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Strain replacement in an epidemic model with super-infection and perfect vaccination

Mimmo Iannelli [a,*], Maia Martcheva [b], Xue-Zhi Li [c]

[a] *Dipartimento di Matematica, Universitá di Trento, 38050 Povo (Trento), Italy*
[b] *Department of Mathematics, University of Florida, Gainesville, FL 32611-8105, USA*
[c] *Department of Mathematics, Xinyang Teachers College, Henan 464000, P.R. China*

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Abstract

Several articles in the recent literature discuss the complexities of the impact of vaccination on competing subtypes of one micro-organism. Both with competing virus strains and competing serotypes of bacteria, it has been established that vaccination has the potential to switch the competitive advantage from one of the pathogen subtypes to the other resulting in pathogen replacement. The main mechanism behind this process of substitution is thought to be the differential effectiveness of the vaccine with respect to the two competing micro-organisms. In this article, we show that, if the disease dynamics is regulated by super-infection, strain substitution may indeed occur even with perfect vaccination. In fact we discuss a two-strain epidemic model in which the first strain can infect individuals already infected by the second and, as far as vaccination is concerned, we consider a best-case scenario in which the vaccine provides perfect protection against both strains. We find out that if the reproduction number of the first strain is smaller than the reproduction number of the second strain and the first strain dominates in the absence of vaccination then increasing vaccination levels promotes coexistence which allows the first strain to persist in the population even if its vaccine-dependent reproduction number is below one. Further increase of vaccination levels induces the domination of the second strain in the population. Thus the second strain replaces the first strain. Large enough vaccination levels lead to the eradication of the disease.

* Corresponding author. Tel.: +39 461 881657; fax: +39 461 881624.
E-mail addresses: iannelli@science.unitn.it (M. Iannelli), maia@math.ufl.edu (M. Martcheva), xzli66@xytc.edu.cn (X.-Z. Li).

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1. Introduction

Vaccination is most effective against those viruses or bacteria that have little tendency to vary antigenically and can only be found in humans. Many of the pathogens, however, are represented by more than one variant. The importance of including subtypes in modeling the development and evolution of the diseases is well recognized. Competitive exclusion and coexistence of strains in gonorrhea and other sexually transmitted diseases are discussed in [10,11]. The re-emergence of tuberculosis and the spread of drug-resistant strains is considered in [4,7,13]. Dengue is represented by four serotypes and infections by some particular sequences of them can be particularly dangerous as they are believed to lead to the deadly haemorrhagic fever. Dengue models with several serotypes are considered in [12,14]. The virus that causes influenza is so highly mutable that it has prompted scientists to create epidemic models where the infected individuals are continuously structured by the phenotype of the virus [17]. Other multi-strain models of influenza are considered in [2,16,8,9]. Epidemic model which investigates multistrain interactions and finds that competitive exclusion is the ultimate outcome is found in [6]. Various mechanisms promote coexistence among the strains. Some of those are super-infection [15,21,26], mutation [5,7,13], coinfection [22], cross-immunity [8,9,12], density-dependent host mortality [3], exponential growth of the host population [1,20] and vaccination [23].

The presence of multiple variants of the pathogen has a very significant impact on vaccination. Typically vaccines contain one or several strains called *vaccine strains*. The current pneumococcal polysaccharide vaccine contains 23 types of pneumococci that cause 90% of the cases of pneumococcal bacteremia and meningitis. Each year CDC determines three strains of influenza virus – two of type A and one of type B, to be included in the vaccine for the next flu season. Thus, vaccines give high level of immunity against the vaccine strains and provide certain degree of protection through cross-immunity against some of the closely related pathogens. Because the vaccines block the spread of the stronger strains, the ones that account for most cases, they free the ecological niche for the development of those strains against which the vaccine provides only partial protection, or no protection at all. Recent reports in the literature reveal that vaccination has lead to the higher presence of subtypes that before vaccination were scarce. A study in Alaska where routine HiB vaccination was initiated in 1991 reports that although the incidence of cases of *Heamophilus influenza*, type b fell 82%, the number of new cases per year of non-type b increases 120% [27]. Another study reports the re-emergence of *Bordella pertussis* in the Netherlands despite high vaccine coverage. Scientists suggest as a possible reason adaptation of the virus to the vaccination which manifests itself in larger divergence between the vaccine strains and the clinical isolates [25]. Invasive meningococcal disease was endemic in Cuba represented mostly by serotype C before widespread vaccination started with the polysaccharide A-C vaccine in 1979. Despite that this vaccination resulted in reduction in meningococci C infections, the incidence continued to rise with prevailing serogroup B [30].

The complexities of the impact of vaccination on the competition and coexistence of two strains is investigated through mathematical models in several articles. The earliest work on that topic appears to be [23] (see also [32]) where the main issue discussed is the possibility of emergence of vaccine-resistant strains of the disease as a result of major vaccination campaigns. In [23] the author considers two models – in the first one the two strain impart total cross-immunity to each other. The vaccine acts by reducing the susceptibility of the vaccinated individuals to each strain, although it may do so by a different amount. In this model coexistence is impossible in the absence of vaccination but it is feasible with vaccination provided the vaccine confers different degree of protection against the two strains. In the second model super-infection is introduced and coexistence of the strains is possible even without vaccination. This model allows for the strain with a lower reproduction number to have higher prevalence. In this case, if one vaccinates against the strain with higher prevalence, one can give the competitive advantage to the strain with higher reproduction number and thus increase the overall number of infectious individuals.

The potential impact of a future HIV vaccine on the dynamics and transmission of two subtypes of HIV are investigated in [28,29]. In their earlier paper Porco and Blower consider a model called a *differential degree model*. Here, as in [23], the vaccine acts by reducing the susceptibility of the vaccinated individuals to both strain, possibly by a different extent. The authors find that, as a consequence of vaccination, either strain can dominate as well as there could be coexistence. Strain replacement is possible if the vaccine is less effective to the invading subtype than to the established one. In their later paper Porco and Blower consider two new HIV models with vaccination so that in each model the vaccine has a different mode of action. The first model, called *differential take model*, allows for coexistence of the two subtypes. In the second model, called *differential reduced infectivity model*, the vaccine provides no protection and coexistence is not possible, while subtype replacement can occur as the vaccine can change the relation between the two reproduction numbers.

Serotype replacement as a result of vaccination is the main topic of discussion in [18,19]. The author discusses a two-serotype model. Host can be colonized by serotype one, serotype two or both serotypes (coinfection). The vaccine provides full protection against the first serotype and can provide no protection, partial protection or full protection against the second serotype. The two serotypes can coexist in the absence of the vaccine but if they cannot coexist in the absence of the vaccine, vaccine that protects completely with respect to both of them cannot promote coexistence. The key prediction of the model is that the increase in the non-targeted serotype is smaller than the decrease in the targeted serotype and thus the vaccine will always lead to overall decrease in the prevalence (at least when only two serotypes are involved). It is used to explain why serotype replacement is observed in trials of vaccines against *Streptococcus pneumoniae* but have not occurred with the use of *Haemophilus influenzae*, type b (HiB) vaccines. Actually, as mentioned previously, more recent studies [27] suggest that serotype replacement occurs with the application of the HiB vaccine.

In this article we investigate the impact of a 'perfect' vaccine, that is a vaccine that confers 100% protection against both strains through which the disease is represented. The main question that we address is whether such a vaccine would still promote strain replacement. Actually we show that, if a perfect vaccine is coupled with the so called super-infection mechanism, vaccination is able to produce stability exchanges, coexistence of strains and switches of strain dominance. This

scenario is related to the reproduction numbers of the two strains and to the invasion numbers of one strain to the other. In fact their dependence on the vaccination rate is not the same for the two strains due to the super-infection mechanism.

In the next section we introduce an SIS mathematical model and its reformulations. Although an SIRS model would be more realistic as most diseases which allow for vaccination impart at least short-term immunity after infection, such a model leads to more complex expressions which obscure the main point. In section three we define the two sets of reproduction numbers: the vaccine-dependent reproduction numbers of the two strains, $\mathscr{R}_1(\psi)$ and $\mathscr{R}_2(\psi)$, and the invasion reproduction numbers of one strain to the other, $\mathscr{R}_1^2(\psi)$ and $\mathscr{R}_2^1(\psi)$. These reproduction numbers control the existence of the steady states. In particular we find that there are four equilibria: the disease-free equilibrium E_0, the dominance equilibrium of strain one E_1, the dominance equilibrium of strain two E_2 and one coexistence equilibrium E_*. In section four we derive condition for local stability of each of these equilibria. Global stability of the disease-free equilibrium is established under appropriate conditions. In section five we consider the impact of vaccination on the competitive exclusion and coexistence of the two strains. In particular we show that if $\mathscr{R}_2(0) > \mathscr{R}_1(0)$ so that the first strain dominates in the absence of vaccination, increasing vaccination levels promotes coexistence of the strains and further increase of vaccination will lead to domination of the second strain. Thus the second strain effectively replaces the first strain. Of course, sufficiently high levels of vaccination eradicate the disease. In section six we discuss our findings and summarize our conclusions.

2. The model formulation

In this section, we introduce a two strain epidemic model with super-infection. We consider a population $N(t)$ whose demography is regulated by a constant birth/recruitment rate Λ and a natural mortality rate μ. The susceptible population $S(t)$ is subjected to a vaccination campaign with vaccination rate ψ. Upon vaccination, individuals move to the vaccinated class where they are completely protected from both strains. However, the vaccine loses its protective properties with time and eventually vaccinated individuals become susceptible again. We call the time individuals spend in the vaccinated class *vaccine-age* and denote it by θ. The newly vaccinated individuals enter the vaccinated class $v(\theta, t)$ with vaccine-age equal to zero. The rate at which the vaccine wanes is denoted by $\alpha(\theta)$. Susceptibles can be infected by strain one at a transmission rate β_1 and go to the class $I(t)$. The infected individuals in class $I(t)$ recover at a rate γ_1 and return to the susceptible class. Alternatively, susceptibles can be infected by strain two at a transmission rate β_2, in which case they go to the class $J(t)$. Infected individuals with strain two recover at a rate γ_2 and upon recovery return to the susceptible class. We assume that those infected with the second strain can come into a contact with infectious individuals with the first strain and become reinfected with the first strain. This process is referred to as *super-infection*. The transmission coefficient in case of super-infection is $\beta_1\delta$ where δ is the coefficient of reduction or enhancement of infection at reinfection. In particular, if $\delta > 1$ then reinfection is more likely than the regular infection while if $0 < \delta < 1$ then reinfection is less likely than the regular infection. If $\delta = 0$ there is no super-infection.

Thus, the model takes the form:

$$\begin{aligned}
S'(t) &= \Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + \psi)S + \gamma_1 I + \gamma_2 J + \int_0^\infty \alpha(\theta) v(\theta, t)\, \mathrm{d}\theta, \\
I'(t) &= \beta_1 \frac{SI}{N} + \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_1) I, \\
J'(t) &= \beta_2 \frac{SJ}{N} - \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_2) J, \\
&\frac{\partial}{\partial t} v(\theta, t) + \frac{\partial}{\partial \theta} v(\theta, t) = -\alpha(\theta) v(\theta, t) - \mu v(\theta, t), \\
&v(0, t) = \psi S(t),
\end{aligned} \tag{1}$$

where

$$N(t) = S(t) + I(t) + J(t) + \int_0^\infty v(\theta, t)\, \mathrm{d}\theta,$$

and is equipped with the following initial conditions:

$$S(0) = S_0, \quad I(0) = I_0, \quad J(0) = J_0, \quad v(\theta, 0) = v_0(\theta).$$

We first note that this problem has a unique solution in the positive cone $S \geqslant 0$, $I \geqslant 0$, $J \geqslant 0$, $v(\theta, t) \geqslant 0$. Also, summing the equations, we have that the total population $N(t)$ satisfies the differential equation

$$N'(t) = \Lambda - \mu N(t)$$

whose solution is given by the formula

$$N(t) = N_0 \mathrm{e}^{-\mu t} + \frac{\Lambda}{\mu}(1 - \mathrm{e}^{-\mu t}).$$

Thus, we can assume that the initial value is

$$N_0 = S_0 + I_0 + J_0 + \int_0^\infty v_0(\theta)\, \mathrm{d}\theta = \frac{\Lambda}{\mu}$$

in order to have a population of constant size $N = \frac{\Lambda}{\mu}$.

Furthermore, integrating the fourth equation in (1) along the characteristic line $t - \theta = \text{constant}$, we get the following formula

$$v(\theta, t) = \begin{cases} v_0(\theta - t) \dfrac{K_0(\theta)}{K_0(\theta - t)} & \text{for} \quad \theta \geqslant t, \\ \psi S(t - \theta) K_0(\theta) & \text{for} \quad \theta < t. \end{cases} \tag{2}$$

where

$$K_0(\theta) = \mathrm{e}^{-\mu\theta - \int_0^\theta \alpha(\tau)\, \mathrm{d}\tau}.$$

Substituting (2) into the first equation in (1) we obtain

$$S'(t) = \Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + \psi)S + \gamma_1 I + \gamma_2 J + \int_0^t K_1(\theta) S(t - \theta)\, \mathrm{d}\theta + F_1(t), \tag{3}$$

where

$$K_1(\theta) = \psi\alpha(\theta)K_0(\theta), \tag{4}$$

$$F_1(t) = \int_t^\infty \alpha(\theta)\frac{K_0(\theta)V_0(\theta - t)}{K_0(\theta - t)}\,\mathrm{d}\theta,$$

and $F_1(t)$ satisfies

$$\lim_{t\to\infty} F_1(t) = 0.$$

Thus we can replace the first equation in (1) by Eq. (3) and study following integro-differential system in the variables $S(t)$, $I(t)$, $J(t)$,

$$\begin{aligned} S'(t) &= \Lambda - \beta_1\frac{SI}{N} - \beta_2\frac{SJ}{N} - (\mu + \psi)S + \gamma_1 I + \gamma_2 J + \int_0^t K_1(\theta)S(t - \theta)\,\mathrm{d}\theta + F_1(t),\\ I'(t) &= \beta_1\frac{SI}{N} + \beta_1\delta\frac{IJ}{N} - (\mu + \gamma_1)I,\\ J'(t) &= \beta_2\frac{SJ}{N} - \beta_1\delta\frac{IJ}{N} - (\mu + \gamma_2)J. \end{aligned} \tag{5}$$

In fact we can disregard the last equation in (1) because the first three do not contain $v(\theta, t)$. Once we have solved (5) we can use (2) to obtain $v(\theta, t)$.

3. Steady states

According to [24], any equilibrium (S^*, I^*, J^*) of the system (5), if it exists, must be a constant solution of the limiting system associated with (5). Thus we have to look for solution of the following system:

$$\begin{aligned} \Lambda &= \beta_1\frac{S^*I^*}{N} + \beta_2\frac{S^*J^*}{N} + (\mu + \psi)S^* - \mathscr{K}_1 S^* - \gamma_1 I^* - \gamma_2 J^*,\\ 0 &= \beta_1\frac{S^*I^*}{N} + \beta_1\delta\frac{I^*J^*}{N} - (\mu + \gamma_1)I^*,\\ 0 &= \beta_2\frac{S^*J^*}{N} - \beta_1\delta\frac{I^*J^*}{N} - (\mu + \gamma_2)J^*, \end{aligned} \tag{6}$$

where

$$\mathscr{K}_1 = \int_0^\infty K_1(\theta)\,\mathrm{d}\theta = \psi - \psi\mu\mathscr{K}_0 \tag{7}$$

and

$$\mathscr{K}_0 = \int_0^\infty K_0(\theta)\,\mathrm{d}\theta.$$

In interpreting these quantities we notice that $\mu\mathscr{K}_0$ is the probability of dying while in the vaccinated class and

$$\int_0^\infty \alpha(\theta)K_0(\theta)\,\mathrm{d}\theta = 1 - \mu\mathscr{K}_0$$

is the probability of leaving the vaccinated class with lost immunity but alive. Thus $\mathscr{K}_1 = \psi(1 - \mu\mathscr{K}_0)$ is the per capita rate at which individuals enter the susceptible class after going through the vaccination class.

We note that any solution of (6) corresponds to the following steady state for the distribution of vaccinate individuals.

$$v^*(\theta) = \psi S^* K_0(\theta).$$

System (6) always has the disease-free equilibrium

$$E_0 = \left(\frac{\Lambda}{\mu(1+\psi\mathscr{K}_0)}, 0, 0\right), \tag{8}$$

while the existence of non-trivial equilibrium will depend on the value of the two parameters

$$\mathscr{R}_1(\psi) = \frac{\beta_1}{(\mu+\gamma_1)(1+\psi\mathscr{K}_0)}, \tag{9}$$

$$\mathscr{R}_2(\psi) = \frac{\beta_2}{(\mu+\gamma_2)(1+\psi\mathscr{K}_0)}, \tag{10}$$

which are the basic reproduction numbers for the strain I and strain J, respectively, and give the average number of secondary infectious cases produced by an infected individual with strain I (respectively, by an infected individual with strain J) during the entire infectious period in a purely susceptible population. We note that the two reproduction numbers are decreasing functions of ψ and can be decreased to zero by the vaccination. In addition

$$\mathscr{R}_1(\psi) < \mathscr{R}_2(\psi) \quad \text{if and only if} \quad \mathscr{R}_1(0) < \mathscr{R}_2(0).$$

Consequently vaccination cannot switch the relationship between the two reproduction numbers.

To understand the form of the reproduction numbers we notice that the time spent in the class I is $\frac{1}{\mu+\gamma_1}$ and therefore $\frac{\beta_1}{\mu+\gamma_1}$ is the number of secondary infections one infectious individual will produce in a completely susceptible population. However, the disease-free population in our case consists of both susceptible individuals whose proportion in the total population is $\frac{1}{1+\psi\mathscr{K}_0}$ and vaccinated individuals with complementary proportion. Thus, the reproduction number is the product of the secondary infections one infectious individual will produce and the probability that an individual chosen at random is susceptible.

Solving system (6) we see that, besides E_0, the following one strain exclusive equilibria are feasible, under some conditions on $\mathscr{R}_1(\psi)$ and $\mathscr{R}_2(\psi)$. Namely we have

(1) The following strain one exclusive equilibrium exists

$$E_1 = (S_1^*, I_1^*, 0),$$

where

$$S_1^* = \frac{N}{\mathscr{R}_1(0)}, \quad I_1^* = N\left(1 - \frac{1}{\mathscr{R}_1(\psi)}\right), \tag{11}$$

if and only if $\mathscr{R}_1(\psi) > 1$;

(2) The following strain two exclusive equilibrium exists

$E_2 = (S_2^*, 0, J_2^*)$,

where

$$S_2^* = \frac{N}{\mathscr{R}_2(0)}, \quad J_2^* = N\left(1 - \frac{1}{\mathscr{R}_2(\psi)}\right), \tag{12}$$

if and only if $\mathscr{R}_2(\psi) > 1$.

Furthermore, the presence of a coexistence equilibrium depends on two other reproduction numbers, namely the *invasion reproduction numbers* $\mathscr{R}_1^2(\psi)$ and $\mathscr{R}_2^1(\psi)$. By definition, the invasion reproduction number of the first strain $\mathscr{R}_1^2(\psi)$ gives the number of secondary infections that one infected individual with the first strain will produce in a population in which the second strain J is at equilibrium. We refer to [28] for the explanation how these numbers are computed. The invasion reproduction number of the first strain in our case is given by (see (12))

$$\mathscr{R}_1^2(\psi) = \frac{\mathscr{R}_1(0)}{\mathscr{R}_2(0)} + \delta\mathscr{R}_1(0)\left(1 - \frac{1}{\mathscr{R}_2(\psi)}\right). \tag{13}$$

We note that the invasion reproduction number of the first strain is a decreasing function of ψ. Thus, vaccination decreases the invasion capabilities of the first strain. Analogously, the invasion reproduction number of the second strain $\mathscr{R}_2^1(\psi)$ gives the number of secondary infections that one infected individual with the second strain will produce in a population in which the first strain I is at equilibrium. The invasion reproduction number of the second strain in our case is given by (see (11))

$$\mathscr{R}_2^1(\psi) = \frac{\mathscr{R}_2(0)}{\mathscr{R}_1(0)} - \frac{\beta_1\delta}{\beta_2}\mathscr{R}_2(0)\left(1 - \frac{1}{\mathscr{R}_1(\psi)}\right). \tag{14}$$

The invasion reproduction number of the second strain increases with ψ. Thus, vaccination facilitates the invasion capabilities of the second strain.

The two invasion number determine the occurrence of one coexistence equilibrium. In fact, solving (6) for non-trivial I^* and J^* we see that it there exists the equilibrium

$E_* = (S^*, I^*, J^*)$

where

$$\begin{aligned} S^* &= \left[\frac{\delta\beta_1 + \gamma_2 - \gamma_1}{\beta_2 - \beta_1 + \beta_1\delta(1 + \psi\mathscr{K}_0)}\right]N, \\ I^* &= \left[\frac{\beta_2(\beta_1\delta + \gamma_2 - \gamma_1)}{\beta_2 - \beta_1 + \beta_1\delta(1 + \psi\mathscr{K}_0)} - (\mu + \gamma_2)\right]\frac{N}{\beta_1\delta}, \\ J^* &= \left[(\mu + \gamma_1) - \frac{\beta_1(\beta_1\delta + \gamma_2 - \gamma_1)}{\beta_2 - \beta_1 + \beta_1\delta(1 + \psi\mathscr{K}_0)}\right]\frac{N}{\beta_1\delta}, \end{aligned} \tag{15}$$

that is feasible if and only if the following condition is satisfied

$$\frac{1}{\mathscr{R}_2(0)} < \frac{\beta_1\delta + \gamma_2 - \gamma_1}{\beta_2 - \beta_1 + \beta_1\delta(1+\psi\mathscr{K}_0)} < \frac{1}{\mathscr{R}_1(0)} \tag{16}$$

Thus we have

(3) If $\delta\beta_1 + \gamma_2 - \gamma_1 > 0$, the coexistence equilibrium (15) exists if and only if the two invasion reproduction numbers are both greater than one, that is if

$$\mathscr{R}_1^2(\psi) > 1 \quad \mathscr{R}_2^1(\psi) > 1. \tag{17}$$

In fact, we can easily check that the upper inequality in (16) is equivalent to the inequality $\mathscr{R}_2^1(\psi) > 1$ while the lower inequality is equivalent to the inequality $\mathscr{R}_1^2(\psi) > 1$.

Moreover we have the following 'complementary' situation that is also easy to check.

(4) If $\delta\beta_1 + \gamma_2 - \gamma_1 < 0$, the coexistence equilibrium (15) exists if and only if the two invasion reproduction numbers are both less than one, that is if

$$\mathscr{R}_1^2(\psi) < 1 \quad \mathscr{R}_2^1(\psi) < 1. \tag{18}$$

We note that feasibility implies

$$\mathscr{R}_1(0) < \mathscr{R}_2(0).$$

We summarize the issues above in the following theorem:

Theorem 1. *Let $\mathscr{R}_1(\psi)$, $\mathscr{R}_2(\psi)$, $\mathscr{R}_1^2(\psi)$, $\mathscr{R}_2^1(\psi)$ be the reproduction numbers respectively defined in (9), (10), (13), (14). Then*

(i) *The linear disease free equilibrium E_0 given in (8) exists for all values of the parameters.*
(ii) *The strain one exclusive equilibrium E_1 given in (11) exists if and only if $\mathscr{R}_1(\psi) > 1$.*
(iii) *The strain two exclusive equilibrium E_2 given in (12) exists if and only if $\mathscr{R}_2(\psi) > 1$.*
(iv) *If $\delta\beta_1 + \gamma_2 - \gamma_1 > 0$, the coexistence equilibrium E^* given in (15) exists if and only if $\mathscr{R}_1^2(\psi) > 1$ and $\mathscr{R}_2^1(\psi) > 1$.*
(v) *If $\delta\beta_1 + \gamma_2 - \gamma_1 < 0$, the coexistence equilibrium E^* given in (15) exists if and only if $\mathscr{R}_1^2(\psi) < 1$ and $\mathscr{R}_2^1(\psi) < 1$.*

We see that though condition (16) shows a rather complicated dependence of coexistence from the parameters, nevertheless there is a simple description in terms of significant parameters such as reproduction numbers and invasion numbers. Since we want to investigate the role of vaccination, we are interested in different scenarios in which coexistence and strain switches occur versus the vaccination rate ψ. We will discuss this aspect in Section 5, while in the next section we preliminarly focus on stability of the equilibria.

4. Stability analysis

In this section we investigate the stability properties of the equilibria whose existence has been stated in the previous analysis. We start with the trivial disease free equilibrium.

Theorem 2. *For any positive solution* $(S(t), I(t), J(t))$ *of system* (5), *if*

$$\mathscr{R}_1(0) < 1 \quad \text{and} \quad \mathscr{R}_2(0) < 1, \tag{19}$$

then the disease free equilibrium E_0 *is a global attractor.*

Proof. Let

$$f_\infty = \lim_{t\to\infty} \inf f(t), \quad f^\infty = \lim_{t\to\infty} \sup f(t).$$

Note that $\frac{S}{N} \leqslant 1$, and

$$J'(t) = \beta_2 \frac{SJ}{N} - \beta_1\delta\frac{IJ}{N} - (\mu+\gamma_2)J \leqslant \beta_2 J - (\mu+\gamma_2)J.$$

From $\mathscr{R}_2(0) = \frac{\beta_2}{\mu+\gamma_2} < 1$ we know that

$$J(t) \to 0 \quad \text{as} \quad t \to \infty.$$

From

$$I'(t) = \beta_1 \frac{SI}{N} + \beta_1\delta\frac{IJ}{N} - (\mu+\gamma_1)I,$$

and $\frac{S}{N} \leqslant 1$, $\frac{I}{N} \leqslant 1$ it follows that

$$I'(t) \leqslant \beta_1 I + \beta_1\delta J - (\mu+\gamma_1)I.$$

Choose a sequence $t_n \to \infty$ such that $I(t_n) \to I^\infty$, and $I'(t_n) \to 0$ (see [31]), note that $J(t_n) \to 0$ as $t_n \to \infty$, then

$$0 \leqslant (\beta_1 - \mu - \gamma_1)I^\infty.$$

Since $\mathscr{R}_1(0) = \frac{\beta_1}{\mu+\gamma_1} < 1$, we have $I^\infty = 0$, therefore $\lim_{t\to\infty} I(t) = 0$.

Finally, we choose the sequences $t_n^1 \to \infty$, $t_n^2 \to \infty$ such that $S(t_n^1) \to S^\infty$, $S(t_n^2) \to S_\infty$, and $S'(t_n^1) \to 0$, $S'(t_n^2) \to 0$. Then, from the first equation in (5), noticing that $J(t)$, $I(t)$ and $F_1(t)$ go to 0 as $t \to \infty$, it follows that

$$0 \leqslant \Lambda - (\mu+\psi)S^\infty + (\psi - \psi\mu\mathscr{K}_0)S^\infty,$$
$$0 \geqslant \Lambda - (\mu+\psi)S_\infty + (\psi - \psi\mu\mathscr{K}_0)S_\infty.$$

So, we get

$$S^\infty = S_\infty = \frac{\Lambda}{\mu(1+\psi\mathscr{K}_0)},$$

and the proof is complete. □

The previous Theorem holds under condition (19), if it is not satisfied we can still prove local stability.

Theorem 3. *If*

$$\mathscr{R}_1(\psi) < 1 \quad \text{and} \quad \mathscr{R}_2(\psi) < 1, \tag{20}$$

then the disease free equilibrium E_0 *is locally stable. If* (20) *is not true* E_0 *is unstable.*

Proof. Taking the linearization of system (5) at the point E_0, we get the following characteristic equation

$$\begin{vmatrix} \lambda+(\mu+\psi)-\widehat{K}_1(\lambda) & \dfrac{\beta_1}{1+\psi\mathscr{K}_0}-\gamma_1 & \dfrac{\beta_2}{1+\psi\mathscr{K}_0}-\gamma_2 \\ 0 & \lambda+\mu+\gamma_1-\dfrac{\beta_1}{1+\psi\mathscr{K}_0} & 0 \\ 0 & 0 & \lambda+(\mu+\gamma_2)-\dfrac{\beta_2}{1+\psi\mathscr{K}_0} \end{vmatrix} = 0.$$

where $\widehat{K}_1(\lambda)$ denotes the Laplace transform of $K_1(\theta)$. This equation is equivalent to

$$[\lambda-(\mu+\gamma_1)(\mathscr{R}_1(\psi)-1)][\lambda-(\mu+\gamma_2)(\mathscr{R}_2(\psi)-1)][\lambda+\mu+\psi-\widehat{K}_1(\lambda)]=0.$$

We see that if $\mathscr{R}_1(\psi)>1$ or $\mathscr{R}_2(\psi)>1$, then at least one solution of this equation has a positive real part, so E_0 is unstable.

If $\mathscr{R}_1(\psi)<1$ and $\mathscr{R}_2(\psi)<1$, then all the solution of the characteristic equation have negative real parts if all the roots of the equation

$$\lambda+\mu+\psi-\widehat{K}_1(\lambda)=0, \tag{21}$$

have negative real parts.

Let $\Re\lambda \geqslant 0$ then we have

$$|\widehat{K}_1(\lambda)| = \left|\psi\int_0^\infty \alpha(\theta)\mathrm{e}^{-\lambda\theta}\mathrm{e}^{-\mu\theta}\mathrm{e}^{-\int_0^\theta \alpha(\tau)\,\mathrm{d}\tau}\,\mathrm{d}\theta\right| < \psi\int_0^\infty \alpha(\theta)\mathrm{e}^{-\int_0^\theta \alpha(\tau)\,\mathrm{d}\tau}\,\mathrm{d}\theta = \psi,$$

but also

$$|\lambda+\mu+\psi| \geqslant \mu+\psi > \psi$$

so that λ cannot be a root of (21). From which we conclude that under (20) all the roots of (21) have non-negative real parts. This completes the proof. □

The theorem below says that each strain can dominate if its reproduction number is larger than one and the other strain cannot invade its equilibrium.

Theorem 4. *The one strain exclusive equilibria satisfy*:

(a) *If* $\mathscr{R}_1(\psi)>1$, *the boundary equilibrium* E_1 *is stable for* $\mathscr{R}_2^1(\psi)<1$ *and unstable for* $\mathscr{R}_2^1(\psi)>1$.
(b) *If* $\mathscr{R}_2(\psi)>1$, *the boundary equilibrium* E_2 *is stable for* $\mathscr{R}_1^2(\psi)<1$ *and unstable for* $\mathscr{R}_1^2(\psi)>1$.

Proof. Let $\mathscr{R}_1(\psi)>1$. Then the equilibrium E_1 exists and the linearization of (5) at E_1 gives the following characteristic equation:

$$\begin{vmatrix} \lambda+\pi_1+\mu+\psi-\widehat{K}_1(\lambda) & \mu & \dfrac{\beta_2}{\mathscr{R}_1(0)}-\gamma_2 \\ -\pi_1 & \lambda & -\delta\pi_1 \\ 0 & 0 & \lambda-(\mu+\gamma_2)(\mathscr{R}_2^1(\psi)-1) \end{vmatrix} = 0, \tag{22}$$

where $\pi_1 = \beta_1(1 - \frac{1}{\mathscr{R}_1(\psi)}) > 0$. One of the roots of this equation is

$$\lambda_1 = (\mu + \gamma_2)(\mathscr{R}_2^1(\psi) - 1)$$

so that, if $\mathscr{R}_2^1(\psi) > 1$ then E_1 is unstable. If instead $\mathscr{R}_2^1(\psi) < 1$ then λ_1 is negative and we have to examine the other two roots of (22) that are given by the equation

$$\lambda^2 + (\lambda + \mu)\pi_1 + \lambda(\mu + \psi - \widehat{K}_1(\lambda)) = 0. \tag{23}$$

Using (4) we have that

$$\widehat{K}_1(\lambda) = \psi - (\lambda + \mu)\psi\widehat{K}_0(\lambda), \tag{24}$$

so that (23) can be written as

$$(\lambda + \mu)[\lambda + \pi_1 + \lambda\psi\widehat{K}_0(\lambda)] = 0. \tag{25}$$

Thus we have another negative root $\lambda_2 = -\mu$ and we are left with the square bracked factor in (25). Using again (24) we need to check the roots of

$$\lambda + \pi_1 + \psi = \widehat{K}_1(\lambda) + \mu\psi\widehat{K}_0(\lambda). \tag{26}$$

Now, if λ is such a root and $\Re\lambda \geqslant 0$, we have

$$\psi < \pi_1 + \psi \leqslant |\lambda + \pi_1 + \psi| = \left|\widehat{K}_1 + \mu\psi\widehat{K}_0(\lambda)\right| \leqslant \mathscr{K}_1 + \mu\psi\mathscr{K}_0 = \psi, \tag{27}$$

where we have used (7). In conclusion, all the roots of (22) have negative real part. Finally, concerning part (b), we note that it can be proved in the same way as we proved part (a). □

Finally we analyze stability of coexistence equilibrium. First we adopt the following condition

$$\beta_1\gamma_2 = \beta_2\gamma_1. \tag{28}$$

We have

Theorem 5. *Assume* $\delta\beta_1 + \gamma_2 - \gamma_1 > 0$, $\mathscr{R}_1^2(\psi) > 1$, $\mathscr{R}_2^1(\psi) > 1$ *and* (28). *Then* E_* *is stable.*

Proof. We note first that if $\mathscr{R}_2^1(\psi) > 1$ we necessarily have $\mathscr{R}_2(0) > \mathscr{R}_1(0)$ that, together with (28), implies $\beta_2 > \beta_1$ and $\gamma_2 > \gamma_1$. Thus we are under the assumptions of item (iv) of Theorem 1 and the equilibrium E_* exists. The linearization of (5) at this point gives the following characteristic equation

$$\begin{vmatrix} \lambda + \beta_1 i^* + \beta_2 j^* + (\mu + \psi) - \widehat{K}_1(\lambda) & \beta_1 s^* - \gamma_1 & \beta_2 s^* - \gamma_2 \\ -\beta_1 i^* & \lambda - \beta_1 s^* - \beta_1\delta j^* + \mu + \gamma_1 & -\beta_1\delta i^* \\ -\beta_2 j^* & \beta_1\delta j^* & \lambda - \beta_2 s^* + \beta_1\delta i^* + \mu + \gamma_2 \end{vmatrix} = 0,$$

where in order to simplify the notations, we have set $i^* = \frac{I^*}{N}$, $j^* = \frac{J^*}{N}$, $s^* = \frac{S^*}{N}$. Now, manipulating the determinant and using (6), the above equation is equivalent to

$$\begin{vmatrix} \lambda+\mu+\psi-\widehat{K}_1(\lambda) & \lambda+\mu & \lambda+\mu \\ -\beta_1 i^* & \lambda & -\beta_1\delta i^* \\ -\beta_2 j^* & \beta_1\delta j^* & \lambda \end{vmatrix} = 0$$

and, using (24), it is equivalent to

$$(\lambda+\mu)\begin{vmatrix} 1+\psi\widehat{K}_0(\lambda) & 0 & 1 \\ -\beta_1 i^* & \lambda+\beta_1\delta i^* & -\beta_1\delta i^* \\ -\beta_2 j^* & -\lambda+\beta_1\delta j^* & \lambda \end{vmatrix} = 0. \tag{29}$$

Now, since we have the root $\lambda = -\mu$, we are left with the analysis of

$$(1+\psi\widehat{K}_0(\lambda))(\lambda^2+(\beta_1\delta)^2 i^* j^*)+\lambda(\beta_1 i^*+\beta_2 j^*)+(\beta_2-\beta_1)\beta_1\delta i^* j^* = 0, \tag{30}$$

that, since $(\lambda+\mu)\psi\widehat{K}_0(\lambda) = \psi - \widehat{K}_1(\lambda)$, can be rewritten as

$$\widehat{K}_1(\lambda) = (\beta_1 i^*+\beta_2 j^*)\times\frac{\lambda+B}{\lambda^2+A}(\lambda+\mu)+\lambda+\mu+\psi, \tag{31}$$

where

$$A = (\beta_1\delta)^2 i^* j^*, \quad B = \frac{(\beta_2-\beta_1)\beta_1\delta i^* j^*}{(\beta_1 i^*+\beta_2 j^*)} \tag{32}$$

We note here that the condition $\beta_1\gamma_2 = \beta_2\gamma_1$ implies $B = \frac{A}{\mu}$. This is a key observation in the proof of stability. Furthermore, if $Re\,\lambda \geqslant 0$, it is easy to see that

$$|\widehat{K}_1| < \psi.$$

Let $Re\,\lambda \geqslant 0$, if we can prove the real parts of

$$Z := \frac{\lambda+B}{\lambda^2+A}(\lambda+\mu)$$

is non-negative, then

$$\left|(\beta_1 i^*+\beta_2 j^*)\times\frac{\lambda+B}{\lambda^2+A}(\lambda+\mu)+\lambda+\mu+\psi\right| \geqslant \mu+\psi,$$

therefore, (31) has no roots with non-negative real parts, and we complete the proof of this theorem. Letting $\lambda = x+\mathrm{i}y$, $x \geqslant 0$, we have

$$\begin{aligned} Re\,Z &= Re\left\{\frac{\lambda+B}{\lambda^2+A}(\lambda+\mu)\right\} = Re\left\{\frac{x+B+\mathrm{i}y}{x^2-y^2+A+2xy\mathrm{i}}(x+\mu+\mathrm{i}y)\right\} \\ &= Re\left\{\frac{(x+\frac{A}{\mu}+\mathrm{i}y)(x^2-y^2+A-2xy\mathrm{i})(x+\mu+\mathrm{i}y)}{(x^2-y^2+A)^2+4x^2y^2}\right\} \end{aligned}$$

$$= \frac{(y^2 - A)^2 + [2x^2 + (\mu + \frac{A}{\mu})x]y^2 + x^4 + (\mu + \frac{A}{\mu})x^3 + 2Ax^2 + (A\mu + \frac{A^2}{\mu})x}{(x^2 - y^2 + A)^2 + 4x^2y^2}$$

$$\geqslant 0.$$

This completes the proof. □

The proof of the previous result has been carried through assuming the special condition (28) that is needed to be technically able to handle the characteristic equation (31). The general case seems difficult to analyze. Another special case for which it is simple to draw a conclusion is the case of $\alpha(\theta) = \alpha$(constant), i.e. the case when the protection from the vaccination decays at a constant rate. In fact with this assumption we have

$$\widehat{K}_0(\lambda) = \int_0^\infty e^{-\lambda\theta} e^{-\mu\theta} e^{-\int_0^\theta \alpha(\tau)\,d\tau}\,d\theta = \int_0^\infty e^{-(\lambda+\mu+\alpha)\theta}\,d\theta = \frac{1}{\lambda+\mu+\alpha}.$$

and the characteristic equation (31) can be rewritten as

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{33}$$

where

$$a_1 = \mu + \alpha + \psi + (\beta_1 i^* + \beta_2 j^*),$$

$$a_2 = (\beta_1\delta)^2 i^* j^* + (\beta_1 i^* + \beta_2 j^*)(\mu + \alpha) + (\beta_2 - \beta_1)\beta_1\delta i^* j^*,$$

$$a_3 = (\beta_1\delta) i^* j^* (\mu + \alpha)[\beta_2 - \beta_1 + \beta_1\delta(1 + \psi\mathscr{K}_0)].$$

and (in view of Routh–Hurwitz Criteria)

$$\begin{aligned} a_1a_2 - a_3 &= (\beta_1 i^* + \beta_2 j^*)(\mu + \alpha + \psi)(\mu + \alpha) + (\beta_2 - \beta_1)\beta_1\delta i^* j^*\psi + (\beta_1 i^* + \beta_2 j^*)[(\beta_1\delta)^2 i^* j^* \\ &\quad + (\beta_1 i^* + \beta_2 j^*)(\mu + \alpha) + (\beta_2 - \beta_1)\beta_1\delta i^* j^*] \\ &> 0. \end{aligned}$$

In fact we see that, if $\beta_2 > \beta_1$, then all these expression are positive and consequently (33) has only roots with negative real parts. Thus we have the additional result:

Theorem 6. *Assume* $\delta\beta_1 + \gamma_2 - \gamma_1 > 0$, $\mathscr{R}_1^2(\psi) > 1$ *and* $\mathscr{R}_2^1(\psi) > 1$. *If* $\alpha(\theta) \equiv \alpha$ *and* $\beta_2 > \beta_1$, *then* E_* *is stable.*

However, the condition $\beta_2 > \beta_1$ does not necessarily occur within the situation envisaged in (iv) of Theorem 1 and, though a_1 and a_3 are always positive, a_2 and/or $(a_1a_2 - a_3)$ may be negative for some values of the parameters. In this case, E^* may lose its stability by Hopf bifurcation. In fact, in Fig. 1 we show some numerical simulation showing existence of periodic solutions. The picture shows the ratios $\frac{I(t)}{N}$ and $\frac{J(t)}{N}$ as a function of time, when the parameters are chosen as indicated in the figure captions.

We note that with this values of the parameters all the conditions of (iv) in Theorem 1 are fulfilled with a_2 and $a_1a_2 - a_3$ negative. Actually, for higher values of the vaccination rates ψ, keeping the values of the other parameters fixed, the coexistence state may become asymptotically stable, as we may see in Fig. 2 where damped oscillations of the strain J are shown.

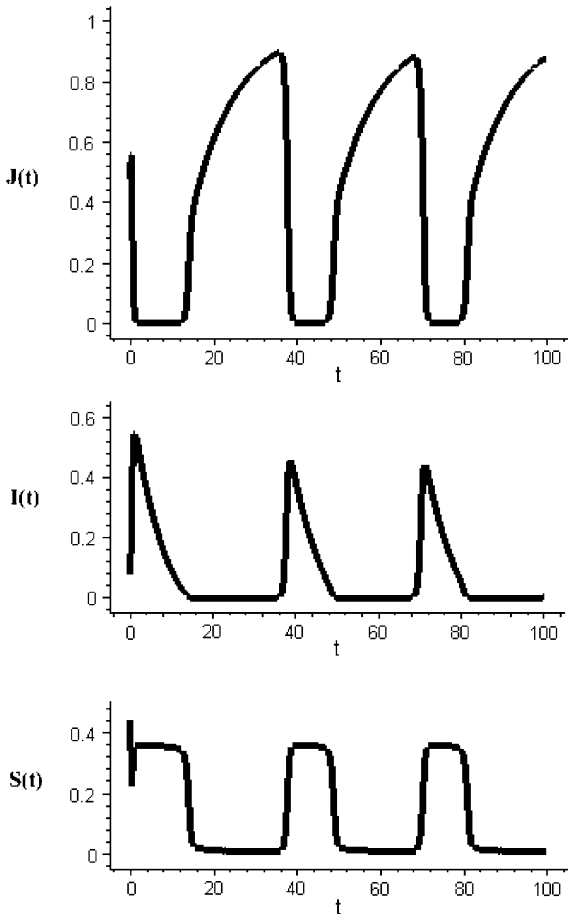

Fig. 1. The case of a constant $\alpha(\theta)$. The parameters of the simulation are $\mu = 0.01$, $\alpha = 0.01$, $\beta_1 = 5.5$, $\beta_2 = 1.8$, $\delta = 0.5$, $\gamma_1 = 1.5$, $\gamma_2 = 0.02$, $\psi = 0.1$.

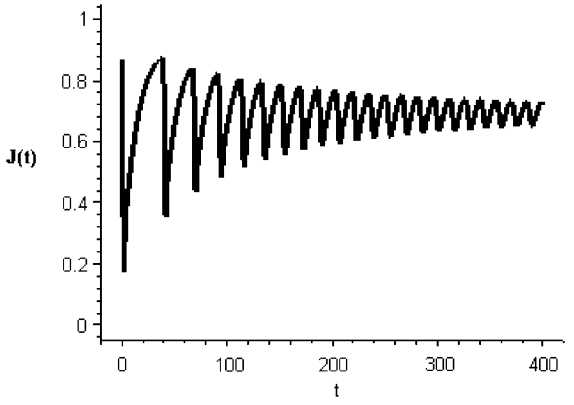

Fig. 2. The case of a constant $\alpha(\theta)$. Here $\psi = 0.35$. The other parameters are chosen as in Fig. 1.

Some more comments should be set forward concerning the case of a non-constant $\alpha(\theta)$. In fact, in this case additional effects may occur, due to a non-exponential kernel $K_0(\theta)$. Adopting the following form for $\alpha(\theta)$

$$\alpha(\theta) = \begin{cases} 0 & \text{if} \quad \theta \leqslant \theta^* \\ \alpha_0 & \text{if} \quad \theta > \theta^*, \end{cases} \tag{34}$$

we may investigate stability as a function of θ^*. In Fig. 3 we show stabilization of the coexistence equilibrium due to large values of θ^*. All the values of the parameters are the same as in the previous examples but for ψ. In fact, since the model actually depends on the product $\psi\mathscr{K}_0$, more than on ψ alone, it is significant to keep this product constant while changing θ^*.

The previous considerations and simulations show that the model may present a complicated dynamics and that existence and stability of equilibria may considerably change with the vaccination rate. A complete detailed exploration of the model goes beyond our purposes in this paper, but we will devote next section to present two particular scenarios that illustrate how vaccination may influence the two strains dynamics.

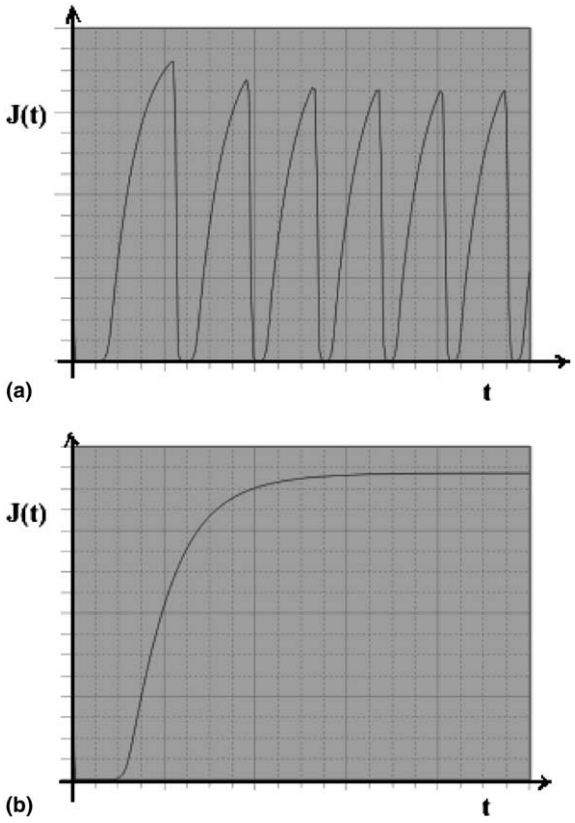

Fig. 3. The case of $\alpha(\theta)$ as given in (34). Here $\mu = 0.01$, $\beta_1 = 5.5$, $\beta_2 = 1.8$, $\delta = 0.5$, $\gamma_1 = 1.5$, $\gamma_2 = 0.02$, $\alpha = 0.01$, $\psi\mathscr{K}_0 = 6$. Case (a) $\theta^* = 0$. Case (b) $\theta^* = 20$.

5. The role of vaccination in the competitive exclusion and coexistence of the strains

In this section we investigate the role that vaccination plays in the dynamical behavior of the system. We will be concerned with the case $\gamma_1 = \gamma_2 = 0$ as this case simplifies the computations without significantly changing the outcomes. In addition, we know from Theorem 5 that the coexistence equilibrium is stable whenever it exists.

Since the stability of the dominance equilibria and the coexistence equilibrium depend on the invasion reproduction numbers, we find vaccination levels ψ_1^* and ψ_2^* such that $\mathscr{R}_1^2(\psi_1^*) = 1$ and $\mathscr{R}_2^1(\psi_2^*) = 1$. Thus,

$$\psi_1^* = \frac{1}{\mathscr{K}_0}\left[\mathscr{R}_2(0) - 1 - \frac{\beta_2 - \beta_1}{\beta_1 \delta}\right] \quad \psi_2^* = \frac{1}{\mathscr{K}_0}\left[\mathscr{R}_1(0) - 1 - \frac{\beta_2 - \beta_1}{\beta_1 \delta}\right]. \tag{35}$$

As $\mathscr{R}_1^2(\psi)$ is a decreasing function of ψ we have that

$$\mathscr{R}_1^2(\psi) > 1 \quad \text{if and only if} \quad \psi < \psi_1^*.$$

On the other hand since $\mathscr{R}_2^1(\psi)$ is an increasing function of ψ we have that

$$\mathscr{R}_2^1(\psi) > 1 \quad \text{if and only if} \quad \psi > \psi_2^*.$$

We also use the vaccination levels ψ^* and ψ^{**} such that $\mathscr{R}_1(\psi^*) = 1$ and $\mathscr{R}_2(\psi^{**}) = 1$. The vaccination levels ψ^* and ψ^{**} are as follows

$$\psi^* = \frac{1}{\mathscr{K}_0}[\mathscr{R}_1(0) - 1] \quad \psi^{**} = \frac{1}{\mathscr{K}_0}[\mathscr{R}_2(0) - 1] \tag{36}$$

We note that some of the vaccination levels defined above may not be feasible because they may not be positive. In correspondence of different values of the levels many situations may occur, we will consider two significant cases.

The case $\mathscr{R}_1(0) > \mathscr{R}_2(0) > 1$.

In this case we also have $\mathscr{R}_1(\psi) > \mathscr{R}_2(\psi)$ for all ψ. We know that here there is no coexistence and competitive exclusion is the ultimate outcome. Since in this case we must have $\beta_1 > \beta_2$ then

$$\psi^* < \psi_2^* \quad \psi^{**} < \psi_1^*$$

which, in particular, means that ψ_1^* and ψ_2^* are positive. From the second inequality we see that, by Theorem 4, E_2 exists only when $\psi < \psi^{**}$ because $\mathscr{R}_2(\psi) > 1$, but it is unstable because $\mathscr{R}_1^2(\psi) > 1$. In addition, we have $\psi_1^* < \psi_2^*$ and $\psi^{**} < \psi^*$. Consequently, we have

$$\psi^{**} < \psi^* < \psi_2^*$$

and ψ_1^* is either in the interval (ψ^{**}, ψ^*) or in the interval (ψ^*, ψ_2^*) but that does not have any impact on the outcome. Thus, we have that for vaccination strategies ψ satisfying $0 \leqslant \psi < \psi^{**}$, equilibria E_0, E_1 and E_2 exist but only E_1 is locally stable ($\mathscr{R}_2^1(\psi) < 1$). Therefore, strain one outcompetes strain two and establishes itself in the population while strain two vanishes. If vaccination is increased further, that is $\psi^{**} < \psi < \psi^*$, then only equilibria E_0 and E_1 exist and only E_1 is locally stable. Consequently, strain one is again the one that dominates. For sufficiently large vaccination strategies, that is $\psi^* < \psi$, only E_0 exists and is stable and the disease is eradicated from the population. We summarize these observations in the proposition:

Proposition 1. *Assume $\mathscr{R}_1(0) > \mathscr{R}_2(0) > 1$. Then, for sufficiently low vaccination strategies, that is vaccination strategies ψ that satisfy $\psi < \psi^*$ only the equilibrium E_1 is stable and the disease establishes itself as strain I. On the other hand, for sufficiently high vaccination strategies, that is vaccination strategies satisfying $\psi > \psi^*$, only E_0 exists and is locally stable and the disease vanishes from the population.*

This result is hardly surprising as strain I is the 'stronger' strain since it can infect even people infected with strain two. Thus, if it dominates in the absence of vaccination it continues to dominate at sufficiently low vaccination levels.

Next we consider the more interesting case

The case $\mathscr{R}_2(0) > \mathscr{R}_1(0) > 1$.

In this case we also have $\mathscr{R}_2(\psi) > \mathscr{R}_1(\psi)$ for all ψ which implies that $\psi^* < \psi^{**}$. Here we may have coexistence as well as competitive exclusion of each strain by the other. First, we notice that

$$\psi_1^* < \psi^{**} \quad \psi_2^* < \psi^*$$

and also

$$\psi_2^* < \psi_1^*.$$

From their respective formulas in (35) we conclude that ψ_1^* and ψ_2^* are not necessarily non-negative. Depending on whether none of them is non-negative, ψ_1^* is non-negative or both are non-negative different outcomes of the competition of the strains are possible.

If $\psi_1^* < 0$ then $\mathscr{R}_1^2(\psi) < 1$ and $\mathscr{R}_2^1(\psi) > 1$ for all ψ, that is strain one cannot invade an equilibrium of strain two but strain two can invade an equilibrium of strain one. Therefore, there is no coexistence equilibrium. For $\psi < \psi^*$, equilibria E_0, E_1 and E_2 exist but only E_2 is locally stable. Consequently, strain two outcompetes strain one and establishes itself in the population. For $\psi^* < \psi < \psi^{**}$ only equilibria E_0 and E_2 exists and E_2 is locally stable. Thus disease stays in the population with strain J. For sufficiently high vaccination strategies, satisfying $\psi > \psi^{**}$ only E_0 exists and is stable. This suggests extinction of the disease.

We summarize this result in the proposition:

Proposition 2. *Assume $\mathscr{R}_2(0) > \mathscr{R}_1(0) > 1$ and $\psi_1^* < 0$. Then, for sufficiently low vaccination strategies, that is vaccination strategies ψ that satisfy $\psi < \psi^{**}$ only the equilibrium E_2 is stable and the disease establishes itself as strain J. On the other hand, for sufficiently high vaccination strategies, that is vaccination strategies satisfying $\psi > \psi^{**}$, only E_0 exists and is locally stable and the disease vanishes from the population.*

If $\psi_2^* < 0 < \psi_1^*$ then $\mathscr{R}_2^1(\psi) > 1$ for all ψ but $\mathscr{R}_1^2(\psi) > 1$ if $\psi < \psi_1^*$ and $\mathscr{R}_1^2(\psi) < 1$ otherwise. Since $\mathscr{R}_2^1(\psi) > 1$ equilibrium E_1 is unstable whenever it exists. Since $\beta_2 > \beta_1$, we have

$$0 < \psi_1^* < \psi^{**} \tag{37}$$

and ψ^* can be in the interval $(0, \psi_1^*)$ or in the interval (ψ_1^*, ψ^{**}). The position of ψ^* changes when E_1 exists but since E_1 is unstable whenever it exists, it doesn't change significantly the dynamical behavior of the system. Consequently, we consider only the two significant intervals for the vaccination strategies ψ given in (37). For vaccination strategies ψ satisfying $0 \leqslant \psi < \psi_1^*$, equilibria E_0, E_1 (possibly for only part of the interval), E_2 and E_* exist but only E_* is locally stable. There-

fore, the two strains coexist in the population. If vaccination levels are increased further, that is $\psi_1^* < \psi < \psi^{**}$, then equilibria E_0 and E_2 exist (E_1 may exist only for part of the interval) but only E_2 is locally stable. Consequently, strain two eliminates strain one and is the one that dominates. For sufficiently large vaccination strategies, that is $\psi^{**} < \psi$, only E_0 exists and is stable and the disease is eradicated from the population. Here we already see that vaccination has a significant impact on the coexistence and competition of strains. In particular, for low vaccination levels there is coexistence, for somewhat higher vaccination levels strain two eliminates strain one and for high levels of vaccination the disease is eradicated as a whole.

We summarize these observations in the proposition:

Proposition 3. *Assume $\mathscr{R}_2(0) > \mathscr{R}_1(0) > 1$ and $\psi_2^* < 0 < \psi_1^*$. Then, for sufficiently low vaccination levels, that is vaccination levels ψ that satisfy $\psi < \psi_1^*$ only the equilibrium E_* is stable and the disease establishes itself with both strains I and J. For medium vaccination levels, that is vaccination levels satisfying $\psi_1^* < \psi < \psi^{**}$, only equilibrium E_2 is locally stable and the disease establishes itself in the population with strain J. Strain I is eliminated. Finally, for sufficiently high vaccination strategies, that is vaccination strategies satisfying $\psi > \psi^{**}$, only E_0 exists and is locally stable and the disease vanishes from the population.*

We conclude with the case $0 < \psi_2^*$ which leads to the most complex impact of vaccination on the competitive exclusion and coexistence of the two strains. With these parameters both invasion reproduction numbers can change their relation to one. In particular, we have that $\mathscr{R}_1^2(\psi) > 1$ if $\psi < \psi_1^*$ and $\mathscr{R}_1^2(\psi) < 1$ otherwise. We also have that $\mathscr{R}_2^1(\psi) > 1$ if $\psi > \psi_2^*$ and $\mathscr{R}_2^1(\psi) < 1$ otherwise. In addition,

$$0 < \psi_2^* < \psi_1^* < \psi^{**}$$

and ψ^* can be either in the interval (ψ_2^*, ψ_1^*) or in the interval (ψ_1^*, ψ^{**}) but as we see later the exact position of ψ^* does not change the dynamical outcome. Consequently, we consider three significant intervals for the vaccination strategy. In particular, for low vaccination levels, or more precisely, vaccination levels ψ satisfying $0 \leqslant \psi < \psi_2^*$ we have that equilibria E_0, E_1 and E_2 exists but only equilibrium E_1 is locally stable as $\mathscr{R}_2^1(\psi) < 1$ here. Thus, for low vaccination levels strain one outcompetes strain two and dominates in the population (see Fig. 4). If the vaccination is increased beyond ψ_2^*, that is for vaccination levels $\psi_2^* < \psi < \psi_1$, equilibria E_0, E_2 and E_* exists as well as E_1 at least for a part of that interval. However, from Theorem 5 it follows that E_* is stable whenever it exists, thus E_* is locally stable.

The remaining equilibria are unstable since both invasion reproduction numbers are larger than one. In this case the two strains coexist in the population (see Fig. 5). If the vaccination levels are increased even further and beyond ψ_1^*, that is vaccination levels are in the interval $\psi_1^* < \psi < \psi^{**}$, then the coexistence equilibrium E_* does not exist any more as $\mathscr{R}_1^2(\psi) < 1$. The equilibria E_0, E_2 exist and possibly E_1 for a part of that interval but only E_2 is locally stable. Thus for these vaccination levels strain two eliminates strain one and establishes itself in the population (see Fig. 6). Finally, if vaccination is increased even further, that is $\psi > \psi^{**}$ then only E_0 exists and is stable and the disease disappears from the population. As we see for these parameter values in absence of vaccination, strain one will dominate. However, introducing vaccination and varying its level has a very dramatic effect on the competition between the strains. Namely, for low vaccination level, strain one continues to dominate, for medium-low vaccination levels, the two strains coexist,

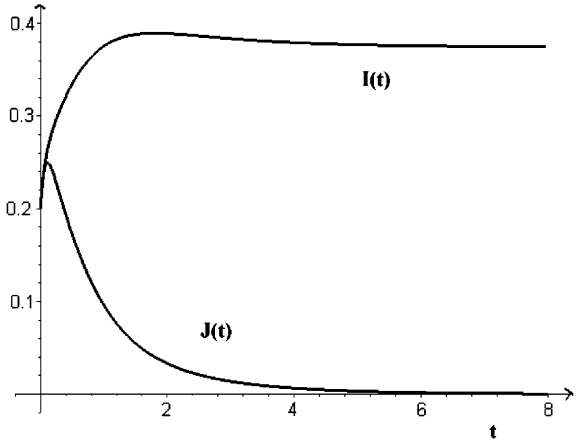

Fig. 4. For low vaccination levels, that is $\psi = 1.5$, strain I eliminates strain J and dominates in the population. The remaining parameters of the simulation are $\beta_1 = 2$, $\beta_2 = 3$, $\mu = 0.5$, $\alpha = 0.5$, $\gamma_1 = \gamma_2 = 0$, $\delta = 0.5$.

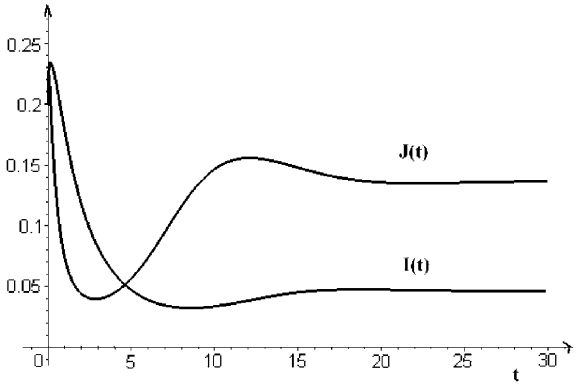

Fig. 5. For medium-low vaccination levels, that is $\psi = 3.5$, strain J invades the equilibrium of strain I and the two strains coexist. The remaining parameters of the simulation are as in Fig. 4. We note that strain I persists in the population despite that its vaccine-dependent reproduction number is $\mathscr{R}_1(\psi) = \frac{8}{9} < 1$. Strain J has the higher reproduction number and higher prevalence.

for medium-high vaccination levels strain two eliminates strain one, and for high vaccination levels the disease is eradicated. This behavior is a result of the fact that vaccination decreases the invasion capabilities of the first strain but increases the invasion capabilities of the second strain which leads to substituting the first strain with the second.

We summarize our findings in the proposition:

Proposition 4. *Assume $\mathscr{R}_2(0) > \mathscr{R}_1(0) > 1$ and $\psi_2^* > 0$. Then, for sufficiently low vaccination levels, that is vaccination levels ψ that satisfy $0 \leqslant \psi < \psi_2^*$ only equilibrium E_1 is stable and strain one dominates in the population. For medium-low vaccination levels satisfying $\psi_2^* < \psi < \psi_1^*$ only the*

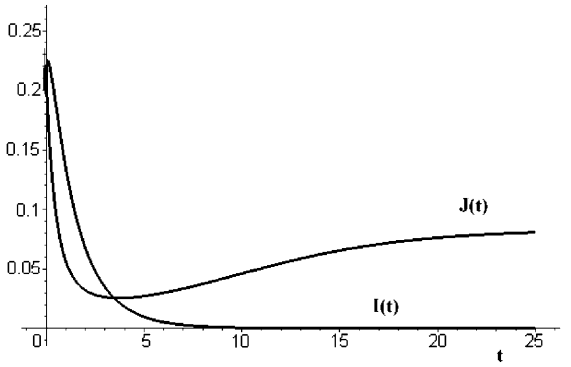

Fig. 6. For medium-high vaccination levels, that is $\psi = 4.5$, strain J eliminates strain I and dominates in the population. Thus, vaccination enables the weaker strain J to replace the stronger strain I in the population. The parameters of the simulation are the same as in Fig. 4.

equilibrium E_* is stable and the disease establishes itself with both strains I and J. For medium-high vaccination levels, that is vaccination levels satisfying $\psi_1^* < \psi < \psi^{**}$ only equilibrium E_2 is locally stable and the disease establishes itself in the population with strain J. Thus strain J eliminates strain I. Finally, for sufficiently high vaccination strategies, that is vaccination strategies satisfying $\psi > \psi^{**}$, only E_0 exists and is locally stable and the disease vanishes from the population.

6. Discussion

In this paper we consider the development and evolution of a disease represented by two strains. We have assumed that the first pathogen can infect individuals already infected by the second, a process called super-infection, while the other way around has such a small incidence that it can be neglected. Altogether, this makes the first strain stronger. Thus, if $\mathscr{R}_1(0) > \mathscr{R}_2(0)$ the first strain dominates. The outcome of the competition between the strains when $\mathscr{R}_1(0) < \mathscr{R}_2(0)$ depends on the two invasion reproduction numbers: the invasion reproduction number of the first strain at equilibrium of the second $\mathscr{R}_1^2(0)$ and the invasion reproduction number of the second strain in the equilibrium of the first $\mathscr{R}_2^1(0)$. If $\mathscr{R}_2^1(0) < 1$ then strain one dominates, if $\mathscr{R}_1^2(0) < 1$ then strain two dominates, if both invasion reproduction numbers are larger than one, then the two strains coexist.

The population described in the model is subjected to vaccination. In the case considered here vaccination can reduce both reproduction numbers to zero and, applied at sufficiently high levels, it can eliminate the disease. It has been observed in previous studies and in practice that vaccination can have a very dramatic effect on the outcome of the competition between the two strains. In some cases it can lead to replacement of one of the pathogens by the other. The main mechanism responsible for the pathogen replacement is indicated to be the fact that the vaccine is not equally efficient with respect to both strains. Vaccination suppresses one of the micro-organisms more than the other, therefore giving opportunity to the second to outcompete and eliminate the first. This process leads to replacement of the first strain by the second. The uneven effect of the vaccine

on the two strains is expressed in the fact that vaccination reduces the two reproduction numbers to a different extent, often leading to a change in the relation between them [23,18].

In this article we are interested in the best case scenario – that is the case when the vaccine provides perfect protection to both strains. Thus, at first sight, the vaccine does not favour any strain and common sense implies that it should not promote replacement. As our discussion shows, however, the impact of the mutual influence of vaccination and the mechanism of interaction of the two strains is much more complicated. One of the outcomes is that the vaccine decreases the invasion reproduction number of the first strain but increases the invasion reproduction number of the second strain. Hence, the vaccine favours the second strain and promotes its dominance. This lack of symmetry seems to follow from the super-infection and we do not expect that it occurs in coinfection. As a result we observe that if in the absence of vaccination only the first strain dominates but $\mathscr{R}_2(0) > \mathscr{R}_1(0) > 1$, as the vaccination levels are increased, the vaccine at first promotes the coexistence of the two strains, and for higher vaccination levels leads to the elimination of strain one and the dominance of strain two. Consequently the vaccine can enable the replacement of the first strain by the second even when vaccination provides perfect protection with respect to both strains.

If strain one is the dominant strain in the absence of vaccination and $1 < \mathscr{R}_1(0) < \mathscr{R}_2(0)$, then the vaccination threshold necessary for the elimination of strain one in the presence of the competition of strain two is ψ_1^* while the vaccination threshold necessary for the elimination of strain one in the absence of the competition of strain two is ψ^*. Since $\psi_1^* < \psi^*$ if and only if $\delta\mathscr{R}_1(0) < 1$, the threshold for elimination of the stronger strain in the presence of the weaker strain is lower if infection with the weaker strain makes infection with the stronger strain much less likely, that is in the context of strong competition between the strains. On the other hand if the competition between the two strains is weak, that is $\delta\mathscr{R}_1(0) > 1$, and particularly when infection with the second strain facilitates infection with the first strain, then $\psi^* < \psi_1^*$ and the threshold for elimination of the first strain in the absence of competition by the second strain is lower. In this situation the presence of the second strain facilitates the existence of the first strain even when its vaccine-dependent reproduction number is below one $\mathscr{R}_1(\psi) < 1$. The two strains share a mutually beneficial relationship.

Looking at the proportions of the two strains i^* and j^* in the coexistence equilibrium we see that, in the case when $\gamma_1 = \gamma_2 = 0$, increasing the vaccination levels decrease i^* but increase j^*. The ratio of the rate of decrease of i^* and the rate of increase of j^*, taken with absolute values, is given by the ratio of the two reproduction numbers in the absence of vaccination $\mathscr{R}_2(0)$: $\mathscr{R}_1(0)$. As $\mathscr{R}_2(0) > \mathscr{R}_1(0)$ infected individuals with strain I at equilibrium experience a larger drop as a result of vaccination than the raise that is achieved by those infected by strain J at equilibrium. This observation was first made in [18] and has been used as a key observation potentially leading to an explanation why in reality vaccination leads to serotype replacement in some pathogens but not in others [18,19].

Studies on the impact of vaccination on competing pathogens have pointed out the complex interactions between two pathogens and the critical impact that vaccination has on these interaction. The different degree of protection that the vaccine offers with respect to the two micro-organisms is the key mechanism that leads to that complex behavior in all those studies. Here we show, that even if we can create vaccines with perfect efficacy, the possibility that they will promote strain replacement and subthreshold coexistence of the strains still exists.

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