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The Loss of Immunity in Directly Transmitted Infections Modeling: Effects on the Epidemiological Parameters

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When directly transmitted infectious diseases are modeled assuming an everlasting induced immunity (and constant contact rate), there are well-established formulas to deal with, which is not true if we include the loss of induced immunity. In general, the immunity induced by the disease is everlasting. We propose a model considering the loss of immunity and present methods for the estimation of two epidemiological parameters: the force of infection and the *basic reproduction ratio*. We also analyze the effects of the loss of immunity on these parameters. Based on these results, we conclude that reinfection can play an important role in highly vaccinated populations.

1. INTRODUCTION

Since the observation that the immunity induced by the natural (environment circulating virus) infection of many directly transmitted infectious diseases may not be an everlasting protection, because the immunity is boosted by secondary infections amongst already exposed individuals Markowitz *et al*. (1990), some efforts have been done to explain its effects on the overall dynamics, e.g. Rouderfer *et al*. (1994).

Nowadays, the question of immunity waning cannot be neglected due to the introduction of mass vaccination strategy, roughly two decades ago, against directly transmitted infections, even though the disease-acquired immunity may appear to be everlasting. There are two failures concerned with vaccination-induced immunity. The first, not considered in this paper, is the vaccination failure to induce the development of the immune response, and the other failure is the initial development of the vaccine-induced immunity that wanes over time (Mathias *et al*., 1989). Due to these failures, the loss of immunity can have a significant impact on vaccination programmes (Rouderfer *et al*., 1994) and, particularly in rubella infection, a non-negligible problem comes out in a highly vaccinated population (Massad *et al*., 1994; Massad *et al*., 1994), because the number of

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congenital rubella syndrome (CRS) could increase when women lose induced immunity during their pregnancy.

When we analyze data on the basis of models assuming that the disease-induced immunity is everlasting, we can apply the classical results to obtain, simultaneously, the following two epidemiological parameters. First, the force of infection can be estimated as the average value of the catalytic approach (Muench, 1959), which is minus the derivative of the logarithm of the estimated age-specific fraction of susceptible individuals, and secondly, the *basic reproduction ratio* which can be derived as the inverse of the estimated fraction of susceptible individuals (Anderson and May, 1991). Both, age-specific and population-related fractions of susceptible individuals, can be derived from seroprevalence. However, if the loss of induced immunity is considered in the model, the catalytic method related to the force of infection cannot be applied, while the formula for the *basic reproduction ratio* remains valid. In other words, when a model with reinfection is considered, we can estimate one of the two epidemiological parameters and, then, we derive the other.

We propose a model considering a constant contact rate taking into account the loss of immunity. We develop it by an age-structured system of partial differential equations (Dietz, 1975), and analyze it in the natural conditions, that is, we restrict ourselves to the assessment of the effects of the loss of immunity on the force of infection and on the *basic reproduction ratio*, as estimated from data in the absence of vaccination strategy. By using a deterministic approach, we are restricted to large-scale patterns. We apply the model to rubella serological survey screened up from a non-vaccinated community of Caieiras City, Brazil (Azevedo Neto *et al*., 1994), to assess both the force of infection and the *basic reproduction ratio* for each possibly attributable value for the loss of immunity parameter (as the true value is unknown).

The above observations underline the importance of this preliminary analysis introducing a methodology to deal with reinfection. In a further paper, we will deal with the estimation of the force of infection and the effective vaccination rate while taking into account the loss of vaccine-induced immunity (Yang *et al*., 1996).

2. THE MODEL

We assume that there is a loss of disease-induced immunity. 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 age-distributed (a) susceptible, latent, infectious and immune individuals at time t. These four groups can be described dynamically

by the following set of partial differential equations,

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

where

$$\lambda(t) = \int_0^L \beta' Y(t,a)da \tag{2}$$

is the natural (in the absence of vaccination strategy) force of infection, μ is the natural mortality rate, σ^{-1} and γ^{-1} are, respectively, the average incubation and recovery periods, β' is the constant contact rate per individual (see Yang *et al.* (Yang, 1997) for the case of an age-specific contact rate) and π is the immunity-loss rate. Finally, L (in average, μ^{-1}) is the human life expectancy of a community. Neither maternally derived antibodies nor disease-induced mortality are considered.

System (1) has the following equation for the total number of individuals,

$$\frac{\partial}{\partial t}N(t,a) + \frac{\partial}{\partial a}N(t,a) = -\mu N(t,a), \tag{3}$$

where $N(t,a) = X(t,a) + H(t,a) + Y(t,a) + Z(t,a)$. If we assume that the mortality is balanced by the natality, then the birth rate at the population level should be given by $N^* = \mu N$, where N is the constant population size.

System (1) is a well-posed problem with the following initial and boundary conditions. The boundary conditions are

$$\begin{cases} X(t,0) = N^* \\ H(t,0) = Y(t,0) = Z(t,0) = 0 \\ X(t,L) = 0 \\ H(t,L) = Y(t,L) = Z(t,L) = 0 \end{cases} \tag{4}$$

since we are not considering the maternally derived antibodies or the loss of immunity. The initial conditions are generically stated as

$$\begin{cases} X(0,a) = X_0(a) \\ H(0,a) = H_0(a) \\ Y(0,a) = Y_0(a) \\ Z(0,a) = Z_0(a), \end{cases} \tag{5}$$

because we do not know how the disease was introduced into the community, but play an important rule when the vaccination strategy is considered.

Observe that the model uses age as a bookkeeping variable, which helps to estimate, in the steady state, the force of infection from age-specific data. But, none of the life history of contact or infectivity/susceptibility parameters is taken to be age-dependent. So, purely within the model, age is irrelevant.

The model incorporating the reinfection is treated as follows. In subsection 2.1 we present the results obtained disregarding the age dependency. This framework, where the *basic reproduction ratio* (R_0) and the force of infection (λ) are calculated from the estimated fraction of susceptible individuals based on a seroprevalence data, is called an R_0 approach. Section 2.2 develops the age-dependent framework in the steady state. In this case, besides the R_0 approach, we have the λ approach, which estimates the force of infection from seroprevalence data.

2.1. ***The age-independent results.*** In this section we outline the age-independent results considering a constant population size. Equations (1) and (3) can be integrated over all ages ($0 \leq a \leq L$, in practice letting $L \to \infty$) using the boundary conditions (4). Then, the dynamics of directly transmitted infections is, according to the model, described by

$$\begin{cases} \dfrac{d}{dt}x(t) &= \mu + \pi z(t) - [\beta y(t) + \mu]x(t) \\ \dfrac{d}{dt}h(t) &= \beta y(t)x(t) - (\sigma + \mu)h(t) \\ \dfrac{d}{dt}y(t) &= \sigma h(t) - (\gamma + \mu)y(t) \\ \dfrac{d}{dt}z(t) &= \gamma y(t) - (\pi + \mu)z(t), \end{cases} \tag{6}$$

where $x(t) = \int_0^\infty X(t,a)da/N$, and $h(t)$, $y(t)$ and $z(t)$ defined similarly as $x(t)$, are the average fractions of individuals in each class. The force of infection, from definition (2), is given by $\lambda(t) = \beta y(t)$, where the transmission coefficient $\beta = \beta' N$ is the total contact rate.

When case notification data are available, then we can use system (6) to estimate the force of infection by applying the non-linear regression method (Bates and Watts, 1988), as Raimundo *et al.* (1996) did to estimate the transmission coefficients of HIV and tuberculosis infections. But we confine ourselves to the steady state analysis.

System (6) has two equilibrium points. The trivial or disease-free equilibrium point is given by $x = 1$ and $h = y = z = 0$. The non-trivial or endemic level

equilibrium point is

$$\begin{cases} x &= \frac{1}{R_0} \\ h &= \frac{\mu(\mu+\sigma)(\mu+\gamma)^2(\mu+\pi)(R_0-1)}{\beta\sigma[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]} \\ y &= \frac{\mu(\mu+\sigma)(\mu+\gamma)(\mu+\pi)(R_0-1)}{\beta[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]} \\ z &= \frac{\mu\gamma(\mu+\sigma)(\mu+\gamma)(\mu+\pi)(R_0-1)}{\beta(\mu+\pi)[(\mu+\sigma)(\mu+\gamma)(\mu+\pi)-\sigma\gamma\pi]}, \end{cases} \tag{7}$$

where the *basic reproduction ratio* R_0 is

$$R_0 = \frac{\beta}{\beta^{th}}, \tag{8}$$

with β^{th} being the threshold contact rate defined by

$$\beta^{th} = \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma}. \tag{9}$$

Hence, as expected, R_0 is clearly independent of the immunity-loss rate.

Liu *et al*. (1987) provided the stability analysis of the dynamics system (6) by means of the characteristic equation. Briefly, they stated that the trivial equilibrium point is stable if $R_0 \leq 1$, and the non-trivial equilibrium point is stable if $R_0 > 1$. Therefore, at $R_0 = 1$ there is bifurcation from the trivial to the non-trivial equilibrium point, and, in this situation, the parasitic specie is capable of invading, and establishing itself within, a host population (Anderson and May, 1991; Diekmann *et al*., 1991).

Observe that, once the fraction x could be estimated, the *basic reproduction ratio* can be calculated as its inverse; and, from the latter value, the force of infection ($\lambda = \beta y$) can be obtained from the third equation of (7), when $R_0 > 1$, through

$$\lambda = \mu \frac{R_0 - 1}{1 - \frac{\sigma\gamma\pi}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}}. \tag{10}$$

We observe that the force of infection depends on the immunity-loss parameter π. This methodology, where the fraction x is estimated, and from which R_0 and λ are derived, is called the R_0 approach.

The major effect of the loss of immunity is to contribute substantially to the increase in the size of the group of susceptible individuals (Rouderfer *et al*., 1994). Then, in proportion to the increasing values assumed by the immunity-loss rate, we must have a low-valued *basic reproduction ratio*, as can be seen from the first relation of (7). Contrarily, the force of infection must assume high value, according to expression (10).

2.2. ***A methodology to deal with reinfection.*** In this section we analyze the endemic level equilibrium point in the steady state taking into account the age structure in the population.

Equations (1) and (3) are combined to yield the system of equations for the fractions of age-structured individuals in the steady state

$$\begin{cases} \dfrac{d}{da}x(a) &= \pi z(a) - \lambda x(a) \\ \dfrac{d}{da}h(a) &= \lambda x(a) - \sigma h(a) \\ \dfrac{d}{da}y(a) &= \sigma h(a) - \gamma y(a) \\ \dfrac{d}{da}z(a) &= \gamma y(a) - \pi z(a), \end{cases} \tag{11}$$

where the age distributed fractions of individuals in each class are $x(a) = X(a)/N(a)$ and $h(a)$, $y(a)$ and $z(a)$ are defined similarly as $x(a)$. Note that the age-distributed population is given by $N(a) = N^* e^{-\mu a}$. As the seroprevalence curve is related to the transmission of the infectious disease irrespective of the vital dynamics, the above definition of the fractions of individuals is different from that used in the preceding section. To obtain the above system of differential equations, we have used the relation, for instance for $X(a)$,

$$\frac{d}{da}x(a) = \frac{1}{N(a)}\frac{d}{da}X(a) + \mu x(a), \tag{12}$$

with equation (3) in the steady state.

By applying the conditions $x(0) = 1$ and $h(0) = y(0) = z(0) = 0$ to system (11), and solving it (see the appendix), we obtain the description of the endemic level in a community (Anderson and May, 1991) by the integral equations

$$\begin{cases} x(a) &= e^{-\lambda a} + \int_0^a B(a-s)x(s)ds \\ h(a) &= e^{-\sigma a}\int_0^a e^{\sigma s}\lambda x(s)ds \\ y(a) &= e^{-\gamma a}\int_0^a e^{\gamma s}\sigma e^{-\sigma\tau}\int_0^\tau e^{\sigma s}\lambda x(s)ds d\tau \\ z(a) &= e^{-\pi a}\int_0^a e^{\pi a'}\gamma e^{-\gamma a'}\int_0^{a'} e^{\gamma s}\sigma e^{-\sigma\tau}\int_0^\tau e^{\sigma s}\lambda x(s)ds d\tau da', \end{cases} \tag{13}$$

where $B(a-s)$, given by

$$B(a-s) \quad = \quad \lambda\sigma\gamma\pi \left\{ \frac{\frac{e^{-\sigma(a-s)}}{(\sigma-\lambda)(\sigma-\pi)} - \frac{e^{-\gamma(a-s)}}{(\gamma-\lambda)(\gamma-\pi)}}{\gamma-\sigma} + \frac{\frac{e^{-\pi(a-s)}}{(\gamma-\pi)(\sigma-\pi)} - \frac{e^{-\lambda(a-s)}}{(\gamma-\lambda)(\sigma-\lambda)}}{\lambda-\pi} \right\}, \tag{14}$$

is the kernel of the integral equations. The first equation is a non-homogeneous Volterra equation. Note that the kernel (14), being a combination of decaying exponential functions, is quadratically integrable (L_2 function) and the equation for $x(a)$ in (13) can be shown to be a contraction (e.g., Coutinho *et al.* (1993)). Then, there exists one and only one solution for $x(a)$ (Griffel, 1981; Tricomi, 1985). Hence, from the solution of $x(a)$ we can obtain age-specific fractions of $h(a)$, $y(a)$ and $z(a)$.

The solution of the first equation of (13), with the kernel (14), depends on two unknown parameters: the age-distributed fraction of susceptible individuals $x(a)$ and the force of infection λ. Nevertheless, we can estimate $x(a)$ from the seroprevalence curve, $S^+(a)$, by the relation

$$x_0(a) \quad = \quad 1 - S^+(a). \tag{15}$$

This result comes from the fact that the age-specific fraction of susceptible individuals plus all other fractions of individual classes, summarized by $S^+(a)$, is unity, by considering that the presence of specific antibodies against a given infectious agent in an individual is interpreted as a previous infection (Azevedo Neto *et al.*, 1994). On the other hand, we can calculate the fraction of susceptible individuals χ as

$$\chi = \langle x_0(a) \rangle \equiv \frac{\int_0^\infty x_0(a) N^* e^{-\mu a} da}{\int_0^\infty N^* e^{-\mu a} da} = \mu \int_0^\infty \left[1 - S^+(a)\right] e^{-\mu a} da, \tag{16}$$

where $\langle \cdot \rangle$ is assigned for the average value regardless of age.

Since $x_0(a)$ and χ are derivable from the seroprevalence data, in the age-structured population analysis we have both R_0 and λ approaches.

First, let us consider the R_0 approach. In this approach we are relating the parameters of the model with the estimated χ. To obtain the fraction of susceptible individuals of the model, we multiply both members of the first equation of (13) by $N(a)$ and integrate over all ages, to obtain

$$\langle x(a) \rangle = \frac{\mu(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}{(\mu+\lambda)(\mu+\sigma)(\mu+\gamma)(\mu+\pi) - \lambda\sigma\gamma\pi}. \tag{17}$$

Observe that if $\lambda = 0$, then $\langle x(a) \rangle = 1$ and all other individual classes must have null values.

The relation (17) can be rewritten, when we substitute $\langle x(a)\rangle$ by the estimated χ, as

$$\lambda = \mu \frac{\chi^{-1} - 1}{1 - \frac{\sigma\gamma\pi}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)}}, \tag{18}$$

which is a well-behaved function in the non-negative range of variations of the force of infection, because the fraction of susceptible individuals assumes, at most, a value equal to unity. Comparing this expression with (10), we note that both are the same if

$$R_0 = \chi^{-1}, \tag{19}$$

which is the first expression of (7). From this expression we note that the effective reproduction ratio is unity in the equilibrium, i.e., $R = R_0\chi = 1$ (see Anderson and May (1991)).

In this approach, for fixed χ and, consequently, also for fixed R_0, we note that for each value attributed to the immunity-loss rate there is a corresponding value for the force of infection. Therefore, for each pair (π,λ) we can generate the corresponding age-specific fraction of susceptible individuals by the first equation of (13). From the uniqueness of the solution for $x(a)$, we can apply the iterative algorithm (Tricomi, 1985) to solve the integral equation for $x(a)$. Hence,

$$x_{j+1}(a) = e^{-\lambda a} + \int_0^a B(a-s)x_j(s)ds, \qquad \text{with} j = 0, 1, 2, \ldots, \tag{20}$$

converges to the unique solution, where $x_j(a)$ and $x_{j+1}(a)$ are the jth and $(j+1)$th iterations of $x(a)$, and the initial value ($j = 0$) is provided by $x(a) = x_0(a)$.

Secondly, let us consider the λ approach. This approach corresponds to calculating the force of infection from the estimated age-specific fraction of susceptible individuals $x_0(a)$ based on a seroprevalence curve. In this case, we fix $x_0(a)$ and for each value attributed to π we calculate λ.

For each pair ($x_0(a)$,π) we can evaluate the force of infection by applying the convergence in the mean theory (Griffel, 1981). This convergence is set as

$$\int_0^\infty |x(a, \lambda^n) - x_0(a)|^2 \, da \to 0, \qquad \text{with } n = 1, 2, \ldots, \tag{21}$$

where λ^n is the nth iteration of λ, with $x(a, \lambda^n)$ being the age-specific fraction of susceptible individuals of the model, and is assessed by Brent's minimization method (Press *et al.*, 1989). For each nth step value of λ in Brent's method, we must evaluate the iterated equation (20) to provide the age-specific fraction of susceptible individuals of the model.

Once the force of infection is evaluated, the *basic reproduction ratio* can be obtained as the inverse of $\langle x(a)\rangle$, which is calculated from (17).

It is worth showing the extreme situations. In the case of the everlasting disease-induced immunity, we obtain, by setting $\pi = 0$ in the above findings,

$$\begin{cases} B(a-s) = 0 \\ \\ \lambda = \mu(R_0 - 1) \\ \\ \langle x(a) \rangle = \dfrac{\mu}{\mu + \lambda}. \end{cases} \tag{22}$$

The latter two formulas of (22) and the expression (9) are the same obtained by Anderson and May (1991) and Coutinho *et al.* (1993). In this case, the force of infection can be related to the age-specific fraction of susceptible individuals by

$$\lambda = \left\langle -\frac{d}{da} \ln[x_0(a)] \right\rangle. \tag{23}$$

This form of evaluating the force of infection is the so-called catalytic approach (Muench, 1959), which comes from the first equation of (11) with $\pi = 0$, and is not valid when reinfection is considered.

At the other extreme is the case where the disease does not induce immunity. This can be obtained by letting $\pi \to \infty$ in the above findings, resulting in:

$$\begin{cases} B(a-s) = \sigma\gamma\pi \left\{ \frac{1}{\gamma-\sigma} \left[-\frac{e^{-\sigma(a-s)}}{\sigma-\lambda} + \frac{e^{-\gamma(a-s)}}{\gamma-\lambda} \right] + \frac{e^{-\lambda(a-s)}}{(\gamma-\lambda)(\sigma-\lambda)} \right\} \\ \lambda = \mu\,(R_0 - 1) \left[\frac{1}{1 - \frac{\gamma}{\beta^{th}}} \right] \\ \langle x(a) \rangle = \frac{\mu}{\mu+\lambda} \left[\frac{1}{1 - \frac{\gamma}{\beta^{th}} \left(\frac{\lambda}{\mu+\lambda} \right)} \right]. \end{cases} \tag{24}$$

Comparing (22) and (24) we observe that, for the same estimated R_0, the force of infection and the fraction of susceptible individuals have the lowest (highest) values for $\pi = 0$ ($\pi \to \infty$).

Up to now we have not used the relation between the force of infection and the contact rate, $\lambda = \beta y$. To do this, we solve (11) in terms of $y(a)$, instead of $x(a)$. Therefore, we obtain in terms of the age-specific fraction of infectious individuals, the expression

$$y(a) \;=\; \lambda\sigma \left[\frac{\frac{e^{-\gamma a}}{\gamma-\lambda} - \frac{e^{-\sigma a}}{\sigma-\lambda}}{\gamma-\sigma} + \frac{e^{-\lambda a}}{(\gamma-\lambda)(\sigma-\lambda)} \right] + \int_0^a B(a-s)y(s)ds, \tag{25}$$

where the kernel is the same defined by (14).

Multiplying both members of equation (25) by $N(a)$ and integrating over all ages, we obtain, for the natural force of infection, the formula (10) with β/β^{th}

in place of R_0. The previous relation (19) was obtained by comparison of the force of infection provided by (18) with that furnished by the age-independent result (10). But, when dealing with the age-specific fraction of infectious individuals, the identification of the *basic reproduction ratio* follows immediately due to definition (8).

In the next section we present some simulations to clarify both approaches.

3. NUMERICAL RESULTS

In this section we apply the above two approaches to rubella infection (Azevedo Neto *et al*., 1994) considering the reinfection. For this purpose we set $\sigma = 52.0$ years^{-1} and $\gamma = 39.0$ years^{-1} (Anderson and May, 1991), $\mu = 0.017$ years^{-1} from actuarial data, and π is made to vary on the range [0.0,0.2]. This range of variations of π corresponds to an average immunity period varying from 5.0 years to infinity (∞).

First, we present the situation where the average fraction of susceptible individuals is estimated and, consequently, the *basic reproduction ratio* is considered as the primary parameter. The R_0 approach disregards the age-structured features of the population and can be used on the case notification records. In this approach, the fraction of susceptible individuals χ is fixed. For a community in Brazil (Azevedo Neto *et al*., 1994), we estimated $\chi = 0.124$ and we calculated $R_0 = 8.097$, from (19).

The effect of immunity-loss rate π on the force of infection λ can be analyzed using (10). In Fig. 1 we show the dependency of the force of infection on the loss of immunity parameter, which are varied from $\pi = 0$ to $\pi = 0.2$ years^{-1}. We note that the force of infection has its lowest value at $\pi = 0$ ($\lambda = 0.121$, both in years^{-1}), and increases proportionally to π, assuming the highest value at $\pi = 0.2$ ($\lambda = 1.526$, both in years^{-1}). When π increases, the fixed χ can be explained by an increase in the force of infection, i.e., due to the infection of individuals that never have had the infection plus the contribution of the reinfection of the susceptible individuals originated from immune individuals who have lost their immunity.

In Fig. 2 we show the age-specific fraction of susceptible individuals considering three fixed forces of infection corresponding to the immunity-loss rate $\pi = 0$, $\pi = 0.1$ ($\lambda = 0.827$) and $\pi = 0.2$ (in years^{-1}). The curves are obtained by the iterative method, according to equation (20). We also show the calculated $x_0(a)$ from estimated $S^+(a)$. We observe that $x_0(a)$, calculated from estimated $S^+(a)$, presents an increasing trend for higher ages. It can be explained either by the loss of immunity or by the sampling effect (Azevedo Neto *et al*., 1994). We noted that the age-specific fraction of susceptible individuals of the model can not explain the reversed sigmoidal shape of the observed one. This shape can be better attained if we consider an age-specific contact rate (Yang, 1997).

In this approach we have fixed the *basic reproduction ratio*. For this reason, let

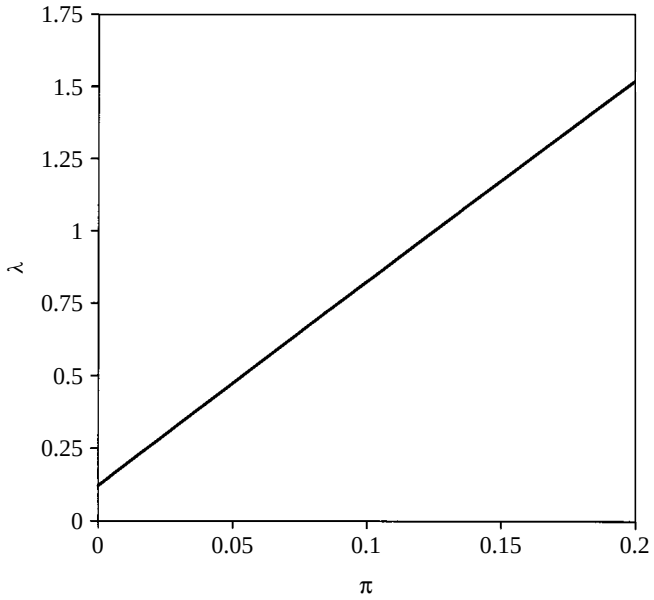

Figure 1. The force of infection λ (years^{-1}) as a function of the loss of immunity parameter on the range $\pi = 0$–0.2 years^{-1}. We fixed $\chi = 0.124$.

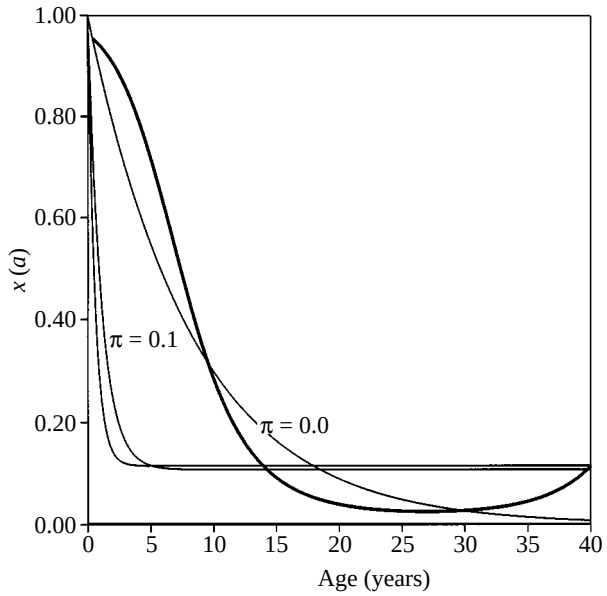

Figure 2. The four age-specific fractions of susceptible individuals $x(a)$: the estimated $x_0(a)$ (thick curve), and for three immunity-loss rates, $\pi = 0$, 0.1, 0.2 years^{-1} (the closest curve to the vertical axis). We fixed $\chi = 0.124$.

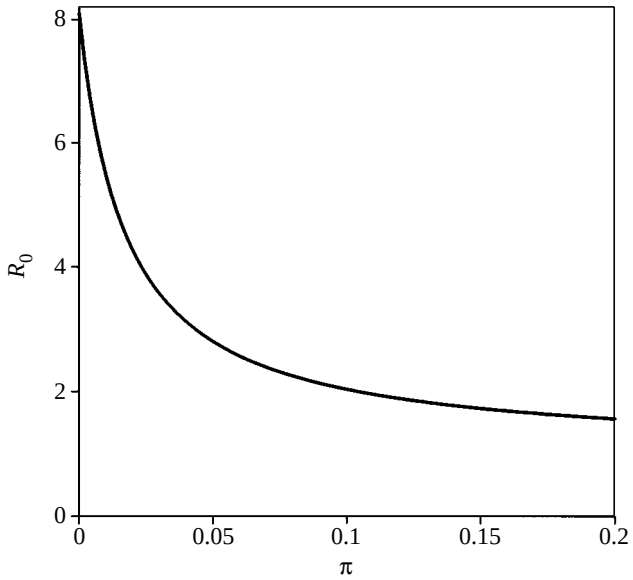

Figure 3. The basic reproduction ratio R_0 as a function of the loss of immunity parameter on the range $\pi = 0$–0.2 years^{-1}. We fixed $\chi = 0.124$ (and $\lambda = 0.121$ years^{-1}).

us consider a hypothetical situation. Suppose several infectious diseases related with different values for the disease-induced immunity-loss rate, but they have the same value for the natural force of infection λ. We set this value as the correspondent to the everlasting immunity, or $\lambda = 0.121$ years^{-1}. Once λ is fixed, we can evaluate $\langle x \rangle$ from expression (17) and then R_0, from (19), for different values assumed by π. In Fig. 3 we show, for this hypothetical situation, the dependency of R_0 as a function of π, from $\pi = 0$ to $\pi = 0.2$ years^{-1}. We observe that, as π decreases, R_0 increases while the fraction of susceptible individuals decreases. The *basic reproduction ratio* varies from 1.56 ($\pi = 0.2$) to 8.10 ($\pi = 0$).

In R_0 approach, by estimating χ, both R_0 and λ are uniquely determined. Hence, we evoked different infectious disease to explain the same seroprevalence curve to show a hypothetical dependency of R_0 on π. In the next approach, this consideration is not necessary.

The second approach is by calculating λ from the fixed $x_0(a)$ for the same community in Brazil (Azevedo Neto *et al.*, 1994), for different values of π. Once λ is calculated for each value of π, we can evaluate $\langle x(a) \rangle$, R_0 and $x(a)$ of the correspondent model. In λ approach, the force of infection is calculated by the convergence in the mean method, according to expression (21).

In Fig. 4 we show the calculated λ and χ ($\equiv \langle x(a) \rangle$) as a function of π. We note that both the force of infection and the fraction of susceptible individuals have their lowest values at $\pi = 0$ ($\lambda = 0.116$, both in years^{-1}, and $\chi = 0.13$), and increase monotonically as π increases, assuming the highest values at $\pi = 0.2$ ($\lambda = 0.274$, both in years^{-1}, and $\chi = 0.44$). We observe that as π increases, the

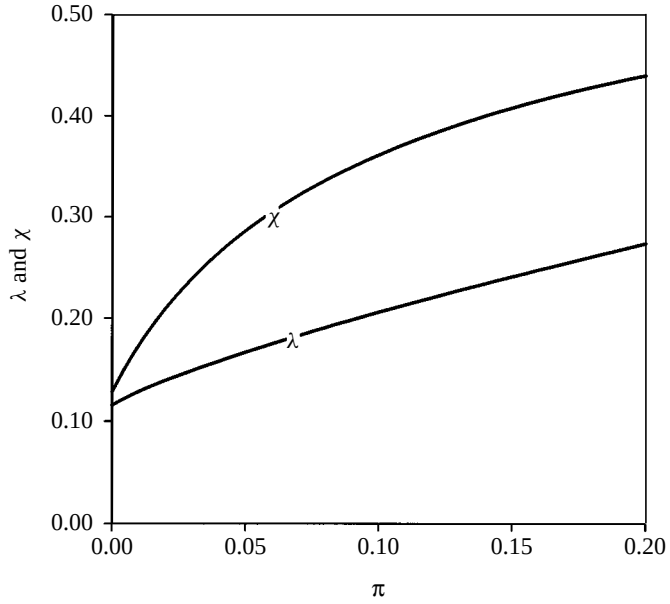

Figure 4. The force of infection λ (years^{-1}) and χ as a function of the loss of immunity parameter on the range $\pi = 0$–0.2 years^{-1}. We fixed $x_0(a)$.

force of infection correlates positively, but not linearly as the preceding approach, with the fraction of susceptible individuals.

In Fig. 5 we show the age-specific fraction of susceptible individuals considering three fixed forces of infection corresponding to the immunity loss rate $\pi = 0$, $\pi = 0.1$ ($\lambda = 0.206$) and $\pi = 0.2$ (in years^{-1}). The curves are obtained by the iterative method, according to equation (20). We observe that the age-specific fractions of susceptible individuals of the model decay more slowly than in the previous approach (see Fig. 2).

In λ approach, there is a natural relation between the *basic reproduction ratio* and the immunity-loss rate. For each π fixed, we estimate λ by the convergence in the mean and, then, R_0 is obtained as χ^{-1}. The result is shown in Fig. 6. We observe that the *basic reproduction ratio* R_0 increases as π decreases, which varies from 2.27 ($\pi = 0.2$) to 7.80 ($\pi = 0$). Note that this range of variation is contained on that found in the previous approach. Here we are explaining a fixed $x_0(a)$ when the immunity-loss rate is varied. In Fig. 3 we fixed χ and λ, and then analyzed the effect of π on R_0. In both situations R_0 increases as π decreases, which agrees with the macroparasite infection, where the acquired immunity provides a much higher estimation for R_0 than that without immunity (Yang and Coutinho, 1998; Yang *et al.*, 1997).

We observed that, comparing the R_0 approach (Figs 1–3, χ fixed) with the λ approach (Figs 4–6, $x_0(a)$ fixed), the former superestimates the epidemiological values, while the latter underestimates them. Nevertheless, the latter approach has an advantage: it can be improved by introducing the age-specific contact rate.

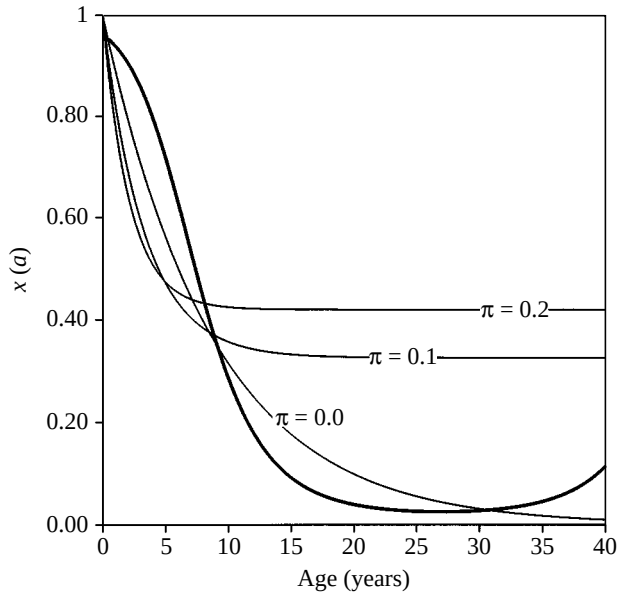

Figure 5. The four age-specific fractions of susceptible individuals $x(a)$: the estimated $x_0(a)$ (thick curve) and for three immunity-loss rates, $\pi = 0$, 0.1, 0.2 years^{-1}. We fixed $x_0(a)$.

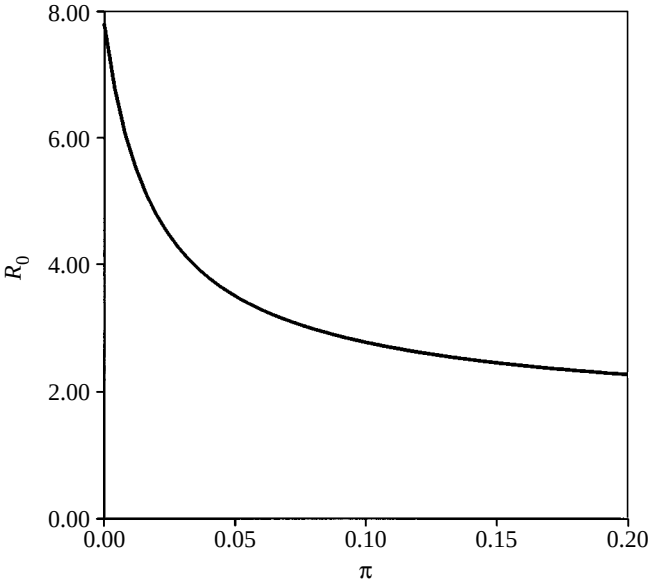

Figure 6. The basic reproduction ratio R_0 as a function of the loss of immunity parameter on the range $\pi = 0$–0.2 years^{-1}. We fixed $x_0(a)$.

4. CONCLUSIONS

We proposed and analyzed an age-structured model to describe directly transmitted infections considering the loss of immunity. We then applied our model to the rubella serological survey, assuming the existence of the loss of immunity induced by the disease, to assess the epidemiological parameters by two approaches. In the R_0 approach, which is a straight analysis, the age structure does not matter. However, in the λ approach a specific methodology must be applied to estimate the parameters by taking into account the age-specific features.

Observe that in the R_0 approach we are estimating the expected number of secondary cases produced per primary case when the infection enters into an entirely susceptible population, from which the force of infection is derived. On the other hand, in the λ-approach we are estimating the probability per unit of time that a susceptible individual becomes infected, and, then, the *basic reproduction ratio* is derived. Comparing the range of variation of the epidemiological parameters, we conjecture that, for a constant contact rate modeling, the true epidemiological values may be situated between estimations provided by both approaches.

The upper bound for the *basic reproduction ratio* is obtained when the induced immunity is everlasting. If the induced immunity wanes, then the estimation of the *basic reproduction ratio* is not only diminished in its value but is also increased in difficulty. As we have stated above, we observed that when π increases, both χ and λ increase, while R_0 diminishes. If only the *basic reproduction ratio* as measuring the controlling effort is taken into account, we can be misled in our understanding, i.e., increasing the immunity-loss rate can lead to an easier control. But the age-structured approach means that both the force of infection (estimated as the inverse of the average age of acquisition of the first infection) and the *basic reproduction ratio* must be taken into account.

For instance, observing that higher estimations of the *basic reproduction ratio* is related to lower fractions of susceptible individuals, then we must have a higher proportion of susceptible individuals covered by vaccination in order to attain eradication (Anderson and May, 1991). On the other hand, higher values assumed by the force of infection is related to the lowering of the average age of acquisition of the first infection. This result, in terms of the eradication conditions, means that the vaccination rate comprised on an age interval must be increased and, also, the vaccination must be carried out in young individuals (Yang, 1997). Therefore, the effort of eradication of directly transmitted infections by vaccination strategy is not an easy task, especially when one takes into account the waning of induced immunity.

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APPENDIX

The kernel $B(a-s)$, given by (14) in the main text, is calculated as follows. The solutions of the system of differential equations (11) can be written as

$$\begin{cases} x(a) &= e^{-\lambda a} + e^{-\lambda a}\int_0^a e^{\lambda s}\pi z(s)ds \\ h(a) &= e^{-\sigma a}\int_0^a e^{\sigma s}\lambda x(s)ds \\ y(a) &= e^{-\gamma a}\int_0^a e^{\gamma s}\sigma h(s)ds \\ z(a) &= e^{-\pi a}\int_0^a e^{\pi s}\gamma y(s)ds. \end{cases} \tag{26}$$

Observe that if we substitute $h(a)$ into the third equation, we have the third equation of (13), which substituted into the fourth equation, we have $z(s)$ given by the fourth equation of (13) as a functional of $x(a)$. From the latter we have, after some arrangement in the limits of the integrations, the first equation of (13), with the kernel given by

$$B(a-s) = \lambda\sigma\gamma\pi e^{\sigma s}\int_0^a\int_0^a\int_0^a e^{(\lambda-\pi)t}e^{(\pi-\gamma)u}e^{(\gamma-\sigma)v}\theta(t-u)\theta(u-v)\theta(v-s)dvdudt, \tag{27}$$

where $\theta(x)$ is the step or Heaviside function. The calculation of the triple integration results in (14).

However, if we substitute the first and the fourth equations of (26) into the third equation of (13), we have the integral equation (25) for the age-specific fraction of infectious individuals in the main text.

The fraction of susceptible individuals, defined by (17) in the main text, is calculated from the first equation of (13), that is,

$$\langle x(a)\rangle = \frac{\int_0^\infty e^{-(\lambda+\mu)a}da + \int_0^\infty e^{-\mu a}\int_0^a B(a-s)x(s)dsda}{\int_0^\infty e^{-\mu a}da}. \tag{28}$$

But, we have the identity

$$\int_0^\infty e^{-\mu a}\int_0^a B(a-s)x(s)dsda = \int_0^\infty x(a)e^{-\mu a}da\int_0^\infty e^{-\mu u}B(u)du, \tag{29}$$

which applied in the previous equation results

$$\langle x(a)\rangle \left[1 - \int_0^\infty e^{-\mu u} B(u)du\right] = \frac{\mu}{\lambda+\mu}. \tag{30}$$

Observe that

$$\int_0^\infty e^{-\mu u} B(u)du = \frac{\sigma\gamma\pi\lambda}{(\mu+\sigma)(\mu+\gamma)(\mu+\pi)(\mu+\lambda)}, \tag{31}$$

which results in (17).

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