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The evolution of pathogen virulence: Effects of transitions between host types

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ABSTRACT

Much of evolutionary epidemiology theory is derived from a perspective in which all hosts, and all parasites, are epidemiologically equivalent. This stands in contrast to the well-documented existence of the numerous processes generating heterogeneity among hosts and parasites that can profoundly influence evolutionary/epidemiological dynamics. Age-related immunological changes, inequities in nutritional status, and interactions between parasites via coinfection are just a few of the many factors that generate heterogeneity among hosts in the ways they express susceptibility to, and respond to infection by, a focal pathogen. Moreover, organisms age, nutritional states improve or worsen, and co-infections can be cleared or acquired, implying that transitions between these different disease states are the rule, rather than the exception, in natural disease systems. Here we develop the theoretical framework for modeling the implications of such transitions in these multi-type host settings for the evolution of virulence. Results show that ignoring these common sources of host heterogeneities in disease characteristics can lead to both quantitatively and qualitatively mischaracterized evolutionary predictions.

1. Introduction

The traditional view of infectious microparasite evolution has long been informed by models in which all heterogeneities are ignored; that is all hosts present identical environments to pathogens, and all pathogens induce the same pathology, while enjoying the identical transmission probability, in all successfully established infections (e.g. Anderson and May, 1982; Frank, 1996; May and Anderson, 1983). In this simple case, the pathogen traits ultimately expected to be favored by selection are those that maximize R_0, typically defined as the total number of secondary infections produced by an infected host introduced into a totally susceptible host population (Keeling and Rohani, 2008), and subject to whatever constraints exist among the pathogen's life history traits (Frank, 1996). As such, the level of exploitation (denoted throughout as ε) by the pathogen that maximizes R_0 is the point at which the (relative) mortality costs (due to increased pathogen virulence) and transmission benefits (due to increased production of transmissible stages) of exploiting the host are balanced (Frank, 1996). This is the pathogen's evolutionarily stable strategy (ESS), one that is unbeatable by any alternative strategy, and thus the strategy expected to eventually be found by natural selection (assuming the conditions for convergence stability are also met (Eshel, 1983; Taylor and Jonker, 1978; Gandon, 2004)).

This simplistic view has made many insights possible, but strictly only holds in the absence of host heterogeneities. Sources of such host heterogeneities are both diverse and commonplace, and are the rule, rather than the exception, that defines the epidemiological reality facing most diseases of natural populations. The existence of super-spreaders (that is, hosts that are more susceptible and/or more infectious than other hosts), for example, is perhaps one of the most recognized forms of heterogeneity in host responses to an infectious agent (Lloyd-Smith et al., 2005). History of exposure, expressed as gradually escalating acquired immunity to a pathogen by a host following repeated bouts of infection also represents a common source of disease-relevant structure being imposed on host populations (Doolan et al., 2009; Hood et al., 1984; Stevenson and Riley, 2004). Other mechanisms capable of generating host-level heterogeneities in disease susceptibility and vulnerability include host age (Thompson et al., 2003), leaky vaccines (Longini et al. 1993), among-host immune-modulating nutritional differences (Scrimshaw et al., 1968), and co-infection with other pathogens that influence immune responses to the pathogen of interest (Cattadori et al., 2007).

Despite the widespread acknowledgement of the conceptual importance and empirical relevance of host heterogeneities for formulating a more general theory of pathogen evolution, the development of theoretical frameworks required to more fully analyze

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the evolutionary implications of host heterogeneities is lagging behind their empirical description. Introducing heterogeneities in host susceptibilities to, or responses following, infection – which stratifies the host population into distinct classes or groups, each with a type-specific response to the pathogen of interest – renders the fitness maximization procedure untenable for identifying the pathogen's evolutionarily stable strategy (ESS) (see, for e.g. Gandon, 2004). This is because, whereas susceptible host density drops out when calculating the ESS in the homogenous case, R_0 is generally a more complex function of the different host densities in the heterogeneous case, which are themselves functions of the resident pathogen exploitation strategy.

Previous theory has considered the case where hosts are partitioned into distinct groups or classes between which no exchange of hosts takes place (Williams, 2012; Williams and Day, 2008). However, most infectious diseases occur in settings where transitions between host types are possible. For example, if HIV is the focal disease and syphilis the secondary disease, an individual who recovers from syphilis via antibiotic treatment would transfer from infected class 2 (the doubly infected hosts) to infected class 1 (those only infected with HIV). Similarly, an HIV positive host who subsequently contracted syphilis would experience a transition from infected class 1–2. Similar observations hold for other kinds of imposed heterogeneity. For example, as an organism ages it may begin to suffer the ill-effects of immunosenescence, where it becomes less able to control the fitness consequences of infection due to age-related corruption of its immune system (Goronzy and Weyand, 2013). In this case age structures the host population, with the young eventually transitioning into older age classes each with their own defining mortality and transmission parameters (Keeling and Rohani, 2008).

Here we develop a general model to investigate the consequences that transitions between host types have for the evolution of pathogen virulence. This model applies to any situation in which host populations are structured into multiple groups, each with their own suites of epidemiological parameters, and for which transitions between these different infected host types occur. It has been shown that, even in the absence of transitions between types, changes in the host population's composition of host types can create important evolutionary feedbacks on the pathogen's force of infection (which is a function of host composition; Williams, 2012). Inclusion of realistic transitions into this framework will help to clarify the evolutionary predictions that result from modeling this phenomenon.

2. Model

A typical starting point for standard explorations of pathogen virulence evolution is with an epidemiological model of the following form:

$$\dot{S} = \Lambda(S, I) - (d + \eta\beta I)S \tag{1}$$

$$\dot{I} = \eta\beta SI - \alpha I$$

here Λ quantifies the input rate of new susceptible (S) hosts, which will typically depend on the number or density of susceptible and infected hosts (I). It will usually arise from a variety of demographic processes, including births and immigration, as well as terms resulting from recovery from the disease of interest through clearance by the immune system (γ). All hosts die at a disease-independent rate, d, with infected hosts dying at an additional rate, v, due to disease. To simplify notation, the total pathogen death rate due to all sources (background mortality, virulence, or immune clearance) has been written as $\alpha = d + v + \gamma$.

Because both uninfected host susceptibility to infection, as well as the transmission probability of those infected, contribute to the process of disease transmission, we model the production of new infections according to a law of mass action and given by $\eta\beta SI$ (McCallum et al., 2001). η is a positive dimensionless parameter that, upon multiplication by S, gives the effective number of susceptible hosts and thus quantifies the degree to which hosts are likely to become infected given contact with an infectious host, with larger values indicating greater susceptibility (Day and Proulx, 2004). Similarly, β, the transmission rate, is the product of the contact rate and transmission probability. While the parameters η and β are usually combined into a single transmission rate parameter in these kinds of models, we keep them separate here in order to emphasize the differences between a model in which all hosts are homogeneous, and one in which host heterogeneities play an important role.

In the above formalism, a life-history tradeoff is typically assumed, wherein transmission rate, β, increases with greater exploitation of the host, ε, while transmission duration decreases via increases in pathogen virulence, v. From this starting point, numerous authors have shown that the ESS level of host exploitation that is expected to evolve, ε^*, is the one that maximizes the basic reproduction ratio, R_0 (Frank, 1996). That is, ε^* is a solution to $z(\varepsilon) = 0$, where

$$z = \frac{\beta'}{\beta} - \frac{\alpha'}{\alpha} = 0 \tag{2}$$

is the difference between the relative transmission benefit and the relative mortality cost of an increase in host exploitation, and X' indicates the derivative of the variable X with respect to a pathogen's exploitation strategy; the ESS occurs at the point of intersection between the marginal benefits, β'/β, and the marginal costs, α'/α, curves, where both are viewed as functions of the degree of pathogen exploitation, ε.

2.1. Transitions between host types

For many types of host heterogeneity, transitions between types arise naturally from the underlying epidemiological dynamics (Fig. 1). These transitions might depend on the degree to which a host is being exploited by the focal pathogen; that is, they might also be functions of a pathogen's host exploitation rate, ε. This is probably quite common in numerous infection-nutrition syndromes, where the most exploitative pathogens (i.e. the ones with the largest ε) exhaust a host's nutritional stores more rapidly than milder pathogens, leading to even further nutritional deficits and subsequently higher virulence (Scrimshaw et al., 1968).

Including these kinds of possibilities in the theory results in an expression determining the ESS host exploitation level given by (see Table 1 for definition of terms)

$$\sum_{j=1}^{n}\left(\frac{\beta'_j}{\beta_j} - \frac{\alpha'_j}{\alpha_j}\right)\hat{f}_j + \sum_{j=1}^{n}\sum_{i=1}^{n}\left(m_{ij} - m_{jj}\right)\frac{t_{ij}}{\alpha_j}\left(\frac{t'_{ij}}{t_{ij}} - \frac{\alpha'_j}{\alpha_j}\right)\hat{f}_j\Bigg|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} = 0. \tag{3}$$

here $m_{ij} = \langle\beta/\alpha\rangle_i/(\beta_j/\alpha_j)$, that is, the ratio of a pathogen's reproductive value in a host from infected group i (which is here a mean value over all groups, indicated by $\langle\cdot\rangle_i$ (see Appendix A)), and the reproductive value of a pathogen in a type j host in the absence of transitions, $t_{ij} = \partial T_i/\partial I_j$ (evaluated at epidemiological equilibrium), and the sum over the i index is for those $t_{ij} \neq 0$. Here, T_i denotes the sum of all transitions into, or out of, the group of type i infected hosts (I_i) (Appendix A). Moreover, since each T_i combines transitions from one infected class to another, $\sum_{i=1}^{n} T_i = 0$. Finally, $f_j = \beta_j I_j/\sum_{k=1}^{n}\beta_k I_k = \beta_j I_j/h$ is group j's relative contribution to the force of infection (at equilibrium).

The contribution of the double summation term in (3) to the ESS determination can best be understood by viewing transitions

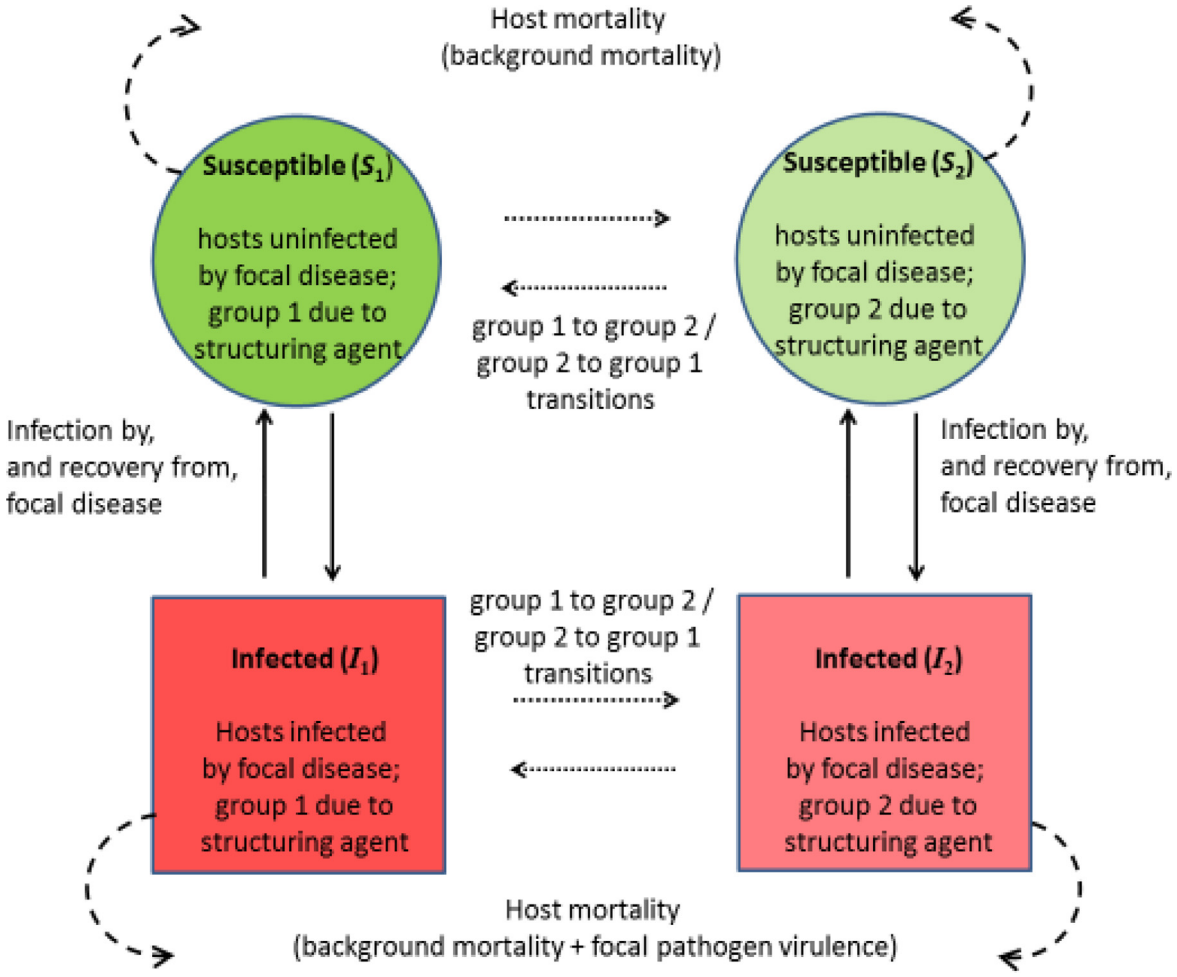

Fig. 1. Flow diagram of one disease, one structuring agent model. Solid black arrows indicate the flow of susceptible hosts, from either group 1 or 2, to the compartments containing hosts infected with the focal disease, following successful transmission. They also indicate the reverse process, where infected hosts from either group recover from the focal infection; dotted black lines indicate transitions between groups 1 and 2, with groups resulting from the presence of a structuring agent; dashed black lines indicate exit rates due to host mortality factors (i.e. disease-independent death, and disease-induced host death or virulence).

Table 1
Notation and definitions of parameters and variables used.

Parameter or variable	Definition
β_j	Transmission rate of type j infected hosts given contact with a susceptible host
α_j	Total per capita exit rate of type j infected hosts from infected class
η_j	Susceptibility of type j hosts to acquiring infection given contact with an infected host
T_i	Transitions into or out of infected class i
h	The sum over all groups of the product between transmission rate (β_k) and the density of infected hosts (I_k)
t_{ij}	Derivative of T_i with respect to I_j
m_{ij}	Ratio of a pathogen's reproductive value in a host from infected group i and the reproductive value of a pathogen in a type j host in the absence of transitions
f_j	Proportion of the force of infection (h) due to host type j
τ_i	Total change in the net rate of transition of infected hosts into or out of group i given a small change in the pathogen's exploitation strategy, weighted by the reproductive value of that group, and then summed over all groups
q_j	A measure of what is gained or lost in reproductive value across all groups through changes in transition rates.
ε	Exploitation strategy of pathogen; determines virulence and transmission probability

as a generalization of the infection process. For fixed i, a type j host can produce a new type i infection at a per capita rate given by t_{ij} and the relative change in this rate given an increase in exploitation is t'_{ij}/t_{ij}. This term plays the role of the 'benefit' of increased exploitation, although in this context it need not be positive. As with the other cases, increased exploitation incurs a relative cost in terms of mortality given by α'_j/α_j. Whether the difference between these component 'cost' and 'benefit' terms contributes a negative or positive term to the cumulative costs and benefits (i.e. the LHS of expression (3)) also depends on the reproductive values of both types involved in the transition. For example, suppose that $t'_{ij} < 0$, so that an increase in exploitation reduces the probability that a type j host will transition into a type i host, implying that the 'costs' minus 'benefits' component is negative. Since $(m_{ij} - m_{jj})$ is proportional to $\langle\beta/\alpha\rangle_i - \langle\beta/\alpha\rangle_j$ Appendix A), multiplying by m_{ij} leaves the sign of the 'cost' minus 'benefit' component term unchanged as long as the transition is to a type with a higher reproductive value ($\langle\beta/\alpha\rangle_i > \langle\beta/\alpha\rangle_j$). The negative value of this weighted 'cost' minus 'benefit' component thus arises because selection acts against increased exploitation, since this decreases the probability of transitioning to a type with a higher reproductive value. On the other hand, if the transition is to a type with a lower reproductive value, the weighted 'cost' minus 'benefit' component will be positive, indicating that selection favors increased exploitation, since this reduces the probability of transitioning to a

class with a lower reproductive value. Expression ((3) then results from summing over all possible transitions, i, for a type j host.

To facilitate comparison with the case where transitions between the different groups of infected types do not occur (see Appendix A), we can write (3) in a slightly modified form:

$$E\left[\frac{\beta'}{\beta} - q\frac{\alpha'}{\alpha}\right] + \frac{\pi}{h}\bigg|_{\tilde{\varepsilon}=\varepsilon=\varepsilon*} = 0, \tag{4}$$

Here the expectation is again taken with respect to, f_j, $q_j = 1 + \sum_{i=1}^{n} m_{ij}\frac{t_{ij}}{\alpha_j}$, and π is the total change in the net rate of transition of infected hosts into or out of group i given a small change in the pathogen's exploitation strategy, $\tau_i = \sum_{j=1}^{n} t'_{ij}\hat{I}_j$, weighted by the reproductive value of that group, $\langle\frac{\beta}{\alpha}\rangle_i$, and then summed over all groups, $\pi = \sum_{i=1}^{n}\langle\frac{\beta}{\alpha}\rangle_i\tau_i$. This thus yields a measure of what is gained or lost in reproductive value across all groups through changes in transition rates.

Consider now the case where transition terms are unaffected by the exploitation strategy employed by a pathogen; that is we assume no interaction between the exploitation strategy and the secondary infection (i.e. $t'_{ij} = 0$). In general, both these rates can depend on the degree of exploitation by the focal mutant pathogen. For example, more exploitative focal pathogens might acquire secondary infections more rapidly, and clear them less efficiently. However, our case does hold for some infectious diseases (for example, some mixed infections of entomopathogenic fungi Thomas et al., 2003) and moreover there is little data to follow in constructing a functional form for such a dependence. Expression ((4) thus becomes:

$$E\left[\frac{\beta'}{\beta} - q\frac{\alpha'}{\alpha}\right]\bigg|_{\varepsilon=\tilde{\varepsilon}=\varepsilon*} = 0, \tag{5}$$

which obviously gives a different prediction for the ESS than a situation without transitions. This example also shows that the simple heuristic device of interpreting each term in the above expectation as the difference between a cost and benefit term on each host type is not easily reconciled in a setting that includes transitions.

As a second example, imagine all groups experience the same clearance, background mortality, and virulence rates, so that $\alpha_j = \alpha$ for all j, while group-specific transmissibility parameters are again given by $\beta_j = \omega_j\beta$, where the ω_j's are constants for all j. When this holds (and $t_{ij} = 0$ for all i and j), expression (3) or (4) collapses to (2), reflecting the fact that this kind of heterogeneity in transmissibility, in the absence of transitions, has no effect on the ESS level of exploitation by the pathogen. In contrast, with transitions, (3) or (4) becomes (see Appendix A)

$$\frac{\beta'}{\beta} - \frac{\alpha'}{\alpha} + \sum_{i=1}^{n} E\left[\frac{\langle\omega\rangle_i}{\omega}\left(\frac{t_i}{\alpha}\right)'\right]\bigg|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} = 0. \tag{6}$$

This second example also makes it clear that the tradeoffs experienced by a given strain of pathogen need not involve just transmission and virulence (or clearance; May and Anderson, 1983), but can be multidimensional, potentially providing many novel routes by which to alter the selection pressures acting on pathogens. Again, in the particular case where transitions between types are independent of host exploitation, (5) becomes

$$\frac{\beta'}{\beta} - E[q]\frac{\alpha'}{\alpha}\bigg|_{\varepsilon=\tilde{\varepsilon}=\varepsilon*} = 0, \tag{7}$$

and transitions still play a role in shaping the ESS via the $E[q]$ term (relative to expression (2) for which it is absent). For instance, assuming typical functional forms for α (i.e. linearly increasing) and β (i.e. non-decreasing, concave down and saturating), when $E[q] < 1$ holds for all ε, the presence of transitions reduces the mortality costs of increased exploitation (α'/α), driving up the ESS level of exploitation relative to a situation without transitions; the opposite conclusion holds true when $E[q]$ is > 1 for all ε. E[q] is a term that emerges when transitions are present and represents an amalgamation of transition and mortality rates.

A final observation also serves to demonstrate the lack of equivalence of certain parameter changes on the ESS when transitions are present. In particular, it is clear from expression (2) that, again in the absence of heterogeneity in virulence, clearance, and disease-independent mortality, multiplicative changes in transmission rate (β) or changes in susceptibility parameters (η) are equivalent, with neither having any effect on the ESS, without transitions. When transitions occur, these two changes are typically not equivalent, with susceptibilities and multiplicative changes in transmission rate both entering into expressions (3)–(7) via the reproductive value weighting terms, but typically not in the same way.

2.2. Example: multiple infections with interactions

To further explore the novel features of the theory presented, a worked example of a two-disease interaction is presented. In this case there are two infected classes of host: those infected with just the focal pathogen, I_1, and those infected with the focal and a secondary pathogen, I_2. Here we assume that the second infection, like some helminth infections, is acquired at a constant per capita rate from the environment. Accounting for the transition rates would then give: $T_1 = -\sigma_1 I_1 + \sigma_2 I_2$, where σ_1 is the per capita rate at which hosts infected with the focal infection acquire the secondary infection and σ_2 is the per capita rate at which the secondary infection is cleared. Note that, in general, both these rates can depend on the degree of exploitation by the focal mutant pathogen. For example, more exploitative focal pathogens might acquire secondary infections more rapidly, and clear them less efficiently, giving $\sigma' > 0$ and $\sigma'_2 < 0$. However, here we assume no interaction between the exploitation strategy and the secondary infection. In any case, this gives rise to the epidemiological situation summarized by the following four equations:

$$\dot{S}_1 = \kappa + \gamma_1 I_1 - (d_1 + h\eta_1)S_1 - \theta S_1 + \mu S_2 \tag{8a}$$

$$\dot{S}_2 = \theta S_1 + \gamma_2 I_2 - (d_2 + h\eta_2)S_2 - \mu S_2 \tag{8b}$$

$$\dot{I}_1 = h\eta_1 S_1 - (d_1 + \nu_1 + \gamma_1)I_1 - \sigma_1 I_1 + \sigma_2 I_2 \tag{8c}$$

$$\dot{I}_2 = h\eta_2 S_2 - (d_2 + \nu_2 + \gamma_2)I_2 + \sigma_1 I_1 - \sigma_2 I_2. \tag{8d}$$

here, κ is a constant input rate of uninfected hosts, γ_1 is the rate of recovery from infection with just the focal pathogen, γ_2 is the rate of recovery of doubly infected hosts from the focal pathogen, d_1 and d_2 are the disease-independent death rates experienced by hosts not infected / infected, respectively, with the secondary pathogen, θ and σ_1 are the per capita rates at which hosts uninfected / infected, respectively, with the focal pathogen contract an infection with the secondary pathogen, and μ and σ_2 are the per capita rates at which hosts that are uninfected / infected with the focal pathogen recover from infection by the secondary pathogen. Following the methodology outlined in Appendix (1), the matrix $[\mathbf{T}]_{ij} = t_{ij} = \partial\dot{I}_i/\partial I_j$ is given by:

$$\mathbf{T} = \begin{bmatrix} -\sigma_1 & \sigma_2 \\ \sigma_1 & -\sigma_2 \end{bmatrix}. \tag{9}$$

The weightings for the mean values $\langle\beta/\alpha\rangle_1$ and $\langle\beta/\alpha\rangle_2$ are given by the first and second columns, respectively, of the matrix $(\mathbf{I} - \mathbf{T}\mathbf{D}^{-1})^{-1}$, where $\mathbf{I}$ is the 2×2 identity matrix, and $\mathbf{D}$ is

the 2×2 diagonal matrix with the total death rate experienced by the pathogen in the host infected by only the focal pathogen, $\alpha_1 = d_1 + \nu_1 + \gamma_1$, in the (1,1) position, and the total death rate experienced by the pathogen in the host infected by both the focal and secondary pathogen, $\alpha_2 = d_2 + \nu_2 + \gamma_2$, in the (2,2) position. These weightings are given by:

$$\rho_{11} = \frac{1 + \frac{\sigma_2}{\alpha_2}}{1 + \frac{\sigma_1}{\alpha_1} + \frac{\sigma_2}{\alpha_2}},\ \rho_{21} = \frac{\frac{\sigma_1}{\alpha_1}}{1 + \frac{\sigma_1}{\alpha_1} + \frac{\sigma_2}{\alpha_2}},$$
$$\rho_{12} = \frac{\frac{\sigma_2}{\alpha_2}}{1 + \frac{\sigma_1}{\alpha_1} + \frac{\sigma_2}{\alpha_2}},\ \rho_{22} = \frac{1 + \frac{\sigma_1}{\alpha_1}}{1 + \frac{\sigma_1}{\alpha_1} + \frac{\sigma_2}{\alpha_2}} \tag{10}$$

(see Appendix 2 for a derivation of these weightings). By including these weightings in expression (5), the ESS expression for this example is:

$$\sum_{j=1}^{2}\left(\frac{\beta'_j}{\beta_j} - \frac{\alpha'_j}{\alpha_j}\right)\hat{f}_j + \rho_{21}(\omega - 1)\left(\frac{\sigma'_1}{\sigma_1} - \frac{\alpha'_1}{\alpha_1}\right)\hat{f}_1 + \rho_{12} \times \left(\frac{1}{\omega} - 1\right)\left(\frac{\sigma'_2}{\sigma_2} - \frac{\alpha'_2}{\alpha_2}\right)\hat{f}_2\Big|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} = 0, \tag{11}$$

where $\omega = (\frac{\beta_2}{\alpha_2})/(\frac{\beta_1}{\alpha_1})$. If we further assume that $\alpha_1 = \alpha_2$ and $\beta_2 = \omega\beta_1$, and that ω and the σ_j's are all independent of exploitation, (13) can then be written as in (9), with $E[q] = (1 + \rho_{21}(\omega - 1))f_1 + (1 + \rho_{12}(\frac{1}{\omega} - 1))f_2$. By choosing parameter values for the various transition and mortality rates, the ESS level of pathogen exploitation can be plotted as a function of the multiplicative constant ω (Fig. 2**a**). When $\omega > 1$, the reproductive values on type 2 hosts (those that are doubly infected) is higher than type 1 hosts (those that are singly infected). Pathogens must thus be restrained in order to limit mortality; hence ESS exploitation (virulence) decreases. When $\omega < 1$, the converse holds and pathogens can be more exploitative (virulent). This is in stark contrast to a situation where transitions are lacking. In this case, there is no difference in reproductive values between host types and, as such, ESS exploitation does not vary.

As $\omega \to 1$ (as would occur in the absence of between-group variation in transmissibility and pathogen mortality), the situation modeled in (13) converges to that of no transitions. This is expected, as transitions become irrelevant in the absence of differences in reproductive values between infected types. By Eq. (7) E[q] scales costs of virulence so when the costs are high ($\omega = 5$) this selects for reduced virulence. Conversely, when $\omega = 1/5$, costs of exploitation are lowered thus selecting for higher virulence (Fig. 2b).

Since it is always true that the weightings determining the reproductive value of a group k infection, $\langle\beta/\alpha\rangle_k$, depend only on pathogen mortality terms and transition rates Appendix A), it follows from expression (5) that, as long as the transition terms do not depend on the equilibrium values of any of the state variables, as in this example, a change in the susceptibility of any host type once again induces no direct evolutionary effect. With the same constraint on the transition terms, the form of the q_j in expression (6) indicates that a uniform multiplicative change in transmission rate also has no direct effect. But both these predictions can fail if the transition terms depend on equilibrium state variable values (as will be the case if the secondary pathogen also spreads as a result of a contact process), since this can allow for some implicit dependence of the weighting terms (the $\rho's$) on any of the η_k or β_k.

3. Discussion

Since heterogeneities are ubiquitous in natural populations, interactions between these structuring agents and a focal disease

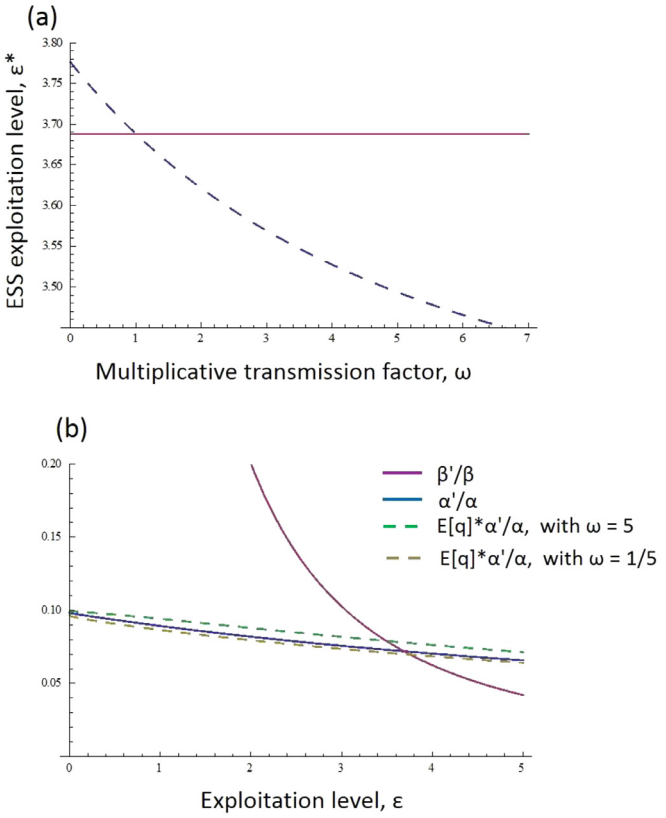

Fig. 2. Example of effect of transitions due to concomitant infection on determination of the ESS level of host exploitation. (a) Solid line plots ESS in the absence of transitions, dashed line the ESS as a function of the multiplicative constant ω with transitions. When $\omega < 1$ the ESS for the case with transitions is higher than for no transitions, while for $\omega > 1$ the ESS is smaller when transitions occur.
(**b**) In the absence of transitions, the ESS occurs at the intersection of the curves $\frac{\beta'}{\beta}$, i.e. the benefit of increased exploitation, and $\frac{\alpha'}{\alpha}$, the cost of increased exploitation. With transitions, multiplication by $E[q]$ moves the costs curve up when $\omega = 5$, in effect increasing the cost of increased exploitation and selecting for reduced exploitation (intersection of solid purple and green dashed line). When $\omega = 1/5$ costs of exploitation are effectively reduced, as multiplication moves the costs curve down, selecting for greater ESS exploitation (intersection of solid purple line and dashed brown line). For all figures $\kappa = 1000$, $\sigma_1 = 0.05$, $\sigma_2 = 0.005$, $\eta_1 = \eta_2 = 0.01$, $\nu_1 = \nu_2 = 0.1\varepsilon$, $\beta_1 = \frac{3\varepsilon}{3\varepsilon + 0.01}$, $\beta_2 = \omega\frac{3\varepsilon}{3\varepsilon + 0.01}$, $\delta_1 = \delta_2 = 0.02$, $\mu = \theta = 0.01$.

of interest, as well as transitions between the generated different host types, are critical components of the selective forces that have shaped, and continue to shape, the evolution of pathogens (Alizon et al., 2013; Cox, 2001; Rigaud et al., 2010). This implies that a mature, predictive theory of virulence evolution must include such realistic and pervasive ecological realities (Cox, 2001).

To this end, expressions (3) or (4) provide a formal partitioning of the terms that contribute to the ESS determination in the presence of multiple host types that can transition into one another. This partitioning explicitly identifies the factors that contribute to the component that arises entirely as a result of host heterogeneity as well as the component shared by homogeneous models. One broad insight that this development affords is that the application of homogeneous theory to heterogeneous hosts will typically result in quantitatively, if not also qualitatively, incorrect predictions.

The influence that interactions between a focal infection and structuring agents can exert on virulence evolution has received some previous attention, at least from the perspective of systems at epidemiological equilibrium and in the absence of transitions between types (Williams, 2012). In this case it is shown that a (small) change in some parameter of interest, p, results in a (pro-

portional) change in the ESS given by

$$\frac{d\varepsilon^*}{dp} \propto E\left[\frac{\partial z}{\partial p}\right] + \mathrm{cov}(z, r), \tag{12}$$

where $r_j = (\beta_j \hat{I}_j)_p / \beta_j \hat{I}_j = (\partial \beta_j / \partial p)/\beta_j + (\partial \hat{I}_j / \partial p)/\hat{I}_j$ is the proportional change in the contribution to the force of infection of pathogens on type j hosts, and where the expectation, '$E[\cdot]$', and covariance, '$\mathrm{cov}(\cdot,\cdot)$', operators are taken with respect to the same distribution as the ESS-determining expectation (i.e. f_j, $j = 1, ..., n$). The covariance term thus measures the evolutionary effect of changes in the contribution to the force of infection, which can, in fact, be the major evolutionary determinant of virulence (just replace p with a parameter that doesn't directly influence the costs and benefits of increased exploitation (z) so that the first term on the right hand side of (13) is zero).

The different predictions that arise from the homogeneous- and heterogeneous-host frameworks, in the absence of transitions, can be interpreted as a form of Simpson's paradox, in which a relationship might appear in two different groups of data, but disappears when the groups are combined, with 'group' as the hidden variable (Astumian, 2005). That is, within each group selection might favor increased exploitation, but the overall mean decreases because of changes in the weightings of the force of infection in each group (Williams and Hastings, 2011). The covariance term in (12) succinctly summarizes this effect when group weighting effects are taken into account. In the present situation, as embodied in equations (5) or (6), transitions between infected types introduce an additional term in the expression governing the definition of the ESS, and hence additional terms in the equations governing the change in the ESS following an environmental change, beyond the indirect changes in host-type composition. This, unfortunately, renders the Simpson's paradox explanation for divergence from the single host-type case incomplete.

This difference between the cases with and without transitions arises because transitions introduce new terms between the one- and multi-type host settings. This departure is quantified by the double summand term in the multi-type host ESS expressions (3) and (4). Without any additional assumptions regarding the forms of transition terms, general predictions regarding how the cumulative 'cost' and 'benefit' terms on each host type change with changes in susceptibility and vulnerability are largely elusive. Applications of the present model need to focus on determining the form of these generalized costs and benefits for particular epidemiological cases, as well as how they change for different pathogen strains (i.e. when pathogen exploitation is altered.)

3.1. Context-dependent tradeoffs and the evolution of exploitation

The applicability of this general theory to any particular system depends largely on the assumption that pathogen exploitation of hosts evolves to balance the 'generalized' benefits of transmission stage production with the 'generalized' costs of reductions in reproductive value. In a critique of the tradeoff perspective, it is suggested that, within heterogeneous host populations, a decoupling of virulence and transmission should often render the formalism untenable (Ebert and Bull, 2003). The scenario envisioned by the authors is that, in such a setting, most transmission might be due to some subset of the population that experiences very little virulence, while those that suffer most from pathogenesis are responsible for very little transmission. They further suggest that little can be achieved by applying a tradeoff model to complex host-pathogen systems under more natural conditions due to the uncertain nature of many of the interactions (Ebert and Bull, 2003). However, the theory presented here suggests that, in many cases, a perspective that utilizes a tradeoff framework is not only useful but, in some clinically relevant situations, required.

For example, HIV satisfies the conditions for a classical tradeoff between transmission rate and infection duration: higher rates of replication lead to higher viral loads and greater transmission efficacy per sexual contact, but also to shorter host survival times (Fraser et al., 2007; Quinn et al., 2000). Moreover, as previously noted, the shape of this tradeoff can be altered in the presence of numerous other pathogens, like *Mycobacterium tuberculosis* (TB) or Herpes simplex virus (HSV), with coinfected hosts exhibiting greater HIV transmission rates and shorter survival times. Since HIV commonly co-occurs within the same host with both these infectious organisms (see (Ellner, 1997) for TB; (Corey et al., 2004) for HSV), any empirically relevant discussion of the evolutionary factors shaping the fitness landscape of HIV needs to consider both plasticity and gene by environment interactions.

More generally, this suggests that natural environmental settings, in which multiple factors are acting to structure host populations and influence transmission and virulence patterns, might provide the conditions under which such context-dependent tradeoffs, masked in more controlled lab settings, are made evident. As noted by Ebert and Bull, 2003), reaction norms for these tradeoffs have hardly been investigated, although a number of studies have investigated virulence reaction norms across gradients of host stress (Restif and Kaltz, 2006; Bedhomme et al., 2004; Blanford et al., 2003; Jokela et al., 1999). Extending these kinds of experimental protocols to investigate the influence of various factors like host age or concomitant infections on transmission-virulence tradeoffs, should be very useful. As well, studies of tradeoffs between other traits that are masked in typical experimental set-ups (cf. expression (5)) could also prove informative. Experiments such as these, as well as explicitly accounting for plasticity in virulence and transmission in modeling efforts, will lead to an improved understanding of how, as well as to which degree, these factors shape pathogen exploitation strategies in nature.

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Appendix A. ESS condition with transitions

Augmenting the system in (1) to allow for multiple host types and for a mutant pathogen (where pathogen traits are indicated by '~') whose transmission rate, β_j, and virulence, v_j, on each host type, $j = 1, ..., n$, depend on its exploitation strategy, $\tilde{\varepsilon}$, gives

$$\dot{\tilde{I}}_j = \tilde{h}\eta_j \hat{S}_j - \left(d_j + \tilde{\nu}_j + \gamma_j\right)\tilde{I}_j + \tilde{T}_j, \tag{A1-1}$$

where $\tilde{h} = \sum_{j=1}^{n} \tilde{\beta}_j \tilde{I}_j$, $\tilde{\beta}_j = \beta_j(\tilde{\varepsilon})$, $\tilde{\nu}_j = \nu_j(\tilde{\varepsilon})$ and $\hat{X}$ indicates an equilibrium value for the state variable X, which is determined, in part, by the resident pathogen's exploitation strategy, ε.

The dynamics of an initially rare mutant pathogen strain can be studied by linearizing (A1-1) in the neighborhood where the numbers of all infected types are vanishingly small. This results in the dynamical system $\dot{\tilde{\mathbf{I}}} = \mathbf{A}\tilde{\mathbf{I}}$, where $[\mathbf{A}]_{ij} = \partial \dot{\tilde{I}}_i / \partial \tilde{I}_j$ evaluated at $\tilde{I}_k = 0$ for all k and $\tilde{\mathbf{I}} = (\tilde{I}_1, ..., \tilde{I}_n)$ is the vector of infected host types. The dominant eigenvalue of this system, $\chi(\tilde{\varepsilon}, \varepsilon)$, gives the invasion exponent of the initially rare pathogen with exploitation strategy, $\tilde{\varepsilon}$, in a resident pathogen population with strategy ε. By an elementary result from linear algebra (Caswell 2001), this is given (implicitly) by

$$\chi(\tilde{\varepsilon}, \varepsilon) = \frac{\tilde{\mathbf{v}}\mathbf{A}\tilde{\mathbf{u}}}{\tilde{\mathbf{v}}\tilde{\mathbf{u}}}, \tag{A1-2}$$

where $\tilde{\mathbf{v}}$ and $\tilde{\mathbf{u}}$ are the dominant left and right, respectively, eigenvectors of the matrix $\mathbf{A}$ corresponding to the eigenvalue χ.

Noting that $\mathbf{A} = \mathbf{B} - \mathbf{D} + \mathbf{T}$, where **B, D** and **T**are matrices defined by $[\mathbf{B}]_{ij} = \eta_i \hat{S}_i \tilde{\beta}_j$, $[\mathbf{D}]_{ij} = \tilde{\alpha}_i \delta_{ij}$ and $[\mathbf{T}]_{ij} = \frac{\partial \tilde{T}_i}{\partial \tilde{I}_j} = \tilde{t}_{ij}$, and δ_{ij} (which is equal to one for $i = j$ and zero otherwise) is the Kronecker delta symbol, the components of the dominant left eigenvector are given by the solution of the system of $\tilde{\mathbf{v}}(\mathbf{B} - \mathbf{D} + \mathbf{T}) = \chi \tilde{\mathbf{v}}$. Solving this (implicitly) gives

$$\tilde{\mathbf{v}} = \phi \tilde{\boldsymbol{\beta}} \bar{\mathbf{D}}^{-1} \left(\mathbf{Id} - \mathbf{T} \bar{\mathbf{D}}^{-1} \right)^{-1}, \tag{A1-3}$$

where $\phi = \sum_{i=1}^{n} \tilde{v}_i \eta_i \hat{S}_i$, $\tilde{\boldsymbol{\beta}} = (\tilde{\beta}_1, \tilde{\beta}_2, ..., \tilde{\beta}_n)$ is the vector giving the transmission rate of the mutant infection in the different host classes, $\bar{\mathbf{D}} = \mathbf{D} + \chi \mathbf{Id}$ and **Id** is the $n \times n$ identity matrix.

We first show that the columns of $(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1}$ are vectors whose components are all nonnegative terms that sum to 1, so that $\tilde{v}_j = \phi \sum_{i=1}^{n} \frac{\tilde{\beta}_i}{\tilde{\alpha}_i + \chi} \rho_{ij}$, where $\sum_{i=1}^{n} \rho_{ij} = 1$ and $\rho_{ij} \geq 0$. To see this, let **1** be the vector of all 1′s and note that, since any given column of **T** sums to zero, it follows that $\mathbf{1} = \mathbf{1}(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1} = \mathbf{1}(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1}$, and all columns of $(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1}$ sum to 1.

To establish the non negativity of $(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1}$, note that the matrix $\bar{\mathbf{D}} - \mathrm{T}$ can be written as the difference between two nonnegative matrices $D - T$, where $D = \bar{\mathbf{D}} - \mathrm{diag}\mathbf{T}$ (this is always nonnegative as long as $\chi \geq 0$), $T = \mathbf{T} - \mathrm{diag}\mathbf{T}$ and *diag***T** is a triangular matrix consisting of the diagonal elements of **T** with zeros as the off-diagonal entries. Therefore we have the equality $(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1} = \bar{\mathbf{D}} D^{-1} (\mathbf{Id} - \mathrm{TD}^{-1})^{-1}$. Since TD^{-1} is a substochastic matrix (a nonnegative matrix with all column sums less than one), and hence has spectral radius less than one (i.e. all eigenvalues are less than one in absolute value), we have that $(\mathrm{TD}^{-1})^k \to 0$ as $k \to \infty$, so that $(\mathbf{Id} - \mathrm{TD}^{-1})^{-1}$ can be written as $\sum_{k=0}^{\infty} (\mathrm{TD}^{-1})^k$ (Ishkhanov 1984). Since $\bar{\mathbf{D}}$, D^{-1} and T are all nonnegative, all entries in $(\mathbf{Id} - \mathbf{T}\bar{\mathbf{D}}^{-1})^{-1}$ must be greater than, or equal to, zero.

By a similar argument the right eigenvector of **A** can be found by (implicitly) solving the vector equation $\mathbf{A}\tilde{\mathbf{u}} = \chi \tilde{\mathbf{u}}$. This gives

$$\tilde{\mathbf{u}} = \vartheta \left(\mathbf{Id} - \bar{\mathbf{D}}^{-1} \mathbf{T} \right)^{-1} \bar{\mathbf{D}}^{-1} \boldsymbol{\eta} \hat{\mathbf{S}}, \tag{A1-4}$$

where $\vartheta = \sum_{i=1}^{n} \tilde{\beta}_i \tilde{u}_i$ and $\boldsymbol{\eta}\hat{\mathbf{S}} = (\eta_1 \hat{S}_1, \eta_2 \hat{S}_2, ..., \eta_n \hat{S}_n)$.

A parasite exploitation strategy, ε^*, is a local evolutionarily stable strategy (ESS) when it cannot be invaded by any small mutations, or when $\chi(\tilde{\varepsilon}, \varepsilon^*) < \chi(\varepsilon^*, \varepsilon^*)$ for all nearby mutant strategies $\tilde{\varepsilon} \neq \varepsilon^*$. χ is therefore maximized in its first argument at $\tilde{\varepsilon} = \varepsilon^*$. Analytically, this means that

$$\left. \frac{\partial \chi}{\partial \tilde{\varepsilon}} \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} = 0 \tag{A1-5a}$$

and

$$\left. \frac{\partial^2 \chi}{\partial \tilde{\varepsilon}^2} \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} < 0. \tag{A1-5b}$$

A final condition, that of convergence stability (Eshel, 1983), must also be met in order to guarantee that the ESS is evolutionarily attainable. This is given by the condition

$$\left. \frac{\partial^2 \chi}{\partial \tilde{\varepsilon}^2} + \frac{\partial^2 \chi}{\partial \varepsilon \partial \tilde{\varepsilon}} \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} < 0. \tag{A1-5c}$$

Evaluating (A1-5a) for the χ given in (A1-2) gives $\mathbf{v}^* (\partial \mathbf{A} / \partial \tilde{\varepsilon}|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}) \mathbf{u}^* = 0$, where $\mathbf{v}^*$ and $\mathbf{u}^*$ are the dominant left and right, respectively, eigenvectors of the matrix $\mathbf{A}|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}$ corresponding to the eigenvalue 0 (the invasion exponent of a mutant pathogen with the identical exploitation strategy as the resident). These eigenvectors correspond to the vector of reproductive values of infections in each host type and the vector giving the stable class distribution, respectively, both calculated with respect to the resident population (Taylor and Frank 1996; Frank 1998). Thus,

$$\begin{aligned} \mathrm{v}_j^* &= \phi \langle \beta/\alpha \rangle_j \big|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}, \text{ where } \langle \beta/\alpha \rangle_j \\ &= \sum_{i=1}^{n} \frac{\beta_i}{\alpha_i} \bigg|_{\tilde{\varepsilon} = \varepsilon^*} \rho_{ij}^* \text{ and } \rho_{ij}^* = \left[\left(\mathbf{Id} - \mathbf{T}\mathbf{D}^{-1} \right)^{-1} \right]_{ij} \bigg|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} \end{aligned} \tag{A1-5d}$$

while $\mathrm{u}_j^* = \hat{I}_j / \sum_{i=1}^{n} \hat{I}_i |_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}$. Substituting these expressions into (A1-5a) results in

$$\left. \sum_{j=1}^{n} \left(\beta'_j \hat{I}_j - \left\langle \frac{\beta}{\alpha} \right\rangle_j \alpha'_j \hat{I}_j + \sum_{i=1}^{n} \left\langle \frac{\beta}{\alpha} \right\rangle_i t'_{ij} \hat{I}_j \right) \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} = 0 \tag{A1-6}$$

where X' indicates a derivative of the quantity X with respect to the mutant strategy $\tilde{\varepsilon}$. Dividing this expression by $\sum_{i=1}^{n} \beta_i \hat{I}_i |_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}$ and letting $f_j = \beta_j \hat{I}_j / \sum_{i=1}^{n} \beta_i \hat{I}_i |_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}$ allows for (A1-6) to be written as

$$\left. \sum_{j=1}^{n} \left(\frac{\beta'_j}{\beta_j} f_j - \left\langle \frac{\beta}{\alpha} \right\rangle_j \frac{\alpha_j}{\beta_j} \frac{\alpha'_j}{\alpha_j} f_j + \sum_{i=1}^{n} \left\langle \frac{\beta}{\alpha} \right\rangle_i \frac{t'_{ij}}{\beta_j} f_j \right) \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} = 0. \tag{A1-7}$$

Using (A1-3) we can calculate that $(\frac{\alpha_j}{\beta_j} \langle \frac{\beta}{\alpha} \rangle_j = 1 + \sum_{i=1}^{n} \langle \frac{\beta}{\alpha} \rangle_i \frac{t_{ij}}{\beta_j}) |_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*}$, so that (A1-7) is equivalent to

$$\left. \sum_{j=1}^{n} \left(\frac{\beta'_j}{\beta_j} - \frac{\alpha'_j}{\alpha_j} \right) f_j + \sum_{j=1}^{n} \sum_{i=1}^{n} \left(\frac{t_{ij}}{\alpha_j} \right)' \left\langle \frac{\beta}{\alpha} \right\rangle_i \frac{\alpha_j}{\beta_j} f_j \right|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} = 0. \tag{A1-8}$$

Finally, since $t_{jj} = -\sum_{i \neq j} t_{ij}$ this can be rewritten as

$$\begin{aligned} &\sum_{j=1}^{n} \left(\frac{\beta'_j}{\beta_j} - \frac{\alpha'_j}{\alpha_j} \right) f_j + \sum_{j=1}^{n} \sum_{i=1}^{n} \\ &\times \left(\left\langle \frac{\beta}{\alpha} \right\rangle_i - \left\langle \frac{\beta}{\alpha} \right\rangle_j \right) \frac{t_{ij}}{\beta_j} \left(\frac{t'_{ij}}{t_{ij}} - \frac{\alpha'_j}{\alpha_j} \right) f_j \Bigg|_{\tilde{\varepsilon} = \varepsilon = \varepsilon^*} = 0, \end{aligned} \tag{A1-9}$$

where the sum over the i index is for those $t_{ij} \neq 0$. This gives the first order expression(s) of the text.

Appendix B. Detailed calculation of worked example

Here we calculate the weighting terms involved in the pathogen reproductive value calculation that appears in the worked example of concomitant infection in the main text. Since there are only two different types each of susceptible and infected host, the transition and mortality matrices, **T** and **D** respectively, are each 2×2 matrices, with $\mathbf{T} = \begin{bmatrix} -\sigma_1 & \sigma_2 \\ \sigma_1 & -\sigma_2 \end{bmatrix}$, $\mathbf{D} = \begin{bmatrix} \alpha_1 & 0 \\ 0 & \alpha_2 \end{bmatrix}$. By Appendix A, the columns of $(\mathbf{Id} - \mathbf{T}\mathbf{D}^{-1})^{-1}$ all have non-negative entries that sum to 1, and hence can be viewed as weighting terms in a mean value calculation. Since $\mathbf{D}^{-1} = \begin{bmatrix} \frac{1}{\alpha_1} & 0 \\ 0 & \frac{1}{\alpha_2} \end{bmatrix}$ it is easy to show $\mathbf{Id} - \mathbf{T}\mathbf{D}^{-1} = \begin{bmatrix} (1 + \frac{\sigma_1}{\alpha_1}) & -\frac{\sigma_2}{\alpha_2} \\ -\frac{\sigma_1}{\alpha_1} & (1 + \frac{\sigma_2}{\alpha_2}) \end{bmatrix}$. Since any invertible 2×2 matrix $\mathbf{X} = \begin{bmatrix} x_{11} & x_{12} \\ x_{21} & x_{22} \end{bmatrix}$ has an inverse that is given

by $\frac{1}{(x_{22}x_{11}-x_{21}x_{12})}\begin{bmatrix} x_{22} & -x_{12} \\ -x_{21} & x_{11} \end{bmatrix}$, we can calculate $(\mathbf{Id}-\mathbf{TD}^{-1})^{-1} = \begin{bmatrix} \rho_{11} & \rho_{12} \\ \rho_{21} & \rho_{22} \end{bmatrix}$ where

$$\rho_{11} = \frac{1+\frac{\sigma_2}{\alpha_2}}{1+\frac{\sigma_1}{\alpha_1}+\frac{\sigma_2}{\alpha_2}},\ \rho_{12} = \frac{\frac{\sigma_2}{\alpha_2}}{1+\frac{\sigma_1}{\alpha_1}+\frac{\sigma_2}{\alpha_2}},$$
$$\rho_{21} = \frac{\frac{\sigma_1}{\alpha_1}}{1+\frac{\sigma_1}{\alpha_1}+\frac{\sigma_2}{\alpha_2}},\ \rho_{22} = \frac{1+\frac{\sigma_1}{\alpha_1}}{1+\frac{\sigma_1}{\alpha_1}+\frac{\sigma_2}{\alpha_2}} \quad \text{(A2-1)}$$

Therefore, with the additional constraint that $\alpha_1 = \alpha_2$, the weightings for the example of concomitant infection appearing in the text are $\rho_{11} = \frac{\alpha+\sigma_2}{\alpha+\sigma_1+\sigma_2}$, $\rho_{12} = \frac{\sigma_2}{\alpha+\sigma_1+\sigma_2}$, $\rho_{21} = \frac{\sigma_1}{\alpha+\sigma_1+\sigma_2}$, and $\rho_{22} = \frac{\alpha+\sigma_1}{\alpha+\sigma_1+\sigma_2}$.

Solving (10) for the equilibrium numbers of susceptible and infected hosts of each type gives:

$$\hat{S}_1 = \frac{1}{\eta_1}\left[\frac{(\alpha_1+\sigma_1)}{\beta_1}\hat{f}_1 - \frac{\sigma_2}{\beta_2}\hat{f}_2\right] \quad \text{(A2-2a)}$$

$$\hat{S}_2 = \frac{1}{\eta_2}\left[\frac{(\alpha_2+\sigma_2)}{\beta_2}\hat{f}_2 - \frac{\sigma_1}{\beta_1}\hat{f}_1\right] \quad \text{(A2-2b)}$$

$$\hat{h} = \frac{\kappa-(d_1+\theta)\hat{S}_1+\mu\hat{S}_2}{\eta_1\hat{S}_1-\frac{\gamma_1}{\beta_1}\hat{f}_1} \quad \text{(A2-2c)}$$

These expressions can be substituted into (8c, d) to give a quadratic in f_1, which can then be solved to yield the (endemic) equilibrium values of the four state variables.

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