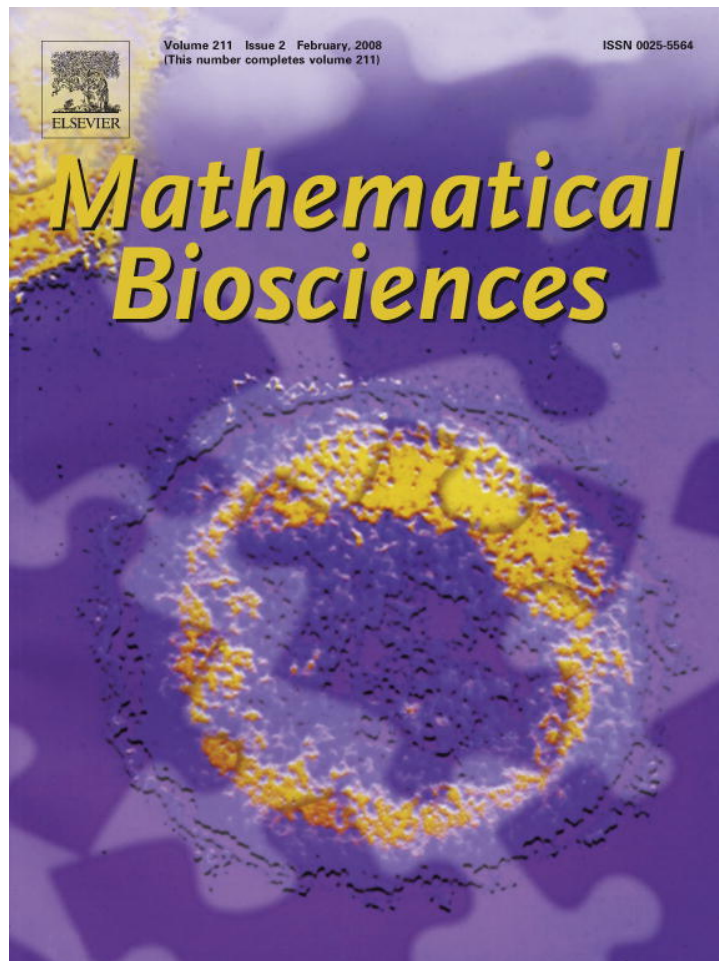


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Vaccinations in disease models with antibody-dependent enhancement

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Abstract

This paper examines the effects of single-strain vaccine campaigns on the dynamics of an epidemic multi-strain model with antibody-dependent enhancement (ADE). ADE is a disease spreading process causing individuals with their secondary infection to be more infectious than during their first infection by a different strain. We follow the two-strain ADE model described in Cummings et al. [D.A.T. Cummings, Doctoral Thesis, Johns Hopkins University, 2004] and Schwartz et al. [I.B. Schwartz, L.B. Shaw, D.A.T. Cummings, L. Billings, M. McCrary, D. Burke, Chaotic desynchronization of multi-strain diseases, *Phys. Rev. E*, 72:art. no. 066201, 2005]. After describing the model and its steady state solutions, we modify it to include vaccine campaigns and explore if there exists vaccination rates that can eradicate one or more strains of a virus with ADE.

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Keywords: Epidemics; Antibody-dependent enhancement; Vaccine

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1. Introduction

Dengue is a serious endemic viral infection found in Africa, the Americas, and Southeast Asia. It is one of the most important emerging tropical diseases at the beginning of the 21st century [10]. There is no vaccine, although clinical trials are underway, nor any preventive medication. The World Health Organization states that approximately 2.5 billion people are at risk for contracting dengue [18] and between 50 and 100 million cases are reported each year [10]. Even though medical treatments for the most severe cases of the disease are effective, dengue is still one of the leading causes of mortality in children in Thailand and the rest of Southeast Asia [19]. Since World War II, the four dengue viruses have progressively spread geographically to virtually all tropical countries to create a global pandemic resulting in several hundred thousand hospitalizations every year [12].

What makes modeling the dengue virus so interesting is that it has developed a sophisticated spreading process. Dengue is known to exhibit as many as four coexisting serotypes (strains) in a region. Once a person is infected and recovered from one serotype, they confer life-long immunity from that serotype. However, the antibodies that the body develops for the first serotype will not counteract a second infection by a different serotype. In fact, due to the nature of the disease, the antibodies developed from the first infection form complexes with the second serotype so that the virus can enter more cells, increasing viral production [8]. This is referred to as heterologous, or secondary, infections. Vaughn et al. [17] reports a 10- to 20-fold increase in viremia titers for secondary infections early in the illness. Viral loads are potentially associated with transmissibility, and we hypothesize that individuals with their secondary infection are more infectious than during their first infection. This increased transmission rate in subsequent infections is known as antibody-dependent enhancement (ADE).

ADE is an alarming evolutionary development in multistrain viruses with respect to vaccines. An optimal vaccination would need to cover all strains of the disease at once, or the vaccinations could increase transmission of the strains not covered. This is particularly dangerous for people who have dengue because the infections are more severe in individuals who already have dengue antibodies. More explicitly, there is evidence that dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are associated with heterologous dengue infections occurring at an interval of a year or more [12]. Treatment of DHF is complicated by the fact that it can progress from a non-specific viral syndrome to irreversible shock and death within a few hours, so hospitalization is required. In large dengue epidemics, there is often chaos, confusion, and increased mortality [10].

Currently, tetravalent vaccines for dengue are in the process of being developed, but an effective dengue vaccine for public use will not be available for 5–10 years [9]. Researchers have developed separate vaccine candidates for each of the four serotypes, for example Steven Whitehead and colleagues [13]. Work on chimeric vaccines, which would protect against combinations of two or more serotypes are still in development. This leads us to examine if there is a way to use the single serotype vaccine safely. It is important to note that administering a single vaccination would only protect the individual against that serotype. A subsequent infection from another serotype would manifest itself as a secondary infection. This is not desirable because secondary infections have higher mortality rates and transmissibility. Therefore, the obvious scenario of using the separate vaccinations in a series is not an option. Therefore, we explore the effect of applying a single cam-

paing of these separate vaccinations to see if we can achieve herd immunity and eradicate the disease.

Motivated by the dengue scenario, this paper examines the effects of single-strain vaccine campaigns on the dynamics of an epidemic model with ADE. To make the analysis more tractable, we follow the two-strain ADE model described in Cummings et al. [3] and Schwartz et al. [14]. After describing the model and its steady state solutions, we modify it to include vaccine campaigns and explore if there exists vaccination rates that can eradicate one or more strains of a virus with ADE.

2. The model

We derive a continuous-time compartmental model involving two co-circulating disease strains with ADE in a homogeneous population, following the work of Cummings et al. [3] and Ferguson et al. [6]. The population affected by the disease will be compartmentalized into discrete categories. Let s be the fraction of the population that is susceptible to the disease, i_j be the fraction infected with strain j but still susceptible to the other strain k , r_j be the fraction of those who have recovered from strain j , and i_{jk} be the fraction of the population previously infected with strain j and now is infected with strain k , where $j = 1, 2$ and $k = 1, 2$ whenever $i \neq k$. The rate of transmission of strain j is β_j . We will assume recovery from one strain implies natural life-long immunity for that strain, concurrent infections with multiple serotypes are not common [11], and that there is no significant disease mortality. The fraction that has recovered from both strains is represented by the variable r_* . The recovery rate from either strain is σ , and μ is the natural death rate which we will set equal to the birth rate. All parameters and variables are assumed to be non-negative, and the total population is assumed to be constant. See the transfer diagram in Fig. 1.

This model does not specifically include the population of mosquitoes because we assume that the short length of time in which viruses could be maintained in the mosquito vector in the absence of human infections (less than 2–3 weeks) would not significantly impact the dynamics. For more details on vector modeling for dengue, see Esteva and Vargas [5]. In another approach, Ferguson et al. [6] includes a background force of infection through stochastic perturbations. The seasonal variations of a mosquito population can also be incorporated into a periodic transmission rate, as described in Schwartz et al. [14]. All are possible directions for enhancement of this model in future research.

Since viral production is increased during a secondary infection due to ADE, we introduce an ADE parameter, ϕ_k , to increase the probability of a person with a secondary infection, i_{jk} , to

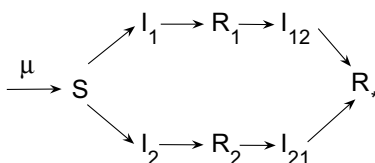


Fig. 1. A transfer diagram for two co-circulating disease strains.

transmit the disease. We are only considering values of ϕ_k greater than one. The full eight-equation system for the two-strain dengue model with ADE is:

$$\begin{aligned}
 \frac{ds}{dt} &= \mu - \beta_1 s i_1 - \beta_2 s i_2 - \phi_2 \beta_2 s i_{12} - \phi_1 \beta_1 s i_{21} - \mu s, \\
 \frac{di_1}{dt} &= \beta_1 s i_1 + \phi_1 \beta_1 s i_{21} - \sigma i_1 - \mu i_1, \\
 \frac{di_2}{dt} &= \beta_2 s i_2 + \phi_2 \beta_2 s i_{12} - \sigma i_2 - \mu i_2, \\
 \frac{dr_1}{dt} &= \sigma i_1 - \beta_2 r_1 i_2 - \phi_2 \beta_2 r_1 i_{12} - \mu r_1, \\
 \frac{dr_2}{dt} &= \sigma i_2 - \beta_1 r_2 i_1 - \phi_1 \beta_1 r_2 i_{21} - \mu r_2, \\
 \frac{di_{21}}{dt} &= \phi_1 \beta_1 r_2 i_{21} + \beta_1 r_2 i_1 - \sigma i_{21} - \mu i_{21}, \\
 \frac{di_{12}}{dt} &= \phi_2 \beta_2 r_1 i_{12} + \beta_2 r_1 i_2 - \sigma i_{12} - \mu i_{12}, \\
 \frac{dr_*}{dt} &= \sigma i_{21} + \sigma i_{12} - \mu r_*.
 \end{aligned} \tag{1}$$

Because the total population is assumed to be constant, we have the relationship

$$s + i_1 + i_2 + r_1 + r_2 + i_{12} + i_{21} + r_* = 1.$$

We can solve directly for r_* and neglect the differential equation dr_*/dt in our analysis of the system (1). We continue with a brief overview of the steady state solutions of this system and their stabilities. These fixed points will be written in the form $(s, i_1, i_2, r_1, r_2, i_{12}, i_{21})$.

The disease free equilibrium (DFE), which represents the die out of both strains, is $E_0 = (1, 0, 0, 0, 0, 0, 0)$. A common method of determining its local stability is finding the basic reproduction number, R_0 , the expected number of secondary infections by a single infected in a susceptible population. We define the basic reproduction number $R_0 = \max\{R_1, R_2\}$, for $R_i = \beta_i / (\sigma + \mu)$.

Proposition 2.1. *If $R_0 < 1$ ($R_0 > 1$), then the DFE is locally asymptotically stable (unstable).*

Proof (Sketch). Following the method described by van den Driessche and Watmough [16], we construct the next generation matrix. From the maximum eigenvalue of this matrix, we find R_0 . Stability can also be determined by linearization. This method evaluates the eigenvalues of the Jacobian matrix evaluated at the fixed point and will provide the same results. \square

Proposition 2.2. *If $R_0 < 1$, $\phi_1 < 1/R_1$, and $\phi_2 < 1/R_2$, the DFE is globally stable.*

Proof. Following the work of Castillo-Chavez, et al. [2], define a Lyapunov function $F = i_1 + i_2 + i_{12} + i_{21}$. Let G be the set on which $F = 0$. Clearly, $F > 0$ for all points in the domain not in G . We now evaluate \dot{F} :

$$\begin{aligned} \dot{F} &= \frac{di_1}{dt} + \frac{di_2}{dt} + \frac{di_{12}}{dt} + \frac{di_{21}}{dt} \\ &= \beta_1 \left(s + r_2 - \frac{1}{R_1} \right) i_1 + \beta_2 \left(s + r_1 - \frac{1}{R_2} \right) i_2 + \beta_2 \left(\phi_2(s + r_1) - \frac{1}{R_2} \right) i_{12} \\ &\quad + \beta_1 \left(\phi_1(s + r_2) - \frac{1}{R_1} \right) i_{21}. \end{aligned} \tag{2}$$

From the assumption that $R_0 < 1$, we know $1/R_1 > 1$ and $1/R_2 > 1$. Also, $0 \leq (s + r_1) \leq 1$ and $0 \leq (s + r_2) \leq 1$. If $\phi_1 < 1/R_1$ and $\phi_2 < 1/R_2$, $\dot{F} < 0$ for all points in the domain not in G . By La Salle’s invariance principle, all points in the domain will asymptotically approach G as $t \rightarrow \infty$ for the given parameter restrictions. For all points in G except the DFE, note that $ds/dt > 0$ and all other non-zero variables are decreasing in Eq. (1). Therefore all points in G monotonically approach the DFE as $t \rightarrow \infty$. \square

The boundary equilibria represent the case when only one of the diseases will persist. In this system, they are of the form

$$E_1 = \left(\frac{\sigma + \mu}{\beta_1}, \frac{(\beta_1 - \sigma - \mu)\mu}{\beta_1(\sigma + \mu)}, 0, \frac{\sigma(\beta_1 - \sigma - \mu)}{\beta_1(\sigma + \mu)}, 0, 0, 0 \right), \tag{3}$$

$$E_2 = \left(\frac{\sigma + \mu}{\beta_2}, 0, \frac{(\beta_2 - \sigma - \mu)\mu}{\beta_2(\sigma + \mu)}, 0, \frac{\sigma(\beta_2 - \sigma - \mu)}{\beta_2(\sigma + \mu)}, 0, 0 \right). \tag{4}$$

Note that E_1 and E_2 only make biological sense when $R_1 > 1$ and $R_2 > 1$, respectively.

Proposition 2.3. E_1 is locally asymptotically stable when

$$R_2 < \frac{R_1}{1 + \frac{\phi_2 \sigma (R_1 - 1)}{\sigma + \mu}} \quad \text{and} \quad R_1 > 1. \tag{5}$$

Similarly, E_2 is locally asymptotically stable when

$$R_1 < \frac{R_2}{1 + \frac{\phi_1 \sigma (R_2 - 1)}{\sigma + \mu}} \quad \text{and} \quad R_2 > 1. \tag{6}$$

Proof (Sketch). The stability is determined by linearization. The inequalities guarantee that the eigenvalues of the Jacobian matrix evaluated at the associated fixed points are negative. \square

In the case where $\beta_1 = \beta_2$, we find that the boundary equilibria, E_1 and E_2 , are never stable. Also, E_1 and E_2 cannot be stable simultaneously.

We continue with a discussion of the endemic equilibrium, or the case when both of the strains persist. Due to the complexity of this system, the endemic fixed point does not have a concise, explicit form, but we can prove its existence and uniqueness for the following parameter restrictions.

Proposition 2.4. If $R_1 > 1$, $R_2 > 1$, $\phi_1 > 1 + \mu/\sigma$ and $\phi_2 > 1 + \mu/\sigma$, then there exists a unique endemic equilibrium in the domain (total population = 1 and variables are non-negative).

Proof. See Appendix A. \square

We investigate the dynamics of the model using the general dengue parameters (for any serotype) in Table 1. The analysis in [7] uses age-specific serological data from Thailand to estimate that the R_0 for dengue is between 4 and 6 (endemic). To begin exploring the dynamics numerically, we set the parameters for each strain to be equal, $\beta_1 = \beta_2 = \beta$ and $\phi_1 = \phi_2 = \phi$. We call this the symmetric parameters case.

In Fig. 2, we set $\phi = 2.63$ and vary β as a comprehensive example of the bifurcation structure, showing parameters where the DFE and endemic equilibria are stable. For values of β which make $R_0 < 1$, the DFE is stable. Two unstable fixed points are created by a bi-unstable saddle–saddle bifurcation at $\beta = 96.758$. The top branch collides with the DFE at $R_0 = 1$ and the DFE loses stability. The bottom branch undergoes a subcritical Hopf bifurcation at

Table 1
Model parameters

Parameter	Value	Reference
μ , 1/host life span, years ⁻¹	0.02	[6]
β , transmission coefficient, years ⁻¹	400	[7]
σ , recovery rate, years ⁻¹	100	[6]
ϕ_i , ADE factor of serotype i	1–5	–

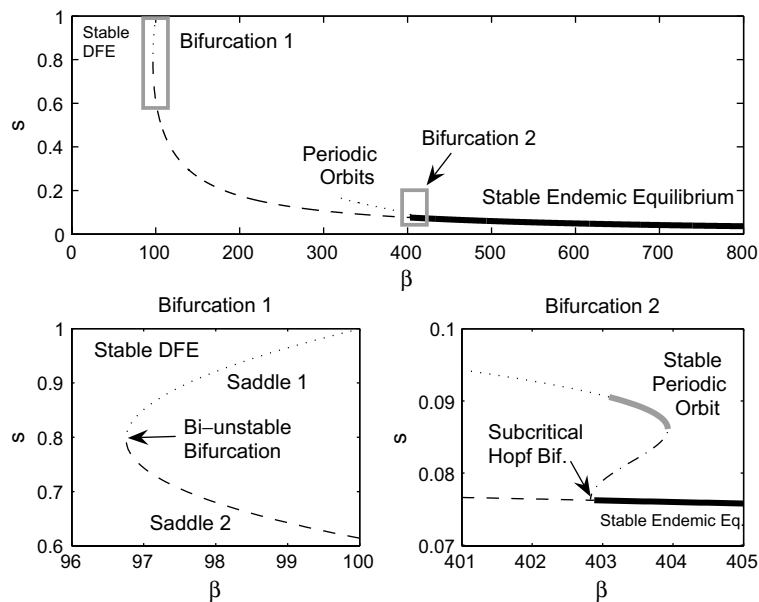


Fig. 2. The bifurcation diagram for the symmetric parameters case. We set $\phi = 2.63$ as we vary β . Stable branches are indicated by thick curves. The fixed points are black and the periodic orbit is gray. A subcritical Hopf bifurcation occurs at $\beta = 402.882$, as shown in the close up box. The steady state branches are created through a bi-unstable saddle–saddle bifurcation at $\beta = 96.758$.

$\beta = 402.882$, where it gains stability. For details of the bifurcation structure, see the close up graphs in Fig. 2. The thick solid black curve indicates where the endemic equilibrium is stable. The thick solid gray curve is a Poincaré cut of the stable periodic orbit. The unstable branches are shown by the dotted and dashed curves.

For $\beta = 400$ and $\phi > 1$, the endemic equilibrium is stable until it loses stability through another subcritical Hopf bifurcation near $\phi = 2.629$. This value was approximated by a linearization of the system and numerically finding the eigenvalues with an error of 10^{-5} using MAPLE. For $\phi > 2.629$, trajectories experience oscillations including periodic, quasiperiodic, and chaotic dynamics. In a similar four strain model, we have numerically analyzed the bifurcation to chaos [1,14]. For that model, we also have explored extinction probabilities [4]. In other work [15], we have analyzed the dynamics for the two and four strain models by a center manifold analysis to derive synchronization properties between the primary and secondary infections.

If we let $\beta_1 \neq \beta_2$, we can add the boundary equilibrium points to the bifurcation diagram. For example, we let $\phi_1 = \phi_2 = 2.63$ in Fig. 3. The boundary for the region of stable endemic equilibrium was approximated by linearization of the system and numerically finding the eigenvalues using MAPLE. The others boundaries are described by Eqs. (5) and (6) and $R_0 = 1$. Notice the large region of oscillatory dynamics. This is the type of behavior we see in time series of disease data such as dengue. The goal in vaccinating is to reduce or remove those outbreak oscillations and make the boundary equilibria or DFE the stable behavior.

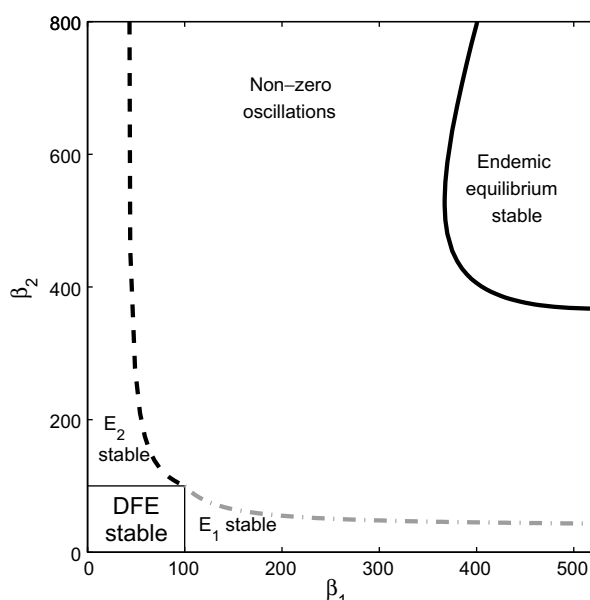


Fig. 3. A graph of the stable regions for the DFE, boundary equilibria, and endemic equilibrium using the full model. We set $\phi_1 = \phi_2 = 2.63$ as we vary β_1 and β_2 .

3. Adding vaccinations

Using our understanding of the bifurcation structure of the model in Eq. (1), we continue by modeling and evaluating the effectiveness of single-strain vaccination strategies. The goal is to determine the set of vaccination rate parameters for which one or both of the virus strains will die out using a single campaign. That is, an individual will only receive one vaccine to one strain over his/her lifetime. These assumptions are motivated by the risks involved with accelerating the acquisition of secondary infections. Secondary cases are associated with higher transmissibility and mortality rates. Mathematically, the optimal solution would prescribe the minimum vaccination rates that make the DFE stable. But if that is not possible, we also consider the cases when the boundary equilibria are stable.

Currently, no dengue vaccine protecting against all four serotypes is available [9]. Recently, however, progress has been made towards developing vaccine candidates for single serotypes [13]. In fact, Steven Whitehead and colleagues have constructed a DEN-4 vaccine candidate which produced 100% neutralizing antibody seroconversion in 24 adult human volunteers [13]. Using this trial as the ideal scenario, we assume we have a vaccine with full efficacy for a single strain. That is, each person vaccinated against one strain will behave as if they have recovered from that strain, and are fully susceptible to the other. We also assume the vaccination occurs at birth, since the goal is to develop a pediatric vaccine for use in endemic countries [10].

Let us first consider a model with a limited number of vaccinations offered for only one strain. More specifically, let v be the percent of the population vaccinated against strain one. Then, $(1 - v)$ percent will enter the susceptible compartment and v percent of the population will enter a new compartment r_1^* . The compartment r_1^* represents the percent of people in the population that have been vaccinated against the first strain. A new compartment i_{12}^* is also required for the percent of the population that has been vaccinated against strain one, but is currently infected with strain two. See the transfer diagram in Fig. 4.

The susceptibles can exit this compartment as before, by coming into contact with an infective. If a susceptible, s , comes in contact with a person that has been vaccinated against one but now has two, they will leave the compartment at a rate of $\theta\beta_2s i_{12}^*$, where β_2 is the contact rate and θ is the ADE factor brought on by the vaccination. We assume $\theta > 1$.

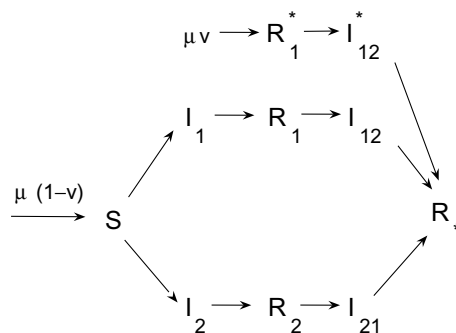


Fig. 4. A transfer diagram for two co-circulating disease strains with vaccinations for one strain only.

Therefore, the system with a vaccination for one strain is:

$$\begin{aligned}
 \frac{ds}{dt} &= (1 - v)\mu - \beta_1 si_1 - \beta_2 si_2 - \phi_2 \beta_2 si_{12} - \phi_1 \beta_1 si_{21} - \theta \beta_2 si_{12}^* - \mu s, \\
 \frac{di_1}{dt} &= \beta_1 si_1 + \phi_1 \beta_1 si_{21} - \sigma i_1 - \mu i_1, \\
 \frac{di_2}{dt} &= \beta_2 si_2 + \phi_2 \beta_2 si_{12} + \theta \beta_2 si_{12}^* - \sigma i_2 - \mu i_2, \\
 \frac{dr_1}{dt} &= \sigma i_1 - \beta_2 r_1 i_2 - \phi_2 \beta_2 r_1 i_{12} - \theta \beta_2 r_1 i_{12}^* - \mu r_1, \\
 \frac{dr_2}{dt} &= \sigma i_2 - \beta_1 r_2 i_1 - \phi_1 \beta_1 r_2 i_{21} - \mu r_2, \\
 \frac{dr_1^*}{dt} &= v\mu - \phi_2 \beta_2 r_1^* i_{12} - \beta_2 r_1^* i_2 - \theta \beta_2 r_1^* i_{12}^* - \mu r_1^*, \\
 \frac{di_{12}}{dt} &= \phi_2 \beta_2 r_1 i_{12} + \beta_2 r_1 i_2 + \theta \beta_2 r_1 i_{12}^* - \sigma i_{12} - \mu i_{12}, \\
 \frac{di_{21}}{dt} &= \phi_1 \beta_1 r_2 i_{21} + \beta_1 r_2 i_1 - \sigma i_{21} - \mu i_{21}, \\
 \frac{di_{12}^*}{dt} &= \beta_2 r_1^* i_2 + \phi_2 \beta_2 r_1^* i_{12} + \theta \beta_2 r_1^* i_{12}^* - \sigma i_{12}^* - \mu i_{12}^*, \\
 \frac{dr^*}{dt} &= \sigma(i_{12} + i_{21} + i_{12}^*) - \mu r^*.
 \end{aligned} \tag{7}$$

The DFE of this system is

$$(s, i_1, i_2, r_1, r_2, r_1^*, i_{12}, i_{21}, i_{12}^*) = (1 - v, 0, 0, 0, 0, v, 0, 0, 0). \tag{8}$$

Proposition 2.5. *The DFE of the single vaccination model is stable when*

$$R_1 < \frac{1}{1 - v} \quad \text{and} \quad R_2 < \frac{1}{1 + v(\theta - 1)}. \tag{9}$$

Proof (Sketch). The stability is determined by linearization. The inequalities guarantee that the eigenvalues of the Jacobian matrix evaluated at the associated fixed points are negative. \square

The relationships in Eq. (9) imply that for the DFE to be stable

$$1 - \frac{1}{R_1} < v < \frac{\frac{1}{R_2} - 1}{\theta - 1}, \tag{10}$$

which puts upper and lower bounds on the vaccination level for it to be effective.

In studying vaccination strategies, we are assuming that both strains are invading the population, so $R_1 > 1$ and $R_2 > 1$. In order for the DFE to be stable, Eq. (9) implies for any vaccination rate $R_2 < 1$. Therefore, the conditions in Eq. (9) cannot be satisfied and strain two can never die out by a vaccination campaign only against strain one. On the other hand, strain one can be eradicated by finding a vaccination rate that would make the boundary equilibrium with the second strain surviving stable.

The two boundary equilibria can be expressed as

$$V_1 = \left(\frac{\sigma + \mu}{\beta_1}, \frac{\mu(\beta_1(1-v) - (\mu + \sigma))}{\beta_1(\sigma + \mu)}, 0, \frac{\sigma(\beta_1(1-v) - (\mu + \sigma))}{\beta_1(\sigma + \mu)}, 0, v, 0, 0, 0 \right) \quad (11)$$

and

$$V_2 = \left(\frac{(1-v)(\sigma + \mu)}{\beta_2(1 + (\theta - 1)v)}, 0, \frac{\mu(1-v)(\beta_2(1 + (\theta - 1)v) - (\mu + \sigma))}{\beta_2(1 + (\theta - 1)v)(\sigma + \mu)}, \right. \\ \left. 0, \frac{\sigma(1-v)(\beta_2(1 + (\theta - 1)v) - (\mu + \sigma))}{\beta_2(1 + (\theta - 1)v)(\sigma + \mu)}, \frac{v(\sigma + \mu)}{\beta_2(1 + (\theta - 1)v)}, \right. \\ \left. 0, 0, \frac{\mu v(\beta_2(1 + (\theta - 1)v) - (\mu + \sigma))}{\beta_2(1 + (\theta - 1)v)(\sigma + \mu)} \right). \quad (12)$$

Note that V_1 and V_2 only make biological sense when $R_1 > 1/(1-v)$ and $R_2 > 1/(1+v(\theta-1))$, respectively. We continue with the scenario of interest, increasing the vaccination rate to see the bifurcation leading to the stabilization of V_2 .

For simplicity, we return the symmetric parameters case, with $\beta_k = \beta$ for $k = 1, 2$, $\phi_k = \phi$ for $k = 1, 2$, and $\theta = \phi$. Linearizing the Jacobian about the boundary equilibrium V_2 shows that it will be stable if

$$\phi < \frac{(\sigma + \mu)(\sigma + \mu v) - \sigma\beta(1-v)^2}{v\sigma\beta(1-v)} \quad (13)$$

and the DFE is unstable. Using the parameters $\beta = 400 \text{ years}^{-1}$, $\phi = 2.63$, $\sigma = 100 \text{ years}^{-1}$, and $\mu = 0.02 \text{ years}^{-1}$, we can find the transfer of stability between the endemic equilibrium and the boundary equilibrium when the vaccination percentage is approximately $v = 0.899$. That is, if more than 89.9% of newborns are vaccinated against strain one, strain one will die out.

For the boundary case with general parameters, the linearization about the V_2 steady state results in a Jacobian with the following eigenvalues

$$\begin{aligned} \lambda_1 &= -\mu, \\ \lambda_2 &= -\sigma - \mu, \\ \lambda_3 &= -\frac{\mu\beta_2(1 + (\theta - 1)v)}{\sigma + \mu}, \\ \lambda_4 &= \frac{\beta_1(\sigma + \mu)(1-v)(\mu + \sigma(1 - \phi_1)) - \beta_2(1 + (\theta - 1)v)((\sigma + \mu)^2 - \phi_1\beta_1(1-v)\sigma)}{\beta_2(1 + (\theta - 1)v)(\sigma + \mu)}, \\ \lambda_5 &= \frac{-\mu\beta_2(1 + (\theta - 1)v) + \sqrt{\mu\beta_2(1 + (\theta - 1)v)((1 + (\theta - 1)v)\mu\beta_2 - 4(\sigma + \mu)^2) + 4\mu(\sigma + \mu)^3}}{2(\mu + \sigma)}, \\ \lambda_6 &= \frac{-\mu\beta_2(1 + (\theta - 1)v) - \sqrt{\mu\beta_2(1 + (\theta - 1)v)((1 + (\theta - 1)v)\mu\beta_2 - 4(\sigma + \mu)^2) + 4\mu(\sigma + \mu)^3}}{2(\mu + \sigma)}. \end{aligned} \quad (14)$$

Here, λ_2 has a multiplicity of three and λ_3 has a multiplicity of two. Notice that the existence of V_2 , with $R_2 > 1/(1 + v(\theta - 1))$, implies that λ_5 and λ_6 have negative real parts. Restricting parameters to positive values and the ADE factors to values greater than one, the stability of the fixed point can be quickly determined from sign of the eigenvalue λ_4 .

Shown in Fig. 5 is an example of the parameter regions for non-symmetric contact rates where one or both strains of the disease will die out. We fix the parameters $\beta_1 = 400 \text{ years}^{-1}$ and $\phi_1 = \theta = 2.63$ and plot the minimum vaccination rate needed as we vary the difference between β_2 and β_1 . Notice that for small β_2 , the inequalities in Eq. (9) are satisfied and the DFE is stable. For larger β_2 , it is only possible to make the boundary equilibrium stable, and strain two will persist.

Fig. 6 is a similar example showing effective vaccination rates as we vary the ADE factor θ for the vaccinated group that is currently infected with strain two. We fix the parameters $\beta_1 = 400$

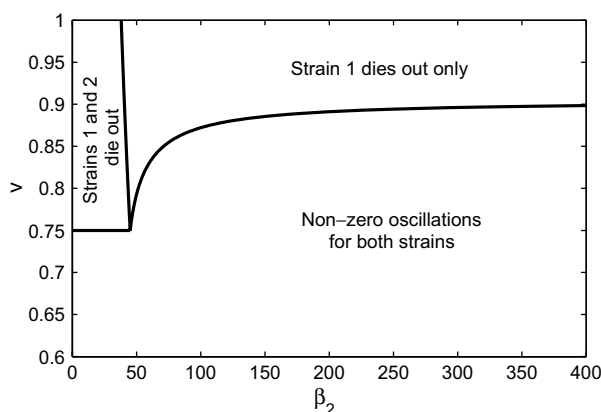


Fig. 5. A graph of the regions of effective vaccination rates against one strain in the non-symmetric contact rate case. We fix the parameters $\beta_1 = 400 \text{ years}^{-1}$ and $\phi_1 = \theta = 2.63$.

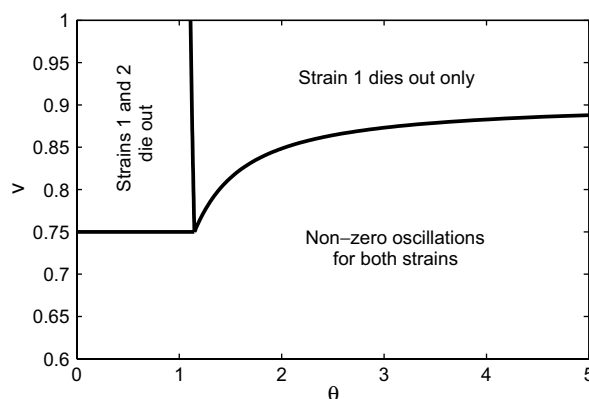


Fig. 6. A graph of the regions of effective vaccination rates against one strain as we vary the ADE factor θ . We fix the parameters $\beta_1 = 400 \text{ years}^{-1}$, $\beta_2 = 90 \text{ years}^{-1}$, and $\phi_1 = 2.63$.

years⁻¹, $\beta_2 = 90$ years⁻¹, and $\phi_1 = 2.63$. Notice that ϕ_2 does not appear in any of the eigenvalues. For small θ , the inequalities in Eq. (9) are satisfied and the DFE is stable. For larger θ , the boundary equilibrium is stable if the real part of λ_5 is negative.

Next, we consider separate vaccinations against both strains. Let v_1 be the percent of the population vaccinated only against strain one and let v_2 be the percent of the population vaccinated only against strain two. We assume there does not exist a single vaccination against both strains simultaneously, and one cannot receive both vaccinations in succession. That is, if a person is vaccinated against one strain, he/she cannot receive the other vaccination. The non-vaccinated population will enter the susceptible compartment at a rate of $(1 - v_1 - v_2)\mu$, while $v_1\mu$ and $v_2\mu$ are the rates that the population enters the vaccinated compartments, called r_j^* for $j = 1, 2$. If the vaccinated population contracts the other strain, they enter the compartment i_{21}^* or i_{12}^* . The ADE created from the vaccine for strain j will be θ_j for $j = 1, 2$. See Fig. 7 for details of the flow between compartments in the two vaccination model.

The system of differential equations for a two strain disease with separate vaccinations against both strains is:

$$\begin{aligned}
 \frac{ds}{dt} &= (1 - v_1 - v_2)\mu - \beta_1 si_1 - \beta_2 si_2 - \phi_2 \beta_2 si_{12} - \phi_1 \beta_1 si_{21} \\
 &\quad - \theta_2 \beta_2 si_{12}^* - \theta_1 \beta_1 si_{21}^* - \mu s, \\
 \frac{di_1}{dt} &= \beta_1 si_1 + \phi_1 \beta_1 si_{21} + \theta_1 \beta_1 si_{21}^* - \sigma i_1 - \mu i_1, \\
 \frac{di_2}{dt} &= \beta_2 si_2 + \phi_2 \beta_2 si_{12} + \theta_2 \beta_2 si_{12}^* - \sigma i_2 - \mu i_2, \\
 \frac{dr_1}{dt} &= \sigma i_1 - \beta_2 r_1 i_2 - \phi_2 \beta_2 r_1 i_{12} - \theta_2 \beta_2 r_1 i_{12}^* - \mu r_1, \\
 \frac{dr_2}{dt} &= \sigma i_2 - \beta_1 r_2 i_1 - \phi_1 \beta_1 r_2 i_{21} - \theta_1 \beta_1 r_2 i_{21}^* - \mu r_2, \\
 \frac{dr_1^*}{dt} &= v_1 \mu - \phi_2 \beta_2 r_1^* i_{12} - \beta_2 r_1^* i_2 - \theta_2 \beta_2 r_1^* i_{12}^* - \mu r_1^*, \\
 \frac{dr_2^*}{dt} &= v_2 \mu - \phi_1 \beta_1 r_2^* i_{21} - \beta_1 r_2^* i_1 - \theta_1 \beta_1 r_2^* i_{21}^* - \mu r_2^*, \\
 \frac{di_{12}}{dt} &= \phi_2 \beta_2 r_1 i_{12} + \beta_2 r_1 i_2 + \theta_2 \beta_2 r_1 i_{12}^* - \sigma i_{12} - \mu i_{12}, \\
 \frac{di_{21}}{dt} &= \phi_1 \beta_1 r_2 i_{21} + \beta_1 r_2 i_1 + \theta_1 \beta_1 r_2 i_{21}^* - \sigma i_{21} - \mu i_{21}, \\
 \frac{di_{12}^*}{dt} &= \beta_2 r_1^* i_2 + \phi_2 \beta_2 r_1^* i_{12} + \theta_2 \beta_2 r_1^* i_{12}^* - \sigma i_{12}^* - \mu i_{12}^*, \\
 \frac{di_{21}^*}{dt} &= \beta_1 r_2^* i_1 + \phi_1 \beta_1 r_2^* i_{21} + \theta_1 \beta_1 r_2^* i_{21}^* - \sigma i_{21}^* - \mu i_{21}^*, \\
 \frac{dr^*}{dt} &= \sigma(i_{12} + i_{21} + i_{12}^* + i_{21}^*) - \mu r^*.
 \end{aligned} \tag{15}$$

The DFE for this system in the form $(s, i_1, i_2, r_1, r_2, r_1^*, r_2^*, i_{12}, i_{21}, i_{12}^*, i_{21}^*)$ is:

$$V_0 = (1 - v_1 - v_2, 0, 0, 0, 0, v_1, v_2, 0, 0, 0, 0, 0). \tag{16}$$

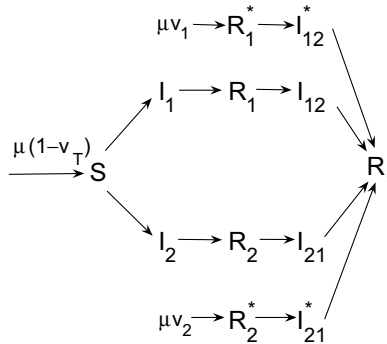


Fig. 7. A transfer diagram for two co-circulating disease strains with vaccinations for both strains.

We linearize the system about the DFE and local stability occurs if

$$v_2 > 1 + v_1(\theta_2 - 1) - \frac{1}{R_2} \tag{17}$$

and

$$v_2 < \frac{v_1 - 1 + \frac{1}{R_1}}{\theta_1 - 1}. \tag{18}$$

Recall that vaccinations cannot be administered simultaneously to the same individual, so we have the additional constraint $v_1 + v_2 \leq 1$.

To find out what vaccination levels are needed for two identical strains, we set the parameters $\beta_k = \beta$ for $k = 1, 2$, $\phi_k = \phi$ for $k = 1, 2$, and $\theta_1 = \theta_2 = \phi$. We find that there exists a set in $v_1 + v_2 \leq 1$ that satisfies Eqs. (17) and (18) only if

$$1 < \phi < \frac{2}{R_0}.$$

For the dengue parameters we are considering, $\beta = 400 \text{ years}^{-1}$, $\mu = 0.02 \text{ years}^{-1}$, $\sigma = 100 \text{ years}^{-1}$, and $R_0 > 2$, there is no set of v_1 and v_2 to make the DFE stable. Therefore, this separate two-strain vaccination strategy cannot eradicate the dengue disease in this population.

As with the one strain vaccination strategy, it is possible to eradicate one strain of the disease using vaccinations. The system has two boundary equilibria, which can be expressed as

$$\begin{aligned}
 W_1 = & \left(\frac{z(\sigma + \mu)}{\beta_1(z + v_2\theta_1)}, \frac{\mu z(\beta_1(z + v_2\theta_1) - (\sigma + \mu))}{\beta_1(z + v_2\theta_1)(\sigma + \mu)}, 0, \frac{\sigma z(\beta_1(z + v_2\theta_1) - (\sigma + \mu))}{\beta_1(z + v_2\theta_1)(\sigma + \mu)}, 0, \right. \\
 & \left. v_1, \frac{v_2(\sigma + \mu)}{\beta_1(z + v_2\theta_1)}, 0, 0, \frac{v_2\mu(\beta_1(z + v_2\theta_1) - (\sigma + \mu))}{\beta_1(z + v_2\theta_1)(\sigma + \mu)}, 0 \right), \\
 W_2 = & \left(\frac{z(\sigma + \mu)}{\beta_2(z + v_1\theta_2)}, 0, \frac{\mu z(\beta_2(z + v_1\theta_2) - (\sigma + \mu))}{\beta_2(z + v_1\theta_2)(\sigma + \mu)}, 0, \frac{\sigma z(\beta_2(z + v_1\theta_2) - (\sigma + \mu))}{\beta_2(z + v_1\theta_2)(\sigma + \mu)}, \right. \\
 & \left. \frac{v_1(\sigma + \mu)}{\beta_2(z + v_1\theta_2)}, v_2, 0, 0, 0, \frac{v_1\mu(\beta_2(z + v_1\theta_2) - (\sigma + \mu))}{\beta_2(z + v_1\theta_2)(\sigma + \mu)} \right).
 \end{aligned} \tag{19}$$

with $z = 1 - v_1 - v_2$. Note that these equilibria make biological sense when the DFE is unstable. As a check, if we let $v_2 = 0$ or $v_1 = 0$ separately, these boundary equilibria may be identified with V_1 or V_2 , the boundary equilibria of the system for vaccinations against one strain.

Using the parameters $\beta_1 = 150 \text{ years}^{-1}$, $\beta_2 = 100 \text{ years}^{-1}$, $\sigma = 100 \text{ years}^{-1}$, and $\mu = 0.02 \text{ years}^{-1}$, $\phi_1 = \theta_1 = 1.2$, and $\phi_2 = \theta_2 = 1.5$ we can numerically find the transfer of stability between the endemic equilibrium, the boundary equilibrium, and the DFE. These values for β_1 and β_2 are used as an example to the regions clearly in one graph in Fig. 8.

4. Discussion

Starting with a basic SIR compartmental model, we designed several systems of differential equations to study the dynamics of a two-strain disease with ADE and vaccinations. Applying standard methods of linearization and numerical techniques, we analyzed the system and found regions of stability for the steady state solutions. The main objective was to determine what vaccination rates in the two scenarios could cause a two-strain disease to die out.

If the population was vaccinated against only one strain, it was determined that this strategy would not eradicate the other strain if that strain was currently in an endemic state. If the population was vaccinated against both strains separately, there exist conditions on vaccination rates that would result in both strains dying out, as shown in Fig. 8. But using standard dengue parameters, this separate two-strain vaccination strategy could not eradicate both strains of dengue if the vaccinations can not be administered in succession.

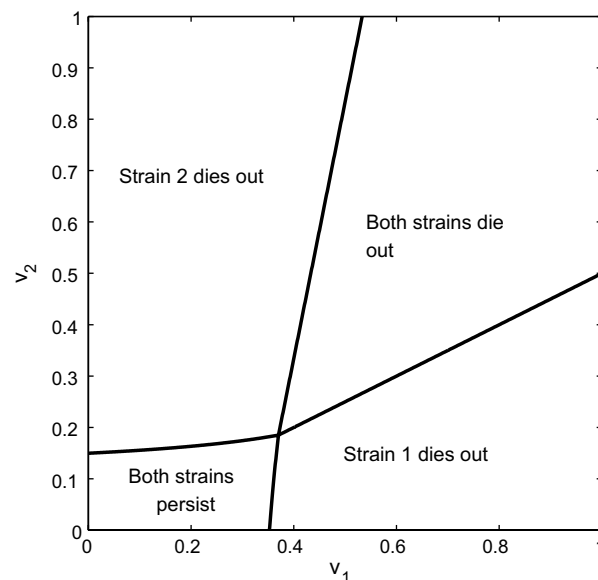


Fig. 8. A graph of the regions of effective vaccination rates using separate vaccinations against both strains. We set the parameters $\beta_1 = 150 \text{ years}^{-1}$, $\beta_2 = 100 \text{ years}^{-1}$, $\phi_1 = \theta_1 = 1.2$, and $\phi_2 = \theta_2 = 1.5$.

These methods and systems can be expanded to diseases with more than two strains with ADE such as the four strain dengue disease, AIDS, and SARS. Numerical techniques would need to be used to analyze these systems.

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Appendix A. Endemic solution

Solving the last six equations of Eq. (1) as a function of s and substituting into the first equation reduces the problem to solving the cubic

$$P(s) = a_3s^3 + a_2s^2 + a_1s + a_0 \quad (\text{A.1})$$

with

$$\begin{aligned} a_3 &= -(\psi_1 - 1)(\psi_2 - 1)R_1R_2, \\ a_2 &= (\psi_1R_1 - 1)(\psi_2R_2 - 1) - (R_1 - 1)(R_2 - 1), \\ a_1 &= R_1 + R_2 - 1, \\ a_0 &= -1 \end{aligned} \quad (\text{A.2})$$

with $\psi_1 = \frac{\sigma\phi_1}{\sigma+\mu}$ and $\psi_2 = \frac{\sigma\phi_2}{\sigma+\mu}$. In this case we assume that the DFE, E_1 , and E_2 are unstable, so $R_1 > 1$ and $R_2 > 1$. If, in addition, we assume $\psi_1 > 1$ and $\psi_2 > 1$, which is equivalent to restricting $\phi_1 > 1 + \mu/\sigma$ and $\phi_2 > 1 + \mu/\sigma$, then we can say the following about the existence and uniqueness of the endemic equilibrium, \hat{s} .

By inspection, $a_3 < 0$, $a_2 > 0$, $a_1 > 0$ and $a_0 < 0$. By Descartes' Rule of signs, the two sign changes imply that there are two or zero real positive roots. Evaluate

$$\begin{aligned} P(0) &= -1, \\ P\left(\frac{1}{R_1}\right) &= \frac{\psi_1}{R_1} \left((R_2 - 1) + \left(1 - \frac{1}{R_1}\right)(\psi_2 - 1)R_2 \right), \\ P\left(\frac{1}{R_2}\right) &= \frac{\psi_2}{R_2} \left((R_1 - 1) + \left(1 - \frac{1}{R_2}\right)(\psi_1 - 1)R_1 \right), \\ P(1) &= (1 + (\psi_1 - 1)R_1)(R_2 - 1) + (R_2 * (\psi_2 - 1) + 1)(R_1 - 1). \end{aligned} \quad (\text{A.3})$$

Since $P(0) < 0$ and $P(1/R_i) > 0$ for $i = 1, 2$, there exists a positive root of P such that $0 < \hat{s} < \min\{1/R_i\}$ for $i = 1, 2$. Because $P(1) > 0$, the second positive root must be greater than 1, outside of the domain $[0, 1]$, and \hat{s} is unique.

To show that the other components of the endemic solution are also positive, we directly observe

$$\begin{aligned}\hat{r}_1 &= \frac{1}{\phi_2} \left(\frac{1}{R_2} - \hat{s} \right) > 0, \\ \hat{r}_2 &= \frac{1}{\phi_1} \left(\frac{1}{R_1} - \hat{s} \right) > 0.\end{aligned}\tag{A.4}$$

The remaining components must satisfy

$$\begin{aligned}\hat{i}_1 &= \frac{\mu R_1 R_2 \hat{s}}{q(\hat{s})(\sigma + \mu)} \left(\frac{1}{R_2} - \hat{s} \right) \left(\hat{s}(\psi_1 - 1) + \frac{1}{R_1} \right), \\ \hat{i}_2 &= \frac{\mu R_1 R_2 \hat{s}}{q(\hat{s})(\sigma + \mu)} \left(\frac{1}{R_1} - \hat{s} \right) \left(\hat{s}(\psi_2 - 1) + \frac{1}{R_2} \right), \\ \hat{i}_{12} &= \frac{\mu R_1 R_2}{q(\hat{s})\phi_2(\sigma + \mu)} \left(\frac{1}{R_1} - \hat{s} \right) \left(\frac{1}{R_2} - \hat{s} \right) \left(\hat{s}(\psi_2 - 1) + \frac{1}{R_2} \right), \\ \hat{i}_{21} &= \frac{\mu R_1 R_2}{q(\hat{s})\phi_2(\sigma + \mu)} \left(\frac{1}{R_1} - \hat{s} \right) \left(\frac{1}{R_2} - \hat{s} \right) \left(\hat{s}(\psi_1 - 1) + \frac{1}{R_1} \right)\end{aligned}\tag{A.5}$$

with $qq(\hat{s}) = R_1 R_2 (\psi_1 \psi_2 - 1) \hat{s}^2 + (R_1 + R_2) \hat{s} - 1$. These components have the same sign as $q(\hat{s})$.

For our parameter assumptions, we know that the quadratic $q(s)$ is concave up and has a positive and negative root. Call the positive root s^* . Because $q(s^*) = 0$, $R_1 R_2 (\psi_1 \psi_2 - 1) (s^*)^2 + (R_1 + R_2) s^* = 1$. Substituting this expression into $P(s^*)$ gives

$$P(s^*) = -s^*(1 + (\psi_2 - 1)R_2 s^*)(1 + (\psi_1 - 1)R_1 s^*) < 0.\tag{A.6}$$

We know

$$\begin{aligned}P(s) &< 0 & 0 \leq s < \hat{s}, \\ P(s) &> 0 & \hat{s} < s \leq 1.\end{aligned}\tag{A.7}$$

Therefore, $s^* < \hat{s}$ and $q(\hat{s}) > 0$. So, all components of the endemic solution are positive.

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