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Modeling directly transmitted infections in a routinely vaccinated population – the force of infection described by a Volterra integral equation ☆

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Abstract

We present the time dependent analysis of a model taking into account a special immunization strategy, that is, susceptible individuals comprised on an age interval are vaccinated. Vaccination is the main protective mechanism against many directly transmitted infections. But, when a vaccination strategy is introduced, the pattern of the disease distribution in a community suffers alterations, which propagate along time until a new equilibrium scenario of the disease is attained. From the model, the time dependent force of infection, described by a non-linear Volterra integral equation, can be obtained by applying the characteristic method to solve a system of partial differential equations. Also the following correlated variables to the force of infection can be obtained: the average age of the acquisition of the first infection, the rate of new cases of infection and, in the case of rubella infection, the risk of infection. From the results, one of the main conclusions relates that the increasing in the average age of the acquisition of the first infection in not always true. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

The introduction of any form of vaccination strategy in a community constitutes a perturbation to a host-parasite system, which leads the epidemiological dynamics to go through unexpected and, sometimes, undesirable patterns like damped oscillations in the force of infection (e.g., [2,17,21,22]). One of the expected effects of any vaccination schedule is a substantial reduction in the force of infection in the new steady state equilibrium value. This reduction should be observed after a variable period of time since the introduction of the vaccine. On the other hand, the reduction in the force of infection increases the average age of the acquisition of the first infection, e.g., [2]. This result was obtained by considering that the force of infection correlates inversely with the average age of the acquisition of the first infection, which is always valid if a vaccination is carried out over all ages. This increase may be considered as an adverse effect, depending on the disease the vaccination strategy is supposed to control. For instance, in the case of rubella, an increase in the average age of the acquisition of the first infection may result in an increased incidence of the congenital rubella syndrome (CRS) when infection occurs in the first trimester of pregnancy.

Almost all papers on directly transmitted infections have used the above analysis considering a mathematical model incorporating a vaccination scheme and comparing between the steady state equilibrium values before and after the introduction of a vaccination strategy [1,4,12]. Two pioneering exceptions are the studies of rubella by Knox [10] and of measles by Cvjetanovic et al. [5], who presented computer-simulated studies, but, according to Anderson and May [2], with some wrong conclusions. Moreover, latter authors analyzed the time dependent vaccination effects.

In this paper we propose a model which considers the vaccination programme being carried out on a fixed age interval. This consideration results in an age structured model consisting of a system of partial differential equations. Trucco [19] applied this time and age dependent system of equations to the cellular growth, and Dietz [6] used, by the first time, these equations for the description of the age dependency in a vaccination programme. Our task is to study the dynamics of directly transmitted infections from the introduction of a vaccination strategy until the system reaches the new equilibrium. System of equations is solved by the characteristic method [20], which results in the force of infection being described by a non-linear Volterra integral equation. The form of the vaccination rate proposed here permits us to verify if a vaccination strategy always increases the average age of the acquisition of the first infection.

We apply this model to study rubella. For this purpose, we use the seroprevalence data for rubella infection obtained from a community never vaccinated [3], in order to provide the initial and boundary conditions needed to

solve system of equations. From the time dependent force of infection we calculate the following time dependent correlated variables: the average age of the acquisition of the first infection (mean age, hereafter), the rate of new cases of infection (new cases, hereafter) and the risk of CRS. Also, the new equilibrium value attained by the dynamics system is calculated.

2. The model

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 number of individuals with age a at time t who are susceptible, non-infectious (latent), infectious and immune. The dynamics of directly transmitted infections can be described by the following set of partial differential equations

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

where

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

is the force of infection, μ the natural mortality rate, σ^{-1} and γ^{-1}, respectively, the average incubation and recovery periods, $v(a)$ the vaccination rate and $\beta'(a,a')$ is the contact rate between susceptible individuals of age a with infectious individuals of age a'. In this model we are not considering the loss of immunity and the maternally derived antibodies.

We consider the dynamics system (1) under the following assumptions:

(a) Individuals comprised on an age interval are under a constant vaccination rate. This assumption can be set as

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

where $\theta(x)$ is the step or Heaviside function, and a_1 and a_2 are, respectively, the lower and upper bounds of the age interval vaccinated. This vaccination scheme generalizes the model analyzed by Anderson and May and by Hethcote. Anderson and May [2] considered in their model a vaccination rate being carried out over a selected proportion p of all susceptible individuals regardless their ages, by letting $a_1=0$ and $a_2\to\infty$. Hethcote [9], in his turn, analyzed a

model where a proportion p of susceptible individuals on a specific age is vaccinated, by letting $a_2 \to a_1$, that is, the vaccination was described by the Dirac delta function $\delta(a - a')$, where a' is the specific age at which the susceptible individuals are vaccinated.

(b) The per capita contact rate is assumed to be constant over all ages, that is,

$$\beta'(a, a') = \beta'. \tag{4}$$

This contact rate, which does not consider the heterogeneously mixing among different age groups (e.g., [1,4,7,16,24,25]), produces an age independent force of infection. However, if seroprevalence data are available, the force of infection can be calculated as the average with respect to age of the estimated age specific force of infection [14].

Under the above assumptions, the first equation of system (1) can be written as

$$\frac{\partial}{\partial t}x(t, a) + \frac{\partial}{\partial a}x(t, a) = -[\mu + \lambda(t) + v\theta(a - a_1)\theta(a_2 - a)]x(t, a), \tag{5}$$

where

$$x(t, a) = \frac{X(t, a)}{N} \tag{6}$$

is the age specific fraction of susceptible individuals, and N is the size of a constant population. The second and the third (this multiplied by β') equations of system (1) can be integrated over all ages, yielding

$$\frac{\mathrm{d}}{\mathrm{d}t}h(t) = \lambda(t)\chi(t) - (\mu + \sigma)h(t), \qquad \frac{\mathrm{d}}{\mathrm{d}t}\lambda(t) = \beta\sigma h(t) - (\mu + \gamma)\lambda(t), \tag{7}$$

where $\beta = \beta' N$ is the contact rate, that is, the number of infectious individuals met by a susceptible individual per year, and

$$\begin{aligned} \chi(t) &= \int_0^\infty x(t, a)\,\mathrm{d}a, \\ h(t) &= \frac{\int_0^\infty H(t, a)\,\mathrm{d}a}{N}, \\ \lambda(t) &= \frac{\beta\int_0^\infty Y(t, a)\,\mathrm{d}a}{N} \end{aligned} \tag{8}$$

are, respectively, the fractions of susceptible and non-infectious individuals and the force of infection. Finally, the fraction of immune individuals, given by

$$z(t) = 1 - \chi(t) - h(t) - \frac{1}{\beta}\lambda(t), \tag{9}$$

is decoupled from system (1).

Note that the vaccination rate considered in this model, given by the expression (3), permits us to analyze the two main objectives of vaccination programme with respect to rubella infection. By an appropriate choice of a_1 and a_2, we can attain the eradication of the disease or the decrease in the number of cases of CRS. Of course, the model proposed by Hethcote also permits this analysis, but the difficult task of vaccinating the individuals exactly at the specific age remains.

3. Time dependent dynamics

In this section we deal with the time dependent epidemiological analysis of directly transmitted infections described by Eqs. (5), (7) and (9). To solve these equations, in Section 3.1 we derive the initial and boundary conditions related to Eq. (5) from rubella seroprevalence survey. In Section 3.2 we calculate the time dependent solution for $x(t,a)$, and substituting it into Eq. (7), we can obtain the force of infection and its correlated variables. Finally, the asymptotic values are given in Section 3.3.

3.1. The initial equilibrium values

In this section we provide the initial and boundary conditions to solve the Eqs. (5) and (7), by assuming that the population was at equilibrium [2] before the introduction of the vaccination strategy.

First, let us consider the necessary conditions to solve uniquely Eq. (5). The boundary condition and the initial age specific fraction of susceptible individuals are given, respectively, by

$$\begin{aligned} &x(t,0) = \mu, \\ &x_0(a) = \mu \exp\left(-(\mu+\lambda_0)a\right), \end{aligned} \tag{10}$$

with λ_0 being the natural (before the introduction of a vaccination strategy) force of infection. Observe that all the new-borns are considered susceptible because we are not considering the maternally derived antibodies. The age specific fraction of susceptible individuals was obtained from Eq. (5) setting $v = 0$.

With respect to the natural force of infection λ_0, we can calculate it from seroprevalence data. Calling the fitted proportion of seropositives as $S^+(a)$, we have, from the catalytic approach [14],

$$\begin{aligned} &\hat{x}_0(a) = 1 - S^+(a), \\ &\hat{\lambda}_0(a) = -\frac{\mathrm{d}}{\mathrm{d}a}\ln[\hat{x}_0(a)]. \end{aligned} \tag{11}$$

On the other hand, we can estimate the average natural force of infection as

$$\lambda_0 = \frac{\int_0^\infty \hat{\lambda}_0(a)\hat{x}_0(a)\,\mathrm{d}a}{\int_0^\infty \hat{x}_0(a)\,\mathrm{d}a}, \tag{12}$$

from the estimated age specific values $\hat{\lambda}_0(a)$ and $\hat{x}_0(a)$. We remark that this catalytic approach does not remain valid when we take into account the loss of immunity [23].

Second, the initial conditions for the fractions of susceptible and non-infectious individuals are given by

$$\begin{aligned} \chi_0 &= \mu/(\mu+\lambda_0), \\ h_0 &= (\mu\lambda_0)/((\mu+\lambda_0)(\mu+\sigma)), \end{aligned} \tag{13}$$

which were obtained by calculating the steady state equilibrium values of system (1) setting $v = 0$.

From the estimated λ_0, we can calculate the contact rate β, because this is closely related with the force of infection, accordingly Eq. (2). Hence, the steady state solution of system (1) with $v = 0$ results in

$$\beta = \frac{(\mu+\lambda_0)(\mu+\sigma)(\mu+\gamma)}{\mu\sigma}. \tag{14}$$

This expression, after rearrangement, relates λ_0 with the *basic reproduction ratio* R_0 through

$$\lambda_0 = \mu[R_0 - 1], \tag{15}$$

where $R_0 = \beta/\beta^{\mathrm{th}}$, with

$$\beta^{\mathrm{th}} = \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma} \tag{16}$$

being the threshold contact rate [2]. Note that if $R_0 > 1$, then we have $\lambda_0 > 0$ (endemicity), and if $R_0 \leqslant 1$, then we have $\lambda_0 = 0$ (disease free).

Finally, we assume that the introduction of a vaccination strategy does not change the contact pattern among individuals in the community, that is, β is unchanged.

3.2. The time dependent force of infection and its correlated variables

In order to obtain the time dependent force of infection, we calculate the age specific fraction of susceptible individuals $x(t,a)$ solving Eq. (5) by applying the characteristic method [20], with the initial and boundary conditions given by the expression (10). The solution can be written as

$$x(t,a) = \begin{cases} \mu \exp(-(\mu+\lambda_0)(a-t)) \exp\left(-\int_0^t [\mu+\lambda(\eta)]\,\mathrm{d}\eta\right) \\ \quad \times \exp\left(-v\int_0^t \theta(\eta+a-t-a_1)\theta(a_2-a+t-\eta)\,\mathrm{d}\eta\right), \quad 0 \leqslant t < a, \\ \mu \exp\left(-\int_0^t [\mu+\lambda(t-a+\eta)]\,\mathrm{d}\eta\right) \\ \quad \times \exp\left(-v\int_0^t \theta(\eta-a_1)\theta(a_2-\eta)\mathrm{d}\eta\right), \quad t \geqslant a, \end{cases}$$

or, by letting $\eta + a - t = y$ in the first and $t - a + \eta = y$ in the second equations, we have

$$x(t,a) = \begin{cases} \mu \exp(-(\mu+\lambda_0)a) \exp(\lambda_0 t) \exp\left(-\int_0^t \lambda(y)\mathrm{d}y\right) \\ \quad \times \exp\left(-v\int_0^a \theta(y-a_1)\theta(a_2-y)\mathrm{d}y\right) \\ \quad \times \exp\left(v\int_0^{a-t} \theta(y-a_1)\theta(a_2-y)\,\mathrm{d}y\right), \quad 0 \leqslant t < a, \\ \mu \exp(-\mu a) \exp\left(-\int_0^t \lambda(y)\,\mathrm{d}y\right) \exp\left(-\int_0^{t-a} \lambda(y)\,\mathrm{d}y\right) \\ \quad \times \exp\left(-v\int_0^a \theta(y-a_1)\theta(a_2-y)\,\mathrm{d}y\right), \quad t \geqslant a. \end{cases} \tag{17}$$

Observe that this equation can be re-written taking into account the relative positions among t, a, a_1 and a_2. The solution (17) can be divided into two cases, depending on the values assigned to a_1 and a_2.

The first case is $a_2 < 2a_1$. The limitation in the value of a_2 may be appropriated to describe a routine vaccination strategy, where individuals on a limited age interval are vaccinated. In this case we have, for $0 \leqslant t < a_1$,

$$x(t,a) = \begin{cases} x_1^a(t,a), & 0 \leqslant a \leqslant t < a_1, \\ x_1^b(t,a), & 0 \leqslant t < a < a_1, \\ x_2^b(t,a), & 0 \leqslant t < a_1 \leqslant a < \min[t+a_1, a_2], \\ x_3^b(t,a), & 0 \leqslant t < a_1 \leqslant \min[t+a_1, a_2] \leqslant a \leqslant a_2, \\ x_4^b(t,a), & 0 \leqslant t < a_1 < a_2 < a < \max[t+a_1, a_2], \\ x_5^b(t,a), & 0 \leqslant t < a_1 < a_2 < \max[t+a_1, a_2] \leqslant a \leqslant t+a_2, \\ x_1^b(t,a), & 0 \leqslant t < a_1 < a_2 < t+a_2 < a, \end{cases} \tag{18}$$

where $\min[x,y]$ is the minimum value between x and y, and $\max[x,y]$ is the maximum value between x and y; for $a_1 \leqslant t \leqslant a_2$,

$$x(t,a) = \begin{cases} x_1^a(t,a), & 0 \leqslant a < a_1 \leqslant t \leqslant a_2, \\ x_2^a(t,a), & a_1 \leqslant a \leqslant t \leqslant a_2, \\ x_2^b(t,a), & a_1 \leqslant t < a \leqslant a_2, \\ x_4^b(t,a), & a_1 \leqslant t \leqslant a_2 < a < t+a_1, \\ x_5^b(t,a), & a_1 \leqslant t \leqslant a_2 < t+a_1 \leqslant a \leqslant t+a_2, \\ x_1^b(t,a), & a_1 \leqslant t \leqslant a_2 < t+a_2 < a \end{cases} \tag{19}$$

and for $t > a_2$,

$$x(t,a) = \begin{cases} x_1^a(t,a), & 0 \leqslant a < a_1 < a_2 < t, \\ x_2^a(t,a), & a_1 \leqslant a \leqslant a_2 < t, \\ x_3^a(t,a), & a_1 < a_2 < a \leqslant t, \\ x_4^b(t,a), & a_1 < a_2 < t < a < t + a_1, \\ x_5^b(t,a), & a_1 < a_2 < t < t + a_1 \leqslant a \leqslant t + a_2, \\ x_1^b(t,a), & a_1 < a_2 < t < t + a_2 < a, \end{cases} \tag{20}$$

where expressions $x_\cdot(t,a)$ are given in Appendix A.

The second case is $a_2 \geqslant 2a_1$. The unbounded value for a_2 may be appropriated to describe a mass vaccination campaign, where individuals comprised on a large age interval are vaccinated. In this case we have, for $0 \leqslant t < a_1$,

$$x(t,a) = \begin{cases} x_1^a(t,a), & 0 \leqslant a \leqslant t < a_1, \\ x_1^b(t,a), & 0 \leqslant t < a < a_1, \\ x_2^b(t,a), & 0 \leqslant t < a_1 \leqslant a < t + a_1, \\ x_3^b(t,a), & 0 \leqslant t < a_1 \leqslant t + a_1 \leqslant a \leqslant a_2, \\ x_5^b(t,a), & 0 \leqslant t < a_1 < a_2 < a \leqslant t + a_2, \\ x_1^b(t,a), & 0 \leqslant t < a_1 < a_2 < t + a_2 < a, \end{cases} \tag{21}$$

for $a_1 \leqslant t \leqslant a_2$,

$$x(t,a) = \begin{cases} x_1^a(t,a), & 0 \leqslant a < a_1 \leqslant y \leqslant a_2, \\ x_2^a(t,a), & a_1 < a \leqslant t \leqslant a_2, \\ x_2^b(t,a), & a_1 \leqslant t < a < \min[t + a_1, a_2], \\ x_3^b(t,a), & a_1 \leqslant t < \min[t + a_1, a_2] \leqslant a \leqslant a_2, \\ x_4^b(t,a), & a_1 \leqslant t \leqslant a_2 < a < \max[t + a_1, a_2], \\ x_5^b(t,a), & a_1 \leqslant t \leqslant a_2 < \max[t + a_1, a_2] \leqslant a \leqslant t + a_2, \\ x_1^b(t,a), & a_1 \leqslant t \leqslant a_2 < t + a_2 < a, \end{cases} \tag{22}$$

and for $t > a_2$ we have the same equations given by the expression (20).

The fraction of susceptible individuals $\chi(t)$ can be obtained by integrating the above age specific fraction $x(t,a)$ over all ages. Hence, we have, for $a_2 < 2a_1$,

$$\chi(t) = \begin{cases} \chi_1^a(t), & 0 \leqslant t \leqslant a_2 - a_1, \\ \chi_1^b(t), & a_2 - a_1 < t < a_1, \\ \chi_2^b(t), & a_1 \leqslant t \leqslant a_2, \\ \chi_3(t), & t > a_2, \end{cases} \tag{23}$$

and, when $a_2 \geqslant 2a_1$, we have

$$\chi(t) = \begin{cases} \chi_1^a(t), & 0 \leqslant t \leqslant a_1, \\ \chi_2^a(t), & a_1 < t < a_2 - a_1, \\ \chi_2^b(t), & a_2 - a_1 \leqslant t \leqslant a_2, \\ \chi_3(t), & t > a_2, \end{cases} \tag{24}$$

where expressions $\chi_\cdot(t)$ are given in Appendix A.

Now, by substituting the above expressions $\chi(t)$, successively, in the first and second equations of (7), with the initial conditions given by the expression (13), after some calculations we obtain the non-linear Volterra integral equation of the second kind [11]. Therefore, the time dependent force of infection is obtained as the solution of

$$\lambda(t) = f(t) + \int_0^t g(t-t')\lambda(t')\chi[t', \Lambda(t')]\,\mathrm{d}t', \tag{25}$$

where $\Lambda(t)$ is the integral function of the force of infection, that is,

$$\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s, \tag{26}$$

$f(t)$ is the transient term

$$f(t) = \left[\lambda_0 - h_0\frac{\beta\sigma}{\gamma-\sigma}\right]\exp\left(-(\mu+\gamma)t\right) + h_0\frac{\beta\sigma}{\gamma-\sigma}\exp\left(-(\mu+\sigma)t\right) \tag{27}$$

and $g(t-t')$ is the integrand of the secular term

$$g(t-t') = \frac{\beta\sigma}{\gamma-\sigma}\left[\exp\left(-(\mu+\sigma)(t-t')\right) - \exp\left(-(\mu+\gamma)(t-t')\right)\right]. \tag{28}$$

Observe that we have used the notation $\chi[t, \Lambda(t)]$ instead of $\chi(t)$. The expressions (27) and (28) are easily modified when $\gamma \to \sigma$. In this case, we must use the approximation $\exp[-(\gamma-\sigma)t] \sim 1-(\gamma-\sigma)t$ in the latter two expressions.

The integral equation (25) shows the following two features.

First, the function $f(t)$ and the kernel $g(t-t') \times \chi[t', \Lambda(t')]$, being a combination of decaying exponential functions, are quadratically integrable (L_2 function) and the kernel for the equation for $\lambda(t)$ can be shown to satisfy the Lipschitz condition with respect to $\lambda(t)$ (e.g., [4]). This implies that the non-linear Volterra Eq. (25) has only one solution [18], and, hence, can be solved numerically by successive iterations.

Second, when the eradication (the main objective of the vaccination strategy) of the disease is feasible, that is, the solution goes to zero when time goes on, we can note that the time to have extinction of the disease, called t_{er}, must be higher than a minimum time t_{m}. This minimum time can be obtained from the transient term of the integral equation

$$f(t_m) = \left[\lambda_0 - h_0 \frac{\beta\sigma}{\gamma - \sigma}\right] \exp\left(-(\mu+\gamma)t_m\right) + h_0 \frac{\beta\sigma}{\gamma-\sigma} \exp\left(-(\mu+\sigma)t_m\right) = \lambda_{er}, \tag{29}$$

where λ_{er} is the value of the force of infection under which the disease can be considered eradicated. For instance, considering $\lambda_0 \sim 0.1\ \mathrm{yr}^{-1}$, $\lambda_{er} \sim 10^{-12}\ \mathrm{yr}^{-1}$, $\gamma \sim 30\ \mathrm{yr}^{-1}$ and $\sigma \gg \gamma$, then we have $t_m \sim 0.4$ yr. In other words, if an appropriate age interval covered by vaccination is considered, then when $v \to \infty$, the force of infection goes to zero only after the period of time t_m has been elapsed.

Once the force of infection was evaluated numerically by the integral equation (25), the following three correlated variables can be derived [2].

The first variable is the mean age $\bar{a}(t)$ defined as

$$\bar{a}(t) = \frac{\int_0^\infty a x(t,a)\lambda(t)\,\mathrm{d}a}{\int_0^\infty x(t,a)\lambda(t)\,\mathrm{d}a}. \tag{30}$$

But, the force of infection can be dropped out from the equation because it does not depend on age. The resulting expression is given in Appendix B.

The second variable represents new cases, defined by

$$\rho(t, A_1, A_2) = \int_{A_1}^{A_2} x(t,a)\lambda(t)\,\mathrm{d}a, \tag{31}$$

where A_1 and A_2 are, respectively, the lower and upper bounds of the age interval considered to calculate the rate of the new cases of infection. When $A_1 = 0$ and $A_2 \to \infty$, the value of the new cases from a vaccination programme is always lower than the value without vaccination. The resulting expression can be found in Appendix C.

Finally, in the case of rubella infection, where the virus seriously affects the fetus, the risk of CRS (a little variation in the definition of the new cases of infection) can be defined as

$$\omega(t, A_1, A_2) = \xi_0\xi_1 \int_{A_1}^{A_2} x(t,a)\lambda(t)R(a)\,\mathrm{d}a, \tag{32}$$

where ξ_0 and ξ_1 are, respectively, the probability that the infection occurs during the first three months of pregnancy and the probability that this infection produces CRS. The fertility function $R(a)$ can be described by

$$R(a) = \eta_2(a-\eta_1)\exp\left(-\eta_2(a-\eta_1)\right)\theta(a-\eta_1), \tag{33}$$

where η_1 is the minimum age women are able to get pregnant and η_2 is the fertility loss rate. From the fertility function we can obtain the probability of

being pregnant on age interval between a and $a + \mathrm{d}a$ by $R(a)\eta_2\,\mathrm{d}a$. The resulting expression is given in Appendix D.

Besides the reduction in the force of infection, which is the main objective of vaccination strategy, the other aim of immunization is the decrease in the number of cases of CRS. These objectives can be analyzed by comparing the steady state equilibrium values before and after introduction of a vaccination strategy.

3.3. Long-term epidemiological variables

In this section, we analyze the steady state equilibrium value of the dynamics system taking into account the immunization in relation to the equilibrium value without vaccination. Setting $t = 0$ as the time at which a vaccination programme is introduced, then, after a sufficient time has been elapsed, the dynamics system attains the long-term equilibrium value.

Both initial and long-term (asymptotic) equilibrium values can be determined analytically. Through an appropriate relation between these two steady state equilibrium values, we can determine the conditions to have either the eradication of the disease or the reduction in the number of cases of CRS or both. The comparison of them provides us the efficiency of the vaccination strategy adopted.

First, from the natural force of infection λ_0, estimated from the seroprevalence data, we can calculate the corresponding correlated variables. They are the mean age, given by

$$\bar{a}_0 = \frac{1}{\mu + \lambda_0}, \tag{34}$$

the new cases, given by

$$\rho_0(A_1, A_2) = \frac{\mu\lambda_0}{\mu + \lambda_0} \exp\left(-(\mu + \lambda_0)A_1\right)\left[1 - \exp\left(-(\mu + \lambda_0)(A_2 - A_1)\right)\right], \tag{35}$$

and the risk of CRS, given by

$$\begin{aligned}\omega_0(A_1, A_2) = {} & \frac{\xi_0\xi_1\mu\lambda_0\eta_2}{(\mu + \lambda_0 + \eta_2)^2} \exp\left(-\eta_2(A_1 - \eta_1)\right) \exp\left(-(\mu + \lambda_0)A_1\right) \\ & \times \{1 + (A_1 - \eta_1)(\mu + \lambda_0 + \eta_2) - [1 + (A_2 - \eta_1)(\mu + \lambda_0 + \eta_2)] \\ & \times \exp\left(-(\mu + \lambda_0 + \eta_2)(A_2 - A_1)\right)\}. \end{aligned} \tag{36}$$

The efficient of a vaccination strategy is assessed in relation to these three variables, together with the decrease in the force of infection.

The perturbation by vaccination, for sufficiently large time ($t \to \infty$), leads the initial steady state equilibrium to the long-term equilibrium. When the Eqs. (5) and (7) reach the long-term equilibrium values, we have the asymptotic force of infection λ_∞ being given by the solution of Eq. (25), or

$$\frac{\mu + \lambda_\infty}{1 - \frac{v \exp(-(\mu+\lambda_\infty)a_1)}{\mu+v+\lambda_\infty}[1 - \exp(-(\mu + v + \lambda_\infty)(a_2 - a_1))]} = \mu + \lambda_0. \tag{37}$$

Note that λ_∞ is related to the natural force of infection λ_0.

From the relation (37) we observe that

(a) The vaccination rate to eradicate the disease can be estimated. Setting $\lambda_\infty = 0$, we have the transcendental equation

$$\frac{\lambda_0}{\mu + \lambda_0}[\mu + v_{\text{th}}] = v_{\text{th}} \exp(-\mu a_1)\{1 - \exp(-[\mu + v_{\text{th}}](a_2 - a_1))\}, \tag{38}$$

where v_{th} is the lower bound of the vaccination rate that must be applied to susceptible individuals to have eradication. If we vaccinate with a rate higher than v_{th}, then the disease can be controlled in a finite time, $t < \infty$.

(b) If we want to control the disease, we must choose adequately the age interval of susceptible individuals to be vaccinated. Setting $v_{\text{th}} \to \infty$ in Eq. (38), we evaluate the maximum value of the lower bound of the age interval to have eradication of the disease as

$$a_1^{\text{th}} = \frac{1}{\mu} \ln\left(\frac{\mu + \lambda_0}{\lambda_0}\right). \tag{39}$$

This expression shows that, if $a_1 > a_1^{\text{th}}$ then eradication cannot be attained even when $v \to \infty$ (if a low value is chosen to the lower bound of the age interval, the threshold vaccination rate can have a lower value). In the case $a_1 = 0$ and $a_2 \to \infty$, from Eq. (38), we have the threshold vaccination rate given by

$$v_{\text{th}} = \lambda_0 \tag{40}$$

and the corresponding proportion of susceptible individuals covered by vaccination is given by

$$p_{\text{th}} = \frac{\lambda_0}{\lambda_0 + \mu}, \tag{41}$$

which is obtained from Eq. (47).

Now, the long-term correlated variables to the force of infection λ_∞ are expressed as ratios in relation to the initial values.

First, the ratio of the mean ages at equilibrium after and before vaccination is given by

$$\frac{\bar{a}_\infty}{\bar{a}_0} = \left(\frac{\mu+\lambda_0}{\mu+\lambda_\infty}\right)^2 - \left(\frac{\mu+\lambda_0}{\mu+\lambda_\infty}\right)^2 \frac{v\exp(-(\mu+\lambda_\infty)a_1)}{\mu+v+\lambda_\infty} \times \left\{ \frac{2(\mu+\lambda_\infty)+v}{\mu+v+\lambda_\infty}[1-\exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] + (\mu+\lambda_\infty)[a_1 - a_2\exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] \right\}, \tag{42}$$

because we have substituted the denominator of Eq. (B.3) by the Eq. (37). If we impose the condition $v \to \infty$ to Eq. (B.3), we have

$$\frac{\bar{a}_\infty}{\bar{a}_0} = \frac{\mu+\lambda_0}{\mu+\lambda_\infty} - \frac{a_1(\mu+\lambda_0)\exp((\mu+\lambda_\infty)a_1)}{1-\exp(-(\mu+\lambda_\infty)a_1)}. \tag{43}$$

If we set $a_1 \to 0$ (due to $a_1^{\text{th}} > 0$, in this situation we have $\lambda_\infty = 0$ whenever $v > v_{\text{th}}$) and $\mu \to \infty$ in Eq. (43), and applying the L'Hôspital rule, we have $\bar{a}_\infty/\bar{a}_0 \to 1 + \lambda_0/\mu$ (see Fig. 2(a)).

Second, the ratio of the new cases is

$$\frac{\rho_\infty(A_1,A_2)}{\rho_0(A_1,A_2)} = \frac{(\mu+\lambda_0)\lambda_\infty}{(\mu+\lambda_\infty)\lambda_0}\exp(-v(a_2-a_1)) \times \frac{\exp(-\lambda_\infty A_1)[1-\exp(-(\mu+\lambda_\infty)(A_2-A_1))]}{\exp(-\lambda_\infty A_1)[1-\exp(-(\mu+\lambda_0)(A_2-A_1))]}. \tag{44}$$

Finally, the ratio of the risks of CRS is

$$\frac{\omega_\infty(A_1,A_2)}{\omega_0(A_1,A_2)} = \left(\frac{\mu+\lambda_0+\eta_2}{\mu+\lambda_\infty+\eta_2}\right)^2 \frac{\lambda_\infty}{\lambda_0}\exp(-v(a_2-a_1))\frac{\exp(-\lambda_\infty A_1)}{\exp(-\lambda_0 A_1)} \times \frac{[1+(A_1-\eta_1)(\mu+\lambda_\infty+\eta_2)] - [1+(A_2-\eta_1)(\mu+\lambda_\infty+\eta_2)]\exp(-(\mu+\lambda_\infty+\eta_2)(A_2-A_1))}{[1+(A_1-\eta_1)(\mu+\lambda_0+\eta_2)] - [1+(A_2-\eta_1)(\mu+\lambda_0+\eta_2)]\exp(-(\mu+\lambda_0+\eta_2)(A_2-A_1))}. \tag{45}$$

Up to now we assessed the vaccination programme taking into account the vaccination rate. However, this rate can be related to the proportion of susceptible individuals vaccinated.

First, when the immunization proportion is related to the susceptible individuals comprised on the age interval vaccinated, then we have

$$p(t) = 1 - \frac{\int_{a_1}^{a_2} x(t,a)\,\mathrm{d}a}{\int_{a_1}^{a_2} x_0(a)\,\mathrm{d}a}, \tag{46}$$

which depends on time. If a vaccination is applied to children under 2 yr old, we can substitute the susceptible individuals by the total number of individuals, which is described by the sum of the 4 equations given in system (1) in the steady state. By doing this, we can find the approximated value of p by solving

$$p \simeq 1 - \frac{\mu}{\mu + \nu} \frac{1 - \exp(-(\mu + \nu)(a_2 - a_1))}{1 - \exp(-\mu(a_2 - a_1))}. \tag{47}$$

This equation becomes more and more imprecise if both a_1 and a_2 assume higher values. Eq. (47) assesses the effective proportion of susceptible individuals covered by vaccination.

Second, when we consider all the susceptible individuals instead of considering only the age interval under vaccination, then we have

$$p' \simeq \frac{\nu \exp(-\mu a_1)}{\mu + \nu}[1 - \exp(-(\mu + \nu)(a_2 - a_1))], \tag{48}$$

which resulted by changing the limits of the definite integration only in the denominator of Eq. (46) by 0 and ∞.

The aim of the approximated proportion p of susceptible individuals covered by vaccination, given by Eqs. (47) or (48), is to furnish a more familiar measure than the vaccination rate ν.

In the next section, the time dependent model is solved numerically to provide us the scenarios when different routine vaccination strategies against rubella are introduced in a community.

4. Numerical results

All the simulations shown in this section were obtained considering the following values for the model's parameters. For rubella infection, we use for the incubation and recovery rates, respectively, $\sigma = 52.0\ \text{yr}^{-1}$ and $\gamma = 39.0\ \text{yr}^{-1}$, and for the contact rate, $\beta = 261.81\ \text{yr}^{-1}$, which was calculated from $\lambda_0 = 0.097\ \text{yr}^{-1}$ [3]. The women related parameters are taken from [12]. We set for the minimum age women are able to get pregnant $\eta_1 = 13.0$ yr, and $\eta_2 = 0.23\ \text{yr}^{-1}$ was chosen to make the fertile function assuming relatively lower values to women with ages greater than 50 yr. We set $A_1 = 18.0$ yr and $A_2 = 45.0$ yr (instead of $A_1 = 13.0$ yr and $A_2 \to \infty$ to cover all the non-negatively defined fertility) to enhance the fact that women usually get pregnant on this age interval. We set $\xi_0 = 0.3$ (three in nine months) and $\xi_1 = 0.5$ (half of infected pregnant women produce CRS). Finally, the morality rate is set as $\mu = 0.017\ \text{yr}^{-1}$. All these parameters are fixed unless explicitly cited.

Using the above values for the parameters, we can calculate some special values related to the model. The threshold contact rate, from Eq. (16), and the maximum value for the lower bound of the age interval covered by vaccination to have eradication, from Eq. (39), are, respectively, $\beta^{\text{th}} = 39.03\ \text{yr}^{-1}$ and $a_1^{\text{th}} = 9.50$ yr. The *basic reproduction ratio* is, from the ratio between β and β^{th}, $R_0 = 6.71$. The threshold values for the vaccination rate and the corresponding

proportion covered by vaccine, in the case when $a_1 = 0$ and $a_2 \to \infty$, are, from Eqs. (40) and (41), $v_{th} = 0.097\ \text{yr}^{-1}$ and $p_{th} = 85.1\ \%$, respectively.

In this section, we present the asymptotic epidemiological values resulting from vaccination divided by their initial equilibrium values, that is, as ratios.

4.1. Long-term results

Just before the introduction of the vaccination strategy (in the initial equilibrium), the epidemiological values, that is, the mean age, the new cases and the risk of CRS are, from Eqs. (34), (35) and (36), respectively, $\bar{a}_0 = 8.77$ yr, $\rho_0(A_1, A_2) = 0.18 \times 10^{-2}\ \text{yr}^{-1}$ and $\omega_0(A_1, A_2) = 0.53 \times 10^{-4}\ \text{yr}^{-1}$. The fraction of susceptible individuals is $\chi_0 = 0.149$.

The vaccination rate described by Eq. (3) can be used to analyze two kinds of vaccination strategies. The first is related to the early vaccination (as adopted in the USA) aiming the eradication, and the other concerns delayed vaccination (adopted in the Great Britain) to reduce the cases of CRS. These vaccination strategies can be analyzed considering the fixed age interval but allowing the lower bound of the age interval to vary.

In order to analyze the two kinds of vaccination strategies, we fix $a_2 - a_1 = 1.0$ yr and we vary a_1, that is, the lower bound of the age interval covered by vaccination is increased. This range of age has practical implications, that is, in a control strategy which aims to vaccine, for instance, 1 yr old children, in this target group can be included children from exactly 1 yr to just below 2 yr old children. Fig. 1 shows this situation.

Fig. 1(a) shows the long-term force of infection λ_∞, by solving Eq. (37). We observe that, for a fixed $a_2 - a_1$, to the increasing a_1 corresponds an increased eradicating vaccination proportion p_{th}, which is given by the intercept of the curve with the p-axis. Consequently, to the same proportion vaccinated we have low decreasing in the force of infection as a_1 is increased. Fig. 1(b) shows the threshold vaccination rate v_{th} and the corresponding threshold proportion vaccinated p_{th}, which were obtained by solving, respectively, Eqs. (38) and (47). According to the Eq. (39), when a_1 is higher than its critical value a_1^{th}, the disease cannot be controlled (the top curve of Fig. 1(a)). In this case, there is not intercept of the curve with the p-axis. Both figures show that when a_1 increases, also the effort to control the disease increases, for the reason that p_{th} increases.

From the force of infection obtained numerically, given in Fig. 1(a), we show in Fig. 2 the ratios of the mean ages, the new cases, and the risks of CRS varying the proportion p of individuals vaccinated, fixing $a_2 - a_1 = 1.0$ yr and varying a_1. Fig. 2(a) shows that, when the lower bound of age interval vaccinated is increased, the peak of the mean age is decreased and moves slightly to right. After the peak this variable drops to zero because the disease was eradicated (mathematically, $\lambda_\infty < 0$), and, therefore, this descending phase,

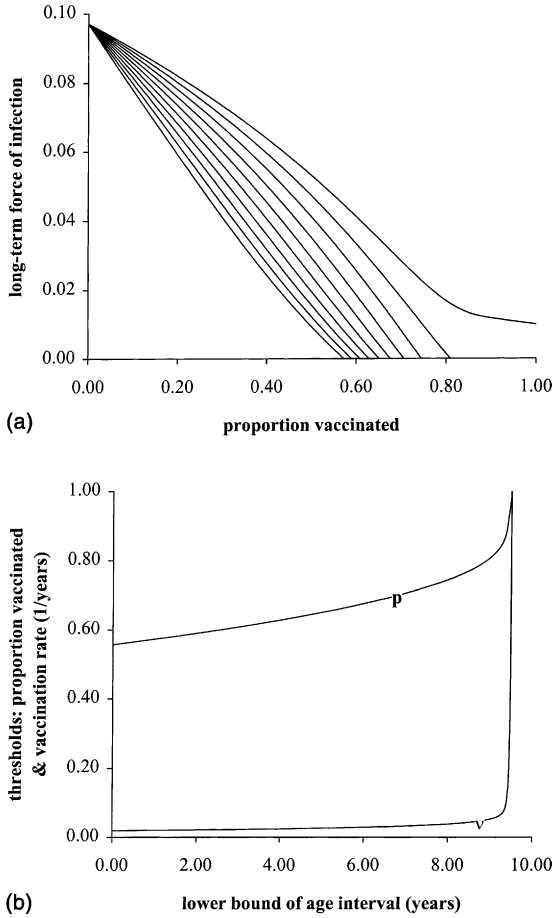

Fig. 1. The force of infection λ_∞ is shown as a function of proportion p of susceptible individuals covered by vaccination (a), for the age intervals: $[1.0, 2.0]$, $[2.0, 3.0]$, $[3.0, 4.0]$, $[4.0, 5.0]$, $[5.0, 6.0]$, $[6.0, 7.0]$, $[7.0, 8.0]$, $[8.0, 9.0]$, $[9.0, 10.0]$ and $[10.0, 11.0]$ (from bottom to top, in yr). The threshold vaccination rate v_{th} ($\times 100$ yr^{-1}) and the corresponding proportion p_{th} are shown as a function of a_1 (b). The vertical asymptote is related to a_1^{th}.

being a mathematical artefact, is not shown. When the eradication is not achieved (bottom curve), the prominent peak is absent and the mean age is decreased in relation to the unvaccinated population. Fig. 2(b) (and (c)) shows that there is an increase in the rate of the new cases of infection for the 3 top curves (to the risk of CRS, the 2 top curves) in relation to the initial value, in the region of low proportion vaccinated. In both cases, there is the crossing-over phenomenon: the vaccination, when carried out in the early ages, produces higher values for the ratio of the new cases (the risks of CRS) than the

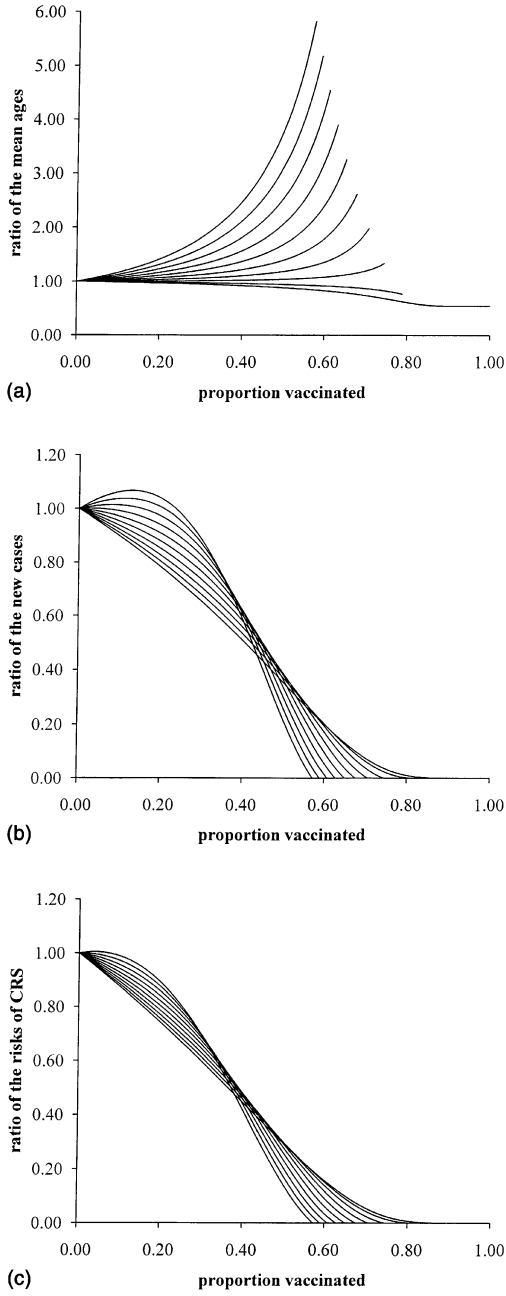

Fig. 2. The ratios of the mean ages (a), the new cases (b) and the risks of CRS (c) are shown as a function of proportion p (from top to bottom in the region where $p \sim 0$), for the age intervals given in Fig. 1.

delayed vaccination strategy in the region of low proportion covered by vaccination, and the opposite relation in the region of high proportion vaccinated. In other words, there is a more quick dropping to zero whenever the peak is attained earlier and in a higher values. Note that when a_1 is greater than 3 yr, both the ratios of the new cases and the risks of CRS never surpasses unity. In the special case when $a_1 > a_1^{\text{th}}$ (the bottom curve), where there is not the possibility of eradication, the region of the low proportion covered by vaccination always produces the best results regarding the reduction in the risk of CRS.

We observed (Fig. 2(a)) that the maximum peak of the ratio between $\bar{a}_\infty$ and $\bar{a}_0$ is about 6.0. This value is, as expected, lower than 6.7, which was obtained from the limiting value $1 + \lambda_0/\mu$, corresponding to $a_1 = 0$ and $v \to \infty$.

All the above figures show the importance of choosing the correct age interval to be vaccinated. If the objective is to reduce the number of the new cases (and the risk of CRS), then the better choice is the delayed vaccination strategy (higher values for a_1), because we have, for all values of the proportion of vaccinated individuals, always these numbers lower than the initial values. If the objective is the eradication of the disease, the better choice is the early vaccination strategy, remembering that the proportion vaccinated must by high.

The analysis of the asymptotic values in relation to the initial values does not give a complete picture. To have a complete view of the transmission of the disease, we must know how the asymptotic situation is reached when a vaccination strategy is introduced in an unvaccinated community.

4.2. Time dependent results

In this section, we study the trajectories followed until the dynamics system attains the long-term value. It is an important analysis because we can observe the effects on the epidemiological parameters induced by the vaccination strategy during the advance in time.

All the simulations below are obtained considering the age interval covered by vaccination between $a_1 = 1.0$ yr and $a_2 = 2.0$ yr. Considering this age interval, the threshold value for the vaccination rate, from Eq. (38), is $v_{\text{th}} = 2.23\ \text{yr}^{-1}$ (corresponding $p_{\text{th}} = 57.26\%$). The ratio relates the time dependent epidemiological parameters in relation to the initial values.

We developed a Fortran coded program to solve the integral equation (25) by an iterative method [8]. We used the extended Simpson's rule [15] for the numerical integration.

First, we analyze a very ineffective vaccination, letting $p = 5.0\%$. The results are shown in Fig. 3.

Fig. 3(a) shows the ratios of the forces of infection, the mean ages, from Eq. (30), and the fractions of susceptible individuals, from Eq. (23). We observe that the ratio of the fractions of susceptible individuals tends to unity, while the

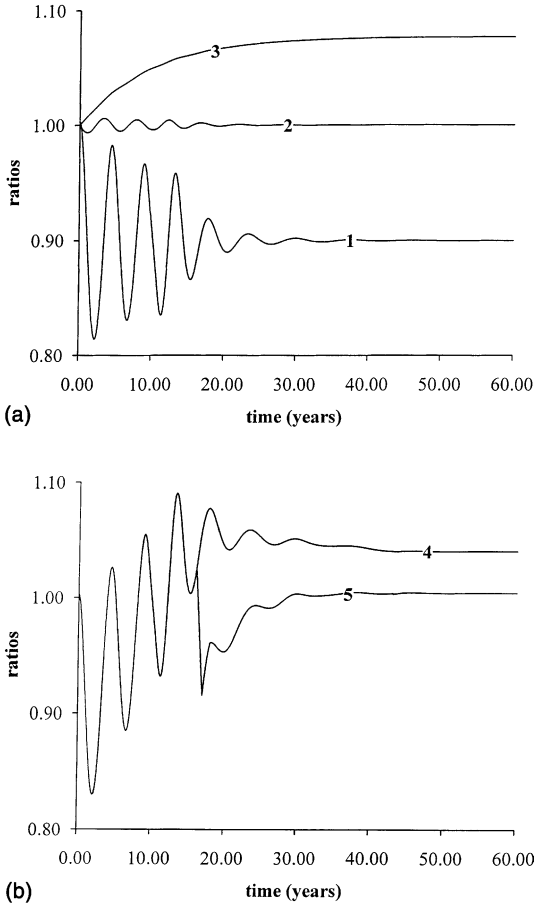

Fig. 3. The ratios of the forces of infection, the fractions of susceptible individuals and the mean ages labeled, respectively, as 1, 2 and 3 (a), and the ratios of the new cases and the risks of CRS labeled, respectively, as 4 and 5 (b) are shown as a function of time t. We considered a low proportion vaccinated, $p = 5\ \%$.

ratio of the mean ages attains a value higher than unity. Fig. 3(b) shows the ratios of the new cases, from Eq. (31), and the risks of CRS, from the Eq. (32). We observe that the initial oscillatory behaviour is practically interrupted after 16 yr since the introduction of the vaccination strategy. Moreover, at this age occurs the splitting of the curves related to the new cases and the risk of CRS. Vaccinating 5.0% of susceptible individuals on this age interval reduces, asymptotically, only the force of infection, but all other variables increase in relation to the initial values. This coverage does not fullfil both two objectives of vaccination strategy.

It is worth discussing the splitting of the curves. Since we are vaccinating on the age interval 1–2 yr, only after 16 yr the immunized individuals in the upper bound of the age interval vaccinated reach 18 yr, which corresponds to the lower bound to assess both the new cases and the risk of CRS. Therefore, in the beginning of the introduction of the vaccination strategy, the immunized individuals affect indirectly (by decreasing the force of infection) the unvaccinated adult individuals on the age 18–45 yr, leading to the same values with respect to the new cases and the risk of CRS. However, the first immunized children (2 yr old) enters the age interval [18,45] after 16 yr from the introduction of the vaccination strategy onwards. For this reason, at this age the splitting of the new cases and the risk of CRS curves occurs, the former assuming values always greater than the latter, but both ratios attain values higher than unity. Observe that the curve of the new cases does not show any abrupt behaviour, which is not true related to the curve of the risk of CRS. Indeed, there is the descending phase in the risk of CRS curve, which comprises the time interval 16–17 yr, which is followed by the ascending phase during 17–18 yr, and thereafter the curve goes its natural way. Observe that the descending phase corresponds to the growing up of the vaccinated children on the whole age interval 1–2 yr, and are entering to the age interval [18,45]. Afterwards, during the time interval 17–18 yr, the increasing risk of CRS is due to the non-vaccinated children on the age interval 0–1 yr entering to the age interval [18,45]. Finally, after 18 yr since the introduction of the vaccination strategy, we observe the trend induced by the vaccination strategy without any other effects on the risk of CRS, because the first 'differentiate wave' of susceptible individuals vaccinated is followed by 'regular waves' of individuals vaccinated.

Second, an intermediary vaccination effort is analyzed, by letting $p = 30.0\%$. The results are shown in Fig. 4. Fig. 4(a) shows the ratios of the forces of infection, the mean ages and the fractions of susceptible individuals. Fig. 4(b) shows the ratios of the new cases and the risks of CRS. We observe quite the same effects as the previous vaccination strategy. The differences are the small number of oscillating waves, and the more strong variations in the beginning of the introduction of the vaccination. This vaccination coverage, asymptotically, diminishes the force of infection by an half, and the ratios of the new cases and the risks of CRS to values lower than unity. This intermediate vaccination fulfills one of the objectives of the vaccination strategy, that is, the reduction in the number of cases of CRS in relation to the absence of vaccination.

For a vaccination strategy above the threshold value, letting $p = 65.21\%$, which corresponds to vaccination rate $v = 2.94\ \mathrm{yr}^{-1}$ [12], the results are shown in Fig. 5. Fig. 5(a) shows the ratios of the forces of infection, the mean ages and the fractions of susceptible individuals. Fig. 5(b) shows the ratios of the new cases and the risks of CRS. The trend of the ratio of the new cases is the same as the risks of CRS, and both are similar with respect to the shape of the force of infection, which decays exponentially. In this case the ratio of the fractions

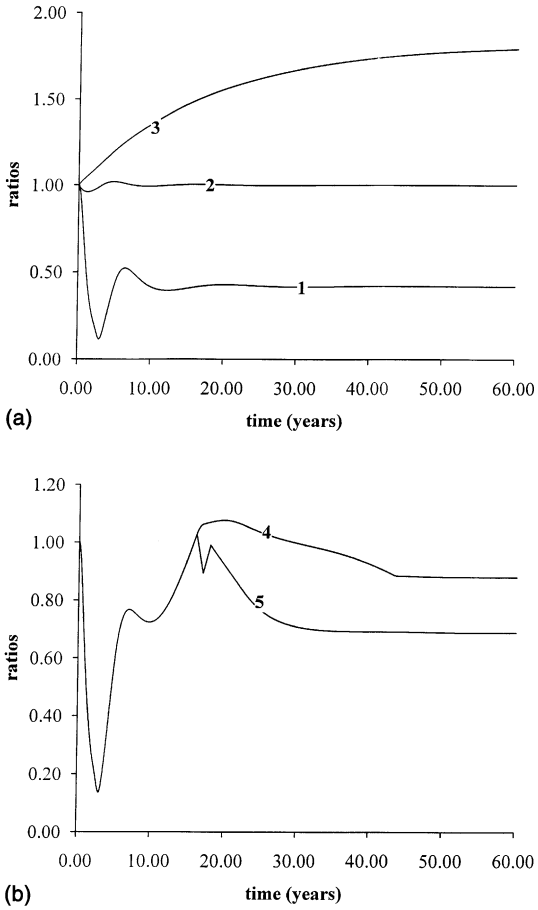

Fig. 4. The ratios of the forces of infection, the fractions of susceptible individuals and the mean ages labeled, respectively, as 1, 2 and 3 (a), and the ratios of the new cases and the risks of CRS labeled, respectively, as 4 and 5 (b) are shown as a function of time t. We considered an intermediate proportion vaccinated, $p = 30\%$.

of susceptible individuals does not attain unity. After 3 yr the force of infection attains zero, which is higher than t_m (see above). In Fig. 5(b) we also present the result of the ratio of the risks of CRS in São Paulo State, Brazil [13] after introduction of mass immunization. The results obtained from the mass vaccination in Brazil can be roughly compared and explained by this routine vaccination. Indeed, the pulse vaccination, when high proportion covered by vaccination is considered, results the same exponentially decreasing force of infection [22]. This vaccination strategy fulfills both objectives of the vaccination strategy.

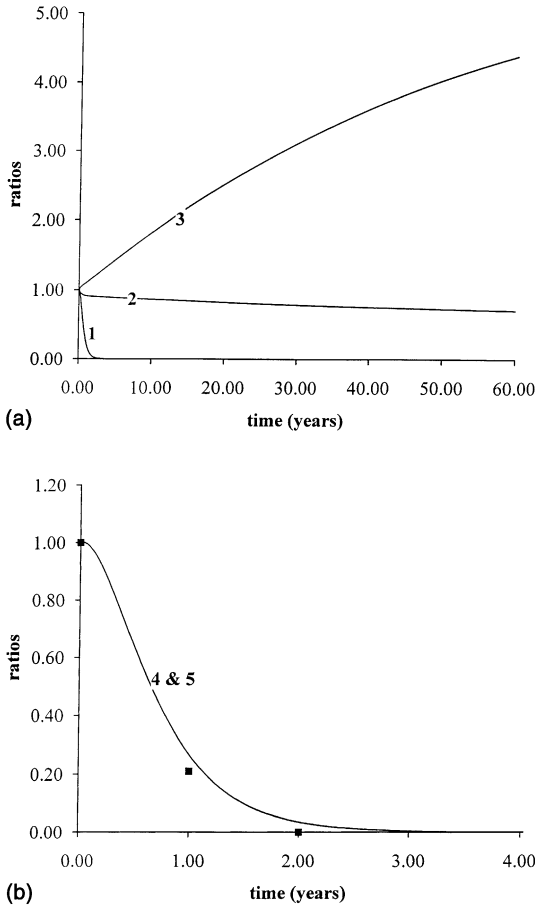

Fig. 5. The ratios of the forces of infection, the fractions of susceptible individuals and the mean ages labeled, respectively, as 1, 2 and 3 (a), and the ratios of the new cases and the risks of CRS labeled, respectively, as 4 and 5 (b) are shown as a function of time t. The three filled squares refer to the observed ratio of the risks of CRS in Great São Paulo, Brazil: time 0 corresponds to the year 1992, 1 to 1993 and 2 to 1994. We considered a high proportion vaccinated, $p = 65.21\%$.

In Figs. 3 and 4 we showed the situation where the disease is in some extent controlled. For this reason, we have the *effective reproduction ratio*, $R = R_0\chi$, equals to unity in the steady state equilibrium values before and after the introduction of the vaccination. However, in Fig. 5 we have the eradication of the disease, therefore, the preceding relation does not remain valid. Hence, the fraction of susceptible individuals asymptotically attains a value below that observed before the vaccination, since the vaccinated individuals are removed directly to the immune status in the absence of natural infection. The vacci-

nation rate is not linked to the force of infection (which assumes zero) and, therefore, the relation (37) is not valid anymore.

As a final example, we consider a vaccination strategy where a_1 is greater than its threshold value a_1^{th}. We consider $a_1 = 10$ yr, $a_2 = 11$ yr and $p = 90\%$ (corresponding $v = 0.84\ \text{yr}^{-1}$), and the results are shown in Fig. 6.

Fig. 6(a) shows the ratios of the forces of infection, the mean ages and the fractions of susceptible individuals. We observe the initial oscillation in the force of infection followed by a monotonically decreasing phase, and the average age of the acquisition of the first infection always decreases in time in

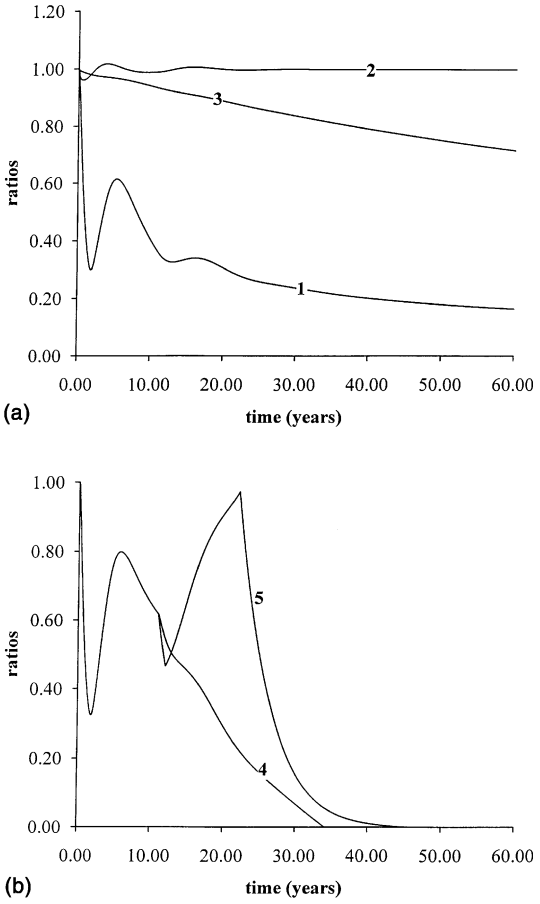

Fig. 6. The ratios of the forces of infection, the fractions of susceptible individuals and the mean ages labeled, respectively, as 1, 2 and 3 (a), and the ratios of the new cases and the risks of CRS labeled, respectively, as 4 and 5 (b) are shown as a function of time t. We considered a very high proportion vaccinated, $p = 90\%$ in a delayed vaccination scheme.

relation to the initial value (see the top curve of Fig. 1(a) and the bottom curve of Fig. 2(a)). Note that the decreasing in both the force of infection and the average age of the acquisition of the first infection show that the inverse relation between them (e.g., Anderson and May [2]) is not always true. Moreover, since the disease cannot be eradicated ($a_1 > a_1^{\text{th}}$), we must have the same value for the fractions of individuals after and before vaccination. Fig. 6(b) shows the ratios of the new cases and the risks of CRS. Only in this case, we considered $A_1 = 22$ yr and $A_2 = 45$ yr. In this situation, both ratios of the new cases and the risks of CRS go to zero. Observe that, in this situation, differently to that shown in Figs. 3(b) and 4(b), we have the risk of CRS assuming values always greater than the new cases of infection. Both results can be compared with Figs. 2(b) and (c). This vaccination strategy is highly advised to reduce the risk of CRS.

In this situation, the splitting of the curves is much more prominent. Since we are vaccinating on the age interval 10–11 yr, and we are assessing both effects on the age interval 22–45 yr, only after 11 yr (the individuals in the upper bound of the age interval vaccinated reach 22 yr) we do have the direct effect of the vaccination strategy on the new cases and the risk of CRS. Therefore at this age we have the splitting in the curves. At this age, the new cases of the infection always decreases. We observe that during the time interval 11–12 yr we have the whole group of immunized young individuals entering to the age interval 22–45 yr, which result in the decreasing in the risk of CRS. This phase is followed by the increasing in the risk of CRS during 12–22 yr, which is the period of time needed to the female new-borns reach 22 yr. Therefore, after 22 yr since the introduction of the vaccination, the risk of CRS decreases abruptly. Obviously, we are not considering the loss of immunity.

Since the introduction of vaccine until the new steady state equilibrium value is attained, there are oscillatory behaviours. However, we observe that, even in the presence of the oscillation in the force of infection in a continuous vaccination strategy, the maximum value is always below to that observed before the introduction of vaccination. Consequently, the new cases and the risk of CRS (when considering all ages) are diminished in relation to the initial values. For this reason, we assigned the special values for A_1 and A_2 to enhance the increasing in the new cases and the risk of CRS.

Finally, when $a_1 < a_1^{\text{th}}$ the average age of the acquisition of the first infection increases monotonically in time until attains its asymptotic value. However, the rates of the new cases of infection and the risk of CRS oscillate in the initial time, and attain their asymptotic values. This behaviour shows that the results of non-eradicating vaccination of children now is reflected more intensively and directly when the children grows up and enter in the age group comprised by A_1 and A_2. However, if there is the eradication, then the direct effects of the vaccination is practically immediate. On the other hand, when $a_1 > a_1^{\text{th}}$, then

the average age of the acquisition of the first infection decreases monotonically in time until it attains the asymptotic value. Both new cases and risk of CRS never surpass the initial values.

5. Conclusions

We proposed a model where a vaccination programme is carried out on a well defined age interval, and applied it to rubella infection. By considering the vaccination of individuals comprised on an age interval, we analyzed the two main objectives of vaccination against rubella infection. However, this model can also be applied to analyze a vaccination strategy against directly transmitted infections, because the immunization is carried out in very young children. For instance, in Brazil, the measles routine vaccination comprises children under 9 months, due to the increased mortality induced by the disease, and this model can be used to assess the effects of the vaccination.

With respect to rubella infection, we compared two kinds of routine vaccination strategies in course in the world: the vaccination of infants implemented in São Paulo State, Brazil (like adopted in the USA), and the vaccination of adolescents implemented in the Great Britain and other developed countries. The former vaccination strategy aims the reduction in the force of infection, while the latter intends to reduce the risk of CRS.

Both strategies were analyzed in the steady state equilibrium values, as shown in Figs. 1(a) to 2(c), and also the time dependent analysis was performed, as shown in Fig. 3(b). The best choice to eradicate (or to control to a very low endemicity) the disease is the vaccination strategy where very young individuals are vaccinated in a high proportion. However, if the goal is the reduction in the risk of CRS, then along with the previous strategy, the vaccination must reach high proportion of young adult female individuals.

By considering a vaccination programme on an age interval, we obtained how the disease progresses along time. We observed that the force of infection, even though undergoes damped oscillations, never surpasses the natural force of infection, which is not true if pulse vaccination is considered [22]. Also, we observed that the average age of the acquisition of the first infection monotonically increases or decreases along time. When the lower bound of the age interval (a_1) is lower than its critical value (a_1^{th}), then the mean age always increases until it attains the asymptotic value, otherwise, decreases. Therefore, the well-established paradigm, which states that the reduction in the force of infection increases the average age of the acquisition of the first infection is not always true. Remember that this assertion was established based on a model where the vaccination is performed over all ages. By allowing the vaccination to be restricted to an age interval, we conclude that the above statement is valid only when $a_1 < a_1^{\text{th}}$, and when $a_1 > a_1^{\text{th}}$, the reduction in the force of infection

leads to the decreasing in the average age of the acquisition of the first infection.

Finally, it is interesting to stress the fact that the routine vaccination must be carried out conveniently. If, for some reason, the vaccination is interrupted, then healthy authorities must be prepared to face an increased incidence of the infection some times later [21]. On the other hand, we did not consider the loss of immunity induced by the vaccine, which increases the difficult of the eradication task.

Appendix A. Susceptible individuals: $x_{\cdot}(t,a)$ and $\chi_{\cdot}(t)$

The expressions for $x_{\cdot}(t,a)$ related in Eqs. (18)–(22) are

$$\begin{aligned} x_1^a(t,a) &= \mu \exp(-\Phi(t)) \exp(\Phi(t-a)), \\ x_2^a(t,a) &= \mu \exp(-\Phi(t)) \exp(\Psi(t-a)) \exp(-v(a_2-a_1)), \\ x_3^a(t,a) &= \mu \exp(-\Phi(t)) \exp(\Phi(t-a)) \exp(-v(a_2-a_1)) \end{aligned} \tag{A.1}$$

and

$$\begin{aligned} x_1^b(t,a) &= \mu \exp(-\Phi(t)) \exp((\mu+\lambda_0)t) \exp(-(\mu+\lambda_0)a), \\ x_2^b(t,a) &= \mu \exp(-\Phi(t)) \exp((\mu+\lambda_0)t) \exp(va_1) \exp(-(\mu+\lambda_0+v)a), \\ x_3^b(t,a) &= \mu \exp(-\Phi(t)) \exp((\mu+\lambda_0)t) \exp(-vt) \exp(-(\mu+\lambda_0)a), \\ x_4^b(t,a) &= \mu \exp(-\Phi(t)) \exp((\mu+\lambda_0)t) \exp(-v(a_2-a_1)) \exp(-(\mu+\lambda_0)a), \\ x_5^b(t,a) &= \mu \exp(-\Phi(t)) \exp((\mu+\lambda_0)t) \exp(-v(t+a_2)) \exp(-(\mu+\lambda_0-v)a), \end{aligned} \tag{A.2}$$

where

$$\begin{aligned} \Phi(y) &= \int_0^y [\mu + \lambda(t)]\,\mathrm{d}t, \\ \Psi(y) &= \int_0^y [\mu + v + \lambda(t)]\,\mathrm{d}t. \end{aligned} \tag{A.3}$$

From Eq. (A.1), letting $t \to \infty$, we can obtain the long-term age specific faction of susceptible individuals, given by

$$x_\infty(a) = \begin{cases} \mu \exp(-(\mu+\lambda_\infty)a), & 0 \leqslant a < a_1, \\ \mu \exp(-(\mu+\lambda_\infty)a) \exp(-v(a-a_1)), & a_1 \leqslant a \leqslant a_2, \\ \mu \exp(-(\mu+\lambda_\infty)a) \exp(-v(a_2-a_1)), & a > a_2. \end{cases} \tag{A.4}$$

The expressions for $\chi_{\cdot}(t)$ related in Eqs. (23) and (24) are

$$\chi_1^a(t) = \mu \exp(-\Phi(t)) \int_0^t \exp(\Phi(t-a))\,\mathrm{d}a + \frac{\mu \exp(-\Phi(t))}{\mu+\lambda_0} \times \left\{1 - v\exp(-(\mu+\lambda_0)(a_1-t))\left[\frac{1-\exp(-(\mu+\lambda_0+v)t)}{\mu+\lambda_0+v} - \exp(-(\mu+\lambda_0)(a_2-a_1))\frac{\exp(-vt)-\exp(-(\mu+\lambda_0)t)}{\mu+\lambda_0-v}\right]\right\},$$

$$\chi_1^b(t) = \mu \exp(-\Phi(t)) \int_0^t \exp(\Phi(t-a))\,\mathrm{d}a + \frac{\mu \exp(-\Phi(t))}{\mu+\lambda_0} \times \left\{1 - v\exp(-(\mu+\lambda_0)(a_1-t))\left[\frac{1-\exp(-(\mu+\lambda_0+v)(a_2-a_1))}{\mu+\lambda_0+v} - \exp(-(\mu+\lambda_0)t)\frac{\exp(-v(a_2-a_1))-\exp(-(\mu+\lambda_0)(a_2-a_1))}{\mu+\lambda_0-v}\right]\right\},$$

$$\chi_2^a(t) = \mu \exp(-\Phi(t))\left[\int_0^{a_1} \exp(\Phi(t-a))\mathrm{d}a + \exp(-v(t-a_1)) \times \int_{a_1}^t \exp(\Psi(t-a))\,\mathrm{d}a\right] + \mu \exp(-\Phi(t)) \times \left\{\frac{\exp(-v(t-a_1))}{\mu+\lambda_0+v}\left[1 + \frac{v\exp(-(\mu+\lambda_0+v)a_2)}{\mu+\lambda_0}\right] + \frac{v\exp(-(\mu+\lambda_0)(a_2-t))}{(\mu+\lambda_0)(\mu+\lambda_0-v)}[\exp(-vt) - \exp(-(\mu+\lambda_0)t)]\right\},$$

$$\chi_2^b(t) = \mu \exp(-\Phi(t))\left[\int_0^{a_1} \exp(\Phi(t-a))\,\mathrm{d}a + \exp(-v(t-a_1)) \times \int_{a_1}^t \exp(\Psi(t-a)),\,\mathrm{d}a\right] + \mu \exp(-\Phi(t))\left\{\frac{\exp(-v(t-a_1))}{\mu+\lambda_0+v} \times \left[1 + \frac{v\exp(-(\mu+\lambda_0+v)(a_2-t))}{\mu+\lambda_0}\right] + \frac{v\exp(-(\mu+\lambda_0)a_1)}{(\mu+\lambda_0)(\mu+\lambda_0-v)} \times [\exp(-v(a_2-a_1)) - \exp(-(\mu+\lambda_0)(a_2-a_1))]\right\} \quad \text{(A.5)}$$

and

$$\chi_3(t) = \mu \exp(-\Phi(t)) \left[\int_0^{a_1} \exp(\Phi(t-a))\,\mathrm{d}a + \exp(-v(t-a_1)) \times \int_{a_1}^{a_2} \exp(\Psi(t-a))\,\mathrm{d}a + \exp(-v(a_2-a_1)) \int_{a_2}^{t} \exp(\Phi(t-a))\,\mathrm{d}a \right] + \mu \exp(-\Phi(t)) \left\{ \frac{\exp(-v(a_2-a_1))}{\mu+\lambda_0} + \frac{v \exp(-(\mu+\lambda_0)a_1)}{\mu+\lambda_0} \times \frac{\exp(-v(a_2-a_1)) - \exp(-(\mu+\lambda_0)(a_2-a_1))}{\mu+\lambda_0-v} \right\}. \tag{A.6}$$

The long-term fraction of susceptible individuals can be obtained from the Eq. (A.6) letting $t \to \infty$, and it is given by

$$\chi_\infty = \frac{\mu}{\mu+\lambda_\infty} \left\{ 1 - \frac{v \exp(-(\mu+\lambda_\infty)a_1)}{\mu+v+\lambda_\infty} \times [1 - \exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] \right\}. \tag{A.7}$$

Appendix B. The average age of the acquisition of the first infection: $\bar{a}(t)$

The analytic expression for the mean age, in the case $2a_1 > a_2$ is, from the Eq. (30):

$$\bar{a}(t) = \begin{cases} \dfrac{A_1^a(t)}{\chi_1^a(t)}, & 0 \leqslant t \leqslant a_2 - a_1, \\ \dfrac{A_1^b(t)}{\chi_1^b(t)}, & a_2 - a_1 < t < a_1, \\ \dfrac{A_2^b(t)}{\chi_2^b(t)}, & a_1 \leqslant t \leqslant a_2, \\ \dfrac{A_3(t)}{\chi_3(t)}, & t > a_2, \end{cases} \tag{B.1}$$

where $A_\cdot^\cdot(t)$ is calculated similar to $\chi_\cdot^\cdot(t)$. The mean age is divided by the fraction of susceptible individuals, which is a function of the force of infection. However, from the assumption of constant contact rate, the force of infection is only time dependent and not age dependent. For this reason, we have, for example,

$$
\begin{aligned}
A_3(t) = \mu \exp(-\Phi(t)) \Bigg[& \int_0^{a_1} \exp(\Phi(t-a))\,\mathrm{d}a + \exp(-v(t-a_1)) \\
& \times \int_{a_1}^{a_2} \exp(\Psi(t-a))\,\mathrm{d}a + \exp(-v(a_2-a_1)) \\
& \times \int_{a_2}^{t} \exp(\Phi(t-a))\,\mathrm{d}a + \frac{t+\frac{1}{\mu+\lambda_0}}{\mu+\lambda_0} \exp(-v(a_2-a_1)) \Bigg] \\
& + \mu \exp(-\Phi(t)) \Bigg\{ \frac{v \exp(-(\mu+\lambda_0)a_1)}{(\mu+\lambda_0)(\mu+\lambda_0-v)} \Bigg[\left(t + \frac{2(\mu+\lambda_0)-v}{(\mu+\lambda_0)(\mu+\lambda_0-v)} \right) \\
& \times (\exp(-v(a_2-a_1)) - \exp(-(\mu+\lambda_0)(a_2-a_1))) \\
& + a_1 \exp(-v(a_2-a_1)) - a_2 \exp(-(\mu+\lambda_0)(a_2-a_1)) \Bigg] \Bigg\}
\end{aligned}
\tag{B.2}
$$

and $\chi_{\cdot}(t)$ was given in Appendix A. The long-term mean age, from Eq. (B.2) letting $t \to \infty$, is given by

$$
\begin{aligned}
\bar{a}_\infty = & \left(\frac{1}{\mu+\lambda_\infty} - \frac{v \exp(-(\mu+\lambda_\infty)a_1)}{\mu+v+\lambda_\infty} \right. \\
& \times \left\{ \frac{2(\mu+\lambda_\infty)+v}{(\mu+\lambda_\infty)(\mu+v+\lambda_\infty)} [1 - \exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] \right. \\
& \left. \left. + [a_1 - a_2 \exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] \right\} \right) \\
& \Bigg/ \left(1 - \frac{v \exp(-(\mu+\lambda_\infty)a_1)}{\mu+v+\lambda_\infty} [1 - \exp(-(\mu+v+\lambda_\infty)(a_2-a_1))] \right).
\end{aligned}
\tag{B.3}
$$

Appendix C. The rate of new cases of infection: $\rho(t, A_1, A_2)$

The semi-analytic expression for the new cases, in the case $2a_1 > a_2$, $A_1 > 2a_2$ and $A_2 - a_2 > A_1$, is, from Eq. (31):

$$
\rho(t, A_1, A_2) = \begin{cases}
\rho_1(t, A_1, A_2), & 0 \leqslant t \leqslant A_1 - a_2, \\
\rho_2(t, A_1, A_2), & A_1 - a_2 < t \leqslant A_1 - a_1, \\
\rho_3(t, A_1, A_2), & A_1 - a_1 < t \leqslant A_1, \\
\rho_4(t, A_1, A_2), & A_1 < t \leqslant A_2 - a_2, \\
\rho_5(t, A_1, A_2), & A_2 - a_2 < t \leqslant A_2 - a_1, \\
\rho_6(t, A_1, A_2), & A_2 - a_1 < t \leqslant A_2, \\
\rho_7(t, A_1, A_2), & t > A_2,
\end{cases}
\tag{C.1}
$$

where, for example, we have

$$\begin{aligned}\rho_1(t,A_1,A_2) &= \mu\exp(-\Phi(t))\lambda(t)\exp(-(\mu+\lambda_0)(A_1-t))\\ &\quad\times\frac{1-\exp(-(\mu+\lambda_0)(A_2-A_1))}{\mu+\lambda_0},\\ \rho_7(t,A_1,A_2) &= \mu\exp(-\Phi(t))\lambda(t)\exp(-v(a_2-a_1))\\ &\quad\times\int_{A_1}^{A_2}\exp(\Phi(t-a))\mathrm{d}a.\end{aligned}\tag{C.2}$$

The long-term new cases of infection, from the second equation of (C.2) letting $t\to\infty$, is given by

$$\begin{aligned}\rho_\infty(A_1,A_2) &= \frac{\mu\lambda_\infty}{\mu+\lambda_\infty}\exp(-v(a_2-a_1))\exp(-(\mu+\lambda_\infty)A_1)\\ &\quad\times[1-\exp(-(\mu+\lambda_\infty)(A_2-A_1))].\end{aligned}\tag{C.3}$$

Appendix D. The risk of CRS: $\omega(t,A_1,A_2)$

The semi-analytic expression for the risk of CRS, in the case $2a_1>a_2$, $A_1>2a_2$, $A_2-a_2>A_1$ and $A_1\geqslant\eta_1>2a_2$, is, from Eq. (32):

$$\omega(t,A_1,A_2)=\begin{cases}\omega_1(t,A_1,A_2), & 0\leqslant t\leqslant A_1-a_2,\\ \omega_2(t,A_1,A_2), & A_1-a_2<t\leqslant A_1-a_1,\\ \omega_3(t,A_1,A_2), & A_1-a_1<t\leqslant A_1,\\ \omega_4(t,A_1,A_2), & A_1<t\leqslant A_2-a_2,\\ \omega_5(t,A_1,A_2), & A_2-a_2<t\leqslant A_2-a_1,\\ \omega_6(t,A_1,A_2), & A_2-a_1<t\leqslant A_2,\\ \omega_7(t,A_1,A_2), & t>A_2,\end{cases}\tag{D.1}$$

where, for example, we have

$$\begin{aligned}\omega_1(t,A_1,A_2) &= \mu\exp(-\Phi(t))\lambda(t)\eta_2^2\exp(-\eta_2(A_1-\eta_1))\\ &\quad\times\exp(-(\mu+\lambda_0)(A_1-t))\\ &\quad\times\left\{\frac{A_1-\eta_1+\frac{1}{\mu+\lambda_0+\eta_2}}{\mu+\lambda_0+\eta_2}-\frac{A_2-\eta_1+\frac{1}{\mu+\lambda_0+\eta_2}}{\mu+\lambda_0+\eta_2}\right.\\ &\qquad\left.\times\exp(-(\mu+\lambda_0+\eta_2)(A_2-A_1))\right\},\end{aligned}\tag{D.2}$$

$$\begin{aligned}\omega_7(t,A_1,A_2) &= \mu\exp(-\Phi(t))\lambda(t)\eta_2^2\exp(-v(a_2-a_1))\\ &\quad\times\int_{A_1}^{A_2}a\exp(\Phi(t-a-\eta_1))\exp(-\eta_2 a)\,\mathrm{d}a.\end{aligned}$$

The long-term risk of CRS, from the second equation of (D.2) letting $t \to \infty$, is given by

$$\omega_\infty(A_1,A_2) = \frac{\mu\lambda_\infty\eta_2^2 \exp(-v(a_2-a_1))\exp(-(\mu+\lambda_\infty)A_1)\exp(-\eta_2(A_1-\eta_1))}{(\mu+\lambda_\infty+\eta_2)^2} \times \{1+(A_1-\eta_1)(\mu+\lambda_\infty+\eta_2)-[1+(A_2-\eta_1)(\mu+\lambda_\infty+\eta_2)] \times \exp(-(\mu+\lambda_\infty+\eta_2)(A_2-A_1))\}. \quad \text{(D.3)}$$

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