Insights From Price's Equation into Evolutionary Epidemiology

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1. Introduction

The basic reproduction number, denoted by R_0, is one of the most important quantities in epidemiological theory ([**11**], [**23**]). It is defined as the expected number of new infections generated by an infected individual in an otherwise wholly susceptible population ([**2**], [**12**], [**23**]). Part of the reason why R_0 plays such a central role in this body of theory undoubtedly stems from its relatively simple and intuitively sensible interpretation as a measure of pathogen reproduction. If R_0 is less than unity then we expect the pathogen to die out since each infected individual fails to generate at least one other infection during the lifetime of the infection.

Given that R_0 is a measure of pathogen reproductive success, it is not surprising that this quantity has also come to form the basis of most evolutionary considerations of host-pathogen interactions ([**1**], [**18**]). For example, mathematical models for numerous epidemiological settings have been used to demonstrate that natural selection is often expected to favour the pathogen strain that results in the largest value of R_0 ([**6**], [**18**]). In more complex epidemiological settings such optimization criteria typically cannot be derived and instead a game-theoretic approach is taken ([**5**]). In this context a measure of the fitness of a rare mutant pathogen strain is used to characterize the evolutionarily stable strain (i.e., the strain that, if present within the population in sufficient numbers, cannot be displaced by any mutant strain that arises). Typically R_0 again plays a central role as the measure of mutant fitness in such invasion analyses ([**10**], [**18**], [**30**]).

In this chapter we consider an alternative approach for developing theory in evolutionary epidemiology. Rather than using the total number of new infections generated by an infected individual (i.e., R_0) as a measure of pathogen fitness we use the instantaneous rate of change of the number of infected hosts instead (see also [**3**], [**18**]). This shifts the focus from a consideration of pathogen reproductive success per generation to pathogen reproductive success per unit time. One very useful result of this change in focus is that we can then model the time dynamics of evolutionary change in the pathogen population simultaneously with the epidemiological dynamics, rather than simply characterizing the evolutionary equilibria that are expected. Even more importantly, however, this seemingly slight change

in perspective can lead to a very different interpretation of what drives pathogen evolution than has been obtained from theory based on R_0. Our contention is thus that this alternative perspective provides a useful complement to theory based on R_0 and that can sometimes yield fresh insights into old questions regarding the evolution of host-pathogen interactions.

Our approach is closely related to that of Day and Proulx ([10]) who developed theory based on the assumption that there is a continuum of pathogen strains. In that publication Day and Proulx likened their approach to quantitative genetic models. Here, however, we assume that there are a finite number of discrete pathogen strains in the population. This provides a much simpler and more general theoretical framework and it allows us to readily extend the approach to models for the evolution of multiple pathogen traits, as well as models for pathogens that can infect multiple host types. This discrete strain approach also provides a simple framework in which models of virulence evolution as well as models of antigenic site evolution and host immunity can be combined ([22]).

2. Price's equation

Price's equation has been used extensively in evolutionary biology to model the dynamics of allele frequencies ([7], [17], [28], [29]). Although the original version of this equation was presented in discrete-time, here we provide a simple and very general continuous-time derivation of Price's equation that also accounts for mutation from one type to another. Similar derivations can be conducted in discrete-time. We then extend these results to allow for multiple habitats.

2.1. Mathematics of selection and mutation. Let's put all epidemiological considerations aside for the moment, and consider a population of asexual individuals of which there are n distinct strains. For example, these might be bacterial strains, asexual *Daphnia* clones, or strains of any other asexual species. Our goal here is derive an equation for the rate of change of the frequency of each strain under the action of natural selection and mutation, in the form of Price's equation. The rate of change of the number of individuals of strain i is assumed to be governed by the following equation:

$$(2.1) \qquad \dot{N}_i = r_i N_i - \mu N_i + \mu \sum_{j=1}^{n} m_{ji} N_j,$$

where r_i is the per capita rate of change of strain i (sometimes referred to as its fitness), μ is the mutation rate for all strains, and m_{ji} is the probability that, if a mutation occurs in an individual of strain j, it mutates to an individual of strain i. Although equations (2.1) are perfectly fine descriptions of the evolutionary dynamics of this system, evolutionary biologists are often more interested in the frequency of different strains rather than their absolute numbers since evolutionary change is defined as a change in the frequency of different alleles. Equation (2.1) can be readily used to derive an equation for the rate of change of the frequency of

strain i, defined as $q_i = N_i/N_T$ where $N_T = \sum_{i=1}^{n} N_i$. We have

$$\dot{q}_i = \frac{\dot{N}_i}{N_T} - q_i \frac{\dot{N}_T}{N_T}$$

(2.2)

$$= q_i \left(r_i - \bar{r} \right) - \mu q_i + \mu \sum_{j=1}^{n} m_{ji} q_j$$

where $\bar{r} = \sum_{j=1}^{n} r_j q_j$ is the average rate of change (i.e., average fitness) of all strains in the population.

Equation (2.2) is the fundamental equation for the rate of change of strain frequencies. Now suppose that we are interested in the evolution of a particular trait, x. An equation for the rate of evolutionary change in the average value of x can be derived as

(2.3)
$$\dot{\bar{x}} = \sum_{i=1}^{n} x_i \dot{q}_i,$$

which, using equation (2.2) gives

(2.4)
$$\dot{\bar{x}} = \left(\sum_{i=1}^{n} q_i x_i r_i - \bar{r}\bar{x} \right) - \mu \left(\bar{x} - \sum_{i,j} x_i m_{ji} q_j \right)$$

$$= \text{cov}\left(x, r \right) - \mu \left(\bar{x} - \bar{x}_m \right).$$

In equations (2.4) $\text{cov}(x, r)$ is the covariance between x and r across all strains, and $\bar{x}_m = \sum_{i,j} x_i m_{ji} q_j$, which is the average trait value of all of mutations that arise. Equation (2.4) is Price's equation with mutation, and it (or its extension: see next section) is the central equation of interest in this chapter.

Price's equation (2.4) has a simple and informative interpretation. The average trait value in the population changes as a result of two different processes. First, the average trait value changes in a direction given by the sign of the covariance between the trait and fitness; if strains with large values of x also have a large fitness, r, then this covariance will be positive and natural selection drives the average of x to higher values. Second, the average trait value changes in a direction governed by any mutational bias that might occur (the second term in (2.4)). Specifically, if the average trait value of mutants that arise is larger than that of the population as a whole at any given time, then the second term in (2.4) will be positive, leading to an evolutionary increase in $\bar{x}$ through mutational bias.

It is only when the average value of the mutants that arise is the same as that of the population that mutation has no directional effect on evolution. Although this is a theoretical possibility, in reality some degree of mutational bias is always expected. For example, even when the mutation rates among the different strains are all equal (i.e., $m_{ji} = 1/n$) we have $\bar{x}_m = \sum_i \frac{1}{n} x_i$, which is the average trait value if all strains were at equal frequency. Consequently, even when mutation is unbiased among the different strains, it will nevertheless impart a directional effect on the mean value of any given trait because selection on this trait will usually not favour equal frequencies of all strains (and hence $\bar{x} \neq \bar{x}_m$).

2.2. An extension to multiple habitats. Before connecting the above results to evolutionary epidemiology, we first generalize equation (2.4) to allow for multiple habitats. For example, a bacterial population of interest might exist in

different habitats connected by migration. Similarly, a *Daphnia* population might inhabit different parts of a lake connected by migration.

To simplify the presentation we consider only two habitats, labeled A and B. The extension to an arbitrary number of habitats will become obvious from this case. The analogs of equation (2.1) for each of the two habitats are

$$(2.5) \qquad \dot{N}_i^A = r_i^{AA} N_i^A - \mu N_i^A + \mu \sum_{j=1}^{n} m_{ji} N_j^A + r_i^{BA} N_i^B$$

$$(2.6) \qquad \dot{N}_i^B = r_i^{BB} N_i^{BB} - \mu N_i^B + \mu \sum_{j=1}^{n} m_{ji} N_j^B + r_i^{AB} N_i^A.$$

In equations (2.5) and (2.6) r_i^{AA} is the per capita rate of production of offspring of strain i by such an individual in habitat A, and that end up in habitat A. On the other hand, r_i^{BA} is the per capita rate of production of offspring of strain i by such an individual in habitat B, that end up in habitat A. Analogous interpretations apply to r_i^{BB} and r_i^{AB}.

From equations (2.5) and (2.6) we can derive the analogues of equation (2.2) as

$$\begin{aligned}
\dot{q}_i^A =& \frac{\dot{N}_i^A}{N_T^A} - q_i^A \frac{\dot{N}_T^A}{N_T^A} \\
=& \frac{r_i^{AA} N_i^A - \mu N_i^A + \mu \sum_{j=1}^{n} m_{ji} N_j^A + r_i^{BA} N_i^B}{N_T^A} \\
& - q_i^A \frac{\sum_i \left(r_i^{AA} N_i^A - \mu N_i^A + \mu \sum_{j=1}^{n} m_{ji} N_j^A + r_i^{BA} N_i^B \right)}{N_T^A}
\end{aligned}$$

which yields

$$\begin{aligned}
\dot{q}_i^A =& r_i^{AA} q_i^A - \mu q_i^A + \mu \sum_{j=1}^{n} m_{ji} q_j^A + \frac{N_T^B}{N_T^A} r_i^{BA} q_i^B - q_i^A \left(\bar{r}^{AA} + \frac{N_T^B}{N_T^A} \bar{r}^{BA} \right) \\
=& q_i^A \left(r_i^{AA} - \bar{r}^{AA} \right) - \mu q_i^A + \mu \sum_{j=1}^{n} m_{ji} q_j^A + \frac{N_T^B}{N_T^A} \left(r_i^{BA} q_i^B - q_i^A \bar{r}^{BA} \right) \\
(2.7) \qquad =& q_i^A \left(r_i^{AA} - \bar{r}^{AA} \right) - \mu q_i^A + \mu \sum_{j=1}^{n} m_{ji} q_j^A + \frac{N_T^B}{N_T^A} q_i^B \left(r_i^{BA} - \bar{r}^{BA} \right) \\
& + \frac{N_T^B}{N_T^A} \bar{r}^{BA} \left(q_i^B - q_i^A \right)
\end{aligned}$$

with an analogous equation for habitat B (not shown). Note that there are two different probability distributions used in the averages calculated in (2.7). For example, the average $\bar{r}^{BA}$ is calculated over the distribution q_i^B whereas the average $\bar{r}^{AA}$ is calculated over the distribution q_i^A.

Finally, we can calculate the equation for the dynamics of the average value of trait x, specific to each habitat as $\dot{\bar{x}}^A = \sum_{i=1}^{n} x_i \dot{q}_i^A$ and $\dot{\bar{x}}^B = \sum_{i=1}^{n} x_i \dot{q}_i^B$. This

gives

$$(2.8) \quad \begin{aligned} \dot{\bar{x}}^A =& \sum_i x_i q_i^A \left(r_i^{AA} - \bar{r}^{AA} \right) - \sum_i x_i \left(\mu q_i^A - \mu \sum_{j=1}^n m_{ji} q_j^A \right) \\ &+ \frac{N_T^B}{N_T^A} \sum_i x_i q_i^B \left(r_i^{BA} - \bar{r}^{BA} \right) + \frac{N_T^B}{N_T^A} \sum_i x_i \bar{r}^{BA} \left(q_i^B - q_i^A \right), \end{aligned}$$

or

$$(2.9) \quad \dot{\bar{x}}^A = \operatorname*{cov}_A \left(x, r^{AA} \right) - \mu \left(\bar{x}^A - \bar{x}_m^A \right) + \frac{N_T^B}{N_T^A} \operatorname*{cov}_B \left(x, r^{BA} \right) + \frac{N_T^B}{N_T^A} \bar{r}^{BA} \left(\bar{x}^B - \bar{x}^A \right).$$

Analogously, we have

$$(2.10) \quad \dot{\bar{x}}^B = \operatorname*{cov}_B \left(x, r^{BB} \right) - \mu \left(\bar{x}^B - \bar{x}_m^B \right) + \frac{N_T^A}{N_T^B} \operatorname*{cov}_A \left(x, r^{AB} \right) + \frac{N_T^A}{N_T^B} \bar{r}^{AB} \left(\bar{x}^A - \bar{x}^B \right).$$

Equations (2.9) and (2.10) are the multiple habitat versions of Price's equation (2.4), and they also have a useful interpretation. Let's focus on (2.9) (equation (2.10) can be interpreted analogously). The average trait value in habitat A changes as a result of four processes, corresponding to the four terms in (2.9). The first two terms are analogous to those of equation (2.4) and represent natural selection and mutational bias specific to habitat A. The third and fourth terms represent the evolutionary change in habitat A that results from migration of individuals from habitat B to habitat A.

Beginning with the fourth term, migration into habitat A causes evolutionary change in $\bar{x}^A$ if the mean trait value differs in the two habitats. The factor $\bar{r}^{BA}$ represents the average per capita rate of such migration, and this is weighted by the relative population sizes of the two habitats, N_T^B / N_T^A, to obtain the absolute effect of migration on the mean trait value. Furthermore, these migrants will cause an evolutionary increase in $\bar{x}^A$ if they have an average trait value larger than that of $\bar{x}^A$ and vice versa. This accounts for the factor $(\bar{x}^B - \bar{x}^A)$ in the fourth term.

Turning to the third term in equation (2.9), migration can also cause an evolutionary effect on $\bar{x}^A$ even if the average trait values in the two habitats are the same (in which case the fourth term disappears). In particular, if those individuals that migrate tend to have higher than average trait values, then this will drive $\bar{x}^A$ toward higher values and vice versa. This is represented by the covariance term $\operatorname*{cov}_A(x, r^{AB})$. Again this is weighted by the relative population sizes of the two habitats, N_T^B / N_T^A, to obtain the absolute effect of migration on the mean trait value.

3. Applying Price's equation to epidemiological models

The above equations are quite general, and track the dynamics of any collection of asexually reproducing entities. Of primary interest here is using this formalism to model the evolutionary dynamics of pathogen populations. To do so, we view the pathogen population from the perspective of infected hosts, and interpret q_i as the frequency of all infected hosts that harbour a pathogen of strain i. This implicitly assumes that a host contains at most a single pathogen strain at any given time. Furthermore, mutation from strain j to strain i in the above formalism

then corresponds to a host infected with strain j "becoming" a host infected with strain i.

Such transitions between infection types are assumed to take place as a result of two processes. First, a mutant pathogen strain must arise within an already infected host. Second, it is assumed that competition between these two pathogen strains then results in competitive exclusion. Thus, as is common in many models of evolutionary epidemiology, we assume that a polymorphism is never maintained within a host ([**4**], [**27**]). In fact, to simplify matters further we assume that the competitive exclusion is effectively instantaneous (i.e., we assume superinfection; ([**27**])). Clearly these assumptions neglect some features of the reality of host-parasite interactions, but they have been used successfully in previous theory to provide considerable insight into evolutionary epidemiology ([**4**], [**21**], [**22**], [**25**], [**27**]). Given the above assumptions, we next need to specify the parameters m_{ji} and r_i.

The parameter m_{ji} is the probability that an infection with strain j undergoes a transition to an infection with strain i. This can be decomposed into the product to two factors: (i) the probability that a strain j pathogen mutates into a strain i pathogen within an infected host, and (ii) the probability that, given strain i has appeared in the host, it competitively excludes the pathogen of strain j. There is no *a priori* reason to expect a particular bias in any of the mutations that arise, and therefore we assume that factor (i) is simply $1/n$ (i.e., strain j gives rise to all other strains with equal probability). Factor (ii) will depend on any competitive asymmetry between strains within a host, and we denote this probability by ρ_{ji}.

The parameter r_i is the per capita rate of change of hosts infected with strain i. This will be determined by the epidemiological dynamics of the host population. To specify r_i we must therefore specify the epidemiological model that is assumed to describe the between-host dynamics of the pathogen. We consider three examples.

3.1. A Simple S-I-R Model. As a very simple example, consider a standard SIR description of the epidemiological dynamics. Specifically, if S, I, and R and the densities of susceptible, infected, and recovered and immune hosts, we suppose

$$(3.1) \qquad \dot{S} = \theta - dS - \beta SI$$

$$(3.2) \qquad \dot{I} = \beta SI - dI - vI - cI$$

$$(3.3) \qquad \dot{R} = cI - dR,$$

where θ is a constant immigration rate of susceptible hosts, d is the per capita mortality rate of hosts in the absence of infection, β is the transmission rate of the infection from infected to susceptible hosts, v is the pathogen-induced host mortality rate (i.e., virulence ([**8**])), and c is the per capita rate of clearance of the infection through host defense mechanisms.

Equations (3.1)–(3.3) implicitly assume that there is only one parasite strain circulating in the host population. To connect this to the earlier results for the evolutionary dynamics of the pathogen population we need to consider how this epidemiological model is extended to multiple strains. If I_i is the number of hosts infected with strain i, then (3.1)–(3.3) extend to

$$(3.4) \qquad \dot{S} = \theta - dS - S \sum_i \beta_i I_i$$

$$(3.5) \qquad \dot{I}_i = S\beta_i I_i - dI_i - v_i I_i - cI_i$$

$$(3.6) \qquad \dot{R} = \sum_i cI_i - dR.$$

Equations (3.4)–(3.6) assume that once a host is infected, it becomes immune to all reinfection regardless of strain type. They also assume that the clearance rate, c, is the same for all strains and that immunity is cross specific.

From equation (3.5) we can now readily identify the per capita rate of change of each strain. Writing this equation as $\dot{I}_i = I_i(S\beta_i - d - v_i - c)$, we can see that $r_i = S\beta_i - d - v_i - c$. We can now apply equation (2.4) to obtain the following equation for the evolutionary dynamics of the two characteristics of the pathogen that are assumed to vary between strains (i.e., the virulence, v and the transmission rate, β). We obtain

$$(3.7) \qquad \dot{\bar{v}} = S\sigma_{\beta v} - \sigma_{vv} - \mu\left(\bar{v} - \bar{v}_m\right)$$

$$(3.8) \qquad \dot{\bar{\beta}} = S\sigma_{\beta\beta} - \sigma_{\beta v} - \mu\left(\bar{\beta} - \bar{\beta}_m\right).$$

Here σ_{xy} is the covariance between x and y across the pathogen strains that are circulating in the population. We can also use equations (3.4)–(3.6) to obtain a system of equations governing the total number of susceptible, infected, and recovered individuals. Defining $I = \sum_i I_i$, we can write the summation in (3.4) as $SI\sum_i \beta_i I_i/I$ or $SI\bar{\beta}$ where $\bar{\beta}$ is the average transmission rate. Performing similar calculations for (3.5), (3.6) yields

$$(3.9) \qquad \dot{S} = \theta - dS - SI\bar{\beta}$$

$$(3.10) \qquad \dot{I} = SI\bar{\beta} - dI - \bar{v}I - cI$$

$$(3.11) \qquad \dot{R} = cI - dR,$$

where all overbars denote an expectation over the distribution of strains in the population.

System (3.7)–(3.11) describes the coupled evolutionary-epidemiological dynamics. Equations (3.7), (3.8) reveal how natural selection and within-host mutation are acting on v and β at each instant in time as a function of the current epidemiological state of the population. Equations (3.9)–(3.11) reveal how the epidemiological state of the population changes over time as a function of the current average value of virulence and transmission, $\bar{v}$ and $\bar{\beta}$. Day and Proulx ([10]) present a similar derivation in which there is a continuum of strain types possible, but interestingly those previous results were based on an assumption of small strain variance whereas the above results are exact and require no such assumption. The difference in the two derivations stems from the fact that Day and Proulx ([10]) tracked the evolution of a single trait only. This typically means that the trait enters the epidemiological model in a nonlinear fashion, and therefore requires a small variance assumption in order to simplify the model. Once multiple trait evolution is considered, however, these nonlinearities often disappear (as above) removing the need for this assumption about the variance.

The variances and covariances in system (3.7)–(3.11) will also change through time, and equations for these dynamics will typically depend on higher moments of the strain distribution. Nevertheless, even in the absence of an explicit model for

these dynamics, system (3.7)–(3.11) can be used to gain some insights into pathogen evolution. It can be helpful to take a geometric approach to this question, by first writing equations (3.7), (3.8) in matrix notation. We obtain:

$$(3.12) \qquad \begin{pmatrix} \dot{\bar{v}} \\ \dot{\bar{\beta}} \end{pmatrix} = \mathbf{G} \begin{pmatrix} -1 \\ S \end{pmatrix} - \mu \begin{pmatrix} \bar{v} - \bar{v}_m \\ \bar{\beta} - \bar{\beta}_m \end{pmatrix}$$

where $\mathbf{G}$ is termed the genetic (co)variance matrix and $\begin{pmatrix} -1 & S \end{pmatrix}^T$ is termed the selection gradient. In general the (co)variances in equations (3.12) are functions of the strain frequencies. It is relatively easy to obtain explicit mathematical expressions for these when there are few strains. For example, the two-strain case is particularly simple and it also provides a natural connection with more standard invasion analyses involving rare mutants. Even in more complex scenarios with many strains, however, expressions (3.12) provide a nice way to interpret the action of natural selection within this epidemiological setting.

The product of G with the selection gradient in equation (3.12) describes the way in which natural selection changes the average level of virulence and transmission in the pathogen population. Natural selection always favours reduced virulence with a strength of -1. On the other hand, natural selection always favours an increased transmission rate with a strength that is proportional to the density of susceptible hosts. At equilibrium the force of mutation must balance the force of natural selection, as mediated through the genetic covariance structure of the pathogen population (Figure 1).

The first interesting insight that Price's equation yields is that, quite generally we expect an intermediate equilibrium level of virulence and transmission regardless of the pattern covariance (i.e., regardless of whether there is a tradeoff between transmission and virulence). This is in contrast to most classical theoretical results that predict virulence will evolve to be zero and transmission rate as large as possible whenever there is no tradeoff (but see [4]). The difference in prediction arises from the inevitable effects of mutational bias (Figure 2). The exact location of the equilibrium will depend on the suite of strains that are possible for a given pathogen species as well as the mutation rate. Higher mutation rates will lead to higher equilibrium levels of virulence. This can be appreciated from Figure 2 by noting that the hollow arrow in Figure 2c will be larger in this case, thereby pulling the population closer to $\bar{x}_m$.

It is also interesting to tie these results to previous research in quasi-species ([26]). In many situations we might expect that, out of all the strains that might exist, relatively few of these will have high fitness (i.e., have zero virulence and very high transmission). This is because there is likely a very specific exploitation strategy that a pathogen must have to gain a high transmissibility while also inducing very little virulence. As such these high fitness strains will be akin to the "master sequences" of quasi-species theory. The vast majority of strains in the population will contain deleterious mutations leading to lower fitness because of a lower transmission rate and/or a higher virulence. Interestingly, as has been well-documented in quasi-species theory, there can be a threshold balance between the strength of selection (which, here, depends on the density of susceptible hosts) and mutation ([26]). When mutation becomes too great (or selection becomes too weak – e.g., which can happen here if S is very small) then an "error threshold" is crossed. This leads to the extinction of the high fitness strain (i.e., the one with low virulence

and high transmissibility). Again this contrasts with classical results which predict that this strain should prevail (Figure 3). For highly mutable pathogens such as RNA viruses this might provide an explanation for the existence of intermediate levels of virulence even in the absence of tradeoffs between pathogen characters.

Aside from the inevitable effects of mutations bias, Price's equation yields other interesting insights and interpretations regarding how natural selection shapes pathogen evolution. Let's ignore the effects of mutation, in which case equations (3.7), (3.8) become

$$(3.13) \qquad\qquad \dot{\bar{v}} = S\sigma_{\beta v} - \sigma_{vv}$$

$$(3.14) \qquad\qquad \dot{\bar{\beta}} = S\sigma_{\beta\beta} - \sigma_{\beta v}.$$

One of the central predictions from the classical theory on virulence evolution is that a heightened background mortality rate of the host will select for increased pathogen virulence (assuming that a tradeoff between transmission rate and virulence exists ([18])). Conceptually, this is explained as resulting from the decreased lifespan of an infected host (see [10] for a comparison of the approach presented here with more classical game-theoretic models of this question). This reduced lifespan of infections reduces the future transmission potential of the pathogen at any given time during an infection, and therefore it selects for an increased emphasis on current transmission. This is realized through the evolution of higher virulence. The same reasoning has been used to predict the evolution of higher virulence in response to any factor that shortens the lifespan of an infected host, including an increased clearance rate as well as the existence of secondary infections (see section 3.2).

Equations (3.13)–(3.14) reveal that there is something amiss with this interpretation. Host background mortality and clearance do not appear in the equations for the evolution of virulence and transmission, and therefore they have no direct effect on evolution. In fact this should be obvious from the outset. Background mortality and clearance are both assumed to act in a fashion that is independent of strain type, and therefore by definition they can play no direct role in the change in frequency of strain types. Both of these factors <u>can</u> have an indirect role in evolution, however, through their influence on the genetic parameters in equations (3.13)–(3.14) and/or their influence on the density of susceptible hosts.

Typically we might expect the influence of clearance and host mortality on the genetic variances and covariances to be relatively minor. They can play a large role, however, in determining the density of susceptible hosts. In standard epidemiological models such as equations (3.9)–(3.11) heightened host mortality or clearance rates lead to a higher density of susceptible hosts. It is this increased benefit of transmission that causes the evolution of higher virulence. This clearly illustrates that virulence evolves to be higher solely because of its positive covariance with transmission. Higher transmission rates are selected for because of the increased density of susceptible hosts, and virulence gets dragged along as a correlated response to selection. Interestingly, in this case the transient evolutionary dynamics occurring from an increased mortality rate can actually be opposite to those occurring from an increased clearance rate despite them reaching the same equilibrium values. This can occur because of differences in the transient dynamics of S that occur from these two different manipulations ([10]).

Perhaps even more significantly, an increased mortality rate of infected hosts does not necessarily lead to the evolution of higher virulence under all epidemiological schemes. For example, if we increased host mortality rate but artificially maintained a constant density of susceptible hosts experimentally, then no evolutionary change in virulence or transmission rate should occur. Thus, rather than viewing host mortality and clearance as factors directly affecting pathogen evolution, we should view them as factors that will affect pathogen evolution only through their influence on the density of susceptible hosts (e.g., Figure 3). Previous theory has focused predominately on cases whether there is a positive relationship between mortality or clearance and the density of susceptible hosts but this need not always be the case. It is also worth noting that the perspective used here to elucidate a qualitative understanding of how various factors affect pathogen evolution does not require that we even attempt to calculate the evolutionarily stable level of virulence. Rather, a general understanding of these issues can be obtained from inspection of the equations governing the evolutionary dynamics.

Finally, by treating the evolution of transmission rate and virulence as distinct traits with some potential genetic covariance, the present approach opens the door to making concrete predictions regarding the magnitude of evolutionary change in response to various manipulations. The lack of these sorts of predictions has led to criticisms of previous theory on virulence evolution ([13]). As an example, Ebert and Mangin ([14]) manipulated background host mortality and then quantified evolutionary changes in transmission rate and virulence. As already mentioned, this manipulation will cause evolution only through its effects on the density of susceptible hosts. Consequently, equations (3.13)–(3.14) predict that the manipulation should cause a stronger evolutionary response in transmission rate than in virulence. The reason is that the response in transmission rate is mediated directly through the genetic variance in transmission rate whereas the response in virulence occurs only indirectly through its genetic covariance with transmission. This difference in evolutionary response does appear to have occurred in the results of Ebert and Mangin ([14]; see their Figure 1).

3.2. An S-I-R Model with Secondary Infections. As a second example, we consider the same model as in section 3.1, but we now allow for secondary infections to occur. Specifically, we allow for hosts that are already infected with a particular strain, to acquire secondary infections as a result of contact with other infected hosts. When such an event occurs, we again suppose that one of the two strains competitively excludes the other instantaneously (i.e., superinfection). This has previously been shown to result in the evolution of higher levels of virulence in many models ([21], [22], [27], [25]).

We begin with model (3.1)–(3.3), and extend this to multiple strains as

$$(3.15) \qquad \dot{S} = \theta - dS - S \sum_i \beta_i I_i$$

$$(3.16) \qquad \dot{I}_i = S\beta_i I_i - dI_i - v_i I_i - cI_i + I_i \sum_j I_j \left(\beta_i \rho_{ji} - \beta_j \rho_{ij} \right)$$

$$(3.17) \qquad \dot{R} = \sum_i cI_i - dR.$$

Equations (3.15)–(3.17) are identical to equations (3.4)–(3.6) except for the inclusion of secondary infection. This is represented in equation (3.16) by terms reflecting the additional way in which infections of type i can be gained and lost. Contacts between hosts infected with strain i and hosts infected with strain j occur at a rate $I_i I_j$ (according to the mass action assumption used implicitly in equations (3.1)–(3.3)). Upon such contact, strain i pathogens are transmitted to the host infected with strain j at a rate β_i, and strain j pathogens are transmitted to the host infected with strain i at a rate β_j. Within-host competition then takes place, and strain i competitively excludes strain j in the j-type host with probability ρ_{ji}, whereas strain j competitively excludes strain i and the i-type host with probability ρ_{ij}. Thus the total rate of change of hosts infected with strain i due to contacts with hosts of strain j is $I_i I_j \left(\beta_i \rho_{ji} - \beta_j \rho_{ij} \right)$. Summing this over all the possible strain types in the population then gives the new term in equation (3.16).

To apply equation (2.4) we need to identify the per capita rate of change of hosts infected with strain i. Using I to denote the total number of infected hosts, we can write equation (3.16) as

$$\dot{I}_i = I_i \left(S\beta_i - d - v_i - c + I \sum_j q_j \left(\beta_i \rho_{ji} - \beta_j \rho_{ij} \right) \right)$$

or

$$\dot{I}_i = I_i \left(S\beta_i - d - v_i - c + I\beta_i \bar{\rho}_{\bullet i} - I\overline{\beta \rho_{i\bullet}} \right),$$

where $\beta_i \bar{\rho}_{\bullet i}$ is the average rate at which strain i infections displace infections of other strains through secondary infection, and $\overline{\beta \rho_{i\bullet}}$ is the average rate at which they themselves are displaced. This illustrates that the per capita rate of change under this model is

$$r_i = S\beta_i - d - v_i - c + I\beta_i \bar{\rho}_{\bullet i} - I\overline{\beta \rho_{i\bullet}} \ .$$

If we further simplify matters by assuming that all strains have equivalent within-host competitive abilities (i.e., $\rho_{ji} \equiv \rho$), we have

$$r_i = S\beta_i - d - v_i - c + I\beta_i \rho - I\bar{\beta}\rho \ .$$

Applying equation (2.4) then gives

$$(3.18) \qquad \dot{\bar{v}} = (S + \rho I)\, \sigma_{\beta v} - \sigma_{vv} - \mu \left(\bar{v} - \bar{v}_m \right)$$

$$(3.19) \qquad \dot{\bar{\beta}} = (S + \rho I)\, \sigma_{\beta\beta} - \sigma_{\beta v} - \mu \left(\bar{\beta} - \bar{\beta}_m \right).$$

Note the similarity between these equations and equations (3.7), (3.8). Secondary infection has a very simple effect on the evolutionary dynamics; it changes S in equations (3.7), (3.8) to $S + \rho I$ in equations (3.18), (3.19). Under secondary infection, hosts that are already infected now represent an additional 'resource' that can be used for transmission, and ρ is a factor that weights the susceptibility of already infected hosts to secondary infections, relative to the susceptibility of hosts with no infection. We can also use equations (3.15)–(3.17) to obtain a system of equations governing the total number of susceptible, infected, and recovered individuals, yielding exactly the same system as before (i.e., equations (3.9)–(3.11)). Secondary infection has no direct effect on the epidemiological dynamics.

Again Price's equation yields some interesting new insights in the case of secondary infection. As mentioned in section 3.1, secondary infection has previously been suggested to cause the evolution of higher virulence because it reduces the

lifespan of an infected host in much the same way that increased mortality or clearance does. The suggestion is that this reduces the future transmission potential of the pathogen at any given time during an infection and therefore it selects for higher virulence. Examination of equations (3.18)–(3.19) reveals that, as with the case of mortality and clearance, this interpretation is incorrect. Secondary infection selects for higher virulence solely because it increases the benefit of transmission, and because transmission is positively genetically correlated with virulence.

Another way to appreciate this difference in interpretation is to imagine conducting an experiment with a host-pathogen system that does not normally have secondary infection (e.g., some phage-bacteria systems; [24]), but in which you can experimentally induce secondary infection. Suppose you maintained a control population with no secondary infection, and an experimental population in which you caused secondary infections with randomly chosen pathogen strains. The loss rate of infected hosts in the experimental population through secondary infection would be elevated, and therefore previous interpretations would lead you to expect the evolution of higher virulence. This will not actually occur, however, and equations (3.18)–(3.19) reveal why. Secondary infection selects for higher virulence solely because it increases the benefit of transmission, and because transmission is positively genetically correlated with virulence. The experimental design suggested here has removed this benefit while maintaining the level of secondary infection. Specifically, strains causing secondary infection are chosen randomly and therefore the covariance between transmission rate and virulence is zero for all secondary infections. In this case equations (3.18), (3.19) reduce to equations (3.7), (3.8) revealing that secondary infection will have no evolutionary consequences.

3.3. The Curse of the Pharaoh. Our final example examines the so-called "Curse of the Pharaoh" hypothesis ([3], [16], [20], [31]). This hypothesis applies to pathogens that have free-existing environmental stages (e.g., spores) such as *Bacillus anthrax* and many of the nucleopolyhedrosis viruses of insects. The hypothesis postulates that long-lasting environmental stages (which we will refer to here as spores) result in the evolution of higher virulence. In such cases the pathogen can kill its host quickly without compromising transmission to other hosts because of the existence of transmissible spores persisting in the environment. The hypothesis derives its name from the suggestion that virulent pathogens with long-lived spores might have been the cause of the mysterious death of Lord Carnarvon after opening the tomb of King Tutankhamen ([3], [20]).

As with the previous two examples, we begin by specifying an epidemiological model. Several authors have examined this hypothesis ([3], [9], [20]), and here we use a special case of the model by [9]:

$$(3.20) \qquad \dot{S} = \Phi$$

$$(3.21) \qquad \dot{I} = \gamma SF - (d + v)I$$

$$(3.22) \qquad \dot{F} = \kappa I + v\omega I - \delta F \ .$$

The variables S, I, and F are the populations sizes of susceptible hosts, infected hosts, and freely-existing spores. We leave the dynamics of the susceptible class unspecified. The parameter γ is the transmission rate of spores from the environment to susceptible hosts, d is the natural host death rate, v is the pathogen-induced death rate (i.e., the virulence), κ is the rate at which infected hosts shed spores

into the environment, ω is the number of spores shed into the environment upon pathogen-induced death of the host, and δ is the per capita loss rate of spores from the environment. Model (3.20)–(3.22) assumes that infections are generated only through contact between susceptible hosts and environmental spores, and that this has a negligible effect on the number of spores in the environment.

Model (3.20)–(3.22) embodies two different pathogen habitats: (i) the host habitat, and (ii) the environmental habitat. As a result, we will need to use the multiple-habitat version of Price's equation to model evolutionary change. Doing so requires that we first extend model (3.20)–(3.22) to multiple strains. Focusing only on equations (3.21), (3.22) gives

$$(3.23) \qquad \dot{I}_i = \gamma S F_i - (d + v_i) I_i$$

$$(3.24) \qquad \dot{F}_i = \kappa_i I_i + v_i \omega I_i - \delta F_i \ .$$

In equations (3.23), (3.24) we have assumed that the rate of transmission of spores to susceptible hosts, γ, is independent of strain type, as is the number of spores produced upon pathogen-induced host death, ω. Model (3.23)–(3.24) does not allow for superinfection, but it can be extended to do so relatively easily. This requires only that equation (3.23) be changed to

$$(3.25) \qquad \dot{I}_i = \gamma S F_i - (d + v_i) I_i + F_i \sum_j I_j \gamma \rho_{ji} - I_i \sum_j F_j \gamma \rho_{ij} \ .$$

The second-to-last term in equation (3.25) represents the influx of strain i infections through secondary infection. It is the rate at which hosts infected with strain j come into contact with spores of strain i (i.e., $F_i I_j$) multiplied by the probability of transmission, γ, and the probability that strain i competitively excludes strain j, ρ_{ji} (summed over all strains j). Similarly, the last term in equation (3.25) represents the loss of strain i infections through secondary infection. It is the rate at which hosts infected with strain i come into contact with spores of strain j (i.e., $F_j I_i$) multiplied by the probability of transmission, γ, and the probability that strain j competitively excludes strain i, ρ_{ij} (summed over all strains j).

To apply Price's equation (2.9)–(2.10) we now need to identify r_i^{II} and r_i^{FI}. These represent the per capita rate of production of strain i infected hosts by strain i infected hosts, and by strain i spores respectively. Similarly, we need to identify, r_i^{IF} and r_i^{FF}, which represent the per capita rate of production of strain i spores by strain i infected hosts and by strain i spores respectively. From equations (3.23)–(3.24) we can see that $r_i^{II} = -(d + v_i)$, $r_i^{FI} = \gamma S$, $r_i^{IF} = \omega_i + v_i \omega$, and $r_i^{FF} = \delta\delta$. If there are secondary infections then r_i^{IF} and r_i^{FF} remain unchanged (because equation (3.24) remains unchanged) while r_i^{II} and r_i^{FI} become $r_i^{II} = -(d + v_i) - F \gamma \bar{\rho}_{i\bullet}$ and $r_i^{FI} = \gamma S + \bar{\rho}_{\bullet i} \gamma I$, where $\bar{\rho}_{i\bullet}$ is the average probability that strain i infections gets competitively excluded during secondary infection, and $\bar{\rho}_{\bullet i}$ is the average probability that strain i secondary infections competitively exclude other strains in secondary infections.

For simplicity we will assume that ρ_{ji} is a constant (and equal to ρ) and we will ignore mutational effects on virulence and focus only on the effects of natural selection. In this case applying equations (2.9)–(2.10) to virulence, v, gives

$$(3.26) \qquad \dot{\bar{v}}^F = \frac{I}{F} \left(\sigma_{\kappa v}^I + \omega \sigma_{vv}^I \right) + \frac{I}{F} \left(\bar{\kappa}^I + \omega \bar{v}^I \right) \left(\bar{v}^I - \bar{v}^F \right)$$

and

$$(3.27) \qquad \dot{\bar{v}}^I = -\sigma_{vv}^I + \frac{F}{I}\gamma S \left(\bar{v}^F - \bar{v}^I \right),$$

where I and F to denote the total population size of all infected hosts and spores respectively. In the case of secondary infection equation (3.26) remains unchanged but equation (3.27) becomes

$$(3.28) \qquad \dot{\bar{v}}^I = -\sigma_{vv}^I + \frac{F}{I}\gamma \left(S + \rho I \right) \left(\bar{v}^F - \bar{v}^I \right).$$

Even though the pathogen spores do not express virulence, each spore can still be characterized by its strain type, which indicates the level of virulence it would cause in a host. Equation (3.26) then gives the dynamics of the average level of virulence in this spore population. Finally, the equations governing the total number of infected hosts and spores are

$$(3.29) \qquad \dot{I} = \gamma SF - (d + \bar{v}^I)I$$

$$(3.30) \qquad \dot{F} = \bar{\kappa}^I I + \bar{v}^I \omega I - \delta F.$$

Equations (3.26)–(3.28) provide an interesting perspective on virulence evolution in spore-producing pathogens. We are primarily interested in the average level of virulence that is expressed when pathogens infect the host, $\bar{v}^I$, and thus equations (3.27) or (3.28) are of most interest. The first term in equation (3.27) or (3.28) (i.e., $-\sigma_{vv}$) shows that virulence is always selected against in the host population regardless of whether there is secondary infection or not. The reason is simply that low virulence strains will persist for longer in the host population than high virulence strains because the latter will kill their hosts quickly and then be shed into the spore population. Indeed the only reason why virulent strains are able to persist in the host population is that they "migrate" into hosts from the spore population.

The average level of virulence in the spore population (even though it is unexpressed) is higher than that in the host population ($\bar{v}^F > \bar{v}^I$). This can be seen directly from equation (3.26), which reveals that $\bar{v}^F$ will always increase above the value of $\bar{v}^I$. Biologically, this occurs because it is the most virulent strains that tend to be shed into the spore population. Thus the second term in equation (3.27) or (3.28) will be positive, and will eventually counterbalance the selection against virulence in the host population. Furthermore, we can see that the strength of this effect of "migration" is determined by the magnitude of the flow of spores into the host population (i.e., the force of infection). This will be higher when there is secondary infection because spores then move into the host population through both susceptible and infected hosts. This is reflected by the fact that the only effect of superinfection is to change S in equation (3.27) to $S + \rho I$ in equation (3.28). This selects for higher virulence in a fashion analogous to that in the model of section 3.2.

We can now ask how the lifespan of spores is expected to affect the evolution of virulence. The Curse of the Pharaoh hypothesis states that an increase in δ (which results in a decreased spore life-span) should lead to the evolution of lower virulence. The parameter δ does not appear anywhere in equations (3.26)–(3.28) and therefore spore lifespan does not have a direct effect on the evolution of virulence. It can nevertheless have an indirect effect, however, because it will affect the values of

S, I, and F. At equilibrium, these epidemiological variables cancel out of the evolutionary equation (3.26) and therefore changes in their values (as a result of changes in δ) will have an evolutionary effect on the average level of virulence only through equation (3.27) or (3.28). We treat each of these in turn.

In the case of no secondary infection equation (3.27) applies and thus we need to know how the value of the quantity FS/I changes as δ is increased. Assuming that the population is at an epidemiological equilibrium, equation (3.29) reveals that the relationship $FS/I = (d + \bar{v}^I)/\gamma$ must always hold. Consequently, even though the equilibrium values of all of the variables S, I, and F change as δ is increased, the ratio FS/I remains constant. As has been noted in previous epidemiological models ([3]), the prediction is therefore that spore lifespan has no effect on the evolution of virulence provided we assume that an epidemiological equilibrium is reached.

In the case of secondary infections equation (3.28) applies and we then need to know how the quantity $F(S + \rho I)/I$ changes. We can re-write this as $FS/I + F\rho$. From the above analysis we know that the first of these two terms remains constant as δ increases, and we expect the second to decrease (the size of the spore population will decrease if its death rate increases). Consequently, there is a lower migration rate of spores into the host population and thus the effect of this migration on maintaining virulence in the host population is diminished; the average level of virulence $\bar{v}^I$ decreases. This is exactly in accord with the Curse of the Pharaoh.

The logic of why the hypothesis holds under superinfection is as follows. The average level of virulence in spore populations is always higher than that in host populations for reasons outlined above. Longer spore life spans also lead to a higher spore population size. So long as secondary infections occur, this larger spore population then results in a greater flux of virulent spore strains into the host population, yielding a higher equilibrium level of virulence. Interestingly, secondary infection has previously been noted to result in predictions consistent with the Curse of the Pharaoh but for different reasons ([20]). In these previous results changes in spore lifespan result in changes in the degree of relatedness among coinfecting pathogens, and it is this effect of relatedness that leads to evolutionary changes in virulence.

Finally, we consider what the model of this section can tell us about virulence evolution in pathogens such as the nucleopolyhedrosis viruses of insects, that release spores only upon pathogen-induced host death. In this case $\kappa = 0$, and we are left with the epidemiological-evolutionary system

$$(3.31) \qquad \dot{I} = \gamma SF - (d + \bar{v}^I)I$$

$$(3.32) \qquad \dot{F} = \bar{v}^I \omega I - \delta F$$

$$(3.33) \qquad \dot{\bar{v}}^F = \frac{I}{F}\omega \left(\sigma^I_{vv} + \bar{v}^I \left(\bar{v}^I - \bar{v}^F \right) \right)$$

$$(3.34) \qquad \dot{\bar{v}}^I = -\sigma^I_{vv} + \frac{F}{I}\gamma S \left(\bar{v}^F - \bar{v}^I \right).$$

We can now use these equations to deduce how the average level of virulence in the host, $\bar{v}^I$, is expected to evolve. Assuming that the epidemiological dynamics are fast relative to evolutionary change, equation (3.31) tells use that $FS\gamma/I = d + \bar{v}^I$.

Thus, equations (3.33), (3.34) become

$$(3.35) \qquad \dot{\bar{v}}^F = \frac{I}{F} \omega \left(\sigma_{vv}^I + \bar{v}^I \left(\bar{v}^I - \bar{v}^F \right) \right)$$

$$(3.36) \qquad \dot{\bar{v}}^I = -\sigma_{vv}^I + \left(d + \bar{v}^I \right) \left(\bar{v}^F - \bar{v}^I \right).$$

As discussed earlier, we always expect $\bar{v}^F > \bar{v}^I$.

Can equations (3.35), (3.36) reach an equilibrium if there is always some genetic variation in the population? If so equation (3.35) requires that $\bar{v}^F - \bar{v}^I = \sigma_{vv}^I / \bar{v}^I$. Substituting this into equation (3.36) and re-arranging shows that, in this case, $\dot{\bar{v}}^I \propto d$. This means that virulence in the host will evolve to be large whenever the level of virulence in the spore population is at equilibrium. Thus there is no joint equilibrium of the two. Once $\bar{v}^I$ increases, $\bar{v}^F$ will evolve to higher values as well leading to yet further evolutionary increases in $\bar{v}^I$.

The above considerations reveal that, for pathogens that release spores only upon pathogen-induced host death, virulence is expected to evolve to be as large as possible. Eventually, however, the inevitable forces of mutational bias outlined earlier will come into play, halting evolutionary change. Moreover, it is possible that other factors not included in the above model would also halt evolution towards extreme virulence. For example, if there were a tradeoff between the speed at which the host is killed and the number of spores produced, this too could result in the evolution of intermediate levels of virulence ([15]).

4. Summary

In this chapter we have presented an alternative theoretical framework for modeling the evolutionary and epidemiological dynamics of host-parasite interactions. The approach is based on using the instantaneous rate of change of infected hosts as a measure of pathogen fitness rather than the more commonly used quantity, R_0. Our alternative approach leads to a number of re-interpretations of predictions derived from previous theory, and it thereby provides a more thorough perspective on how various factors affect pathogen evolution. It also provides a relatively straightforward approach for modeling the dynamics of evolutionary change in pathogen populations when it cannot be assumed that the epidemiological dynamics occur on a time scale that is fast relative to that of the evolutionary dynamics (see also [10]).

The approach used here is also more amenable to integrating the somewhat disparate bodies of theory that have developed in the study of the evolutionary ecology of host-parasite interactions. For example, there is a large body of theory devoted to understanding the evolution of the harm that pathogens induce on their hosts (i.e., virulence as defined here). There is also a large and relatively independent body of theory that is focused on predicting the evolutionary dynamics of antigenic matching and avoidance between host and pathogen (e.g., gene-for-gene and matching-allele models; [19]). The approach based on Price's equation that we have developed here offers one framework in which these two bodies of theory might be integrated. Similarly, we have illustrated how the ideas of quasispecies theory can be integrated into theory on the evolution of virulence using this framework as well.

There are several potentially important areas for future development, but there is one in particular that is especially important. All of the theory developed and

discussed here has assumed that the transmission rate and virulence of difference pathogen strains are determined by their genotypes alone. In reality the extent to which a pathogen strain causes mortality and is transmitted is a function of both its genotype and that of its host. Developing models that elucidate the additional complexities of such coevolutionary dynamics will be an important challenge for future research.

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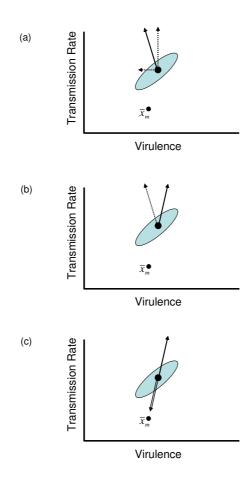   *E-mail address*: `gandon@mpl.ird.fr`

FIGURE 1. A schematic representation of a pathogen population at evolutionary and epidemiological equilibrium. The dot next to $\bar{x}_m$ denotes the mean transmission rate and virulence of all mutations that arise. The shaded ellipse represents the contour within which 95% of the pathogen genotypes lie, and the dot in its center is the mean transmission rate and virulence of the population. The fact that the major axis of the 95% ellipse has a positive slope implies a positive genetic covariance between transmission rate and virulence. (a) Dashed arrows represent the direction of selection on transmission rate and virulence, and the solid arrow is the net direction of selection. (b) Dashed arrow is the net direction of selection from panel (a) and the solid arrow is the direction of evolutionary change that results from this selection when mediated through the positive genetic covariance between transmission rate and virulence. (c) Solid arrow is the direction of evolution change from selection from panel (b) and the hollow arrow is the force of mutational bias that exactly balances this at equilibrium.
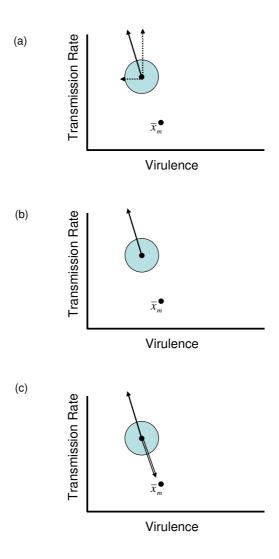
FIGURE 2. A schematic representation of a pathogen population
at evolutionary and epidemiological equilibrium as in Figure 1 but
with no covariance between transmission rate and virulence. The
dot next to denotes the mean transmission rate and virulence of
all mutations that arise. The shaded circle represents the contour
within which 95% of the pathogen genotypes lie, and the dot in
its center is the mean transmission rate and virulence of the pop-
ulation. (a) Dashed arrows represent the direction of selection on
transmission rate and virulence, and the solid arrow is the net di-
rection of selection. (b) Solid arrow is the direction of evolutionary
change is the same as in panel (a) because there is no covariance
between transmission rate and virulence. (c) Solid arrow is the di-
rection of evolution change from selection from panel (b) and the
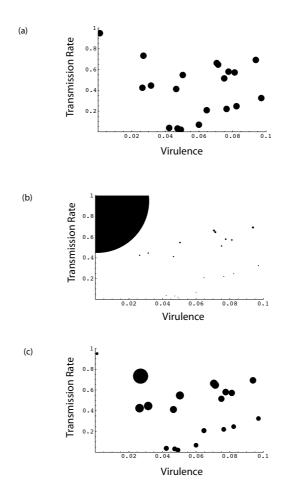hollow arrow is the force of mutational bias that exactly balances
this at equilibrium.

FIGURE 3. An example of how an intermediate level of virulence and transmission rate can evolve in the absence of tradeoffs as a result of crossing an error threshold. One pathogen strain was assigned high fitness parameters (i.e., high transmission rate and low virulence) and 19 others were assigned low fitness values of these parameters at random. These are represented by the dots plotted in each of the panels. Model (3.4)–(3.6) of the text was then used to simulate the evolutionary and epidemiological outcome under different conditions. Parameter values were $\theta = 10$, $\mu = .13$, and $d = 0$ or $d = 1$. Size of dots depict relative equilibrium frequency in the population. (a) all strains are introduced at equal frequency at time 0. (b) When $d = 1$. The equilibrium density of susceptible hosts is high and thus the fitness difference between the high fitness strain and the deleterious mutants outweighs mutational loss, causing the high fitness strain to prevail. (c) When $d = 0$. The equilibrium density of susceptible hosts is low and thus the fitness difference between the high fitness strain and the deleterious mutants is not enough to outweigh mutational loss. The error threshold is crossed and the high fitness strain goes extinct, leading to an intermediate average value of virulence and transmission rate.