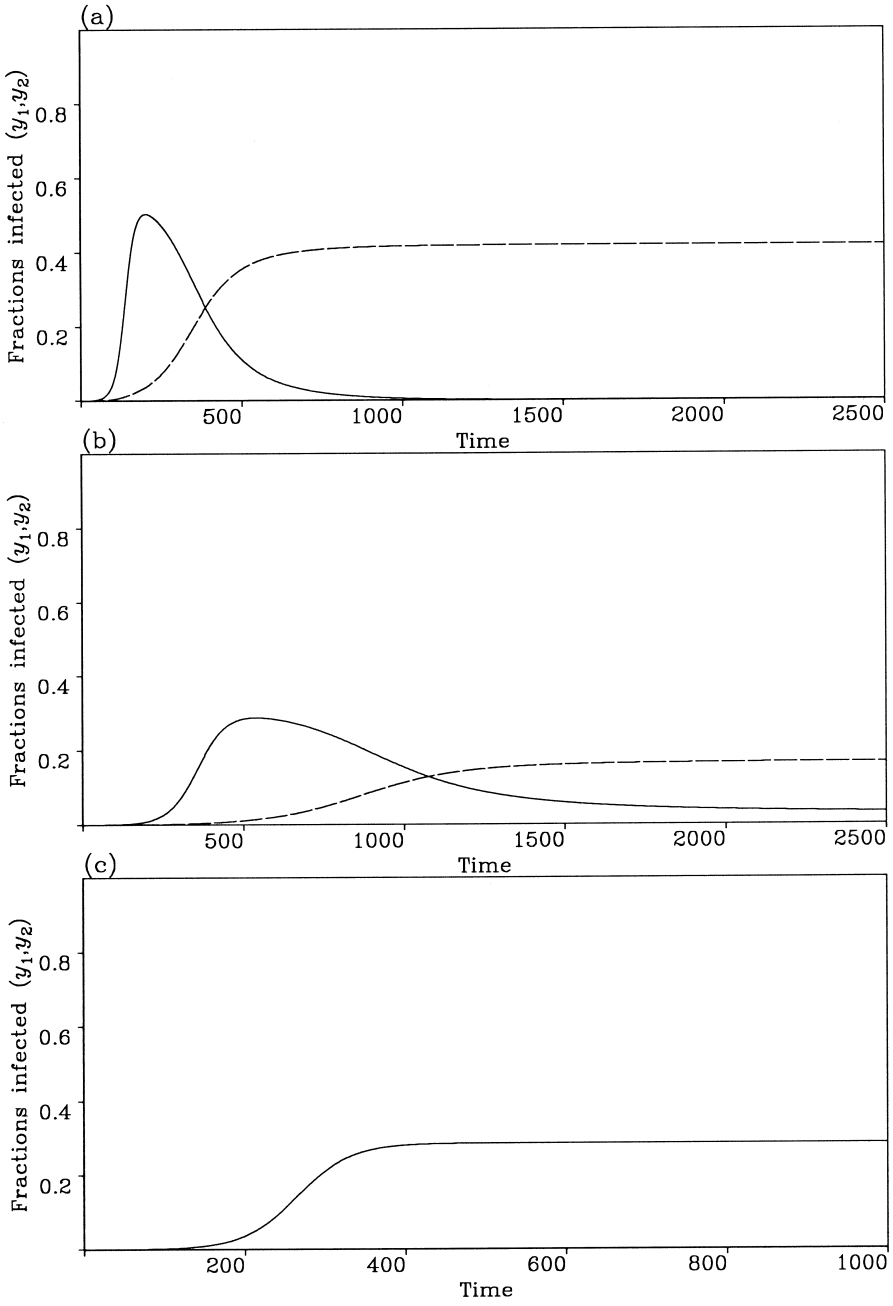

FIG. 2. Three possible dynamical patterns in competition between two strains in an exponentially growing host population. Shown are frequencies of infecteds carrying each strain over time. (a) After an epidemic of the more-virulent strain, the less-virulent strain establishes an endemic frequency equilibrium ($k=0.05$, $c=0.85$). (b) Again, the more-virulent strain has an epidemic increase, but an equilibrium coexistence is established between the two strains ($k=0.05$, $c=0.69$). (c) The less-virulent strain is unable to invade, as the more-virulent strain spreads quickly and maintains an endemic equilibrium ($k=0.075$, $c=0.82$). Other parameters are as in Fig. 1.

The more contagious, more virulent strain does best when potential new hosts are plentiful, since its transmission advantage is fully realized. Accordingly, it suffers as hosts become rarer and new infections fail to keep pace with host deaths. In ecological terms, the more virulent strain is "*r*-selected" (MacArthur & Wilson 1967), i.e. fast at colonizing "empty" or uninfected populations. The less virulent strain will infect the population more slowly initially, but may, under certain conditions, nonetheless do better at high rates of infection, where susceptibles are scarce and the ability to keep the current host alive is more important than the ability to transmit infections rapidly. Mathematically, we can see this effect by considering

the ratio between hosts infected with strains 1 and 2. Define the ratio

$$\rho := \frac{Y_1}{Y_2}\left(=\frac{y_1}{y_2}\right)$$

and the total fraction of the population infected

$$y := \frac{Y_1 + Y_2}{N} = y_1 + y_2.$$

Then rate of change of the ratio ρ:

$$\dot{\rho} = \frac{\mathrm{d}\rho}{\mathrm{d}t} = \rho[c(1-y)(\beta_1 - \beta_2) - (v_1 - v_2)]. \qquad (10)$$

From eqn (10), it is clear that the more virulent strain does better when c is high and susceptibles are plentiful (y is low).

Specifically, the relative frequency of the more virulent strain 1 increases ($\dot{\rho} > 0$) when

$$c > c_{\mathrm{crit}},$$

where

$$c_{\mathrm{crit}} := \frac{v_1 - v_2}{(1-y)(\beta_1 - \beta_2)}.$$

As we noted earlier, changing c has no effect on the relative R_0 of two strains; however, it does have an effect on the initial success of the two strains spreading in a relatively uninfected population. Thus it is possible for an epidemic of a more virulent strain to occur in a newly infected population, despite the fact that this more virulent strain will eventually be excluded.

From these observations we can draw two conclusions

(i) introduction of a pathogen into an uninfected population can favor the evolution of more virulent strains, even if such strains were not viable in an equilibrium population from which they came;

(ii) host populations in which the rate of new partner acquisition is higher can sustain an initial epidemic of the more virulent strain up to a higher level of infection.

We now look more specifically at the effect of new partner acquisition rate on epidemics.

5.2. EFFECT OF CONTACT RATE ON EPIDEMIC SIZE AND DURATION

The behavior of the system away from eqilibrium depends on the magnitude of A, which decreases as the rate c increases. When $A > 1$, the less virulent strain 2 will outcompete the more virulent strain 1, because $\dot{\rho}$ is negative at all levels of infection prevalence y. If, however, $A < 1$, then the more virulent strain will outcompete the less virulent one while $y < 1 - A$ but will lose when $y > 1 - A$. In this case, the more virulent strain will increase faster than the less virulent one at first, thanks to the surplus of susceptible hosts; according to the conditions in the previous section, the more virulent strain will either maintain its advantage [Fig. 2(c)] or lose it [Fig. 2(a)].

The growth rate per capita per unit time of strain i [from eqns (5) and (6)] is

$$\frac{\dot{Y}_i}{Y_i} = c\beta_i(1-y) - v_i - \mu.$$

Consider the situation in which $\dot{Y}_1/Y_1 \gg \dot{Y}_2/Y_2$, i.e. $c \gg v_1 - v_2/\beta_1 - \beta_2$. Then we can ignore the growth of strain 2 and approximate eqn (8) as

$$\dot{y}_1 \approx y_1[c\beta_1 - v_1 - k - (c\beta_1 - v_1)y_1],$$

which is a logistic growth equation, so y_1 asymptotically approaches its maximum of $y_{1\max} = 1 - k/(c\beta_1 - v_1)$.

Two analytical features are important: The first can be seen by solving the logistic equation and finding the time t^* required for the more virulent strain to reach nearly its maximum prevalence $-y_{1\mathrm{nearmax}} = (1-\epsilon)y_{1\max,}$. Using equation (2.22) of May *et al*. (1988), this is:

$$t^* = \frac{1}{c\beta_1 - v_1 - k}\left[\ln\frac{1-\epsilon}{\epsilon} + \ln\frac{1}{y_1(0)} + \ln\left(1 - y_1(0) - \frac{k}{c\beta_1 - v_1}\right)\right]. \qquad (11)$$

For sufficiently small values of ϵ and $y_1(0)$, this value decreases with c: by speeding the spread of the more virulent strain, faster rates of new partner acquisition make the epidemic reach its peak faster. Note that in Fig. 2(a)–(c), the more virulent strain increases initially, regardelss of its eventual fate. This occurs because $c > (v_1 - v_2)/(\beta_1 - \beta_2)$; in Fig. 1 these parameter combinations lie above the horizontal, dashed line.

Second, increasing c increases the more virulent strain's maximum prevalence $y_{1\max}$; the faster transmission that results from high rates of new partner acquisition permits more severe epidemics.

6. Extension: Vertical Transmission/Reduced Fertility of Infecteds

6.1. GENERAL MODEL

Many features of the model considered in Section 4 arise from the fact that the host population maintains exponential growth (or decline) even as the epidemic

spreads. In this section we test the sensitivity of these conclusions by considering the possibility that infecteds do not have offspring (new susceptibles) as fast as uninfecteds. This effect may arise from a combination of factors: infected people may choose not to have children, and vertically transmitted AIDS may kill the children of infecteds before they reach the sexually active population.

We assume that hosts infected with strain i have $1-\delta_i$ offspring who survive to enter the sexually active, susceptible population for every one born to an uninfected host. We further assume that $\delta_1 \geqslant \delta_2$: the more virulent strain has at least as great a chance of transmission to offspring or effect on fertility as the less virulent one. This modifies eqns (4), (5), and (6) to read:

$$\dot{X} = \frac{dX}{dt} = k(N - \delta_1 Y_1 - \delta_2 Y_2) - X\left[\frac{c(\beta_1 Y_1 + \beta_2 Y_2)}{N} + \mu\right] \quad (12)$$

$$\dot{Y}_1 = \frac{dY_1}{dt} = Y_1\left(\frac{c\beta_1}{N} X - v_1 - \mu\right) \quad (13)$$

$$\dot{Y}_2 = \frac{dY_2}{dt} = Y_2\left(\frac{c\beta_2}{N} X - v_2 - \mu\right), \quad (14)$$

which is equivalent to

$$\dot{N} = \frac{dN}{dt} = N[k - \mu - (v_1 + \delta_1 k)y_1 - (v_2 + \delta_2 k)y_2] \quad (15)$$

$$\dot{y}_1 = \frac{dy_1}{dt} = y_1[r_1 - k + (\delta_1 k - r_1)y_1 + (\delta_2 k + v_2 - c\beta_1)y_2] \quad (16)$$

$$\dot{y}_2 = \frac{dy_2}{dt} = y_2[r_2 - k + (\delta_2 k - r_2)y_2 + (\delta_1 k + v_1 - c\beta_2)y_1]. \quad (17)$$

As before, there are four equilibria:

Coexistence:

$$\left(\hat{y}_1 = \frac{kc(\beta_1 - \beta_2) - r_2(v_1 - v_2) - k\delta_2(r_1 - r_2)}{c(\beta_1 - \beta_2)(v_1 - v_2 + k(\delta_1 - \delta_2))}, \quad \hat{y}_2 = \frac{r_1(v_1 - v_2) - kc(\beta_1 - \beta_2) + k\delta_1(r_1 - r_2)}{c(\beta_1 - \beta_2)(v_1 - v_2 + k(\delta_1 - \delta_2))}\right)$$

More-virulent only:

$$\left(\hat{y}_1 = \frac{k - r_1}{k\delta_1 - r_1}, \hat{y}_2 = 0\right)$$

Less-virulent only:

$$\left(\hat{y}_1 = 0, \hat{y}_2 = \frac{k - r_2}{k\delta_2 - r_2}\right)$$

Zero:

$$(\hat{y}_1 = 0, \hat{y}_2 = 0).$$

Any effect that lowers the number of new susceptibles will favor the less virulent strain in competition with the more virulent strain. Thus, it is clear that increases in the δ_i's will favor the less virulent strain in competition. However, the more virulent strain may attain a higher equilibrium presence when δ_1 increases, since the rate of dilution by new susceptibles is lower.

In the Appendix, we derive the existence and stability conditions for each of the four equilibria, as shown in Table 1. When $\delta_1 = \delta_2 = 0$, these conditions reduce to the conditions of Section 4, above.

As shown in Fig. 3, the effect of vertical transmission (where this amounts to partial sterilization of infecteds,

TABLE 1
Stability conditions for frequency equilibria

Equilibrium	Stability conditions
More-virulent only	$k < r_1$
	$k > r_1(v_1 - v_2)/[\delta_1(r_2 - r_1) + c(\beta_1 - \beta_2)]$
Coexistence	$\frac{r_1(v_1 - v_2)}{\delta_1(r_2 - r_1) + c(\beta_1 - \beta_2)} > k > \frac{r_2(v_1 - v_2)}{\delta_2(r_2 - r_1) + c(\beta_1 - \beta_2)}$
Less-virulent only	$k < r_2$
	$k < r_2(v_1 - v_2)/[\delta_2(r_2 - r_1) + c(\beta_1 - \beta_2)]$
Zero	$k > \max\{r_1, r_2\}$

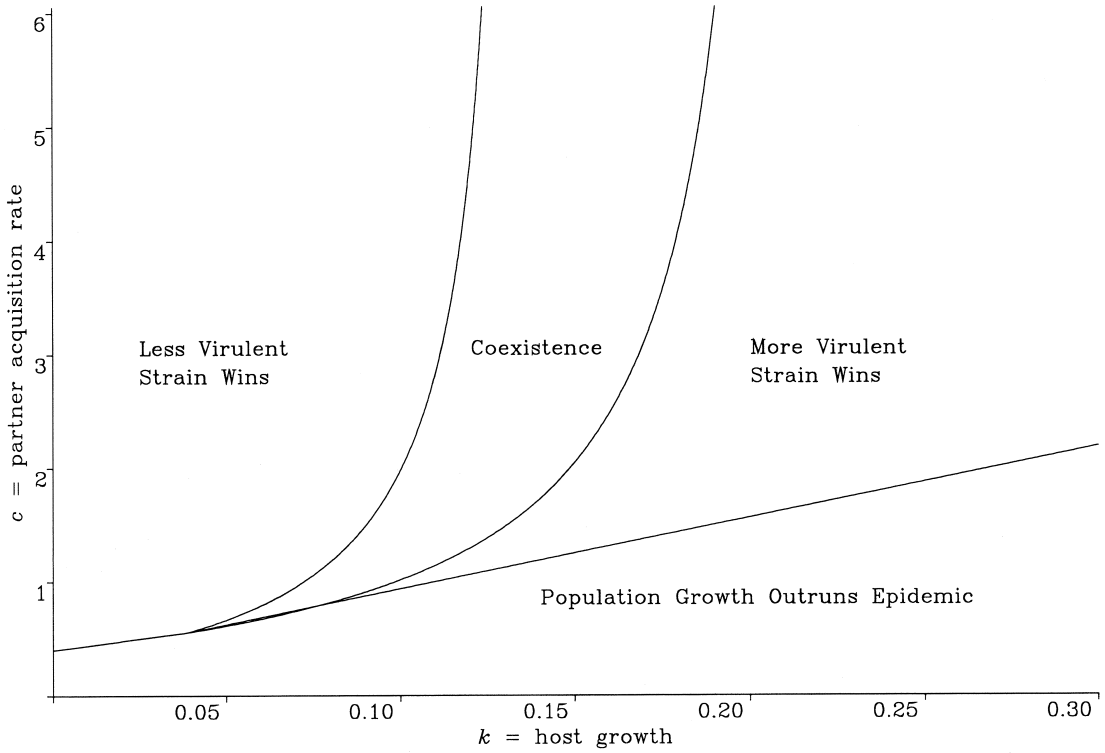

FIG. 3. Vertical transmission favors the less-virulent strain. Shown is the phase plane for frequency equilibria expected when vertical transmission is included. Parameters are as in Fig. 1, except that infecteds contribute only 65% as many offspring as uninfecteds (due to reduced fertility or to AIDS death of offspring before they reach the sexually active class); in the terms of the model, $\delta_1 = \delta_2 = 0.35$. The structure of the phase plane is similar to Fig. 1, except that the less-virulent only and coexistence equilibria have gained at the expense of the more-virulent only equilibrium.

since their offspring do not reach the sexually active class) is to enlarge the parameter region for which the less virulent strain predominates. This form of vertical transmission limits the number of new susceptibles, and this shifts the balance toward the less virulent, less transmissible strain.

In the limit of full vertical transmission ($\delta_1 = \delta_2 = 1$), the more virulent strain dies out, regardless of other parameters, because of scarcity of susceptibles. This can be seen from the conditions for the stability of the more-virulent only equilbriium in Table 1, which become self-contradictory when $\delta_1 = 1$.

7. Extension: Within-host Strain Takeover

As noted in the introduction, HIV shows substantial variability during the course of a single infection, and a fuller explanation of the evolution of HIV must take this phenomenon into account. In this section we make the simplest possible modification of the model to allow for evolution within the host, and we show that while the behaviour of the system changes, the directional effects of the host birth rate (k) and new partner acquisition rate (c) remain the same.

Here we assume that at some rate q, the more virulent strain (strain 1) takes over in individuals infected with strain 2. Since strain 1 is assumed to replicate faster within the individual (thus creating both high viral loads and harming the patient more quickly), it is reasonable to think that it would have a competitive advantage within a patient, and, if produced by mutation, would outcompete the original strain.

This modification changes eqns (5) and (6) to the following:

$$\dot{Y}_1 = \mathrm{d}Y_1/\mathrm{d}t = Y_1\left(\frac{c\beta_1}{N}X - v_1 - \mu\right) + qY_2 \qquad (18)$$

$$\dot{Y}_2 = \mathrm{d}Y_2/\mathrm{d}t = Y_2\left(\frac{c\beta_2}{N}X - v_2 - \mu - q\right) \qquad (19)$$

7.1. DENSITY EQUILIBRIA

In the density-regulated case, with a constant supply of new susceptibles, there are two nontrivial equilibria:

strain 1 alone, and coexistence of strains 1 and 2. Strain 2 cannot exist alone, since strain 2 infections give rise to strain 1 infections at the rate q. Assuming that either strain is viable alone in the population ($R_0>1$ for both strains, where $R_2=c\beta_2/(v_2+\mu+q)$ and R_1 is as above), coexistence occurs whenever

$$q<q_c=\frac{\beta_2}{\beta_1}(v_1+\mu)-(v_2+\mu).$$

The condition $q<q_c$ also specifies that strain 2 can invade an equilibrium population consisting of only susceptibles and strain 1 infecteds. Thus, there are the following possibilities:

(i) If $R_2>1$ and $q<q_c$, then there is coexistence between strains 1 and 2.
(ii) If $R_2>1$ and $q>q_c$ then strain 1 replaces strain 2.
(iii) If $R_1<1$ and $R_2<1$ then both strains die out.

As before, the critical condition that determines the outcome of competition, $q>q_c$, is independent of k and c for density-regulated equilibrium.

7.2. FREQUENCY EQUILIBRIA

In the case of a per-capita supply of new susceptibles, eqns (8) and (9) are modified as follows:

$$\dot{y}_1=\mathrm{d}y_1/\mathrm{d}t=y_1[r_1-k-r_1y_1+(v_2-c\beta_1)y_2]+qy_2. \tag{20}$$

$$\dot{y}_2=\mathrm{d}y_2/\mathrm{d}t=y_2[r_2-k-q-r_2y_2+(v_1-c\beta_2)y_1]. \tag{21}$$

Again, strain 2 cannot exist alone; the two possible nonzero equilibria are strain 1 alone and coexistence of the strains. Assuming that both strains have $R_0>1$, the equilibrium $(1-k/r_1, 0)$ can be invaded by strain 2 when

$$q<q_c=v_1-v_2-kc(\beta_1-\beta_2)/(c\beta_1-v_1). \tag{22}$$

As in the simpler case without mutation, increasing c and decreasing k favor the less virulent strain 2 by raising the value of q_c, which is the maximum takeover rate at which strain 2 can persist. Figure 4 shows a sample phase plane for $q>0$.

8. Discussion

A general mathematical model of the dynamics of two strains of a sexually transmitted pathogen in

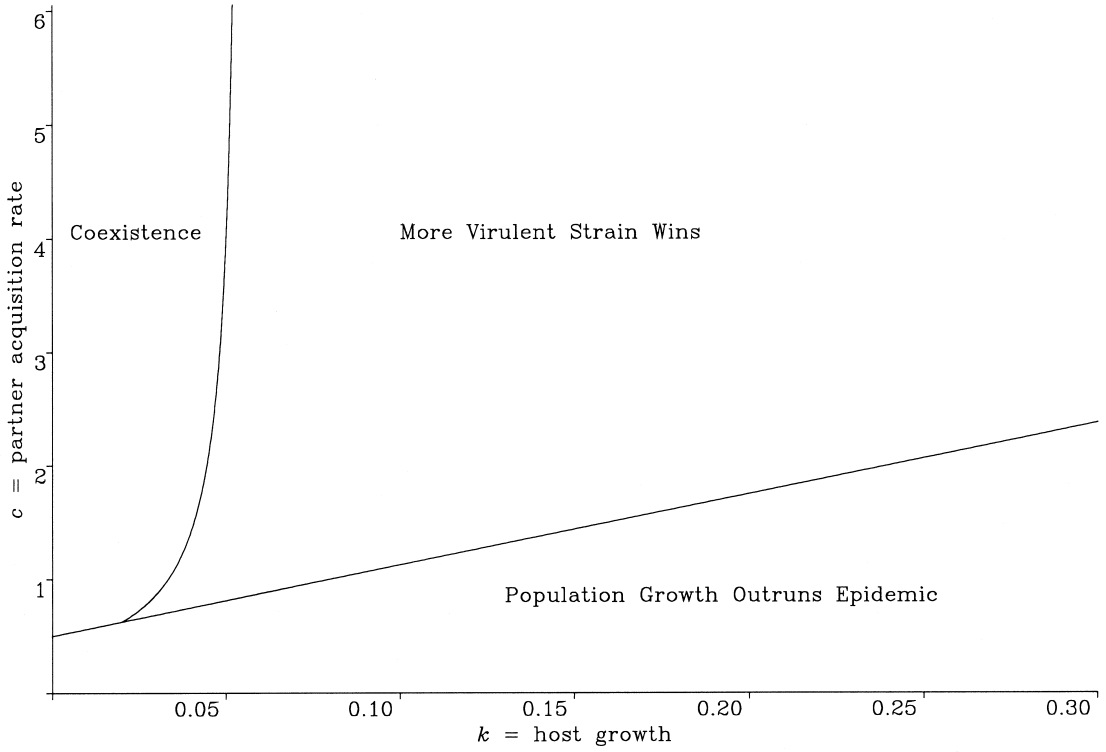

FIG. 4. The c–k phase plane when there is within-host evolution and conversion to the more virulent strain. Parameters as in Fig. 1, except that hosts infected with the less virulent strain convert to the more virulent one at rate $q=0.03$/yr.

a human population indicates that the effects of host sexual behavior on the evolution of pathogen virulence are complex and dependent on the demographic details of the population. In a newly infected population, where more virulent, more transmissible strains have an advantage due to the availability of susceptible hosts, faster acquisition of new partners by the hosts magnifies that advantage. In an exponentially growing population in which the frequency of individuals infected with each strain has reached equilibrium, the opposite effect occurs: faster acquisition of new partners favors less virulent, less transmissible strains. This occurs because by increasing the transmission rate, faster acquisition of new partners limits the supply of new susceptibles, which in turn limits the advantage of the more transmissible strain. Finally, in a density-limited population at equilibrium, new partner acquisition rates are irrelevant to the success of different strains, because here the most successful strain is the one with the highest R_0, which scales directly with c for all strains; hence relative magnitudes of R_0 are unaffected by c.

Two extensions to the model, to include vertical transmission and within-host evolution, confirm the robustness of our conclusions. Although restricting the range of outcomes, mutation does not change the qualitative conclusions of the model: in density-limited populations, c has no effect on the outcome of competition between strains, while in exponentially growing ones, increasing c favors the less virulent strain. Likewise, vertical transmission at moderate rates leaves the qualitative behavior of the model the same, and as in the original model, increasing c and decreasing k favor the less virulent strain.

The short-term conclusions about the evolution of virulence in newly infected populations hold regardless of whether transmission is sexual or airborne, and regardless of the population growth function. In the short term (epidemic phase), populations with more diverse contacts (greater c) will certainly favor the evolution of more virulent strains. But as the pathogen becomes endemic, the evolutionary gains from faster transmission will be lost and may have perverse effects, as this model shows. In the very long term, when the host population is limited to an equilibrium level, host partner change rates should become irrelevant to the evolution of virulence.

Ewald (1991) has argued that greater "sexual contact diversity" is likely to increase the virulence of sexually transmitted pathogens. Since his terms are unclearly defined, it is difficult to know exactly what predictions he would make. These simple models suggest that his predictions may be correct in the short-run; when invading uninfected populations, more virulent pathogens do better when transmission is faster, as it is when hosts acquire partners more rapidly. The short-run evolution of the pathogen may be of the greatest public-health interest, as it corresponds to an epidemic. However, for the more general problem of understanding the evolutionary relationship between virulence and host population characteristics, our model suggests that the intuitively plausible effects emphasized by Ewald (1991, 1992) are in fact not predicted. Depending on the nature of host population growth, faster acquisition of new partners may either favor less virulent strains or have no effect at all on competition between strains.

Our model also shows that even if Ewald (1992) is correct that HIV became more pathogenic when it was introduced into western, urban populations, it is unneccessary to invoke differences in rates of sexual partner acquisition to explain an increase in virulence. As shown in Figs 2(a) and 2(b), more virulent, transmissible strains can spread rapidly and reach high levels of prevalence after introduction into uninfected populations, even if in the long run they will be outcompeted by less virulent strains. This corresponds to the finding by Lenski & May (1994), (see also Bull, 1994 and Levin *et al*., 1994), that the optimal virulence for a parasite peaks at the beginning of the epidemic, when infected hosts are rare, then declines as the infection reaches a higher level of prevalence. It may also account for the observed phenomenon that diseases newly introduced to a population are often more deadly in that population than they were in their original host population: the plethora of new susceptibles may give the more virulent strain a temporary advantage.

A unique feature of this model is that it shows that under certain conditions, different strains can coexist, temporarily at least, in the competition for hosts. Previous models of the evolution of parasites show that the strain that wins in competition for hosts is the strain with the greatest basic reproductive number R_0. When R_0 determines the outcome of competition, host contact and growth rates are irrelevant, since neither can change the relative magnitudes of R_0. In a growing population (such as many contemporary human populations), both of these factors are important because the pathogen's evolutionary success is decoupled from R_0; a more virulent strain with a higher R_0 can lose if host growth is sufficiently low and new partner acquisition sufficiently fast, while a less virulent strain with a higher R_0 can lose if host growth is sufficiently high and new partner acquisition sufficiently slow.

The decoupling of evolutionary success from R_0, and hence the features observed here—the possibility of

coexistence, and the negative relationship between contact rates and virulence at equilibrium—are dependent on two assumptions: (i) epidemiological dynamics with sexual transmission (mathematically, the N in the denominator of the expression for λ_i); and (ii) constant per-capita host population growth (kN, rather than some constant term, in the expression for dN/dt).

If either sexual transmission or constant per capita host growth, or both, are missing, then at equilibrium the strain with the higher R_0 will be fixed in the population, and it can be replaced only by a strain with still higher R_0. In other words, the frequency equilibria described in Section 4 are possible only when population growth is exponential and transmission is frequency-, not density-dependent. Hence, for non-sexually transmitted diseases or in populations whose growth is a constant immigration each year, host contact and growth rates have no effect on the evolution of virulence in the long run.

The authors thank Robert May, Sebastian Bonhoeffer, Richard Lenski, Bruce Levin, Jim Bull, Joel Cohen, and E. Allen Herre for helpful discussions. M.L. is a Rhodes Scholar. M.A.N. is a Wellcome Trust Senior Research Fellow and E. P. Abraham Junior Research Fellow of Keble College, Oxford.

REFERENCES

Anderson, R. M. & May, R. M. (1979). Population biology of infectious diseases: Part 1. *Nature* **280,** 361–367.

Anderson, R. M. & May, R. M. (1981). The population dynamics of microparasites and their invertebrate hosts. *Phil. Trans. R. Soc. Lond.* **B291,** 451–524.

Anderson, R. M. & May, R. M. (1982). Coevolution of hosts and parasites. *Parasitology* **85,** 411–426.

Antia, R., Levin, B. & May, R. M. (1994). Within-host population dynamics and the evolution and maintenance of microparasite virulence. *Am. Nat.* **144,** 457–472.

Ashton, L. J., Learmont, J., Luo, K., Wylie, B., Stewart, G. & Kaldor, J. M. (1994). HIV infection in recipients of blood products from donors with known duration of infection. *The Lancet* **344,** 718–720.

Bonhoeffer, S. & Nowak, M. A. (1994). Intra-host vs. inter-host selection: viral strategies of immune function impairment. *Proc. Natn. Acad. Sci. U.S.A.* **91,** 8062–8066.

Bremermann, H. J. & Pickering, J. (1983). A game-thoretical model of parasite virulence. *J. theor. Biol.* **100,** 411–426.

Bremermann, H. J. & Thieme, H. R. (1989). A competitive exclusion principle for pathogen virulence. *J. math. Biol.* **27,** 179–90.

Bull, J. J. (1995). Virulence. *Evolution*, **48,** 1423–1437.

Bull, J. J., Molineux, I. J., & Rice, W. R. (1991). Selection of benevolence in a host-parasite system. *Evolution* **45,** 875–82.

Clayton, D. H. & Tompkins, D. M. (1994). Ectoparasite virulence is linked to mode of transmission. *Proc. R. Soc. Lond.* **B,** 256, 211–217.

DeCock, K. M., Adjorlolo, G., Ekpini, E., Sibailly, T., Kouadio, J., Maran, M., Brattegaard, K., Vetter, K. M., Doorly, R. & Gayle, H. D. (1993). Epidemiology and transmission of HIV-2: why there is no HIV-2 pandemic. *JAMA* **270,** 2083–2086.

Eigen, M. & Nieselt-Struwe, K. (1990). how old is the immunodeficiency virus? *AIDS* **4**(suppl 1), S85–S93.

European Collaborative Study (1992). Risk factors for mother-to-child transmission of HIV-1. *Lancet* **339,** 1007–1012.

Ewald, P. W. (1983). Host-parasite relations, vectors, and the evolution of disease severity. *Ann. Rev. Ecol. Syst.* **14,** 465–485.

Ewald, P. W. (1991). Transmission modes and the evolution of virulence: with special reference to cholera, influenza, and AIDS. *Human Nature* **2,** 1–30.

Ewald, P. W. (1992). Evolution of HIV in Africa. *Science* **257,** 10.

Fischl, M. A., Richman, D. D., Grieco, M. H., Gottlieb, M. S. Volberding, P. A., Caskin, O. L., Leedon, J. M., Groopman, J. E., Mildvan, D., Schooley, R. T., Jackson, G. G., Durack, D. T. & King, D. (1987). The efficiency of AZT in treatment of patients with AIDS and AIDS-related complex—a double-blind, placebo-controlled trial. *N. Eng. J. med.* **317,** 185–191.

Frank, S. A. (1992). A kin selection model for the evolution of virulence. *Proc. R. Soc. Lond.* **B250,** 195–197.

Getz, W. M. & Pickering, J. (1983). Epidemic models: thresholds and population regulation. *Am. Nat.* **121,** 892–8.

Gupta, P., Kingsley, L., Armstrong, J., Ding, M., Cottrill, M. & Rinaldo, C. (1993). Enhanced expression of human immunodeficiency virus type 1 correlates with development of AIDS. *Virology* **196,** 586–595.

Hahn, B. H., Shaw, G. M., Taylor, M. E., Refield, R. R., Markham, P. D., Salahuddin, S. Z., Wong-Staal, F., Gallo, R. C., Parks, E. S. & Parks, W. P. (1986). Genetic variation in HTLV-III/LAV over time in patients with AIDS or at risk for AIDS. *Science* **232,** 1548–1553.

Herre, E. A. (1993). Population structure and the evolution of virulence in nematode parasites of fig wasps. *Science* **259,** 1442–5.

Holmes, E. C., Zhang, L. Q., Simmonds, P., Ludlam, C. A. & Leigh Brown, A. J. (1992) Convergent and divergent sequence evolution in the surface envelope glycoprotein of HIV-1 within a single infected patient. *Proc. natn. Acad. Sci. U.S.A.* **89,** 4835–4839.

Kellam, P., Boucher, C. & Larder, B. A. (1992). Fifth mutation in HIV-1 reverse transcriptase contributes to the development of high-level resistant zidovudine. *Proc. natn. Acad. Sci. U.S.A.* **89,** 1934–1938.

Knolle, H. (1989). Host density and the evolution of parasite virulence. *J. theor. Biol.* **136,** 199–207.

Lenski, R. & May, R. M. (1995). The evolution of virulence: a reconciliation between two conflicting hypotheses. *J. theor. Biol.* **169,** 253–265.

Levin, B. R. & Bull, J. J. (1994). Short-sighted evolution and the virulence of pathogenic microorganisms. *Trends Microbiol.* **2,** 76–81.

Levin, B. R., Bull, J. J. & Stewart, F. M. (1995). The intrinsic rate of increase of HIV/AIDS: epidemiological and evolutionary implications. *Math. Biosci.*, in press.

Levin, S. & Pimentel, D. (1981). Selection of intermediate rates of increase in parasite-host systems. *Am. Nat.* **117,** 308–315.

Li, W-H., Taimura, M. & Sharp, P. M. (1988). Rates and dates of divergence between AIDS virus nucleotide sequences. *Molec. Biol. Evol.* **5,** 313–330.

Lipsitch, M., Herre, E. A. & Nowak, M. A. (1995). Host population structure and the evolution of parasite virulence: a law of diminishing returns. *Evolution*, in press.

Lipsitch, M., Nowak, M. A., Ebert, D. & May, R. M. (1995). The population dynamics of vertically and horizontally transmitted infections. *Proc. R. Soc. Lond.* **B,** in press.

MacArthur, Robert H. & Wilson, E. O. (1967). *The Theory of Island Biogeography*. Princeton, NJ: Princeton University Press.

May, R. M. & Anderson, R. M. (1983). Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. R. Soc. Lond* **B219,** 281–313.

May, R. M. & Anderson, R. M. (1987). Transmission dynamics of HIV infection. *Nature* **326,** 137–142.

May, R. M. Anderson, R. M. & McLean, A. R. (1988). Possible demographic consequences of HIV/AIDS epidemics: I. Assuming HIV infection always leads to AIDS. *Math. Biosci.* **90,** 475–505.

McLean, A. R. & Nowak, M. A. (1992). Competition between

zidovudine-sensitive and zidovudine-resistant strains of HIV. *AIDS* **6,** 71–79.
Nowak, M. A. (1990). HIV mutation rate [letter]. *Nature* **347,** 522.
Nowak, M. A. (1991). The evolution of viruses. Competition between horizontal and vertical transmission of mobile genes. *J. theor. Biol.* **150,** 339–347.
Nowak, M. A. & May R. M. (1993). AIDS pathogenesis: mathematical models of HIV and SIV infections. *AIDS* **7**(suppl. 1), S3–S18.
Nowak, M. A. & May, R. M. (1994). Superinfection and the evolution of virulence. *Proc. R. Soc. Lond.* **B255,** 81–89.
Nowak, M. A., Anderson, R. M., McLean, A. R., Wolfs, T. F. W., Goudsmit, J. & May, R. M. (1991). Antigenic diversity thresholds and the development of AIDS. *Science* **254,** 963–9.
Phillips, R. E., Rowland-Jones, S., Nixon, D. F., Gotch, F. M., Edwards, J. P., Ogunlesi, A. O., Elvin, J. G., Rothbard, J. A., Bangham, C. R. M., Rizza, C. R. & McMichael, A. J. (1991). Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition. *Nature* **354,** 453–9.
Preston, B. D., Poiesz, B. J. & Loeb, L. A. (1988). Fidelity of HIV-1 reverse transcriptase. *Science* **242,** 1168–1171.
Roberts, J. D., Bebenek, K. & Kunkel, T. A., (1988). The accuracy of reverse transcriptase from HIV-1. *Science* **242,** 1171–1173.
St. Clair, M. H., Marlin, J. L., Tudor-Williams, G., Back, M. C., Vavro, C. L., King, D. M., Kellam, P., Kemp, S. D. & Larder, B. A. (1991). Resistance to ddI and sensitivity to AZT induced by a mutation in HIV-1 reverse transcriptase. *Science* **253,** 1557–1559.
Stewart, F. M. & Levin, B. R. (1984). The population biology of bacterial viruses: why be temperate? *Theor. Popul. Biol.* **26,** 93–117.

APPENDIX

Equilibria and Stability

Here we derive the existence and stability conditions for eqns (16) and (17) in the main text. The more specific case, with zero vertical transmission [eqns (8) and (9), in the text] is obtained by setting $\delta_1=\delta_2=0$ in what follows.

The equations can be rewritten as follows:

$$\dot{y}_1 = y_1(P_1 - Q_{11}y_1 - Q_{12}y_2) \tag{A.1}$$

$$\dot{y}_2 = y_2(P_2 - Q_{21}y_1 - Q_{22}y_2), \tag{A.2}$$

where $P_i = r_i - k$, and $Q_{ij} = c\beta_i - v_j - \delta_j k$.

We now consider existence and stability conditions at each of the four equilibria $(\hat{y}_1, \hat{y}_2)$.

COEXISTENCE

$([P_1Q_{22}-P_2Q_{12}]/D, [P_2Q_{11}-P_1Q_{21}]/D)$, where $D = Q_{11}Q_{22}-Q_{12}Q_{21}$.

Initially, note that our assumption $\delta_1 \geqslant \delta_2$ implies that $D>0$.

Existence conditions: $P_1Q_{22}-P_2Q_{12}>0$, *and* $P_2Q_{11}-P_1Q_{21}>0$.

In the original notation, these reduce to the condition:

$$\frac{r_2(v_1-v_2)}{c(\beta_1-\beta_2)-\delta_2(r_1-r_2)} < k < \frac{r_1(v_1-v_2)}{c(\beta_1-\beta_2)-\delta_1(r_1-r_2)} \tag{A.3}$$

Stability conditions

The equilibrium is stable when the real parts of both eigenvalues λ given by:

$$\begin{vmatrix} -Q_{11}\hat{y}_1-\lambda & -Q_{12}\hat{y}_1 \\ -Q_{21}\hat{y}_2 & -Q_{22}\hat{y}_2-\lambda \end{vmatrix} = 0$$

are negative. The characteristic equation is:

$$\lambda^2 + \lambda(Q_{11}\hat{y}_1 + Q_{22}\hat{y}_2) + \hat{y}_1\hat{y}_2 D = 0,$$

so the equilibrium is stable when $D>0$ and $Q_{11}\hat{y}_1 + Q_{22}\hat{y}_2 > 0$. We have seen that $D>0$ by assumption. The other stability condition is implied by inequality (A.3). Hence, condition (A.3) is necessary and sufficient for existence and stability of the coexistence equilibrium.

MORE-VIRULENT ONLY: $(P_1/Q_{11}, 0)$

This equilibrium exists when $P_1/Q_{11}>0$. It is stable, by inspection of the equations, when $P_1>0$ and $P_2 - Q_{21}P_1/Q_{11}<0$.

But $P_1<Q_{11}$ by definition, so the combined existence and stability conditions are $P_1>0$ and $P_2Q_{11}-P_1Q_{21}<0$. In the original notation, these conditions are: $k<r_1$ and $k>(r_1(v_1-v_2))/c(\beta_1-\beta_2) - \delta(r_1-r_2)$. In the case $\delta_1=0$, the latter reduces to $k>Ar_1$.

LESS-VIRULENT ONLY: $(0, P_2/Q_{22})$

This equilibrium exists when $P_2/Q_{22}>0$. It is stable, by inspection of the equations, when $P_2>0$ and $P_1 - Q_{12}P_2/Q_{22}<0$.

But $P_2<Q_{22}$ by definition, so the combined existence and stability conditions are $P_2>0$ and $P_1Q_{22}-P_2Q_{12}<0$. In the original notation, these conditions are: $k<r_2$ and $k<(r_2(v_1-v_2))/c(\beta_1-\beta_2) - \delta_2(r_1-r_2)$. In the case $\delta_2=0$, the latter reduces to $k<Ar_2$.

ZERO: (0, 0)

This is stable when $P_1<0$ and $P_2<0$. In the original notation, it is stable when $k>r_1$ and $k>r_2$.