Mathematical Techniques in the Evolutionary Epidemiology of Infectious Diseases

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Abstract: I provide a brief introduction to two complimentary mathematical approaches for incorporating evolution into epidemiological models. These are referred to as the invasion-analysis technique and the Price-equation technique.

1. Introduction

The epidemiology of infectious diseases is a vibrant and growing area of research. Mathematics has come to play a central role in this field because it allows one to better understand disease dynamics and to assess the utility of different potential control measures. There have been many new developments and extensions of epidemiological models in recent years, including the development of models that account for pathogen evolution. In this chapter I provide a brief overview of two different ways in which the dynamics of pathogen evolution can be incorporated into epidemiological models.

The need for incorporating evolution into epidemiological models of infectious disease stems, in part, from the high levels of genetic variation that are often generated through mutation and recombination during individual infections. These different genetic strains can have very different epidemiological characteristics, and therefore an accurate prediction of the epidemiological dynamics often cannot be made without accounting for this variation.

Most epidemiological models follow the seminal work of Kermack and McKendrick [12] and are referred to as compartment models [11]. In such models, the host population is divided into mutually exclusive classes (e.g., susceptible, infected, recovered etc), and dynamical equations are developed to model the flow of individual among the different classes. In this way, the dynamics of the pathogen itself are not explicitly modeled, but rather the epidemiological consequences at the level of the host population are tracked, and related to various aspects of infection at the level of the

individual host (e.g., transmission rate between hosts, parasite induced mortality rate, recovery rate etc).

Most epidemiological models of pathogen evolution have been developed from compartment models, because the ultimate interest again is typically the epidemiological dynamics at the level of the host population. The challenge, therefore, has been to bridge the scale of pathogen replication and evolution within hosts (which is where all genetic variation is generated), to the scale of pathogen evolution and replication between hosts. Some strains of pathogens might be very good competitors within hosts but very poor at transmitting to new hosts and vice versa. In evolutionary terms, selection on the pathogen population acts at different levels of biological organization (i.e., within-host level and the between-host level).

One of the key obstacles to developing a complete theory for the evolution of infectious diseases is this complexity of "multi-level selection". To make any progress, some simplifications are necessary. Because this chapter is meant to be an introductory overview, I will make an extreme simplification and assume that selection acts only at the between-host level. In other words, I will suppose that any given infected host harbours only a single strain of pathogen at any given time. This strain type might change due to mutation, but I assume that if a mutant strain ever does arise within a host, it either dies out, our it displaces the original strain instantaneously [2, 18, 4]. Consequently, the evolution of the pathogen population occurs solely as a results of differences among strains in their ability to transmit from host-to-host, as well as differences in the mortality they induce and their susceptibility to clearance by host immunological responses. More realistic extensions of the techniques to be presented here have been developed [19, 18, 4, 16, 5], but this simple case is sufficient for introductory purposes.

2. Mathematical Models of Pathogen Evolution

The two approaches for modeling pathogen evolution to be presented will be referred to as the 'Invasion-analysis' technique and the 'Price-equation' technique. The invasion-analysis approach is based on an assumption that evolutionary change is very slow relative to the timescale of the epidemiological dynamics. More specifically, it assumes that the epidemiological dynamics always reach their limiting behaviour (typically assumed to be a point equilibrium) in between the appearance of successive mutations. As a result, there is only ever at most two-strains circulating in the population at any given time. The other key feature of this approach is that it typically seeks to identify the endpoints of evolution only (as will be described below) but not to provide any information about the evolutionary dynamics that occur along the way. These simplifications allow for a relatively complete mathematical analysis of evolution in many contexts.

The Price-equation technique is more complex but allows for any time scale of evolutionary change. It supposes that there are multiple strains present at any given time, and that mutations continually occur among these. It then tracks the simultaneous epidemiological and evolutionary dynamics. This is clearly a more realistic approach, but

it comes with the drawback that rarely can a complete mathematical analysis be conducted. Rather, this approach is best suited towards providing qualitative insights into the epidemiological and evolutionary dynamics, although numerical analysis can also sometimes be used to gain quantitative insights as well.

The above distinction is a bit artificial, and one can readily imagine constructing models with elements of both approaches. Nevertheless this distinction is useful because, in practice, most published models tend to use one or the other approach.

In what follows I will use a very simple toy epidemiological model to highlight the main ingredients of each of these two approaches. To give the examples a concrete grounding in some epidemiological question of interest, I will focus on the issue of virulence evolution. This has been a question of considerable interest in evolutionary epidemiology, and is one for which both of the approaches have been used.

2.1 The Underlying Epidemiological Model

Many pathogens infect their hosts without causing substantial damage (e.g., many rhinoviruses that cause the common cold) while others induce higher levels of mortality (e.g., flavivurses that cause dengue fever). One explanation for this variation in pathogen virulence is that the costs and benefits of pathogen-induced mortality vary among pathogens, and this has resulted in the evolution of different levels of virulence. I will work with a simple epidemiological model that is meant to explore this possibility, and to allow predictions of the level of virulence that we expect to evolve.

Consider a simple SI model, where S and I are the numbers of susceptible and infected hosts respectively:

$$\frac{dS}{dt} = \theta - \mu S - S\beta I$$
$$\frac{dI}{dt} = S\beta I - (\mu + v)I \qquad (2.1)$$

The parameter θ is the immigration rate of susceptible hosts, μ is the per capita background mortality rate of hosts, v is the increased mortality rate of hosts due to infection (the virulence), and β is the transmission rate (assuming mass-action transmission). This model has two equilibria, one in which the pathogen is absent $E_1 := (\theta/\mu, 0)$ and the other in which the pathogen is endemic $E_2 := ((\mu + v)/\beta, \frac{\theta}{\mu + v} - \frac{\mu}{\beta})$. The disease-free equilibrium, E_1, is always biologically feasible, whereas the endemic equilibrium, E_2, is feasible if and only if $R_0 > 1$ where $R_0 = \frac{\theta}{\mu}\frac{\beta}{\mu + v}$. Furthermore, it can be shown (e.g., by the method of Lyapunov functions; [13]; Appendix) that, when E_2 is feasible, it is globally asymptotically stable. Otherwise, E_1 is globally asymptotically stable. It is this model that will be used in presenting the two techniques below.

2.2 Invasion analysis technique

The technique of invasion analysis a quite general approach for modeling evolution (see [20]) but here I will discuss it within the context of the above epidemiological model. Suppose that all pathogen strains can be characterized by their transmission rate, β, as well as the level of virulence, v, that they induce. Thus, there is also a value of R_0 specific to each strain. I will restrict attention to those strains having a value of R_0 larger than one.

The underlying logic of invasion analysis is as follows. Suppose that a single strain is currently present in the population, and that it has reached its endemic steady state of (2.1). Now imagine that a small number of individuals carrying a second strain are introduced into the population. An invasion analysis seeks to determine whether or not this new strain invades or dies out. More specifically, it seeks to determine if there is a strain that, once present at endemic levels, can resist invasion by all possible mutants that might arise. If so, it is reasoned that this is a plausible endpoint of evolution because, once here, no further evolutionary change can occur. Such strains are said to be evolutionarily stable (ES).

To look for an ES strain for model (2.1) we need to augment this model to allow for a second strain. Using a subscript 'm' to denote the mutant parameter values, we have

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \theta - \mu S - S\beta I - S\beta_m I_m \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= S\beta I - (\mu + v)I \\
\frac{\mathrm{d}I_m}{\mathrm{d}t} &= S\beta_m I_m - (\mu + v_m)I_m
\end{aligned} \qquad . \qquad (2.2)$$

System (2.2) implicitly assumes that the only way in which the two strains interact is through competition for the infection of a common pool of susceptible hosts. As expected, one equilibrium of the augmented system (2.2) is $\hat{S} = \frac{\mu + v}{\beta}$, $\hat{I} = \frac{\theta}{\mu + v} - \frac{\mu}{\beta}$, and $\hat{I}_m = 0$, and it is the stability of this equilibrium that determines whether or not the mutant strain can invade. If and only if this equilibrium is stable for all possible mutants is the resident strain ES.

Model (2.2) is simple enough that a complete, global analysis is possible (Appendix). For most models, however, only a local analysis can be done and therefore I will focus on such local results here to illustrate the general approach. A linear stability analysis of system (2.2) at the equilibrium $\hat{S} = \frac{\mu + v}{\beta}$, $\hat{I} = \frac{\theta}{\mu + v} - \frac{\mu}{\beta}$, $\hat{I}_m = 0$ yields the following Jacobian matrix;

$$\begin{pmatrix} -\mu - \hat{I}\,\beta & -\hat{S}\,\beta & -\hat{S}\,\beta_m \\ \hat{I}\,\beta & -\mu - v + \hat{S}\,\beta & 0 \\ 0 & 0 & -\mu - v_m + \hat{S}\,\beta_m \end{pmatrix}. \tag{2.3a}$$

To appreciate its structure, rewrite matrix (2.3a) in a way that emphasizes its block-triangular form:

$$\begin{pmatrix} \mathbf{J}_{res} & \vec{u} \\ \vec{0} & \mathbf{J}_{mut} \end{pmatrix} \tag{2.3b}$$

where $\vec{0} := \begin{pmatrix} 0 & 0 \end{pmatrix}$, $\vec{u} := \begin{pmatrix} -\hat{S}\,\beta_m \\ 0 \end{pmatrix}$, $\mathbf{J}_{mut} := -\mu - v_m + \hat{S}\,\beta_m$, and $\mathbf{J}_{res}$ is given by

$$\mathbf{J}_{res} := \begin{pmatrix} -\mu - \hat{I}\,\beta & -\hat{S}\,\beta \\ \hat{I}\,\beta & -\mu - v + \hat{S}\,\beta \end{pmatrix}. \tag{2.4}$$

Thus, the eigenvalues of (2.3a) are simply the eigenvalues of the diagonal blocks, $\mathbf{J}_{res}$ and $\mathbf{J}_{mut}$.

The notation $\mathbf{J}_{res}$ emphasizes the fact that, a linear stability analysis of system (2.1) at the endemic equilibrium E_2 yields a Jacobian matrix that is exactly (2.4). Because we have assumed that the epidemiological dynamics reach a stable equilibrium when only the resident strain is present, we know that the eigenvalues of (2.4) have negative real parts (barring the possibility that one or more eigenvalues are zero). Therefore, the stability of the equilibrium when we introduce the mutant type is completely determined by the leading eigenvalue of the submatrix $\mathbf{J}_{mut}$. In this case, this submatrix is simply a single element and thus the eigenvalue is trivially equal to $r := -\mu - v_m + \hat{S}\beta_m$.

Now, as mentioned, the resident strain is ES if and only if this equilibrium is stable. Thus, we have (locally in this case)

$$\begin{aligned} &ES \Leftrightarrow -\mu - v_m + \hat{S}\beta_m < 0 \\ &ES \Leftrightarrow \frac{1}{\hat{S}} > \frac{\beta_m}{\mu + v_m} \\ &ES \Leftrightarrow R > R_m \end{aligned} \tag{2.5}$$

where *ES* is shorthand for the statement "The resident strain is evolutionarily stable", and where I have defined $R = \beta/(\mu + v)$ and $R_m = \beta_m/(\mu + v_m)$. Thus, the resident strain is

evolutionarily stable if and only if it has the largest value of $\beta_i/(\mu + v_i)$ of all possible strains, *i*. Incidentally, these results can be shown to hold globally for this particular model as well (Appendix).

This general approach has been used in a very wide variety of epidemiological models to characterize evolutionarily stable strains (see references in [5]). In the present case, we have seen that evolution maximizes a quantity (*R* in this case) and we can use this fact to elucidate important properties of pathogen evolution. In other more complex models, however, there need not be a simple maximization principle such as this. Rather, the inequality in (2.5) for more complex models often cannot be separated into terms solely involving mutant parameters on one side and resident parameters on the other. In this case, slightly more sophisticated analyses are required that are beyond the scope of this overview (interested readers should consult Otto and Day 2007).

Let's now see how the above maximization principle can be used to understand pathogen evolution. To begin, we can immediately see that strains with very high transmission and very low virulence will be best (i.e., they have the largest value of *R*). For some pathogens, however, it is not possible for a strain to have a high transmission rate without also inducing a high mortality rate [6, 1, 15, 17, 14, 7]. The simplest way to account for this constraint is to suppose that transmission rate is an increasing function of virulence. In this case we can then seek the level of virulence that maximizes $R = \beta(v)/(\mu + v)$. So long as the function $\beta(v)$ increases at a diminishing rate (i.e., $\mathrm{d}^2\beta/\mathrm{d}v^2 < 0$), *R* will be maximized at an intermediate level of virulence, *v**. Furthermore, under these conditions it is easy to see that the ES level of virulence is an increasing function of host mortality rate, μ. In particular, *v** must satisfy the following, first order necessary condition:

$$\frac{\mathrm{d}\beta}{\mathrm{d}v} = \frac{\beta(v)}{\mu + v}. \qquad (2.6)$$

Since $\mathrm{d}\beta/\mathrm{d}v$ decreases with increasing *v* (i.e., $\mathrm{d}^2\beta/\mathrm{d}v^2 < 0$), a simple implicit differentiation argument using (2.6) shows that that value of *v* satisfying (2.6) is larger, for larger values of μ. Thus, host species with high levels of natural mortality are predicted to harbour highly virulence pathogens.

2.3 Price equation technique

Price's equation has been widely used in evolutionary biology to model the dynamics of allele frequencies [22, 3, 8, 21]. Recently, however, it has been adapted to model the dynamics of the frequency of different pathogen strains in epidemiological models as well [4, 5]. To describe this approach let's return to the toy model (2.1) and first extend it to allow for *n* pathogen strains. We have

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \theta - \mu S - S\sum\nolimits_i \beta_i I_i \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= S\beta_i I_i - (\mu + v_i) I_i \qquad \forall i \in \{1,2,...,n\}\end{aligned} \tag{2.7}$$

System (2.7) consists of n +1 equations; one for each type of infected host, and one for the dynamics of susceptible hosts.

To maintain genetic variation in strains within the population, we now further extend system (2.7) to allow for the occurrence of mutation. Biologically, when mutations arise, they do so in a host that is already infected with some other genotype of pathogen. This then creates a host harbouring more than one type of pathogen. In order to maintain a simplified model in which hosts only ever contain a single pathogen, we therefore assume that such mutations either die out or supplant the original strain instantaneously. 'Mutation' in the model therefore really represents a change from one genotype of infection to another. Thus, as is common in many models of evolutionary epidemiology, we assume that a polymorphism is never maintained within a host [2, 19, 9, 10, 18].

Extending system (2.7) to incorporate this type of mutation, we have

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \theta - \mu S - S\sum\nolimits_i \beta_i I_i \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= S\beta_i I_i - (\mu + v_i) I_i - \eta I_i + \eta \sum\nolimits_j m_{ji} I_j \qquad \forall i, j \in \{1,2,...,n\}\end{aligned} \tag{2.8}$$

Here η is the rate at which infections change genotype through mutation, and m_{ji} is the probability that, given such a change, an infection of genotype j changes to one of genotype i.

System (2.8) completely specifies the dynamics of the different strain types. From an evolutionary standpoint, however, it is often more useful to change variables and to track these dynamics in terms of the frequencies of the different strain types. Defining $q_i := I_i / I_T$ as the frequency of strain type i, where $I_T = \sum_i I_i$, we have

$$\begin{aligned}\frac{\mathrm{d}q_i}{\mathrm{d}t} &= \frac{\mathrm{d}I_i/\mathrm{d}t}{I_T} - q_i \frac{\mathrm{d}I_T/\mathrm{d}t}{I_T} \\ &= q_i(r_i - \bar{r}) - \eta q_i + \eta \sum\nolimits_j m_{ji} q_j\end{aligned} \tag{2.9}$$

where $r_i = S\beta_i - \mu - v_i$ is referred to as the 'fitness' of strain *i*, and $\bar{r} := \sum_i q_i r_i$ is the mean fitness of all strains.

Let's now step back for a moment and see what we have done. Given *n* strains of pathogen, we now have *n* – 1 equations for the dynamics of their frequencies (since $\sum_i q_i = 1$). To completely specify system (2.8) in these new variables, however, we must also track the dynamics of the total number of infected individuals, as well as the number of susceptible individuals. Using (2.8) this gives

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \theta - \mu S - S\bar{\beta} I_T \\ \frac{\mathrm{d}I_T}{\mathrm{d}t} &= S\bar{\beta} I_T - (\mu + \bar{v}) I_T \end{aligned} \qquad (2.10)$$

where $\bar{x} := \sum_i q_i x_i$, and where I have made use of the fact that $\sum_i m_{ji} = 1$. System (2.10) provides the final two equations required to completely specify the dynamics (bringing the total number of equations back to *n* +1).

At this stage it might seem strange to employ this change of variables because it has resulted in a system of equations that is more complex than the original system (2.7). In fact, if we were primarily interested in the dynamics of the number of each strain type this would not be a useful change of variables. If, however, we are primarily interested in the evolution of some characteristic of the pathogen (e.g., its transmission rate or its virulence) then this change of variables does prove to be useful because we can now readily derive equations for the dynamics of the average value of these characteristics across all pathogens. Furthermore, this change of variables has also separated the epidemiological dynamics of the system (given by equations 2.10) from the evolutionary dynamics of the system (given by equations 2.9). As we will see, this is also a useful thing to do.

To derive equations for the evolutionary dynamics of the mean level of virulence and transmission, we simply need to differentiate $\bar{v} = \sum_i q_i v_i$ and $\bar{\beta} = \sum_i q_i \beta_i$ with respect to time. Doing so, and using (2.9) to simplify the result, we get [4]

$$\begin{aligned} \frac{\mathrm{d}\bar{v}}{\mathrm{d}t} &= \mathrm{cov}(v_i, r_i) - \eta(\bar{v} - \bar{v}_m) \\ \frac{\mathrm{d}\bar{\beta}}{\mathrm{d}t} &= \mathrm{cov}(\beta_i, r_i) - \eta(\bar{\beta} - \bar{\beta}_m) \end{aligned} \qquad (2.11a)$$

or

$$\frac{\mathrm{d}\bar{v}}{\mathrm{d}t} = S\sigma_{\beta v} - \sigma_{vv} - \eta\left(\bar{v} - \bar{v}_m\right)$$
$$\frac{\mathrm{d}\bar{\beta}}{\mathrm{d}t} = S\sigma_{\beta\beta} - \sigma_{\beta v} - \eta\left(\bar{\beta} - \bar{\beta}_m\right) \qquad (2.11b)$$

Here σ_{xy} is the covariance between x and y across the pathogen strains that are circulating in the population, and $\bar{x}_m := \sum_{i,j} x_i m_{ji} q_j$ is the average value of trait x among all new mutations. Equations (2.11) are versions of Price's equation [22, 3, 8, 21] and each has a useful interpretation. The average trait value in the population changes as a result of two processes. First, the average trait value changes in a direction given by the sign of the covariance between the trait and fitness. For example, the average value of transmission is driven upward by the fact that strains with large values of transmission, β, tend to have higher fitness (the term $S\sigma_{\beta\beta}$), but it is also affected by the fact that strains with high virulence have lower fitness, and virulence might be genetically correlated with transmission across parasite strains (the term $-\sigma_{\beta v}$). Second, the average trait value changes in a direction governed by any mutational bias that might occur (e.g., the term $-\eta(\bar{\beta} - \bar{\beta}_m)$ for the dynamics of $\bar{\beta}$).

The variances and covariances in system (2.11), σ_{xy}, will also change through time, and equations for these dynamics will typically depend on higher moments of the strain distribution. So in this sense, equations (2.11) cannot be immediately solved to obtain the evolutionary dynamics of the average values of v and β. Nevertheless, system (2.11) can be used to gain some important insights into pathogen evolution without requiring a full solution. To see how, it is useful to write equations (2.11) in matrix notation:

$$\begin{pmatrix} \frac{\mathrm{d}\bar{v}}{\mathrm{d}t} \\ \frac{\mathrm{d}\bar{\beta}}{\mathrm{d}t} \end{pmatrix} = \mathbf{G}\begin{pmatrix} -1 \\ S \end{pmatrix} - \eta\begin{pmatrix} \bar{v} - \bar{v}_m \\ \bar{\beta} - \bar{\beta}_m \end{pmatrix} \qquad (2.12)$$

where **G** is the genetic (co)variance matrix and $\begin{pmatrix} -1 & S \end{pmatrix}^T$ is termed the selection gradient. The product of **G** with the selection gradient in equation (2.12) describes the way in which natural selection changes the average level of virulence and transmission in the pathogen population. Natural selection always favours reduced virulence with a strength of -1. On the other hand, natural selection always favours an increased transmission rate with a strength that is proportional to the density of susceptible hosts, *S*. At equilibrium the force of mutation must balance the force of natural selection, as mediated through the genetic covariance structure of the pathogen population [4]. Interestingly, this formulation also separates the effects of the epidemiological dynamics on evolution (represented here by the selection gradient vector) and the genetic structure of the pathogen population (represented here by the genetic covariance matrix).

In the invasion analysis approach, we were only able to infer properties of the endpoint of evolution, and therefore we needed to make an assumption of a tradeoff between virulence and transmission for such an endpoint to exist. Here, however, we can make predictions about the evolutionary dynamics regardless of whether such tradeoffs exist. Of course, we still do not expect there to be an intermediate equilibrium level of virulence unless, ultimately, some sort of constraint between ever increasing transmission and ever decreasing virulence occurs. In the Price-equation approach, this would be manifest as a positive covariance between the two traits.

Let's now suppose such a constraint occurs, and return to the question of how natural host mortality rate affects virulence evolution using the Price equation approach. We saw previously (using an invasion analysis) that high mortality selects for the evolution of high virulence. An examination of equations (2.11) however, reveals that host mortality μ does not enter directly into the evolutionary dynamics. Therefore, such mortality affects virulence evolution only if it indirectly affects either the genetics of the pathogen population, or the selection gradient $\begin{pmatrix} -1 & S \end{pmatrix}^T$.

We typically do not expect host mortality to significantly alter the genetics of the pathogen population, and therefore the only way in which host mortality affects virulence evolution is indirectly through the epidemiological dynamics. For example, if we assume that the epidemiological dynamics are always approximately at equilibrium (as in the invasion analysis), then from (2.10) we have $S \approx (\mu + \bar{v})/\bar{\beta}$. Thus, higher host mortality rates lead, indirectly, to a higher number of susceptible hosts. This, in turn, increases the advantage of strains with higher transmission rate, and to the extent that transmission and virulence are positively correlated with one another, this leads to the evolution of higher virulence. Thus, the Price equation approach provides a more mechanistic picture of the factors that govern the evolution of pathogen populations. For example, if we were to test these predictions by experimentally elevating host mortality rate and measuring evolutionary changes in pathogen virulence, the invasion analysis would lead us to believe that higher virulence is always expected. The Price equation approach, however, reveals that this will only be true if our experimental manipulation allows this change in host mortality to indirectly feed back, through the epidemiological dynamics, to elevate the number of susceptible hosts (something that might well not occur in all experimental systems).

3. Discussion

This chapter has presented a brief overview of two different approaches to modeling evolutionary epidemiology. I have concentrated on a very simple toy epidemiological model that is not meant to represent the dynamics of any particular disease. Rather, it is simply meant as a tool to elucidate the similarities and differences of the two techniques. The interested reader should consult [4, 5] for more complex and realistic examples.

The invasion analysis technique presented is somewhat restricted in its scope and does not provide complete information about the mechanistic details driving evolution in pathogen populations. It main advantage, however, is that it provides an analytically tractable approach for modeling pathogen evolution. The Price equation approach is more general in the sense that it makes fewer restrictive assumptions, and it also provides a more complete description of the mechanistic details of evolution. Its primary drawback, however, is that it rarely allows for a complete, analytical treatment of pathogen evolution. Rather, it is best at providing qualitative insights. As such these two approaches are best viewed as complimentary techniques.

Appendix

Consider the following function

$$V(S,I) = S - \hat{S}\ln\left(S/\hat{S}\right) + I - \hat{I}\ln\left(I/\hat{I}\right) \tag{A1}$$

where $\hat{S}$ and $\hat{I}$ are the equilibrium values of S and I at the endemic equilibrium, E_2. Expression (A1) is a Lyapunov function for system (2.1) [13]. To see this, note that this function has a unique minimum in S and I at the equilibrium values $\hat{S}$ and $\hat{I}$. Therefore, all we need to show is that $\mathrm{d}V/\mathrm{d}t \le 0$ along all trajectories of system (2.1), with equality holding only when $S = \hat{S}, I = \hat{I}$. Differentiating (A1), and using equations (2.1) gives

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} &= \left(1 - \frac{\hat{S}}{S}\right)\frac{\mathrm{d}S}{\mathrm{d}t} + \left(1 - \frac{\hat{I}}{I}\right)\frac{\mathrm{d}I}{\mathrm{d}t} \\ &= \theta\left(1 - \frac{\hat{S}}{S}\right) - \mu S + \mu\hat{S} - \beta S\hat{I} + (\mu + v)\hat{I}\end{aligned} \tag{A2}$$

Now, using the fact that $\beta S\hat{I} = \beta\hat{S}\hat{I}\dfrac{S}{\hat{S}} = (\theta - \mu\hat{S})\dfrac{S}{\hat{S}}$ and $\theta = \mu\hat{S} + (\mu + v)\hat{I}$, (A2) can be re-written as

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \theta\left(2 - \frac{\hat{S}}{S} - \frac{S}{\hat{S}}\right) \le 0, \tag{A3}$$

with equality holding only when $S = \hat{S}$.

We can also use an extension of the Lyapunov function provided by [13] to demonstrate that the local results given in (2.5) of the text, hold globally as well. Consider the following function

$$V(S,I,I_m) = S - \hat{S}\ln\left(S/\hat{S}\right) + I - \hat{I}\ln\left(I/\hat{I}\right) + I_m \tag{A4}$$

where $\hat{S}$ and $\hat{I}$ are the equilibrium values of S and I at the endemic equilibrium, E_2. Expression (A4) has a unique minimum in S,I, and I_m at $(\hat{S},\hat{I},0)$. The time derivative of (A4) along trajectories of system (2.2) is

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} &= \theta\left(2-\frac{\hat{S}}{S}-\frac{S}{\hat{S}}\right)+\beta_m\hat{S}I_m-(\mu+\nu_m)I_m \\ &= \theta\left(2-\frac{\hat{S}}{S}-\frac{S}{\hat{S}}\right)-\beta_m I_m\left(\frac{R-R_m}{RR_m}\right)\end{aligned} \qquad \text{(A5)}$$

Now suppose that $R > R_m$. Expression (A5) is then clearly negative everywhere except when $S=\hat{S}$, $I_m=0$, in which case it is zero. Thus, (A4) is a Lyapunov function for equilibrium $(\hat{S},\hat{I},0)$ of system (2.2) if $R > R_m$. If $R < R_m$, then we already know that the equilibrium $(\hat{S},\hat{I},0)$ is unstable. Thus, result (2.5) of the text holds globally.

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