doi:10.1111/evo.137

Why is sterility virulence most common in sexually transmitted infections? Examining the role of epidemiology

David V. McLeod[1,2] and Troy Day[3]

[1] Institute of Integrative Biology, ETH Zürich, Zürich, Switzerland

[2] E-mail: david.mcleod@env.ethz.ch

[3] Department of Mathematics and Statistics, Department of Biology Queen's University, Kingston, Ontario, Canada

Received July 10, 2018
Accepted February 6, 2019

Sterility virulence, or the reduction in host fecundity due to infection, occurs in many host–pathogen systems. Notably, sterility virulence is more common for sexually transmitted infections (STIs) than for directly transmitted pathogens, while other forms of virulence tend to be limited in STIs. This has led to the suggestion that sterility virulence may have an adaptive explanation. By focusing upon finite population models, we show that the observed patterns of sterility virulence can be explained by consideration of the epidemiological differences between STIs and directly transmitted pathogens. In particular, when pathogen transmission is predominantly density invariant (as for STIs), and mortality is density dependent, sterility virulence can be favored by demographic stochasticity, whereas if pathogen transmission is predominantly density dependent, as is common for most directly transmitted pathogens, sterility virulence is disfavored. We show these conclusions can hold even if there is a weak selective advantage to sterilizing.

KEY WORDS: Infectious disease, sexually transmitted infections, sterility, stochasticity, virulence evolution.

Sterility virulence, defined to be any reduction in host fecundity due to pathogen infection (including complete sterility), occurs in many host–pathogen systems (Lockhart et al. 1996; Apari et al. 2014; Abbate et al. 2015) but is more commonly associated with sexually transmitted infections (STIs; Lockhart et al. 1996). Interestingly, sterilizing STIs tend to cause limited virulence other than sterility (Lockhart et al. 1996; Antonovics et al. 2011), whereas sterilizing non-STIs tend to be associated with high overall levels of virulence (Apari et al. 2014). In combination, this evidence has led to the suggestion that sterility virulence may be a "targeted" pathogen strategy with an adaptive explanation (Apari et al. 2014), rather than simply a physiological by-product of STIs being localized to the reproductive organs (Antonovics et al. 2011). In particular, it has been hypothesized that by causing host reproductive failure, sterility virulence may promote host sexual activity and thus increase STI transmission (Apari et al. 2014). However, this explanation requires individuals to have both the ability to detect reproductive failure (e.g., a species with long-term pair bonds) and the capacity to act upon this information (e.g., divorce and find new mate), and so the hypothesis is primarily targeted toward humans (Apari et al. 2014). Yet as Apari et al. (2014) noted, sterilizing STIs are neither restricted to humans nor species with long-term pair bonds (Smith and Dobson 1992; Lockhart et al. 1996; Knell and Webberley 2004), limiting the generality of this explanation. For example, the two-spot ladybird and koala are both highly promiscuous with no long-term pair bonds, yet experience high rates of infection by sterilizing STIs (Weigler et al. 1988; Hurst et al. 1995).

One key difference between STIs and other directly transmitted pathogens is the epidemiology of transmission. For pathogens transmitted by direct (nonsexual) contact, transmission is generally density dependent as contacts between individuals tend to increase with density (Anderson and May 1979; Begon et al. 2002; McCallum et al. 2017). For STIs, however, transmission tends to be mainly frequency dependent as sex acts and reproduction are largely determined by mating system, and only weakly depend upon population density in the absence of Allee effects (May and Anderson 1987; Anderson

and May 1991; Lockhart et al. 1996; Lloyd-Smith et al. 2004; Antonovics et al. 2011). Although the form of transmission has clear epidemiological consequences (Getz and Pickering 1983; de Castro and Bolker 2005), in deterministic models with large (ideally infinite) population sizes, if sterility virulence causes any increase in transmissibility, sterilizing pathogens are favored, irrespective of the form of transmission (Jaenike 1996; O'Keefe and Antonovics 2002; O'Keefe 2005). Indeed, evolutionary theory on sterility virulence has focused almost exclusively upon such models (Jaenike 1996; O'Keefe and Antonovics 2002; Best et al. 2010; Ashby and Boots 2015; Lion and Gandon 2015; McLeod and Day 2015), ignoring the evolutionary consequences of epidemiology in finite populations. Instead these previous studies have focused upon how spatial structure (O'Keefe and Antonovics 2002; Lion and Gandon 2015) or host coevolution (Best et al. 2010; Ashby and Boots 2015; McLeod and Day 2015) can limit the evolution of sterility virulence, without considering why sterility virulence is more common for STIs than directly transmitted pathogens.

Here, we consider how the interaction between epidemiology and demographic stochasticity can explain the observed patterns of sterility virulence in finite populations. Our analysis shows that when transmission is mainly density invariant and infected individuals experience some density-dependent mortality, pathogen strains causing some degree of sterility tend to be favored. If instead transmission is mainly density dependent or infected individuals do not experience density-dependent mortality, then pathogen strains causing no sterility virulence are favored. Hence, the interaction between epidemiology and demographic stochasticity can help explain why sterility virulence is more commonly associated with STIs than directly transmitted pathogens. To explore the robustness of our results to the inclusion of the possibility of other selective effects of sterility virulence, we also consider the possibility of a (weak) selective advantage to sterility virulence (i.e., transmissibility increases with sterility virulence). When this occurs, both demographic stochasticity and selection favor sterility virulence in STIs. However, for directly transmitted pathogens sterility virulence is disfavored by demographic stochasticity but favored by selection. We provide the conditions under which demographic stochasticity nevertheless overcomes selection to disfavor sterility virulence in directly transmitted pathogens. Taken as a whole, our results provide a novel explanation for why sterility virulence is more commonly seen in STIs, and why directly transmitted pathogens should not cause sterility, even when favored to by selection.

Model

Consider a susceptible-infected host population with horizontal transmission, no multiple infection, and no recovery. Let the density of susceptible hosts and hosts infected with strain $i = 1, 2$ at time t be $x(t)$ and $y_i(t)$, respectively, and take $\mathbf{x} = (x, y_1, y_2)$. Susceptible and infected hosts die at a per capita rate of $d(\mathbf{x})$ and $\mu(\mathbf{x})$, respectively, and mortality is a nondecreasing function of population density ($\partial d/\partial \mathbf{x}_i \geq 0$, $\partial \mu/\partial \mathbf{x}_i \geq 0$). Susceptible hosts are born at rate $b(\mathbf{x})$, which may be regulated by density-dependent processes (e.g., logistic growth), while the fecundity of a host infected with strain i is reduced by a factor of $1 - \delta_i$ due to sterility virulence: if $\delta_i = 1$, sterility virulence is maximal and strain i fully sterilizes the host, whereas if $\delta_i = 0$, strain i causes no sterility virulence. Thus, if strain i is present in the population, $\partial b/\partial \delta_i < 0$. The per capita transmission rate of strain i is $\beta_i(\mathbf{x})$ and due to pathogen mutation (and strain replacement at the within-host level), strain i infected hosts transition to strain j infected hosts at a per capita rate ν; as this is assumed to be rare, $\nu \ll 1$. For brevity, we will refer to ν as mutation rate. We will assume strain 1 causes less host sterility than strain 2, $\delta_1 < \delta_2$, but may have reduced transmissibility, $\beta_1(\mathbf{x}) = \beta(\mathbf{x})(1 - \varepsilon)$, $\beta_2(\mathbf{x}) = \beta(\mathbf{x})$, and that selection on sterility virulence through transmission is weak, $0 \leq \varepsilon \ll 1$. Note that the assumption of weak selection places no restrictions upon the between-strain difference in sterility virulence, so in the most extreme case, it is possible one strain fully sterilizes while the other causes no sterility virulence, that is, $\delta_1 = 0$, $\delta_2 = 1$.

Under these assumptions, the population dynamics can be described using the following system of stochastic differential equations (SDEs):

$$\begin{aligned} dx &= [b(\mathbf{x}) - d(\mathbf{x})x - \beta_1(\mathbf{x})y_1 - \beta_2(\mathbf{x})y_2]dt + \Omega^{-1/2}M_x, \\ dy_1 &= [(\beta_1(\mathbf{x}) - \mu(\mathbf{x}))y_1 + \nu(y_2 - y_1)]dt + \Omega^{-1/2}M_{y_1}, \\ dy_2 &= [(\beta_2(\mathbf{x}) - \mu(\mathbf{x}))y_2 + \nu(y_1 - y_2)]dt + \Omega^{-1/2}M_{y_2}, \end{aligned} \quad (1)$$

where Ω is habitat size, and so controls the likelihood of interactions between hosts, regardless of infection status, while M_x and M_{y_i} are unbiased stochastic noise terms. Critically, these noise terms arise naturally from the individual birth, death, and transmission events from the full stochastic process underlying the approximation given by (1), and so are dependent upon the population demographics in a well-defined fashion (see Supporting Information 1 for the full derivation). As habitat size becomes large ($\Omega \to \infty$), we will be left with a system of ordinary differential equations (ODEs). In the absence of mutations ($\nu = 0$), the ODE system predicts the strain with higher transmissibility (strain 2) will fix in the population, irrespective of the form of the transmission function, $\beta(\mathbf{x})$, or the between-strain difference in sterility virulence. This can be seen by considering the conditions under which strain i can invade a monomorphic strain j population at equilibrium: from (1), strain i will have a

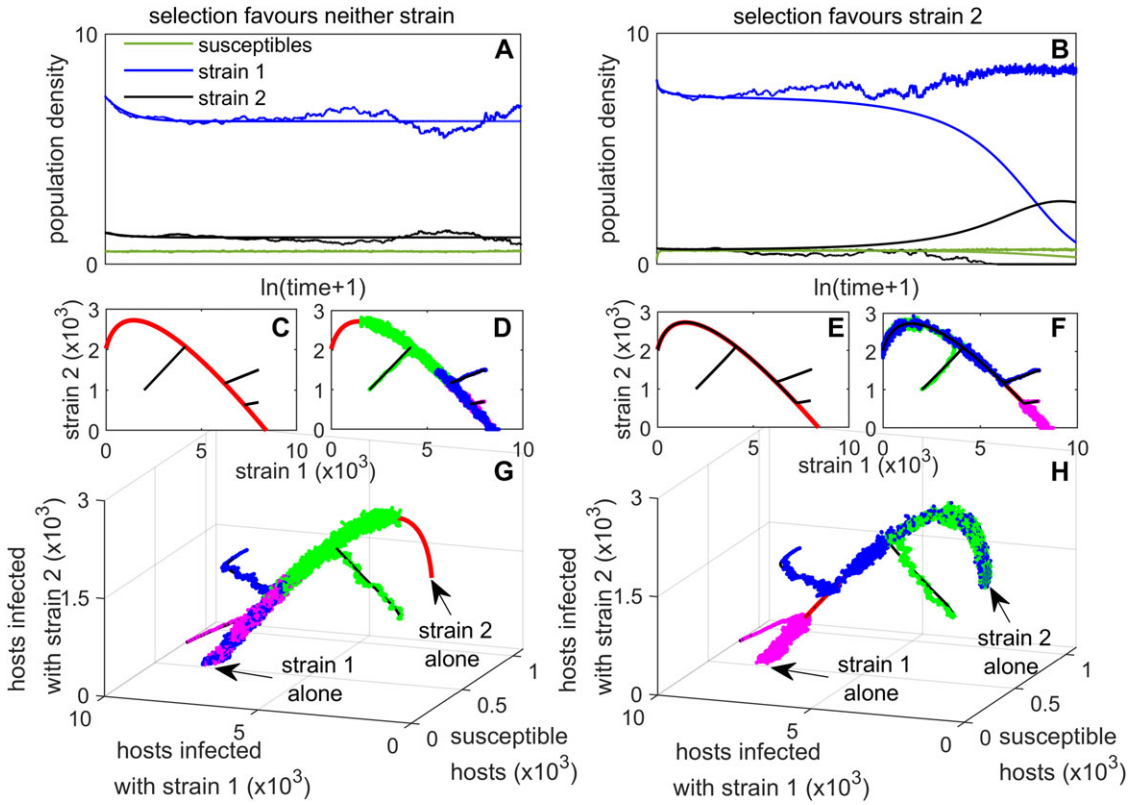

Figure 1. **Illustration of the fast- and slow-timescales associated with system (1). Subplots (A) and (B) show sample trajectories of the deterministic dynamics (smooth curves) and stochastic dynamics (rough curves) of the full stochastic process approximated by (1); time has been rescaled so that both the fast- and slow-timescales are visible. Initially, the expected change in (1) is the dominant force and so there is a close match between the deterministic and stochastic dynamics (fast-timescale). However, once the system has moved into the vicinity of the slow manifold, demographic stochasticity comes into play and the stochastic trajectories diverge from the deterministic trajectories. Subplots (G) and (H) show these dynamics in (x, y_1, y_2)-space, while subplots (C–F) show the view from the (y_1, y_2)-plane. In subplots (C–H), the red curve is the slow manifold, the black curves are deterministic trajectories, and the rough curves are stochastic trajectories. Subplots (A), (C), (D), and (G) assume there is no selection, while subplots (B), (E), (F), and (G) assume weak selection favoring strain 2 ($\varepsilon = 0.005$). For these examples, $\beta_1(\mathbf{x}) = 8x(1-\varepsilon)$, $\beta_2(\mathbf{x}) = 8x$, $b(\mathbf{x}) = 5(x + y_1 + 0.25y_2)$, $d(\mathbf{x}) = 0.25 + 0.5(x + y_1 + y_2)$, and $\mu(\mathbf{x}) = 0.25 + d(\mathbf{x})$, with $\Omega = 10^3$ and no mutation ($\nu = 0$).**

positive per capita growth when rare if $\beta_i(\mathbf{x}) > \mu(\mathbf{x})$. Since at the monomorphic strain j equilibrium we have $\beta_j(\mathbf{x}) = \mu(\mathbf{x})$, at equilibrium the condition $\beta_i(\mathbf{x}) > \mu(\mathbf{x})$ becomes $\beta_i(\mathbf{x}) > \beta_j(\mathbf{x})$, and so whichever strain has the higher transmissibility is favored. If instead the two strains have the same transmissibility, but different sterility virulence, then in the ODE model with no mutation

$$\frac{dy_1/dt}{dy_2/dt} = \frac{(\beta(\mathbf{x}) - \mu(\mathbf{x}))y_1}{(\beta(\mathbf{x}) - \mu(\mathbf{x}))y_2} = \frac{y_1}{y_2}, \tag{2}$$

and so it follows that $y_1 = C_0 y_2$, that is, the density of strain 1 is a linear function of the density of strain 2, with the slope determined by the initial state of the population at $t = 0$, that is, $C_0 = y_1(0)/y_2(0)$. It follows that the fraction of infected hosts that are infected by strain 1 will remain constant over time and is set by the initial state of the population at $t = 0$, that is, $\frac{y_1(t)}{y_1(t)+y_2(t)} = \frac{y_1(0)}{y_1(0)+y_2(0)}$, and so the between-strain difference in sterility virulence is selectively neutral with respect to the deterministic evolutionary dynamics.

Because system (1) is a set of coupled SDEs, as currently written, it does not provide much insight into the evolutionary process. Therefore, we wish to reduce it to a more tractable form. To do so, we observe that since selection is weak and mutations are rare, system (1) admits what is commonly referred to as a "slow manifold" (Berglund and Gentz 2006; Parsons and Rogers 2017), which in this case is a curve in (x, y_1, y_2)-space satisfying $\beta(\mathbf{x}) = \mu(\mathbf{x})$. The reason that this curve is referred to as a slow manifold is that in the vicinity of this curve, the per capita growth rate of the different pathogen strains is very small (since mutations are rare and selection is weak), and so changes in the composition of the pathogen population occur slowly. As a result, system (1) has a fast timescale and a slow timescale (Fig. 1). The fast timescale corresponds to demographic processes (e.g., transmission, birth, and death events) driven mainly by the terms in (1) multiplied

by dt; the effect of these processes is to push the system into the vicinity of the slow manifold. In this fast timescale regime, stochasticity has a weak effect, and the dynamics of (1) are very similar to the dynamics of the set of ordinary differential equations (obtained in the limit of $\Omega \to \infty$; see Fig. 1). Once in the vicinity of the slow manifold, however, the system slowly moves along the slow manifold as the composition of the pathogen population changes due to mutation, selection, and stochasticity (this is the slow timescale; see Fig. 1).

As our interest is the evolution of the pathogen, we are primarily interested in the dynamics on the slow timescale, and so we wish to transform system (1) to a simpler form in which the fast timescale dynamics are eliminated. Let $p \equiv y_1/(y_1 + y_2)$ be the proportion of infected hosts that are infected with strain 1. Then using methods outlined in recent work (Constable et al. 2016; Parsons and Rogers 2017), which built off of standard techniques (Katzenberg 1991; Berglund and Gentz 2006), the slow timescale dynamics of p are governed by the stochastic differential equation (SDE)

$$dp = \underbrace{(\nu(1-2p) - \varepsilon\beta(\mathbf{x}_p)p(1-p))}_{a(p)}\,dt + \underbrace{\left(\frac{p(1-p)}{\Omega}\mathfrak{R}(\mathbf{x}_p)\right)}_{\sigma^2(p)}^{1/2} dW_t, \tag{3}$$

where dW_t is a Gaussian random variable with mean zero and variance dt (see Supporting Information 2 for details). In (3), $\mathbf{x}_p = [x_p, p\mathcal{I}(p), (1-p)\mathcal{I}(p)]$ is the vector of population densities evaluated on the slow timescale, so x_p and $\mathcal{I}(p)$ are the density of susceptible hosts and total density of infected hosts, respectively, on the slow timescale for a given p, and

$$\mathfrak{R}(\mathbf{x}_p) = \frac{\beta(\mathbf{x}_p) + \mu(\mathbf{x}_p)}{\mathcal{I}(p)}. \tag{4}$$

Associated with (3) is a diffusion process with infinitesimal mean $a(p)$ and infinitesimal variance $\sigma^2(p)$ (Ewens 2004; Gardiner 2009; Etheridge 2012). In this context, $a(p)$ represents directional biases favoring a particular strain (through either mutation or selection), whereas $\sigma^2(p)$ represents nondirectional (or unbiased) evolutionary noise due to demographic stochasticity.

As we will see, when selection is sufficiently weak, demographic stochasticity plays a key role in the evolutionary process, even in large populations. This may seem surprising: typically, demographic stochasticity is viewed as a small effect unless population size is also very small (Lande et al. 2003). In our model, this is true when we are dealing with processes operating on the fast timescale of (1): in that case, the dynamics are largely driven by the expected change (the terms multiplied by dt) since the stochastic noise terms are scaled by $\Omega^{-1/2}$ (which is small for large population sizes). However, when the system is in the vicinity of the slow manifold, the expected change in population density becomes smaller and smaller (since on the slow manifold $\beta(\mathbf{x}) = \mu(\mathbf{x})$), whereas this is not true for the stochasticity. Thus, if selection is weak and mutations are rare, on the slow timescale the effects of selection and mutation are of comparable magnitude to the effect of demographic stochasticity, and so demographic stochasticity can play a significant role (Fig. 1)

Results

We wish to use (3) to understand how selection, stochasticity, and epidemiology interact to shape the evolution of sterility virulence. To do so, we adopt the approach we used elsewhere (McLeod and Day 2019), and ask what is the likelihood of observing the stochastic process in a particular state? If we are more likely to observe the process in a state in which strain i is most frequent, then we will say strain i is favored. In what follows, we provide a brief summary of our analysis, with an emphasis on providing intuition for our results; the full analysis can be found in the Supporting Information 3. Our first objective will be to understand the evolution of sterility virulence when there is no link between sterility virulence and transmission (i.e., $\varepsilon = 0$), to see how epidemiology alone can impact which strain is favored. We will then briefly consider the possibility of a link between transmission and sterility virulence to understand how robust our predictions are in the presence of selection.

When there is no link between transmission and sterility virulence ($\varepsilon = 0$), then there are only two factors in (3): (i) unbiased mutations, pushing the population toward $p = 1/2$, and (ii) the role played by the infinitesimal variance, $\sigma^2(p)$, which need not be symmetric and instead will vary in magnitude dependent upon the pathogen population composition. But when the infinitesimal variance is large (resp. small), evolutionary noise will be large (resp. small), causing the system to exhibit more variation. As a consequence, the stochastic process will spend less time in states with large evolutionary noise (large $\sigma^2(p)$) and so will be less likely to be observed in these states. Hence, in the absence of selection, the pathogen strain minimizing $\sigma^2(p)$ is stochastically favored (Supporting Information 3). Since the factor $p(1-p)/\Omega$ in $\sigma^2(p)$ is symmetric in p, the strain minimizing $\sigma^2(p)$ will be the strain that minimizes $\mathfrak{R}(\mathbf{x}_p)$ (see also Supporting Information 3).

The biological importance of $\mathfrak{R}(\mathbf{x}_p)$ can be easily understood. The numerator of $\mathfrak{R}(\mathbf{x}_p)$, $\beta(\mathbf{x}_p) + \mu(\mathbf{x}_p)$, represents the variance in per capita pathogen growth rate at selective neutrality. As the variance in per capita growth increases, pathogen population turnover also increases, causing the population composition to change more

rapidly. Counteracting this force is the effect of total pathogen population density, $\mathcal{I}(p)$ (the denominator of $\mathfrak{R}(\mathbf{x}_p)$): the larger the pathogen population (as measured by $\mathcal{I}(p)$), the more robust the population is to demographic fluctuations since the net change in population composition due to a strain i infected host being replaced by a strain j infected host will be smaller. These two effects can be understood by analogy to a random walk where the walker's position is p: if we increase the variance in per capita growth rate, we decrease time between steps taken by the walker, whereas if we decrease population size, we increase the size of each step. A walker taking larger, more frequent steps will exit a region more rapidly, despite having no directional bias in its movement, and so will be less likely to be observed in such a region. Thus, the ratio of the variance in per capita growth rate to total population size can be roughly thought of as a measure for how rapidly the stochastic process moves on the evolutionary timescale. The strain whose sterility virulence "slows" this process the most will be favored. This is because if the stochastic process gets "bogged down" for a particular strain composition and so population composition changes slowly, then we will be more likely to observe this strain composition in the evolving population at any given point in time. With this in mind, we now consider how epidemiology alters the level of sterility virulence that minimizes $\mathfrak{R}(\mathbf{x}_p)$.

ROLE OF EPIDEMIOLOGY

We are interested in how epidemiology affects the level of sterility virulence minimizing $\mathfrak{R}(\mathbf{x}_p)$. To determine this, assume the two pathogen strains are selectively neutral ($\varepsilon = 0$) and are nearly identical in sterility virulence, $\delta_1 = \delta$ and $\delta_2 = \delta + \Delta\delta$ with $\Delta\delta \approx 0$. Then, to determine which strain minimizes $\mathfrak{R}(\mathbf{x}_p)$, a first-order Taylor expansion of $\mathfrak{R}(\mathbf{x}_p)$ in $\Delta\delta$ reveals that it is sufficient to consider the sign of $d\mathfrak{R}/d\delta$, evaluated when $\delta_1 = \delta_2 = \delta$. In particular, if $d\mathfrak{R}/d\delta > 0$, pathogen strains causing less host sterility will be favored, whereas if $d\mathfrak{R}/d\delta < 0$, pathogen strains causing greater host sterility will be favored. Thus, we wish to determine the sign of $d\mathfrak{R}/d\delta$. For this analysis, since neither $\mathcal{I}(p)$ nor x_p will depend upon the composition of the pathogen population, p, to distinguish this case from the more general case, we let $\mathcal{I}(p) = \bar{\mathcal{I}}$ and $x_p = \bar{x}$.

To determine the sign of $d\mathfrak{R}/d\delta$, we will focus upon the transmission function $\beta(\mathbf{x}) = Bx/(x + y + c)$, where $y = \sum_i y_i$ and B and c are constants. The motivation for choosing this transmission function is that by varying the parameters B and c, we can investigate everything from exclusively frequency-dependent transmission ($c = 0$) to exclusively density-dependent transmission ($c \to \infty$). Note that when we take the limit as $c \to \infty$, we assume that B increases in proportion to c so that the ratio B/c is a nonzero, finite constant. Using this transmission function, by implicit differentiation (see Supporting Information 4), we can compute

$$\frac{d\mathfrak{R}}{d\delta} \propto \left[-\frac{x+y}{x+y+c} x \frac{\partial \mu}{\partial x} + \frac{y+c}{x+y+c}\left(\mu(x,y) - x\frac{\partial \mu}{\partial x} - y\frac{\partial \mu}{\partial y}\right)\right]_{-x=\bar{x}\,y=\bar{\mathcal{I}}}, \quad (5)$$

where proportionality is up to a positive factor. From equation (5), we see that there are two primary factors determining whether sterility virulence is stochastically favored or disfavored: (i) the influence of density-dependent mortality (controlled by the derivatives $\frac{\partial \mu}{\partial x}$, $\frac{\partial \mu}{\partial y}$), and (ii) the degree to which transmission is either frequency or density dependent (controlled by c). Clearly, if mortality is unaffected by population density (i.e., $\partial\mu/\partial x = \partial\mu/\partial y = 0$), then $d\mathfrak{R}/d\delta > 0$ and so sterility virulence is never stochastically favored. However, as the strength of density-dependent mortality increases, so too do the potential benefits of sterility virulence. If mortality is positively density dependent (i.e., $\partial\mu/\partial x > 0$, $\partial\mu/\partial y > 0$), then as transmission becomes increasingly frequency dependent ($c \to 0$), the likelihood that $d\mathfrak{R}/d\delta < 0$ increases. This can be shown by computing the derivative of (5) with respect to c (while holding all else constant): doing so, we see that if $\mu(x, y) + \frac{\partial \mu}{\partial x} y > \frac{\partial \mu}{\partial y} y$, then (5) is a monotonically increasing function of c. The condition $\mu(x, y) + \frac{\partial \mu}{\partial x} y > \frac{\partial \mu}{\partial y} y$ will hold for most, if not all, biologically plausible mortality functions; for example, susceptible hosts being equal or superior competitors to infected hosts is sufficient (e.g., $\mu(\mathbf{x}) = a_0 + a_1 x + a_2(y_1 + y_2)$ with $a_1 \geq a_2$).

To understand these results, observe that to minimize $\mathfrak{R}(\mathbf{x}_p)$, the pathogen strain needs to reduce its variance in per capita growth (the numerator of $\mathfrak{R}(\mathbf{x}_p)$), while simultaneously increasing its equilibrium density (the denominator of $\mathfrak{R}(\mathbf{x}_p)$). It can be shown that the variance in per capita growth is a non-increasing function of sterility virulence (Supporting Information 4). The intuitive reason for this is that increasing sterility virulence reduces the density of susceptibles, lowering the rate at which transmission and death events occur, thereby decreasing the variance in per capita growth of the pathogen. Because increasing sterility virulence reduces the variance in per capita growth (decreasing the numerator of $\mathfrak{R}(\mathbf{x}_p)$) and so favoring sterility virulence, the necessary (but not sufficient) condition for sterility to be stochastically disfavored is that an increase in sterility virulence must also decrease pathogen density (decrease the denominator of $\mathfrak{R}(\mathbf{x}_p)$). As sterility virulence only indirectly affects pathogen density through its negative effect on susceptible density, pathogen density is reduced by sterility virulence only if a decrease in susceptible density has a greater impact upon transmission, $\beta(\mathbf{x})$, than on infected host mortality, $\mu(\mathbf{x})$. The likelihood of this will increase as the degree to which transmission is density dependent increases, and the weaker the dependence of host mortality

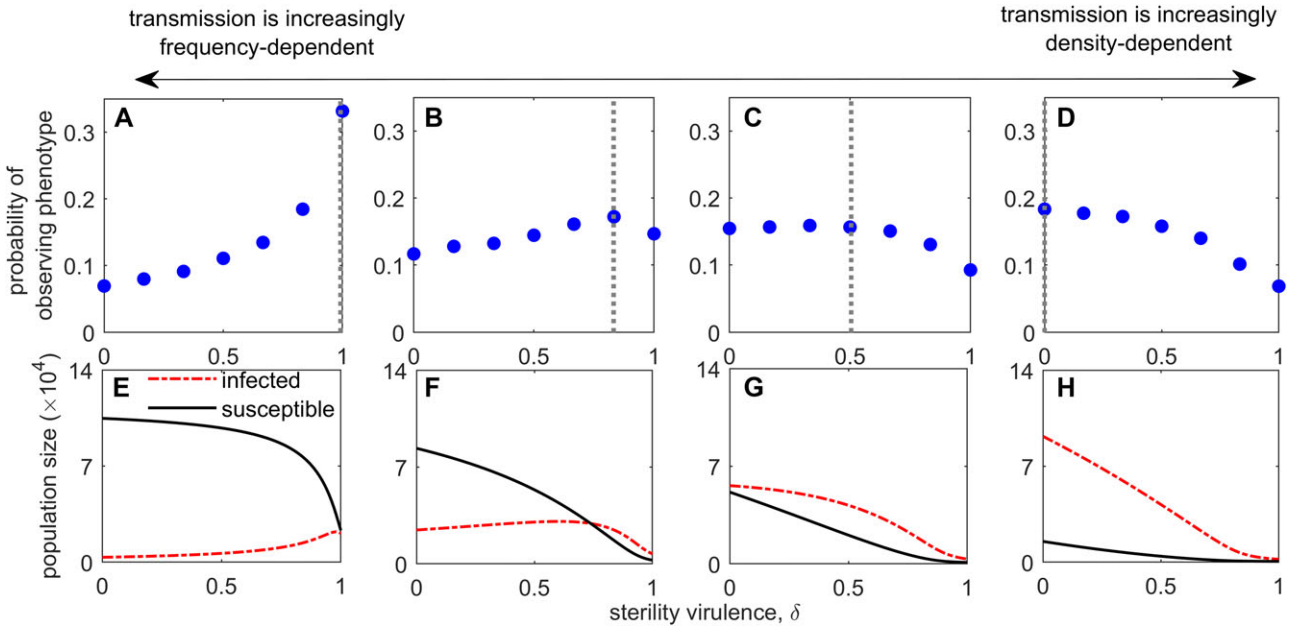

Figure 2. **The favored level of sterility virulence depends upon the epidemiology of transmission. As pathogen transmission transitions from mainly frequency dependent (subplot A,E) to mainly density dependent (subplot (D) and (H)), the favored sterility virulence phenotype transitions from one causing complete sterility to one causing no sterility in agreement with analytic predictions (the level of sterility virulence that minimizes $\Re(\mathbf{x}_p)$ is the dashed vertical line in subplots (A–D)). The blue circles in subplots (A–D) are the stationary distribution obtained from 2.5×10^4 runs of the multistrain model with $N = 7$ (see system (8)) simulated using Euler–Maruyama method (see Supporting Information 5). Subplots (E–H) show the expected number of susceptible and infected hosts for the sterility virulence indicated by the *x*-axis. Each column corresponds to a different value of q: from subplot (A) to (D), q was taken to be 3.9216, 3.125, 1.9048, and 0.5, respectively. The choice of q was made to show the range of potential optimal sterility virulence phenotypes. Parameter values used were $\{B, \alpha, m, \kappa, \tilde{b}, \nu, \Omega\} = \{16.8, 0.05, 0.75, 0.3, 4, 10^{-6}, 10^4\}$.**

upon susceptible density, in agreement with our analysis of (5) (Fig. 2E–H).

The other thing to note is that (5) only indirectly depends upon the birth and death rates of the susceptible population. As a result, the birth and death rates of susceptibles can assume any form satisfying the assumptions leading to model (1) and the results from consideration of (5) will not be altered. However, in order for sterility virulence to be favored by frequency-dependent transmission, the "strength" of density-dependent mortality cannot be too weak. In some populations, population size will be primarily regulated by density-dependent fecundity and only weakly impacted by density-dependent mortality. In this circumstance, it can be shown that if the basic reproductive ratio of the pathogen approaches unity, sterility virulence is favored for frequency-dependent transmission (Supporting Information 4).

To provide a concrete example of when sterility virulence is favored or disfavored, consider the model

$$\begin{aligned} b(\mathbf{x}) &= \tilde{b}(x + \textstyle\sum_i [1 - \delta_i] y_i), \\ d(\mathbf{x}) &= m + \kappa(x + \textstyle\sum_i y_i), \\ \mu(\mathbf{x}) &= \alpha + d(\mathbf{x}), \end{aligned} \tag{6}$$

where $\tilde{b}$ is the per capita rate of reproduction, m is natural mortality, α is virulence-related mortality, and κ controls the magnitude of density-dependent mortality. Set $y = \sum_i y_i$ and suppose that $\delta_i = \delta$ for all i, so that all strains have equal sterility virulence. Then from (5), if transmission is exclusively density-dependent, $\beta(\mathbf{x}) = Bx$ (so $c \to \infty$ in (5)), this leaves (5) equal in the limit of $c \to \infty$ to $\alpha + m$. Hence, for density-dependent transmission, pathogens causing no sterility are favored. Conversely, if transmission is exclusively frequency dependent, $\beta(\mathbf{x}) = Bx/(x + y)$, the level of sterility minimizing $\Re(\mathbf{x}_p)$ can be computed directly by solving $[d\Re/d\delta]_{\delta=\delta^*} = 0$ for δ^*: as the quantities are evaluated for $\delta_1 = \delta_2 = \delta$, on the slow timescale this will not depend upon p (nor will $\Re(\mathbf{x}_p)$). Doing so yields

$$\delta^* = 1 - \frac{(B - \alpha - \tilde{b})(m + \alpha + \sqrt{B(m + \alpha)})}{\tilde{b}(B - m - \alpha)}, \tag{7}$$

and so pathogens causing some level of sterility are stochastically favored, and the optimal level of sterility is δ^*.

Although our analytic predictions have focused upon the two-strain case, we can extend (1) to include N strains, each with

a different sterility virulence, such that

$$\begin{aligned} dx &= \left[b(\mathbf{x}) - d(\mathbf{x})x - \textstyle\sum_i \beta(\mathbf{x})y_i\right]dt + \Omega^{-1/2}M_x \\ dy_i &= \left[(\beta(\mathbf{x}) - \mu(\mathbf{x}))y_i + \nu(\textstyle\sum_j y_j - Ny_i)\right]dt + \Omega^{-1/2}M_{y_i}, \\ & \qquad i = 1, 2, \ldots, N \end{aligned} \tag{8}$$

where y_i is the density of the i-th strain, $\mathbf{x} = (x, y_1, y_2, \ldots, y_N)$, and M_x and M_{y_i} are stochastic unbiased noise terms (see Supporting Information 5 for full details). Note that in equation (8), we have assumed that strain i mutates to strain j at a per capita rate ν, and so the total per capita rate at which strain i will mutate to a different strain is $\nu(N-1)$, however, if we were to instead use a single-step mutational scheme it will not qualitatively change our results (see Supporting Information 5). In Figure 2, we simulate system (8) with $N = 7$ using the Euler–Maruyama method (Allen 2011; see also Supporting Information 5), where we have used the model specified by equation (6) with $\beta(\mathbf{x}) = \frac{Bx}{1+q(x+\sum_i y_i)}$. Hence, as we decrease q from subplot **a** to subplot **d**, transmission becomes increasingly density dependent. The simulation results show that the predictions of our two-strain model scale as expected when there are more strains present in the population. In particular, when transmission is predominantly frequency dependent (Fig. 2A), fully sterilizing pathogens are favored, whereas when transmission is increasingly density dependent (Fig. 2D), sterility virulence becomes disfavored, in agreement with our general predictions obtained from consideration of (5). Additionally, the stochastically favored level of sterility virulence, δ^*, for the N strain model matches well with the level of virulence minimizing $\mathfrak{R}(\mathbf{x}_p)$ obtained in the two-strain case.

Now, when the population becomes infinitely large, $\Omega \to \infty$, demographic stochasticity is negligible, and so each pathogen phenotype is equally likely to be observed in the population, irrespective of its sterility virulence. Thus we may ask how small populations have to be for demographic stochasticity to have an appreciable effect. In Figure 3, we simulate the multistrain model (8) as presented in Figure 2, for a range of population sizes (by varying Ω), revealing that even in large populations, demographic stochasticity can play the role predicted by our analysis of the two-strain model. Note as well that the impact of demographic stochasticity inversely scales with the magnitude of directional biases (the strength of selection and the frequency of mutations). If there is a strong link between sterility virulence and transmission (so selection is strong), or mutations are too frequent, demographic stochasticity will play a limited role. This can be seen more explicitly by considering (3): since dW_t is a Gaussian random variable with mean zero and variance dt, $dW_t = \mathcal{O}(\sqrt{dt})$. Therefore, if selection or mutation is strong (i.e., $\varepsilon \gg 1/\Omega$ or $\nu \gg 1/\Omega$), the influence of the directional biases in (3) (as measured by $a(p)$) will greatly exceed the influence of stochasticity (as measured by $\sigma^2(p)$).

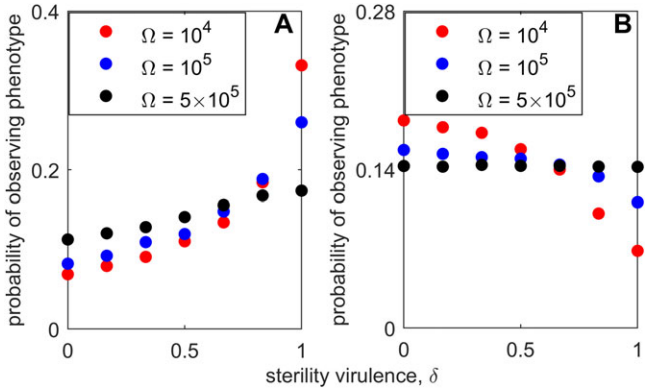

Figure 3. The relationship between population size (controlled by habitat size, Ω) and the strength of demographic stochasticity. In subplot (A), transmission is mainly frequency dependent, whereas in subplot (B), transmission is mainly density dependent. The circles are the stationary distribution for three different values of Ω, obtained from 2.5 × 10^4 runs of model (8) with $N = 7$ using Euler–Maruyama method. Parameter values used were $\{B, \alpha, m, \kappa, b, \nu, \Omega\} = \{16.8, 0.05, 0.75, 0.3, 4, 10^{-6}, 10^4\}$, with $q = 3.9216$ for subplot (a) and $q = 0.5$ for subplot (b).

WHAT HAPPENS WHEN TRANSMISSIBILITY AND STERILITY VIRULENCE ARE LINKED?

Thus far we have assumed there is no link between sterility virulence and transmissibility, that is, sterility virulence is selectively neutral. This was purposeful: (i) the evidence for a transmission–sterility virulence tradeoff is limited (Abbate et al. 2015), and (ii) we wanted to understand the effect of demographic stochasticity upon the likelihood of observing different pathogen phenotypes in the population. The results of the previous section showed that demographic stochasticity tends to favor sterility virulence as transmission becomes increasingly frequency dependent, provided mortality is also density dependent. However, we may ask how robust this conclusion is if, as previous studies have considered (Jaenike 1996; O'Keefe and Antonovics 2002; O'Keefe 2005), there is a positive link between sterility–virulence and transmission. Because in well-mixed populations susceptible hosts represent a public good freely available to all competing pathogen strains, the deterministic model ($\Omega \to \infty$) predicts pathogens should sterilize (Jaenike 1996; O'Keefe and Antonovics 2002; O'Keefe 2005). This result holds irrespective of whether transmission is predominantly frequency or density dependent.

If the strain at the selective disadvantage also minimizes $\mathfrak{R}(\mathbf{x}_p)$, however, then demographic stochasticity will act in opposition to selection. This occurs if transmission is predominantly density dependent, or mortality is independent of

population density. In this circumstance, we may ask how weak does selection have to be relative to the effect of demographic stochasticity. This can be thought of as asking how small the between-strain difference in transmissibility has to be relative to the between-strain difference in sterility virulence. Our purpose here is not to consider different possible tradeoff functions, or to construct a stochastic analogue of adaptive dynamics. Rather, our objective is to consider how robust the effects of demographic stochasticity are relative to selection, when they act in opposition.

To do so, we suppose strain 2 has the transmission advantage, $\beta_1(\mathbf{x}) = \beta(\mathbf{x})(1-\varepsilon)$, $\beta_2(\mathbf{x}) = \beta(\mathbf{x})$, and causes increased sterility virulence, such that $\delta_2 = \delta$ and $\delta_1 = \delta - \omega\varepsilon$ with $\omega\varepsilon \in [0, \delta]$. Here, ω is a positive scaling factor (so $\delta_1 < \delta_2$) linking between-strain differences in transmissibility to between-strain differences in sterility (i.e., if $\omega = 1$, then a one unit change in between-strain transmissibility corresponds to a one unit change in between-strain sterility). We provide a more comprehensive analysis in the Supporting Information 3, but here we focus only upon the case in which mutations are very rare as the qualitative patterns are similar for larger mutation rates. In this regime, assuming selection is weak, the strain with lower transmission and lower sterility virulence (strain 1) is favored if

$$\frac{\omega}{2\Omega}\left.\frac{\partial \mathfrak{R}}{\partial \delta}\right|_{\varepsilon=0} > \beta(x_0), \tag{9}$$

where x_0 is the density of susceptibles when $\varepsilon = 0$. If the value of ω/Ω required to satisfy (9) decreases, either by reducing population size (by decreasing habitat size, Ω) or through increasing the between-strain difference in sterility virulence relative to the between-strain difference in transmissibility (by increasing ω), then there is a corresponding decline in the likelihood of the evolution of more transmissible pathogens (with higher sterility virulence). Note that the critical value of ω/Ω required to satisfy (9) can be related to the strength of selection by observing that by definition of ω, we must have $\omega \leq \delta/\varepsilon$. This in turn implies that $\omega/\Omega \leq \delta/[\varepsilon\Omega]$, and so if, for example, $\varepsilon = 1/\Omega$, then a stochastic reversal would require both (9) to be satisfied, and $\omega/\Omega < \delta$. Thus the between-strain difference in transmissibility (the selective advantage of sterility virulence) must be small in order for the effects of selection to be overturned by demographic stochasticity.

The biological interpretation of (9) is clear: the right-hand side is the (selective) transmission costs paid by the less sterilizing strain (the between-strain difference in transmissibility is $\varepsilon\beta(x_0)$, but as everything in (9) is first-order in ε, ε cancels from both sides; Supporting Information 3), while the left-hand side are any nonselective benefits of reduced sterility. To satisfy (9), at minimum the strain with reduced sterility virulence must minimize the ratio $\mathfrak{R}(\mathbf{x}_p)$, that is $\frac{\partial \mathfrak{R}}{\partial \delta} > 0$. Hence, we can conceptually view inequality (9) as asking when a strain paying a directional bias cost (right-hand side of (9)) can be stochastically favored by "slowing" the stochastic process through minimizing $\mathfrak{R}(\mathbf{x}_p)$ (left-hand side of (9)).

To gain some more insight into (9) and what favors or disfavors a reversal of selection, focus again upon the model specified by (6) with density-dependent transmission, $\beta(\mathbf{x}) = Bx$. Our previous analysis showed that for this model, nonsterilizing pathogens minimize $\mathfrak{R}(\mathbf{x}_p)$. Treating inequality (9) as an equality and solving for the critical ratio ω/Ω, it can be shown that as the basic reproductive ratio, $R_0 = B(\tilde{b} - m)/(\kappa[\alpha + \tilde{b}])$, of the (neutral) pathogen strain becomes small ($R_0 \to 1$), sterilizing pathogens are increasingly likely to be disfavored (Fig. 4D–F). This could occur by increasing mortality (increasing α, m, or κ; Fig. 4B and C) or by decreasing transmissibility (decreasing B; Fig. 4A). On the other hand, if R_0 becomes large, then a variety of outcomes are possible, depending upon which demographic quantity is manipulated to increase R_0. If we increase transmissibility, then for large (and small) R_0, sterilizing pathogens are increasingly likely to be disfavored (Fig. 4D). Conversely, if we decrease natural- and virulence-related mortality, then whether reductions in mortality (and so increases in R_0) cause sterilizing pathogens to be increasingly favored or disfavored depends upon a complex interaction with the other parameters (Fig. 4E and F). That these predictions depend upon what assumptions are made about the underlying population demographics emphasizes that not all forms of density dependence are equivalent, and that how density dependence is modeled can lead to very different conclusions (Mylius and Diekmann 1995; Metz et al. 2008).

Finally, we note that although we assumed a positive link between sterility virulence and transmission in keeping with previous work (Jaenike 1996; O'Keefe and Antonovics 2002; O'Keefe 2005), if instead there was a negative link between sterility virulence and transmission, then whenever $\partial\mathfrak{R}/\partial\delta > 0$, selection and demographic stochasticity work together to disfavor sterility virulence. Conversely, if $\partial\mathfrak{R}/\partial\delta < 0$, then selection and demographic stochasticity work in opposition. In this situation, whenever $-\beta(x_0) < \frac{\omega}{2\Omega}\frac{\partial\mathfrak{R}}{\partial\delta}|_{\varepsilon=0}$ the influence of demographic stochasticity can reverse selection, leading to sterility virulence being stochastically favored. This can be shown by slightly modifying the arguments used to derive (9).

Discussion

The fact that sterility virulence is common for STIs but rare for other directly transmitted pathogens, while other forms of virulence tend to be limited for STIs (Lockhart et al. 1996; Antonovics et al. 2011), has led to the suggestion that sterility virulence may have an adaptive explanation and be "targeted" (Apari et al. 2014). In particular, it has been hypothesized that by sterilizing, STIs may

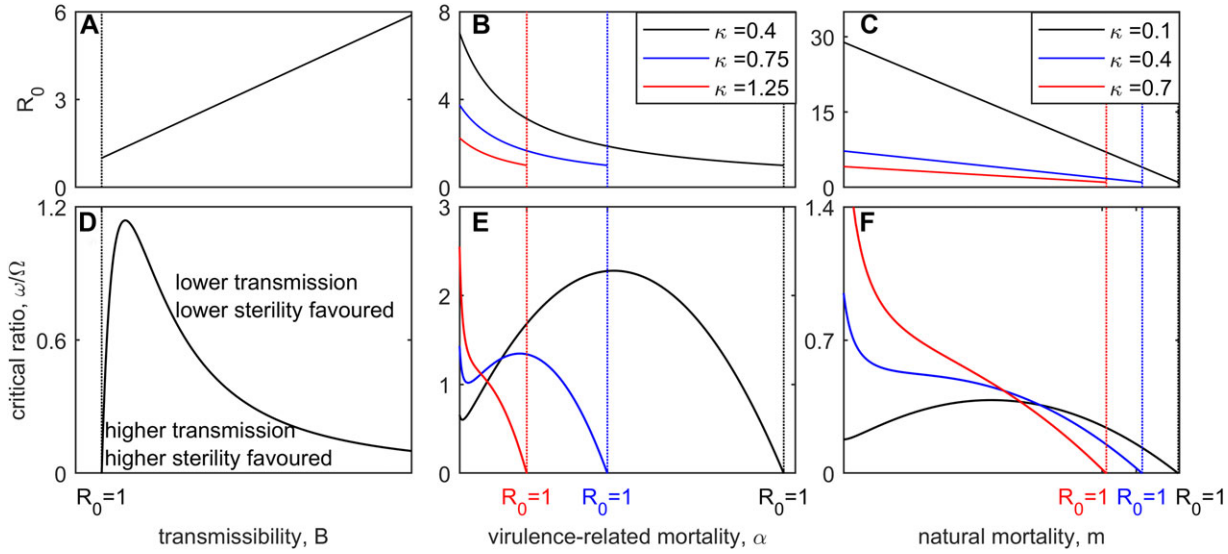

Figure 4. Example behavior of critical ratio ω/Ω (subplots (D–F)) and basic reproductive number, R_0 (subplots A-C), as demographic parameters, B, α, and m are varied. In subplots (D–F), for values of ω/Ω above (resp. below) the various curves, the strain with decreased transmission and decreased sterility virulence is favored (resp. disfavored). Thus when the critical ratio ω/Ω is small, strains causing no sterility virulence are increasingly stochastically favored, despite being selected against. No matter what demographic quantity is varied (B, α, m), as $R_0 \to 1$ (dashed vertical lines correspond to $R_0 = 1$, subplots (A–C)), the value of ω/Ω required to favor reduced sterility virulence also decreases. For this model, the density of susceptibles is an increasing function of α and m and a decreasing function of B, and so as $R_0 \to 1$, the density of susceptibles becomes maximal.

promote host sexual activity (Apari et al. 2014), and so adaptively increase STI transmission. However, this hypothesis requires a number of assumptions (e.g., pair bonds, ability to divorce and remate) that are not commonly associated with host–STI systems, limiting its explanatory power.

One epidemiological difference between STIs and directly transmitted pathogens is the form of transmission: STIs tend to exhibit frequency-dependent transmission, whereas directly transmitted pathogens tend to exhibit mainly density-dependent transmission (e.g., Antonovics et al. 2011). This is because the number of sexual partners an individual has usually depends upon mating system and is only weakly affected by population density (McCallum et al. 2001), and in many sexually reproducing species, mating rate is limited by breeding season, pair formation, and gestation period, and not population density (Lockhart et al. 1996). Indeed, the relationship between frequency-dependent transmission and STIs can be derived from first principles (Lloyd-Smith et al. 2004), but is also supported by models fit to data (May and Anderson 1987; Anderson and May 1991; Augustine 1998; Webberley et al. 2006; Ryder et al. 2014). Here, we have shown that sterility virulence may indeed be "targeted" to STIs as argued elsewhere (Apari et al. 2014), but that such a relationship can be explained by consideration of the transmission differences between STIs and directly transmitted pathogens alone. In particular, provided there is some density-dependent mortality, frequency-dependent transmission tends to favor sterility virulence whereas density-dependent transmission disfavors sterility virulence. Our results can be applied to more complex combinations of frequency- and density-dependent transmission that sometimes better fit empirical data (e.g., Ryder et al. 2005; Smith et al. 2009; McCallum et al. 2017) such that "mainly" frequency-dependent transmission favors sterility virulence whereas "mainly" density-dependent transmission disfavors sterility (Fig. 2). Moreover, we have shown that even if there is a (weak) selective advantage to sterilizing in terms of increased transmissibility, stochasticity can be sufficient to overcome selection (Fig. 4), and that this is most likely to occur for pathogens with either low R_0 or high transmissibility.

Although our prediction that stochasticity favors sterilizing STIs requires some form of density-dependent mortality of infected individuals, we suggest that this is likely not an overly stringent assumption. Not only are STIs commonly associated with low levels of virulence (other than sterility; Lockhart et al. 1996; Antonovics et al. 2011; Apari et al. 2014), they are often chronic (Antonovics et al. 2011) and so we should not expect being infected to shield or remove individuals from intraspecific competition that would otherwise occur. As such, it seems reasonable to expect that infected hosts will be subject to the same demographic forces as susceptible hosts, and many populations are known to be subject to density-dependent adult mortality, through, for example, predation (e.g., lemmings; Gilg et al. 2003), or intraspecific competition and aggression over territories (e.g.,

wolves; Cubaynes et al. 2014) and resources (e.g., red deer and birds; Clutton-Brock et al. 2002; Saether et al. 2016).

Examining the role played by different demographic assumptions has a long history in life history modeling, with the focus typically upon when evolution admits an optimization principle (Mylius and Diekmann 1995; Metz et al. 2008). Applications to host–pathogen systems have considered deterministic models, and so the primary interest is when demographic feedbacks can create the potential for adaptive diversification and evolutionary branching (e.g., Pugliese 2002; Best et al. 2009; Boldin and Kisdi 2012; Cortez 2013), rather than the interplay between population demography and stochasticity, as we have considered here. Our work thus suggests an additional implication of demographic assumptions for host–pathogen evolution when finite population sizes are considered; moreover, the framework we have employed here may be used to investigate other forms of less commonly considered pathogen virulence (such as morbidity) that often have limited evolutionary implications in standard, deterministic host–pathogen models.

Existing theory has tended to focus upon determining what factors select against sterility virulence without explicitly addressing why sterility virulence is more commonly associated with STIs than directly transmitted pathogens. However, a central assumption of existing models is that population size is large (ideally infinite) and so stochasticity is ignored. As a result, epidemiological differences between STIs and other directly transmitted pathogens, such as the form of transmission function, tend to play a limited evolutionary role. By focusing upon finite population sizes, here we have shown the importance of epidemiology upon the evolution of sterility virulence.

AUTHOR CONTRIBUTIONS

D.V.M. and T.D. designed study, analyzed model, and wrote paper.

ACKNOWLEDGMENTS

Financial support was provided by an ETH Zürich postdoctoral fellowship (to D.V.M.). All simulations were run on the HPC cluster at ETH Zürich.

DATA ARCHIVING

Data associated with this manuscript can be found at https://datadryad.org/resource/doi:10.5061/dryad.70423j5

LITERATURE CITED

Abbate, J. L., S. Kada, and S. Lion. 2015. Beyond mortality: sterility as a neglected component of parasite virulence. PLoS Pathog. 11:e1005229.

Allen, L. J. S. 2011. An Introduction to Stochastic Processes with Applications to Biology. CRC Press, Boca Raton, FL.

Anderson, R. M., and R. M. May. 1979. Population biology of infectious diseases: Part I. Nature 280:361–367.

———. 1991. Infectious diseases of humans: dynamics and control. Oxford Univ. Press, Oxford, UK.

Antonovics, J., M. Boots, J. Abbate, C. Baker, Q. McFrederick, and V. Panjeti. 2011. Biology and evolution of sexual transmission. Ann. N.Y. Acad. Sci. 1230:12–24.

Apari, P., J. D. de Sousa, and V. Muller. 2014. Why sexually transmitted infections tend to cause infertility: an evolutionary hypothesis. PLoS Pathog. 10:e1004111.

Ashby, B., and M. Boots. 2015. Coevolution of parasite virulence and host mating strategies. Proc. Natl. Acad. Sci. 112:13290–13295.

Augustine, D. J. 1998. Modelling *Chlamydia*–koala interactions: coexistence, population dynamics and conservation implications. J. Appl. Ecol. 35:261–272.

Begon, M., M. Bennett, R. G. Bowers, N. P. French, S. M. Hazel, and J. Turner. 2002. A clarification of transmission terms in host–microparasite models: numbers, densities and areas. Epidemiol. Infect. 129:147–153.

Berglund, N., and B. Gentz, 2006. Noise-induced phenomena in slow-fast dynamical systems. Springer, New York, New York.

Best, A., A. White, and M. Boots. 2009. The implications of coevolutionary dynamics to host-parasite interactions. Am. Nat. 173:779–791.

———. 2010. Resistance is futile but tolerance can explain why parasites do not always castrate their hosts. Evolution 64:348–357.

Boldin, B., and E. Kisdi. 2012. On the evolutionary dynamics of pathogens with direct and environmental transmission. Evolution 66:2514–2527.

Clutton-Brock, T. H., T. N. Coulson, E. J. Milner-Gulland, D. Thomson, and H. M. Armstrong. 2002. Sex differences in emigration and mortality affect optimal management of deer populations. Nature 415:633–637.

Constable, G. W. A., T. Rogers, A. J. McKane, and C. E. Tarnita. 2016. Demographic noise can reverse the direction of deterministic selection. Proc. Natl. Acad. Sci. 113:E4745–E4754.

Cortez, M. H. 2013. When does pathogen evolution maximize the basic reproductive number in well-mixed host-pathogen systems? J. Math. Biol. 67:1533–1585.

Cubaynes, S., D. R. MacNulty, D. R. Stahler, K. A. Quimby, D. W. Smith, and T. Coulson. 2014. Density-dependent intraspecific aggression regulates survival in northern Yellowstone wolves (*Canis lupus*). J. Anim. Ecol. 83:1344–1356.

de Castro, F., and B. Bolker. 2005. Mechanisms of disease-induced extinction. Ecol. Lett. 8:117–126.

Etheridge, A. 2012. Some mathematical models from population genetics. Springer-Verlag, New York, New York.

Ewens, W. J. 2004. Mathematical population genetics I: theoretical introduction. Springer: Interdisciplinary Applied Mathematics, New York, New York.

Gardiner, C. W. 2009. Handbook of stochastic methods. Springer: Complexity, Berlin, Germany.

Getz, W. M., and J. Pickering. 1983. Thresholds and population regulation. Am. Nat. 121:892–898.

Gilg, O., I. Hanski, and B. Sittler. 2003. Cyclic dynamics in a simple vertebrate predator-prey community. Science 302:866–868.

Hurst, G. D. D., R. G. Sharpe, A. H. Broomfield, L. E. Walker, T. M. O. Majerus, I. A. Zakharov, and M. E. N. Majerus. 1995. Sexually transmitted disease in a promiscuous insect, *Adalia bipunctata*. Ecol. Entomol. 20:230–236.

Jaenike, J. 1996. Suboptimal virulence of an insect-parasitic nematode. Evolution 50:2241–2247.

Katzenberg, G. S. 1991. Solutions of a stochastic differential equation forced onto a manifold by a large drift. Ann. Probab. 19:1587–1628.

Knell, R. J., and K. M. Webberley. 2004. Sexually transmitted diseases of insects: distribution, evolution, ecology and host behaviour. Biol. Rev. 79:557–581.

Lande, R., S. Engen, and B. Saether, 2003. Stochastic population dynamics in ecology and conservation. Oxford Univ. Press, Oxford, UK.

Lion, S., and S. Gandon. 2015. Evolution of spatially structured host–parasite interactions. J. Evol. Biol. 28:10–28.

Lloyd-Smith, J. O., W. M. Getz, and H. V. Westerhoff. 2004. Frequency-dependent incidence in models of sexually transmitted diseases: portrayal of pair-based transmission and effects of illness on contact behaviour. Proc. R. Soc B. 271:625–635.

Lockhart, A. B., P. H. Thrall, and J. Antonovics. 1996. Sexually transmitted diseases in animals: ecological and evolutionary implications. Biol. Rev. 71:415–471.

May, R. M., and R. M. Anderson. 1987. Transmission dynamics of HIV infection. Nature 326:137–142.

McCallum, H., N. Barlow, and J. Hone. 2001. How should pathogen transmission be modelled? Trends Ecol. Evol. 16:295–300.

McCallum, H., A. Fenton, P. J. Hudson, B. Lee, B. Levick, R. Normal, S. E. Perkins, M. Viney, A. J. Wilson, and J. Lello. 2017. Breaking beta: deconstructing the parasite transmission function. Phil. Trans. R. Soc. B 372:20160084.

McLeod, D. V., and T. Day. 2015. Pathogen evolution under host avoidance plasticity. Proc. R. Soc B. 282:20151656.

———. 2019. Social evolution under demographic stochasticity. PLoS Comp. Biol. 15:1–13.

Metz, J. A. J., S. D. Mylius, and O. Diekmann. 2008. When does evolution optimize? Evol. Ecol. Res. 10:629–654.

Mylius, S. D., and O. Diekmann. 1995. On evolutionarily stable life histories, optimization and the need to be specific about density dependence. Oikos 74:218–224.

O'Keefe, K. J. 2005. The evolution of virulence in pathogens with frequency-dependent transmission. J. Theor. Biol. 233:55–64.

O'Keefe, K. J., and J. Antonovics. 2002. Playing by different rules: the evolution of virulence in sterilizing pathogens. Am. Nat. 159:597–605.

Parsons, T. L., and T. Rogers. 2017. Dimension reduction for stochastic dynamical systems forced onto a manifold by large drift: a constructive approach with examples from theoretical biology. J. Phys. A: Math. Theor. 50:415601.

Pugliese, A. 2002. On the evolutionary coexistence of parasite strains. Math. Biosci. 177:355–375.

Ryder, J., M. Hoare, D. Pastok, M. Bottery, M. Boots, A. Fenton, D. Atkinson, R. J. Knell, and G. D. D. Hurst. 2014. Disease epidemiology in arthropods is altered by the presence of nonprotective symbionts. Am. Nat. 183:E89–E104.

Ryder, J. J., K. M. Webberley, M. Boots, and R. J. Knell. 2005. Measuring the transmission dynamics of a sexually transmitted disease. Proc. Natl. Acad. Sci. 102:15140–15143.

Saether, B., G. V., S. Engen, T. Coulson, P. R. Grant, M. E. Visser, J. E. Brommer, B. R. Grant, L. Gustafsson, B. J. Hatchwell, et al. 2016. Demographic routes to variability and regulation in bird populations. Nat. Comm. 7:12001.

Smith, G., and A. P. Dobson. 1992. Sexually transmitted diseases in animals. Parasitol. Today 8:159–166.

Smith, M., S. Telfer, E. R. Kallio, S. Burthe, A. R. Cook, X. Lambin, and M. Begon. 2009. Host–pathogen time series data in wildlife support a transmission function between density and frequency dependence. Proc. Natl. Acad. Sci. USA 106:7905–7909.

Webberley, K. M., J. Buszko, V. Isham, and G. D. D. Hurst. 2006. Sexually transmitted disease epidemics in a natural insect population. J. Anim. Ecol. 75:33–43.

Weigler, B. J., A. A. Girjes, N. A. White, N. D. Kunst, F. N. Carrick, and M. F. Lavin. 1988. Aspects of the epidemiology of *Chlamydia psittaci* infection in a population of koalas (*Phascolarctos cinereus*) in southeastern Queensland, Australia. J. Wildlife Dis. 24:282–291.

Associate Editor: F. Debarre
Handling Editor: Mohamed A.F. Noor

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure 1. Behaviour of model $b(\mathbf{x}) = b(x + y_1 + 0.25y_2)$, $d(\mathbf{x}) = 0.25 + 0.5(x + y_1 + y_2)$, $\mu(\mathbf{x}) = d(\mathbf{x}) + 0.25$, $\beta(\mathbf{x}) = 8x/(x + y_1 + y_2 + c)$, with $\Omega = 10^3$ and $\varepsilon = 0$.

Figure 2. Change in $\Theta(a_0, a_1)$ as we manipulate a_0 and a_1.

Figure 3. Comparison of the stationary distributions between the model where phenotypes mutate to any other phenotype with equal probability (random mutation; blue circles) and the model where phenotypes mutate to neighbouring phenotypes with equal probability (single-step mutation; red circles).