The Price equation and evolutionary epidemiology

Troy Day[1,2], Todd Parsons[3], Amaury Lambert[3] and Sylvain Gandon[4]

[1]Department of Mathematics and Statistics, and [2]Department of Biology, Queen's University, Jeffery Hall, Kingston, Ontario, Canada K7L 3N6
[3]Sorbonne Université, Laboratoire de Probabilités, Statistique et Modélisation (LPSM), CNRS UMR 8001, 75005 Paris, France
[4]CEFE UMR 5175, CNRS – Université de Montpellier – Université Paul-Valéry Montpellier – EPHE, 1919, route de Mende, 34293 Montpellier Cedex 5, France

TD, 0000-0002-1052-6140; TP, 0000-0002-2599-8415; SG, 0000-0003-2624-7856

The Price equation has found widespread application in many areas of evolutionary biology, including the evolutionary epidemiology of infectious diseases. In this paper, we illustrate the utility of this approach to modelling disease evolution by first deriving a version of Price's equation that can be applied in continuous time and to populations with overlapping generations. We then show how this version of Price's equation provides an alternative perspective on pathogen evolution by considering the epidemiological meaning of each of its terms. Finally, we extend these results to the case where population size is small and generates demographic stochasticity. We show that the particular partitioning of evolutionary change given by Price's equation is also a natural way to partition the evolutionary consequences of demographic stochasticity, and demonstrate how such stochasticity tends to weaken selection on birth rate (e.g. the transmission rate of an infectious disease) and enhance selection on mortality rate (e.g. factors, like virulence, that cause the end of an infection). In the long term, if there is a trade-off between virulence and transmission across parasite strains, the weaker selection on transmission and stronger selection on virulence that arises from demographic stochasticity will tend to drive the evolution of lower levels of virulence.

This article is part of the theme issue 'Fifty years of the Price equation'.

1. Introduction

The Price equation has come to be regarded as one of the most general descriptions of evolution by natural selection [1–4]. Most applications of this equation are to models of evolution that are formulated in discrete time and that assume non-overlapping generations (but see [5–7] for examples involving discrete time with overlapping generations). One area in which the application of Price's results to continuous-time models has been relatively well developed is the study of infectious disease dynamics [8–10]. Several processes have been examined in this context, including the evolution of pathogen virulence, transmissibility, coinfection and antigenicity [11–15].

The use of Price's equation in studies of evolutionary epidemiology has provided an alternative way to conceptualize the evolution of infectious diseases, and one that is tied to very general evolutionary principles as well as to the population-genetic literature [14]. Perhaps more importantly, it has also provided fresh insight into the underlying causes of evolutionary change by clearly separating the direct effects of natural selection from those that arise through epidemiological feedbacks, and by allowing these feedbacks to occur on a timescale that is comparable with that of evolutionary change. For example, studies have shown that very different evolutionary outcomes are expected for epidemic versus endemic diseases [7,11,16–18], that transient evolutionary changes in traits like virulence or transmission rate can be in a direction opposite to that of their long-term change [8,9,11,18–20], and that the short-term evolutionary consequences of interventions like vaccination can be very different from the long-term outcome [13].

Nevertheless, in virtually all of these examples, the full power of Price's results has not been used because most of these analyses have focused only on the so-called 'first term' or covariance term of Price's equation. As will be seen more clearly below, biologically this means that these studies have mostly focused on cases where natural selection acts only at the between-host level and where mutation is neglected.

In this paper, we have three goals. First, for completeness, we derive a general form of the Price equation in continuous time that allows for non-overlapping generations and show how evolutionary change can be partitioned into three distinct terms [7]. Biologically, these terms correspond to the effect of differences among types in reproductive success, differences among types in the fidelity of replication, and differences among types in how they change over time if they survive. Second, we show how this equation provides an alternative way to view the evolutionary epidemiology of infectious diseases, and how each of the three terms represents an important process in pathogen evolution; namely, differences among strains in their ability to spread among susceptible hosts, differences among strains in their mutation rate, and differences among strains in their ability at within-host competition. Third, we extend these results to incorporate demographic stochasticity and show that the way in which the Price equation partitions evolutionary processes into three terms is also a natural way to partition the evolutionary consequences of demographic stochasticity.

2. A continuous-time Price equation

Consider a population with a discrete set of kinds of individuals and suppose that each individual is characterized by some quantity z. For example, z might be a quantitative trait of an individual or it might be an indicator variable that takes a value of 1 if some characteristic of interest is present and 0 otherwise. The value of z for a type i individual is denoted z_i and the average value of z in the entire population is $\bar{z}$. We use n_i to denote the number of individuals of type i. In a small interval of time, Δt, we assume that each type i individual produces $b_i \Delta t$ descendants and itself survives with probability $1 - d_i \Delta t$. We refer to b_i as the birth rate of type i, d_i as the death rate of type i, and we define the net reproductive rate as $r_i = b_i - d_i$.

Now suppose that descendants of a type i individual might be of a different type $j \neq i$ such that the average value of z across all descendants of a type i individual is $z_i + \Delta z_i$, where Δz_i is the difference (on average) in the z-value between a type i 'parent' and all of its descendants. In a similar way, if an individual of type i itself survives the interval of time Δt it might also change in type and thus in its value of z. To account for this, we define $z_i^s(\Delta t)$ to be the expected value of z for an individual of type i that has survived a duration Δt. Note that $z_i^s(0) = z_i$, meaning that if no time elapses, an individual of type i will necessarily still be of type i and thus have a trait value of z_i.

We now seek an equation that governs the time dynamics of $\bar{z}$. At time $t + \Delta t$ (where Δt is small) we have

$$\bar{z}(t+\Delta t) = \frac{\overbrace{\sum_i n_i b_i \Delta t (z_i + \Delta z_i)}^{\text{reproduction}} + \overbrace{\sum_i n_i (1 - d_i \Delta t) z_i^s(\Delta t)}^{\text{survival}}}{\sum_i n_i (b_i \Delta t + (1 - d_i \Delta t))} + o(\Delta t),$$
(2.1)

where the first term in the numerator accounts for all new births and the second term accounts for the survival of existing individuals. Approximating everything to first order in Δt we obtain

$$\bar{z}(t+\Delta t) \approx \bar{z}(t)$$
$$+ \frac{\sum_i n_i b_i (z_i + \Delta z_i) - \sum_i n_i d_i z_i^s(0) + \sum_i n_i (dz_i^s/dt)(0)}{\sum_i n_i} \Delta t$$
$$- \frac{\sum_i n_i z_i^s(0) \sum_i (n_i r_i)}{\sum_i n_i^2} \Delta t,$$
(2.2)

which can be rearranged (using $z_i^s(0) = z_i$) to give

$$\bar{z}(t+\Delta t) - \bar{z}(t) \approx \frac{\sum_i n_i z_i (b_i - d_i)}{\sum_i n_i} \Delta t - \bar{z}\bar{r}\Delta t + \frac{\sum_i n_i b_i \Delta z_i}{\sum_i n_i} \Delta t$$
$$+ \frac{\sum_i n_i (dz_i^s/dt)(0)}{\sum_i n_i} \Delta t,$$
(2.3)

where all overbars denote an expectation taken over the distribution $n_i / \sum_i n_i$. Dividing by Δt and taking the limit $\Delta t \to 0$ then gives the following differential equation governing the rate of change of the average value $\bar{z}$:

$$\frac{d\bar{z}}{dt} = \text{cov}[z, r] + \mathbb{E}[b\Delta z] + \mathbb{E}\left[\frac{dz^s}{dt}\right],$$
(2.4)

where dz^s/dt is evaluated at $\Delta t = 0$ and again the expectations and covariance are taken over all types in the population (i.e. over the distribution $n_i / \sum_i n_i$).

Equation (2.4) reveals that there are three separate effects that govern the evolutionary dynamics [7]. The first term accounts for differences among types in reproductive success. For example, if types with large values of z tend to have high net reproductive rates, r, then the covariance will be positive and this will tend to increase the average value of z in the population. The second term accounts for differences among types in the fidelity of replication. For example, if offspring tend to have a higher value of z than their parents, then the second term will be positive and this will tend to increase the average value of z in the population. The third term accounts for differences among types in how they change over time if they survive. For example, if the value of z of an individual tends to increase over time then the third term will be positive and this will tend to increase the average value of z in the population.

Also notice that the first term in the Price equation (2.4) results from both birth and death events, the second term results only from birth events, and the third term does not involve either. As will be seen shortly, these differences in how the demographic events affect the evolutionary dynamics are also central to understanding how demographic stochasticity affects evolutionary change.

3. Evolutionary epidemiology

Our main goal in this article is to illustrate how the above general formalism of Price's equation connects to mathematical models for the evolutionary epidemiology of infectious diseases. To do so, here we begin by constructing a model for the evolution of an infectious disease using a standard multi-strain compartment model [9,21–23]. In the next section, we then use a change of variables [9,14] to recast this model in the context of Price's equation.

Consider a compartment model in which there are two pathogen strains. Hosts infected with each strain generate new infections through contact with susceptible hosts, and mutation can also occur during the transmission process. We allow for secondary infection and the resultant within-host competition in the simplest possible way by using a superinfection assumption [24,25]. Under this assumption, when a secondary infection occurs, it is assumed that within-host competition resolves the multiple infection instantly such that the host either switches to another kind of infection or remains as it was.

Under these assumptions, a simple model for the time dynamics of the density, I_i, of hosts infected with strain i is

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = h_i S - (\mu + v_i)I_i + \sigma h_i I_j \rho_{ij} - \sigma h_j I_i \rho_{ji}, \tag{3.1}$$

where $j \neq i$ and i and j take values in $\{1, 2\}$. Here $h_i = (\beta_i I_i (1 - \tau_i) + \beta_j I_j \tau_j)$ and is called the 'force of infection' for strain i. The constant β_i is the transmission rate of strain i from such infected hosts and τ_i is the probability that, when a type i host transmits a parasite propagule, this propagule has mutated to the other type. Therefore, h_i represents the rate at which type i infectious propagules are being generated, both by type i parasites that do not mutate (the component $\beta_i I_i (1 - \tau_i)$) and by type j parasites that mutate to type i (the component $\beta_j I_j \tau_j$). As a result, the term $h_i S$ is the rate at which type i infections are generated through transmission of the parasite to susceptible hosts. The terms $\sigma h_i I_j \rho_{ij}$ and $-\sigma h_j I_i \rho_{ji}$ represent the rates of gain and of loss, respectively, of type i infections through secondary infection. The positive constant σ scales the efficacy of secondary infection relative to infection of susceptible hosts, and ρ_{ij} is the probability that, given a secondary infection occurs, the type i parasite out-competes the type j parasite instantly via superinfection. Finally, v_i is the pathogen-induced mortality rate (i.e. virulence) for strain i and μ is the background host mortality rate.

Equation (3.1) must also be supplemented with an equation governing the time dynamics of susceptible hosts, S, as well as any other host categories that might be relevant (e.g. recovered and immune hosts). To keep things as clear as possible, we will focus on a simple SIS (susceptible–infected–susceptible) model, and in this case the above two equations for I_1 and I_2 are coupled to a single additional equation of the form

$$\frac{\mathrm{d}S}{\mathrm{d}t} = B - \mu S - \sum_i \beta_i I_i S, \tag{3.2}$$

where B is a function specifying the total rate of influx of new susceptible hosts through birth and immigration.

The above model (equations (3.1) and (3.2)) can be analysed using a variety of techniques to determine how the strain composition of the population evolves [9,22]. For example, one of the most common techniques is to use an adaptive dynamics approach, which implicitly assumes that the evolutionary dynamics occur on a much slower timescale than the epidemiological dynamics [26]. Often, however, evolution and epidemiology occur on similar time-scales and in this case recasting the model using a change of variables can be helpful to gain insight [9,14]. This change of variables separates the evolutionary and epidemiological components of the dynamics, with the evolutionary part

being given by a form of Price's equation. We illustrate how to do this next.

4. Connecting price and evolutionary epidemiology

Here, we take equations (3.1) and (3.2) and re-write them with a change of variables, tracking the total number of infected hosts, $I = I_1 + I_2$, and the frequency, p, of these that are infected with strain 1 (i.e. $p = I_1/(I_1 + I_2)$) [9,14]. We get

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \bar{\beta}SI - (\mu + \bar{v})I \tag{4.1}$$

and

$$\frac{\mathrm{d}S}{\mathrm{d}t} = B - \mu S - \bar{\beta}IS \tag{4.2}$$

along with

$$\frac{\mathrm{d}p}{\mathrm{d}t} = p(1-p)((\beta_1 - \beta_2)S - (v_1 - v_2)) + (1-p)\beta_2 S\tau_2 - p\beta_1 S\tau_1$$
$$+ \sigma h_1(1-p)\rho_{12} - \sigma h_2 p\rho_{21}, \tag{4.3}$$

where the overbars denote an average of the parameters over the two different kinds of infected hosts (e.g. $\bar{\beta} = p\beta_1 + (1-p)\beta_2$, etc.).

Equations (4.1) and (4.2) specify the epidemiological dynamics while equation (4.3) separates out from this the evolutionary dynamics. Notice that equation (4.1) for the total abundance of infected hosts I simplifies considerably from equation (3.1) because mutation and secondary infection affect the kinds of infections that occur but they do not affect total number of all infections.

We can also see from equation (4.3) that the evolutionary dynamics are governed by three processes. The first process is captured by the term $p(1-p)((\beta_1 - \beta_2)S - (v_1 - v_2))$ and represents the difference between strains in their ability to infect susceptible hosts as well as the difference in the rates at which each type of infection ends. The second process is captured by the terms $(1-p)\beta_2 S\tau_2 - p\beta_1 S\tau_1$ and represents mutation between the two strains during the process of infection of susceptible hosts. Finally, the third process is captured by the terms $\sigma h_1(1-p)\rho_{12} - \sigma h_2 p\rho_{21}$ and represents the gain and loss of strain 1 infections through secondary infection.

Equations (4.1)–(4.3) allow one to see how evolution proceeds when coupled to the epidemiological dynamics, and also clearly illustrate the different factors that affect evolutionary change. Furthermore, equation (4.3) is precisely a special case of the Price equation (2.4). To see this, we need to identify z, b and d from equation (2.4) in the context of the above model.

To begin, we take $z = \mathbb{1}_1$, the indicator variable for type 1. In other words, $z_1 = 1$ and $z_0 = 0$. Thus, in this context $\bar{z}$ is just the frequency of type 1 infections because $\bar{z} = \bar{\mathbb{1}}_1 = p \cdot 1 + (1-p) \cdot 0 = p$. Furthermore, the birth rate of strain i is $b_i = \beta_i S$ while the death rate is $d_i = \mu + v_i$ (recall that, from the standpoint of Price's equation, b_i is the total birth rate for a type i parent regardless of the type of offspring that are produced). Therefore, the first term of Price's equation (2.4) is

$$\mathrm{cov}[z, r] = p(1-p)((\beta_1 - \beta_2)S - (v_1 - v_2)) \tag{4.4}$$

or more simply

$$\mathrm{cov}[z, r] = p(1-p)(r_1 - r_2), \tag{4.5}$$

where $r_i = \beta_i S - (\mu + v_i)$. This is exactly the first term of equation (4.3).

The second term of Price's equation (2.4) accounts for the fidelity of transmission. To compute it, we need to compute the expected difference in type between a parent and its offspring, Δz, for both types of infection. We then multiply these by b_i and average them over the entire population.

Consider the offspring of type 1 infections. With probability $1 - \tau_1$ no mutation occurs and so there is no change in type. With probability τ_1 a mutation occurs and so z changes from $z_1 = 1$ to $z_2 = 0$. Therefore, using a subscript on Δz to indicate type, we have

$$\Delta z_1 = (1 - \tau_1) \cdot 0 + \tau_1(-1) = -\tau_1 \tag{4.6}$$

and similarly,

$$\Delta z_2 = (1 - \tau_2) \cdot 0 + \tau_2(1) = \tau_2. \tag{4.7}$$

Therefore, together we get

$$\mathbb{E}[b\Delta z] = p\beta_1 S(-\tau_1) + (1-p)\beta_2 \tau_2, \tag{4.8}$$

which is exactly the second term of equation (4.3).

Finally, for the third term of Price's equation (2.4) we need to specify the instantaneous rate at which the expected value of z for type 1 infections changes as a result of type 1 infections switching to type 2 through secondary infection (and *vice versa*). These must then be averaged over the two types of infected hosts.

Since z is an indicator variable with $z_1 = 1$ and $z_0 = 0$, the rate at which the expected value of z changes during survival for a type 1 infection is simply the rate at which a type 1 infection becomes a type 2 infection through superinfection. This is given by

$$\frac{\mathrm{d}z_1^s}{\mathrm{d}t}(0) = -\sigma I p(\beta_1 p \tau_1 + \beta_2(1-p)(1-\tau_2))\rho_{21}. \tag{4.9}$$

Likewise, the rate at which the expected value of z changes during survival for a type 2 infection is simply the rate at which a type 2 infection becomes a type 1 infection through superinfection, and is given by

$$\frac{\mathrm{d}z_2^s}{\mathrm{d}t}(0) = \sigma I(1-p)(\beta_1 p(1-\tau_1) + \beta_2(1-p)\tau_2)\rho_{12}. \tag{4.10}$$

Therefore, we have

$$\mathbb{E}\left[\frac{\mathrm{d}z^s}{\mathrm{d}t}\right] = -(1-p)\sigma I p(\beta_1 p \tau_1 + \beta_2(1-p)(1-\tau_2))\rho_{21}$$
$$+ p\sigma I(1-p)(\beta_1 p(1-\tau_1) + \beta_2(1-p)\tau_2)\rho_{12} \tag{4.11}$$

or

$$\mathbb{E}\left[\frac{\mathrm{d}z^s}{\mathrm{d}t}\right] = \sigma h_1(1-p)\rho_{12} - \sigma h_2 p\rho_{21}, \tag{4.12}$$

which is exactly the third term of equation (4.3).

To summarize, the above considerations show that we can rewrite the evolutionary-epidemiological model given by equations (3.1) and (3.2) in terms of Price's

equation (2.4) as

$$\frac{\mathrm{d}S}{\mathrm{d}t} = B - \mu S - \bar{\beta}IS \tag{4.13}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \bar{\beta}SI - (\mu + \bar{v})I \tag{4.14}$$

and $\quad \dfrac{\mathrm{d}p}{\mathrm{d}t} = \mathrm{cov}[z, \beta S - v] + \mathbb{E}[\beta S \Delta z] + \mathbb{E}\left[\dfrac{\mathrm{d}z^s}{\mathrm{d}t}\right]. \tag{4.15}$

The system of equations (4.13)–(4.15) also illustrates another interesting feature of the application of Price's equation to evolutionary epidemiology. In most applications of Price's results there is no explicit modelling of demography and so no feedback between evolution and demography. However, this kind of epi-evolutionary feedback is at the core of most models in infectious disease evolution and so when such models are cast in terms of Price's results, one typically obtains a coupled system of equations whereby Price's equation is coupled to equations governing the demography of the population. For example, in the above model Price's equation (4.15) involves the density of susceptible hosts S as well as the total number of infected hosts I (see equation (4.12)). Each of these variables changes through time as specified by equations (4.13) and (4.14), and these equations are coupled to Price's equation (4.15) because $\bar{\beta}$ and $\bar{v}$ both depend on p.

The fact that there is an epi-evolutionary feedback between Price's equation and the equations for population demography highlights that the direction and speed of evolution can be influenced by the number of different kinds of hosts in the population and how these numbers change over time. The above equations (4.13) and (4.14) are adequate for capturing these demographic dynamics provided the number of individuals in the population is large enough that this deterministic description is appropriate. For smaller population sizes, however, we need to account for demographic stochasticity. Moreover, because the evolutionary dynamics are coupled to the population dynamics, demographic stochasticity will presumably alter how evolution proceeds as well. In the next section, we examine this in detail.

5. Including demographic stochasticity

Here, we extend the above epidemiological model to include demographic stochasticity and so demonstrate how Price's equation is altered. As we will show, the particular partitioning of evolutionary processes in Price's equation is also a natural way to partition the evolutionary consequences of demographic stochasticity.

Our approach to including demographic stochasticity is based on a continuous-time Markov chain model for the epidemiological dynamics (appendix A). The model treats population size as being integer-valued and tracks the *number* of hosts in each of the three classes (susceptible or infected by strain 1 or 2). We also specify the area of the habitat, A, in which the population lives so that we can transform the stochastic process into one that tracks population *density* (recall that the deterministic model is formulated in terms of density). Then, by assuming that the habitat size is relatively large, we can obtain a diffusion approximation for the density of the three classes of individuals (S, I_1 and I_2, [27]). If we describe this diffusion process using stochastic differential equations (SDEs), we obtain the following SDE for the

evolutionary dynamics of the frequency of type 1 infections (appendix A):

$$\frac{dp}{dt} = p(1-p)\left((\beta_1 - \beta_2)S\left(1 - \frac{1}{AI}\right) - (v_1 - v_2)\left(1 + \frac{1}{AI}\right)\right)$$
$$+ ((1-p)\beta_2\tau_2 - p\beta_1\tau_1)S\left(1 - \frac{1}{AI}\right)$$
$$\times \sigma h_1(1-p)\rho_{12} - \sigma h_2 p\rho_{21}$$
$$+ D, \tag{5.1}$$

where D is a noise term that has a mean value of 0 and that is approximately a diffusion. The remaining terms in equation (5.1) represent the *expected* change in the frequency of type 1 infection. Equation (5.1) is also coupled to SDEs for S and I but we do not present these here since our primary focus is on Price's equation for the evolutionary dynamics (but see [27]).

The notation dp/dt in equation (5.1) is non-standard because the frequency p is not a differentiable function of time, but this notation facilitates comparison with the deterministic case in equation (4.3). Specifically, we can directly compare the first line of equation (5.1) with the first term given in equation (4.3) as given by equation (4.4). We see that, in comparison with equation (4.4), the 'birth' part of the SDE (5.1) is multiplied by $(1 - 1/AI)$ while the 'death' part is multiplied by $(1 + 1/AI)$. This makes the birth component in the SDE smaller than that of the deterministic case, while the death component in the SDE is larger than that of the deterministic case. This means that demographic stochasticity diminishes the evolutionary importance of differences in birth rates between strains and it enhances the evolutionary importance of differences in death rates. At first this asymmetry seems surprising until we recognize that evolution is a change in the *frequency* of different types. When a new infection (i.e. a birth) occurs, the *number* of infections goes from AI to $AI+1$ and thus the change in *frequency* due to adding an additional infection gets smaller (it goes from $1/AI$ to $1/(AI+1)$). Conversely, when a death occurs, the *number* of infections goes from AI to $AI-1$ and thus the change in *frequency* due to removing an individual through death gets larger (it goes from $1/AI$ to $1/(AI-1)$). Appendix B makes this idea more precise.

The second line of the SDE (5.1) can be compared with the second component of equation (4.3) as given by equation (4.8). Again we see that the SDE version is multiplied by $(1 - 1/AI)$. As with the birth component above this makes the effect of this second term smaller in the presence of demographic stochasticity. The reason is the same as above—this second term accounts for mutation during the generation of new infections, and the evolutionary consequences of new infections (in terms of the frequency p) show diminishing returns as the number of infections increases.

The third line of the SDE (5.1) can be compared with equation (4.12) and we see that they are identical—demographic stochasticity does not alter how superinfection affects the evolutionary dynamics. The reason is that superinfection does not result in a change in the total number of infections. As a result, when the *number* of type 1 infections changes owing to superinfection, the effect on the *frequency* of type 1 infections remains the same (the frequency always changes by the reciprocal of the total number of infected hosts). Finally, the noise term D can be decomposed into

the various demographic processes as well but we put aside this analysis for future work.

Taken together, we can therefore write a version of Price's equation (2.4) for this epidemiological model under demographic stochasticity. Neglecting the noise term, we have

$$\frac{d\bar{z}}{dt} = \text{cov}[z, b]\left(1 - \frac{1}{AI}\right) - \text{cov}[z, d]\left(1 + \frac{1}{AI}\right)dt$$
$$+ \mathbb{E}[b\Delta z]\left(1 - \frac{1}{AI}\right) + \mathbb{E}\left[\frac{dz^s}{dt}\right]. \tag{5.2}$$

6. Discussion

The Price equation has found widespread use in many different areas of evolutionary biology. Here, we have illustrated how it can also provide useful insight into the evolutionary biology of infectious diseases. Although classical multi-strain compartment models in epidemiology can be analysed in a variety of ways, the change of variables used here that recasts such models in terms of Price's equation represents an interesting complement to these modelling techniques. One of its main features is that it separates the epidemiological dynamics from the evolutionary dynamics and so more clearly illustrates how there is a reciprocal feedback between the two. It also thereby lends itself to exploring how the evolutionary outcome depends on the relative rates at which epidemiological and evolutionary processes occur. For example, the Price equation approach has been used to show that very different evolutionary outcomes are expected for epidemic versus endemic diseases [7,11,17,18], that transient evolutionary changes in traits like virulence or transmission rate can be in a direction opposite to that of their long-term change [8,9,11], and that the short-term evolutionary consequences of interventions like vaccination can be very different from the long-term outcome [11,13,18,20]. This theoretical framework has also inspired evolution experiments with microbes in the laboratory [18,20] and provided some insights on the understanding of the epidemiology and evolution of pathogens at a global scale [28].

The particular decomposition of evolutionary change that is highlighted by the Price equation also provides an interesting perspective on the evolution of infectious diseases. We have shown that for populations with overlapping generations (as is the case for most epidemiological models) there are three components to evolutionary change (see equation (4.15)). The first term (the covariance term) of equation (4.15) stems from differences among strains in the net rate at which hosts infected with each strain is changing. This net rate of change is made up of two broad classes of demographic events: (i) births—the generation of new infections through transmission to susceptible hosts, βS; and (ii) deaths—the loss of existing infections through host mortality, $\mu + v$. Not all new infections caused by a particular strain will be infections by that same strain, however, because of mutation. The second term of Price's equation (4.15) accounts for this potential lack of fidelity of transmission and so it involves demographic processes associated with births but not deaths (i.e. it involves βS but not $\mu + v$). Finally, the third term of equation (4.15) accounts for changes in type of existing infections as a result of secondary infection (within-host mutation and subsequent within-host

competition would also be captured by a term of this type). Since this process involves a change of one infection type to another rather than the generation of a new infection, it does not involve births, βS, nor deaths, $\mu + v$. Note that each of the above three processes is affected by the epidemiological dynamics as well, through their dependence on S and/or I. This kind of epi-evolutionary (or eco-evolutionary) feedback is something not often appearing in traditional applications of the Price equation.

The above partitioning of the evolutionary processes by Price's equation (4.15) also provides a natural way to partition the evolutionary consequences of demographic stochasticity when the population size is small. Specifically, our analysis demonstrates that demographic stochasticity tends to diminish the evolutionary importance of differences in birth rates between strains and it tends to enhance the evolutionary importance of differences in death rates. This is because births (i.e. the generation of a new infection) increase the number of infections by 1, and so decrease the effect that changes in number have on the frequency of the different strains. Likewise, deaths (i.e. the loss of an infection) decrease the number of infections by 1, and so increase the effect that changes in number have on the frequency of the different strains. Both effects appear in the covariance term of Price's equation (5.2) while only the birth effect appears in the mutation term. Neither effect appears in the term accounting for secondary infection, because this process does not result in a change in the total number of infections.

These results on the evolutionary consequences of demographic stochasticity parallel previous findings arguing that selection favours reduced variance in fitness when there is demographic stochasticity [4,27,29–31]. To see this we can combine the first two terms of Price's equation (5.2) to get

$$\frac{\mathrm{d}\bar{z}}{\mathrm{d}t} = \mathrm{cov}\left[z, b - d - \frac{b+d}{AI}\right] + \mathbb{E}[b\Delta z]\left(1 - \frac{1}{AI}\right) + \mathbb{E}\left[\frac{\mathrm{d}z^s}{\mathrm{d}t}\right].$$
(6.1)

We can see that the 'measure of fitness' that appears in the covariance term is then $b - d - (b+d)/AI$. In other words, selection will tend to increase $\bar{z}$ if high values of z are associated with high values of $b - d - (b+d)/AI$. The quantity $b - d$ is simply the net rate of increase, or expected fitness, while the quantity $b + d$ is the rate at which birth or death events happen and can also be viewed as the variance in fitness [27]. Therefore, selection will tend to increase $\bar{z}$ if high values of z are associated with high expected fitness and low variance in fitness. While this is a well-known finding, the derivation used here (including that in appendix B) provides a more mechanistic understanding of where this result comes from.

The effect of demographic stochasticity on evolutionary dynamics has been explicitly discussed within the Price equation framework by Rice [32]. Rice [32] considered a discrete-time version of the Price equation and introduced demographic stochasticity by allowing fitness to be a random variable. There is no explicit description of demography, but mean fitness (i.e. a measure of the growth rate of the population) drops when the variance in fitness increases (see also [29,30]). This effect is akin to the process mediated by the change in population size following a birth or a death event that we discuss above. In our formalism, the link between evolutionary change and stochastic demography is more explicit, but the incorporation of other forms of stochasticity (e.g. environmental stochasticity) remains to be investigated in the epi-evolutionary framework with SDEs.

These findings regarding demographic stochasticity have interesting implications for the study of infectious disease evolution. The above results mean that demographic stochasticity will tend to weaken selection on transmission rate and enhance selection on factors that cause the end of an infection (like virulence). Thus, if there is a trade-off between virulence and transmission across parasite strains, the weaker selection on transmission and stronger selection on virulence that arises from demographic stochasticity means that such stochasticity will tend to drive the evolution of lower levels of virulence [27,33,34].

The study of the joint epidemiological and evolutionary dynamics of pathogens yields multiple theoretical challenges. Once again, the Price equation provides a very useful framework to identify distinct processes acting on evolutionary dynamics. This partitioning has the remarkable ability to account for a seemingly endless amount of biological complexity.

Appendix A

Here, we derive a version of the epidemiological model presented in the main text that accounts for demographic stochasticity. We use a continuous-time Markov chain where the state space is the integer-valued set of all possible numbers of susceptible hosts as well as the number of hosts infected with strain 1 or strain 2. As such the system remains in its current state for an exponentially distributed amount of time, after which some event occurs (e.g. a new infection, a host death, a superinfection, etc.). Furthermore, the number times each event has occurred by time t is given by an inhomogeneous Poisson process. Therefore, we define $P_i(t)$ to be a Poisson counting process for event i that has unit intensity. Likewise, we define $P_i^*(t) = P_i(t) - t$ to be the corresponding mean-centred process. With this notation, if there are $I_1(0)$ hosts infected with strain 1 at time $t = 0$, then the number of hosts infected by strain 1 at time t, $X_1(t)$, can be written as

$$
\begin{aligned}
X_1(t) = X_1(0) &+ P_1\left(\int_0^t \hat{\beta}_1 Y X_1(1-\tau_1)\,\mathrm{d}s\right) + P_2\left(\int_0^t \hat{\beta}_2 Y X_2 \tau_2\,\mathrm{d}s\right) \\
&- P_3\left(\int_0^t \mu X_1\,\mathrm{d}s\right) - P_4\left(\int_0^t v_1 X_1\,\mathrm{d}s\right) \\
&- P_5\left(\int_0^t \sigma \hat{\beta}_1 X_1^2 \tau_1 \rho_{21}\,\mathrm{d}s\right) - P_6\left(\int_0^t \sigma \hat{\beta}_2 X_1 X_2(1-\tau_2)\rho_{21}\,\mathrm{d}s\right) \\
&+ P_7\left(\int_0^t \sigma \hat{\beta}_1 X_1 X_2(1-\tau_1)\rho_{12}\,\mathrm{d}s\right) + P_8\left(\int_0^t \sigma \hat{\beta}_2 X_2^2 \tau_2 \rho_{12}\,\mathrm{d}s\right),
\end{aligned}
$$
(A 1)

where $Y(t)$ is the number of susceptible hosts at time t. All of the notation in equation (A 1) is the same as the main text

except we have defined $\hat{\beta} = \beta/A$ because β in the main text is specific to population *densities* and we are tracking population *numbers* in equation (A 1). So, for example, $\hat{\beta}$ should be smaller if the same number of individuals are occupying a larger area because their effective contact rate *per individual* would be lower. An analogous equation holds for $X_2(t)$, and a similar equation can also be written for $Y(t)$. Now using the definition of $P_i^*(t)$ we get

$$
\begin{aligned}
X_1(t) = X_1(0) &+ \int_0^t \hat{\beta}_1 Y X_1(1-\tau_1)\,\mathrm{d}s + \int_0^t \hat{\beta}_2 Y X_2 \tau_2\,\mathrm{d}s \\
&- \int_0^t \mu X_1\,\mathrm{d}s - \int_0^t v_1 X_1\,\mathrm{d}s \\
&- \int_0^t \sigma\hat{\beta}_1 X_1 X_1 \tau_1 \rho_{21}\,\mathrm{d}s - \int_0^t \sigma\hat{\beta}_2 X_1 X_2(1-\tau_2)\rho_{21}\,\mathrm{d}s \\
&+ \int_0^t \sigma\hat{\beta}_1 X_1 X_2(1-\tau_1)\rho_{12}\,\mathrm{d}s + \int_0^t \sigma\hat{\beta}_2 X_2 X_2 \tau_2 \rho_{12}\,\mathrm{d}s \\
&+ P_1^*\left(\int_0^t \hat{\beta}_1 Y X_1(1-\tau_1)\,\mathrm{d}s\right) + P_2^*\left(\int_0^t \hat{\beta}_2 Y X_2 \tau_2\,\mathrm{d}s\right) \\
&- P_3^*\left(\int_0^t \mu X_1\,\mathrm{d}s\right) - P_4^*\left(\int_0^t v_1 X_1\,\mathrm{d}s\right) \\
&- P_5^*\left(\int_0^t \sigma\hat{\beta}_1 X_1^2 \tau_1 \rho_{21}\,\mathrm{d}s\right) - P_6^*\left(\int_0^t \sigma\hat{\beta}_2 X_1 X_2(1-\tau_2)\rho_{21}\,\mathrm{d}s\right) \\
&+ P_7^*\left(\int_0^t \sigma\hat{\beta}_1 X_1 X_2(1-\tau_1)\rho_{12}\,\mathrm{d}s\right) + P_8^*\left(\int_0^t \sigma\hat{\beta}_2 X_2^2 \tau_2 \rho_{12}\,\mathrm{d}s\right).
\end{aligned}
\tag{A 2}
$$

We then divide by the habitat area A, and define $I_i = X_i/A$ and $S = Y/A$, and $\beta_i = A\hat{\beta}_i$ to get

$$
\begin{aligned}
I_1(t) = I_1(0) &+ \int_0^t \beta_1 S I_1(1-\tau_1)\,\mathrm{d}s + \int_0^t \beta_2 S I_2 \tau_2\,\mathrm{d}s \\
&- \int_0^t \mu I_1\,\mathrm{d}s - \int_0^t v_1 I_1\,\mathrm{d}s \\
&- \int_0^t \sigma\beta_1 I_1 I_1 \tau_1 \rho_{21}\,\mathrm{d}s - \int_0^t \sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}\,\mathrm{d}s \\
&+ \int_0^t \sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}\,\mathrm{d}s + \int_0^t \sigma\beta_2 I_2 I_2 \tau_2 \rho_{12}\,\mathrm{d}s \\
&+ \frac{1}{A}P_1^*\left(A\int_0^t \beta_1 S I_1(1-\tau_1)\,\mathrm{d}s\right) + \frac{1}{A}P_2^*\left(A\int_0^t \beta_2 S I_2 \tau_2\,\mathrm{d}s\right) \\
&- \frac{1}{A}P_3^*\left(A\int_0^t \mu I_1\,\mathrm{d}s\right) - \frac{1}{A}P_4^*\left(A\int_0^t v_1 I_1\,\mathrm{d}s\right) \\
&- \frac{1}{A}P_5^*\left(A\int_0^t \sigma\beta_1 I_1^2 \tau_1 \rho_{21}\,\mathrm{d}s\right) - \frac{1}{A}P_6^*\left(A\int_0^t \sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}\,\mathrm{d}s\right) \\
&+ \frac{1}{A}P_7^*\left(A\int_0^t \sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}\,\mathrm{d}s\right) + \frac{1}{A}P_8^*\left(A\int_0^t \sigma\beta_2 I_2^2 \tau_2 \rho_{12}\,\mathrm{d}s\right).
\end{aligned}
\tag{A 3}
$$

So far everything is expressed in terms of Poisson processes but we can model these with diffusion processes if the habitat area A is relatively large, using the approximation [27,35,36]

$$
\frac{1}{A}P^*(Ag(t)) \approx \frac{1}{\sqrt{A}}W(g(t))
$$

where $g(t)$ is a function of time and $W(t)$ is a standard Wiener process. Therefore, we have

$$
\begin{aligned}
I_1(t) \approx I_1(0) &+ \int_0^t \beta_1 S I_1(1-\tau_1)\,\mathrm{d}s + \int_0^t \beta_2 S I_2 \tau_2\,\mathrm{d}s \\
&- \int_0^t \mu I_1\,\mathrm{d}s - \int_0^t v_1 I_1\,\mathrm{d}s \\
&- \int_0^t \sigma\beta_1 I_1 I_1 \tau_1 \rho_{21}\,\mathrm{d}s - \int_0^t \sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}\,\mathrm{d}s \\
&+ \int_0^t \sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}\,\mathrm{d}s + \int_0^t \sigma\beta_2 I_2 I_2 \tau_2 \rho_{12}\,\mathrm{d}s \\
&+ \frac{1}{\sqrt{A}}W_1\left(\int_0^t \beta_1 S I_1(1-\tau_1)\,\mathrm{d}s\right) + \frac{1}{\sqrt{A}}W_2\left(\int_0^t \beta_2 S I_2 \tau_2\,\mathrm{d}s\right) \\
&- \frac{1}{\sqrt{A}}W_3\left(\int_0^t \mu I_1\,\mathrm{d}s\right) - \frac{1}{\sqrt{A}}W_4\left(\int_0^t v_1 I_1\,\mathrm{d}s\right) \\
&- \frac{1}{\sqrt{A}}W_5\left(\int_0^t \sigma\beta_1 I_1^2 \tau_1 \rho_{21}\,\mathrm{d}s\right) - \frac{1}{\sqrt{A}}W_6\left(\int_0^t \sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}\,\mathrm{d}s\right) \\
&+ \frac{1}{\sqrt{A}}W_7\left(\int_0^t \sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}\,\mathrm{d}s\right) + \frac{1}{\sqrt{A}}W_8\left(\int_0^t \sigma\beta_2 I_2^2 \tau_2 \rho_{12}\,\mathrm{d}s\right)
\end{aligned}
\tag{A 4}
$$

and upon computing the differential we get

$$
\begin{aligned}
\mathrm{d}I_1 =\ & \beta_1 S I_1(1-\tau_1)\,\mathrm{d}t + \beta_2 S I_2 \tau_2\,\mathrm{d}t - (\mu+v_1)I_1\,\mathrm{d}t \\
&- \sigma\beta_1 I_1 I_1 \tau_1 \rho_{21}\,\mathrm{d}t - \sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}\,\mathrm{d}t \\
&+ \sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}\,\mathrm{d}t + \sigma\beta_2 I_2 I_2 \tau_2 \rho_{12}\,\mathrm{d}t \\
&+ \frac{\sqrt{\beta_1 S I_1(1-\tau_1)}}{\sqrt{A}}\,\mathrm{d}W_1 + \frac{\sqrt{\beta_2 S I_2 \tau_2}}{\sqrt{A}}\,\mathrm{d}W_2 - \frac{\sqrt{\mu I_1}}{\sqrt{A}}\,\mathrm{d}W_3 \\
&- \frac{\sqrt{v_1 I_1}}{\sqrt{A}}\,\mathrm{d}W_4 - \frac{\sqrt{\sigma\beta_1 I_1^2 \tau_1 \rho_{21}}}{\sqrt{A}}\,\mathrm{d}W_5 - \frac{\sqrt{\sigma\beta_2 I_1 I_2(1-\tau_2)\rho_{21}}}{\sqrt{A}}\,\mathrm{d}W_6 \\
&+ \frac{\sqrt{\sigma\beta_1 I_1 I_2(1-\tau_1)\rho_{12}}}{\sqrt{A}}\,\mathrm{d}W_7 + \frac{\sqrt{\sigma\beta_2 I_2^2 \tau_2 \rho_{12}}}{\sqrt{A}}\,\mathrm{d}W_8.
\end{aligned}
\tag{A 5}
$$

An analogous equation holds for I_2, providing a stochastic version of equation (3.1) for the case where the habitat area A is large. Finally, defining $p = I_1/(I_1+I_2)$ and using Ito's lemma we get equation (5.1) of the main text.

Appendix B

In this appendix, we formalize the intuition behind the different effects of demographic stochasticity. Recall that demographic stochasticity affects those parts of the evolutionary process that are driven by new infections (the first two lines of the Price equation (5.1) but it has no effect on those parts driven by secondary infections (the third line of Price's equation (5.1)). The key to understanding this difference is to note that processes associated with the first two lines result in a change in the total number of infected hosts (increasing from births and decreasing from deaths), whereas processes associated with the third line do not alter the total number of infected hosts (instead one type of host changes to another).

To explore this idea more broadly, consider a simple generic model in which there are just births or deaths. We assume that one event happens at a time and the rate at which events happen is proportional to the total population size. To illustrate the above points, we will consider two different demographic schemes: (1) the total population size is fixed by ensuring that any birth or death event is

compensated for by randomly adding or removing another individual as necessary (this corresponds to the processes embodied by the third line of Price's equation (5.1)); and (2) the total population size changes as a result of births and deaths (this corresponds to the processes embodied by the first two lines of Price's equation (5.1)).

Let X denote the number of type 1 individuals, p the frequency of type 1 individuals, and N the total population size. Also, let b_i be the birth rate of type i and d_i the death rate. As an example, with this set-up, if we condition on a birth or death event occurring, it will be a birth of type 1 with probability

$$\frac{pb_1}{pb_1 + (1-p)b_2 + pd_1 + (1-p)d_2}$$

and so forth. The total rate at which events happen is $N(pb_1 + (1-p)b_2 + pd_1 + (1-p)d_2)$, and for simplicity of notation we will define $\alpha = pb_1 + (1-p)b_2 + pd_1 + (1-p)d_2$, which is the average rate of events ($N\alpha$ is the total rate of events).

(a) Scheme 1 (N is a fixed constant)

Each birth replaces a type 1 individual with probability p and a type 2 individual with probability $1-p$. Likewise, the vacancy created by each death event is filled by a type 1 individual with probability p and a type 2 individual with probability $1-p$. Given an event occurs, we therefore have the following table of possibilities:

event	probability	expected change in p
birth of type 1	$\frac{b_1 p}{\alpha}$	$(1-p)\frac{X+1}{N} + p\frac{X}{N} - \frac{X}{N} = (1-p)\frac{1}{N}$
birth of type 2	$\frac{b_2(1-p)}{\alpha}$	$(1-p)\frac{X}{N} + p\frac{X-1}{N} - \frac{X}{N} = -p\frac{1}{N}$
death of type 1	$\frac{d_1 p}{\alpha}$	$(1-p)\frac{X-1}{N} + p\frac{X}{N} - \frac{X}{N} = -(1-p)\frac{1}{N}$
death of type 2	$\frac{d_2(1-p)}{\alpha}$	$(1-p)\frac{X}{N} + p\frac{X+1}{N} - \frac{X}{N} = p\frac{1}{N}$

The expected change in p in a small interval of time Δt is therefore

$$\mathbb{E}[\Delta p] = (1 - N\alpha\Delta t)\cdot 0$$
$$+ N\alpha\Delta t\frac{1}{\alpha}\left(b_1 p(1-p)\frac{1}{N} - b_2(1-p)p\frac{1}{N}\right.$$
$$\left. - d_1 p(1-p)\frac{1}{N} + d_2(1-p)p\frac{1}{N}\right) \qquad (B\ 1)$$

or

$$\mathbb{E}[\Delta p] = p(1-p)((b_1 - b_2) - (d_1 - d_2))\Delta t.$$

Thus, if the total population size does not change as a result

of births or deaths, then the expected change in frequency in a small interval of time does not depend on population size. Instead, this expected change is exactly the same as the change in frequency predicted by a deterministic model. This is why the third line of SDE (5.1) is identical to that of the deterministic model.

(b) Scheme 2 (N changes with births and deaths)

In this case, we do not replace individuals upon births nor fill empty spots upon deaths but instead allow the total population size to change. Given an event occurs, we therefore have the following table of possibilities:

event	probability	expected change in p
birth of type 1	$\frac{b_1 p}{\alpha}$	$\frac{X+1}{N+1} - \frac{X}{N} = (1-p)\frac{1}{N+1}$
birth of type 2	$\frac{b_2(1-p)}{\alpha}$	$\frac{X}{N+1} - \frac{X}{N} = -p\frac{1}{N+1}$
death of type 1	$\frac{d_1 p}{\alpha}$	$\frac{X-1}{N-1} - \frac{X}{N} = -(1-p)\frac{1}{N-1}$
death of type 2	$\frac{d_2(1-p)}{\alpha}$	$\frac{X}{N-1} - \frac{X}{N} = p\frac{1}{N-1}$

The expected change in p in a small interval of time Δt is therefore

$$\mathbb{E}[\Delta p] = (1 - N\alpha\Delta t)\cdot 0$$
$$+ N\alpha\Delta t\frac{1}{\alpha}\left(b_1 p(1-p)\frac{1}{N+1} - b_2(1-p)p\frac{1}{N+1}\right.$$
$$\left. - d_1 p(1-p)\frac{1}{N-1} + d_2(1-p)p\frac{1}{N-1}\right)$$
$$(B\ 2)$$

or

$$\mathbb{E}[\Delta p] = p(1-p)\left((b_1 - b_2)\frac{N}{N+1} - (d_1 - d_2)\frac{N}{N-1}\right)\Delta t.$$

In this case, because the total population size changes as a result of births or deaths, the expected change in frequency changes as well in a way that depends on what the current population size is. For example, the increase in frequency of type 1 due to the birth of a type 1 individual is smaller than the decrease in frequency of type 1 due to the death of a type 1 individual.

We can take this a bit further in drawing a connection to the main text by noting that, if N is large, then to first order in $1/N$ we get

$$\mathbb{E}[\Delta p] = p(1-p)\left((b_1 - b_2)\left(1 - \frac{1}{N}\right) - (d_1 - d_2)\left(1 + \frac{1}{N}\right)\right)\Delta t,$$

which has exactly the same form as the third line of SDE (5.1).

References

1. Price GR. 1970 Selection and covariance. *Nature* **227**, 520–521. (doi:10.1038/227520a0)
2. Price GR. 1972 Extension of covariance selection mathematics. *Ann. Hum. Genet.* **35**, 485–490. (doi:10.1111/j.1469-1809.1957.tb01874.x)
3. Frank SA. 1995 George Price's contributions to evolutionary genetics. *J. Theor. Biol.* **175**, 373–388. (doi:10.1006/jtbi.1995.0148)
4. Rice S. 2004 *Evolutionary theory: mathematical and conceptual foundations*. Oxford, UK: Oxford University Press.
5. Taylor PD. 1990 Allele-frequency change in a class-structured population. *Am. Nat.* **135**, 95–106. (doi:10.1086/285034)
6. Coulson T, Tuljapurkar S. 2008 The dynamics of a quantitative trait in an age-structured population living in a variable environment.
Am. Nat. **172**, 599–612. (doi:10.1086/591693)
7. Day T, Bonduriansky R. 2011 A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. *Am. Nat.* **178**, E18–E36. (doi:10.1086/660911)
8. Day T, Gandon S. 2006 Insights from Price's equation into evolutionary epidemiology. In *Disease evolution: models, concepts, and data analysis* (eds Z

Feng, U Dieckmann, S Levin), pp. 23–43. Providence, RI: AMS and DIMACS.

9. Day T. 2009 Mathematical techniques in the evolutionary epidemiology of infectious diseases. In *Modeling and dynamics of infectious diseases* (*Series in Contemporary Applied Mathematics*, vol. 11), (eds Z Ma, Y Zhou, J Wu), pp. 136–149. Contemporary Applied Mathematics. Singapore: World Scientific Press.

10. Alizon S. 2009 The Price equation framework to study disease within-host evolution. *J. Evol. Biol.* **22**, 1123–1132. (doi:10.1111/j.1420-9101.2009.01726.x)

11. Day T, Proulx SR. 2004 A general theory for the evolutionary dynamics of virulence. *Am. Nat.* **163**, E40–E63. (doi:10.1086/382548)

12. Boni M, Gog J, Andreasen V, Feldman MW. 2006 Epidemic dynamics and antigenic evolution in a single season of influenza A. *Proc. R. Soc. B* **273**, 1307–1316. (doi:10.1098/rspb.2006.3466)

13. Gandon S, Day T. 2007 The evolutionary epidemiology of vaccination. *J. R. Soc. Interface* **4**, 803–817. (doi:10.1098/rsif.2006.0207)

14. Day T, Gandon S. 2007 Applying population genetic models in theoretical evolutionary epidemiology. *Ecol. Lett.* **10**, 876–888. (doi:10.1111/j.1461-0248.2007.01091.x)

15. Alizon S. 2013 Co-infection and super-infection models in evolutionary epidemiology. *Interface Focus* **3**, 20130031. (doi:10.1098/rsfs.2013.0031)

16. Bull JJ, Ebert D. 2008 Invasion thresholds and the evolution of nonequilibrium virulence. *Evol. Appl.* **1**, 172–182. (doi:10.1111/j.1752-4571.2007.00003.x)

17. Mideo N, Nelson WA, Reece SE, Bell AS, Read AF, Day T. 2011 Bridging scales in the evolution of infectious disease life histories: application. *Evolution* **65**, 3298–3310. (doi:10.1111/j.1558-5646.2011.01382.x)

18. Berngruber TW, Froissart R, Choisy M, Gandon S. 2013 Evolution of virulence in emerging epidemics. *PLoS Pathog.* **9**, e1003209. (doi:10.1371/journal.ppat.1003209)

19. Bolker BM, Nanda A, Shah D. 2009 Transient virulence of emerging pathogens. *J. R. Soc. Interface* **7**, 811–822. (doi:10.1098/rsif.2009.0384)

20. Berngruber TW, Lion S, Gandon S. 2015 Spatial structure, transmission modes and the evolution of viral exploitation strategies. *PLoS Pathog.* **11**, e1004810. (doi:10.1371/journal.ppat.1004810)

21. Kermack WO, McKendrick AG. 1927 A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond. A* **115**, 700–721. (doi:10.1098/rspa.1927.0118)

22. Bremermann HJ, Thieme HR. 1989 A competitive exclusion principle for pathogen virulence. *J. Math. Biol.* **27**, 179–190. (doi:10.1007/BF00276102)

23. Hethcote HW. 2000 The mathematics of infectious diseases. *SIAM Rev.* **42**, 599–653. (doi:10.1137/S0036144500371907)

24. Nowak MA, May RM. 1994 Superinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond. B* **255**, 81–89. (doi:10.1098/rspb.1994.0012)

25. Mosquera J, Adler FR. 1998 Evolution of virulence: a unified framework for coinfection and superinfection. *J. Theor. Biol.* **195**, 293–313. (doi:10.1006/jtbi.1998.0793)

26. Geritz SAH, Kisdi E, Meszéna G, Metz JAJ. 1998 Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evol. Ecol.* **12**, 35–57. (doi:10.1023/A:1006554906681)

27. Parsons TL, Lambert A, Day T, Gandon S. 2018 Pathogen evolution in finite populations: slow and steady spreads the best. *J. R. Soc. Interface* **15**, 20180135. (doi:10.1098/rsif.2018.0135)

28. Gandon S, Day T, Metcalf CJE, Grenfell BT. 2016 Forecasting epidemiological and evolutionary dynamics of infectious diseases. *Trends Ecol. Evol.* **31**, 776–788. (doi:10.1016/j.tree.2016.07.010)

29. Gillespie JH. 1974 Natural selection for within-generation variance in offspring number. *Genetics* **76**, 601–606.

30. Frank SA, Slatkin M. 1990 Evolution in a variable environment. *Am. Nat.* **136**, 244–260. (doi:10.1086/285094)

31. Parsons TL, Quince C, Plotkin JB. 2010 Some consequences of demographic stochasticity in population genetics. *Genetics* **185**, 1345–1354. (doi:10.1534/genetics.110.115030)

32. Rice SH. 2008 A stochastic version of the Price equation reveals the interplay of deterministic and stochastic processes in evolution. *BMC Evol. Biol.* **8**, 262. (doi:10.1186/1471-2148-8-262)

33. Kogan O, Khasin M, Meerson B, Schneider D, Myers CR. 2014 Two-strain competition in quasineutral stochastic disease dynamics. *Phys. Rev. E* **90**, 042149. (doi:10.1103/PhysRevE.90.042149)

34. Humplik J, Hill AL, Nowak MA. 2014 Evolutionary dynamics of infectious diseases in finite populations. *J. Theor. Biol.* **360**, 149–162. (doi:10.1016/j.jtbi.2014.06.039)

35. Kurtz TG. 1981 *Approximation of population processes*, vol. 36. Philadelphia, PA: Society for Industrial and Applied Mathematics.

36. Ethier SN, Kurtz TG. 1986 *Markov processes: characterization and convergence*. New York, NY: John Wiley and Sons.