ON THE MECHANISM OF STRAIN REPLACEMENT IN EPIDEMIC MODELS WITH VACCINATION

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Abstract. Strain replacement is the effect of substitution of a strain of higher prevalence in the population with another. Differential effectiveness of the vaccines is thought to be the mechanism responsible for the replacement effect. Recent theoretical study shows that differential effectiveness of the vaccine may not be necessary and other trade-off mechanisms can lead to it even when the vaccine is "perfect". We suggest that the mechanism of strain replacement is the reciprocal effect of vaccination on the fitness of the strains as measured by their invasion reproduction numbers. This mechanism is responsible for the substitution of one strain with another to occur both when the vaccine is perfect and when it is imperfect. We review various well-known trade-off mechanisms and investigate whether they lead to replacement effect in conjunction with "perfect" vaccination. We find that in contrast to imperfect vaccination which leads to replacement of a strain with larger intrinsic reproduction number with a strain with a lower intrinsic reproduction number, "perfect" vaccination seems to have opposite effect on the intrinsic reproduction numbers.

Keywords: multiple pathogen variants, strain replacement, coinfection, cross-immunity, vaccination, coexistence, invasion.

1. Introduction

In response to selective pressures from the host immune system pathogens vary their genetic characteristics to escape recognition. Thus the evolution and replacement of pathogen types is a continuous process mediated by the host immunity. The rate at which a pathogen mutant obtains dominance in the individual host is highest at intermediate level of immunity of the host [12]. Vaccination has direct impact on host immunity and is therefore intimately connected to the evolution of pathogens on the within-host level. Furthermore, vaccination changes dynamically the susceptible pool for the pathogen variants on population level and is a mechanism that favors the population distribution of a certain strain. The process through which the establishment of a particular pathogen variant on within host level is related to the establishment of this or other pathogen variant on the population level but this relation is not well understood. Phylogenies of specific highly mutable pathogens (such as HIV) show significant differences in the evolution on the within-host and between-host levels [12].

Vaccination plays distinctive role in the evolution of the pathogens on each level [23], but its role as an evolutionary agent is better understood on population level. Empirical evidence in terms of clinical trials and surveillance [4, 15] as well as theoretical research [19, 20, 8, 27, 28] point to the fact that while vaccination leads to elimination of certain strains also facilitates the emergence at higher prevalence of strains which previously were not widely spread. This phenomenon is now called *the replacement effect* [24]. The replacement effect has been drawing significant attention in the literature because it diminishes the effect of vaccination, particularly for diseases caused by pathogens of considerable genetic diversity. Clearly, vaccines should be developed in a way that minimizes the possibility for substitution of the current strains with others. This, in turn, requires that we understand what causes this effect.

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The primary reason for strain replacement to occur is that vaccines do not equally well protect against all strains – a property referred to as *differential effectiveness*. In a recent article we [16] showed, however, that differential effectiveness may not be necessary for the replacement to occur. This raises the question of the mechanism of strain replacement – a mechanism that can explain its occurrence both in the presence and the absence of differential effectiveness. In this article, namely in the next section, we discuss such a mechanism strictly in the case of *strong replacement effect* – that is, replacement effect in which the dominance of one strain is exchanged with dominance of the other.

Further we observe that what is necessary for replacement to occur is the action of some sort of *trade-off mechanism* – a mechanism that allows for coexistence. In section 3 we show that differentially effective vaccines themselves are a trade-off mechanism while equally effective, and in particular "perfect" vaccines, that provide complete protection, lead to competitive exclusion. That observation explains why equally effective vaccines when acting outside of other trade-off mechanisms cannot cause replacement. However, the results in [16] show that equally effective vaccines can act synergistically with some other trade-off mechanism (super-infection in that case) to lead to strain replacement. Can all trade-off mechanisms fill that role or there is something special about super-infection? We devote the rest of the paper to answering this question. In section 4 we investigate coinfection coupled with "perfect" vaccination and we find that strain replacement can also occur. In section 5 we investigate cross-immunity and we touch on mutation. We find that with these two trade-off mechanisms strain replacement in its strong form does not occur. Our results are in accord with those in [13] where cross-immunity has been found to lead to selection for a subdominant strain only in presence of imperfect vaccine.

Strain replacement signifies pathogen evolution under the influence of vaccination. One of the questions that arise in that context concerns the direction of this evolution. Is it possible that through vaccination we may be selecting for a more virulent strain? We do not address this question here but it has been investigated for incompletely effective vaccines in [11] where it has been observed that virulence can evolve towards increased virulence or decreased virulence depending on whether the vaccine blocks pathogen growth or infection. Here we observe that the direction of evolution of the pathogen's intrinsic reproduction number (the reproduction number in the absence of vaccination) depends on whether the vaccine is differentially effective or not. Imperfect vaccines seem to lead to evolution towards lower intrinsic reproduction numbers while "perfect" vaccines lead to evolution to higher reproduction numbers. In section 6 we summarize our results and discuss the differences in the the replacement effect for perfect and imperfect vaccines.

2. The mechanism of strain replacement

Intuitively, replacement on population level of one pathogen strain with another suggests exchange of prevalence between the two strains. Such exchange of prevalence is a result of vaccination and can occur under several scenarios which are mathematically distinct.

- **Scenario 1:** The strains coexist both before and after vaccination but before vaccination strain one is more prevalent while after vaccination strain two is more prevalent. We will refer to this replacement as *weak replacement*.
- **Scenario 2:** Strain one dominates (persists alone) before vaccination but after vaccination the two strains coexist but strain two has higher prevalence. An analogous scenario occurs if both strains coexist before vaccination with strain one being more prevalent, while after vaccination strain two dominates.
- **Scenario 3:** Strain one dominates (persists alone) before vaccination while after vaccination strain two dominates. We will call this strain replacement *strong replacement*.

Replacement in all those three scenarios may or may not be epidemiologically significant. Replacement will be epidemiologically significant if the prevalence of the second strain after vaccination is about or higher than the prevalence of the first strain before vaccination, or, in other words, the prevalence of the replacing strain is sufficiently high.

Mathematically scenario 3 is easier to investigate than scenarios one and two because we have strict rigorous conditions which allow the prediction of which strain will dominate. On the other hand to investigate the other two scenarios we need to know which strain will have higher prevalence if the two coexist – something that is not that well understood.

The conditions that govern the dominance of one strain or another are based on the invasion reproduction numbers – the number of cases strain i will generate when strain j is at equilibrium. We denote the invasion reproduction number of strain i by $\hat{\mathcal{R}}_i$. Thus, strain one dominates if strain one can invade the equilibrium of strain two, $\hat{\mathcal{R}}_1 > 1$ while strain two cannot invade the equilibrium of strain one, $\hat{\mathcal{R}}_2 < 1$. Analogous condition determine the dominance of strain two. The two invasion reproduction numbers depend on the vaccination level ψ: $\hat{\mathcal{R}}_i(\psi)$. Suppose that strain one dominates in the absence of vaccination, that is, $\hat{\mathcal{R}}_1(0) > 1$ while $\hat{\mathcal{R}}_2(0) < 1$. In order for strain two to dominate at a certain vaccination level $\hat{\psi}$ we need that strain one cannot invade the equilibrium of strain two, $\hat{\mathcal{R}}_1(\hat{\psi}) < 1$, and that strain two can invade the equilibrium of strain one, $\hat{\mathcal{R}}_2(\hat{\psi}) > 1$. If such a vaccination level $\hat{\psi}$ exists, strong replacement will occur. In other words we need vaccination to reduce the invasion capabilities of the first strain and to increase invasion capabilities. Without such reciprocal effect of vaccination, strong replacement cannot occur.

Fitness is defined as the expected number of offspring contributed to the next generation and is typically computed as the product of survival and average number of offspring. For that reason fitness of pathogens is often identified as their reproduction number. However, the reproduction numbers are a measure of the reproductive success of the pathogen in an entirely susceptible population, and, in a presence of a competitor, higher reproduction number may not even lead to persistence [25, 21].

The invasion reproduction numbers, on the other hand, measure reproductive success when the competitor is established, and guarantee persistence (at the very least). Thus, they reflect better the fitness of the pathogens. If we take the invasion reproduction numbers for a measure of the fitness, then the mechanism for strain replacement says that vaccination must have a reciprocal (differential in direction) effect on the fitness of the pathogens for strong replacement to occur. Strong replacement cannot occur without such differential in direction effect on the fitness of the pathogens.

3. Differential effectiveness of the vaccine and strain replacement

In this section we show two things. First, that equally effective vaccines cannot cause coexistence, that is, if competitive exclusion is the norm in the absence of vaccination, it is also the only outcome in the presence of vaccination with equally effective vaccine. In contrast, differentially effective vaccines can cause coexistence, even if in the absence of vaccination competitive exclusion is the only outcome, that is differential effectiveness of the vaccine is a trade-off mechanism in its own right. Second, we show that differential effectiveness of the vaccine alone leads to reciprocal impact of vaccination on the invasion reproduction numbers of the pathogens and therefore, to strain replacement. Consequently, differential effectiveness of the vaccine is one manifestation of the main mechanism causing strain replacement.

We consider a host population of total size at time t given by $N(t)$ that is being recruited at a rate Λ and dies at a natural death rate μ. The number of healthy individuals who are susceptible to the disease at time t is denoted by $S(t)$. Healthy individuals can get infected by strain one at a transmission rate β_1 and enter the class of individuals infected and infectious

with strain one. This class is of total size $I(t)$. Independently, healthy individuals can get infected by strain two at a transmission rate β_2 and enter the class of individuals infected and infectious with strain two whose total size is given by $J(t)$. Infected individuals with strain one recover at a recovery rate γ_1 while infected individuals with strain two recover at a recovery rate γ_2. Recovered individuals comprise the class $R(t)$. Finally, susceptible individuals are vaccinated at a vaccination rate ψ and enter the class of vaccinated individuals, $V(t)$. We assume that vaccinated individuals can get infected by strain one at a rate $\beta_1\delta_1$ where δ_1 is the coefficient of reduction of transmission of strain one provided by the vaccine. Similarly, vaccinated individuals can get infected by strain two at a rate $\beta_2\delta_2$ where δ_2 is the coefficient of reduction of transmission of strain two provided by the vaccine. We will consider two cases mainly.

(1) The vaccine is equally effective with respect to both strains, that is, $\delta_1 = \delta_2 = \delta$ which may or may not be zero.

(2) The vaccine has differential effectiveness. In particular, we will assume that the vaccine is nearly perfect with respect to one of the strains, say strain two. That means that $\delta_2 = 0$. In contrast, the vaccine is only partially effective with respect to strain one, that is, $\delta_1 \neq 0$. We denote $\delta_1 = \delta$.

We consider the following two-strain model with vaccination [14].

$$\begin{aligned} S' &= \Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu+\psi)S \\ I' &= \beta_1 \frac{SI}{N} + \beta_1\delta_1 \frac{IV}{N} - (\mu+\gamma_1)I \\ J' &= \beta_2 \frac{SJ}{N} + \beta_2\delta_2 \frac{JV}{N} - (\mu+\gamma_2)J \\ R' &= \gamma_1 I + \gamma_2 J - \mu R \\ V' &= \psi S - \beta_1\delta_1 \frac{IV}{N} - \beta_2\delta_2 \frac{JV}{N} - \mu V \end{aligned} \tag{3.1}$$

Since vaccines are generally assumed to reduce transmission we must have $0 \leq \delta_1, \delta_2 \leq 1$. The reproduction numbers of the two strains are given by

$$\mathcal{R}_1(\psi) = \frac{\beta_1\mu + \beta_1\delta_1\psi}{(\mu+\psi)(\mu+\gamma_1)} \qquad \mathcal{R}_2(\psi) = \frac{\beta_2\mu + \beta_2\delta_2\psi}{(\mu+\psi)(\mu+\gamma_2)} \tag{3.2}$$

We note that both reproduction numbers are decreasing functions of the vaccination rate ψ. We denote the value of the reproduction numbers in the absence of vaccination, $\mathcal{R}_i(0)$ at $\psi = 0$, with $\mathcal{R}_i$ and we call those *intrinsic reproductive numbers*. Furthermore, the value at maximal vaccination levels, $\psi \to \infty$, is $\mathcal{R}_i(0)\delta_i$, and may or may not be under one. This reflects the fact that imperfect vaccines may not be able to reduce the reproduction number below one, and may not lead to eradication. The system above always has a disease-free equilibrium (each equilibrium is given in terms of the proportions of susceptible, infectives with each strain, recovered and vaccinated individuals – $\mathcal{E} = (s, i, j, r, v)$):

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

and a unique dominance equilibrium corresponding to each strain. The dominance equilibrium of the first strain is

$$\mathcal{E}_1 = \left(\frac{\mu}{\beta_1 i + \mu + \psi}, i, 0, \frac{\gamma_1 i}{\mu}, \frac{\psi\mu}{(\beta_1\delta_1 i + \mu)(\beta_1 i + \mu + \psi)}\right)$$

and it exists when $\mathcal{R}_1(\psi) > 1$. The proportion of infected with strain one i in $\mathcal{E}_1$ is given by the unique solution of the following equation:

$$\frac{\mathcal{R}_1\mu}{\beta_1 i + \mu + \psi}\left[1 + \frac{\delta_1\psi}{\beta_1\delta_1 i + \mu}\right] = 1. \tag{3.3}$$

The dominance equilibrium of the second strain, correspondingly, is

$$\mathcal{E}_2 = \left(\frac{\mu}{\beta_2 j + \mu + \psi}, 0, j, \frac{\gamma_2 j}{\mu}, \frac{\psi\mu}{(\beta_2\delta_2 j + \mu)(\beta_2 j + \mu + \psi)}\right)$$

and it exists when $\mathcal{R}_2(\psi) > 1$. The system (3.1) may or may not have coexistence equilibria.

Our first result testifies to the fact that competitive exclusion is the only outcome in the absence of vaccination.

Proposition 3.1. *Assume $\psi = 0$. Then, if $\max\{\mathcal{R}_1, \mathcal{R}_2\} > 1$, a competitive exclusion principle holds, that is, the strain with the larger reproduction number persists, while the other one is eliminated.*

This results follows from the observation that $\psi = 0$ implies that $V(t) \to 0$ as $t \to \infty$. The rest of the system is similar to the one studied in [3] and the result follows from there. Our next result shows that an equally effective vaccine $\delta_1 = \delta_2 = \delta$ also leads to competitive exclusion, namely,

Proposition 3.2. *Assume that the vaccine is equally effective with respect to both strains, that is, $\delta_1 = \delta_2 = \delta$. Then, if $\max\{\mathcal{R}_1(\psi), \mathcal{R}_2(\psi)\} > 1$, a competitive exclusion principle holds, that is, the strain with the larger reproduction number persists, while the other one is eliminated.*

Proof. Assume without loss of generality that $\mathcal{R}_1(\psi) > \mathcal{R}_2(\psi)$. As a result of the assumption that $\delta_1 = \delta_2 = \delta$ this inequality is equivalent to the inequality $\beta_1(\mu+\gamma_2) > \beta_2(\mu+\gamma_1)$. Consider the function $\xi(t) = I^{\beta_2}(t)/J^{\beta_1}(t)$. Differentiating ξ with respect to t we see that it satisfies the following differential equation $\xi'(t) = \alpha\xi(t)$ where the constant α is given by

$$\alpha = [\beta_1(\mu + \gamma_2) - \beta_2(\mu + \gamma_1)] = \frac{\mu + \psi}{\mu + \delta\psi}[\mathcal{R}_1(\psi) - \mathcal{R}_2(\psi)] > 0$$

Consequently, $\xi(t) \to \infty$ as $t \to \infty$, and since $I(t)$ is bounded, we must have $J(t) \to 0$ and $t \to \infty$. That implies persistence of $I(t)$ (at least in a weak sense) because if we assume $I(t) \to 0$, then the solutions of the system (3.1) approach the disease-free equilibrium, which on the other hand can be shown to be unstable because at least one of the reproduction numbers is above one. Therefore, the assumption that $I(t) \to 0$ is not correct. □

Now we turn to the scenario (2): differential effectiveness of the vaccine. We work under the conditions $\delta_2 = 0$ and $\delta_1 = \delta$. The model (3.1) takes the form:

$$\begin{aligned}
S' &= \Lambda - \beta_1\frac{SI}{N} - \beta_2\frac{SJ}{N} - (\mu + \psi)S \\
I' &= \beta_1\frac{SI}{N} + \beta_1\delta\frac{IV}{N} - (\mu + \gamma_1)I \\
J' &= \beta_2\frac{SJ}{N} - (\mu + \gamma_2)J \\
R' &= \gamma_1 I + \gamma_2 J - \mu R \\
V' &= \psi S - \beta_1\delta\frac{IV}{N} - \mu V
\end{aligned} \tag{3.4}$$

In this case equation (3.3) for j simplifies and gives the following solution:

$$j = \frac{(\mu + \psi)(\mathcal{R}_2(\psi) - 1)}{\beta_2}$$

and dominance equilibrium $\mathcal{E}_2$ takes the form

$$\mathcal{E}_2 = \left(\frac{1}{\mathcal{R}_2}, 0, \frac{(\mu+\psi)(\mathcal{R}_2(\psi)-1)}{\beta_2}, \frac{\gamma_2}{\mu}\frac{(\mu+\psi)(\mathcal{R}_2(\psi)-1)}{\beta_2}, \frac{\psi}{\mathcal{R}_2\mu}\right).$$

To investigate the possible presence of a coexistence equilibrium, we introduce the invasion reproduction numbers. The invasion reproduction number of the first strain at the equilibrium of the second strain $\hat{\mathcal{R}}_1(\psi)$ is the number of secondary infections one individual infected with the first strain can produce when the second strain is at equilibrium in the population. This number under scenario (2) takes the form

$$\hat{\mathcal{R}}_1(\psi) = \frac{\mathcal{R}_1(\mu+\delta\psi)}{\mathcal{R}_2\mu} = \frac{\mathcal{R}_1(\psi)}{\mathcal{R}_2(\psi)} \tag{3.5}$$

where $\mathcal{R}_i = \mathcal{R}_i(0)$ for $i = 1, 2$. Similarly, the invasion reproduction number of the second strain at the equilibrium of the first strain $\hat{\mathcal{R}}_2(\psi)$ is the number of secondary infections one individual infected with the second strain can produce when the second strain is at equilibrium in the population. The invasion reproduction number of the second strain under scenario (2) takes the form

$$\hat{\mathcal{R}}_2(\psi) = \frac{\mathcal{R}_2\mu}{\beta_1 i + \mu + \psi} \tag{3.6}$$

where i is the solution of (3.3). First we show that under scenario (2) competitive exclusion is not necessarily the outcome, and coexistence is possible. In other words unequally effective vaccines represent a trade-off mechanism which allows for coexistence. The following result testifies to the presence of a nontrivial region of the parameter space where coexistence may occur.

Proposition 3.3. *If $\mathcal{R}_2 > \mathcal{R}_1$, and each strain can invade the equilibrium of the other, that is*

$$\hat{\mathcal{R}}_1(\psi) > 1 \qquad\qquad \hat{\mathcal{R}}_2(\psi) > 1$$

then there exists a unique coexistence equilibrium $\mathcal{E}^* = (s^*, i^*, j^*, r^*, v^*)$.

Proof. The values of the coexistence equilibrium can be computed as follows

$$\begin{aligned} s^* &= \frac{1}{\mathcal{R}_2} \\ i^* &= \frac{\mathcal{R}_2\mu(\hat{\mathcal{R}}_1(\psi)-1)}{(\mathcal{R}_2-\mathcal{R}_1)\beta_1\delta} \\ j^* &= \frac{1}{\beta_2}\left[\mathcal{R}_2\mu - (\beta_1 i^* + \mu + \psi)\right] \\ r^* &= \frac{\gamma_1 i^*}{\mu} + \frac{\gamma_2 j^*}{\mu} \\ v^* &= \frac{\mathcal{R}_2 - \mathcal{R}_1}{\delta\mathcal{R}_1\mathcal{R}_2} \end{aligned} \tag{3.7}$$

which gives the uniqueness. The existence will follow if all values above are positive. This is straight forward to see under the assumptions of the this proposition for all values except j^*. To see that $j^* > 0$ consider the left-hand side of equation (3.3) as follows:

$$f(x,y) = \frac{\mathcal{R}_1\mu}{\beta_1 x + \mu + \psi}\left[1 + \frac{\delta\psi}{\beta_1\delta y + \mu}\right].$$

The fact that i - the proportion of infectives with strain one in $\mathcal{E}_1$ - means that i satisfies equation (3.3), that is $f(i,i) = 1$. On the other hand if i^* is the proportion of infectives in the coexistence equilibrium $\mathcal{E}^*$, then we have

$$\beta_1\delta i^* + \mu = \frac{\delta\psi\mathcal{R}_1}{\mathcal{R}_2 - \mathcal{R}_1}$$

and consequently, $f(i, i^*) = \hat{\mathcal{R}}_2(\psi) > 1$. Therefore, $f(i, i) < f(i, i^*)$. But $f(x, y)$ is a decreasing function of y which gives $i^* < i$. Then,

$$j^* = \frac{\beta_1 i^* + \mu + \psi}{\beta_2}\left[\frac{\mathcal{R}_2\mu}{\beta_1 i^* + \mu + \psi} - 1\right] > \frac{\beta_1 i^* + \mu + \psi}{\beta_2}\left[\hat{\mathcal{R}}_2(\psi) - 1\right] > 0.$$

The persistence of both strains in this case can be observed in simulations. □

Several remarks are in order. First, we note that $\hat{\mathcal{R}}_1(\psi) > 1$ is equivalent to $\mathcal{R}_1(\psi) > \mathcal{R}_2(\psi)$. This, in particular means that in the absence of vaccination, $\psi = 0$, the conditions of this proposition are inconsistent and coexistence does not occur. If we have $\mathcal{R}_2 > \mathcal{R}_1$ we need the vaccination level $\psi > \psi^*$, where the threshold vaccination level ψ^* is given by

$$\psi^* = \frac{(\mathcal{R}_2 - \mathcal{R}_1)\mu}{\mathcal{R}_1\delta}$$

so that $\mathcal{R}_1(\psi) > \mathcal{R}_2(\psi)$. Second, $\hat{\mathcal{R}}_2(\psi) > 1$ implies that $\mathcal{R}_2(\psi) > 1$. Thus, the conditions of the proposition imply that both reproduction numbers are above one. Consequently subthreshold coexistence does not occur.

Next, we turn our attention to strain replacement. First, we note that vaccination has a reciprocal effect on the two invasion reproduction numbers. In particular, $\hat{\mathcal{R}}_1(\psi)$ is a linearly increasing function of the vaccination rate ψ such that $\hat{\mathcal{R}}_1(0) = \frac{\mathcal{R}_1}{\mathcal{R}_2}$. That is, under one of the assumptions for coexistence, $\mathcal{R}_2 > \mathcal{R}_1$, the invasion reproduction number of the first strain in the absence of vaccination is smaller than one. It is somewhat complicated to express the invasion reproduction number of the second strain as a function of the vaccination rate. Instead, we will use an upper and a lower bound of that number as follows:

$$\frac{\mathcal{R}_2\mu}{\beta_1 + \mu + \psi} \le \hat{\mathcal{R}}_2(\psi) \le \frac{\mathcal{R}_2\mu}{\mu + \psi} \tag{3.8}$$

From these inequalities, it can be seen that $\hat{\mathcal{R}}_2(\psi) \to 0$ as $\psi \to \infty$ although it may not do so monotonically. This, in particular, implies that vaccination has a reciprocal effect on the invasion capabilities of the two strains – it increases the invasion capabilities of the first strain, and decreases the invasion capabilities of the second strain. We illustrate in Figure 1 the graph of the invasion reproduction number of the first strain and we plot the upper bound and the lower bound from (3.8) to limit the region that contains the invasion reproduction number of the second strain.

In the case of absence of vaccination, $\psi = 0$, the proportion infectives i can be easily computed from (3.3) and it can be seen that $\hat{\mathcal{R}}_2(0) = \frac{\mathcal{R}_2}{\mathcal{R}_1}$. That is, under one of the assumptions for coexistence, $\mathcal{R}_2 > \mathcal{R}_1$, the invasion reproduction number of the second strain in the absence of vaccination is greater than one. Consequently, in the absence of vaccination we have the second strain dominating in the population. As the vaccination levels increase, the invasion capabilities of the first strain grow while the invasion capabilities of the second decline until, at some vaccination level $\hat{\psi}$ we have $\hat{\mathcal{R}}_1(\hat{\psi}) > 1$ and $\hat{\mathcal{R}}_2(\hat{\psi}) < 1$, that is the first strain dominates in the population. Looking at Figure 1 we can choose $\hat{\psi}$ to be any value greater than seven. A replacement effect has occurred.

4. Coinfection, perfect vaccination and strain replacement

In an earlier article [16] we have reported that super-infection as a trade-off mechanism can lead to strain replacement, even when the vaccine is assumed perfect with respect to both strains, that is, it protects all vaccinated individuals completely from infection with either strain. In super-infection one of the strains (say, strain one) wins instantaneously the within-host competition and displaces the other strain (say, strain two) in infected individuals thus turning individuals infected with the second strain into individuals infected with the first strain

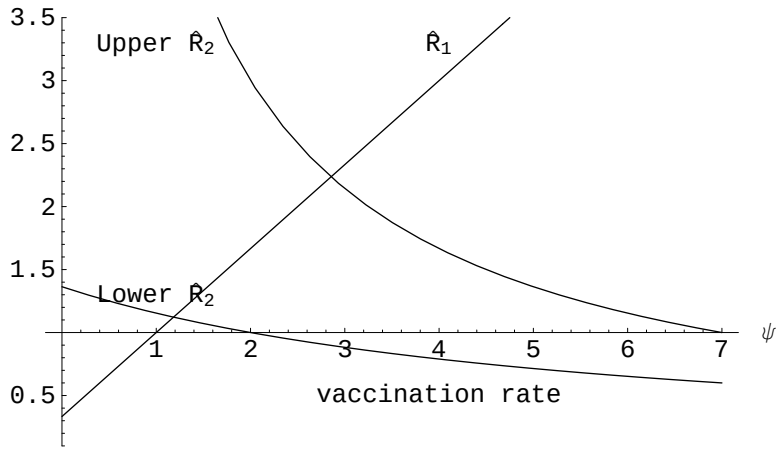

FIGURE 1. The figure illustrates the graph of the invasion reproduction number $\hat{\mathcal{R}}_1(\psi)$ and Upper $\hat{\mathcal{R}}_2(\psi)$ give the upper bound while Lower $\hat{\mathcal{R}}_2(\psi)$ gives the lower bound in (3.8). The parameters are chosen as follows: $\beta_1 = 5$, $\beta_2 = 15$, $\gamma_1 = 0.5$, $\gamma_2 = 0.5$, $\delta = 1$, $\mu = 0.5$ which give $\mathcal{R}_1 = 5$ and $\mathcal{R}_2 = 15$.

[25]. If the second strain has better reproduction rate and would be the dominant strain in the absence of vaccination and super-infection, super-infection as a trade-off mechanism might be strengthening the first strain to coexist with the second strain, or even replace it as a dominant strain. When vaccination is applied against the first strain, it weakens the first strain and the second strain can again take over, that is, dominate. One question we want to address in this section is whether coinfection, as another trade-off mechanism [**?**] can lead to strain replacement even when the vaccine is perfect. In coinfection the strains are seemingly symmetrical – they can both infect individuals infected with the other strain and then they coexist in the host and the host can transmit both. As a trade-off mechanism coinfection can also allow the weaker strain – the one that will be eliminated in the absence of coinfection – to persist either jointly with the stronger strain or even alone, eliminating the stronger strain from the population [21]. When vaccination is applied, even vaccination equally effective against both strains, it weakens the trade-off mechanism and restores the dominance of the strain with the larger reproduction number in absence of vaccination. Thus the same effect is observed when the trade-off mechanism is coinfection and leads to strain replacement as we show below.

We consider again a host population of total size at time t given by $N(t)$ in which individuals are recruited at a total recruitment rate Λ and die at a natural death rate μ. The number of healthy individuals who are susceptible to the disease at time t is denoted by $S(t)$. Healthy individuals can get infected by strain one at a transmission rate β_1 and enter the class of individuals infected and infectious with strain one. This class is of total size $I_1(t)$. Independently, healthy individuals can get infected by strain two at a transmission rate β_2 and enter the class of individuals infected and infectious with strain two whose total size is given by $I_2(t)$. Individuals, infected with strain one can get infected with strain two from those infected with strain two only at a rate δ_1 while individuals infected with strain two can get infected with strain one from those infected with strain one only at a rate δ_2 – those individuals become jointly infected with both strains and enter the class $J(t)$. Jointly infected individuals infect susceptibles with strain one at a rate γ_1 and those in the I_1 class with strain two – at a rate η_1. Similarly, jointly infected individuals infect susceptibles with strain two at a rate γ_2 and those in the I_2 class with strain one – at a rate η_2. Infected with strain one recover at a rate α_1, those infected with strain two – at a rate α_2 and those jointly infected recover approximately

at the same time from both strains at a rate ν. All recovered individuals make up the class $R(t)$. Finally, susceptible individuals are vaccinated at a vaccination rate ψ and enter the class of vaccinated individuals, $V(t)$. We note that all vaccinated individuals are fully protected against all strains in the system, that is, we assume "perfect" vaccination. The model takes the form:

$$\begin{aligned}
S' &= \Lambda - \beta_1 \frac{SI_1}{N} - \beta_2 \frac{SI_2}{N} - (\gamma_1 + \gamma_2)\frac{SJ}{N} - (\mu + \psi)S \\
I_1' &= \beta_1 \frac{SI_1}{N} + \gamma_1 \frac{SJ}{N} - (\mu + \alpha_1)I_1 - \delta_1 \frac{I_1 I_2}{N} - \eta_1 \frac{I_1 J}{N} \\
I_2' &= \beta_2 \frac{SI_2}{N} + \gamma_2 \frac{SJ}{N} - (\mu + \alpha_2)I_2 - \delta_2 \frac{I_1 I_2}{N} - \eta_2 \frac{I_2 J}{N} \\
J' &= \delta_1 \frac{I_1 I_2}{N} + \eta_1 \frac{I_1 J}{N} + \delta_2 \frac{I_1 I_2}{N} + \eta_2 \frac{I_2 J}{N} - (\mu + \nu)J \\
R' &= \alpha_1 I_1 + \alpha_2 I_2 + \nu J - \mu R \\
V' &= \psi S - \mu V
\end{aligned} \tag{4.1}$$

The existence of equilibria depends on the reproduction numbers of the two strains which are symmetrical:

$$\mathcal{R}_1(\psi) = \frac{\beta_1 \mu}{(\mu + \psi)(\mu + \alpha_1)} \qquad \mathcal{R}_2(\psi) = \frac{\beta_2 \mu}{(\mu + \psi)(\mu + \alpha_2)} \tag{4.2}$$

We note again that both reproduction numbers are decreasing functions of the vaccination rate ψ. In this case both can be decreased to zero by vaccination. The system (4.1) has the disease-free equilibrium

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

where each equilibrium consists of the proportion of susceptible, proportion of infected with the first strain, proportion infected with the second strain, proportion of jointly infected, proportion recovered, and proportion vaccinated individuals: $\mathcal{E} = (s, i_1, i_2, j, r, v)$. The system has two dominance equilibria - one for each strain. The dominance equilibrium of strain one exists if and only if $\mathcal{R}_1(\psi) > 1$ and is given by:

$$\mathcal{E}_1 = \left(\frac{1}{\mathcal{R}_1}, \frac{\mu}{\mu + \alpha_1} \left(1 - \frac{1}{\mathcal{R}_1(\psi)} \right), 0, 0, \frac{\alpha_1}{\mu + \alpha_1} \left(1 - \frac{1}{\mathcal{R}_1(\psi)} \right), \frac{\psi}{\mu \mathcal{R}_1} \right)$$

Similarly, dominance equilibrium of strain two exists if and only if $\mathcal{R}_2(\psi) > 1$ and is given by:

$$\mathcal{E}_2 = \left(\frac{1}{\mathcal{R}_2}, \frac{\mu}{\mu + \alpha_2} \left(1 - \frac{1}{\mathcal{R}_2(\psi)} \right), 0, 0, \frac{\alpha_2}{\mu + \alpha_2} \left(1 - \frac{1}{\mathcal{R}_2(\psi)} \right), \frac{\psi}{\mu \mathcal{R}_2} \right)$$

Denote by $q_i = \frac{\eta_i}{\mu + \nu}$ and $r_i = \frac{\gamma_i}{\mu + \nu}$ for $i = 1, 2$. The invasion reproduction number of the first strain at the equilibrium of the second is given by

$$\hat{\mathcal{R}}_1(\psi) = \frac{\beta_1 s + r_1 s(\delta_1 + \delta_2) i_2 + q_2(\mu + \alpha_1 + \delta_1 i_2) i_2}{\mu + \alpha_1 + \delta_1 i_2 + q_2 i_2 \beta_1 s} \tag{4.3}$$

where s and i_2 have the corresponding values from $\mathcal{E}_2$. Analogously, the reproduction number of the second strain at the equilibrium of the first is given by

$$\hat{\mathcal{R}}_2(\psi) = \frac{\beta_2 s + r_2 s(\delta_1 + \delta_2) i_1 + q_1(\mu + \alpha_2 + \delta_2 i_1) i_1}{\mu + \alpha_2 + \delta_2 i_1 + q_1 i_1 \beta_2 s} \tag{4.4}$$

where s and i_1 have the corresponding values from $\mathcal{E}_1$. Both invasion reproduction numbers depend on ψ only through i_1 and i_2. Both i_1 and i_2 are decreasing functions of ψ but the

dependence of the invasion reproduction numbers on i_1 and i_2 may be non-monotone. In particular, the dependence of the invasion reproduction numbers on i_1 and i_2 may be monotonely decreasing, monotonely increasing or first monotonely decreasing and then monotonely increasing. That translates to exactly opposite dependence of the invasion numbers on ψ. First, we will assume without loss of generality that

$$\mathcal{R}_1 < \mathcal{R}_2.$$

This, in particular means that in the absence of the trade-off mechanism (coinfection in this case) strain two will dominate in the population both in absence and in presence of vaccination of any level. Second, since the intrinsic reproduction number of the second strain is larger, to break the symmetry of the strains we make the following assumptions that strengthen strain one and weaken strain two:

ASSUMPTION 4.1. (1) *Suppose that strain one can coinfect individuals infected with strain two but strain two cannot coinfect individuals infected with strain one. That, in particular, means that we are assuming:*

$$\delta_1 = 0, \qquad \eta_1 = 0 \ (q_1 = 0).$$

(2) *Suppose that jointly infected individuals, that is those in class J cannot infect with strain two, that is,*

$$\gamma_2 = 0 \ (r_2 = 0).$$

Under these assumptions the invasion reproduction numbers become:

$$\hat{\mathcal{R}}_1(\psi) = \frac{\beta_1 s + r_1 s\delta_2 i_2 + q_2(\mu+\alpha_1)i_2}{\mu + \alpha_1 + q_2 i_2 \beta_1 s} \tag{4.5}$$

The reproduction number of the second strain at the equilibrium of the first becomes:

$$\hat{\mathcal{R}}_2(\psi) = \frac{\beta_2 s}{\mu + \alpha_2 + \delta_2 i_1} \tag{4.6}$$

The invasion reproduction number of the second strain $\hat{\mathcal{R}}_2(\psi)$ is now a decreasing function of i_1, and consequently, an increasing function of ψ. On the other hand, the derivative of $\hat{\mathcal{R}}_1(\psi)$ with respect to i_2 is

$$\frac{\partial \hat{\mathcal{R}}_1(\psi)}{\partial i_2} = \frac{r_1\delta_2(\mu+\alpha_1)s + q_2(\mu+\alpha_1)^2\left[1 - \left(\frac{\mathcal{R}_1}{\mathcal{R}_2}\right)^2\right]}{(\mu + \alpha_1 + q_2 i_2 \beta_1 s)^2} > 0$$

Consequently, $\hat{\mathcal{R}}_1(\psi)$ is an increasing function of i_2 and therefore a decreasing function of ψ. This implies that vaccination has reciprocal effect of the invasion reproduction numbers. In particular, it decreases the invasion capabilities of the first strain and increases the invasion capabilities of the second strain. Thus, if coinfection allows the first strain to dominate in the population when no vaccination is present, that is, $\hat{\mathcal{R}}_1(0) > 1$ while $\hat{\mathcal{R}}_2(0) < 1$, increasing vaccination levels may lead to the fact that at some vaccination level $\hat{\psi}$ we have $\hat{\mathcal{R}}_1(\hat{\psi}) < 1$ and $\hat{\mathcal{R}}_2(\hat{\psi}) > 1$, that is strain two dominates in the population. Replacement of strain one with strain two has occurred. We illustrate that in Figure 2. We note that in Figure 2 we have the case when $\mathcal{R}_2 > \mathcal{R}_1$, and consequently, in the absence of coinfection strain two will be dominating (with or without vaccination). In the absence of vaccination $\psi = 0$, the trade-off mechanism is strong enough to allow for the strain with the lower reproduction number to persist while the one with the larger reproduction number is eliminated. That is a result of the fact that the first strain can invade the equilibrium of the second $\hat{\mathcal{R}}_1(0) = 1.44$ while the second cannot invade the equilibrium of the first $\hat{\mathcal{R}}_2(0) = 0.9091$. This outcome is a result of our Assumptions 4.1 that strengthen the first strain in its interaction with the second.

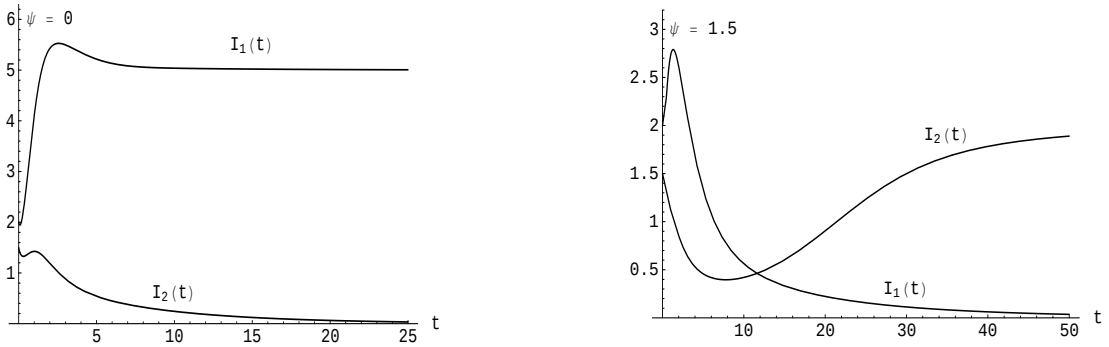

FIGURE 2. The figure shows that strain replacement occurs in the model with coinfection (4.1). The left figure shows that strain one dominates while strain two is eliminated when there is no vaccination $\psi = 0$. The right figure shows that strain two dominates while strain one is eliminated when vaccination is at level $\psi = 1.5$. The remaining parameters in this figure are chosen as follows: $\beta_1 = 6$, $\beta_2 = 5$, $\mu = 0.5$, $\gamma_1 = 8$, $\gamma_2 = 0$, $\delta_1 = 0$, $\delta_2 = 1.5$, $\alpha_1 = 1$, $\alpha_2 = 0.5$, $\nu = 0.5$, $\eta_1 = 0$, $\eta_2 = 0$, $\Lambda = 10$. These give $\mathcal{R}_1 = 4$ and $\mathcal{R}_2 = 5$.

Furthermore, vaccination decreases the impact of the trade-off mechanism and restores the strain with the larger intrinsic reproduction number to dominate in the population.

This example raises several questions: Is it absolutely necessary that the trade-off mechanism is strong enough to allow the strain with the lower reproduction number to dominate in the population. Super-infection [25] and coinfection [21] are two such mechanism which are known to generate this effect but not all trade-off mechanisms can be readily associated with it. In particular, we have previously observed that cross-immunity as a trade-off mechanism always leads to dominance of the strain with the largest reproduction number [26]. Before we address the question whether cross-immunity may trigger strain replacement, we will investigate whether strain replacement may be exhibited under a different scenario. In particular, assume it is possible that the trade-off mechanism is weak and does not lead to dominance of the strain with the smaller intrinsic reproduction number. Is it possible that a "perfect" vaccination works in such a way that it strengthens this weak trade-off mechanism so that at some higher vaccination levels this mechanism allows for the strain with the lower intrinsic reproduction number to dominate? In the case of coinfection we could answer this question negatively only for a special case.

Proposition 4.2. *Assume that jointly infected individuals cannot coinfect already infected individuals, that is $\eta_1 = \eta_2 = 0$. Assume that in the absence of vaccination ($\psi = 0$) the strain with the larger reproduction number persists while the other is eliminated. Then strain replacement cannot occur in model (4.1).*

Proof. Assume without loss of generality that $\mathcal{R}_1 > \mathcal{R}_2$, and that $\hat{\mathcal{R}}_1(0) > 1$ while $\hat{\mathcal{R}}_2(0) < 1$. The invasion reproduction number of the first strain at the equilibrium of the second in this case becomes

$$\hat{\mathcal{R}}_1(\psi) = \frac{\beta_1 s + r_1 s(\delta_1 + \delta_2) i_2}{\mu + \alpha_1 + \delta_1 i_2} \tag{4.7}$$

where we recall that s and i_2 have the corresponding values from $\mathcal{E}_2$. Analogously, the invasion reproduction number of the second strain at the equilibrium of the first is given by

$$\hat{\mathcal{R}}_2(\psi) = \frac{\beta_2 s + r_2 s(\delta_1 + \delta_2) i_1}{\mu + \alpha_2 + \delta_2 i_1} \tag{4.8}$$

where we recall s and i_1 have the corresponding values from $\mathcal{E}_1$. The derivatives of the two invasion reproduction numbers with respect to i_2 and i_1 respectively, are given by

$$\frac{\partial\hat{\mathcal{R}}_1(\psi)}{\partial i_2}=\frac{r_1 s(\delta_1+\delta_2)(\mu+\alpha_1)-\delta_1\beta_1 s}{(\mu+\alpha_1+\delta_1 i_2)^2}=\frac{s(\mu+\alpha_1)[r_1(\delta_1+\delta_2)-\delta_1\mathcal{R}_1]}{(\mu+\alpha_1+\delta_1 i_2)^2}$$

Analogously,

$$\frac{\partial\hat{\mathcal{R}}_2(\psi)}{\partial i_1}=\frac{r_2 s(\delta_1+\delta_2)(\mu+\alpha_2)-\delta_2\beta_2 s}{(\mu+\alpha_2+\delta_2 i_1)^2}=\frac{s(\mu+\alpha_2)[r_2(\delta_1+\delta_2)-\delta_2\mathcal{R}_2]}{(\mu+\alpha_2+\delta_2 i_1)^2}$$

Assume that replacement occurs. That implies that there exists a vaccination level ψ^* such that $\hat{\mathcal{R}}_1(\psi^*)=1$ becoming from larger than one to smaller than one. This equality can be rewritten to give

$$(\mu+\alpha_1)\left[\frac{\mathcal{R}_1}{\mathcal{R}_2}-1\right]=i_2[\delta_1-r_1 s(\delta_1+\delta_2)]$$

From our assumption that $\mathcal{R}_1>\mathcal{R}_2$ it follows that the left-hand side of this equality is positive. Since $i_2>0$, that means that we must have

$$\delta_1>r_1 s(\delta_1+\delta_2)$$

which implies that

$$\delta_1\mathcal{R}_2>r_1(\delta_1+\delta_2)$$

or that $\frac{\partial\hat{\mathcal{R}}_1(\psi)}{\partial i_2}<0$ leading to the fact that $\hat{\mathcal{R}}_1(\psi)$ is an increasing function of ψ starting from a value above one and cannot be equal to one for any ψ. That is a contradiction. Consequently, strain replacement does not occur. □

5. Cross-immunity and strain replacement

Cross-immunity is the phenomenon where an infection with one strain gives partial protection to infection with other strains. Cross-immunity has been primarily investigated in connection with influenza [1, 5, 6] and dengue [7, 17, 10]. It is well known that it can cause coexistence of the strains. Imperfect vaccination can lead to strain replacement in conjunction with cross-immunity only if the strains provide sufficient level of protection against each other, that is, when the competition among them is high [8, 13]. Here we investigate the possibility that cross-immunity as a trade-off mechanism may cause replacement in the context of "perfect" vaccination. From the analysis in [26] we know that the boundaries of the coexistence region do not cross the bisector $\mathcal{R}_1=\mathcal{R}_2$. That, in particular, implies that only the strain with the higher reproduction number dominates. Here, we use a cross-immunity model similar to the one in [5, 6] and somewhat simpler than the one in [26]. We use that model to show that "perfect" vaccination combined with cross-immunity in its simplest form cannot lead to strain replacement. This suggests that not all trade-off mechanisms necessarily induce replacement effect.

We consider again a host population of total size at time t given by $N(t)$ with recruitment Λ and natural death rate μ. The class of susceptible to the disease individuals at time t is denoted by $S(t)$. Healthy individuals who previously were never infected by any of the strains can get infected by strain one at a rate β_1 and enter the class of individuals infected and infectious with strain one $I_1(t)$. Those recover at a rate γ_1 and enter the recovered class $R_1(t)$. Recovered individuals in class $R_1(t)$ cannot get infected with strain one any more but they can get infected by strain two at a somewhat reduced rate $\beta_2\sigma$, where σ is the cross-immunity coefficient, and move to the class of individuals currently infected and infectious with strain two who were previously infected with train one $J_2(t)$. Individuals who recover from $J_2(t)$ enter the class of fully immune individuals $W(t)$ at a rate γ_2. This same process can be symmetrically undergone through a first infection with strain two giving rise to the analogous classes $I_2(t)$,

$R_2(t)$, and $J_1(t)$. Finally, susceptible individuals are vaccinated at a vaccination rate ψ and enter the class of vaccinated individuals, $V(t)$. We note that all vaccinated individuals are fully protected against all strains in the system, that is, we again assume "perfect" vaccination. We obtain the following model:

$$
\begin{aligned}
S' &= \Lambda - \beta_1 \frac{S(I_1+J_1)}{N} - \beta_2 \frac{S(I_2+J_2)}{N} - (\mu+\psi)S \\
I_1' &= \beta_1 \frac{S(I_1+J_1)}{N} - (\mu+\gamma_1)I_1 \\
R_1' &= \gamma_1 I_1 - \beta_2 \sigma R_1 \frac{(I_2+J_2)}{N} - \mu R_1 \\
J_1' &= \beta_1 \sigma R_2 \frac{(I_1+J_1)}{N} - (\mu+\gamma_1)J_1 \\
I_2' &= \beta_2 \frac{S(I_2+J_2)}{N} - (\mu+\gamma_2)I_2 \\
R_2' &= \gamma_2 I_2 - \beta_1 \sigma R_2 \frac{(I_1+J_1)}{N} - \mu R_2 \\
J_2' &= \beta_2 \sigma R_1 \frac{(I_2+J_2)}{N} - (\mu+\gamma_2)J_2 \\
W' &= \gamma_1 J_1 + \gamma_2 J_2 - \mu W \\
V' &= \psi S - \mu V
\end{aligned}
\tag{5.1}
$$

The reproduction numbers of the two strains are the same as in the coinfection case and are symmetrical:

$$
\mathcal{R}_1(\psi) = \frac{\beta_1 \mu}{(\mu+\psi)(\mu+\alpha_1)} \qquad \mathcal{R}_2(\psi) = \frac{\beta_2 \mu}{(\mu+\psi)(\mu+\alpha_2)} \tag{5.2}
$$

The system (5.1) has the disease-free equilibrium

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

where each equilibrium consists of the following proportions: $\mathcal{E} = (s, i_1, r_1, j_1, i_2, r_2, j_2, w, v))$. The system has two dominance equilibria - one for each strain. The dominance equilibrium of strain one exists if and only if $\mathcal{R}_1(\psi) > 1$ and is given by:

$$
\mathcal{E}_1 = \left(\frac{1}{\mathcal{R}_1}, \frac{\mu}{\mu+\gamma_1}\left(1 - \frac{1}{\mathcal{R}_1(\psi)}\right), \frac{\gamma_1}{\mu+\alpha_1}\left(1 - \frac{1}{\mathcal{R}_1(\psi)}\right), 0, 0, 0, 0, 0, \frac{\psi}{\mu \mathcal{R}_1} \right)
$$

Similarly, the dominance equilibrium of strain two exists if and only if $\mathcal{R}_2(\psi) > 1$ and is given by:

$$
\mathcal{E}_2 = \left(\frac{1}{\mathcal{R}_2}, 0, 0, 0, \frac{\mu}{\mu+\gamma_2}\left(1 - \frac{1}{\mathcal{R}_2(\psi)}\right), \frac{\gamma_2}{\mu+\gamma_2}\left(1 - \frac{1}{\mathcal{R}_2(\psi)}\right), 0, 0, \frac{\psi}{\mu \mathcal{R}_2} \right)
$$

The invasion reproduction number of the first strain at the equilibrium of the second strain is given by

$$
\hat{\mathcal{R}}_1(\psi) = \frac{\mathcal{R}_1}{\mathcal{R}_2} + \frac{\mathcal{R}_1 \sigma \gamma_2}{\mu+\gamma_2}\left(1 - \frac{1}{\mathcal{R}_2(\psi)}\right) \tag{5.3}
$$

The invasion reproduction number of the second strain at the equilibrium of the first strain is given by

$$
\hat{\mathcal{R}}_2(\psi) = \frac{\mathcal{R}_2}{\mathcal{R}_1} + \frac{\mathcal{R}_2 \sigma \gamma_1}{\mu+\gamma_1}\left(1 - \frac{1}{\mathcal{R}_1(\psi)}\right) \tag{5.4}
$$

Clearly both invasion reproduction numbers are decreasing functions of the vaccination rate and thus vaccination does not have a reciprocal effect on the invasion capabilities of the strains. In fact, it decreases both. Consequently, strain replacement in the strong form that we are considering in this article – the dominance of one strain is replaced by dominance of the other – does not occur. It is possible that *weak replacement* in the form of Scenario 1 or Scenario 2 may occur. For instance, it is possible that one of the strains has a much higher prevalence but the other has a much lower prevalence while the two strains coexist and with increased vaccination levels the strain with the higher prevalence gets eliminated first and the other strain dominates.

In this context, strain replacement in the stronger sense considered here does not occur in the presence of another trade-off mechanism – mutation – defined as one strain changing its genetic characteristic to become another (and the host infected with it becomes a host host infected with the new strain) [2]. It is well known that mutation leads to coexistence, but the newly obtained mutant strain cannot exist by itself, that is, it cannot be a dominant strain [9]. Therefore, in the case of mutation strain replacement in the strong sense considered here does not occur.

6. Discussion

In this article we investigate the role of vaccination in strain replacement. We understand the replacement effect in a strong sense: we assume that one of the strains dominates in the absence of vaccination, while in the presence of vaccination – the other strain dominates. We call this vaccine induced replacement effect since vaccination is necessary to bring about the other strain.

The replacement effect has been thoroughly investigated in the literature – there are both plenty of empirical evidence and theoretical studies. Mathematical models have been used to investigate how and why it occurs. It has been suggested that the replacement effect is a result of the differential effectiveness of the vaccine.

In this article we add to an already existing theoretical evidence that differential effectiveness of the vaccine may not be necessary for a vaccine induced replacement effect to occur. We suggest a new mechanism that may explain why strain replacement under vaccination may occur. In particular, we suggest that vaccination leads to exchange in the dominance of strains because it has a reciprocal effect on the fitness of the strains, that is because it decreases the fitness of the strain dominating in the absence of vaccination, and it increases the fitness of the strain dominating in the presence of vaccination. We define the fitness of the strain as its capability to invade the equilibrium of the other strain, that is, its reproduction number when the other strain is at equilibrium, given by the invasion reproduction number.

Furthermore, exchange of dominance of the strains through vaccination appears to be possible only if the strains have the ability to coexist. Therefore, exchange of dominance is strongly connected to the action of some trade-off mechanism. In fact, in all known theoretical cases that detect the phenomenon, stable coexistence of the strains is also possible as well as competitive exclusion. To support that claim we establish that differential effectiveness is a trade-off mechanism itself by showing that in the absence of other known trade-off mechanisms equally effective vaccines lead to competitive exclusion of the strain with the lower reproduction number. On the other hand, differential effectiveness of the vaccine leads to (locally stable) coexistence. From this perspective it is hardly surprising that some other trade-off mechanisms in combination with equally effective, and even "perfect", vaccines can also lead to strain replacement. We observed it an epidemic model with perfect vaccination and super-infection as a trade-off mechanism. We show that confection as a trade-off mechanism combined with "perfect" vaccination can also lead to strain replacement in the strong sense we consider here.

On the other hand strain replacement in the strong sense does not occur with perfect vaccination in the presence of several well-known trade-off mechanisms, such as cross-immunity and mutation. Perhaps, it may occur in some weakened sense where the strains coexist but exchange their position as the most prevalent strain. We did not explore that further because such exploration requires knowledge of the mechanism that governs higher prevalence during coexistence.

So which trade-off mechanisms can lead to strain replacement in the presence of equally effective vaccines and which cannot? We surmise that the trade-off mechanism should be strong enough to be capable to allow a strain with a lower intrinsic reproduction number to dominate in the population. Both super-infection and coinfection are known to lead to extinction of the strain with the maximal reproduction number even in the absence of vaccination. On the other hand, there is no evidence that cross-immunity may cause such effect.

"Perfect" vaccination coupled with either super-infection or coinfection seems to lead to strain replacement through exactly the same sequence of steps: The strain with the largest intrinsic reproduction number will dominate in the absence of vaccination and the trade-off mechanism. However, in the presence of the trade-off mechanism but in the absence of vaccination – the strain with the lower intrinsic reproduction number dominates and the strain with the larger reproduction is eliminated. Vaccination weakens the effect of the trade-off mechanism and at some vaccination level the dominance of the strain with the larger intrinsic reproduction number is restored. Thus we see replacement of the dominance of the strain with the lower intrinsic reproduction number with the strain with the larger intrinsic reproduction number. We have not been able to show that "perfect" vaccination can lead to replacement of the strain with the larger intrinsic reproduction number by a strain with a lower intrinsic reproduction number. We have been able to rule out this possibility for a special case of coinfection, however, ruling it out for the more general cases remains an open problem.

This is where the replacement effect that occurs with differential effectiveness of the vaccine differs significantly compared to the one that occurs with "perfect" vaccines. Aside the fact that most vaccines are indeed unequally effective against different strains – differential effectiveness leads to the replacement of the strain with the higher reproduction number which dominates in the absence of vaccination (when competitive exclusion is the only outcome) with the strain with a lower reproduction number (when unequally effective vaccine acts as a trade-off mechanism). Another marked difference is that even if "perfect" vaccines can cause replacement, that can only happen for a certain range of vaccination levels. If the vaccination level is sufficiently high – both strains will be eliminated from the population. That may not be the case with differentially effective vaccines. If the reproduction number of the strain, not primarily targeted by the vaccine, cannot be reduced below one, no matter how high the vaccination levels, that strain will persist, even if we successfully vaccinate all individuals in the population.

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