Seasonality and the Coexistence of Pathogen Strains

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Online Supplement For "Seasonality and the Coexistence of Pathogen Strains"

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Appendix

The Single-Strain Model Has a Single, Stable Equilibrium

To analyze the single-strain model, we rewrite the model as;

$$I_{n+1} \quad = \quad Wi(I_n), \tag{S1}$$

Here I_n is the initial density of the pathogen in generation n; in the main text we write this as $I_n(0)$, but for convenience here we simplify our notation. Also, W is the inter-epidemic survival rate of the pathogen, and $i(I_n)$ is the cumulative fraction infected i at the burnout equilibrium, which we write here as;

$$1 - i(I_n) \quad = \quad \exp\left[-R_0\{(1-I_n)i(I_n) + I_n\}\right]. \tag{S2}$$

To show that this model has a stable equilibrium, we use linearity stability analysis. From equation (S1), the equilibrium value of $\hat{I}$ is calculated as;

$$\hat{I} \quad = \quad W\hat{i}, \tag{S3}$$

where $\hat{i}$ is calculated from (S2) when $I_n = \hat{I}$.

An immediate difficulty is that we cannot write down an explicit expression for $\hat{I}$, but we can show that the model has a single non-zero equilibrium. To do this, we rewrite the burnout equation (S2) as;

$$1 - \hat{i} \quad = \quad \exp\left[-R_0\{(1-W\hat{i})\hat{i} + W\hat{i}\}\right]. \tag{S4}$$

To show that there is only one equilibrium, we show that the two sides of the above equation

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only intersect once. To do this, we define the two sides of the equation as;

$$g(i) \equiv 1 - i, \tag{S5}$$

$$f(i) \equiv \exp\left[-R_0\{(1 - Wi)i + Wi\}\right] \tag{S6}$$

We then observe that $g(0) = f(0) = 1$, corresponding to a disease-free equilibrium, while $g(1) = 0$ and $f(1) > 0$. It follows that if $g'(0) = -1 > f'(0)$, then $g(i)$ and $f(i)$ must intersect at least once, corresponding to an endemic equilibrium. We then further observe that,

$$f'(i) = -R_0\left(1 + W(1 - 2i)\exp\left[-R_0\{(1 - Wi)i + Wi\}\right]\right. . \tag{S7}$$

Because $f'(0) = -R_0(1 + W)$, $f'(0) < -1$ as long as $R_0(1 + W) > 1$. The condition that $R_0 > 1$ is thus sufficient for there to be at least one intersection of $g(i)$ and $f(i)$. It is then straightforward to show that, for all i and W, $f'(i) < 0$ and $f''(i) > 0$. It follows that $g(i)$ and $f(i)$ only intersect once, and so there is only one equilibrium. It is worth noting however, that because of the importance of inter-epidemic survival there is still an equilibrium even if $1/(1 + W) < R_0 < 1$.

To show that the equilibrium is stable, it suffices to show that the first derivative of the right-hand side of the model equation (S1) is greater than -1 and less than 1. To do this, we implicitly differentiate both sides of the burnout equation (S2) with respect to I_n, and evaluate at $\hat{I} = W\hat{i}$, to get;

$$W\frac{di}{dI_n}|_{\hat{I}} = \frac{WR_0(1 - \hat{i})\exp\left[-R_0\{(1 - W\hat{i})\hat{i} + W\hat{i}\}\right]}{1 + WR_0(1 - W\hat{i})\exp\left[-R_0\{(1 - W\hat{i})\hat{i} + W\hat{i}\}\right]} \tag{S8}$$

Visual inspection makes clear that the right-hand side of the above equation is positive as long as $\hat{i} < 1$ and $W < 1$. By definition, $\hat{i} < 1$, and we assume that $W < 1$ throughout. To further

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show that the right-hand side is less than 1, we write;

$$\frac{WR_0(1-\hat{i})\exp\left[-R_0\{(1-W\hat{i})\hat{i}+W\hat{i}\}\right]}{1+WR_0(1-W\hat{i})\exp\left[-R_0\{(1-W\hat{i})\hat{i}+W\hat{i}\}\right]} \quad < \quad 1. \tag{S9}$$

Rearranging produces the expression;

$$R_0\exp\left[-R_0\{(1-W\hat{i})\hat{i}+W\hat{i}\}\right](W-1) \quad < \quad 1. \tag{S10}$$

This expression clearly holds for all $W < 1$. The single-strain version of our model thus has a single, stable equilibrium point for all values of the reproductive number $R_0 > 1$ and the inter-epidemic survival rate $W < 1$.

Swapping the Resident and the Invader

Figs. S1 and S2 show mirror-image versions of the invasions in figs. 3 and 4 in the main text. What this means is that in fig. S1 we switched the parameters of the resident and the invader relative to fig. 3, and likewise for fig. S2 relative to fig. 4. Note that in both of figs. S1 and S2 the equilibrium fraction infected with each pathogen strain is the same as in the corresponding figure in the main text.

Multiple Time-Scale Analysis

Here we present the details of our multiple time-scale analysis, which we used to derive equations (22) and (23) in the main text. For convenience, we express the state variables as functions of the fraction of hosts that are no longer susceptible $x \equiv 1 - S$. Note that for the model with no effect of the invader on the susceptible population $x \equiv Z_r + I_r$; x is thus more concise than the expression $Z_r + I_r$. Near the end of the epidemic $x \approx Z_r$, but at the onset of the epidemic $Z_r(0) = 0$, and so at that point $x = I_r(0)$.

At the beginning of an invasion, the fraction infected by the invader will inevitably be far

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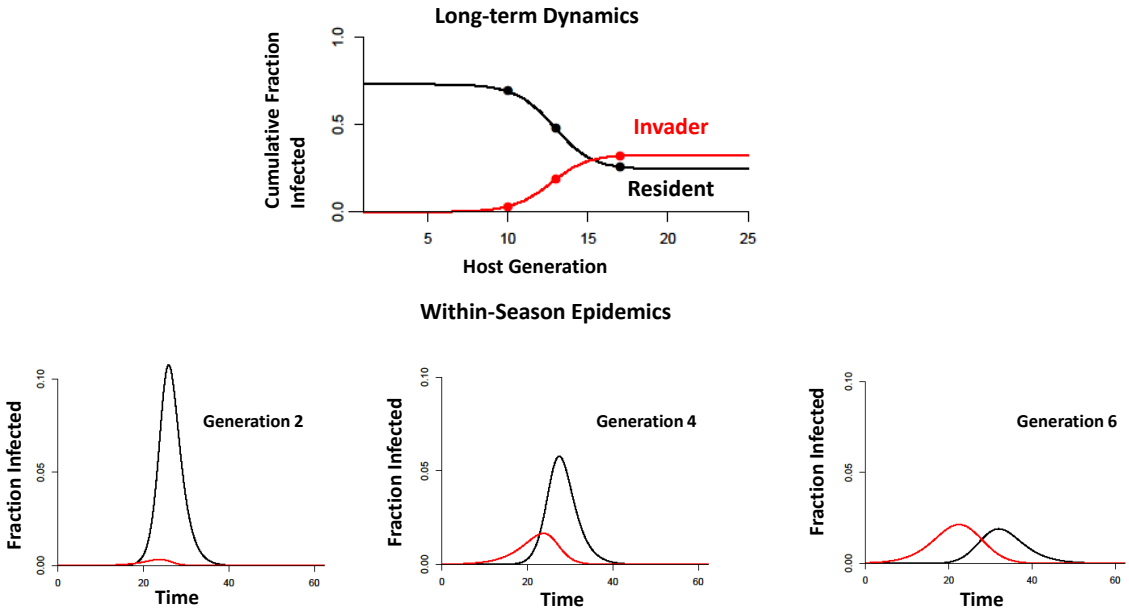

Figure S1: Coexistence resulting from an epidemic-equilibrium invasion. Here we follow fig. 3 in the main text, except that here the roles of the invader and the resident are reversed. As in fig. 3, at the beginning of the simulation the resident's initial infection rate is equal to its single-strain equilibrium, while the invader's initial infection rate is 10^{-8}. In contrast to fig. 3, however, here the resident has transmission rate $\beta_r = 1.8$, removal rate $\mu_r = 1$, and inter-epidemic survival $W_i = 10^{-9}$, while the invader has transmission rate $\beta_r = 1.25$, removal rate $\mu_r = 1$, and inter-epidemic survival $W_r = 10^{-3}$. The reproductive numbers of the resident and invader are thus $R_{0,i} = 1.8/1 > 1.25/1 = R_{0,i}$, so that the invader has a higher reproductive number than the resident. Because the resident's inter-epidemic survival rate is very low, the invader has an advantage early in the epidemic, allowing it to invade and ultimately to reach the coexistence equilibrium. Note that the cumulative infection rates of the two pathogens reach the same coexistence equilibrium as in fig. 3.

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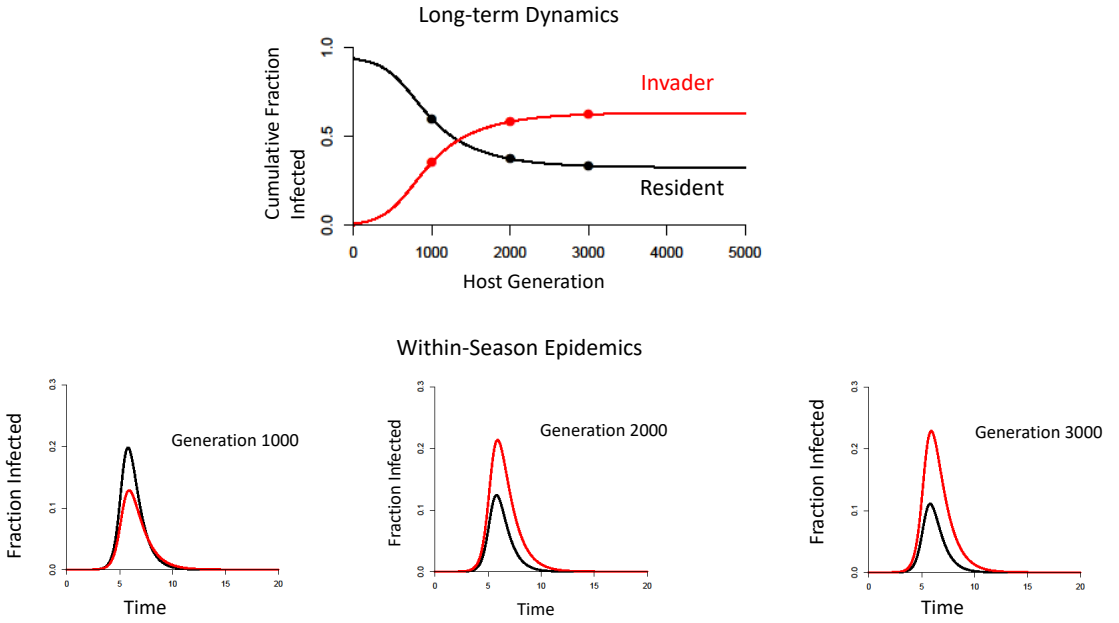

Figure S2: Model simulations showing how coexistence can occur through an epidemic-transient invasion, as in fig. 4 in the main text, except that here the roles of the invader and the resident are reversed. As in fig. 4, at the beginning of the simulation the resident's initial infection rate is equal to its single-strain equilibrium, while the invader's initial infection rate is 10^{-8}. In contrast to fig. 4, however, here the invader has transmission rate $\beta_i = 4$, removal rate $\mu_i = 1.3$, and inter-epidemic survival $W_i = 4.05 \times 10^{-7}$, while the resident has transmission rate $\beta_r = 3.5$, removal rate $\mu_r = 1$, and inter-epidemic survival $W_r = 1.1 \times 10^{-6}$. Because the invader thus has lower initial epidemic fitness than the resident, such that $\lambda_{0,i} = 2.5 < 2.7 = \lambda_{0,r}$, the invader has a disadvantage early in the epidemic. The invader nevertheless has higher reproductive number than the resident, such that $R_{0,i} = 4 > 3.5 = R_{0,r}$, and it is thus able to infect more hosts over the entire course of the epidemic, and therefore it can successfully invade. Note that the cumulative infection rates of the two pathogens reach the same coexistence equilibrium as in fig. 4.

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lower than the fraction infected by the resident. As a first step in analyzing transient dynamics during epidemics, we therefore assume that the invader does not contribute to the depletion of susceptible hosts, and consequently we can set the invader's fraction infected $I_i(t) = 0$ in the susceptible-host equation (10), so that only the resident affects the host;

$$\frac{dS}{dt} = -R_{0,r} S I_r. \tag{S11}$$

Given this simplification, we can write down a highly accurate approximation to the dynamics of the invader in the early stages of the invasion: this approximation then allows us to understand the conditions under which invasions are driven by the transient dynamics of epidemics.

The simplification that the fraction infected by the invader $I_i(t) = 0$ allows us to (temporarily) eliminate the time dependence of the model using the chain rule. To do this, we divide the full-model equations (11)-(18) by the approximate equation (S11) for the susceptible population. We can then express our model equations as functions of the fraction non-susceptible x instead of as functions of time t;

$$I_r'(x) = -\frac{R_{0,r}(1-x)I_r - I_r}{-R_{0,r}(1-x)I_r}, \tag{S12}$$

$$I_i'(x) = -\frac{R_{0,i}u(1-x)I_i - uI_i}{-R_{0,r}(1-x)I_r}, \tag{S13}$$

$$Z_i'(x) = -\frac{uI_i}{-R_{0,r}(1-x)I_r}. \tag{S14}$$

This change of variables means that we can integrate over the interval $x_0 \leq x \leq x_\infty$, where $x_0 = I_r(0)$ and x_∞ denotes the cumulative fraction infected at the end of the epidemic (in the main text we instead use $Z_r(\infty)$). Integrating over time t in contrast requires that we integrate over the interval $t = 0$ to $t = \infty$; in practice, of course, this means integrating from $t = 0$ to some large but arbitrary value of t. In addition to allowing us to write down an invasion criterion, integrating over x is thus a first step towards greater computational convenience.

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To calculate the initial conditions for the above equations we must also take into account how the state variables I_r, I_i and Z_i in equations (S12)-(S14) depend on x instead of t. We thus have an unusual looking set of initial conditions:

$$I_r(x_0) = I_r(0), \tag{S15}$$

$$I_i(x_0) = 1, \tag{S16}$$

$$Z_i(x_0) = 0. \tag{S17}$$

On the right hand side of equation (S15), I_r is a function of time, while on the left hand side of the equation $I_r(x_0)$ is a function of the cumulative fraction infected x, as are I_i and Z_i in equations (S16) and (S17).

We set the initial fraction infected with the invader $I_i(0) = 1$ because as we will shortly explain our approximate equation for $I_i'(x)$ is a linear function of I_i; accordingly, just as the equation for exponential growth $dN/dt = rN$ implies that the solution $N(t) = N(0)\exp(rt)$ is proportional to $N(0)$, the linearity of our differential equation for $I_i(x)$ means that its solution is proportional to $I_i(0)$, as we show below. This means that for now we can use any non-zero value for $I_i(0)$, because later we can switch back to assuming that $I_i(0) \ll 1$. Also, because our ultimate interest is in what happens at $t = \infty$, and because the cumulative fraction infected $Z_r(\infty) \equiv x_\infty$, we have omitted explicit reference to Z_r.

Given these initial conditions, we can integrate (solve) equation (S12) to produce an explicit expression for $I_r(x)$, the fraction infected by the resident, in terms of x, the overall fraction no longer susceptible:

$$I_r(x) = x + \frac{1}{R_{0,r}} \log_e \frac{(1-x)}{(1-I_r(0))}. \tag{S18}$$

Substituting this expression into the invader equation (S13) eliminates the fraction infected by

the resident $I_r(t)$ from that equation:

$$\frac{dI_i}{dx} = \frac{u(R_{0,i}(1-x)-1)I_i}{(1-x)(R_{0,r}x + \log_e(1-x) - \log_e(1-I_r(0))}. \tag{S19}$$

The above equation for $I_i(x)$ is linear, homogeneous and first-order, which means that in principle we can easily solve it by a technique known as separation of variables. The resulting solution, however, would be almost completely uninformative, in the sense that it would not allow us to directly relate the effects of the model parameters to the fraction infected by the invader. In pursuing an alternative analysis, we note first that, as we described in the main text, a particularly important issue is how the initial fraction infected with the resident $I_r(0)$ affects the cumulative fraction infected with the invader $Z_i(\infty)$. Because at the beginning of the invasion $I_r(0)$ is determined by the reproductive number $R_{0,r}$ and the inter-epidemic survival W_r of the invader, understanding the effects of $I_r(0)$ on invader fitness would allow us to understand the effects of $R_{0,r}$ and W_r on the likelihood of a successful invasion. A key goal of our alternative analysis is thus to relate $Z_i(\infty)$ to $I_r(0)$, where $I_r(0)$ is (temporarily) represented by $\epsilon = I_r(0)/\gamma_0$.

A complication for our alternative analysis is that equation (S19)'s denominator vanishes at $x = x_0 = I_r(0) \ll 1$. To cope with this problem, we first simplify the equation by noting that when $I_r(0)$ is small, then $\log_e(1-I_r(0)) \approx I_r(0)$, giving us;

$$\frac{dI_i}{dx} = \frac{u(R_{0,i}(1-x)-1)I_i}{(1-x)(R_{0,r}x + \log_e(1-x) + I_r(0))}. \tag{S20}$$

If we define $\omega \equiv u(R_{0,i}-1)$, this equation further simplifies to

$$I_i'(x) = \frac{dI_i}{dx} = \frac{1 - \frac{1}{R_{0,i}-1}\frac{x}{1-x}}{\frac{I_0}{\omega} + \frac{R_{0,r}x}{\omega} + \frac{\log_e(1-x)}{\omega}} I_i. \tag{S21}$$

Next, for convenience we define the function $\phi(x) \equiv (x + \log_e(1-x))/x^2$. An important point in what follows is that it is possible to use L'Hôpital's rule to show that $\phi(x)$ has a finite,

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non-zero limit as $x \to 0$: $\lim_{x\to 0} \phi(x) = -1/2$. Also, recall that the initial relative fitness of the invader is $\gamma_0 \equiv (\beta_i - \mu_i)/(\beta_r - \mu_r) = u(R_{0,i} - 1)/(R_{0,r} - 1)$. We then express the initial density of the resident in terms of the small parameter $\epsilon = I_r(0)/\omega \ll 1$, so that we can replace equation (S21) with the following:

$$I_i'(x) = \frac{1 - \frac{1}{R_{0,i}-1}\frac{x}{1-x}}{\epsilon + x/\gamma_0 + x^2\phi(x)/\omega} I_i. \tag{S22}$$

We now proceed to analyze the above equation.

Because we assume that $I_r(0) \ll 1$, we can assume that $\epsilon \ll 1$. The observation that $\epsilon \ll 1$ immediately suggests that we should try the standard approach of looking for solutions in terms of a power series in ϵ. We therefore express the fraction infected with the invader I_i in terms of a power series in ϵ and a set of functions $Y_m(x)$. To simplify the problem, we focus on the two lowest-order terms, for which $m = 0, 1$ respectively. Our power series is thus:

$$I_i(x) = Y_0(x) + \epsilon Y_1(x) + \text{higher order terms.} \tag{S23}$$

As we will show, it turns out to be the case that the above power-series solutions do not exist. Counter-intuitively, however, showing that the power-series solutions do not exist is a useful approach because the failure of the power-series approach points us towards an alternative solution that does exist. Accordingly, we use equation (S23) to look for solutions to equation (S22), beginning with the case for which $\epsilon = 0$. In that case, $I_i(x) = Y_0(x)$; substituting $Y_0(x)$ into equation (S22) and rearranging gives;

$$\left(x/\gamma_0 + x^2\phi(x)/\omega\right) Y_0' = \left(1 - \frac{1}{R_{0,i} - 1}\frac{x}{1-x}\right) Y_0, \tag{S24}$$

with $Y_0(0) = 1$.

A difficulty here is that the left hand side of equation (S24) is zero at the initial value of the cumulative fraction infected $x = 0$ and at the resident's burnout value $x = x_\infty$, and so the

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derivative in the equation is infinite at $x = 0$ and $x = x_\infty$. These so-called "singular points" are natural consequences of our re-parameterization $t \mapsto x$, because $I_r(x) \to 0$ for both $x \to 0$ and for $x \to x_r(\infty)$. To better understand this problem, we define $f(x)$ to be the factor on the right-hand side of equation (S22) that multiplies $I_i(x)$, and we set $\epsilon = 0$;

$$f(x) = \frac{1 - \frac{1}{R_{0,i}-1}\frac{x}{1-x}}{x/\gamma_0 + x^2\phi(x)/\omega}$$

Focusing on $x = 0$, we notice first that the function $f(x)$ goes to infinity as $x \to 0$, and that $f(x)$ therefore cannot be represented as a Taylor series near $x = 0$. The function $xf(x)$ in contrast approaches the initial relative epidemic fitness γ_0 as $x \to 0$, and it is then easy to verify that $xf(x)$ can be represented as a Taylor series near $x = 0$. The function $xf(x)$ is therefore what is known mathematically as an "analytic function".

In the context of the differential equation (S22), a singular point with this property is said to be a "regular singular point". The observation that $x = 0$ is a regular singular point allows us to apply a classical result by Fuchs (Bender and Orszag, 1978), which states that equation (S24) has a solution of the form;

$$Y_0 = x^\alpha A(x). \tag{S25}$$

Here $A(x)$ is analytical in a neighborhood of $x = 0$ and the "indicial exponent" α can be determined by matching Y_0 and Y_0' at $x = 0$ (see Bender and Orszag (1978, Chap. 3)). In our case, this will turn out to mean that $\alpha = \gamma_0$, where $\gamma_0 = (\beta_i - \mu_i)/(\beta_r - \mu_r)$ is again the initial relative fitness of the invader. Fuchs's theorem does not explain how to find $A(x)$, but the theorem is nevertheless useful because the knowledge that the solution has the form shown in the equation allows us to find $A(x)$, as we will eventually show.

The problem is that, although equation (S24) is linear and has a regular singular point, implying that equation (S25) provides a useful solution to equation (S24), in practice any such solution will have initial condition $Y_0(0) = 0$. Such a solution therefore cannot satisfy our initial condition $I_i(0) = 1$ (or for that matter any other non-zero initial condition on $I_i(0)$, but

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again 1 is most convenient). It follows that near $x = 0$ even the lowest order of the solution must depend on $\epsilon \neq 0$, and so setting $\epsilon = 0$ is insufficient to solve equation (S22). We conclude that solutions to equation (S22) cannot be expressed as a power series, and thus that the power-series approach has failed. We repeat that this failed attempt is still useful because it has at least shown that that for $x \ll \epsilon$ the solutions should have a structure similar to that of equation (S25).

We therefore attempt to find another kind of solution to equation (S19) that has a different dependence on ϵ. To do this, we apply the method of multiple time scales. (Although our independent variable x does not represent actual time, we will follow standard practice and refer to x as time; moreover, x is in any case implicitly dependent on time t, and therefore in a sense functions as a proxy for t.) On the long time scale, for which which $x > 0$, we still expect that the solution will be close to a function of the form (S25); on the short-time scale, however, finding a solution means that we must change time scales, and focus on a boundary layer close to $x = 0$. Because of the importance of this boundary layer, we refer to this solution as Y_b. On this new time scale, $\tau = x/\epsilon$, and so our approximate differential equation (S24) for the invader infection rate I_i simplifies to,

$$\frac{dY_b}{d\tau} = \epsilon \frac{dY_b}{dx} = \epsilon \frac{1 - \frac{1}{R_{0,i}-1}\frac{x}{1-x}}{\epsilon + x/\gamma_0 + x^2\phi(x)/\omega} Y_b = \epsilon \frac{1 - \frac{1}{R_{0,i}-1}\frac{\epsilon\tau}{1-\epsilon\tau}}{\epsilon + \epsilon\tau/\gamma_0 + (\epsilon\tau)^2\phi(\epsilon\tau)/\omega} Y_b.$$

If we take the limit as $\epsilon \to 0$ on the right-hand side of this equation and apply l'Hôpital's rule multiple times, we have

$$\frac{dY_b}{d\tau} = \frac{Y_b}{1 + \tau/\gamma_0} + O(\epsilon). \tag{S26}$$

Here $O(\epsilon)$ is the Landau order statistic, which is a function such that;

$$\lim_{\epsilon \to 0} \frac{O(\epsilon)}{\epsilon} = 0.$$

The function $O(\epsilon)$ thus represents higher order terms, which approach 0 as ϵ approaches 0.

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Equation (S26) can be solved using methods from introductory calculus. In our case we are looking for a solution with initial condition;

$$Y(x_0) = Y(I_0) = Y(\epsilon\omega) = 1,$$

and so the solution is;

$$Y_b(x) = \left(\frac{x/\gamma_0 + \epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0}. \tag{S27}$$

This equation provides an expression for $I_i(x)$ on the short time scale, meaning the early phase of the epidemic when $x \approx 0$. Because $\epsilon = I_r(0)/\omega$, the short time scale solution is the part of the solution that allows us to understand the effects of the resident's initial fraction infected $I_r(0)$. As we explained in the main text, the dominant effect of $I_r(0)$ in determining invader fitness during the epidemic means that the short time scale solution largely determines whether an invasion can occur. As we further explain in the main text, the short time scale solution also plays the counter-intuitive role of connecting the initial part of the epidemic with the long-term dynamics of the pathogen.

Although the above expression for $I_i(x)$ is useful when x is close to 0, we of course want to know the dynamics of $I_i(x)$ over the entire epidemic. To achieve this understanding, we must combine the short-term solution with a long-term solution (here "short-term" and "long-term" refer only to the early and late phases of a single epidemic, not to the much longer time scales that include the inter-epidemic period). We therefore propose a solution that matches our information about the model behavior on the short and long time scales. Our earlier failed attempt to solve equation (S25) is useful in constructing this proposed solution, because it suggests that to cover both the short and long time scales we should combine the short-term solution in equation (S27) with an (as yet) unknown function $\xi(x)$, as follows;

$$Y(x) = \left(\frac{x/\gamma_0 + \epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0} \xi(x). \tag{S28}$$

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Our next step is to determine what $\xi(x)$ must be. To do this, we note that,

$$Y'(x) = \frac{1}{R_{0,r}\epsilon}\left(\frac{x/\gamma_0+\epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0-1}\xi(x) + \left(\frac{x/\gamma_0+\epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0}\xi'(x). \tag{S29}$$

Because the right hand side of equation (S28) for $Y(x)$ is a solution to our differential equation (S22) for $I_i(t)$, we can substitute equation (S28) into the right-hand side of equation (S22). Equating the result to the left-hand side of equation (S29) gives,

$$\frac{1}{R_{0,r}\epsilon}\left(\frac{x/\gamma_0+\epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0-1}\xi(x) + \left(\frac{x/\gamma_0+\epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0}\xi'(x) = \frac{1-\frac{1}{R_{0,i}-1}\frac{x}{1-x}}{\epsilon+x/\gamma_0+x^2\phi(x)/\omega}\left(\frac{x/\gamma_0+\epsilon}{R_{0,r}\epsilon}\right)^{\gamma_0}\xi.$$

We now have a differential equation that serves to determine what $\xi(x)$ must be:

$$\xi'(x) = \left(\frac{1-\frac{1}{R_{0,i}-1}\frac{x}{1-x}}{\epsilon+x/\gamma_0+x^2\phi(x)/\omega} - \frac{1}{x/\gamma_0+\epsilon}\right)\xi \tag{S30}$$

Taking the limit as $\epsilon \to 0$ gives,

$$\xi'(x) \approx \frac{\frac{u}{x-1}-\gamma_0\phi(x)}{R_{0,r}-1+x\phi(x)}\xi. \tag{S31}$$

This differential equation has the initial condition $\xi(0) = 1$, matching our requirement. Also, the equation no longer has a singularity at $x = 0$, but it still has a singularity at $x = x_\infty$. This latter problem can be solved by matching the function and its derivative at x_∞; we then find that, near x_∞, $\xi \sim |x - x_\infty|^{\alpha_\infty}$, where the indicial exponent is

$$\alpha_\infty = u\frac{R_{0,i}(1-x_\infty)-1}{R_{0,r}(1-x_\infty)-1}.$$

Recall that $1 - x_\infty$ is the final size of the susceptible population after an epidemic of the resident strain r, and that $u = \mu_i/\mu_r$ We then note that $R_{0,r}(1-x_\infty)$ is the effective reproductive number of strain r after the epidemic, so that $R_{0,r}(1-x_\infty) < 1$. The effective reproductive number of the invading strain i is less than 1 exactly when strain i cannot have an epi-

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demic when strain r is at its burnout equilibrium. Because this condition must be true for an epidemic-transient invasion to occur, we have $\alpha_\infty > 0$.

We now have a differential equation for $\xi(x)$, which we can combine with our short-term solution (S27) to create an approximation to our differential equation for $Y(x)$, which in turn approximates $I_i(x)$. Remembering that the solution of $I_i(x)$ is in fact proportional to $I_i(0) \ll 1$ (we are thus no longer assuming that $I_i(0) = 1$), and combining our short-term solution equation (S27) and our long-term solution equation (S31), we can therefore write $I_i(x)$ in terms of $\xi(x)$;

$$I_i(x) = \frac{(x+\epsilon\gamma_0)^{\gamma_0}}{R_{0,r}\gamma_0\epsilon}\xi(x)I_i(0). \tag{S32}$$

If we substitute $\epsilon = I_{0,r}/\omega$ and take the limit as $\epsilon \to 0$, the above equation becomes:

$$I_i(x) = I_i(0)\left(\frac{x}{I_r(0)R_{0,r}/(R_{0,r}-1)}\right)^{\gamma_0}\xi(x). \tag{S33}$$

Rearranging this equation gives the term in the integral in equation (22) in the main text.

Testing the accuracy of our approximations, and changing the variable of integration

Equation (S33) allows us to compare the accuracy of our approximate solution $\xi(x)$ to the corresponding value obtained by solving the full model. To carry out this comparison, we first note that by solving equation (S33) for ξ, we get

$$\xi(x) = \frac{I_i(x)}{I_i(0)}\left(\frac{x}{I_r(0)R_{0,r}/(R_{0,r}-1)}\right)^{-\gamma_0}. \tag{S34}$$

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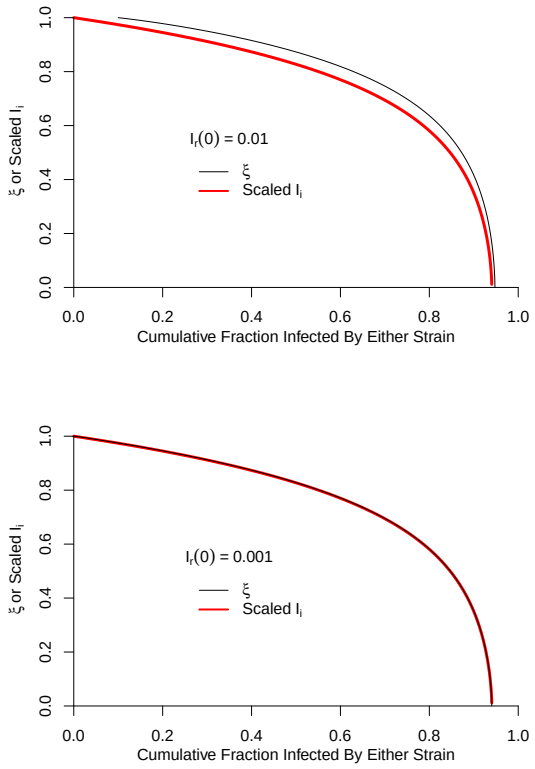

Figure S3: A test of the accuracy of our approximate model. Here we compare the fraction infected by the invader $I_i(x)$ versus the cumulative fraction infected by both strains, as calculated by the approximate model equation (S33), which uses $\xi(x)$, and by the full model equations (11)-(14) and (S11) which we use to calculate the scaled value of I_i. Here the reproductive number for the resident $R_{0,r} = 3$, the reproductive number for the invader $R_{0,i} = 1.5$, the ratio of removal rates $u = 0.5$, and the initial fraction infected with the invader $I_i(0) = 10^{-10}$.

Next we solve the full model (10)-(14) to find $(S(t), I_r(t), I_i(t))$. If we let t vary, we then obtain the following curve in two dimensions;

$$\left((1 - S(t), \frac{I_i(t)}{I_i(0)} \left(\frac{1 - S(t)}{I_r(0) R_{0,r}/(R_{0,r} - 1)}\right)^{-\gamma_0}\right)$$

From equation (S34), we know that $\xi(x)$ versus x is an approximation to this curve.

Because our calculation of ξ is based on the assumption that $I_r(0) \ll 1$, the smaller $I_r(0)$ the better the approximation. As fig. (S3) shows, however, the approximation is remarkably accurate even for $I_r(0) = 10^{-3}$, and only begins to break down for $I_r(0) = 10^{-2}$.

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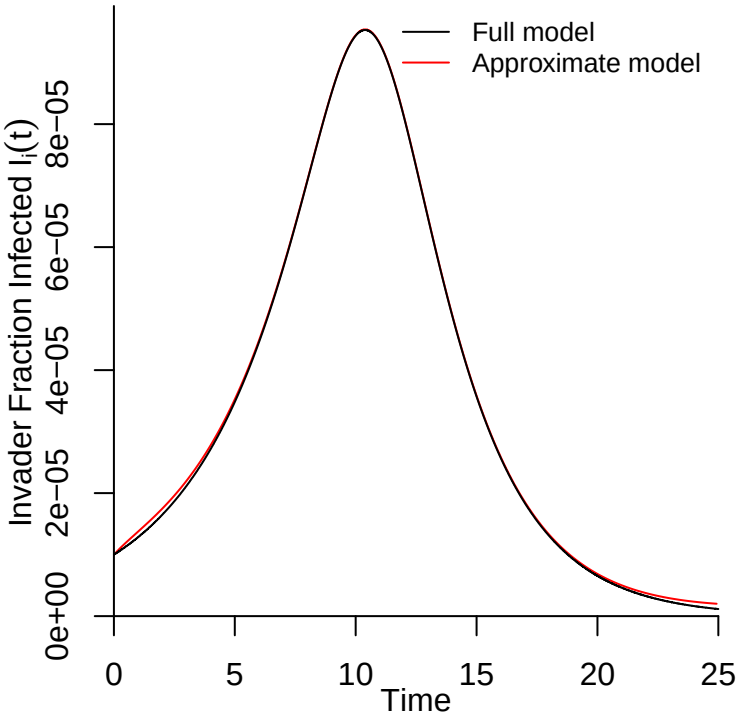

Figure S4: An additional test of the accuracy of our approximate model. Here we compare the fraction infected by the invader $I_i(t)$ as calculated by the approximate model equation (S33) and the full model equations (11)-(14) and (S11). Here the resident's reproductive number $R_{0,r} = 2$, the invader's reproductive number $R_{0,i} = 1.5$, and the relative removal rate $u = 0.7$.

Fig. S3 thus indicates that the approximation is highly accurate, but plots of ξ versus x are somewhat abstract. To focus on a more understandable quantity, we compare our approximate equation (S33) for $I_i(t)$ to the corresponding exact equation (11) for $I_i(t)$ in the full model in the main text. In carrying out this second comparison, a complication is that the approximate equation (S33) expresses the fraction infected with the invader $I_i(x)$ as a function of x, whereas equation (11) from the full model of course describes the dynamics of the invader $I_i(t)$ as a function of time. To generate a prediction for $I_i(t)$ from equation (S33), we therefore numerically solved both equation (S33) and the full model equations (10)-(14), and then we aligned the values of x_r in the two models. Fig. S4 then shows that our approximate version of $I_i(t)$ is also very close to the value of $I_i(t)$ from the full model.

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Both comparisons would seem to cast doubt on the usefulness of equation (S33) by requiring that we solve the full model equations (10)-(14). Equation (S33) is nevertheless useful because our ultimate interest is in long-term dynamics; we are therefore not interested in how the infection rate changes during a single epidemic, but rather in the cumulative infection rate over the entire epidemic. We can thus eliminate the dependence of the equation on x by integrating over time without losing any information. To see this, remember that the integral over time enters the model when we calculate the invader's cumulative fraction infected $Z_i(\infty)$;

$$Z_i(\infty) = u \int_0^\infty I_i(t)dt. \tag{S35}$$

It turns out to be the case that we can replace $I_i(t)$ with $I_i(x)$ in the above equation by changing the variable of integration in the integral from t to x. To do this we first write time t as a function of x, so that $t = t(x)$. By the chain rule, $dt = t'(x)dx$. We then have;

$$\int_0^\infty I_i(t)dt = \int_0^\infty I_i(x)t'(x)dx.$$

Because $dt = t'(x)dx$, and because the cumulative fraction infected $x = 1 - S$ it follows that;

$$\frac{1}{t'(x)} = \frac{dx}{dt} = -\frac{dS}{dt}.$$

We then have $dt = (-1/(dS/dt))dx$. This is useful because at the start of the invasion $I_i(t) \ll 1$, and so we know that $dS/dt \approx -R_{0,r}SI_r$. Also, we know that when $t = 0$ then $x = 0$, and that when $t = \infty$ then $x = x_r^*(\infty)$, allowing us to change the bounds of integration. We can then carry out a change of variables in equation (S35) to get;

$$Z_i(\infty) \approx u \int_0^{x_r^*(\infty)} \frac{I_i(x)}{R_{0,r}(1-x)I_r(x)}\, dx. \tag{S36}$$

As a final check on the accuracy of our approximations, in fig. (S5), we show the effects

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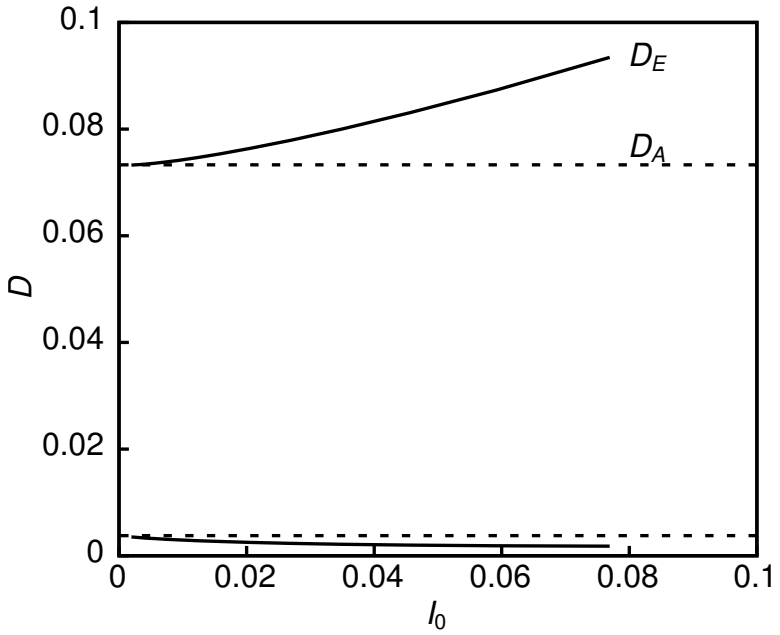

Figure S5: A final test of the accuracy of our approximate model. Here we show the scaling factor $D_i = Z_i(\infty)I_r(0)^{-\gamma_0}$ for the annual growth rate of the invading strain, versus the corresponding exact scaling factor D_E from the full model, equations (S11), (11), and (12). Here D_A is the approximate factor obtained from assuming that $I_r(0) \ll 1$. For the top curves, the parameters are $R_{0,r} = 2.0, R_{0,i} = 4.0, u = 3.0$. For the bottom curves: $R_{0,r} = 2.0, R_{0,i} = 2.5, u = 2.0$.

of increasing $I_r(0)$ on the difference between our approximate calculation of the function $D_i(R_{0,r}, \gamma_0, u)$ and the corresponding exact calculation that uses the full model equations (10)-(14). As the figure shows, the discrepancy rises as $I_r(0)$ increases, as we expect, but the agreement for small $I_r(0)$ is excellent.

Effects of the model parameters on the invader's increase during the epidemic

To understand the effects of the resident's reproductive number $R_{0,r}$ and the relative removal rate u on the invader's rate of increase during the epidemic, in fig. S6 we present an expanded version of fig. 5 in the main text. As in fig. 5, we plot increases in invader fitness as measured by $Z_i(\infty)/I_i(0)$, together with the fitness components $I_r(0)^{-\gamma_0}$ and $D_i(R_{0,r}, \gamma_0, u)$, versus the invader's initial relative fitness γ_0. Fig. S6 then shows that, as we stated in the main text,

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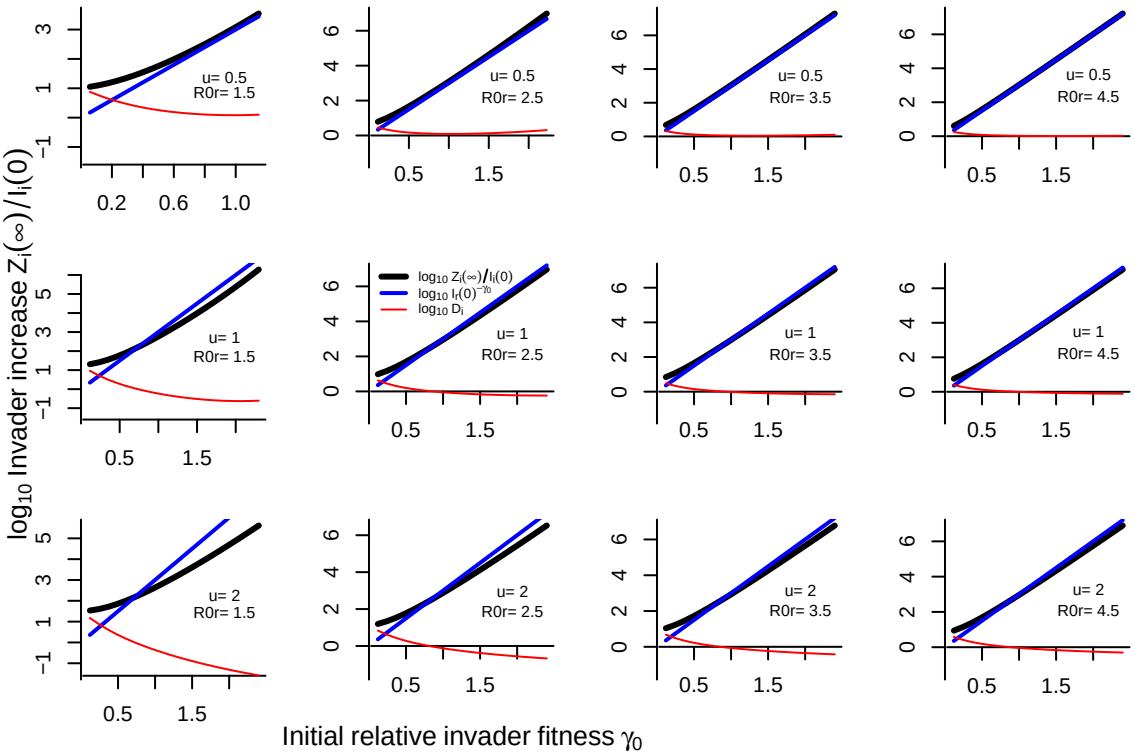

Figure S6: Effects of the model parameters on the change in invader fitness and on the two components of the change in invader fitness. Here we show the change in the invader's infection rate $Z_i(\infty)/I_i(0)$ over the entire epidemic, and the two components of the invader's increase in fitness, the initial resident frequency raised to the power of the initial relative fitness $I_r(0)^{-\gamma_0}$ and the function that describes the dynamic effects of competition $D(R_{0,r}, \gamma_0, u)$. Each plot is calculated for a different value of the ratio of removal rates $u = \mu_i/\mu_r$ and the resident's reproductive number $R_{0,r}$, such that in each column we used a different value of $R_{0,r}$ and in each row we used a different value of u.

$Z_i(\infty)/I_i(0)$ always increases with increasing invader initial fitness $\lambda_{0,i}$. More broadly, the figure confirms that the patterns seen in fig. 5 hold for a wide range of parameters, confirming that the term $I_r(0)^{-\gamma}$ generally plays the most important role in determining the rate at which the increase in the invader's fitness increases with increasing relative initial invader fitness.

The Upper Limit on the Survival Rate of the More Infectious Strain

In the main text, we used a coexistence criterion to show that coexistence through epidemic-transient invasions requires that the difference in inter-epidemic survival rates between the

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invader and the resident must be 2 to 4 orders of magnitude. Although we cannot write down an analogous criterion for the difference in inter-epidemic survival rates that permits coexistence through epidemic-equilibrium invasions, we can use simulations to roughly determine the upper limit on the survival of the more infectious strain, below which coexistence is possible and above which coexistence is impossible.

In fig. S7 we therefore use simulations to roughly approximate this upper limit. The figure shows that, as in the case of epidemic-transient invasions, the upper limit on the survival rate of the more infectious strain is orders of magnitude smaller than the inter-epidemic survival rate of the less infectious strain. The resulting difference in inter-epidemic survival rates between the more infectious strain and the less infectious strain, however, is generally much larger than the difference necessary for coexistence through epidemic-transient invasions, as we described in the main text.

A caveat to this general conclusion is that the upper limit on the survival rate of the more infectious strain increases very rapidly with increasing inter-epidemic survival of the less infectious strain; as a result, for high values of the inter-epidemic survival of the less infectious strain the difference between the survival rates of the two strains that is necessary for coexistence to occur through epidemic-equilibrium invasions is in some cases smaller than the difference that is necessary for coexistence to occur through epidemic-transient invasions (compare fig. S7 to fig. 8 in the main text). We repeat, however, that this result holds only for high survival rates of the less infectious strain.

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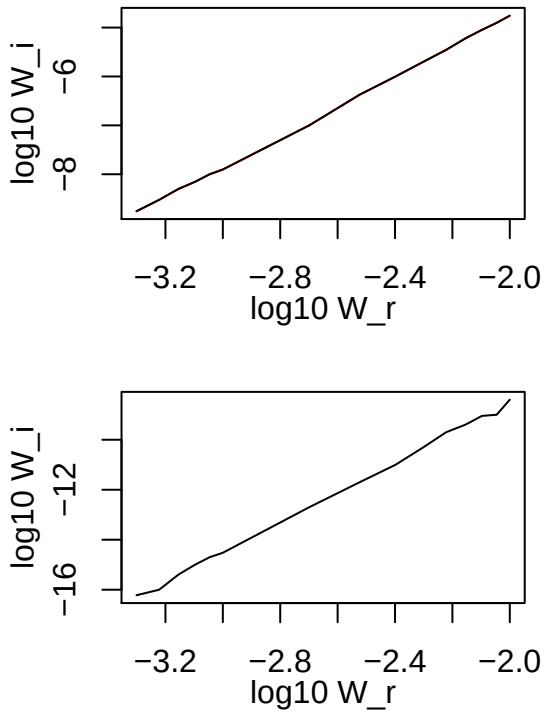

Figure S7: The upper limit on the survival rate of the more infectious pathogen strain for which coexistence is possible through epidemic-equilibrium invasions. In each plot the black line is the highest value of the invader's inter-epidemic survival rate that allows for coexistence. Because the upper limit on the survival rate of the more infectious strain increases very sharply with increases in the survival rate of the resident, to allow for straightforward comparison of the invader and resident survival rates we plotted the survival rates of both strains on a $\log_{10}$ scale. In the upper panel, the resident's reproductive number $R_{0,r} = \beta_r/\mu_r = 1.25/1.0 = 1.25$, and the invader's reproductive number $R_{0,i} = 1.8/1.0 = 1.8$, as in fig. 3 in the main text. In the lower panel, the resident's reproductive number $R_{0,r} = \beta_r/\mu_r = 1.6/1.25 = 1.2$, and the invader's reproductive number $R_{0,i} = 3.6/1.5 = 2.4$. The invader is thus the more infectious strain in both cases, but as with our other results, this result is the same if the resident is the more infectious strain. To illustrate the influence of epidemic length on the coexistence boundary, we note that in the lower panel epidemic lengths of 25 and 250 time units gave essentially identical results, whereas for resident survival rates below $W_r < 10^{-3}$ in the upper panel the upper limit was slightly lower for an epidemic length of 25 time units than for an epidemic length of 250 time units.

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