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Modelling the effects of temporary immune protection and vaccination against infectious diseases ☆

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Abstract

In this paper, we develop a mathematical model to describe the dynamics of reinfection under the assumption that immune protection may wane over time. As a disease control strategy a schedule of primary and secondary (booster) vaccination is studied, with vaccine induced immunity declining over time. A distinction is made between infection in immunological naive individuals (primary infection) and infection in individuals whose immune system has been primed by vaccination or infection (reinfection). Using the model we analyze the association between prevalence of infection and immunity, induced either by infection or by vaccine. The model shows that eradication depends on vaccination coverage as well as on vaccine efficacy.

Keywords: Epidemic model; Vaccination; Booster; Vaccination coverage; Immunological memory

1. Introduction

The basic question of how we acquire immunity has been investigated for a century or more. Even so, several concepts in immunology still remain unclear. For instance, it is known that the first exposure of an individual to an antigen elicits a primary response, the initial antigen response. The primary immune response combats the infection with the production of antibodies, which appears after a time lag of a few days. After recovering from an infection, the concentration of antibodies against the infectious agent gradually declines over time, but the individual is often still protected against a second occurrence of the disease. That is, the person is immune. When an individual is exposed to the same antigen for a second time, a much larger number of antibodies is produced quickly to combat the infection. The response elicited when the individual encounters the same antigen at a later time is the secondary immune response. This mechanism is possible because the primary immune response produces memory cells, which are specialized to mount an immune response against

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the same antigen. Memory is, therefore, a central characteristic of immune responses [27]; its advantages discussed so far include protection from reinfection, control of chronic infection, and the transfer of immune function to the next generation [30]. The exact process by which immunological memory evolves is not fully known. Immunological memory is defined as the duration of which hosts are protected from re [20] and provides the basis for the use of vaccines [28,29].

When individuals are immunized, the vaccine induces their immune system to respond and produce antibodies against the 'virus' in the vaccine. These antibodies then destroy the vaccine virus, but the immune system 'remembers' the virus so that it can fight off infection if the individual is ever exposed to the natural virus (the ones that cause the disease). Because the virus in the vaccine and the natural virus are very similar, the immune system responds to both. This means that if an immunized person is ever exposed to the circulating virus, the immune system responds immediately and large amounts of antibodies are produced to overcome the infection. The level of effectiveness varies with the different components of a vaccines. Also, it is not known exactly why some people do not respond well and develop immunity against a disease as intended.

One of the aim of vaccination programmes is to reduce the prevalence of an infectious disease and ultimately to eradicate it. In other words, the vaccination is a mechanism that attempts to lower the degree of susceptibility of healthy individuals against a particular pathogenic agent. Since this decrease of susceptibility occurs in a population, the overall effect of vaccination is to decrease the proportion of contacts with infected individuals. Thus, an efficient vaccination campaign acts to reduce the number of infectious individuals below its critical level. At the population level, one wishes to identify the critical vaccination rate necessary to eradicate the disease or prevent infection (epidemic outbreak). Hence, it is important to address the required level of intervention in order to eradicate disease, that is, the threshold at which the disease dies out.

Mathematical models of epidemics have been used to determine the ability of vaccines to control infectious diseases and to contribute to the understanding of the impact of vaccination programs [2,3,11,26,15–19,22]. These models discuss the effects of a single-dose vaccination schedule. Also, a few studies of mathematical models with multiple-dose vaccines are available in the literature [7,21]. In particular, Alexander et al. [1] developed a mathematical model for the transmission dynamics of some vaccine-preventable infectious disease, assuming that both recovered and booster vaccinated individuals become permanently immune to the disease. In the model presented here, it is assumed that the booster immunization as well as the natural infection induce only temporary immunity to the disease. Hence, both recovered and vaccinated individuals will never become permanently immune, since they are at risk of reinfection. But this reinfection will occur at a lower rate of infectiousness than those of the susceptible individuals who never have been either vaccinated or infected.

Our main assumption is that the transmission dynamics of a childhood disease in the presence of a preventive vaccine is such that immunity may wane in time, allowing recurrent infections. A mathematical model with multiple immunization schedules (two-dose vaccination) is proposed to show the effect of vaccine immunity waning in time on the dynamics of a disease that also fails to elicit lifelong protective immunity. A distinction is made between infection in immunologically naive individuals (primary infection) and infection in individuals whose immune system has been primed by vaccination or infection (secondary infection).

The dynamics of the model is governed by ordinary differential equations. This paper is organized as follows. In Section 2 we develop the model based on biological features of the transmission of diseases where both multiple immunization schedules and reinfection are in course; Section 3 presents the analysis of the trivial and the endemic equilibrium points, the study of the trivial point of the model is to addresses the question of whether single-dose vaccination could ever completely stop the spread of infection in a population; Section 4 presents the numerical results and epidemiological implications; finally, in Section 5 are the conclusion.

2. Formulation of the model

To build the model and set up the differential equation we divide the total population (N) into six classes. Namely, S_1', the naive susceptible individuals; V', the vaccinated individuals; I_1', the primary infectious individuals; S_2', the susceptible individuals that developed an immune response (by natural infection and primary vaccination) lost after a certain period of time and need second vaccine dose or may be reinfected; I_2', the secondary infectious individuals; and finally R', the recovered individuals. We will call S_1' a naive susceptible, and S_2' a susceptible individuals.

The model will include the vital dynamics, that is the natural mortality rate (μ) and the positive and constant recruitment rate μN so that it balances natural deaths, for the total population to be of constant size N. The interaction between the classes will be assumed as follows. The naive susceptible individuals (S_1') are rapidly shifted to the vaccinated class (V') by routine immunization at the rate υ_1. The naive susceptible individuals (S_1') may also become primary infectious (I_1') following the true mass-action incidence [14]. The incidence is the infection rate of susceptible individuals through their contacts with infectives, such that the number of primary infectious individuals (I_1') produced by adequate contacts is $\frac{\beta_1 S_1'(I_1'+I_2')}{N}$, where β_1 is the transmission coefficient of the disease at primary infection.

It is realistically assumed that the vaccine induces less protection than does the natural infection itself, and the immunity (induced in response to both vaccination and natural infection) may diminish over time resulting in a different class of susceptible individuals (S_2'). These susceptible individuals developed immunological memory since they already had contact with the virus either by vaccination or by disease (wild virus). These susceptible individuals had rid themselves from the antibodies against both wild and vaccine virus, but due to their immunological memory they are able to elicit very quickly an immune response, so their reinfection rate is lower rate than that of the naive susceptible individuals S_1'. In such a situation, the number of new infectious produced by adequate contacts is $\frac{\beta_2 S_2'(I_1'+I_2')}{N}$, where $\beta_2 = \sigma\beta_1$ is the transmission coefficient of the disease at reinfection and $0 \leqslant \sigma \leqslant 1$. Parameter σ illustrates the effect of immunological memory, so it is the factor that reduces the risk of reinfection (σ) measures the susceptibility to reinfection. In the case $\sigma = 0$, both vaccine and infection are totally effective, the immunological memory developed against reinfection does not wane over time, and our model reduces to an *SIRS* type model with vaccination; whereas $\sigma = 1$, implies that both vaccine and infection are totally useless to induce immunological memory. From now on we make the realistic assumption that both vaccination and infection elicit immune response, but they fail to offer long-lasting protection against reinfection, that is, $0 < \sigma < 1$.

Vaccine-induced and wild virus-induced (natural) immunity against infection are assumed to be lost at per-capita rates ρ_1 and ρ_2, respectively. Thus, ρ_1 is the rate at which the vaccine protection wanes and ρ_2 is the rate at which the natural protection wanes, with $\rho_1 > \rho_2$. The average duration of immune protection ($\mathscr{D}$) [30] acquired either by preventive vaccine or infection is $\mathscr{D}_1 = 1/\rho_1$, $\mathscr{D}_2 = 1/\rho_2$, respectively. This duration is predicted to evolve asymptotically towards infinity, but in reality it is of course finite, determined by reproductive tradeoffs not included in the model. We refer to this as the maximum memory outcome.

The model assumes that both primary and secondary infectious individuals (I_1' and I_2') recover with rate constants $\gamma_1 > 0$ and $\gamma_2 > 0$. The recovering period of the secondary infectious individuals is a little shorter than that of the primary one ($\gamma_1 < \gamma_2$). It is therefore plausible that in effect, secondary infected individuals will be more actively cleansing the pathogen than the primary infected individuals because the immunological memory responds faster and more strongly to new infections. The recovered individuals ($R\prime$) move back to class S_2' by waning protection both to natural infection and reinfection [10], however the susceptible individuals S_2' no longer move back to naive class S_1' because the immunological memory was induced and the immune system can remember the identity of a pathogen. Finally, we assume that individuals in S_2' class may either be revaccinated at rate υ_2 or become infectious again (I_2').

The transfer diagram of the temporary immunity model [8] is shown in Fig. 1.

The model is governed by the system of ordinary differential equations:

$$\begin{cases} \frac{dS_1'}{dt} = bN - (v_1+\mu)S_1' - \frac{\beta_1 S_1'}{N}(I_1'+I_2'), \\ \frac{dV'}{dt} = v_1 S_1' - (\rho_1+\mu)V' + v_2 S_2', \\ \frac{dI_1'}{dt} = \frac{\beta_1 S_1'}{N}(I_1'+I_2') - (\gamma_1+\mu)I_1', \\ \frac{dS_2'}{dt} = \rho_1 V' + \rho_2 R' - (v_2+\mu)S_2' - \frac{\beta_2 S_2'}{N}(I_1'+I_2'), \\ \frac{dI_2'}{dt} = \frac{\beta_2 S_2'}{N}(I_1'+I_2') - (\gamma_2+\mu)I_2', \\ \frac{dR'}{dt} = \gamma_1 I_1' + \gamma_2 I_2' - (\rho_2+\mu)R', \end{cases} \tag{1}$$

with nonnegative initial conditions and $N(0) > 0$.

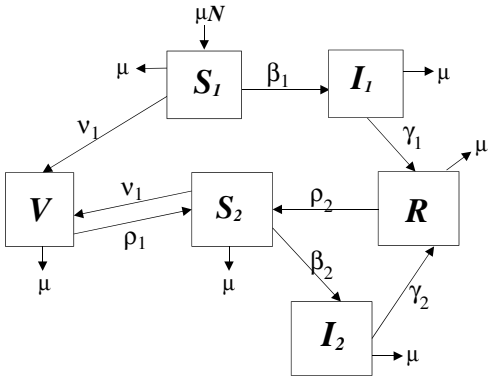

Fig. 1. The flow diagram for the model. Individuals are classified as naive susceptible and susceptible (S_1 and S_2), primary and secondary infectious (I_1 and I_2), vaccinated (V) and recovered (R).

System (1) is well posed, since solutions remain nonnegative for nonnegative initial conditions. The demographic equation for the dynamics of the total population size is given by $\mathrm{d}N/\mathrm{d}t = bN - \mu N$. As said before, we set $b = \mu$, so that the total population remains constant (N). Since the model is homogeneous of degree one, the variables can be normalized by setting $S_1 = S_1'/N$; $V = V'/N$; $I_1 = I_1'/N$; $S_2 = S_2'/N$; $I_2 = I_2'/N$ and $R = R'/N$, which leads to the normalized system

$$\begin{cases} \frac{\mathrm{d}S_1}{\mathrm{d}t} = \mu - (v_1 + \mu)S_1 - \beta_1 S_1(I_1 + I_2), \\ \frac{\mathrm{d}V}{\mathrm{d}t} = v_1 S_1 - (\rho_1 + \mu)V + v_2 S_2, \\ \frac{\mathrm{d}I_1}{\mathrm{d}t} = \beta_1 S_1(I_1 + I_2) - (\gamma_1 + \mu)I_1, \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} = \rho_1 V + \rho_2 R - (v_2 + \mu)S_2 - \beta_2 S_2(I_1 + I_2) \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} = \beta_2 S_2(I_1 + I_2) - (\gamma_2 + \mu)I_2, \\ \frac{\mathrm{d}R}{\mathrm{d}t} = \gamma_1 I_1 + \gamma_2 I_2 - (\rho_2 + \mu)R, \end{cases} \tag{2}$$

where each variable denotes a fraction of the total individuals, so that $S_1 + V + I_1 + S_2 + I_2 + R = N$, with $N = 1$ and, $\frac{\mathrm{d}N}{\mathrm{d}t} = 0$.

3. Analysis of the model

System (2), which includes immunization schedules, predicts vaccination strategy and changes in qualitative behavior that result from such a control. To develop the framework for predicting conditions for disease eradication associated with a vaccination program the following cases are considered: (a) two-dose immunization schedule ($v_1 \neq 0$ and $v_2 \neq 0$) recommended for diseases as measles, mumps and rubella (MMR), pertussis and polio and hepatitis B; (b) only primary immunization schedule ($v_1 \neq 0$ and $v_2 = 0$) recommended for diseases like varicella, influenza (Flu).

Next, system (2) together with these immunization schedules will be qualitatively analyzed so as to find the conditions for existence and stability of a disease free equilibrium point. The analysis allows us to determine the optimal vaccine coverage level needed for disease eradication and to find the basic reproductive number, commonly denoted by $\mathscr{R}_0$ in mathematical epidemiology [6,12]. The concept of $\mathscr{R}_0$, introduced by Ross in 1909 [23], is defined in epidemiological modelling as the average number of infected individuals produced by one infected individual introduced in a population completely susceptible. Thus, if $\mathscr{R}_0 < 1$, the disease dies out, and if $\mathscr{R}_0 > 1$, the disease spreads in the population and goes to an endemic level. For a disease that confers immunity in which the susceptible population is vaccinated it has been demonstrated that under certain parameter conditions there is a dependence of the reproductive number on the vaccination rate. In such a case, the reproduction ratio $\mathscr{R}_{\mathrm{vac}}$, which is the basic reproduction ratio $\mathscr{R}_0$ modified by vaccination, must be reduced below one in order to ensure that the disease dies out [15,16]. If there is no vaccination, then $\mathscr{R}_{\mathrm{vac}} = \mathscr{R}_0$. There-

fore, the aim of the vaccination campaign against childhood diseases must be to reduce $\mathscr{R}_{\text{vac}}$ below one, and to provide prolonged protection against both clinical disease and (ideally) natural infection and reinfection.

3.1. Disease-free equilibrium point

For system (2) always exists a disease-free or trivial equilibrium point (DFE), $P^* = (S_1^*, V^*, 0, S_2^*, 0, 0)$, with

$$\begin{cases} S_1^* = \frac{\mu}{(\nu_1+\mu)}, \\ V^* = \frac{1}{(\rho_1+\mu)}\left[\frac{\nu_1\mu}{(\nu_1+\mu)} + \frac{\rho_1\nu_1\nu_2}{(\nu_1+\mu)(\nu_2+\rho_1+\mu)}\right], \\ S_2^* = \frac{\nu_1\rho_1}{(\nu_1+\mu)(\nu_2+\rho_1+\mu)}. \end{cases} \tag{3}$$

The Jacobian matrix of system (2) evaluated at the DFE is

$$A_0 = \begin{bmatrix} a_{11} & 0 & 0 & 0 & 0 & 0 \\ \nu_1 & a_{22} & 0 & \nu_2 & 0 & 0 \\ 0 & 0 & a_{33} & 0 & \beta_1 S_1^* & 0 \\ 0 & \rho_1 & -\sigma\beta_1 S_2^* & a_{44} & -\sigma\beta_1 S_2^* & 0 \\ 0 & 0 & \sigma\beta_1 S_2^* & 0 & a_{55} & 0 \\ 0 & 0 & \gamma_1 & 0 & \gamma_2 & a_{66} \end{bmatrix}, \tag{4}$$

where

$$\begin{aligned} a_{11} &= -(\mu+\nu_1), \quad a_{44} = -(\mu+\nu_2), \\ a_{22} &= -(\mu+\rho_1), \quad a_{55} = \sigma\beta_1 S_2 - (\gamma_2+\mu), \\ a_{33} &= \beta_1 S_1 - (\mu+\gamma_1), \quad a_{66} = -(\mu+\rho_2). \end{aligned}$$

Two of the eingenvalues of A_0 are straightforwardly determined: $\tau_1 = -(\mu+\nu_1)$ and $\tau_2 = -(\mu+\rho_2)$. The other four are expressed as the roots of the equation

$$A_{22}\{[\sigma\beta_1 S_2^* - (\gamma_2+\mu) - \tau][\beta_1 S_1^* - (\gamma_1+\mu) - \tau] - \sigma(\beta_1)^2 S_1^* S_2^*\} = 0, \tag{5}$$

where

$$A_{22} = \begin{bmatrix} -(\rho_1+\mu) - \tau & \nu_2 \\ \rho_1 & -(\nu_2+\mu) - \tau \end{bmatrix}.$$

Since $\operatorname{tr} A_{22} < 0$ and $\det A_{22} > 0$, A_{22} has two negative eingenvalues. The other two eingenvalues associated with the second degree equation in (5) are negative when

$$R_{\text{vac}} = \mathscr{R}_0 \times f < 1, \tag{6}$$

where $\mathscr{R}_0$ is the threshold quantity or the basic reproductive number of the disease, and it is defined as

$$\mathscr{R}_0 = \frac{\beta_1}{(\gamma_1+\mu)}, \tag{7}$$

also,

$$f = \frac{p\nu_1 + \mu}{\nu_1 + \mu}, \tag{8}$$

with,

$$p = \frac{\sigma\rho_1(\gamma_1+\mu)}{(\gamma_2+\mu)(\nu_2+\rho_1+\mu)}. \tag{9}$$

Since $\gamma_1 < \gamma_2$, $\rho_1 < \rho_2$ and $0 < \sigma < 1$, we have $p < 1$ and, as a consequence $f < 1$. Hence, the DFE (3) is locally asymptotically stable when condition (6) holds. Setting $R_{vac} = 1$, and solving Eq. (6) for ν_1, the threshold vaccination rate is found to be

$$v_1^C(v_2) = \frac{\mu(\mathscr{R}_0 - 1)}{1 - p \cdot \mathscr{R}_0}. \tag{10}$$

Hence, for $\mathscr{R}_0 < 1$, the DFE is stable. For $\mathscr{R}_0 > 1$, $v_1^C(v_2)$ is positive if and only if $p < \frac{1}{\mathscr{R}_0}$. In this situation, the disease is eradicated when $v_1 > v_1^C(v_2)$. Otherwise, when $v_1 < v_1^C(v_2)$, the disease stay in the community.

From Eq. (9), $v_1^C(v_2)$ decreases when v_2 increases, now, Eq. (8) tells that reinfection may be strong if both infection and vaccine have not induced efficient immunological memory (large σ). So, one possible way to eradicate the disease would be to proportionally increase v_2 in the second dose. If increasing v_2, the disease can still be eradicated if reinfection is weak. Long-term immunological memory (small σ) is one way in this direction. In this way, double-dose vaccination not only allows for disease eradication but also offsets immunity loss given by ρ_1.

If the vaccine has no effect, $\rho_1 \to \infty$ (immune protection duration, $\mathscr{D} \to 0$), then $p \to \frac{\sigma(\gamma_1+\mu)}{(\gamma_2+\mu)} < \sigma$. If the vaccine induces lifelong immunity, then $\rho_1 = 0(\mathscr{D} \to \infty), p = 0$ and disease eradication is attainable with a single-dose vaccination. Now, the impact of double-dose vaccination can be assessed using Eq. (10), since for $p > \frac{1}{\mathscr{R}_0}$ a single vaccine dose will not eradicate the disease when $\rho_1 \to \infty$ or $0 < \sigma \leqslant 1$. Under these conditions, a second dose must be administered only if $\rho_1 > 0$. However, the basic problem is to find out the minimum value of parameter ρ_1 (that is, when does the first dose lose effectiveness) so that a second dose becomes necessary to eradicate the disease. To find out the critical value of ρ_1, one sets $v_2 = 0$. Now, if $v_1 \to \infty$, the conditions for disease eradication are $f = \mathrm{p}$ and $R_{\mathrm{vac}} = p \times \mathscr{R}_0 < 1$. Setting $p \times \mathscr{R}_0 = 1$, one gets $\rho_1^c = \frac{(\gamma_2+\mu)\mu}{\beta_2-(\gamma_2+\mu)}$, and the disease can be eradicated with a single-dose vaccination if $\rho_1 < \rho_1^c$. For weak reinfection, $\beta_2 < (\gamma_2 + \mu)$, then $\rho_1^c < 0$, and the disease can be eradicated with a single vaccination dose. Finally, for $\rho_1 > \rho_1^c$, condition (6) becomes necessary for the two-dose vaccination program to be successful.

Single-dose vaccination program can be studied setting $v_2 = 0$ in Eq. (3). It can be seen that the DFE is locally asymptotically stable when $R_{\mathrm{vac}} < 1$. As before, the threshold vaccination rate is now given by Eq. (10) when setting $v_2 = 0$. Thus, for all $v_1 > v_1^C(0, \mathscr{R}_0)$, that is, if vaccination coverage level is above the thresh, the disease can be eradicated from the population. On the other hand, for all $v_1 < v_1^C(0, \mathscr{R}_0)$, the disease can not be eradicated.

The model demonstrates that when there is vaccine immunity loss ($\rho_1 > 0$), single-dose vaccination can only eradicate the disease if reinfection is weak (large σ) and $\rho_1 < \rho_1^c$. However, if $\rho_1 > \rho_1^c$, a second-dose vaccination becomes necessary to eradicate the disease.

It must be noted that since the immunological memory may not protect the hosts from reinfection, a two-dose program is recommended in many European countries as well as in the United States to try to achieve eradication [4,5,13,25].

Finally, setting $v_1 = 0$ and $v_2 = 0$, for system (2), the DFE always exists and it is given by $P_o^* = (1, 0, 0, 0, 0, 0)$. The eingenvalues of the Jacobian matrix (4) of the linearized system (2) evaluated at the DFE are $\tau_1 = \tau_2 = -\mu$; $\tau_3 = -(\mu + \rho_1)$; $\tau_4 = -(\mu + \gamma_2)$; $\tau_5 = -(\mu + \rho_2)$; and $\tau_6 = [\beta_1 - (\gamma_1 + \mu)] < 0$ if $\beta_1 < (\gamma_1 + \mu)$. Thus, the DFE is locally asymptotically stable if $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$, with $\mathscr{R}_0$ defined by Eq. (7). If $\mathscr{R}_0 > 1$, the disease can go to an endemic level and it becomes necessary to implement control strategies to eradicate the disease or at least to lower its prevalence to reasonable levels. Such strategies include treatments to cure or increase the life expectancy of infected individuals, and vaccination as a prophylactic measure to prevent infection.

3.2. Endemic equilibrium point

When the disease is present in the population one has $I^* \neq 0$. There may be several critical points where $I^* \neq 0$, which are the endemic equilibrium points (EEP) of the model. These points will be denoted by $P_e^* = (S_1^*, V^*, I_1^*, S_2^*, I_2^*, R^*)$, which are determined from system (2) as follows:

$$\begin{cases} \mu - (v_1 + \mu)S_1^* - (\gamma_1 + \mu)I_1^* = 0, \\ v_1 S_1^* + v_2 S_2^* - (\rho_1 + \mu)V^* = 0, \\ \beta_1 S_1^*(I_1^* + I_2^*) - (\gamma_1 + \mu)I_1^* = 0, \\ \rho_1 V^* + \rho_2 R^* - (v_2 + \mu)S_2^* - (\gamma_2 + \mu)I_2^* = 0, \\ \gamma_1 I_1^* + \gamma_2 I_2^* - (\rho_2 + \mu)R^* = 0, \\ \beta_2 S_2^*(I_1^* + I_2^*) - (\gamma_2 + \mu)I_2^* = 0. \end{cases} \tag{11}$$

From the first, second and fifth equation one has, respectively,

$$\begin{cases} S_1^* = \frac{\mu-(\mu+\gamma_1)I_1^*}{(\nu_1+\mu)}, \\ V^* = \frac{\nu_1 S_1^* + \nu_2 S_2^*}{(\rho_1+\mu)}, \\ R^* = \frac{\gamma_1 I_1^* + \gamma_2 I_2^*}{(\rho_2+\mu)}. \end{cases} \tag{12}$$

Negative values of the variables have no biological meaning. Thus, one needs

$$S_1^* > 0 \Longleftrightarrow I_1^* < \frac{\mu}{(\mu+\gamma_1)}. \tag{13}$$

Now replacing the expression for V^* and R^* in the fourth equation of (11), one gets

$$S_2^* = \frac{(\mu+\rho_1)}{\mu(\mu+\nu_2+\rho_1)}[k_0 + k_1 I_1^* - k_2 I_2^*], \tag{14}$$

where

$$\begin{cases} k_0 = \frac{\rho_1 \nu_1 \mu}{(\mu+\rho_1)(\mu+\nu_1)}, \\ k_1 = \frac{\gamma_1\rho_2}{(\mu+\rho_2)} - \frac{\rho_1\nu_1(\mu+\gamma_1)}{(\mu+\rho_1)(\mu+\nu_1)}, \\ k_2 = \frac{\mu(\mu+\rho_2+\gamma_2)}{(\mu+\rho_2)}. \end{cases} \tag{15}$$

Since all parameters are positive, from expression (14), we always have $S_2^* \neq 0$, and $S_2^* > 0$, if $k_0 > k_1 I_1^* - k_2 I_2^*$.

Let us now find the expressions for I_1^* and I_2^* that satisfy system (11) and give $S_2^* > 0$ and $S_1^* > 0$. Replacing the expression for S_1^* in the third equation of (11), an expression for I_1^* is obtained as

$$(I_1^*)^2 + BI_1^* + C = 0, \tag{16}$$

where

$$\begin{aligned} B &= \frac{\mu}{(\mu+\gamma_1)}\left[\frac{(\nu_1+\mu)}{\mu\mathscr{R}_0} + \frac{(\mu+\gamma_1)}{\mu} I_2^* - 1\right], \\ C &= -\frac{\mu}{(\mu+\gamma_1)} I_2^*. \end{aligned} \tag{17}$$

Let us now determine the conditions under which the quadratic equation (16) has positive real roots. We can either have $I_2^* = 0$ or $I_2^* > 0$.

If $I_2^* = 0$, Eq. (16) turns into

$$(I_1^*)^2 + \frac{\mu}{(\mu+\gamma_1)}\left[\frac{(\nu_1+\mu)}{\mu\mathscr{R}_0} - 1\right] I_1^* = 0, \tag{18}$$

and we have either $I_1^* = 0$ or $I_1^* = \frac{\mu}{(\mu+\gamma_1)}\left[\frac{(\nu_1+\mu)}{\mu\mathscr{R}_0} - 1\right]$. Note that $I_1^* > 0 \Longleftrightarrow \mathscr{R}_0 < \frac{(\nu_1+\mu)}{\mu}$. Thus, if $I_1^* = 0$, from Eq. (14), $S_2^* = \frac{\nu_1\rho_1}{(\nu_1+\mu)(\nu_2+\rho_1+\mu)} > 0$. If $I_1^* = \frac{\mu}{(\mu+\gamma_1)}\left[\frac{(\nu_1+\mu)}{\mu\mathscr{R}_0} - 1\right]$, then from the last condition of (11), one gets, $S_2^* = 0$, which contradicts (14), or $S_2^* \neq 0$.

Therefore, for $I_2^* = 0$ and $I_1^* = 0$, a single biologically viable equilibrium point exists, which is the disease free equilibrium $P_{\nu_1} = (S_1^*, V^*, 0, S_2^*, 0, 0)$ whose coordinates are given by expression (3); and for $I_2^* = 0$ and $I_1^* > 0$, there is no equilibrium point that satisfy system (11).

For $I_2^* > 0$ and $I_1^* > 0$, the EEP is biologically viable only if $S_2^* > 0$ and $0 < I_1^* < \frac{\mu}{(\mu+\gamma_1)}$. Note that for each positive value of I_2^*, Eq. (16) has a unique positive solution for I_1^*, that does not depend on B, since $C < 0$. We will show later that indeed there is a single positive solution of Eq. (16).

Now, from Eq. (16) we have

$$I_2^* = \frac{I_1^*\left[I_1^* + \frac{\mu}{(\mu+\gamma_1)}\left(\frac{(\nu_1+\mu)}{\mu\mathscr{R}_0} - 1\right)\right]}{\left[\frac{\mu}{(\mu+\gamma_1)} - I_1^*\right]}. \tag{19}$$

Hence, for $0 < I_1^* < \frac{\mu}{(\mu+\gamma_1)}, I_2^* > 0$ if $\mathscr{R}_0 < \frac{(\nu_1+\mu)}{\mu}$, and $I_2^* < 0$ if $\mathscr{R}_0 > \frac{(\nu_1+\mu)}{\mu}$, that is, $\mathscr{R}_0 > 1$.

Replacing in the last equation of system (11) I_2^* by its expression in (19) and S_2^* by its expression in (14), one gets a quadratic equation for I_1^*.

$$P(I_1^*) = AI_1^{*2} + BI_1^* + C = 0, \tag{20}$$

with

$$\begin{aligned} A &= R_{\text{vac}} - \mathscr{R}_0\left\{k_3\left[\frac{\gamma_1\rho_2}{\mu(\mu+\rho_2+\gamma_2)} + 1\right]\right\}, \\ B &= \frac{\mu}{(\mu+\gamma_1)}\left\{-A - \frac{(\mathscr{R}_0)^2 k_3\mu(\mu+\gamma_1)}{(\mu+\nu_1)} - (R_{\text{vac}} - 1)\right\}, \\ C &= \frac{\mu^2}{(\mu+\gamma_1)^2}(R_{\text{vac}} - 1), \end{aligned} \tag{21}$$

where $k_3 = \frac{\sigma(\mu+\rho_1)}{(\mu+\gamma_2)(\mu+\rho_1+\nu_2)}k_2 > 0$ and k_2 is given by Eq. (15).

Next, we search for multiple endemic equilibria of system (2). These points are determined by the positive real solutions of quadratic equation (20). Since the expression for the discriminant of this quadratic equation is very complex, we will analyze the signs of its coefficients (21) to ensure the existence of real solutions. In this way, the conditions under which this equation has zero, one or two positive real roots will be determined, and these results translated into endemic equilibria of the system (2) that are biologically feasible.

As mentioned before, for $I_2^* > 0$ and $I_1^* > 0$, the EEP is biologically viable only if $S_2^* > 0$ and $0 < I_1^* < \frac{\mu}{(\mu+\gamma_1)}$. Assume that the quadratic equation has two positive real solutions, let them be I^* and I^{**} being the smaller and higher value of I_1^*, respectively. When $I^* < \frac{\mu}{(\mu+\gamma_1)}$ and $I^{**} > \frac{\mu}{(\mu+\gamma_1)}$, a unique EEP exists, which is biologically viable. When $I^* > \frac{\mu}{(\mu+\gamma_1)}$ and $I^{**} > \frac{\mu}{(\mu+\gamma_1)}$, neither endemic equilibria are biologically viable, and the unique equilibrium is the DFE. In this way, the system (2) presents one of the following dynamics: (a) only the DFE which is locally asymptotically stable; (b) the unstable DFE, a smaller positive EEP which is locally asymptotically stable, and the higher positive EEP which is unstable; and (c) the stable DFE which is locally asymptotically stable plus two positive (smaller and higher) endemic equilibria not biologically viable and, therefore, unstable. It follows that for $R_{\text{vac}} > 1$, the system (2) has a unique EEP which is locally asymptotically stable and for $R_{\text{vac}} < 1$ it has a stable DFE. Therefore, if there exists a nontrivial equilibrium which is

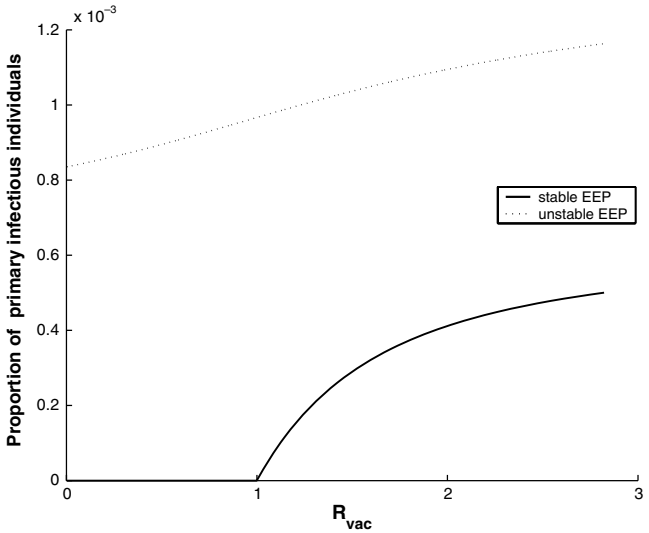

Fig. 2. Forward bifurcation in the $(R_{\text{vac}}(\beta_1), I_1^*)$ -plane, $\nu_1 \neq 0$ and $\nu_2 \neq 0$. The solid curve is the locally stable EEP, the dashed curve is the unstable EEP and it is not biologically viable.

biologically viable, $P_e^* = (S_1^*, V^*, I_1^*, S_2^*, R^*, I_2^*)$, then it is unique, locally asymptotically stable, and also a forward bifurcation is present (Fig. 2). Unfortunately, this equilibrium cannot be studied from its closed form, so, we will discuss its local stability using numerical methods. The results are provided next.

4. Numerical verification

The numerical analysis of the stability of the endemic equilibria was done with the parameters of the model fixed at the values indicated in Table 1, also, the rate of loss of vaccine-induced immunity (ρ_1) and the rate of recovery from primary infection (γ_1) are chosen to represent measles [24]. We explore the implications of variable vaccination coverages (v_1, v_2) and transmission coefficients (β_1, β_2). The parameters σ, $\rho_2(< \rho_1)$ and $\gamma_2(> \gamma_1)$ are chosen for simulations purposes only, so we can illustrate our results. To show the theoretical results of the paper, we used the same set of biologically-feasible control strategies previously presented.

First let us study the two-dose immunization schedule, $v_1 \neq 0$ and $v_2 \neq 0$. Following Eq. (20) we will provide a discussion of two specific cases that represent the quantitative and biological aspects of the model (2).

Table 1
Parameter values used in simulations

	Definition	Value
μ	Death and birth rate	1/65 years^{-1}
β_1	Coefficient transmission	Variable
β_2	Coefficient transmission	Variable
v_1	Vaccination coverage (first dose)	Variable
v_2	Vaccination coverage (second dose)	Variable
ρ_1	Rate of wanning of immunity induced by vaccination	1/20 years^{-1}
ρ_2	Rate of wanning of immunity induced by infection	1/25 years^{-1}
γ_1	Rate of recovery from primary infection	26 (14 days)
γ_2	Rate of recovery from reinfection	36.5 (10 days)

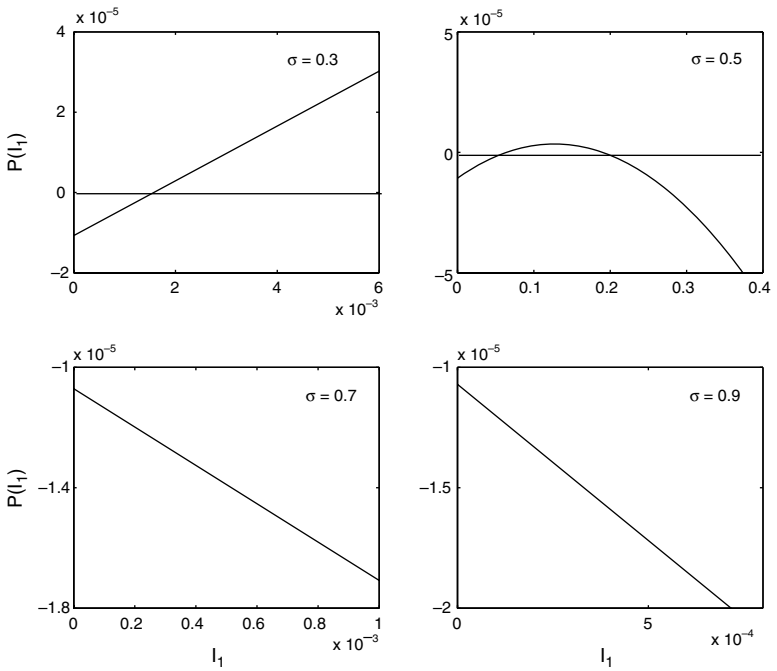

Fig. 3a. The quadratic $P(I_1^*)$ is plotted versus I_1^*, with increasing values of $\sigma = 0.3, 0.5, 0.7, 0.9$, corresponding to one, two or zero positive real roots, which are not biologically relevant.

When $R_{vac} < 1 (C < 0)$, if $A > 0$, then Eq. (20) has a positive $I_1^* > \frac{\mu}{(\mu+\gamma_1)}$ and a negative real solutions, independently of the value of B. On the other hand, if $A < 0$, for $B > 0$, Eq. (20) has either two positive real solutions ($I^* > \frac{\mu}{(\mu+\gamma_1)}$ and $I^{**} > \frac{\mu}{(\mu+\gamma_1)}$) or two complex solutions; for $B < 0$, one has either two negative real or two complex solutions of Eq. (20). This means that, for $R_{vac} < 1$ there is an unique equilibrium locally asymptotically stable, which is the DFE.

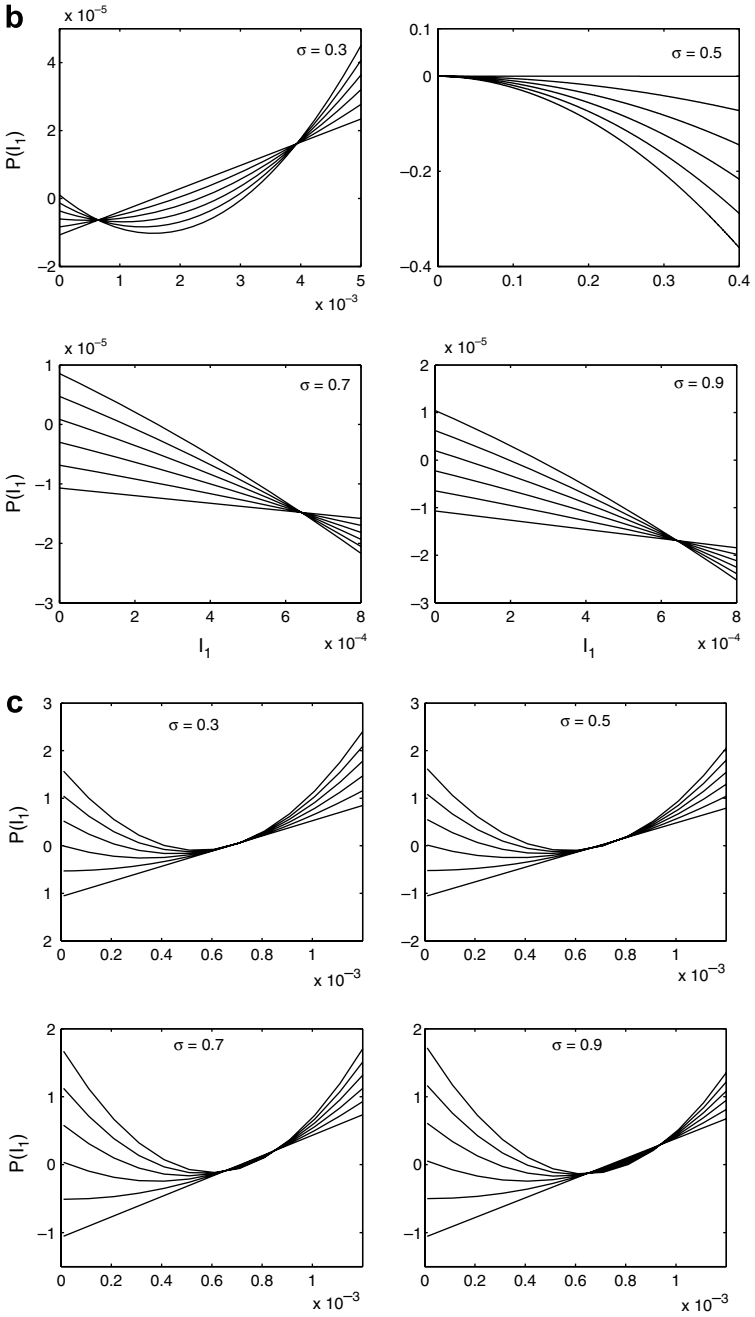

Fig. 3b and c. The quadratic $P(I_1^*)$ is plotted versus I_1^*, with increasing values of $\sigma = 0.3, 0.5, 0.7, 0.9$, corresponding to one, two or zero positive real roots with the global situation with increasing values of $\beta_1 = 0.01, 20, 40, 60, 80, 100$ describing a weak or strong reinfection.

Now, for $R_{vac} > 1 (C > 0)$, one has $B < 0$. If $A < 0$ then Eq. (20) has a positive real solution, $I_1^* < \frac{\mu}{(\mu+\gamma_1)}$, and a negative real solution. If $A > 0$ then Eq. (20) has two positive real solutions, $I^* < \frac{\mu}{(\mu+\gamma_1)}$ and $I^{**} > \frac{\mu}{(\mu+\gamma_1)}$. Therefore, for $R_{vac} > 1$ there is an unique EEP locally asymptotically stable.

In either case, a forward bifurcation occurs, that is, for $R_{vac} < 1$, the DFE is locally asymptotically stable, and for $R_{vac} > 1$, the EEP is locally asymptotically stable (stable EEP). The diagram of the forward bifurcation corresponding to Eq. (20) as a function of R_{vac} is depicted in Fig. 2. The dashed curve is the unstable EEP which is not biologically viable $(I^{**} > \frac{\mu}{(\mu+\gamma_1)})$. The solid curve is the locally stable EEP $\left(I^* < \frac{\mu}{(\mu+\gamma_1)}\right)$.

Fig. 3 shows the graph of Eq. (20), with $P(I_1^*)$ plotted versus I_1^*. Fig. 3a shows this graph for $v_1 = 0.095$, $v_2 = 0$ and $\beta_1 = 0.04$. One can see either one ($\sigma = 0.3$), two ($\sigma = 0.5$) or zero ($\sigma = 0.7$ and $\sigma = 0.9$) real positive roots of this equation. For $\sigma = 0.3$ we have one positive root, but not biologically relevant ($I^* = 0.0016$). For $\sigma = 0.5$, there are two roots, but they are not biologically viable, ($I^* = 0.1900$ and $I^* = 0.0642$) and for $\sigma = 0.7, 0.9$ no root is biologically viable. Thus, the unique locally asymptotically stable equilibrium point is the DFE. In this way, if reinfection is weak, $\sigma\beta_1 < (\gamma_2 + \mu) = 36.5167$, the eradication of the disease is possible with a single-dose vaccination.

Fig. 3b and c describes the global situation of weak or strong reinfection using increasing values of $\beta_1 = 0.01, 20, 40, 60, 80, 100$. In both figures, $P(I_1^*)$ is plotted versus I_1^*. In Fig. 3b this is done for $v_1 = 0.095$ and $v_2 = 0$, with increasing values of β_1 at left, from bottom to top, for $\sigma = 0.3, 0.7, 0.9$, and, from top to bottom for $\sigma = 0.5$. Using as example the situation $\sigma = 0.3$: for $\beta_1 = 0.01$, $I_1^* = 0.0016$; for $\beta_1 = 20, I_1^* = 0.0019$; for $\beta_1 = 40, I_1^* = 0.0023$; for $\beta_1 = 60, I_1^* = 0.0026$; for $\beta_1 = 80, I_1^* = 0.0029$ and, for $\beta_1 = 100$; we have $I_1^* = 0.0030$ and $I_1^{**} = 0.00007$. In all situations I_1^{**} has negative values, whereas the values of I_1^*, except the last one, are not biologically viable since they are above the value of $I_1^* = \frac{\mu}{(\mu+\gamma_1)} = 0.0006419$ (13). Therefore, if reinfection is weak, that is if $\beta_2 < (\gamma_2 + \mu) = 36.5167$, DFE is a unique equilibrium locally asymptotically stable, and the disease can be eradicated with a single-dose vaccination.

If reinfection is strong, there is a need for second vaccine dose to eradicate the disease. For instance, if $v_1 = 0.095$, $v_2 = 0.15$, and increasing values of $\beta_1 = 0.01, 20, 40, 60, 80, 100$. Set $\sigma = 0.3$, for $\beta_1 = 0.01$, we get $I_1^* = 0.000791$; for $\beta_1 = 20$, we get $I_1^* = 0.0007913$; for $\beta_1 = 40$, we get $I_1^* = 0.000798$; for $\beta_1 = 60$, we get $I_1^* = 0.0008$; for $\beta_1 = 80$, we get $I_1^* = 0.000812$ and, for $\beta_1 = 100$; we get $I_1^* = 0.000819$. If $v_1 > v_1^C(v_2)$ and $\rho_1^c < 0$, then $I_1^* > 0.0006419$ and $I_1^{**} < 0$.

Let us set $\sigma = 0.9$ now, for $\beta_1 = 0.01$, we get $I_1^* = 0.00141$; for $\beta_1 = 20$, we get $I_1^* = 0.00165$; for $\beta_1 = 40$,we get $I_1^* = 0.0019$; for $\beta_1 = 60$, we get $I_1^* = 0.0021$; for $\beta_1 = 80$, we get $I_1^* = 0.0023$. So we have $I_1^* > 0.0006419$ and $I_1^{**} < 0$ or $I_1^{**} > 0.0006419$. Therefore, DFE is an unique equilibrium, which is locally asymptotically stable, and the disease may be eradicated from the population with a second vaccine dose. However, for $\beta_1 = 100$ we have $I_1^* = 0.0024$ and $I_1^{**} = 0.00004$, but $v_1 < v_1^C(v_2) = 0.11, \rho_1^c > 0$ and $\rho_1 > \rho_1^c$, and the reinfection is strong, $\beta_2 > (\gamma_2 + \mu)$. In this situation, it is necessary to go by condition (6) so that the two-dose vaccination can succeed. Increasing the vaccine effort for the dose, v_1, it is still possible to eradicate the disease. For

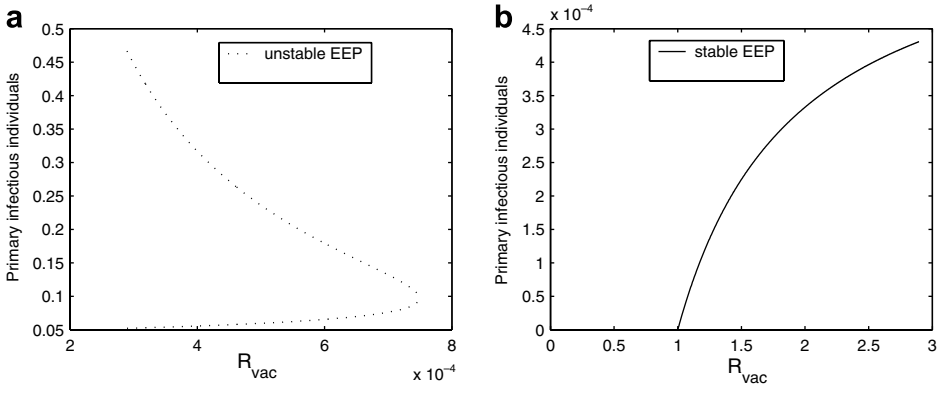

Fig. 4. (a) For $R_{vac} < 1$, the two real positive roots of Eq. (20) are larger than the value given by the biological condition (13), namely, $I_1^* < 0.0006419$. Hence, DFE is an unique equilibrium locally asymptotically stable for $R_{vac} < 1$ and EEP is locally asymptotically stable for $R_{vac} < 1$.

instance, with $v_1 = 0.115, I_1^* = 0.00363$ and $I_1^{**} < 0$, which makes the only stable existing equilibrium point precisely DFE.

In Fig. 3c, we set $v_1 = 0.0095$, $v_2 = 0.15$, showing increasing values of $\beta_1 = 0.01, 20, 40, 60, 80, 100$, at left, from bottom to top, for $\sigma = 0.3, 0.5, 0.7, 0.9$. As before, we get one, two or zero real positive roots of Eq. (20). For example if $\sigma = 0.3$, for $\beta_1 = 0.01$, we get $I_1^* = 0.00067$ and $I_1^{**} < 0$; for $\beta_1 = 20$, we get $I_1^* = 0.0006716$ and $I_1^{**} < 0$; for $\beta_1 = 40$, we get $I_1^* = 0.000005$ and $I_1^{**} = 0.000672$; for $\beta_1 = 60$, we get $I_1^* = 0.00023$ and $I_1^{**} = 0.000673$; for $\beta_1 = 80$, we get $I_1^* = 0.00034$ and $I_1^{**} = 0.000675$ and, for $\beta_1 = 100$; we get $I_1^* = 0.00041$ and $I_1^{**} = 0.000676$. In the same way we have, $\rho_1 > \rho_1^c$, and the disease may be eradicated increasing v_1.

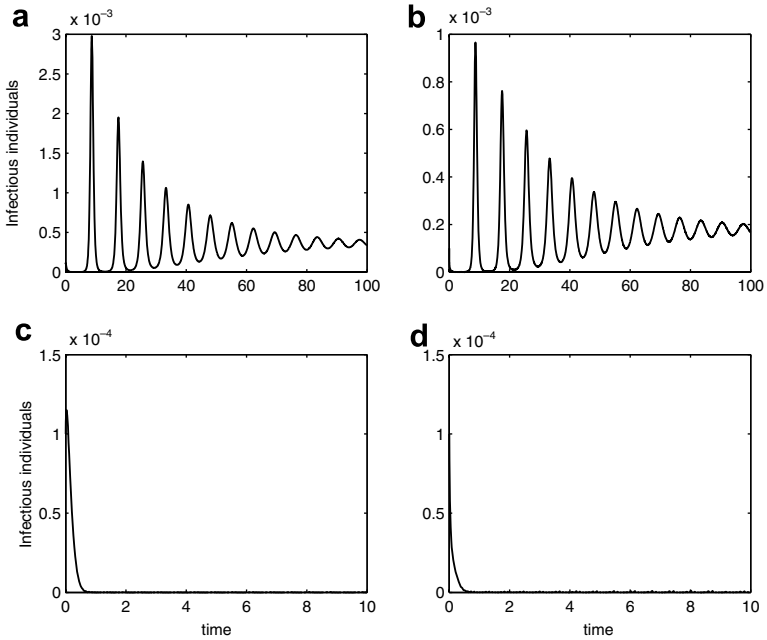

Fig. 5. Profile of populations for proportion of primary (a,c) and secondary (b,d) infectious individuals, where (a, b) $v_1 < v_1^C$: disease persistence; (c,d) $v_1 > v_1^C$: disease eradicated.

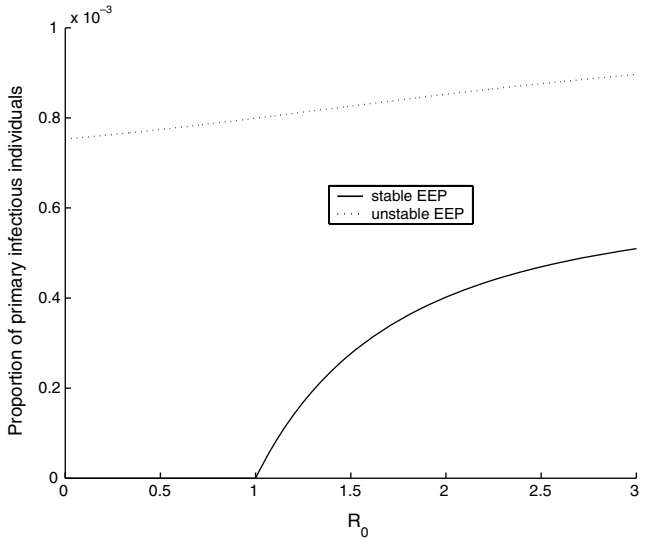

Fig. 6. Forward bifurcation in the $(R_0(\beta_1), I_1^*)$-plane, $v_1 = v_2 = 0$. The solid curve is the locally stable EEP, the dashed curve is the unstable EEP and it is not biologically viable.

In Fig. 4a, we set $v_1 = 0.095$, $v_2 = 0$ and $\sigma = 0.5$; for $R_{vac} < 1$, the two real positive roots of Eq. (20) are larger than the value obtained from the condition of existence (13), namely, $I_1^* < 0.0006419$. Hence, the disease free equilibrium (DFE) is an unique equilibrium locally asymptotically stable, such that the disease is eradicated.

Fig. 4b shows the situation that prevails when the bifurcation is a classical forward bifurcation. In this case, taking $v_1 = 0.095$ and $v_2 = 0$, for $R_{vac} > 1$, there are two real roots of $P(I^*)$, but one of them is negative. Thus, for $R_{vac} > 1$, we expect stability of the endemic equilibrium point (EEP) for the positive I_1^* value, so that the disease is maintained into the population.

Fig. 5 shows the profile of populations for proportion of primary and secondary infectious individuals. If , $v_1 < v_1^C$, the disease can not be eradicated and invade the population (Fig. 5a,b). On the other hand, for all $v_1 > v_1^C$ the disease can be eradicated from the population (Fig. 5c,d).

In Fig. 6, taking $v^1 = 0$, $v_2 = 0$ and $\sigma = 0.5$, the forward bifurcation is present. The DFE is locally asymptotically stable if $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$.

5. Conclusion

In this paper we studied qualitatively and quantitatively a six-dimensional deterministic model for the transmission dynamics of a childhood disease in the presence of a preventive vaccine that may wane over time. The model incorporates the assumption that the disease does not confer permanent immunity, thus, reinfection is possible.

Gomes et al. [8,9] considered the existence of a reinfection threshold in models with temporary immunity. Regardless of the terminology used to describe this phenomenon, we determined a critical value, $\beta_2^C = (\gamma_2 + \mu)$, for reinfection. We showed (by a different path than [1]) that eradication may depend on the primary immunization when the target vaccination coverage for eradication is met ($v_1 > v_1^C$) and reinfection is weak ($\beta_2 < \beta_C$). When a secondary immunization program is associated with the primary one, then even with strong reinfection ($\beta_2 > \beta_C$) the eradication may depend only on the primary vaccination coverage ($v_1 > v_1^C(v_2)$).

The important observation from our results is that waning of immunity is a major obstacle to the eradication of infectious diseases with just a single-dose vaccination program. An epidemiological consequence of this result is that, for relatively low coverage v_1, a booster program (two-dose) may fail to control the disease. More importantly, the probability of failure of a booster program increases as primary vaccination coverage decreases. Hence, with $v_1 > v_1^C$ and a second-dose immunization, the disease can be controlled by vaccination, and immunity loss can be balanced increasing vaccination coverage.

The local stability of the model reveals that the disease-free equilibrium is stable provided that the vaccination coverage exceeds a certain threshold. We determined qualitatively this threshold for controlling or eradicating the disease, and using an analytical study of the model we demonstrated that if there exist vaccination, then the disease can be eradicated even if the basic reproduction number is greater than one, $\mathscr{R}_0 > 1$. For a single-dose vaccination eradication can only occur if reinfection is weak (β_2) and that coverage exceeds its critical value v^C.

Since not all children receive the first dose of vaccine, and for some of those who do, the vaccine does not work well, the number of children susceptible to any disease will increase, each year. So, a second immunization is needed to protect those children who did not respond to the first dose, and provides an opportunity to give a first dose to children who did not receive the vaccine earlier. Overall, about 40% of children need some or all parts of a second dose of vaccine. This means that even if everyone gets immunized, there will always be 5–10% who are not protected against disease, and if there are outbreaks, some of those people will become infected. This is one of the main reasons why children are given a booster before they go to school.

Also, when $\mathscr{R}_{vac} > 1$, there is a single nontrivial equilibrium point that is biologically viable. That is even if eradication is not achieved an epidemic can be avoided with booster vaccination.

Our model (2) shows that the duration of memory can protect the hosts from reinfection and that longer duration of memory is always advantageous for them. The duration of memory can regulate the degree of competition between the pathogens. If the duration of memory is short and the population of immune hosts becomes susceptible again at a fast rate (low value of $\mathscr{D}$), the hosts are not protected against reinfection, and the intra-specific competition between pathogens is strong and the superior pathogen wins excluding the

inferior one. On the other hand, the long duration of protection (higher value of $\mathscr{D}$) is advantageous because it provides lasting protection against reinfection, the intra-specific competition is weaker and coexistence of the pathogens can be observed.

References

[1] M.E. Alexander, S.M. Moghadas, P. Rohani, A.R. Summers, Modelling the effect of a booster vaccination on disease epidemiology, J. Math. Biol. 52 (2006) 290–306.

[2] J. Arino, C.C. Mccluskey, P. Van Den Driessche, Global results for a epidemic model with vaccination that exhibits backward bifurcation, SIAM J. Appl. Math. 64 (1) (2003) 260–276.

[3] J. Arino, K.L. Cooke, P. Van Den Driessche, J. Velasco-Hernández, An epidemiology model that includes a leaky vaccine with a general waning function, Discret. Contin. Dyn. Syst. Ser. B 4 (2) (2004) 479–495.

[4] M. Böttiger, M. Forsgren, Twenty years experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old girls and of women postpartum) and 13 years of a general two-dose vaccination, Vaccine 15 (1997) 1538–1544.

[5] I. Davidikin, M. Valle, Vaccine-induced measles virus antibodies after two doses of combined measles, mumps and rubella vaccine: a 12-year follow-up in two cohorts, Vaccine 16 (1998) 2052–2057.

[6] O. Diekmann, J.A.P. Heesterbeek, J.A.J. Metz, On the definition and computation of the basic reproduction ratio $\mathscr{R}_0$ in models for infectious diseases in heterogeneous populations, J. Math. Biol. 28 (4) (1990) 365–382.

[7] K. Dietz, The evaluation of rubella vaccination strategies, The Mathematical Theory of the Dynamics of Biology Population II, Academic Press, NY, 1981.

[8] M.G.M. Gomes, L.J. White, G.F. Medley, Infection, reinfection, and vaccination under suboptimal immune protection: epidemiological perspectives, J. Theor. Biol. 228 (2004) 539–549.

[9] M.G.M. Gomes, L.J. White, G.F. Medley, The reinfection threshold, J. Theor. Bol. 236 (2005) 111–113.

[10] B.T. Grenfell, R.M. Anderson, Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination, Proc. Roy. Soc. London B 236 (1989) 213–252.

[11] A.B. Gumel, S.M. Moghadas, A qualitative study of a vaccination model with non-linear incidence, Appl. Math. Comput. 143 (2003) 409–419.

[12] H.W. Hethcote, Qualitative analysis of communicable disease models, Math. Biosci. 28 (1976) 335–356.

[13] H.W. Hethcote, Simulations of pertussis epidemiology in the United States: effects of adult booster vaccinations, Math. Biosci. 158 (1) (1999) 47–73.

[14] M.C.M. de Jong, O. Diekmann, J.A.P. Heesterbbeek, How does transmission of infection depend on population size? in: D. Mollison (Ed.), Epidemic Models: Their Structure and Relation to Data, vol. 5, Cambridge University, Cambridge, 1994, p. 84.

[15] C.M. Kribs-Zaleta, J.X. Velasco-Hernández, A simple vaccination model with multiple endemic states, Math. Biosci. 164 (2000) 183–201.

[16] C.M. Kribs-Zaleta, M. Martcheva, Vaccination strategies and backward bifurcation in an age-since-infection structured model, Math. Biosci. 177 & 178 (2002) 317–332.

[17] E. Massad, M.N. Burattini, R.S. Azevedo-Neto, H.M. Yang, D.M.T. Zanetta, F.A.B. Coutinho, A model-based design of a vaccination strategy against rubella in a non-immunized community of São Paulo State, Brazil. Epidemiol. Infect. 112 (1994) 579–594.

[18] S.M. Moghadas, A.B. Gumel, A mathematical study of a model for childhood diseases with non-permanent immunity, J. Comput. Appl. Math. 157 (2003) 347–363.

[19] S.M. Moghadas, Modelling the effect of imperfect vaccines on disease epidemiology, Discret. Contin. Dyn. Syst. Ser. B 4 (4) (2004) 999–1012.

[20] K. Murali-Krishna, L.L. Lau, S. Sambhara, F. Lemonnier, J. Altman, R. Ahmed, Persistence of memory CD* T cells in MHC class I-deficient mice, Science 286 (1999) 1377–1381.

[21] A.C. Paulo, M.C. Gomes, A.C. Casinhas, A. Horta, Multiple dose vaccination against childhoold disease: high coverage with the first dose remains crucial for eradication, IMA J. Math. Appl. Med. Biol. 17 (2000) 201–212.

[22] S.M. Raimundo, E. Massad, R.S. Azevedo Neto, The impact of reinfection on the control of rubella: a mathematical model approach, in: Proceedings of the Abstracts Eighth International Congress on Infectious Diseases, Boston, Massachusets, USA, 1998, pp. 212.

[23] R. Ross, The Prevention of Malaria, Murray, London, 1909.

[24] A. Scherer, A. McLean, Mathematical models of vaccination, Br. Med. Bull. 62 (2002) 187–199.

[25] M. Toyoda, T. Ihara, T. Nakano, M. Ito, H. Kamiya, Expression of interleukin-2 receptor a and CD45RO antigen on T lymphocytes cultured with rubella virus antigen, compared with humoral immunity in rubella vaccines, Vaccine 17 (1999) 2051–2058.

[26] H.M. Yang, Mathematical modeling of the infectious diseases considering the Re-infection and the vaccine failures, in: Proceedings of the Mathematical Modelling and Computing in Biology and Medicine, ESMTB Fifth Conference, Milano, Italy, 2002.

[27] R.M. Zinkernagel, M.F. Bachmann, T.M. Kundig, S. Oehen, H. Pirchet, H. Hengartner, On immunological memory, Ann. Rev. Immunol. 14 (1996) 333–367.

[28] R.M. Zinkernagel, On differences between immunity and immunological memory, Curr. Opin. Immunol. 14 (2002) 523–536.

[29] R.M. Zinkernagel, What is missing in immunology to understand immunity? Nat. Immunol. 1 (2000) 181–185.

[30] D. Wodarz, Evolution of immunological memory and the regulation of competition between pathogens, Curr. Biol. 13 (18) (2003) 1648–1652.