

## VIRULENCE EVOLUTION IN EMERGING INFECTIOUS DISEASES

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**Abstract.**—Models of virulence evolution generally consider the outcome of competition between resident and mutant parasite strains at or near endemic equilibrium. Less studied is what happens during the initial phases of invasion and adaptation. Understanding initial adaptive dynamics is particularly important in the context of emerging diseases in wildlife and humans, for which rapid and accurate intervention may be of the essence. To address the question of virulence evolution in emerging diseases, we employ a simple stochastic modeling framework. As is intuitive, the pathogen strains most likely to emerge are those with the highest net reproductive rates ( $R_0$ ). We find, however, that stochastic events shape the properties of emerging pathogens in sometimes unexpected ways. First, the mean virulence of emerging pathogens is expected to be larger in dense host populations and/or when transmission is high, due to less restrictive conditions for the spread of the pathogen. Second, a positive correlation between average virulence and transmissibility emerges due to a combination of drift and selection. We conclude that at least in the initial phases of adaptation, special assumptions about constraints need not be invoked to explain some virulence-transmission correlations and that virulence management practices should consider how residual variation in transmission and virulence can be selected to reduce the prevalence and/or virulence of emerging infectious diseases.

**Key words.**—Branching process, demographic stochasticity, emerging pathogens, life history, trade-offs, virulence evolution.

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Numerous infectious diseases emerge in human populations following exposure to an animal reservoir (e.g., Murphy 1998; Woolhouse 2002), from other human populations (e.g., Diamond 1997), or after the appearance of a parasite mutant, resisting treatment (Heinemann 1999) or escaping immunization (Earn et al. 2002). The immunological and epidemiological reasons for these jumps are largely unknown (Woolhouse 2002). A first and necessary step towards their management is to understand their ecology and evolutionary biology at different steps of the invasion process.

Much of our knowledge of pathogen evolution is based on optimality approaches and the attainment of evolutionary equilibria (e.g., Anderson and May 1983; Antia et al. 1994; Bull 1994; van Baalen and Sabelis 1995; Frank 1996; van Baalen 1998; Gandon et al. 2001; André et al. 2003). With rare exception, these studies assume that virulence and transmission are properties of the parasite alone (but see Antia et al. 1994; André et al. 2003; Restif and Koella 2003). Both empirical and theoretical studies suggest that this is an oversimplification for many systems. Parasite strains will be selected based on their ability to withstand the vagaries of the environment, penetrate their host's lines of defense, and proliferate and exit (often at the expense of) the host. Given the multitude of steps in even the simplest parasite life cycle (Hochberg 1998; Day and Proulx 2004), and the diverse constraints on each of these steps (e.g., trade-offs), predicting the trajectory of adaptation and ensuing impact on individual and population health will prove to be a daunting challenge.

The patterns of pathogen transfer between species, or populations of the same species, are ostensibly determinant to the subsequent stages of invasion. A key feature of emerging diseases that is not captured by optimality approaches is the triage of sparse enemy strains in a largely susceptible host population. We might expect that given the presence of ran-

dom, residual genetic variation for virulence and transmissibility, initially maladapted pathogens will be subject to (perhaps intense) natural selection in newly challenged host populations. Here, deterministic optimality approaches could be misleading because some variants, which would otherwise be deemed as maladaptive, may persist solely due to chance effects. What is required in these initial steps of the invasion process is the explicit accounting of successful and missed opportunities for each candidate pathogen strain. Given the probabilistic nature of initial events, stochastic modeling approaches are required to capture the ensuing dynamics (see Dieckmann and Heesterbeek 2000, pp. 6–9; Antia et al. 2003; Iwasa et al. 2004).

We investigate the relative effects of selection and demographic stochasticity in the initial stages of pathogen invasion, as might be relevant to certain emerging wildlife and human diseases. A simple model of the probability of pathogen emergence is developed and analyzed under the assumption that there are no a priori relationships between virulence and transmissibility of the pathogen. We show that selection and drift act in characteristic ways to produce predictable patterns in virulence, and result in an apparent trade-off between virulence and transmissibility. Finally, we discuss the implications of our results for disease spread and virulence management.

### MODEL DEVELOPMENT

#### *Emergence of a Novel Pathogen in a Virgin Host Population*

Consider a focal pathogen that has just been introduced into a host population of size  $n$ . Every host is assumed to be susceptible to infection (initial density  $S = n$ ). Evidently, as

the pathogen spreads, the density of infected hosts ( $I$ ) increases and the density of susceptibles ( $S$ ) decreases.

Now consider a focal infection by this pathogen. Per unit of time, the infection has a probability  $d = \delta + \alpha$  to be interrupted (by immune clearance or host death), and a probability  $b = \beta S$  to generate a new infection by transmission to a susceptible host (density  $S$ ). The basic reproductive ratio of the pathogen is defined as the expected total number of secondary infections generated if one introduces a single infected host in the population, or  $R_0 = \beta n/d$  (Anderson and May 1991). If this ratio is lower than one, then the pathogen cannot invade the population. (We define invasion as the growth and persistence of the pathogen population). Whereas  $R_0 > 1$  guarantees invasion in deterministic models, we show below that this is not necessarily the case when demographic stochasticity acts (see also Dieckmann and Heesterbeek 2000, pp 6–9; Iwasa et al. 2004). Here, individual infected hosts produce, 0, 1, 2, etc. new infections, which follow some kind of probability distribution with an expected mean greater than one. By “chance” the initially small numbers of infected hosts may produce too few new infections, dooming the invasion. Our aim in this study is to derive both the probability that an invasion fails due to stochastic effects and the probability that the pathogen actually provokes an epidemic (hereafter called the “probability of emergence” sensu Antia et al. 2003).

For analytical tractability, we assume first that the reproductive ratio of the pathogen is large, or  $\beta n \gg d$ . (This assumption will be relaxed in numerical studies given below). Under these conditions, emerging pathogens attain high prevalences given by  $1 - 1/R_0$  at equilibrium.

Consider a single, given infection, present at time  $t$  in the population. We call  $Q(t)$  the probability that this infection, together with all its descendants, ultimately disappears without provoking an epidemic. Note that the probability of emergence of this infection is then just  $P = 1 - Q$ . Note that  $Q(t)$  can be expressed as a function of  $Q(t + dt)$  by considering all the events that may occur on the focal infection during the infinitesimal period  $dt$ :

$$Q(t) = b \times dt \times [Q(t + dt)]^2 + d \times dt + Q(t + dt)(1 - b \times dt - d \times dt). \quad (1)$$

In the first term, the infection reproduces by transmission to a susceptible host (with a probability  $b \times dt$ ), and it will ultimately be lost if the two “daughter” infections are ultimately lost (probability  $[Q(t + dt)]^2$ ). In the second term, the infection goes extinct owing to immune clearance or host death (probability  $d \times dt$ ). In the third term, the infection neither reproduces nor dies (probability  $1 - b \times dt - d \times dt$ ), and it will ultimately be lost with a probability  $Q(t + dt)$ . Equation (1) cannot be solved directly, because  $b$  is not constant through time (it depends on the density of susceptible hosts:  $b = \beta S$ ) and therefore  $Q(t)$  is not constant ( $Q[t] \neq Q[t + dt]$ ).

However, the branching argument enables the simplification that  $b$  and  $Q$  can be approximately considered as constant during the emergence process (see Iwasa et al. 2004; but see also Fisher 1922, 1930, pp. 73–83; Haldane 1927; Dieckmann and Heesterbeek 2000, pp. 6–9; Antia et al. 2003 for discrete

time versions of branching processes). The argument stems from the separation of the emergence process into two distinct phases. The first phase is the very beginning of introduction, when the number of infected hosts is very low. At this stage, stochasticity plays a major role in the fate of the pathogen and extinction is still a possible outcome of the process. The second phase is reached afterward, if the pathogen succeeds in infecting a relatively large number of hosts. At this stage, because the number of infected hosts is large, pathogen’s demography is almost deterministic and extinction is a very unlikely outcome. As a result, the probability that the pathogen emerges can be approximated by the mere probability that it succeeds in reaching this second phase, which can be relatively easy to derive, as we shall see in the following.

The branching approximation appears in the following step of the argument. The idea is to consider that, all along the first phase of emergence, the host’s demography is unaffected by parasites (i.e., the density of susceptible hosts remains approximately equal to the total host density,  $S \approx n$ ). In other words, the pathogen is spreading in a constant environment (a susceptible host population of size  $n$ ). In consequence, the reproduction rate of infections is constant ( $b = \beta n$ ), and so is the probability of emergence. Thanks to this approximation Equation (1) can be simplified and solved to give

$$b \times Q^2 - (b + d) \times Q + d = 0, \quad \text{or} \quad Q = d/b. \quad (2)$$

Because the probability of emergence is  $P = 1 - Q$ , this yields the final expression

$$P = 1 - \frac{\delta + \alpha}{\beta n} = 1 - \frac{1}{R_0}, \quad (3)$$

which is obtained also by Iwasa et al. (2004), as well as by Dieckmann and Heesterbeek (2000, pp. 6–9) in a discrete time setting.

The above approximation is valid under certain conditions. It implies that the pathogen either has a high basic reproductive ratio ( $\beta n \gg d$ ) and/or that the host population is large (large  $n$ ). To the extent that the former is true, the number of infected hosts needed for the deterministic phase to be reached will be relatively low and will only affect marginally the demography of susceptible hosts. In the same way, if the host population is large, then the pathogen potentially reaches high densities and yet has a negligible impact on host demography.

In order to test for the robustness of the branching approximation, we performed Monte-Carlo simulations as follows. Each numerical experiment is initiated with one infected host introduced into a system of  $n$  susceptible hosts. At each subsequent time step, demographic stochasticity acts through one of the following events chosen at random: either (1) loss of an infection (clearance or host death), or (2) reproduction of an infection (transmission to a susceptible host). The probability of an infection occurring is given by the mass action model, or  $b = \beta S$ . The total number of hosts  $n$  is assumed constant, but the number of susceptible hosts ( $S$ ) is calculated at each step of the simulation as the difference between the total number of hosts and the current number of infections ( $S = n - I$ ). Therefore, the reproduction rate of pathogens ( $b = \beta S$ ) is a dynamic variable, and as a consequence the simulations relax the branching assumption.

If the pathogen actually emerges, then at equilibrium the number of infected hosts reaches the deterministic quantity  $\hat{I} = n(1 - 1/R_0)$ . We consider the pathogen to have emerged when the density of infected hosts ( $I$ ) equals or exceeds the arbitrarily high level of 99% of this final equilibrium value. Simulations accurately reflected analytical results (Eq. 3) over a wide range of situation conditions (not shown).

*Expected Virulence of Outbreaks and Correlation with Transmissibility*

Consider a pathogen that has just been introduced into a completely susceptible host population. Assume that the overall extinction rate of infections by this pathogen is  $d$  and their transmissibility is  $\beta$ . In the following,  $b$  refers to the birth rate of the pathogen just after introduction ( $b = \beta n$ ). Conditional on the introduction of a pathogen with phenotype ( $b, d$ ), the probability of an epidemic is

$$p_e(b, d) = \begin{cases} 1 - d/b, & \text{for } b \geq d \\ 0, & \text{for } b < d. \end{cases} \quad (4)$$

Assume now that a parasite strain is introduced with a probability  $u$  at each time unit. These strains represent a subset of those present in the surrounding environment. Their phenotypes are chosen at random from a two-dimensional uniform distribution, with birth rates between 0 and a maximum  $b_m = \beta_m \times n$ , and extinction rates between  $\delta$  and  $d_m = \delta + \alpha_m$ . Thus, importantly, our model assumes no a priori trade-offs between virulence and transmissibility. Neglecting immune clearance,  $\delta$  can be interpreted as the host background mortality rate and  $\alpha_m$  as the maximal attainable virulence of introduced pathogens. If the host is able to clear the infection at a constant rate, then  $\delta$  is merely the sum of clearance rate and background mortality. The joint uniform distribution of  $b$  and  $d$  is described by a density function

$$\varphi(b, d) = \begin{cases} 0 & \text{if } b \notin [0, b_m] \text{ or } d \notin [0, d_m], \\ \frac{1}{b_m(d_m - \delta)} & \text{if } b \in [0, b_m] \text{ and } d \in [0, d_m]. \end{cases} \quad (5)$$

The overall probability that an epidemic occurs per unit of time is therefore

$$p(E) = P_e = u\varphi \iint p_e(b, d) db dd. \quad (6)$$

So far, we have obtained an expression for the probability of epidemic, conditional on the fact that pathogen phenotype is ( $b, d$ ) (Eq. 4). Employing a Bayesian argument (Bayes 1763), we can reverse the conditionality and derive the probability that the pathogen’s phenotype is ( $b, d$ ), conditional on the fact that this pathogen has actually provoked an epidemic. Specifically, what we obtain is a density function giving the distribution of the phenotypes of epidemic strains:

$$\psi(b, d | E) = p(E | b, d) \times \frac{\varphi}{p(E)}, \quad (7)$$

where  $p(E|b, d) = u \times P_e(b, d)$  represents the probability that an epidemic occurs, conditional on the potentially introduced strain having the phenotype ( $b, d$ ).

From Equation (7), the expected virulence of an emerging strain,  $E(\alpha) = E(d) - \delta$ , is found by integration as  $E(\alpha) = \{\iint d \times \psi([b, d] | E) db dd\} - \delta$ , simplifying to

$$E(\alpha) = \frac{\iint d \times p_e(b, d) db dd}{\iint p_e(b, d) db dd} - \delta. \quad (8)$$

The expected transmissibility,  $E(\beta) = E(b)/n$ , is calculated in the same way as

$$E(\beta) = \frac{1}{n} \frac{\iint b \times p_e(b, d) db dd}{\iint p_e(b, d) db dd}, \quad (9)$$

and the expectation of the virulence-transmissibility product,  $E(\alpha \times \beta) = E[(d - \delta)(b/n)]$ , is given by

$$E(\alpha \times \beta) = \frac{1}{n \iint p_e(b, d) db dd} \times \left[ \iint b \times d \times p_e(b, d) db dd - \delta \iint b \times p_e(b, d) db dd \right].$$

The variance of distributions of  $b$  and  $d$  can be derived also in the same way as  $V(x) = E(x^2) - E(x)^2$  and, from them, the variance of distributions of  $\alpha$  and  $\beta$  are given by  $V(\alpha) = V(d)$  and  $V(\beta) = V(b)/n^2$ . Finally, the correlation coefficient between the transmissibility and the virulence of emerging pathogens is found to be

$$\begin{aligned} \text{corr}(\alpha, \beta) &= \frac{\text{cov}(\alpha, \beta)}{\sqrt{V(\alpha)} \times \sqrt{V(\beta)}} \\ &= \frac{E(\alpha \times \beta) - E(\alpha) \times E(\beta)}{\sqrt{V(\alpha)} \times \sqrt{V(\beta)}}. \end{aligned} \quad (10)$$

RESULTS

*Virulence of Emerging Pathogens*

In a given host population of size  $n$ , all potential pathogens do not emerge with equal probabilities (see Eqs. 3 and 4), and those that do emerge are nonrandomly distributed in virulence–transmission life-history space. Below, we analyse how our simple model produces such trends.

We find that the size of the completely susceptible host population in which parasites are emerging ( $n$ ) is a key parameter (see Eq. 3), because invasion is always more likely in a dense population. This turns out to have important consequences for the mean expected virulence of emerging pathogens.

In Figure 1 we plot the probability of emergence of a pathogen, as a function of its virulence. Less virulent pathogens are always more likely to emerge. Further, and more

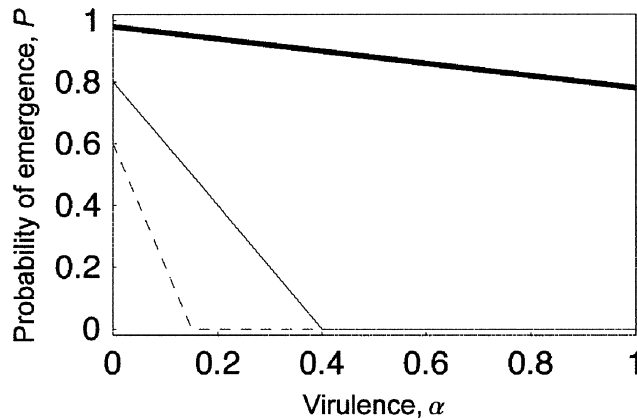


FIG. 1. Analytical results for the probability of an epidemic, as a function of a pathogen's virulence. Background host mortality is  $\delta = 0.1$ ; pathogen transmissibility is  $\beta = 5 \cdot 10^{-4}$ ; population size is  $n = 500$  (dashed line); 1000 (plain line); or 10000 (thick line). The probability of emergence decreases with virulence, in a more rapid way if population is small.

interestingly, in small host populations (small  $n$ ), the reduction of the probability of emergence owing to virulence is much stronger than in large host populations (compare the curves in Fig. 1). As a result, host population size affects the average virulence of emerging strains, as shown in Figure 2.

Emerging strains are on average more virulent as host density increases (larger  $n$ ). This occurs because the presence of a large susceptible host population guarantees numerous reproductive opportunities for parasites. As a result, virulence becomes a nearly neutral trait as host density increases. In small, and particularly very small, host populations, transmission opportunities are more limited and chance effects mean that highly virulent pathogens may drive both their hosts and themselves extinct and no emergence occurs. We also find that emerging strains are on average more virulent when maximum transmissibility  $\beta_m$  is large (not shown). This occurs because pathogens with low transmissibility are constrained by virulence as compared with those with high  $\beta_m$ . Given their similar effects, both maximum transmissibility and host population size can usefully be aggregated into a single parameter: the maximum parasite reproduction rate  $b_m = \beta_m n$ . When this parameter is large, parasites have numerous reproductive opportunities (i.e., environmental conditions are favourable); hence even highly virulent strains may spread.

#### Correlation between Virulence and Transmissibility

A further analysis of the properties of emerging pathogens reveals that correlations between transmissibility and virulence may arise in the complete absence of explicit relationships between the two. In Figure 3, we show the probability of emergence of a pathogen as a function of its virulence and transmissibility (Eq. 3). Highly virulent pathogens need to be particularly well transmitted in order to attain a given probability of emergence. Differential selection against low transmission/high virulence pathogens, in combination with neutral selection differentials between a range of high transmission/high virulence and low transmission/low virulence pathogens generates a positive correlation between virulence

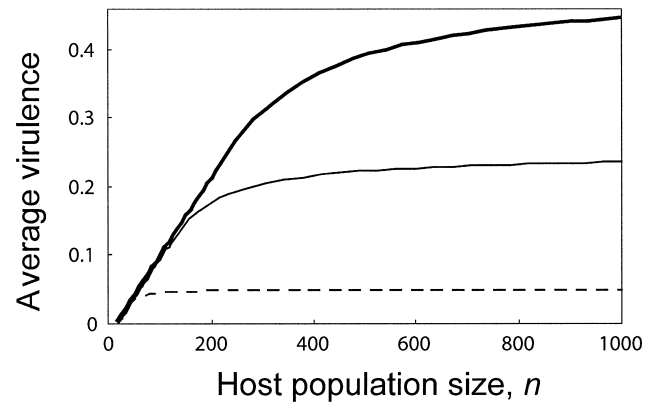


FIG. 2. Mean virulence of epidemics as a function of host density. Mean virulence is higher when population size is larger or transmission higher. The basic interruption rate of infections is  $\delta = 0.1$ ; the maximal attainable transmissibility is  $\beta_{\max} = 5 \cdot 10^{-3}$ ; the maximum virulence is  $\alpha_{\max} = 1$  (thick line); 0.5 (plain line); or 0.1 (dashed line).

and transmissibility in emerging pathogens. This correlation coefficient can be derived mathematically (Eq. 10). From numerical evaluation of Eq. (10), we find that it is always positive and may attain about 40% (Fig. 4). As a result, if several parasite strains are emerging in a given host population or in different host populations, the better-transmitted ones are also, on average, the most virulent.

The strength of the correlation between transmission and virulence varies curvilinearly with available host numbers. This can be understood from the observation of Figure 5, showing the probability of emergence of a pathogen as a function of its transmissibility, for various population sizes and virulence. If very few hosts are available (Fig. 5a), then the range of virulence levels allowing emergence is reduced. As a consequence, the variance in virulence is small, and so is thus the correlation with transmissibility. In contrast, in very large host populations (Fig. 5c) all pathogens with sufficiently high transmissibility are certain to emerge, whatever be their virulence (i.e., the rapid saturation in Fig. 5c). Therefore, here also, the correlation is weak between the virulence and transmissibility of emerging pathogens. With intermediate population size (Fig. 5b), any virulence level may potentially emerge, but the virulence of a pathogen affects strongly the minimal transmissibility needed for emergence to occur (compare the various curves of Fig. 5b). As a result, the correlation between virulence and transmission rate is maximal at intermediate densities of available hosts. This intermediate density decreases with the maximal attainable transmissibility  $b_m$  (compare the three curves in Fig. 4) and increases with maximal attainable virulence  $\alpha_m$  (not shown). In general terms, the less likely pathogens are to spread (the lower  $\beta_m$  and the larger  $\alpha_m$ ), the higher is the correlation between transmissibility and virulence even in dense host populations (e.g., dashed line in Fig. 4). Finally, it is important to note that maximum correlations are always high (always greater than 30% with all tested parameters).

Note that, qualitatively, the same correlation between virulence and transmissibility arises if one does not consider the true probability of emergence of each pathogen strain

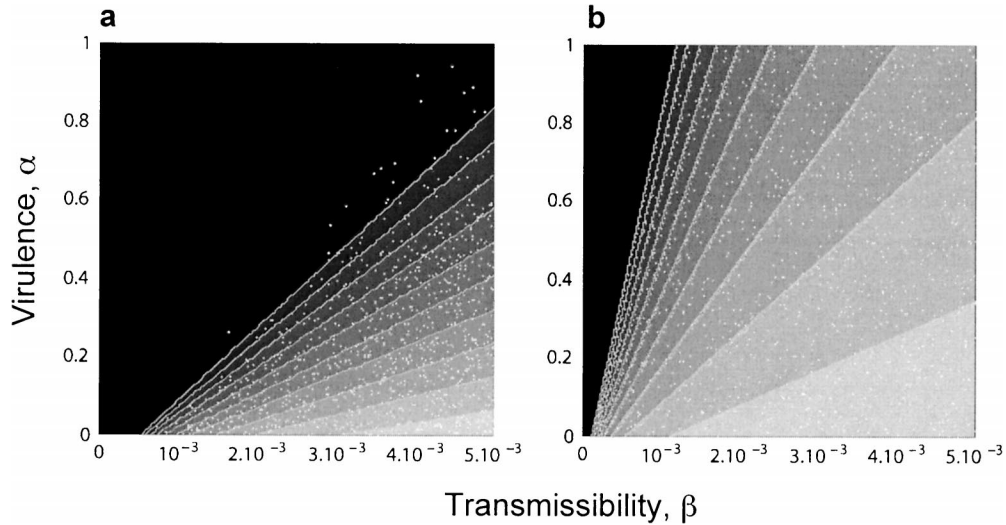


FIG. 3. Emergence of introduced pathogens. Light intensity is proportional to the probability of emergence of pathogens with given transmissibility and virulence, as calculated from Eq. (3). White dots indicate emerging pathogens in stochastic simulations where strains are introduced with random transmissibility and virulence (see main text for methods). Background host mortality is  $\delta = 0.1$ ; host population size is  $n = 200$  (a) or  $1000$  (b).

(Eq. 3), but considers instead that any pathogen with  $R_0 > 1$  spreads with the same probability. Indeed, even in this case, very well transmitted pathogens can afford a larger virulence and spread all the same, while weakly transmitted ones must be weakly virulent as well (see discussions by Bonhoeffer et al. 1996; Day 2003).

#### DISCUSSION

Virulence–transmission trade-offs are one of the cornerstones in evolutionary theories of disease virulence (e.g., Anderson and May 1983; Antia et al. 1994; Bull 1994; van Baalen and Sabelis 1995; Frank 1996; van Baalen 1998; Gandon et al. 2001; Ganusov and Antia 2003). The prevailing view is that trade-offs occur either as a consequence of host and pathogen physiologies, such that higher within-host replication of parasites implies more certain and/or rapid host

death (e.g., Antia et al. 1994; Ganusov et al. 2002; André et al. 2003), or as a result of ecology, such that hosts exposed to more transmissible pathogens incur more infections and hence increased negative effects on host fitness and per capita infecting pathogen fitness (Hochberg 1998; Ebert et al 2000). Experimentally differentiating tradeoffs implicating within-host processes (e.g., Antia et al. 1994; Frank 1996; Gandon et al. 2001; Day 2003), between-host effects (Hochberg 1998) and demographic stochasticity (this study) is an important challenge for future research.

Our study highlights demographic stochasticity as a mechanism generating correlations between virulence and transmission in the early stages of an invasion. The relaxed selection associated with stochastic emergence results in differential selection against highly virulent, low transmissible pathogens. In deterministic models (e.g., optimality approaches), both these and strains with low transmission/low virulence and high transmission/high virulence are rapidly eliminated by selection. It is the maintenance of these less optimal types by stochastic forces that creates the association between transmission and virulence in the context of emerging pathogens. We would expect that, in addition to its pertinence for cross-species jumps, demographic stochastic effects on emerging pathogens could play a role in boom and bust epidemics in spatially extended systems (e.g., metapopulations). Our expectation is that chance effects foster parasite maladaptation in the initial stages of an epidemic.

We have also shown that the expected mean virulence of emerging pathogens should be affected by both transmissibility and initial host population size. If transmissibility (or host density) is low, then this places a constraint on the level of virulence resulting in successful pathogen spread, whereas if transmissibility (or host density) is high then a wide range of virulences may be associated with emerging pathogens. These results may explain certain observations of high virulence in the initial stages of epidemics, followed by atten-

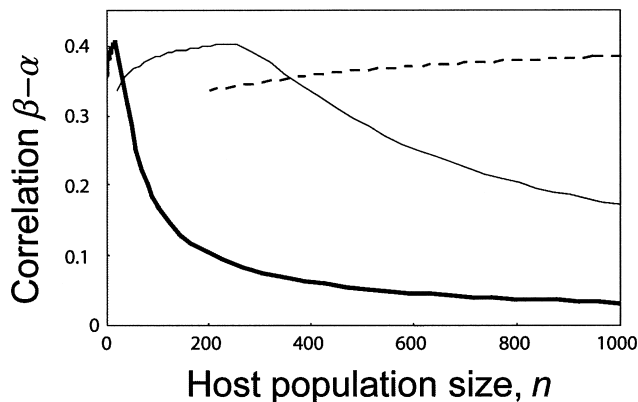


FIG. 4. Correlations between the virulence and transmissibility of emerging pathogens. The most transmissible pathogens are always, on average, also the most virulent. Parameters are as in Figure 3. Except the maximum attainable transmissibility, which is  $\beta_m = 5.10^{-4}$  (dashed line),  $5.10^{-3}$  (plain line), or  $5.10^{-2}$  (thick line).

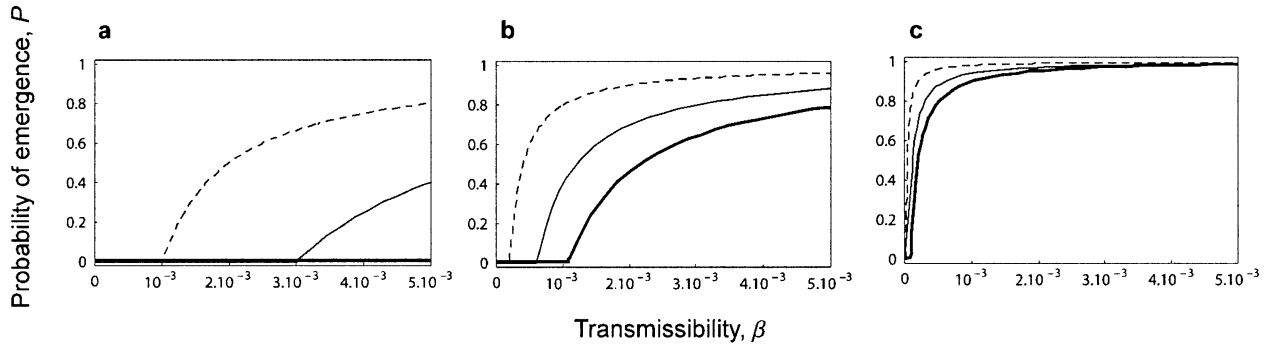


FIG. 5. Probability of emergence, as a function of pathogen's transmissibility. Background host mortality is  $\delta = 0.1$ ; host population size is  $n = 200$  (a), 1000 (b), and 10,000 (c). Virulence is  $\alpha = 1$  (dashed lines), 0.5 (plain lines), or 0.1 (thick lines).

uation of virulence in the absence of host evolution (Fenner and Ratcliffe 1965).

The initial stages of pathogen invasion could set the stage for dynamics occurring over longer time scales, eventually leading to selection-driven stable optima (e.g., Frank 1992, 1996; van Baalen 1998; Gandon et al. 2001), or cycles (van Baalen 1998; Sasaki and Godfray 1999; Gomulkiewicz et al. 2000), or drift-driven maladaptation (Hochberg and Moller 2001). Which of these long-term dynamics transpire should depend importantly on the mutation dynamics of emerging pathogens, the population dynamics of host and pathogen populations, and on the evolutionary response of the host itself. Of particular interest here is the implications for human interventions such as virulence management (Dieckmann et al. 2002), where epidemiological parameters are altered with the aim of reducing the harmful effects of infectious disease. Our results suggest that residual variation in low transmission/low virulence pathotypes may be the target of positive selection in certain virulence management campaigns.

Our model did not consider interference between parasite strains (i.e., multiple or co-infections), which is considered to be an important force in maintaining intermediate levels of virulence (e.g., Mosquera and Adler 1998; Day and Proulx 2004). Although this remains to be studied formally, we would predict that including competition between parasites should further increase observed levels of virulence in the initial stages of invasion. Thus, as the initial emergence of virulent pathogens proceeds, increasing numbers of multiple and co-infections will occur, either breaking expected attenuation or actually increasing virulence. Virulence management measures taken very early in an epidemic may thereby be decisive for curbing subsequent prevalence and pathology.

Our analyses were couched in the context of emerging infectious diseases, but we suggest that this type of phenomenon may be more general to a range of species life-history trade-offs. Given that transmission–virulence trade-offs are special cases of associations between dispersal ability (ecological) or individual growth rates (physiological) and habitat exploitation (virulence), we suspect that the initial stages of habitat invasion, be it by primary producers, predators, or herbivores, could exhibit dynamics that are broadly similar to those described in our study.

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