IMA Journal of Mathematics Applied in Medicine and Biology (2002) **19**, 113–135

The effects of re-infection in directly transmitted infections modelled with vaccination

HYUN MO YANG†

Universidade Estadual de Campinas, IMECC - Departamento de Matemática Aplicada, Caixa Postal 6065, CEP: 13081-970, Campinas, S.P., Brazil

[Received on 25 July 2000; revised on 11 December 2001; accepted on 6 September 2002]

We propose a mathematical model to deal with directly transmitted infections incorporating the loss of immunity. The model is developed taking into account a constant contact rate among individuals and an age-dependent vaccination rate. Based on this model, we analyse the effects of re-infection in a community under a vaccination strategy.

Keywords: force of infection; vaccination; re-infection; mathematical model.

1. Introduction

Mathematical models have been proved to be useful tools for quantitative epidemiology, producing many important results. In this way, previously developed mathematical models to describe directly transmitted infections assuming lifelong immunity produced some interesting results. One of them states that the introduction of any form of perturbation in the host–parasite system, like vaccination, leads the dynamical system through unexpected, and sometimes undesirable, patterns such as damped oscillations in the force of infection (Schwartz & Smith, 1983; Yang, 1997, 1998, 2001). Another result establishes the shift of the average age of the acquisition of the first infection to elder ages (Anderson & May, 1991). However, this paradigm does not remain valid if the vaccination is carried out on an age interval such that the lower bound of the age interval under vaccination is higher than the natural (without vaccination) average age of the acquisition of the first infection (Yang, 2001).

The scenario is quite different when the vaccine does not induce lifelong immunity, even though the disease-induced immunization may appear to be everlasting (Rouderfer *et al.*, 1994). For this reason, the loss of immunity can play an important role in a highly vaccinated population by increasing the number of susceptible individuals. For instance, when we consider the vaccination of very young children against rubella (Massad *et al.*, 1994, 1995), we could have an increase in the number of cases of congenital rubella syndrome (CRS) due to the fact that women may lose the induced immunization during the fertile age. Several papers have dealt with the rubella infection considering a mathematical model without considering the loss of immunity, but incorporating a vaccination schedule (Anderson & May, 1985; Coutinho *et al.*, 1993; Greenhalgh, 1990; Massad *et al.*, 1995). One further example is related to measles. In Brazil, the actually

†Email: hyunyang@ime.unicamp.br

adopted routine vaccination scheme is the first dose at nine months and the second at 15 months. Besides this scheme, several national vaccination campaigns occurred in 1980, 1987, 1990 and 1992. In the last campaign approximately 48 million children under 15 years were covered. Even this great effort to control the disease did not prevent a severe measles outbreak in 1997, infecting a higher fraction of elder individuals (Guerra L.M. Paiva *et al.*, 1999).

In this paper we propose a mathematical model to describe directly transmitted infections taking into account the loss of immunity. The model assumes a constant contact rate among individuals in the community and a vaccination programme which is carried out on a fixed age interval. These considerations result in an age-structured system of partial differential equations (Trucco, 1965b), which is analysed in the steady state. Trucco (1965a) applied this time- and age-dependent system of equations to cellular growth, and Dietz (1975) used for the first time for the description of an age-dependent vaccination programme. Yang & Silveira (1998) considered a particular application of the model proposed here by taking into account a community which was not vaccinated against rubella. They fitted the model to serological data for rubella obtained from Caieiras City, Brazil (Azevedo Neto *et al.*, 1994), before the introduction of a vaccination strategy. A mathematical model considering a fixed latent period and nonpermanent immunity was treated by Greenhalgh (1997), while both periods were treated as delays by Cooke & van den Driessche (1996).

For the re-infection model, we present a methodology to assess the effects of vaccination and loss of immunity on the force of infection and on the *basic reproduction ratio*. In Section 2 we present the re-infection model, where the boundary and initial conditions and the steady-state values are given, respectively, in Sections 2.1 and 2.2. In Section 3 we present the analysis of the steady states before and after the introduction of a vaccination, respectively, in Sections 3.1 and 3.2, and the effects of a vaccination strategy are presented in Section 3.3. Finally, in Section 4 we present a brief conclusion.

2. The model

In this section we develop a model for directly transmitted infections encompassing loss of immunity. We assume the very simple hypothesis that vaccine-induced immunity and disease-induced immunity protect the individual for the same amount of time. The reason behind this simplification, which results in a unique loss of immunity rate for the immune individuals, consists of the possibility of obtaining an analytical approach to treat the model (at least we can obtain an integral equation). However, Rouderfer *et al.* (1994) dealt with a more elaborate model considering different loss rates for the induced and acquired immunities and also a boosting of the waning of immunity by re-infection or vaccination.

Let us consider a closed community divided into four groups: $X(t,a)$, $H(t,a)$, $Y(t,a)$ and $Z(t,a)$ which are, respectively, the densities depending on age a at time t of susceptible, exposed (latent), infectious and recovered (immune) individuals. When the entire population is subdivided into four non-intercepting compartments according to the infection status considering re-infection, we are dealing with the SEIRS model. Therefore, these four compartments are described dynamically by the following set of

partial differential equations:

$$\begin{cases} \frac{\partial}{\partial t}X(t,a) + \frac{\partial}{\partial a}X(t,a) &= \pi Z(t,a) - [\mu + \lambda(t) + \nu(a)]\, X(t,a) \\ \frac{\partial}{\partial t}H(t,a) + \frac{\partial}{\partial a}H(t,a) &= \lambda(t)X(t,a) - (\mu + \sigma)\, H(t,a) \\ \frac{\partial}{\partial t}Y(t,a) + \frac{\partial}{\partial a}Y(t,a) &= \sigma H(t,a) - (\mu + \gamma)\, Y(t,a) \\ \frac{\partial}{\partial t}Z(t,a) + \frac{\partial}{\partial a}Z(t,a) &= \nu(a)X(t,a) + \gamma Y(t,a) - (\mu + \pi)\, Z(t,a), \end{cases} \tag{1}$$

where

$$\lambda(t) = \int_0^\infty \beta' Y(t,a)\, \mathrm{d}a \tag{2}$$

is the force of infection, μ is the natural mortality rate, σ^{-1} and γ^{-1} are, respectively, the average incubation and recovery periods, $\nu(a)$ is the age-dependent vaccination rate, β' is the constant contact rate per individual and π is the immunity loss rate. Maternally derived antibodies are not considered, nor are the boosting of immunity by vaccination or secondary infections (Rouderfer *et al.*, 1994). See Yang (1997, 1999a,b) for an age-structured contact rate model.

We analyse a vaccination strategy described by the equation

$$\nu(a) = \nu\theta\,(a - a_1)\,\theta\,(a_2 - a)\,, \tag{3}$$

where $\theta(x)$ is the Heaviside or step function and ν is a constant vaccination rate applied on the range [a_1,a_2], where a_1 and a_2 are, respectively, the lower and upper bounds of the age interval vaccinated. This function describes the vaccination of individuals comprised on a fixed age interval. We use the term 'vaccination of individuals' to mean vaccination of both individuals susceptible from birth and of immune individuals who lose the induced immunity (technically these individuals are under re-vaccination).

The system of (1) can be summed up to generate the equation for the density dependent on age $N(t,a)$ of the total number of individuals, with $N(t,a) = X(t,a) + H(t,a) + Y(t,a) + Z(t,a)$. By doing this we are disregarding the distribution of the infection in the community to deal only with the age distribution of the individuals in the community, which is given by

$$\frac{\partial}{\partial t}N(t,a) + \frac{\partial}{\partial a}N(t,a) = -\mu N(t,a). \tag{4}$$

This equation shows the effect of a constant mortality rate amongst individuals of all ages. Greenhalgh analysed the effects of a density-dependent mortality rate on the disease propagation (Greenhalgh, 1997).

The system of partial differential equations (1) is mathematically well-posed if we provide the initial and boundary conditions. Instead of solving numerically the dynamical system, we are interested only in the equilibrium values. For this reason, in the next sections we provide the initial and boundary conditions, which correspond to the natural equilibrium values, and the equilibrium values under a vaccination programme.

2.1 *The boundary and initial conditions—the natural equilibrium values*

First, let us determine the boundary conditions, which are the values assigned to the dynamic variables at birth ($a = 0$) and at maximum attainable age ($a = \infty$). In the model, we are not taking into account the immigration and the passage of the virus through placenta (vertical transmission). Therefore, all new-borns are considered susceptible to the virus and there is no input rate related to immigration into any compartment, hence the boundary conditions are given by

$$\begin{cases} X(t,0) = N^* \\ H(t,0) = 0 \\ Y(t,0) = 0 \\ Z(t,0) = 0, \end{cases} \tag{5}$$

where N^* is the total birth rate which can be related to the (per capita) natality rate. If we assume that the number of new-borns in a given time interval is equal to the number of individuals who die in that given time interval then we must have $N^* = \mu N$, with N being the constant population size. The set of boundary conditions given at $a = \infty$ is $X(t,\infty) = H(t,\infty) = Y(t,\infty) = Z(t,\infty) = 0$. As we can see later, these conditions are automatically satisfied by the system (1).

Second, let us consider the initial conditions. The main goal in dealing with the system (1) is the analysis of a vaccination strategy, described by (3). For this reason the initial conditions are taken as the natural equilibrium values, corresponding to the endemic equilibrium of this system before the introduction of vaccination ($\nu = 0$), designed as

$$\begin{cases} X(0,a) = X_0(a) \\ H(0,a) = H_0(a) \\ Y(0,a) = Y_0(a) \\ Z(0,a) = Z_0(a), \end{cases} \tag{6}$$

which are determined next. These equations state that at $t = 0$ a vaccination programme is introduced in a community in equilibrium.

The equilibrium values obtained before the introduction of the vaccination are given by the system (1) dropping out the partial derivative of the dynamic variables with respect to time and setting $\nu = 0$. Instead of the age distributions of the individuals, we use the age-specific fractions of individuals $x_0(a)$, $h_0(a)$, $y_0(a)$ and $z_0(a)$, where, for instance, $x_0(a) = X_0(a)/N_0(a)$ is the age-specific fraction of susceptible individuals and analogously for other compartments. For the age-structured population we have $N_0(a) = N^* e^{-\mu a}$, which is the solution of (4) at the equilibrium. Therefore, combining (1) and (4) in the steady

state, we have the system of equations

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}a}x_0(a) &= \pi z_0(a) - \lambda_0 x_0(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}h_0(a) &= \lambda_0 x_0(a) - \sigma h_0(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}y_0(a) &= \sigma h_0(a) - \gamma y_0(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}z_0(a) &= \gamma y_0(a) - \pi z_0(a), \end{cases} \tag{7}$$

where the natural (without vaccination) force of infection is given by $\lambda_0 = \beta' N^* \int_0^\infty y_0(a)\mathrm{e}^{-\mu a}\,\mathrm{d}a$, which is (2) in the equilibrium.

Observe that the mortality rate μ does not appear in the system of differential equations (7). This fact results from the identity

$$\frac{\mathrm{d}}{\mathrm{d}a}x_0(a) \equiv \frac{\mathrm{d}}{\mathrm{d}a}\left[\frac{X_0(a)}{N_0(a)}\right] = \frac{1}{N_0(a)}\frac{\mathrm{d}}{\mathrm{d}a}X_0(a) + \mu x_0(a)$$

for the age-specific fraction of susceptible individuals, and the corresponding identities for the other three classes. We use correspondingly this equation with the equations of system (1), at equilibrium without vaccination, divided by $N_0(a)$. To solve the system (7) given by the fractions of individuals, we use the initial conditions $x_0(0) = 1$ and $h_0(0) = y_0(0) = z_0(0) = 0$, which are the boundary conditions given by (5) divided by N^*.

The solutions of the system of differential equations (7) can be obtained in terms of the age-specific fraction of susceptible individuals. The solutions, which correspond to the natural endemic equilibrium (in the absence of vaccination), are

$$\begin{cases} x_0(a) &= \mathrm{e}^{-\lambda_0 a} + \pi \int_0^a B(a-s)x_0(s)\,\mathrm{d}s \\ h_0(a) &= \mathrm{e}^{-\sigma a}\int_0^a \mathrm{e}^{\sigma s}\lambda_0 x_0(s)\,\mathrm{d}s \\ y_0(a) &= \mathrm{e}^{-\gamma a}\int_0^a \mathrm{e}^{\gamma\tau}\sigma\mathrm{e}^{-\sigma\tau}\int_0^\tau \mathrm{e}^{\sigma s}\lambda_0 x_0(s)\,\mathrm{d}s\,\mathrm{d}\tau \\ z_0(a) &= \mathrm{e}^{-\pi a}\int_0^a \mathrm{e}^{\pi a'}\gamma\mathrm{e}^{-\gamma \mathrm{e}a'}\int_0^{a'} \mathrm{e}^{\gamma\tau}\sigma\mathrm{e}^{-\sigma\tau}\int_0^\tau \mathrm{e}^{\sigma s}\lambda_0 x_0(s)\,\mathrm{d}s\,\mathrm{d}\tau\,\mathrm{d}a', \end{cases} \tag{8}$$

where the kernel $B(a-s)$ is given by

$$B(a-s) = \lambda_0\sigma\gamma\left\{\frac{\frac{\mathrm{e}^{-\sigma(a-s)}}{(\sigma-\lambda_0)(\sigma-\pi)} - \frac{\mathrm{e}^{-\gamma(a-s)}}{(\gamma-\lambda_0)(\gamma-\pi)}}{\gamma-\sigma} + \frac{\frac{\mathrm{e}^{-\pi(a-s)}}{(\gamma-\pi)(\sigma-\pi)} - \frac{\mathrm{e}^{-\lambda_0(a-s)}}{(\gamma-\lambda_0)(\sigma-\lambda_0)}}{\lambda_0-\pi}\right\}. \tag{9}$$

This kernel can be derived from (13) in the next section, by changing λ to λ_0 and letting $\nu = 0$.

The solutions given by (8) are completely determined if we have $x_0(a)$. On the other hand, the solution for $x_0(a)$ can be obtained from the first equation of system (8) when an estimated value for λ_0 is available; reciprocally, if we have an estimated $x_0(a)$ then we can calculate λ_0. Moreover, the first equation of system (8) determining the age-specific fraction of susceptible individuals is a non-homogeneous linear Volterra integral equation, and the kernel given by (9) is quadratically integrable (L_2-*function*) on $[0,a]\times[0,a]$. Therefore, this Volterra integral equation has only one solution for $x_0(a)$ (Tricomi, 1985).

2.2 *The equilibrium values under vaccination*

The system (1) can be solved to obtain the equilibrium values after the introduction of the vaccination. The calculations in order to obtain the solutions are analogous to those presented in the preceding section. Equations (1) and (4) are combined, in the steady state, to result in the system of equations

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}a}x(a) &= \pi z(a) - [\lambda + \nu(a)]\,x(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}h(a) &= \lambda x(a) - \sigma h(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}y(a) &= \sigma h(a) - \gamma y(a) \\ \frac{\mathrm{d}}{\mathrm{d}a}z(a) &= \nu(a)x(a) + \gamma y(a) - \pi z(a), \end{cases} \tag{10}$$

where $x(a)$, $h(a)$, $y(a)$ and $z(a)$ are the age-specific fractions of individuals, for instance $x(a) = X(a)/N(a)$ and so on, while the age-structured population density is given by $N(a) = N_0(a) = N^*\mathrm{e}^{-\mu a}$, since we are not considering the differential mortality due to the disease. The force of infection in the presence of vaccination is given by $\lambda = \beta' N^* \int_0^\infty y(a)\mathrm{e}^{-\mu a}\,\mathrm{d}a$. The initial conditions are obtained from (5) divided by N^*, that is $x(0) = 1$ and $h(0) = y(0) = z(0) = 0$.

The steady-state system of (10), with the vaccination rate given by (3), is solved in terms of the age-specific fraction of susceptible individuals. The resulting integral equations are

$$\begin{cases} x(a) = \mathrm{e}^{-\lambda a - \phi(a)} + \pi \int_0^a [B_1(a,s) + B_2(a,s)]\,x(s)\,\mathrm{d}s \\ h(a) = \mathrm{e}^{-\sigma a}\int_0^a \mathrm{e}^{\sigma s}\lambda x(s)\,\mathrm{d}s \\ y(a) = \mathrm{e}^{-\gamma a}\int_0^a \mathrm{e}^{\gamma\tau}\sigma\mathrm{e}^{-\sigma\tau}\int_0^\tau \mathrm{e}^{\sigma s}\lambda x(s)\,\mathrm{d}s\,\mathrm{d}\tau \\ z(a) = \mathrm{e}^{-\pi a}\left[\int_0^a \mathrm{e}^{\pi s}\nu(s)x(s)\,\mathrm{d}s + \int_0^a \mathrm{e}^{\pi a'}\gamma\mathrm{e}^{-\gamma a'}\int_0^{a'}\mathrm{e}^{\gamma\tau}\sigma\mathrm{e}^{-\sigma\tau}\int_0^\tau \mathrm{e}^{\sigma s}\lambda x(s)\,\mathrm{d}s\,\mathrm{d}\tau\,\mathrm{d}a'\right], \end{cases} \tag{11}$$

where the function $\phi(a)$ is given by

$$\phi(a) = [\nu\,(a - a_1)]\,\theta\,(a - a_1)\,\theta\,(a_2 - a) + [\nu\,(a_2 - a_1)]\,\theta\,(a - a_2)\,, \tag{12}$$

which results from $\phi(a) = \int_0^a \nu(s)\,\mathrm{d}s$, and the kernels $B_1(a,s)$ and $B_2(a,s)$ are obtained from the equations

$$\begin{cases} B_1(a,s) &= \mathrm{e}^{-\lambda a - \phi(a)}\nu(s)\mathrm{e}^{\pi s}\int_s^a \mathrm{e}^{(\lambda-\pi)t + \phi(t)}\,\mathrm{d}t \\ B_2(a,s) &= \gamma\sigma\lambda\mathrm{e}^{-\lambda a - \phi(a)}\mathrm{e}^{\sigma s}\int_0^a\int_0^a\int_0^a \mathrm{e}^{(\lambda-\pi)t+\phi(t)}\mathrm{e}^{(\pi-\gamma)a'}\mathrm{e}^{(\gamma-\sigma)\tau} \\ &\qquad\qquad \times\theta\left(t - a'\right)\theta\left(a' - \tau\right)\theta\,(\tau - s)\,\mathrm{d}\tau\,\mathrm{d}a'\,\mathrm{d}t \\ &= \gamma\sigma\lambda\mathrm{e}^{-\lambda a - \phi(a)}\mathrm{e}^{\sigma s}\int_s^a\int_\tau^a\int_{a'}^a \mathrm{e}^{(\gamma-\sigma)\tau + (\pi-\gamma)a' + (\lambda-\pi)t + \phi(t)}\,\mathrm{d}\tau\,\mathrm{d}a'\,\mathrm{d}t. \end{cases} \tag{13}$$

These integrals can be calculated taking into account the relative positions among the ages a, s, t, a', τ, a_1 and a_2.

The kernels $B_1(a,s)$ and $B_2(a,s)$ can be written as

$$B_1(a,s)=\nu\left\{\left[\frac{e^{-\pi(a-s)}-e^{-(\lambda+\nu)(a-s)}}{\lambda+\nu-\pi}\right]\theta(a-a_1)\,\theta(a_2-a)-\left[\frac{\nu e^{-\lambda(a-a_2)}e^{-\pi(a_2-s)}}{(\lambda-\pi)(\lambda+\nu-\pi)}\right.\right.$$
$$\left.\left.+\frac{e^{-\nu(a_2-s)}e^{-\lambda(a-s)}}{\lambda+\nu-\pi}-\frac{e^{-\pi(a-s)}}{\lambda-\pi}\right]\theta(a-a_2)\right\}\theta(s-a_1)\,\theta(a_2-s) \qquad (14)$$

and

$$B_2(a,s)=\lambda\sigma\gamma\{[b_0(a-s)\,\theta(a_1-s)]\,\theta(a_1-a)+[b_1(a,s)\,\theta(a_1-s)$$
$$+b_2(a-s)\,\theta(s-a_1)\,\theta(a_2-s)]\,\theta(a-a_1)\,\theta(a_2-a)$$
$$+[b_3(a,s)\,\theta(a_1-s)+b_4(a,s)\,\theta(s-a_1)\,\theta(a_2-s)$$
$$+b_0(a-s)\,\theta(s-a_2)]\,\theta(a-a_2)\}, \qquad (15)$$

where the auxiliary functions $b_0(a-s)$, $b_1(a,s)$, $b_2(a-s)$, $b_3(a,s)$ and $b_4(a,s)$ are given by

$$b_0(a-s)=\frac{\frac{e^{-\sigma(a-s)}}{(\pi-\sigma)(\lambda-\sigma)}-\frac{e^{-\gamma(a-s)}}{(\pi-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{\frac{e^{-\pi(a-s)}}{(\gamma-\pi)(\sigma-\pi)}-\frac{e^{-\lambda(a-s)}}{(\gamma-\lambda)(\sigma-\lambda)}}{\lambda-\pi},$$

$$b_1(a,s)=\frac{\frac{e^{-\sigma(a-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)}-\frac{e^{-\gamma(a-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)}}{\gamma-\sigma}+\frac{e^{-\pi(a-s)}}{(\lambda+\nu-\pi)(\gamma-\pi)(\sigma-\pi)}+e^{-(\lambda+\nu)(a-a_1)}$$
$$\times\left[\frac{\frac{\nu e^{-\sigma(a_1-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)(\lambda-\sigma)}-\frac{\nu e^{-\gamma(a_1-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{\frac{\nu e^{-\pi(a_1-s)}}{(\lambda+\nu-\pi)(\gamma-\pi)(\sigma-\pi)}-\frac{e^{-\lambda(a_1-s)}}{(\gamma-\lambda)(\sigma-\lambda)}}{\lambda-\pi}\right],$$

$$b_2(a-s)=\frac{\frac{e^{-\sigma(a-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)}-\frac{e^{-\gamma(a-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)}}{\gamma-\sigma}+\frac{\frac{e^{-\pi(a-s)}}{(\gamma-\pi)(\sigma-\pi)}-\frac{e^{-(\lambda+\nu)(a-s)}}{(\gamma-\lambda-\nu)(\sigma-\lambda-\nu)}}{\lambda+\nu-\pi},$$

$$b_3(a,s)=\frac{\frac{e^{-\sigma(a-s)}}{(\pi-\sigma)(\lambda-\sigma)}-\frac{e^{-\gamma(a-s)}}{(\pi-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{\frac{e^{-\pi(a-s)}}{(\gamma-\pi)(\sigma-\pi)}-\frac{e^{-\nu(a_2-a_1)}e^{-\lambda(a-s)}}{(\gamma-\lambda)(\sigma-\lambda)}}{\lambda-\pi}$$
$$+\nu e^{-\lambda(a-a_2)}\left[e^{-(\lambda+\nu)(a_2-a_1)}\frac{\frac{e^{-\sigma(a_1-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)(\lambda-\sigma)}-\frac{e^{-\gamma(a_1-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}\right.$$
$$\left.-\frac{\frac{e^{-\sigma(a_2-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)(\lambda-\sigma)}-\frac{e^{-\gamma(a_2-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{e^{-(\lambda+\nu)(a_2-a_1)}e^{-\pi(a_1-s)}-e^{-\pi(a_2-s)}}{(\lambda+\nu-\pi)(\gamma-\pi)(\sigma-\pi)(\lambda-\pi)}\right]$$

and

$$b_4(a,s)=\frac{\frac{e^{-\sigma(a-s)}}{(\pi-\sigma)(\lambda-\sigma)}-\frac{e^{-\gamma(a-s)}}{(\pi-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{e^{-\pi(a-s)}}{(\lambda-\pi)(\gamma-\pi)(\sigma-\pi)}-e^{-\lambda(a-a_2)}$$
$$\times\left[\frac{\frac{\nu e^{-\sigma(a_2-s)}}{(\pi-\sigma)(\lambda+\nu-\sigma)(\lambda-\sigma)}-\frac{\nu e^{-\gamma(a_2-s)}}{(\pi-\gamma)(\lambda+\nu-\gamma)(\lambda-\gamma)}}{\gamma-\sigma}+\frac{\frac{\nu e^{-\pi(a_2-s)}}{(\gamma-\pi)(\sigma-\pi)(\lambda-\pi)}+\frac{e^{-(\lambda+\nu)(a_2-s)}}{(\gamma-\lambda-\nu)(\sigma-\lambda-\nu)}}{\lambda+\nu-\pi}\right].$$

Note that all the auxiliary functions are combinations of exponentially decaying functions.

As in the preceding section, the solution for $x(a)$ is obtained from the first equation of the system (11) if we have estimated values for λ and ν; reciprocally, if we have an estimated $x(a)$ then we can calculate λ and ν. Moreover, the first equation of the system (11) is a non-homogeneous linear Volterra integral equation with respect to the unknown variable $x(a)$. Additionally, the kernels $B_1(a, s)$ and $B_2(a, s)$ are piecewise continuous with respect to the ages a and s, which make them quadratically integrable functions (L_2-*functions*) on $[0, a] \times [0, a]$. Therefore, we have only one solution for $x(a)$ (Tricomi, 1985) when a finite vaccination rate is considered.

Observe that the system of integral equations (8) of the preceding section can be obtained from the system of equations (11) letting $\nu = 0$, and the kernel given by (9) corresponds to the auxiliary function $b_0(a - s)$, if we substitute λ by λ_0.

The new equilibrium value, given by the system of integral equations (11), can be either trivial (eradication of the disease) or non-trivial (disease controlled at a low prevalence) with respect to the force of infection. In the next section we show more details about these two equilibrium points.

3. Analysis of the model

We supposed that a vaccination strategy is introduced in a community originally at a natural endemic equilibrium, and we scaled the initial time, $t = 0$, with the beginning of the vaccination programme. The new equilibrium values corresponding to the system of equations (1) were determined. We present more results related to the equilibrium values.

3.1 *Before the introduction of a vaccination strategy*

We took the natural endemic situation in the community (Anderson & May, 1985), just before introduction of a vaccination programme, as the initial conditions given by (6). Hence, from the first equation of (8) we can obtain the fraction of susceptible individuals x_0 in the community as

$$x_0 = \frac{\int_0^\infty x_0(a) N_0(a)\, \mathrm{d}a}{\int_0^\infty N_0(a)\, \mathrm{d}a}, \tag{16}$$

where $N_0(a)$ was previously defined, and $x_0(a)$ is given by the first equation of system (8).

The fraction of susceptible individuals before the introduction of a vaccination strategy can be easily calculated. The value for $\int_0^\infty x_0(a) N_0(a)\, \mathrm{d}a$ can be obtained by multiplying both sides of the first equation of (8) by $N_0(a)$ and performing the integration, which is easily done, since the kernel is a function of difference between ages a and s, and is given by

$$x_0 = \frac{\mu(\mu + \sigma)(\mu + \gamma)(\mu + \pi)}{(\mu + \lambda_0)(\mu + \sigma)(\mu + \gamma)(\mu + \pi) - \lambda_0 \sigma \gamma \pi}. \tag{17}$$

This formula can be rewritten setting the average natural force of infection λ_0 as a function

of the fraction of susceptible individuals x_0, resulting in

$$\lambda_0 = \mu \frac{x_0^{-1} - 1}{1 - \frac{\sigma\gamma\pi}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}}. \tag{18}$$

This relation shows clearly the dependency of the force of infection with the loss of immunity rate π.

On the other hand, the average natural force of infection can be obtained from its definition given by (2). In order to do this, we solve the equilibrium system (10), with $\nu = 0$, in terms of $y_0(a)$, which results in the non-homogeneous linear Volterra integral equation

$$y_0(a) = \lambda_0\sigma \left[\frac{\frac{e^{-\gamma a}}{\gamma-\lambda_0} - \frac{e^{-\sigma a}}{\sigma-\lambda_0}}{\gamma-\sigma} + \frac{e^{-\lambda_0 a}}{(\gamma-\lambda_0)(\sigma-\lambda_0)} \right] + \pi \int_0^a B(a-s) y_0(s)\, ds. \tag{19}$$

Again, this equation can be integrated over all ages because the kernel B is a function of the difference between ages a and s. Therefore, substituting this equation into (2) in the steady state, and calculating the integration, we have

$$\lambda_0 = \mu \frac{R_0 - 1}{1 - \frac{\sigma\gamma\pi}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}}. \tag{20}$$

In this case, the *basic reproduction ratio* R_0 is given by

$$R_0 = \frac{\beta}{\beta^{\text{th}}}, \tag{21}$$

where the total contact rate $\beta = \beta' N$ is the number of infectious individuals met by all the susceptible individuals per year, and its threshold value β^{th} is defined by

$$\beta^{\text{th}} = \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma}. \tag{22}$$

We note that the *basic reproduction ratio* does not depend explicitly on the immunity loss rate (Anderson & May, 1991), although the average natural force of infection depends on this parameter.

Comparing formulae related to the average natural force of infection, given by (18) and (20), we can relate the *basic reproduction ratio* R_0 with the proportion of susceptible individuals x_0 by

$$R_0 = \frac{1}{x_0}. \tag{23}$$

This relation is valid only when the disease is endemic in the population. On the other way, this identity can be obtained considering that in the equilibrium, the *effective reproduction ratio* R, which obeys the relation $R = R_0 x_0$, is unity. The parameter R_0 is essentially a mathematical parameter since it cannot be measured directly from the field data, although it plays an important role in the stability analysis of the equilibrium points.

The solutions given by the system (8) were obtained supposing that $\lambda_0 > 0$ (according to (20) we must have $R_0 > 1$), which is always true if we have $x_0 < 1$, according to (23), or $\beta > \beta^{\text{th}}$, according to (21). When $\lambda_0 = 0$, the solutions become $x_0(a) = 1$ and $h_0(a) = y_0(a) = z_0(a) = 0$, and the age-density of susceptible individuals is given by $X_0(a) = N_0(a) = N^* e^{-\mu a}$. This case corresponds to $R_0 = x_0 = 1$ or $\beta = \beta^{\text{th}}$. Next, we treat the question about the stability of the trivial and non-trivial (with respect to the force of infection) equilibrium points.

Without a vaccination strategy, the system (1) does not depend on age. By integrating over all ages and dividing by the total population size, for instance $\bar{x}_0(t) = \int_0^\infty X_0(t, a)\, da/N$, the resulting system is given by

$$\begin{cases} \frac{d}{dt}\bar{x}_0(t) &= \mu + \pi\bar{z}_0(t) - [\beta\bar{y}_0(t) + \mu]\,\bar{x}_0(t) \\ \frac{d}{dt}\bar{h}_0(t) &= \beta\bar{y}_0(t)\bar{x}_0(t) - (\sigma + \mu)\,\bar{h}_0(t) \\ \frac{d}{dt}\bar{y}_0(t) &= \sigma\bar{h}_0(t) - (\gamma + \mu)\,\bar{y}_0(t) \\ \frac{d}{dt}\bar{z}_0(t) &= \gamma\bar{y}_0(t) - (\pi + \mu)\,\bar{z}_0(t), \end{cases} \tag{24}$$

where the force of infection is given by $\lambda_0(t) = \beta\bar{y}_0(t)$. This set of equations can be obtained from the system (30) given in the next section by letting $\nu = 0$.

The system of equations (24) has two equilibrium points. The first is given by the trivial equilibrium point ($\lambda_0 = 0$), with coordinates $\bar{x}_0 = 1$ and $\bar{h}_0 = \bar{y}_0 = \bar{z}_0 = 0$, and the non-trivial equilibrium point ($\lambda_0 > 0$), with coordinates

$$\begin{cases} \bar{x}_0 &= \frac{1}{R_0} \\ \bar{h}_0 &= \frac{\mu(\mu+\sigma)(\mu+\gamma)^2(\mu+\pi)(R_0-1)}{\beta\sigma[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]} \\ \bar{y}_0 &= \frac{\mu(\mu+\sigma)(\mu+\gamma)(\mu+\pi)(R_0-1)}{\beta[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]} \\ \bar{z}_0 &= \frac{\mu\gamma(\mu+\sigma)(\mu+\gamma)(R_0-1)}{\beta[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]}, \end{cases} \tag{25}$$

where R_0 is given by (21). The non-trivial equilibrium point is valid only for $R_0 > 1$, and for $R_0 \leqslant 1$ we have the trivial equilibrium point.

The stability of the above two equilibrium points is assessed by the eigenvalues related to the Jacobian matrix obtained from the system (24). Note that the above results are a particular form of the detailed solutions given in the next section by setting $\nu = 0$, hence we give a brief description about the stability. If $R_0 < 1$, then the trivial equilibrium point is locally asymptotically stable. Otherwise, the non-trivial equilibrium point is locally asymptotically stable.

The discussions about the methods to estimate the force of infection and the *basic reproduction ratio*, considering re-infection, were treated elsewhere (Yang & Silveira, 1998). In that paper the effects of the re-infection on the force of infection and on the *basic reproduction ratio* were analysed. All the results were applied to rubella considering the seroprevalence curve obtained from a community before the introduction of immunization against the rubella virus (Azevedo Neto *et al.*, 1994). Briefly, Yang & Silveira (1998) showed that the re-infection consideration resulted in two approaches: the calculation of

λ_0 from estimated $\hat{x}_0(a)$ and the calculation of R_0 from estimated $\hat{x}_0$. Both approaches depend on the seroprevalence survey before the introduction of the vaccination $S_0^+(a)$, from which they derived $\hat{x}_0(a)$ and $\hat{x}_0$, respectively, by the relations $1 - S_0^+(a)$ and $\int_0^\infty \left[1 - S_0^+(a)\right] N(a)\, \mathrm{d}a/N$.

We present two special cases with respect to the loss of immunity parameter. When $\pi = 0$, we have

$$\begin{cases} x_0(a) &= \mathrm{e}^{-\lambda_0 a} \\ x_0 &= \dfrac{\mu}{\mu + \lambda_0}, \end{cases} \tag{26}$$

and when $\pi = \infty$,

$$\begin{cases} x_0(a) &= \mathrm{e}^{-\lambda_0 a} + \pi \displaystyle\int_0^a \bar{B}(a-s) x_0(s)\, \mathrm{d}s \\ x_0 &= \dfrac{\mu\,(\mu+\sigma)\,(\mu+\gamma)}{(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\lambda_0) - \sigma\gamma\lambda_0}, \end{cases} \tag{27}$$

where

$$\bar{B}(a-s) = \lambda_0 \sigma \gamma \left[\frac{\mathrm{e}^{-\sigma(a-s)}}{(\sigma-\lambda_0)\,(\sigma-\lambda_0)} + \frac{\mathrm{e}^{-\gamma(a-s)}}{(\gamma-\lambda_0)\,(\gamma-\sigma)} + \frac{\mathrm{e}^{-\lambda_0(a-s)}}{(\gamma-\lambda_0)\,(\sigma-\lambda_0)} \right]$$

is the kernel.

3.2 *After the introduction of a vaccination strategy*

In the preceding section, we obtained the equilibrium values of the system (1) with vaccination rate given by (3). From the age-specific fraction of susceptible individuals in the equilibrium $x(a)$, given by the first equation of (11), we can calculate the fraction of susceptible individuals in the community x using (16) and substituting $x_0(a)$ by $x(a)$.

The fraction of susceptible individuals in the community under a vaccination strategy is given by

$$x = x_1 + \pi\,(x_2 + x_3)\,, \tag{28}$$

where x_1, x_2 and x_3 are

$$\begin{cases} x_1 &= \frac{\mu}{\mu+\lambda} \left\{ 1 - \frac{\nu \mathrm{e}^{-(\mu+\lambda)a_1}}{\mu+\nu+\lambda} \left[1 - \mathrm{e}^{-(\mu+\nu+\lambda)(a_2-a_1)} \right] \right\} \\ x_2 &= \nu\mu \int_{a_1}^{a_2} x(s) \mathrm{e}^{-\mu s} \left\{ \frac{1}{(\mu+\nu+\lambda)(\mu+\pi)} + \frac{\nu \left[\frac{\mathrm{e}^{-(\mu+\pi)(a_2-s)}}{\mu+\pi} - \frac{\mathrm{e}^{-(\mu+\nu+\lambda)(a_2-s)}}{\mu+\nu+\lambda} \right]}{(\lambda+\nu-\pi)(\mu+\lambda)} \right\} \mathrm{d}s \\ x_3 &= \mu\lambda\sigma\gamma \left[\int_0^{a_1} x(s) \mathrm{e}^{-\mu s} c_1(s)\, \mathrm{d}s + \int_{a_1}^{a_2} x(s) \mathrm{e}^{-\mu s} c_2(s)\, \mathrm{d}s \right. \\ &\quad \left. + \int_{a_2}^{\infty} \frac{x(s) \mathrm{e}^{-\mu s}}{(\mu+\lambda)(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}\, \mathrm{d}s \right], \end{cases} \tag{29}$$

with the auxiliary functions $c_1(s)$ and $c_2(s)$ given by

$$
\begin{aligned}
c_1(s) = {} & \frac{1}{(\mu+\lambda)(\mu+\sigma)(\mu+\gamma)(\mu+\pi)} - \frac{\nu}{\mu+\lambda+\nu} \\
& \times \left[\frac{\frac{e^{-(\mu+\sigma)(a_1-s)}}{(\mu+\sigma)(\lambda-\sigma)(\pi-\sigma)} - \frac{e^{-(\mu+\gamma)(a_1-s)}}{(\mu+\gamma)(\lambda-\gamma)(\pi-\gamma)}}{\gamma-\sigma} \right. \\
& \left. + \frac{\frac{e^{-(\mu+\pi)(a_1-s)}}{(\mu+\pi)(\gamma-\pi)(\sigma-\pi)} - \frac{e^{-(\mu+\lambda)(a_1-s)}}{(\mu+\lambda)(\gamma-\lambda)(\sigma-\lambda)}}{\lambda-\pi} \right] + \frac{\nu^2 e^{-(\mu+\lambda+\nu)(a_2-a_1)}}{(\mu+\lambda+\nu)(\mu+\lambda)} \\
& \times \left[\frac{e^{-(\mu+\pi)(a_1-s)}}{(\lambda+\nu-\pi)(\lambda-\pi)(\gamma-\pi)(\sigma-\pi)} \right. \\
& \left. + \frac{\frac{e^{-(\mu+\sigma)(a_1-s)}}{(\lambda+\nu-\sigma)(\lambda-\sigma)(\pi-\sigma)} - \frac{e^{-(\mu+\gamma)(a_1-s)}}{(\lambda+\nu-\gamma)(\lambda-\gamma)(\pi-\gamma)}}{\gamma-\sigma} \right] + \frac{\nu}{\mu+\lambda} \\
& \times \left[\frac{\frac{e^{-(\mu+\sigma)(a_2-s)}}{(\mu+\sigma)(\lambda+\nu-\sigma)(\pi-\sigma)} - \frac{e^{-(\mu+\gamma)(a_2-s)}}{(\mu+\gamma)(\lambda+\nu-\gamma)(\pi-\gamma)}}{\gamma-\sigma} \right. \\
& + \frac{e^{-(\mu+\pi)(a_2-s)}}{(\mu+\pi)(\lambda+\nu-\pi)(\gamma-\pi)(\sigma-\pi)} \\
& \left. + \frac{e^{-\nu(a_2-a_1)} e^{-(\mu+\lambda)(a_2-s)}}{(\mu+\lambda+\nu)(\pi-\lambda)(\gamma-\lambda)(\sigma-\lambda)} \right]
\end{aligned}
$$

and

$$
\begin{aligned}
c_2(s) = {} & \frac{1}{(\mu+\lambda+\nu)(\mu+\sigma)(\mu+\gamma)(\mu+\pi)} \\
& + \nu \left[\frac{\frac{e^{-(\mu+\sigma)(a_2-s)}}{(\mu+\sigma)(\lambda+\nu-\sigma)(\pi-\sigma)} - \frac{e^{-(\mu+\gamma)(a_2-s)}}{(\mu+\gamma)(\lambda+\nu-\gamma)(\pi-\gamma)}}{(\mu+\lambda)(\gamma-\sigma)} \right. \\
& \left. + \frac{\frac{e^{-(\mu+\pi)(a_2-s)}}{(\mu+\pi)(\gamma-\pi)(\sigma-\pi)} - \frac{e^{-(\mu+\lambda+\nu)(a_2-s)}}{(\mu+\lambda+\nu)(\gamma-\lambda-\nu)(\sigma-\lambda-\nu)}}{(\mu+\lambda)(\lambda+\nu-\pi)} \right].
\end{aligned}
$$

As the auxiliary functions related to the kernels, we have again a combination of exponentially decaying functions.

The above results were obtained considering the loss of immunity and a strategy where vaccination is applied to susceptible individuals in the age interval $[a_1,a_2]$. In order to present analytical results related to the stability of the equilibrium points, we consider a particular form for the vaccination rate, letting $a_1 = 0$ and $a_2 = \infty$ in (3).

The dynamical system corresponding to a constant vaccination applied at all ages is obtained by integrating the system of equations (1)–(4). The system of equations in terms

of the fractions of each class of individuals is given by

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t}\bar{x}(t) &= \mu + \pi\bar{z}(t) - [\beta\bar{y}(t) + \nu + \mu]\,\bar{x}(t) \\ \frac{\mathrm{d}}{\mathrm{d}t}\bar{h}(t) &= \beta\bar{y}(t)\bar{x}(t) - (\sigma + \mu)\,\bar{h}(t) \\ \frac{\mathrm{d}}{\mathrm{d}t}\bar{y}(t) &= \sigma\bar{h}(t) - (\gamma + \mu)\,\bar{y}(t) \\ \frac{\mathrm{d}}{\mathrm{d}t}\bar{z}(t) &= \nu\bar{x}(t) + \gamma\bar{y}(t) - (\pi + \mu)\,\bar{z}(t), \end{cases} \tag{30}$$

where $\bar{x}(t) = \int_0^\infty X(t,a)\,\mathrm{d}a/N$, and so on for other three compartments, and the force of infection is given by $\lambda(t) = \beta\bar{y}(t)$.

When there is a vaccination strategy, the new equilibrium values of the dynamical system (30) are

$$\begin{cases} \bar{x} &= \frac{(\mu+\sigma)(\mu+\gamma)}{\beta\sigma} \equiv \frac{1}{R_0} \\ \bar{h} &= \frac{\mu(\mu+\sigma)(\mu+\gamma)^2(\mu+\nu+\pi)}{\beta\sigma[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]}\,(R_\nu - 1) \\ \bar{y} &= \frac{\mu(\mu+\sigma)(\mu+\gamma)(\mu+\nu+\pi)}{\beta[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]}\,(R_\nu - 1) \\ \bar{z} &= \frac{\nu(\mu+\sigma)(\mu+\gamma)}{\beta\sigma(\mu+\pi)} + \frac{\mu\gamma(\mu+\sigma)(\mu+\gamma)(\mu+\nu+\pi)}{\beta(\mu+\pi)[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]}\,(R_\nu - 1)\,, \end{cases} \tag{31}$$

where R_ν is the *reproduction ratio* given by

$$R_\nu = \frac{\beta}{\beta_\nu^{\mathrm{th}}}, \tag{32}$$

with the threshold being given by

$$\beta_\nu^{\mathrm{th}} = \frac{(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\nu+\pi)}{\sigma\,(\mu+\pi)}\,. \tag{33}$$

Observe that we have the relation $R_\nu = R_0\,(\mu+\pi)\,/\,(\mu+\nu+\pi)$. The non-trivial force of infection is attained if we have $R_\nu > 1$, otherwise we have $\lambda = 0$. Observe the equality between the fractions of susceptible individuals before and after the introduction of a vaccination if $\lambda > 0$. When the vaccination eradicates the disease, we have

$$\begin{cases} \bar{x} &= \frac{\mu+\pi}{\mu+\nu+\pi} \\ \bar{z} &= \frac{\nu}{\mu+\nu+\pi} \end{cases} \tag{34}$$

and $\bar{h} = \bar{y} = 0$. This is the situation when the disease is eradicated by vaccination programme, and, hence, the resulting proportion of susceptible individuals is not equal to the value found before the introduction of the vaccination.

The stability of the trivial and non-trivial equilibrium points of the dynamical system (30) can be assessed by the roots (eigenvalues) of the characteristic equation $\Phi(\varphi)$

$$\Phi(\varphi) = \det(\mathbf{J} - \varphi\mathbf{I}) = 0,$$

where **I** is a 4×4 identity matrix and **J** is the Jacobian matrix obtained from the linearization of the system (30). The Jacobian matrix is given by

$$\mathbf{J} = \begin{bmatrix} -(\mu+\nu)-\beta\bar{y}(t) & 0 & -\beta\bar{x}(t) & \pi \\ \beta\bar{y}(t) & -(\mu+\sigma) & \beta\bar{x}(t) & 0 \\ 0 & \sigma & -(\mu+\gamma) & 0 \\ \nu & 0 & \gamma & -(\mu+\pi) \end{bmatrix},$$

which must be evaluated at the equilibrium point.

With respect to the stability of the trivial equilibrium point, substituting the coordinates of the trivial equilibrium point (which are given by (34) and $\bar{h} = \bar{y} = 0$), into the Jacobian, we can calculate the roots of the characteristic equation. The eigenvalues are

$$\begin{cases} \varphi_1 = -\mu \\ \varphi_2 = -(\mu+\nu+\pi) \end{cases}$$

plus the roots of the second-order polynomial

$$\varphi^2 + (2\mu+\sigma+\gamma)\,\varphi + (\mu+\sigma)\,(\mu+\gamma)\,(1-R_\nu) = 0.$$

The remaining two eigenvalues have negative real part if and only if $R_\nu < 1$. Therefore, the trivial equilibrium point is locally asymptotically stable if $R_\nu < 1$. Note that the condition $R_0 < 1$ in the absence of the vaccination can be obtained straightforwardly.

With respect to the stability of the non-trivial equilibrium point, we substitute the coordinates given by (31) into the Jacobian and calculate the roots of the characteristic equation given by

$$\begin{aligned} \Phi(\varphi) = &\left\{[(\mu+\sigma)+\varphi]\,[(\mu+\gamma)+\varphi] - \frac{\beta\sigma}{R_0}\right\} \\ &\times \{[(\mu+\pi)+\varphi]\,[(\mu+\nu+\beta A(R_\nu-1))+\varphi] - \pi\nu\} \\ &+\beta\sigma A\left\{\frac{\beta\,[(\mu+\pi)+\varphi]}{R_0} - \gamma\pi\right\}(R_\nu-1) = 0, \end{aligned}$$

where the positively defined A is given by

$$A = \frac{\mu\,(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\nu+\pi)}{\beta\,[(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\pi) - \sigma\gamma\pi]}.$$

This fourth-order polynomial has the φ–independent term given by the coefficient

$$c_0 = \mu\beta\sigma A\left[(\mu+\gamma+\pi) + \frac{(\mu+\gamma)\,(\mu+\pi)}{\sigma}\right](R_\nu-1),$$

which is positively defined if and only if $R_\nu > 1$. According to the conjecture given in Leite *et al.* (2000), the non-trivial equilibrium point is locally asymptotically stable

if $R_\nu > 1$. Note that the condition $R_0 > 1$ in the absence of the vaccination can be obtained straightforwardly. The stability analysis of a more elaborated mathematical model considering a fixed latent and nonpermanent immunity was made by Greenhalgh (1997), which, due to other non-linearities besides the product $\bar{x}(t)\bar{y}(t)$, presents a more extended stability analysis.

Note that the trivial equilibrium point is stable if $R_\nu < 1$, and the non-trivial equilibrium point is stable if $R_\nu > 1$. Therefore, the bifurcation from the trivial equilibrium point to the non-trivial equilibrium point occurs at the value $R_\nu = 1$.

We obtained two equations describing the distribution of the infection in the community: the age-specific fraction of susceptible individuals $x(a)$, given by (11), and the fraction of susceptible individuals in the community x, given by (28). Both quantities depend on the unknown force of infection λ and the vaccination rate ν. We must, therefore, consider a suitable device to estimate these unknown parameters.

To estimate the force of infection λ and the vaccination rate ν, we must be able to derive the quantities $\hat{x}(a)$ and $\hat{x}$. Both quantities can be derived from a seroprevalence survey $S^+(a)$ from a community under vaccination, supposing that the perturbation introduced by a vaccination strategy in the host–parasite system drove the system to the new steady state. Hence, $\hat{x}(a)$ and $\hat{x}$ can be obtained by the relations, respectively, $1 - S^+(a)$ and $\int_0^\infty \left[1 - S^+(a)\right] N(a)\, \mathrm{d}a/N$. Note that such a seroprevalence curve with regard to the vaccination in a steady state is not available, although the seroprevalence curve just after the introduction of the vaccination was obtained (Massad *et al.*, 1995). However, this kind of data is not appropriate to be used in the model, as in the initial moments just after the introduction of a vaccination there is an enhanced alteration in the force of infection (Yang, 1998).

The values related to the natural endemic situation can be compared with the equilibrium situation after the introduction of the vaccination. The link between the situations before and after the introduction of a vaccination strategy is dealt with in the next section.

3.3 *The effects of a vaccination strategy*

The steady states considering a vaccination strategy and a natural distribution of the infection in the community are linked by the system of partial differential equations (1). For this reason, the natural endemic situation is taken as the initial conditions, given by (6), which is modified each time constrained by the perturbed (by vaccination) system of dynamical equations (1) until the new equilibrium is reached. Note that the first equation of the system (11) and the equation (28) do not depend on the initial force of infection. Therefore, we must relate the new (under vaccination) equilibrium value with the natural (without vaccination) endemic situation. By the foregoing results, the natural endemic situation was characterized by a single force of infection λ_0 parameter, while the new steady state was characterized either by a singe vaccination rate ν parameter or by both vaccination rate ν and force of infection λ parameters. The first situation represents the eradication of the disease by vaccination while the last shows a vaccination controlling the disease to some extent.

Let us analyse the last case, when we must have two equations to estimate the unknown variables λ and ν. The first equation comes from the well known paradigm

which establishes that the equilibrium fractions of susceptible individuals before and after introduction of vaccination strategy (when the eradication of the disease is not achieved) are equal. Note that this relation can be seen clearly by comparing the first equations of the systems of solutions (25) and (31). The second equation is provided by the first equation of the system of integral equations (11).

To relate the known natural force of infection λ_0 with the unknown force of infection λ and vaccination rate ν, we equate (17) and (28) (Anderson & May, 1985) Yang (1997). This results in a transcendental equation

$$\frac{\mu\,(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\pi)}{(\mu+\lambda_0)\,(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\pi)-\lambda_0\sigma\gamma\pi} = x_1+\pi\,(x_2+x_3)\,, \tag{35}$$

where x_1, x_2 and x_3 are given by (29) and depend on λ and ν. From this equation we can obtain numerically, for instance, the vaccination rate for each value of the force of infection, that is, $\nu(\lambda)$.

Let us suppose that we can obtain an age-specific fraction of susceptible individuals $\hat{x}(a)$ from available seroprevalence data (at equilibrium). With the aim of calculating the force of infection in the presence of vaccination, we apply the convergence in the mean theory Tricomi (1985), that is

$$\int_0^\infty \left|x^j(a)-\hat{x}(a)\right|^2 \mathrm{d}a \to 0\,, \text{ with } j=0,1,2,\ldots, \tag{36}$$

where the λ-parametrized $x(a)$ forms a sequence of functions $\{x(a)\}$ provided by the first equation of the system (11) for each λ^j. This convergence in the mean can be treated as one-dimensional minimization (in relation to λ) based on the λ-parametrized function $x(a)$ with respect to the target function $\hat{x}(a)$ (Yang & Silveira, 1998). The value of λ that minimizes $\int_0^\infty \left|x(a)-\hat{x}(a)\right|^2 \mathrm{d}a$ can be calculated by the Brent method (Press *et al.*, 1989).

During the jth step in the Brent method, we must calculate $x^j(a)$ for each λ^j. First, the vaccination rate ν can be calculated for each λ^j using (35) to obtain $\nu(\lambda^j)$. Second, both λ^j and $\nu(\lambda^j)$ are used to calculate $x^j(a)$. This function can be obtained by the iterative method, because $x(a)$ is a unique solution of the non-homogeneous linear Volterra integral equation, given by the first equation of the system (11) with the kernels given by (14) and (15). Therefore, we can calculate the age-specific fraction of susceptible individuals by the iterative equation

$$x^j_{n+1}(a) = \mathrm{e}^{-\lambda^j a-\phi^j(a)} + \pi\int_0^a \left[B_1(a,s)+B_2(a,s)\right] x^j_n(s)\,\mathrm{d}s,$$
$$\text{with } n=0,1,2,\ldots,\ \text{for a fixed } j, \tag{37}$$

where $\phi^j(a)$ is calculated only in terms of $\nu(\lambda^j)$. On the other hand $x^j_{n+1}(a)$, $x^j_n(a)$ (which are, respectively, the $(n+1)$th and nth iterations of the age-specific fraction of susceptible individuals) and the kernels $B_1(a,s)$ and $B_2(a,s)$ are calculated in terms of λ^j and $\nu(\lambda^j)$. The initial approximation is given by $x^j_0(a) = x^{j-1}(a)$ (when $j=0$, we can use $x^0_0(a) = \hat{x}(a)$ as the initial approximation).

The natural force of infection can be calculated using (36) and (37) setting $\nu = 0$ (Yang & Silveira, 1998). For the age-specific fraction of susceptible individuals in a community prior to the start of vaccination, we use (8).

Next, if the vaccination rate is such that we could reach the condition of the eradication of the disease, then (35) does not remain valid any more, and we must estimate only the vaccination rate, setting $\lambda = 0$ in the first equation of (11). Therefore, the vaccination rate ν can be calculated by the minimization of $\int_0^\infty \left|x(a, \nu^j) - \hat{x}(a)\right|^2 \mathrm{d}a$, where $x(a, \nu^j)$ is given by the first equation of (11), with ν^j being the vaccination rate corresponding to the jth step of the Brent method. For each ν^j calculated in the minimization method, we can obtain the age-specific fraction of susceptible individuals by the iterative equation

$$x_{n+1}^j(a) = \mathrm{e}^{-\phi^j(a)} + \pi \int_0^a B_1(a, s) x_n^j(s)\,\mathrm{d}s, \quad \text{with } n = 0,1,2,\ldots, \text{ for a fixed } j, \tag{38}$$

where $\phi^j(a)$, $x_{n+1}^j(a)$, $x_n^j(a)$ (respectively, the $(n+1)$th and nth iterations of the age-specific fraction of susceptible individuals) and $B_1(a, s)$ are calculated in terms of ν^j.

Since the only available rubella seroprevalence survey is related to the moment just after the introduction of the vaccination (Massad *et al.*, 1995), we present two easy analytical examples.

3.3.1 *Vaccination of susceptible individuals of all ages.* We consider a vaccination scheme where the age interval vaccinated is given by $a_1 = 0$ and $a_2 = \infty$. By doing this, we can retrieve the classical results.

A vaccination carried out on all ages is described by the age-specific fraction of susceptible individuals obeying

$$x(a) = \mathrm{e}^{-(\lambda+\nu)a} + \pi \int_0^a \hat{B}(a - s) x(s)\,\mathrm{d}s, \tag{39}$$

where

$$\hat{B}(a - s) = \nu \frac{\mathrm{e}^{-\pi(a-s)} - \mathrm{e}^{-(\lambda+\nu)(a-s)}}{\lambda + \nu - \pi} + \lambda\sigma\gamma b_2\,(a - s)\,. \tag{40}$$

Integrating (39), the fraction of susceptible individuals in a community results in

$$x = \frac{\mu\,(\mu + \sigma)\,(\mu + \gamma)\,(\mu + \pi)}{(\mu + \lambda + \nu)\,(\mu + \sigma)\,(\mu + \gamma)\,(\mu + \pi) - \pi\,[\nu\,(\mu + \sigma)\,(\mu + \gamma) + \lambda\sigma\gamma]}. \tag{41}$$

These expressions can be related to the natural equilibrium values.

The equality of the susceptible individuals before and after the vaccination, which are given, respectively, by (41) and (17), results in

$$\lambda = \lambda_0 \left(1 - \frac{1}{R_\nu}\right), \tag{42}$$

where R_ν is the *reproduction ratio* when there is a vaccination strategy, given by

$$R_\nu = \frac{\nu^{\text{th}}}{\nu}, \tag{43}$$

with the threshold value for the vaccination rate ν^{th} being

$$\nu^{\text{th}} = \lambda_0 \left[1 + \pi \frac{(\mu + \sigma + \gamma)}{(\mu + \sigma)(\mu + \gamma)} \right]. \tag{44}$$

This *reproduction ratio* is given in terms of the force of infection λ_0, which is the same as (32) given in terms of the contact rate β. Note that $\lambda = \lambda_0$ for $\nu = 0$, and $\lambda = 0$ for all $\nu \geqslant \nu^{\text{th}}$. Observe that the minimum vaccination effort ν^{th} to reach the eradication of the disease increases linearly with the loss of immunity parameter.

Note that the solution given by (39) depends on the force of infection and the vaccination rate. Unless we have an infinite vaccination rate (while π is maintained finite), the age-specific fraction of the susceptible individuals is not a zero function. However, we note that the force of infection can be diminished down to zero.

We present two special cases with respect to the loss of immunity parameter. When $\pi = 0$, we have

$$\begin{cases} x(a) = \mathrm{e}^{-(\lambda+\nu)a} \\ x = \dfrac{\mu}{\mu + \lambda + \nu}, \end{cases}$$

and if we apply the equality of the fractions of susceptible individuals before and after the introduction of the vaccination, we have the same equations (42) and (43). However, (44) becomes

$$\nu^{\text{th}} = \lambda_0,$$

for the threshold vaccination rate. Finally, the *reproduction ratio* is given by

$$R_\nu = R_0 \frac{\mu}{\mu + \nu},$$

which comes from (46).

On the other extreme, when $\pi = \infty$, we have

$$\begin{cases} x(a) = \mathrm{e}^{-(\lambda+\nu)a} + \displaystyle\int_0^a \tilde{B}(a-s)x(s)\,\mathrm{d}s \\ x = \dfrac{\mu(\mu+\sigma)(\mu+\gamma)}{(\mu+\sigma)(\mu+\gamma)(\mu+\lambda) - \sigma\gamma\lambda}, \end{cases}$$

where

$$\tilde{B}(a-s) = \lambda\sigma\gamma \left[\frac{\mathrm{e}^{-\sigma(a-s)}}{(\sigma-\gamma)(\sigma-\lambda-\nu)} + \frac{\mathrm{e}^{-\gamma(a-s)}}{(\gamma-\lambda-\nu)(\gamma-\sigma)} + \frac{\mathrm{e}^{-(\lambda+\nu)(a-s)}}{(\lambda+\nu-\gamma)(\lambda+\nu-\sigma)} \right]$$
$$+ \nu \mathrm{e}^{-(\lambda+\nu)(a-s)}$$

TABLE 1 *The results related to the classical models are presented. We have the models SEIR, SEIRS and SEIS represented by the loss of immunity rate assuming, respectively, the values* $\pi = 0, 0 < \pi < \infty$ *and* $\pi = \infty$

SEIR	SEIRS	SEIS
$\lambda_0 = \mu\,(R_0 - 1)$	$\lambda_0 = \frac{\mu(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi}\,(R_0 - 1)$	$\lambda_0 = \frac{(\mu+\sigma)\,(\mu+\gamma)}{\mu+\sigma+\gamma}\,(R_0 - 1)$
$\lambda = \lambda_0\left(1 - \frac{\nu}{\nu^{\text{th}}}\right)$	$\lambda = \lambda_0\left(1 - \frac{\nu}{\nu^{\text{th}}}\right)$	$\lambda = \lambda_0$
$\nu^{\text{th}} = \lambda_0$	$\nu^{\text{th}} = \lambda_0\left[1 + \pi\frac{(\mu+\sigma+\gamma)}{(\mu+\sigma)(\mu+\gamma)}\right]$	$\nu^{\text{th}} = \infty$

is the kernel. If we apply the equality of the fractions of susceptible individuals before and after the introduction of the vaccination, we have

$$\lambda = \lambda_0,$$

which implies that (44) must be given by

$$\nu^{\text{th}} = \infty,$$

for the threshold vaccination rate. This shows clearly that the vaccination as a eradicating mechanism is related only to those infections which induce to some degree of immunity.

For a strategy that vaccinates susceptible individuals at all ages, the classical results can be retrieved from the above equations. In Table 1 we summarize the results related to SEIR, SEIRS and SEIS models.

Note that we have $R_\nu^{-1} = \nu/\nu^{\text{th}}$ and $R_0 = 1/x_0$. From Table 1, which presents the results related to a vaccination carried out over all ages, we can assess some effects of the re-infection in the distribution of an infection in a community.

First, the force of infection increases monotonically and reaches the asymptote with increasing loss of immunity rate. If $\sigma = \gamma = 30 \gg \mu = 1/60$ (in years^{-1}), the asymptotic force of infection (related to $\pi = \infty$) is around 900 times greater than the force of infection related to the lifelong immunity ($\pi = 0$). However, the *basic reproduction ratio* is not affected by the loss of immunity rate and maintains its value (consequently the fraction of susceptible individuals is also fixed) whatever the force of re-infection that is taken into account. Therefore, for a fixed *basic reproduction ratio* value (the contact rate is then fixed), the increase in the force of infection with increasing loss of immunity rate is explained by an increase in the number of infectious individuals circulating in a community. Hence, if the disease does not induce immunity, we must have an increase in the number of infectious individuals circulating in the community around 900 times the one obtained when considering the lifelong immunity, while the number of recovered individuals goes to zero.

Second, the threshold vaccination rate increases linearly with the increasing loss of immunity rate. Considering the above values for σ, γ and μ, we have a small value (0·067) for the inclination of the line. This has important implications when vaccination strategy is considered to eradicate a disease. With the increasing loss of immunity rate, the great number of infectious individuals leads to an increase of the required vaccination effort

(higher number of susceptible individuals must be protected) for the eradication of the disease.

Suppose that we have a seroprevalence curve obtained from field data. Then, we can calculate the fraction of susceptible individuals x_0 in this community, and the *basic reproduction ratio* R_0 can be calculated as its inverse. If we do not have any kind of information about the loss of acquired immunity, then we must theoretically assess the possible scenarios due to the re-infection. Since R_0 is fixed, the contact rate β is also fixed and the force of infection increases due to the increase in the number of infectious individuals in the community. Note that the loss of immunity results in the increasing number of susceptible individuals. However, these increased susceptible individuals are removed to other compartments by the high number of infectious individuals, in order to maintain the fraction of susceptible individuals at a fixed value. Therefore, the force of infection, given by (18), can be rewritten as

$$\lambda_0 = \lambda_0^0 + \lambda_0^\pi,$$

where $\lambda_0^0 = \mu\,(R_0 - 1)$ corresponds to the force of infection without loss of immunity, and

$$\lambda_0^\pi = \frac{\pi\sigma\gamma\mu\,(R_0 - 1)}{(\mu+\sigma)\,(\mu+\gamma)\,(\mu+\pi) - \sigma\gamma\pi}$$

is the additional force of infection due to the loss of immunity. In a naive interpretation, this additional force of infection exhausts the part of the susceptible individuals increased by the loss of immunity, while the first λ_0^0 acts on the susceptible new-borns.

3.3.2 *Vaccination of susceptible individuals for an age interval without loss of immunity.* Let us consider the case where the infection and the vaccine induce lifelong immunity and the vaccination is carried out on an age interval.

In this situation we have

$$x(a) = \mathrm{e}^{-\lambda a - \phi(a)}$$

for the age-specific fraction of susceptible individuals, and

$$x = \frac{\mu}{\mu+\lambda}\left\{1 - \frac{\nu \mathrm{e}^{-(\mu+\lambda)a_1}}{\mu+\nu+\lambda}\left[1 - \mathrm{e}^{-(\mu+\nu+\lambda)(a_2-a_1)}\right]\right\}$$

for the fraction of susceptible individuals in a community. Suppose that $\lambda > 0$ and the fractions of susceptible individuals before and after the introduction of vaccination are equal. Therefore, we have the relation

$$\mu + \lambda_0 = \frac{\mu+\lambda}{1 - \frac{\nu \mathrm{e}^{-(\mu+\lambda)a_1}}{\mu+\nu+\lambda}\left[1 - \mathrm{e}^{-(\mu+\nu+\lambda)(a_2-a_1)}\right]}, \tag{45}$$

which shows that $\lambda = 0$ can be achieved with finite value of ν if we choose a_1 appropriately and $a_2 > a_1$ (Yang, 1997).

The *basic reproduction ratio* R_0 does not depend on the loss of immunity parameter and this is given by (21). When a vaccination strategy is introduced in a community, we can calculate the *reproduction ratio*, denoted by R_ν. This calculation is based on the spectral radius theory (Dezotti & Yang, 2000), and is given by

$$R_\nu = R_0 \left\{ 1 - \frac{\nu \mathrm{e}^{-\mu a_1}}{\mu + \nu} \left[1 - \mathrm{e}^{-(\mu+\nu)(a_2 - a_1)} \right] \right\}. \tag{46}$$

Note that we have $R_{\nu=0} = R_0$. We can calculate the threshold vaccination rate ν^{th} above which the disease can be eradicated setting $R_\nu = 1$ in the equation. Note that this threshold value can also be obtained if we change appropriately (45) letting $\lambda = 0$.

4. Conclusion

We have proposed and analysed a model taking into account the loss of immunity induced by both vaccine and natural infection. The framework presented here was essentially theoretical due to the fact that we do not have any seroprevalence data after the introduction of vaccination. However, we presented some results related to the effects of the re-infection on the epidemiological values.

Theoretically, we showed that when a vaccination strategy results in the eradication of the disease, an appropriate methodology is related to the application of the convergence in the mean theory on the age-specific fraction of susceptible individuals. But, when a vaccination strategy does not eradicate the disease, we must relate the force of infection before the vaccination with the force of infection after the vaccination and the corresponding vaccination rate. An appropriate methodology consists in applying the equality of the fractions of susceptible individuals before and after the introduction of the vaccination and, then, we apply the convergence in the mean theory on the age-specific fraction of susceptible individuals. Note that the target age-specific fraction of susceptible individuals must be obtained from steady-state seroprevalence data.

When vaccine is applied to susceptible individuals in all ages, we showed that the natural force of infection λ_0 and the vaccination effort ν^{th} increase proportionally to the loss of immunity parameter π, while the *basic reproduction ratio* R_0 remains unaltered. The constant R_0 means that we have the same amount of the secondary cases generated by a primary case for all values of the loss of immunity rate, but the number of infectious individuals increases. For this reason, we have a higher incidence rate with the increasing loss of immunity rate.

When we consider the question of the re-infection we conclude that the eradication effort depends not only on the *basic reproduction ratio*, but also on the force of infection. This can be seen clearly from the relation of the force of infection with the threshold vaccination rate, which increases with increasing loss of immunity rate. Consequently, we must obtain information about the period of time that the immunity can protect individuals in order to determine a suitable vaccination strategy.

Since we dealt with a constant contact rate at all ages, the force of infection does not depend on age, and the corresponding age-specific fraction of susceptible individuals is an exponentially decaying function. We can improve this model by taking into account a more realistic age-dependent contact rate (Yang, 1999a). The methodology presented here

to calculate the force of infection by the convergence in the mean theory can also be a suitable device to estimate the immunity loss rate, together with the parameters related to the age-dependent contact rate (Yang, 1999b).

Acknowledgements

We wish to thank the anonymous referee's helpful comments, which greatly helped to clarify this paper. Financial support was received from CNPq grant # 300627/93-9 (RE).

References

ANDERSON, R. M. & MAY, R. M. (1985) Age-related change in the rate of disease transmission: Implications for design of vaccination programmes. *J. Hyg. Camb.*, **94**, 364–436.

ANDERSON, R. M. & MAY, R. M. (1991) *Infectious diseases of humans: Dynamics and control*. Oxford: Oxford University Press.

AZEVEDO NETO, R. S., SILVEIRA, A. S. B., NOKES, D. J. YANG, H. M. *et al.* (1994) Rubella seroepidemiology in a non-immunized population of São Paulo State, Brazil. *Epidemiol. Infect.*, **113**, 161–173.

COOKE, K. L. & VAN DEN DRIESSCHE, P. (1996) Analysis of an SEIRS epidemic model with two delays. *J. Math. Biol.*, **35**, 240–260.

COUTINHO, F. A. B., MASSAD, E., BURATTINI, M. N., YANG, H. M. & AZEVEDO NETO, R. S. (1993) Effects of vaccination programmes on transmission rates of infections and related threshold conditions for control. *IMA J. Math. Appl. Med. Biol.*, **10**, 187–206.

DEZOTTI, C. H. & YANG, H. M. (2000) *Teoria do raio espectral e o esforço de vacinação mínimo para infecções de transmissão direta, In: Proceedings—XXII CNMAC, Santos, S.P., 13–17 de Setembro de 1999* pp. 45–59.

DIETZ, K. (1975) Transmission and control of arbovirus diseases. *Proceedings of SIMS Conference on Epidemiology, Alta, Utah, July 8–12, 1974* (D. Ludwig & K. L. Cooke, eds). SIAM, PA, pp. 104–121.

GREENHALGH, D. (1990) Vaccination campaigns for common childhood diseases. *Math. Biosc*, **100**, 201–240.

GREENHALGH, D. (1997) Hopf bifurcation in epidemic models with a latent period and nonpermanent immunity. *Math. Comput. Modelling*, **25**, 85–107.

GUERRA L.M. PAIVA, A. L., ROSSI, A. JR. PAVIA, L. M. *et al.* (1999) Prevalence of antibodies against measles among pediatricians in a teaching hospital. *Rev. Saúde Pública*, **33**, 374–378.

LEITE, M. B. F., BASSANEZI, R. C. & YANG, H. M. (2000) The *basic reproduction ratio* for a model of directly transmitted infections considering the virus charge and the immunological response. *IMA J. Math. Appl. Med. Biol.*, **17**, 15–31.

MASSAD, E., BURATTINI, M. N., AZEVEDO NETO, R. S., YANG, H. M., COUTINHO, F. A. B. & ZANETTA, D. M. T. (1994) A model-based design of a vaccination strategy against rubella in a non-immunized community of São Paulo State, Brazil. *Epidemiol. Infect.*, **112**, 579–594.

MASSAD, E., AZEVEDO NETO, R. S., BURATTINI, M. N., ZANETTA, D. M. T., COUTINHO, F. A. B. YANG, H. M. *et al.* (1995) Assessing the efficacy of a mixed vaccination strategy against rubella in São Paulo, Brazil. *Intern. J. Epidemiol.*, **24**, 842–850.

PRESS, W. H., FLANNERY, B. P., TEUKOLSKY, S. A. & VETTERLING, W. T. (1989) *Numerical recipes: The art of scientific computing (FORTRAN Version)*. Cambridge: Cambridge University Press.

ROUDERFER, V., BECKER, N. G. & HETHCOTE, H. W. (1994) Waning immunity and its effects on vaccination schedules. *Math. Biosc.*, **124**, 59–82.

SCHWARTZ, I. B. & SMITH, H. L. (1983) Infinite subharmonic bifurcation in an SEIR epidemic model. *J. Math. Biology*, **18**, 233–253.

TRICOMI, F. G. (1985) *Integral equations*. New York: Dover.

TRUCCO, E. (1965a) Mathematical model for cellular system. The von Foerster equations, Part I. *Math. Bioph.*, **27**, 285–303.

TRUCCO, E. (1965b) Mathematical model for cellular system. The von Foerster equations, Part II. *Math. Bioph.*, **27**, 449–471.

YANG, H. M. (1997) Impacto da vacinação nas infecções de transmissão direta—Epidemiologia através de modelo matemático (port.) Thesis: IMECC—UNICAMP.

YANG, H. M. (1998) Modelling vaccination strategy against directly transmitted diseases using a series of pulses. *J. Biol. Systems*, **6**, 187–212.

YANG, H. M. & SILVEIRA, A. S. B. (1998) The loss of immunity in directly transmitted infections modeling: Effects on the epidemiological parameters. *B. Math. Biol.*, **60**, 355–372.

YANG, H. M. (1999a) Directly transmitted infections modeling considering age-structured contact rate. *Math. Comput. Modelling*, **29**, 39–48.

YANG, H. M. (1999b) Directly transmitted infections modeling considering age-structured contact rate - Epidemiological analysis. *Math. Comput. Modelling*, **29**, 11–30.

YANG, H. M. (2001) Modeling directly transmitted infections in a routinely vaccinated population—The force of infection described by Volterra integral equation. *Appl. Math. Comput.*, **122**, 27–58.