SEROTYPE REPLACEMENT OF VERTICALLY TRANSMITTED DISEASES THROUGH PERFECT VACCINATION

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Abstract. Strain replacement occurs when after a vaccination campaign one (or more) strains decline in prevalence while another strain (or strains) rise in prevalence. Differential effectiveness of the vaccine is the widely accepted and the most important mechanism which leads to this replacement effect. Recent theoretical studies have suggested that strain replacement may occur even if the vaccine is perfect, that is, the vaccine is completely effective with respect to all strains present. It has already been shown that perfect vaccination, along with a trade-off mechanism, such as co-infection or cross-immunity, lead to strain replacement. In this paper, we examine the hypothesis that strain replacement with perfect vaccination occurs only with trade-off mechanisms which allow a strain with a lower reproduction number to eliminate a strain with a higher reproduction number in the absence of vaccination. We test this hypothesis on a two-strain model with vertical transmission. We first show that vertical transmission as a trade-off mechanism can lead to dominance of a strain with suboptimal reproduction number. Based on the hypothesis we expect, and we show, that strain replacement occurs with vertical transmission.

Keywords: differential effectiveness, trade-off mechanism, vertical transmission, "perfect" vaccination, strain replacement.

1. Introduction

Vaccination provides protection against a pathogen, specific to the pathogen strain that created it. For many diseases whose causative agents are represented by multiple strains, the protection of a vaccine is only partial. For instance, *Streptococcus pneumoniae* is represented by more than 90 serotypes while the most comprehensive vaccine covers only 23 serotypes. When a vaccination campaign is carried out with such a vaccine, vaccinated individuals are protected against the strains included in the vaccine, but not against the remaining strains. Consequently, the prevalence of the vaccine strains declines while the prevalence of some of the non-vaccine strains rises. This phenomenon is known as *strain replacement*. Multiple studies exist reporting rise in the prevalence of non-vaccine strains (see [3, 5, 14, 15] for examples concerning *S. pneumoniae* and [13] for a review). Strain replacement occurs primarily because the vaccine protects against some strains but not others, that is, because of the differential effectiveness of the vaccine. The fact that differential effectiveness of the vaccines leads to strain replacement has been supported by a number of experimental results and mathematical studies [7, 8, 11, 19, 20]. More recently, theoretical studies have suggested that strain replacement may occur even if the vaccine is perfect, that is, if the vaccine provides full

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protection against all strains involved [6]. Perfect vaccines can lead to strain replacement if there is some trade-off mechanism that allows for the strains to coexist in the presence, or in the absence of vaccination.

The trade-off mechanism considered in [6] is super-infection, defined as the ability of one strain to infect individuals infected with the other, and immediately take over the host. Other mechanisms, such as coinfection, defined as the ability of two strains to coexist in one host, have also been found to lead to strain replacement with perfect vaccination [12, 13]. Not all trade-off mechanisms, however, can lead to strain replacement with perfect vaccination. For example, it has been shown that in the most basic models involving cross-immunity as a trade-off mechanism, strain replacement will not occur with perfect vaccination [12]. So what makes super-infection and coinfection different from cross-immunity?

When a number of strains compete for a single resource, namely susceptible individuals, in the most general case the only outcome of the competition is competitive exclusion. Under this scenario, one strain persists, while the others are eliminated. The strain that outcompetes and eliminates the rest is the one that can persist on the lowest number of susceptibles, that is, the strain with the largest reproduction number [1].

A trade-off mechanism may allow a strain with smaller reproduction number to coexist with the strain that has a larger reproduction number. In fact, all trade-off mechanisms allow for coexistence of strains with different reproduction numbers, and therefore allow for persistence of a competitively inferior strain together with the competitively superior strain. Some trade-off mechanisms, however, may also allow a strain with smaller reproduction number to take over and eliminate a strain with a larger reproduction number. For instance, assume $\mathcal{R}_1 > \mathcal{R}_2$ where $\mathcal{R}_1$ and $\mathcal{R}_2$ are the reproduction numbers of the two strains, respectively. In the absence of a trade-off mechanism, strain one eliminates strain two. However, in the presence of some trade-off mechanisms strain two may be able to eliminate strain one, regardless of the fact that strain one has a larger reproduction number. Not all trade-off mechanisms have this property. It has been shown that super-infection and coinfection do [16, 17], while cross-immunity does not [18].

In this paper we consider the following hypothesis: *Strain replacement with perfect vaccination occurs in conjunction with trade-off mechanisms that allow a strain with lower reproduction number to dominate and eliminate a strain with a higher reproduction number in the absence of vaccination.* Proving this hypothesis independently of the model may be difficult, so we consider a specific model in which the strains can be transmitted horizontally, as well as vertically. Vertical transmission occurs when a pathogen is transmitted from parent to offspring (e.g. HIV can be transmitted from a mother to a newborn). A wide range of microparasites can be transmitted both vertically and horizontally [2, 9]. Vertical transmission is a known mechanism that leads to coexistence between the pathogen strains. Moreover, it has been suggested that it may allow a strain with a lower reproduction number to outcompete and eliminate a strain with a higher reproduction number [10]. We consider a model with vertical transmission without vaccination in Section 2 and show that this is indeed the case. Based on our hypothesis we expected that if we introduce perfect vaccination to the baseline model, strain replacement will occur. We show in Section 3 that the model with vertical transmission and perfect vaccination allows for strain replacement. That is, if strain

one dominates in the absence of vaccination, at certain vaccination levels, strain two eliminates strain one and dominates by itself. Section 4 summarizes our results.

2. A Model Without Vaccination or Healthy Births From Infected Individuals (Model 1)

In this section, we introduce a model with vertical and horizontal transmission without vaccination. We consider a population, with respect to time, of total size $N(t)$, which is then divided into three different classes. The number of susceptibles, uninfected with either of the two strains, is denoted by $S(t)$. The two infected classes are represented by $I(t)$, for those infected with strain one, and $J(t)$, for those infected with strain two.

In addition to the different classes, there are many different parameters included in the model. The per capita birth rate of individuals into the susceptible class is expressed by b_x. Also, the per capita birth rates of uninfected newborns from the infected classes I and J into the susceptible class are represented by η_1 and η_2 respectively. The rate of vertical transmission of the disease into the infected classes I and J is given by b_1 and b_2 respectively. On the other hand, the rate of horizontal transmission of susceptible individuals becoming infected with strain one is given β_1. Symmetrically, β_2 signifies this rate with the exception that it deals with strain two. Typically, an individual infected with a particular virus has a higher death rate than an individual in the susceptible class. Since we have assigned the natural death rate to be μ; α_1 and α_2 are disease-induced death rates and give us the ability to increase the death rates within the two infected classes. These parameters can be referenced in Table 1.

Table 1: Parameter meanings for the model

Parameter	Description
b_x	per capita birth rate into the susceptible class
b_1	per capita birth rate of infected newborns into infected class I
b_2	per capita birth rate of infected newborns into infected class J
η_1	per capita birth rate of uninfected newborns from infected class I
η_2	per capita birth rate uninfected newborns from infected class J
η_3	per capita birth rate of susceptible newborns from vaccinated class (to be used in the vaccination model)
β_1	transmission rate of strain 1
β_2	transmission rate of strain 2
μ	per capita death rate
α_1	disease-induced per capita death rate of infected class I
α_2	disease-induced per capita death rate of infected class J
ψ	per capita vaccination rate (to be used in the vaccination model)

This model is as follows:

$$\begin{aligned} \frac{dS}{dt} &= (b_x S + \eta_1 I + \eta_2 J)(1 - S - I - J) - \mu S - \beta_1 IS - \beta_2 JS \\ \frac{dI}{dt} &= I[b_1(1 - S - I - J) - (\mu + \alpha_1) + \beta_1 S] \\ \frac{dJ}{dt} &= J[b_2(1 - S - I - J) - (\mu + \alpha_2) + \beta_2 S] \end{aligned} \tag{2.1}$$

We represent the model using a flow chart in Figure 1.

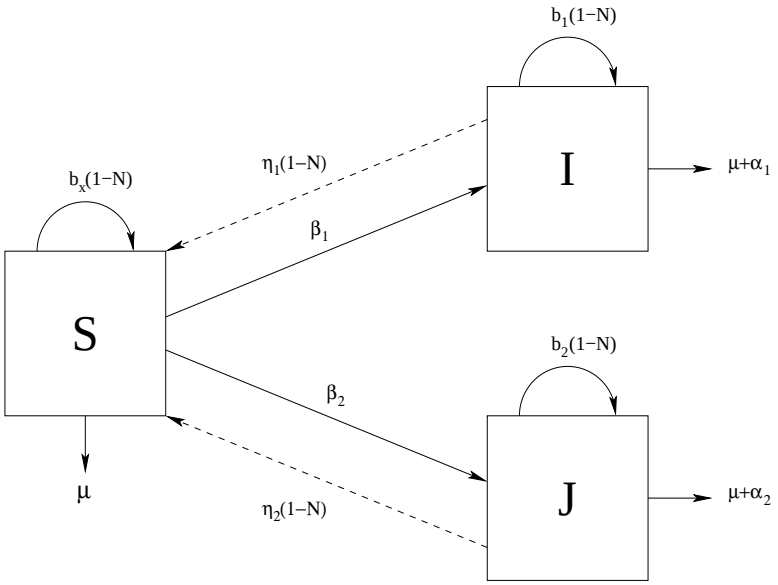


FIGURE 1. Flow chart of the model without vaccination.

From a biological standpoint, it is reasonable to assume that the birth rate of new individuals from either of the infected classes is less than that of the healthy population. To represent this assumption with parameters, we have: $\eta_1 + b_1 < b_x$ and $\eta_2 + b_2 < b_x$.

The term $(1 - S - I - J)$ is a logistic term and accounts for population size limitation due to crowding. The carrying capacity has been rescaled to one. The total population $N(t) = S(t) + I(t) + J(t)$ satisfies the following differential equation:

$$\frac{dN}{dt} = (b_x S + \eta_1 I + \eta_2 J + b_1 I + b_2 J)(1 - S - I - J) - \mu N - \alpha_1 I - \alpha_2 J. \tag{2.2}$$

$$\begin{aligned} &\leq b_x N(1-N) - \mu N && \text{(Logistic Equation)} \\ &= (b_x - \mu)N && \text{(Malthus Equation)} \end{aligned}$$

$$\Rightarrow N(t) \leq N_0 e^{(b_x - \mu)t} \tag{2.3}$$

From the preceding calculations, we make certain parameter assumptions to be held throughout this paper. In order for the entire population not to die out, we assume $b_x > \mu$.

For the remainder of this paper, we will assume η_1, $\eta_2 = 0$. However, we will come back to the original model (2.1) in the discussion. This model has been considered in an article by Lipsitch *et al.* [10].

2.1. **Disease-Free Equilibrium and Reproduction Numbers.** The disease free equilibrium (DFE) of the model (2.1) is computed to be: $\mathcal{E}_0 = \left(\frac{b_x - \mu}{b_x}, 0, 0\right)$. The reproduction numbers follow as:

$$\mathcal{R}_1 = \frac{b_1\mu + \beta_1(b_x - \mu)}{b_x(\mu + \alpha_1)} \qquad \mathcal{R}_2 = \frac{b_2\mu + \beta_2(b_x - \mu)}{b_x(\mu + \alpha_2)} \tag{2.4}$$

The two reproduction numbers are symmetric. This follows from the fact that the two infected classes have similar structures (with the exception of the parameters).

Analyzing the reproduction numbers further, we can obtain expressions for the rate of each type of transmission, whether it be horizontal or vertical. Analyzing the reproduction number of strain one, we can express it as:

$$\mathcal{R}_1 = \frac{b_1}{\mu+\alpha_1}\frac{\mu}{b_x} + \frac{\beta_1}{\mu+\alpha_1}\left(1-\frac{\mu}{b_x}\right)$$

Different parts of this expression have different significance. The reproduction number is a weighted average of the reproduction number of vertical transmission ($\tilde{\mathcal{R}}_1$) and the reproduction number of horizontal transmission ($\tilde{\tilde{\mathcal{R}}}_1$), where

$$\tilde{\mathcal{R}}_1 = \frac{b_1}{\mu+\alpha_1} \qquad \tilde{\tilde{\mathcal{R}}}_1 = \frac{\beta_1}{\mu+\alpha_1}.$$

Notice that the reproduction number of strain one, $\mathcal{R}_1$, is a convex combination of $\tilde{\mathcal{R}}_1$ and $\tilde{\tilde{\mathcal{R}}}_1$. This, in particular means that the value of $\mathcal{R}_1$ is between the values of $\tilde{\mathcal{R}}_1$ and $\tilde{\tilde{\mathcal{R}}}_1$. So now, we will impose another parameter assumption to be held true for the vertical transmission reproduction numbers of both strains. We will assume that vertical transmission is of relatively small significance or:

$$\tilde{\mathcal{R}}_1 = \frac{b_1}{\mu+\alpha_1} < 1 \qquad \tilde{\mathcal{R}}_2 = \frac{b_2}{\mu+\alpha_2} < 1 \tag{2.5}$$

Theorem 2.1. *The following conditions give the stability of the DFE.*

a.) *If* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 < 1$ *then DFE is locally asymptotically stable (l.a.s.).*
b.) *If* $\mathcal{R}_1 > 1$ *or* $\mathcal{R}_2 > 1$ *then DFE is an unstable saddle.*

2.2. **Strain 1 and strain 2 dominance equilibrium.** We can compute the strain one and strain two dominance equilibrium as the ordered triples:

$$\mathcal{E}_1 = (S_1^*, I_1^*, 0) = \left(1-\frac{\mu}{b_x} - \frac{(b_x+\beta_1)(\mu+\alpha_1)(\mathcal{R}_1-1)}{\beta_1(b_x+\beta_1-b_1)}, \frac{b_x(\mu+\alpha_1)(\mathcal{R}_1-1)}{\beta_1(b_x+\beta_1-b_1)}, 0\right) \tag{2.6}$$

$$\mathcal{E}_2 = (S_2^*, 0, J_2^*) = \left(1-\frac{\mu}{b_x} - \frac{(b_x+\beta_2)(\mu+\alpha_2)(\mathcal{R}_2-1)}{\beta_2(b_x+\beta_2-b_2)}, 0, \frac{b_x(\mu+\alpha_2)(\mathcal{R}_2-1)}{\beta_2(b_x+\beta_2-b_2)}\right) \tag{2.7}$$

Theorem 2.2. *Assume* $\tilde{\mathcal{R}}_1 < 1$ *and* $\tilde{\mathcal{R}}_2 < 1$.

a.) $\mathcal{E}_1$ *exists iff* $\mathcal{R}_1 > 1$.
b.) $\mathcal{E}_2$ *exists iff* $\mathcal{R}_2 > 1$.

See appendix for justification.

2.3. **Invasion Reproduction Numbers.** The invasion numbers are computed as the following:

$$\hat{\mathcal{R}}_1 = \frac{b_1(1-S_2^*-J_2^*)+\beta_1 S^*}{\mu+\alpha_1} \qquad \hat{\mathcal{R}}_2 = \frac{b_2(1-S_1^*-I_1^*)+\beta_2 S^*}{\mu+\alpha_2} \tag{2.8}$$

The biological interpretation of the invasion reproduction numbers is as follows. The invasion reproduction number of strain one is the number of secondary cases that one infected individual will produce in a population where strain two is at equilibrium. $\hat{\mathcal{R}}_1$ measures the invasion capabilities of strain one. Similarly, $\hat{\mathcal{R}}_2$ is this measure for strain two.

Furthermore, we can obtain expressions of the invasion numbers in terms of parameter values.

$$\hat{\mathcal{R}}_1 = \mathcal{R}_1 + \frac{b_1\beta_2 - \beta_1(b_x+\beta_2)}{\mu+\alpha_1}\frac{(\mu+\alpha_2)(\mathcal{R}_2-1)}{\beta_2(\beta_2+b_x-b_2)} \tag{2.9}$$

$$\hat{\mathcal{R}}_2 = \mathcal{R}_2 + \frac{b_2\beta_1 - \beta_2(b_x+\beta_1)}{\mu+\alpha_2}\frac{(\mu+\alpha_1)(\mathcal{R}_1-1)}{\beta_1(\beta_1+b_x-b_1)} \tag{2.10}$$

This is a result of substituting the values from (2.6) and (2.7) for the expressions $(1-S^*-J^*)$ and S^*.

Theorem 2.3. *Assume $\mathcal{R}_1 > 1$ and $\tilde{\mathcal{R}}_1 < 1$.*

a.) *$\mathcal{E}_1$ is locally asymptotically stable if $\hat{\mathcal{R}}_2 < 1$.*

b.) *$\mathcal{E}_1$ is unstable if $\hat{\mathcal{R}}_2 > 1$.*

Similarly, we have:

Theorem 2.4. *Assume $\mathcal{R}_2 > 1$ and $\tilde{\mathcal{R}}_2 < 1$.*

a.) *$\mathcal{E}_2$ is locally asymptotically stable if $\hat{\mathcal{R}}_1 < 1$.*

b.) *$\mathcal{E}_2$ is unstable if $\hat{\mathcal{R}}_1 > 1$.*

Proof is technical and is omitted.

2.4. **Parametric Plot.** In order to define and plot the boundaries of local stability of $\mathcal{E}_1$ and $\mathcal{E}_2$, we consider a parametric plot in the $(\mathcal{R}_1, \mathcal{R}_2)$ plane. To do so, we need to express the invasion numbers from (2.9) and (2.10) in terms of $\mathcal{R}_1$ and $\mathcal{R}_2$. To this end, we eliminate α_1 and α_2. From the expressions for the reproduction numbers (2.4) we have $(\mu+\alpha_1)$ and $(\mu+\alpha_2)$ in terms of the remaining parameter values and the reproduction numbers. Replacing those expressions into (2.9) and (2.10) we express the two invasion numbers as:

$$\hat{\mathcal{R}}_1 = \mathcal{R}_1 + \frac{\mathcal{R}_1[b_1\beta_2 - \beta_1(b_x+\beta_2)][b_2\mu+\beta_2(b_x-\mu)]}{[b_1\mu+\beta_1(b_x-\mu)][\beta_2(\beta_2+b_x-b_2)]}\left(1-\frac{1}{\mathcal{R}_2}\right) \tag{2.11}$$

$$\hat{\mathcal{R}}_2 = \mathcal{R}_2 + \frac{\mathcal{R}_2[b_2\beta_1 - \beta_2(b_x+\beta_1)][b_1\mu+\beta_1(b_x-\mu)]}{[b_2\mu+\beta_2(b_x-\mu)][\beta_1(\beta_1+b_x-b_1)]}\left(1-\frac{1}{\mathcal{R}_1}\right) \tag{2.12}$$

With the invasion numbers in terms of the reproduction numbers, we can now generate parametric plots from the invasion numbers. We consider the $(\mathcal{R}_1, \mathcal{R}_2)$ plane. Since $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$ are functions of $\mathcal{R}_1$ and $\mathcal{R}_2$, the equations $\hat{\mathcal{R}}_1 = 1$ and $\hat{\mathcal{R}}_2 = 1$ define two curves in the $(\mathcal{R}_1, \mathcal{R}_2)$ plane. From the first invasion number $\hat{\mathcal{R}}_1 = 1$, we can express the reproduction number $\mathcal{R}_1$ as a function of $\mathcal{R}_2$. Similarly, from $\hat{\mathcal{R}}_2 = 1$, we can express $\mathcal{R}_2$ as a function of $\mathcal{R}_1$.

To make this process easier, we will take all the parameters of the invasion numbers $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$, and symbolize them as single constants $\mathcal{K}_1$ and $\mathcal{K}_2$ respectively.

$$\mathcal{K}_1 = \frac{[b_1\beta_2 - \beta_1(b_x+\beta_2)][b_2\mu+\beta_2(b_x-\mu)]}{[b_1\mu+\beta_1(b_x-\mu)][\beta_2(\beta_2+b_x-b_2)]}$$

$$\mathcal{K}_2 = \frac{[b_2\beta_1 - \beta_2(b_x+\beta_1)][b_1\mu+\beta_1(b_x-\mu)]}{[b_2\mu+\beta_2(b_x-\mu)][\beta_1(\beta_1+b_x-b_1)]}$$

Starting with (2.11) and (2.12), we can express $\hat{\mathcal{R}}_1 = 1$ as $\mathcal{R}_1 = g(\mathcal{R}_2)$ and $\hat{\mathcal{R}}_2 = 1$ as $\mathcal{R}_2 = f(\mathcal{R}_1)$. Utilizing the substitutions for $\mathcal{K}_1$ and $\mathcal{K}_2$ we can express $\mathcal{R}_i$ in terms of $\mathcal{R}_j$, with $i, j = 1, 2$ and $i \neq j$ as follows:

$$\mathcal{R}_1 = \frac{1}{1 + \mathcal{K}_1(1 - \frac{1}{\mathcal{R}_2})} = g(\mathcal{R}_2) \qquad \mathcal{R}_2 = \frac{1}{1 + \mathcal{K}_2(1 - \frac{1}{\mathcal{R}_1})} = f(\mathcal{R}_1)$$

Using these two functions, we can now plot the curves in the $(\mathcal{R}_1, \mathcal{R}_2)$ plane, which yields the parametric plot, Figure 2.

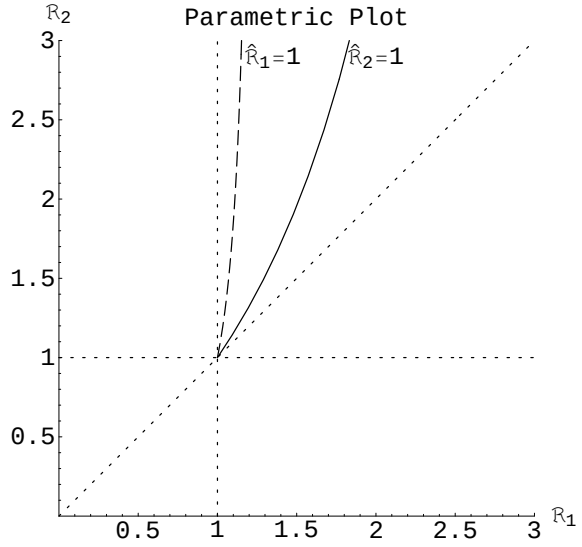


FIGURE 2. Parametric plot of the invasion numbers $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$ expressed as the reproduction numbers. Parameter values used for this plot: $b_x = 0.7791$, $b_1 = 0.4261$, $b_2 = 0.6864$, $\beta_1 = 0.2396$, $\beta_2 = 0.765$, and $\mu = 0.0713$. These parameter values yield $\mathcal{K}_1 = -0.19$ and $\mathcal{K}_2 = -1.47$.

The main goal in Section 2 is to show that a strain with a lower reproduction number can dominate and persist, while the strain with larger reproduction number can be eliminated. Different regions of Figure 2 yield particular outcomes of the system. To distinguish the importance between each region of Figure 2, we will shade various sections differently in Figure 3.

The white area of Figure 3 is where both reproduction numbers are less than one. This in most cases will lead to both strains dying out. We will not consider this area any further.

One of the more important areas of this plot is the darker gray area (in the upper left of Figure 3). Here we have the invasion number $\hat{\mathcal{R}}_2 > 1$, while $\hat{\mathcal{R}}_1 < 1$, so strain two has the ability to invade strain one, but not vice versa. For this reason, reproduction numbers with values within this area will yield a system in which strain two will be the dominant strain, and strain one will be eliminated.

Similarly, in the light gray area (towards the right of Figure 3), we have a similar scenario with the other strain. In this area $\hat{\mathcal{R}}_2 < 1$ and $\hat{\mathcal{R}}_1 > 1$, which leads us to conclude strain one will dominate, while strain two will be eliminated.

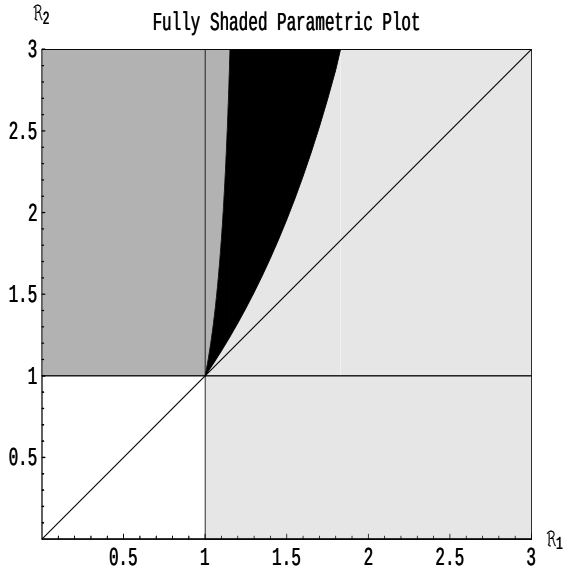


FIGURE 3. Shaded parametric plot of *Model 1* to distinguish between different areas.

The third area of importance is the black region. Here we have that both invasion numbers are greater than one, or that each strain has the ability to invade the other strain. Since both invasion reproduction numbers are greater than one, we expect that coexistence of the two strains will occur. So for the reproduction numbers, $\mathcal{R}_1$ and $\mathcal{R}_2$, whose values fall within this area, both strains will coexist within the population.

With the role of the different regions explained, we now focus on the most important information that this parametric plot offers us. Recall, the main goal with this model (Section 2) is to show that a strain with a suboptimal reproduction number can dominate, while the other strain is eliminated. For this reason, in addition to plotting the two functions of the invasion numbers, we have also plotted a few other lines to serve as guides. In particular, the diagonal line gives the value where $\mathcal{R}_1 = \mathcal{R}_2$. We note that in the area above this line we have $\mathcal{R}_1 < \mathcal{R}_2$, and in the area below $\mathcal{R}_1 > \mathcal{R}_2$. Looking back at Figure 3, we see that in general the strain with the higher reproduction number dominates. This is particularly the case with strain two whose region of dominance (dark gray area in Figure 3) lies entirely above the line $\mathcal{R}_1 = \mathcal{R}_2$, that is, it occurs when $\mathcal{R}_1 < \mathcal{R}_2$. This is also true to a large extent for strain one. Most of its region of dominance (light gray area in Figure 3) is below the line $\mathcal{R}_1 = \mathcal{R}_2$, that is $\mathcal{R}_1 > \mathcal{R}_2$. However, a part of the light gray area lies above the line $\mathcal{R}_1 = \mathcal{R}_2$. Figure 4 highlights the area where strain one dominates, yet it has a lower reproduction number.

Referencing this parametric plot, we know that it is possible to obtain a situation where the strain with suboptimal reproduction number dominates, while the other strain dies out. In what follows, we describe the approach that lead us to these plots. To obtain dominance of a strain with suboptimal reproduction number, we need that the boundary of its region of dominance lies on the opposite side of the line $\mathcal{R}_1 = \mathcal{R}_2$. To show that this situation will occur, we will examine the constant values of $\mathcal{K}_1$ and $\mathcal{K}_2$, which encompass all the parameter values of the invasion numbers. From Theorem 2.3, we know that if $\hat{\mathcal{R}}_2 < 1$, then strain two cannot invade the equilibrium of strain one. In other words,

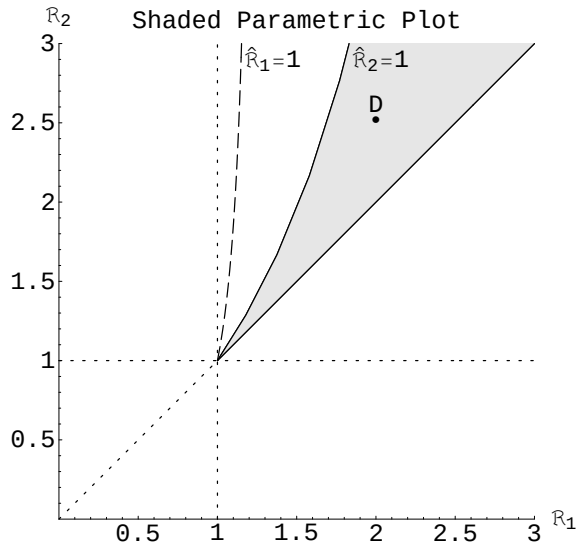


FIGURE 4. Parametric plot highlighting the area of greatest importance.

strain one dominates. Moveover, strain one has the ability to dominate with a smaller reproduction number if $\mathcal{R}_2 > \mathcal{R}_1$, or when $f(\mathcal{R}_1) > \mathcal{R}_1$. In order to get this situation on a parametric plot, we need the curve $f(\mathcal{R}_1)$ to be above the line $\mathcal{R}_1 = \mathcal{R}_2$. For this to occur we want that:

$$\frac{1}{1+\mathcal{K}_2(1-\frac{1}{\mathcal{R}_1})} \geq \mathcal{R}_1 \tag{2.13}$$

Notice that $f(\mathcal{R}_1)$ is a decreasing function of $\mathcal{R}_1$ if $\mathcal{K}_2 > 0$, and $f(\mathcal{R}_1)$ is an increasing function of $\mathcal{R}_1$ if $\mathcal{K}_2 < 0$. Also, if $\mathcal{K}_2 > 0$, the largest value of $f(\mathcal{R}_1)$ is $f(1) = 1 \Rightarrow f(\mathcal{R}_1) < \mathcal{R}_1$ for all $\mathcal{R}_1 > 1$. So the condition in (2.13) will never hold.

Now, take $\mathcal{K}_2 < 0 \Rightarrow f(\mathcal{R}_1)$ is an increasing function of $\mathcal{R}_1$. So $f(1) = 1 \Rightarrow f(\mathcal{R}_1) > 1$ for all $\mathcal{R}_1$, so the condition in (2.13) may hold. There are two distinct cases that we will examine to determine exactly when (2.13) holds.

In the first case we will assume $1 + \mathcal{K}_2 > 0$. Then $1 + \mathcal{K}_2(1 - \frac{1}{\mathcal{R}_1}) > 0$ for all $\mathcal{R}_1 \geq 1$. To see this, notice that $1 + \mathcal{K}_2(1 - \frac{1}{\mathcal{R}_1})$ is a decreasing function of $\mathcal{R}_1$, so the smallest value is when $\mathcal{R}_1 \to \infty$. To find this value explicitly, we evaluate the following limit.

$$\lim_{\mathcal{R}_1 \to \infty} \left(1 + \mathcal{K}_2\left(1 - \frac{1}{\mathcal{R}_1}\right)\right) = 1 + \mathcal{K}_2$$

If $1 + \mathcal{K}_2 > 0$, then $f(\mathcal{R}_1)$ is a continuous positive function of $\mathcal{R}_1$ for all $\mathcal{R}_1 > 1$. From this, we can see directly that (2.13) will not hold.

$$\begin{aligned} \frac{1}{1+\mathcal{K}_2(1-\frac{1}{\mathcal{R}_1})} &\geq \mathcal{R}_1 \\ 1 &\geq \mathcal{R}_1\left[1 + \mathcal{K}_2\left(1 - \frac{1}{\mathcal{R}_1}\right)\right] \\ &= (1+\mathcal{K}_2)\mathcal{R}_1 - \mathcal{K}_2 \end{aligned}$$

This is a convex combination of $\mathcal{R}_1$ and one, so its value is always greater than one and we will never be able to attain the condition.

In the second case we assume $1+\mathcal{K}_2 < 0$. But, with this assumption, the denominator of $f(\mathcal{R}_1)$ may become zero. This is because for some value of $\mathcal{R}_1$, denoted by $\mathcal{R}_1^*$, the equality $1 + \mathcal{K}_2(1 - \frac{1}{\mathcal{R}_1}) = 0$ holds. This value can be calculated as:

$$\mathcal{R}_1^* = \frac{\mathcal{K}_2}{\mathcal{K}_2 + 1}$$

Clearly, $\mathcal{R}_1^* > 0$, as both the numerator and the denominator are negative. Moreover, $\mathcal{R}_1^* > 1$, since the numerator is larger than the denominator. We notice that:

$$\lim_{\mathcal{R}_1 \to \mathcal{R}_1^{*-}} \frac{1}{1 + \mathcal{K}_2(1 - \frac{1}{\mathcal{R}_1})} \geq \mathcal{R}_1^*$$

Therefore, there are values of $\mathcal{R}_1$ for which $f(\mathcal{R}_1) > \mathcal{R}_1$. Thus, the inequality (2.13) can hold.

It is understood, as we increase the values of $\mathcal{R}_1$ and $\mathcal{R}_2$ in the parametric plot, the value of one of the curves will not be defined for all values of the corresponding reproduction number that is larger than one. By evaluating the above limit, we see that (2.13) will hold, but only for some finite $\mathcal{R}_1$, specifically when $\mathcal{R}_1 < \mathcal{R}_1^*$.

With a better understanding of the parameter situations needed to show strain replacement, we will use a point labeled "D" corresponding to an ordered pair $(\mathcal{R}_1, \mathcal{R}_2)$. We will choose parameter values in such a way that the two reproduction numbers will correspond to the point "D", which will fall within the shaded area of Figure 4. To obtain these parameter values, we generated a random search until all given assumptions and conditions were met.

After these parameters are determined, we demonstrate that the strain with suboptimal reproduction number dominates in Figure 5.

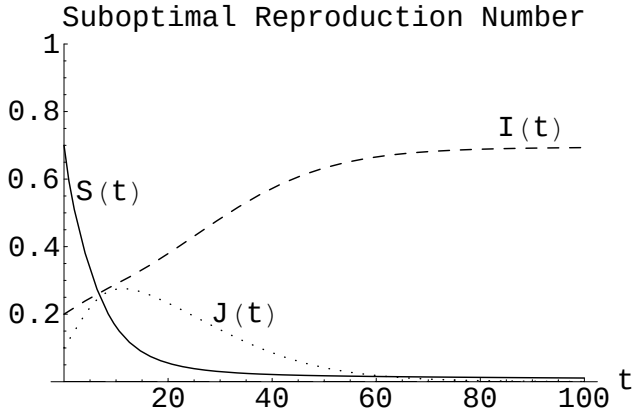


FIGURE 5. Simulation of *Model 1* when the strain with lower reproduction number, $I(t)$, dominates a strain with a higher reproduction number, $J(t)$. Parameter values used for this plot: $b_x = 0.7791$, $b_1 = 0.4261$, $b_2 = 0.6864$, $\beta_1 = 0.2396$, $\beta_2 = 0.765$, $\mu = 0.0713$, $\alpha_1 = 0.057$, and $\alpha_2 = 0.2311$. The reproduction numbers follow as: $\mathcal{R}_1 = 2.00$ and $\mathcal{R}_2 = 2.51$.

In Figure 5 we have the reproduction number of strain one, $\mathcal{R}_1 = 2.00$, while the reproduction number of strain two, $\mathcal{R}_2 = 2.51$. Yet, strain one, represented by $I(t)$, is the dominant strain, while strain two, represented by $J(t)$, is eliminated. Therefore, the principle that the strain with higher reproduction number excludes the strain with lower reproduction number is not valid in this model [1].

Using the parametric plot in Figure 2, we were able to show that dominance of a strain with suboptimal reproduction number, can be attained. But just as importantly, we can also use the analysis to choose parameter values which do not provide us with this situation. To generate these plots, it must be the case that one of the assumptions on the parameters values is no longer held. For this example, we will assume that $b_x \not> b_1$. We find $\mathcal{K}_1 = 1.75$ and $\mathcal{K}_2 = 5.62$, so both values are positive and generate the plot Figure 6.

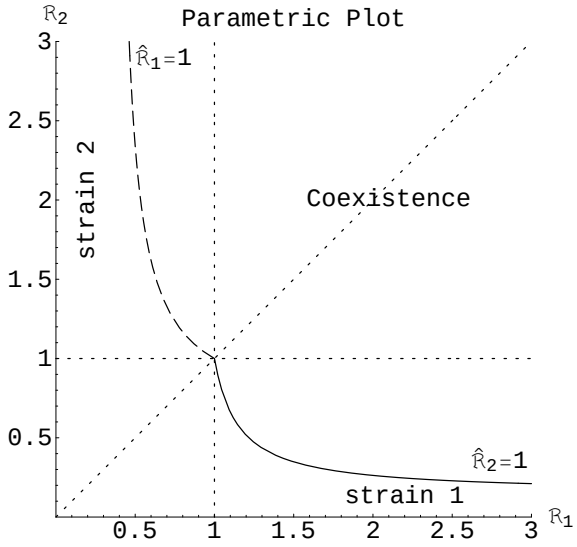


FIGURE 6. Parametric plot of *Model 1* when we do not get the situation of the strain with suboptimal reproduction number being dominant. Parameter values used for this plot: $b_x = 0.423$, $b_1 = 0.5945$, $b_2 = 0.3808$, $\beta_1 = 0.0572$, $\beta_2 = 0.1094$, and $\mu = 0.1458$

Unlike Figure 2, in Figure 6 there is no region which suggests that a strain with suboptimal reproduction number dominates a strain with a higher reproduction number. This is because in Figure 6 the area underneath the $\hat{\mathcal{R}}_2 = 1$ curve would be dominated by strain one. Also, the region to the left of $\hat{\mathcal{R}}_1 = 1$ curve would be dominated by strain two. Finally, the region between the two curves represents coexistence. Thus, there is no such area as in Figure 4, where a strain with a lower reproduction number would dominate a strain with a higher reproduction number.

3. A Vaccination Model Without Healthy Births From Both Infected Individuals (Model 2)

In this section we introduce a model similar to that in section 2, however now we include a vaccinated class, which is represented by $V(t)$. The birth rate of susceptible newborns from the vaccinated class is represented by η_3. It is reasonable to expect that the per capita birth rate of susceptible and vaccinated individuals is the same. Therefore, we will take $\eta_3 = b_x$. The per capita vaccination rate is represented by ψ. All other parameters have the same meaning as in *Model 1*, so we can use Table 1 as a reference. With this, the general model that includes vaccination is:

$$
\begin{aligned}
\frac{dS}{dt} &= (b_x S + \eta_1 I + \eta_2 J + \eta_3 V)(1 - S - I - J - V) - (\mu + \psi)S - \beta_1 IS - \beta_2 JS \\
\frac{dI}{dt} &= I[b_1(1 - S - I - J - V) - (\mu + \alpha_1) + \beta_1 S] \\
\frac{dJ}{dt} &= J[b_2(1 - S - I - J - V) - (\mu + \alpha_2) + \beta_2 S] \\
\frac{dV}{dt} &= \psi S - \mu V
\end{aligned}
\tag{3.1}
$$

The vaccination within this model is assumed to be "perfect", or that it is one-hundred percent effective against both strains in the system. Thus, we note that all individuals in the vaccinated class are completely protected against both strains and are not subject to any further infections. Furthermore, using the results from section 2, which showed that a strain with suboptimal reproduction number can dominate, while the other strain dies out, in this section, we conjecture and show that strain replacement occurs through perfect vaccination.

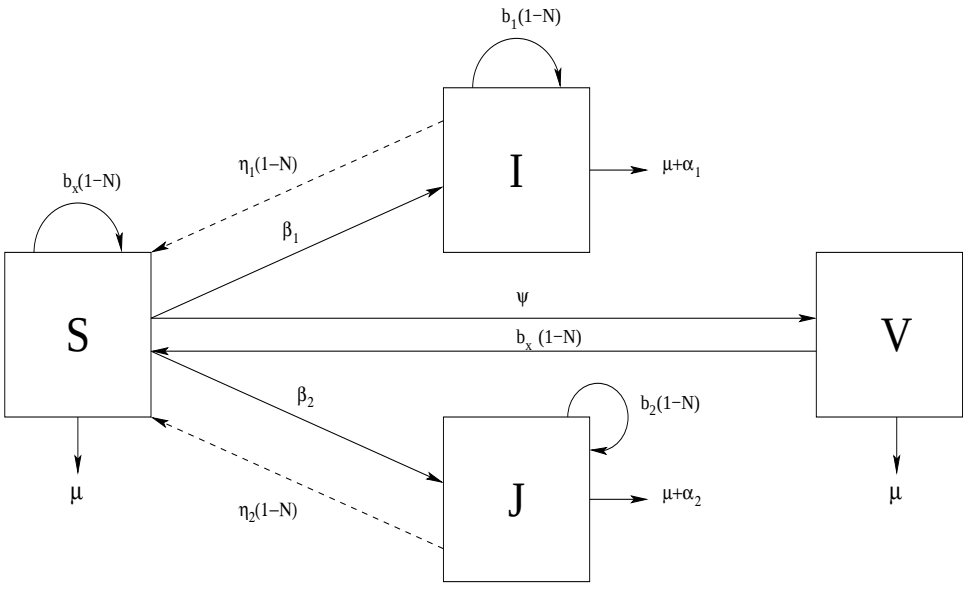


Figure 7. Flow chart of the model with vaccination.

Similar to the first model, we again assume η_1 and η_2 to be zero. The vaccine-dependent reproduction numbers of the two strains are given by:

$$\mathcal{R}_1(\psi) = \frac{b_1(\frac{\mu}{b_x}) + \beta_1(\frac{\mu}{\mu+\psi})(1-\frac{\mu}{b_x})}{\mu+\alpha_1} \qquad \mathcal{R}_2(\psi) = \frac{b_2(\frac{\mu}{b_x}) + \beta_2(\frac{\mu}{\mu+\psi})(1-\frac{\mu}{b_x})}{\mu+\alpha_2} \tag{3.2}$$

With a vaccinated class, the reproduction number values depend on the value of ψ. In fact, the reproduction numbers are decreasing functions with respect to ψ. In the absence of vaccination ($\psi = 0$), the reproduction numbers are identical to the reproduction numbers (2.4) in section 2. Moreover we observe, $\mathcal{R}_1(0) = \mathcal{R}_1$ and $\mathcal{R}_2(0) = \mathcal{R}_2$. The fraction $\frac{\mu}{(\mu+\psi)}$ is the proportion of susceptible individuals in a disease-free population subjected to vaccination at rate ψ. The system (3.1) always has a disease-free equilibrium which can be found as:

$$\mathcal{E}_0 = \left(\left(1-\frac{\mu}{b_x}\right)\frac{\mu}{\mu+\psi}, 0, 0, \left(1-\frac{\mu}{b_x}\right)\frac{\psi}{\mu+\psi}\right)$$

The system (3.1) also has one equilibrium corresponding to each strain: $\mathcal{E}_1 = (S_1^*, I^*, 0, V_1^*)$ and $\mathcal{E}_2 = (S_2^*, 0, J^*, V_2^*)$. The values of I^* and J^* are as follows:

$$I^* = \frac{(\frac{b_1\mu}{b_x} + \frac{\beta_1\mu}{\mu+\psi}(1-\frac{\mu}{b_x}))[1-\frac{1}{\mathcal{R}_1(\psi)}]}{\frac{\beta_1\mu}{\mu+\psi}[1+\frac{\mu\beta_1}{b_x(\mu+\psi)}-\frac{b_1}{b_x}]} = \frac{\mathcal{C}_1[1-\frac{1}{\mathcal{R}_1(\psi)}]}{\mathcal{C}_2} \tag{3.3}$$

$$J^* = \frac{(\frac{b_2\mu}{b_x} + \frac{\beta_2\mu}{\mu+\psi}(1-\frac{\mu}{b_x}))[1-\frac{1}{\mathcal{R}_2(\psi)}]}{\frac{\beta_2\mu}{\mu+\psi}[1+\frac{\mu\beta_2}{b_x(\mu+\psi)}-\frac{b_2}{b_x}]} = \frac{\mathcal{D}_1[1-\frac{1}{\mathcal{R}_2(\psi)}]}{\mathcal{D}_2} \tag{3.4}$$

As before, we will represent the values of I^* and J^* as functions of the reproduction numbers $\mathcal{R}_1(\psi)$ and $\mathcal{R}_2(\psi)$, eliminating α_1 and α_2 in the process from (3.2). For simplicity we lump all the remaining parameters in appropriately defined constants, $\mathcal{C}_1$, $\mathcal{C}_2$, $\mathcal{D}_1$, and $\mathcal{D}_2$.

Linearizing around the equilibrium $\mathcal{E}_2$, we find the invasion reproduction number of strain one in the presence of vaccination as $\hat{\mathcal{R}}_1$. Similarly, linearizing around $\mathcal{E}_1$, we find $\hat{\mathcal{R}}_2$.

The expressions for I^* and J^* become important substitutions into the invasion numbers, which are computed as:

$$\hat{\mathcal{R}}_1 = \frac{\frac{b_1\mu}{b_x} + \frac{\beta_1\mu}{\mu+\psi} - \frac{\beta_1\mu\mu}{b_x(\mu+\psi)} + \frac{\mu}{(\mu+\psi)}(\frac{b_1\beta_2}{b_x} - \beta_1 - \frac{\mu\beta_1\beta_2}{b_x(\mu+\psi)})J^*}{\mu+\alpha_1} \tag{3.5}$$

$$\hat{\mathcal{R}}_2 = \frac{\frac{b_2\mu}{b_x} + \frac{\beta_2\mu}{\mu+\psi} - \frac{\beta_2\mu\mu}{b_x(\mu+\psi)} + \frac{\mu}{(\mu+\psi)}(\frac{b_2\beta_1}{b_x} - \beta_2 - \frac{\mu\beta_1\beta_2}{b_x(\mu+\psi)})I^*}{\mu+\alpha_2} \tag{3.6}$$

As before, for simplification reasons, we take groups of parameters in the expressions for $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$ and represented them as constants. We can do that since all of these parameter values are constant, do not depend on $\mathcal{R}_1(\psi)$ and $\mathcal{R}_2(\psi)$, and do not include α_1 or α_2. The following shows the constants $\mathcal{M}_1$ and $\mathcal{M}_2$, used for simplification in $\hat{\mathcal{R}}_1$.

$$\mathcal{M}_1 = \frac{b_1\mu}{b_x} + \frac{\beta_1\mu}{\mu+\psi} - \frac{\beta_1\mu\mu}{b_x(\mu+\psi)}$$

$$\mathcal{M}_2 = \frac{\mu}{(\mu+\psi)}\left(\frac{b_1\beta_2}{b_x} - \beta_1 - \frac{\mu\beta_1\beta_2}{b_x(\mu+\psi)}\right)$$

The same can be done for the parameters in $\hat{\mathcal{R}}_2$ using the constants $\mathcal{N}_1$ and $\mathcal{N}_2$. With these substitutions, the invasion numbers can be expressed as:

$$\begin{aligned} \hat{\mathcal{R}}_1 &= \frac{\mathcal{M}_1 + \mathcal{M}_2 J^*}{\mu + \alpha_1} \\ \hat{\mathcal{R}}_2 &= \frac{\mathcal{N}_1 + \mathcal{N}_2 I^*}{\mu + \alpha_2} \end{aligned} \tag{3.7}$$

It is now necessary to generate the parametric plots for this model. To do so, we must find the expressions $\hat{\mathcal{R}}_1(\psi) = F(\mathcal{R}_1(\psi), \mathcal{R}_2(\psi))$ and $\hat{\mathcal{R}}_2(\psi) = G(\mathcal{R}_1(\psi), \mathcal{R}_2(\psi))$. After we have these expressions, just as we did in section 2, we will need to represent the reproduction numbers as functions of one another. For example, we will show how to obtain $\mathcal{R}_1(\psi) = f(\mathcal{R}_2(\psi))$, while the second expression will follow by symmetry.

To start, we set the invasion number $\hat{\mathcal{R}}_1 = 1$. After substituting the values for J^* and $(\mu + \alpha_1)$ from (3.4) and (3.2) respectively, into (3.7), we obtain:

$$\begin{aligned} \hat{\mathcal{R}}_1 &= \left(\mathcal{M}_1 + \mathcal{M}_2 \frac{\mathcal{D}_1[1 - \frac{1}{\mathcal{R}_2(\psi)}]}{\mathcal{D}_2} \right) \frac{\mathcal{R}_1(\psi)}{\mathcal{M}_1} = 1 \\ \mathcal{R}_1(\psi) &= \frac{1}{1 + \frac{\mathcal{M}_2 \mathcal{D}_1}{\mathcal{M}_1 \mathcal{D}_2}[1 - \frac{1}{\mathcal{R}_2(\psi)}]} \end{aligned}$$

Again, since $\mathcal{M}_i$ and $\mathcal{D}_i$ are constants (with $i = 1$ or 2), we can simplify the expression even more, by defining a new constant $\mathcal{K}$, where $\mathcal{K} = \frac{\mathcal{M}_2 \mathcal{D}_1}{\mathcal{M}_1 \mathcal{D}_2}$. Thus, the expression $\mathcal{R}_1(\psi) = f(\mathcal{R}_2(\psi))$ is:

$$\mathcal{R}_1(\psi) = \frac{1}{1 + \mathcal{K}[1 - \frac{1}{\mathcal{R}_2(\psi)}]} \tag{3.8}$$

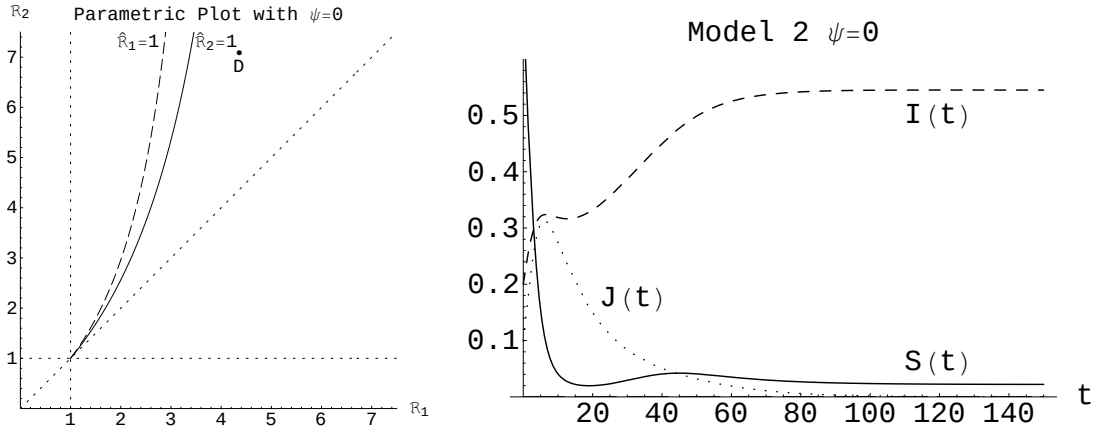
Similarly, this same process is used to find $\mathcal{R}_2(\psi) = g(\mathcal{R}_1(\psi))$ with the exception that the constant will now be labeled as $\mathcal{L}$.

$$\mathcal{R}_2(\psi) = \frac{1}{1 + \mathcal{L}[1 - \frac{1}{\mathcal{R}_1(\psi)}]} \tag{3.9}$$

Now, using these two functions, we generate a parametric plot of the two curves. However, since we have vaccination in the model, these plots will fluctuate depending on the level of vaccination. We will use this to demonstrate how specific areas of dominance within the parametric plot change with increasing levels of vaccination.

3.1. **Simulation Results.** The following simulations of *Model 2* provide evidence of strain replacement with increasing levels of vaccination. With each of the simulation plots, there exists a corresponding parametric plot. However, since the reproduction numbers are decreasing functions of ψ, increasing the level of vaccination changes the values of the reproduction numbers. In addition to this, the parametric plots will also change.

Given a set of parameter values, we can use (3.8) and (3.9) to generate a parametric plot. From the given parameters, along with the level of vaccination, we can choose specific values of the reproduction numbers $\mathcal{R}_1(\psi)$ and $\mathcal{R}_2(\psi)$. With these values, we then obtain an ordered pair $(\mathcal{R}_1(\psi), \mathcal{R}_2(\psi))$, with ψ being fixed. These reproduction numbers are the coordinates of the point "D" in the parametric plot. Depending on



(a) Parametric Plot (b) Simulation

FIGURE 8. Parametric and corresponding simulation plot of *Model 2* when $\psi = 0$. The reproduction numbers of I and J are: $\mathcal{R}_1 = 4.36$ and $\mathcal{R}_2 = 7.05$ respectively.

the location of the point "D", we will obtain different outcomes from the competition between the strains.

The parameters used for the simulations in Figure 8, Figure 9, and Figure 10 are: $b_x = 0.732$, $b_1 = 0.197$, $b_2 = 0.0652$, $\beta_1 = 0.440$, $\beta_2 = 0.876$, $\mu = 0.0771$, $\eta_1 = \eta_2 = 0$, $\eta_3 = b_x$, $\alpha_1 = 0.0179$, and $\alpha_2 = 0.0349$.

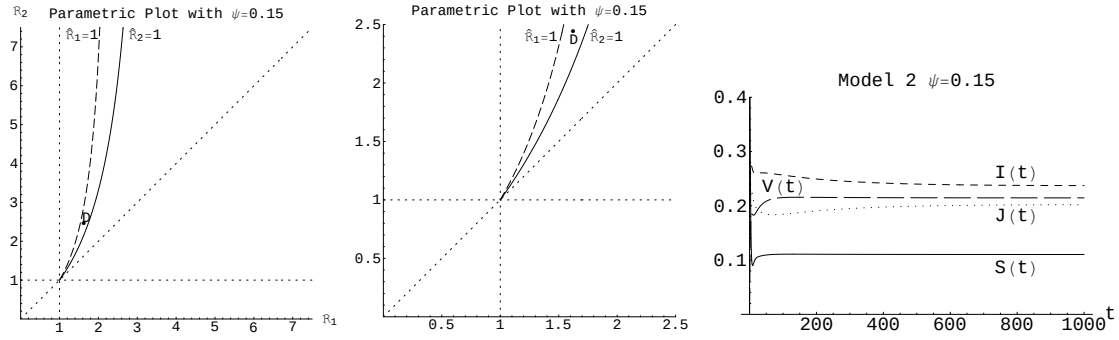
In the first of three series of simulation plots for this model, Figure 8, we take vaccination to be zero, or $\psi = 0$. To understand how the system may react, we generate the parametric plot, Figure 8(a), using the fixed parameter values above. Even though this parametric plot is not an exact copy as in section 2, it is similar and offers us the opportunity to reference Figure 3, to understand the distinct areas where a particular strain will dominate.

The positioning of the point "D" in the parametric plot, Figure 8(a), suggests that strain one, which has suboptimal reproduction number, will dominate. We confirm this conjecture with the outcome of the dynamic simulation, Figure 8(b), of the system.

As we increase vaccination to a level of $\psi = 0.15$, not only do the reproduction numbers change, but also the position of the point "D" and the boundary curves $\hat{\mathcal{R}}_1 = 1$ and $\hat{\mathcal{R}}_2 = 1$. Now this point falls in a region where the strains coexist. This is shown in the second simulation, Figure 9.

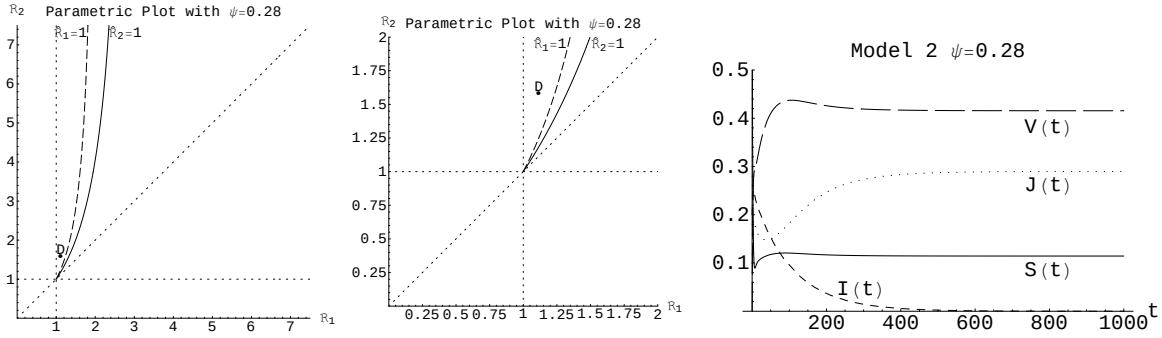
Finally, in the third simulation plot, Figure 10, we increase vaccination even further to a level of $\psi = 0.28$. Even though there is not much change in the parametric plot, Figure 10(b), the values of the reproduction numbers and therefore the coordinates of "D" change. That proves to be very important. Now, this point falls into a region where the opposing strain, namely the one which was eliminated with zero vaccination, is now the dominant strain.

Through this sequence of plots, we see that strain replacement has occurred in the model with perfect vaccination (3.1) where healthy births from infected individuals are not permitted.



(a) Parametric plot (b) Enlarged view (c) Simulation

FIGURE 9. Parametric and corresponding simulation plot of *Model 2* when $\psi = 0.15$. The reproduction numbers are: $\mathcal{R}_1(\psi) = 1.63$ and $\mathcal{R}_2(\psi) = 2.44$.



(a) Parametric plot (b) Enlarged view (c) Simulation

FIGURE 10. Parametric and corresponding simulation plot of *Model 2* when $\psi = 0.28$. The reproduction numbers are: $\mathcal{R}_1(\psi) = 1.11$ and $\mathcal{R}_2(\psi) = 1.57$.

4. DISCUSSION

In this paper we consider a model with two strains and vertical transmission as a trade-off mechanism. We address the following hypothesis: since vertical transmission is a trade-off mechanism which leads to the dominance of a strain with suboptimal reproduction number, it will also lead to strain replacement with perfect vaccination. We first show that vertical transmission is a trade-off mechanism that allows a strain with suboptimal reproduction number to dominate. We do that in the case when healthy births from the infected classes are not allowed ($\eta_1 = \eta_2 = 0$). We obtain the result by computing invasion reproduction numbers $\hat{\mathcal{R}}_1$ and $\hat{\mathcal{R}}_2$. The equalities $\hat{\mathcal{R}}_1 = 1$ and $\hat{\mathcal{R}}_2 = 1$ define curves in the $(\mathcal{R}_1, \mathcal{R}_2)$ plane. Dominance of a strain with lower reproduction number occurs when the dominance region of this strain intersects the line $\mathcal{R}_1 = \mathcal{R}_2$. We develop the analytical techniques to detect such a scenario. We show both analytically and graphically that this situation can occur in our model in the case when healthy births from the infected classes are not allowed ($\eta_1 = \eta_2 = 0$). We have also investigated

the case where healthy births from the infected classes are permitted ($\eta_1 \neq 0, \eta_2 \neq 0$) and we have obtained a similar result [22]. Furthermore, we conjectured that a trade-off mechanism that allows a strain with suboptimal reproduction number to dominate will lead to strain replacement with perfect vaccination. To address this question, we consider the model with perfect vaccination. We define again the invasion reproduction numbers in the presence of vaccination and the corresponding graphic interpretation of the equalities $\hat{\mathcal{R}}_1 = 1$ and $\hat{\mathcal{R}}_2 = 1$. Strain replacement with perfect vaccination does indeed occur for the case where healthy births from the infected classes are not permitted ($\eta_1 = \eta_2 = 0$) under the following scenario. As a starting point, we first consider a situation where in the absence of vaccination ($\psi = 0$) dominance of a strain with suboptimal reproduction number occurs. Then, increasing the vaccination level leads to coexistence of the two strains. Further increase of the vaccination level leads to elimination of the strain which dominated originally and persistence of the strain which was eliminated in the absence of vaccination. The case ($\eta_1 \neq 0, \eta_2 \neq 0$) is again considered through simulations in [22] and similar results are obtained. We summarize the trade-off mechanisms and whether each of them leads to dominance of a strain with a lower reproduction number and/or to strain replacement in Table 2.

Table 2. Trade-off mechanism overview

Trade-off mechanism	$\mathcal{R}_1 > \mathcal{R}_2$, **but strain 2 excludes strain 1**	**Strain replacement with perfect vaccination**	**Reference**
Model 2 ($\eta_1 = \eta_2 = 0$)	Yes	Yes	[10, 22]
Model 2 ($\eta_1 \neq 0, \eta_2 \neq 0$)	Yes	Yes	[10, 22]
Super-infection	Yes	Yes	[6]
Co-infection	Yes	Yes	[12]
Mutation	No	No	[12]
Cross-immunity	No	No	[12]

Since our model includes virulence, one may draw some conclusions about the impact of vaccination on the evolution of virulence. This is particularly shown in the special case when the two strains transmit with the same transmission rates, $\beta_1 = \beta_2$. Then $\mathcal{R}_1 < \mathcal{R}_2$ if and only if $\alpha_1 > \alpha_2$. Thus, in the absence of vaccination a strain with higher virulence may dominate. After vaccination, however, this strain will be replaced by a lower-virulence strain. Thus, perfect vaccination against vertically transmitted strains may reduce virulence. To translate these results to the more general and more realistic case when $\beta_1 \neq \beta_2$ one has the use methodology of adaptive dynamics [21]. The impact of imperfect vaccines and their mode of action on pathogen evolution and virulence was more thoroughly addressed in [4].

The main conclusion from this investigation is that significant evidence exist that a trade-off mechanism can lead to strain replacement with perfect vaccination if and only if it allows for a less fit strain, a strain with a lower reproduction number, to dominate in the absence of vaccination. Future work may be able to establish rigorously this result. The main biological implication of our work is that efforts directed to elimination of the differential effectiveness of the vaccine cannot be expected to eradicate

strain replacement. Such efforts may be more successful with non-vertically transmitted pathogens whose strains are not subjected to interactions such as coinfection and superinfection.

Acknowledgments

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5. APPENDIX

Proof of Theorem 2.2.

a.) For these equilibria to exist, we need to be certain the equilibria are valid, or in other words, they must be nonnegative. Since we used substitutions to find expressions for these equilibria, it is necessary for S^*, J^*, $(1-S^*)$, and $(1-S^*-J^*)$ all to be positive.

Show $J^* > 0$ when J^* is expressed as:

$$\begin{aligned} J^* &= \frac{b_x(\mu+\alpha_2)(1-\mathcal{R}_2)}{\beta_2(b_2-b_x-\beta_2)} \\ &= \frac{b_x(\mu+\alpha_2)(\mathcal{R}_2-1)}{\beta_2(\beta_2+b_x-b_2)} \end{aligned}$$

Examining the individual signs of the numerator and denominator:

$$\begin{aligned} b_x(\mu+\alpha_2)(\mathcal{R}_2-1) &> 0 \qquad \text{(as the parameters are all positive)} \\ \beta_2(\beta_2+b_x-b_2) &> 0 \qquad \text{(by assumption } b_2 < b_x\text{)} \end{aligned}$$

Therefore, the overall value of $J^* > 0$.

Next, we will do the same for S^* which is the expression:

$$\begin{aligned} S^* &= 1-\frac{\mu}{b_x}-\frac{b_x+\beta_2}{b_x}J^* \\ &= 1-\frac{\mu}{b_x}-\frac{b_x+\beta_2}{b_x}\frac{b_x(\mu+\alpha_2)(\mathcal{R}_2-1)}{\beta_2(\beta_2+b_x-b_2)} \\ &= 1-\frac{\mu}{b_x}-\frac{(b_x+\beta_2)(\mu+\alpha_2)}{\beta_2(\beta_2+b_x-b_2)}\left(\frac{b_2\mu+\beta_2(b_x-\mu)}{b_x(\mu+\alpha_2)}-1\right) \\ &= 1-\frac{\mu}{b_x}-\frac{b_x+\beta_2}{\beta_2(\beta_2+b_x-b_2)}\left(b_2\frac{\mu}{b_x}+\beta_2\left(1-\frac{\mu}{b_x}\right)-(\mu+\alpha_2)\right) \end{aligned}$$

Notice the denominator of this term is positive. Thus, in the next step, after taking a common denominator, it is left out as it has no influence to the overall sign of the

expression. The numerator is left to be:

$$\begin{aligned} &= \beta_2(\beta_2 + b_x - b_2)\left(1 - \frac{\mu}{b_x}\right) - (b_x + \beta_2)\left[b_2\frac{\mu}{b_x} + \beta_2\left(1 - \frac{\mu}{b_x}\right) - (\mu + \alpha_2)\right] \\ &= -\beta_2 b_2\left(1 - \frac{\mu}{b_x}\right) - (b_x + \beta_2)b_2\frac{\mu}{b_x} + (b_x + \beta_2)(\mu + \alpha_2) \\ &= -b_2(\beta_2 + \mu) + (b_x + \beta_2)(\mu + \alpha_2) \\ &= -b_2\beta_2 - \mu(b_2 - b_x) + \beta_2(\mu + \alpha_2) + b_x\alpha_2 \end{aligned}$$

Using the assumptions in Section 2, we get the expression, $\mu(b_2 - b_x) < 0$. In addition to this, since all of the values for the parameters are positive, $b_x\alpha_2 > 0$. With these individual expressions positive, just as we did with the denominator, we will leave them out of the remaining steps:

$$\begin{aligned} &= \beta_2(-b_2 + (\mu + \alpha_2)) \\ &= \beta_2(\mu + \alpha_2)\left(\frac{-b_2}{\mu + \alpha_2} + 1\right) \\ &= \beta_2(\mu + \alpha_2)(1 - \tilde{\mathcal{R}}_1) \\ &> 0 \end{aligned}$$

This follows from assumption dealing with the vertical transmission, which then implies that $S^* > 0$.

Finally, we will examine $(1 - S^*)$ and $(1 - S^* - J^*)$, which are expressed as:

$$\begin{aligned} 1 - S^* &= \frac{\mu}{b_x} + \left(\frac{b_x + \beta_2}{b_x}\right)J^* \\ 1 - S^* - J^* &= \frac{\mu}{b_x} + \left(\frac{b_x + \beta_2}{b_x}\right)J^* - J^* \\ &= \frac{\mu}{b_x} + \left(\frac{b_x + \beta_2}{b_x}\right)J^* - \frac{b_x J^*}{b_x} \\ &= \frac{\mu}{b_x} + \frac{\beta_2}{b_x}J^* \\ &> 0 \end{aligned}$$

With all positive parameter values we can conclude that these expressions are positive.

Therefore, by showing these four expressions S^*, J^*, $(1 - S^*)$, and $(1 - S^* - J^*)$ all to be positive with the assumption $\mathcal{R}_2 > 1$ and $\tilde{\mathcal{R}}_2 < 1$, we have a valid strain two equilibrium. Hence, $\mathcal{E}_2$ exists.

b.) It follows analogously from part (a) to prove $\mathcal{E}_1$ exists when $\mathcal{R}_1 > 1$ and $\tilde{\mathcal{R}}_1 < 1$.

■

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