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A model-based design of a vaccination strategy against rubella in a non-immunized community of São Paulo State, Brazil

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SUMMARY

A mixed vaccination strategy against rubella is proposed. We describe how the vaccination strategy was designed with the help of mathematical techniques. The strategy was designed for application in a non-immunized community of the State of São Paulo, Brazil, and was implemented by local health authorities in 1992. This strategy comprises a pulse vaccination campaign, covering the age interval between 1 and 10 years, followed by the introduction of the vaccine in the immunization calendar at 15 months of age. The expected impact of the proposed strategy is discussed.

INTRODUCTION

By the end of the 1960s the development of new vaccines against several childhood infections resulted in modifications in the epidemiology of those diseases. The efficacy of the vaccines allowed public health authorities to aim for eradication. However, in spite of great efforts worldwide, eradication of no infection, with the exception of smallpox, has been achieved. Difficulties in attaining high vaccination coverages, multiple changes in the calendar, problems with storage (including cold-chain), difficulties with the distribution of vaccines, lack of political/administrative endurance, are amongst the probable causes in the failure to eradicate childhood infections. The above-mentioned difficulties are particularly cumbersome in developing countries. Also, there is still a gap in the theoretical knowledge about the existence of sufficient conditions for eradication of such infection. Some theoretical eradication conditions have recently been demonstrated [1].

The methods by which optimal control strategies for childhood infections can be determined using mathematical models have been thoroughly discussed in the literature [1–11].

In the State of São Paulo, Brazil, routine measles vaccine was introduced in 1973. However, despite high official coverage rates, recurrent epidemic outbreaks

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occurred regularly until 1986. This led local health authorities to carry out a major vaccination campaign against measles in 1987. This campaign was aimed at the entire population between 9 months and 15 years of age, covering around 90% of the target population [12]. After the intervention, the average seroprevalence raised to 96% and the incidence of measles dropped from 3666 cases/year to 254 cases/year. The deaths attributable to measles dropped from 145/year to 4 deaths/year [13].

Amongst the so-called childhood infections, rubella is considered to be the most likely candidate for eradication through vaccination, second only to poliomyelitis. This is probably due to its relatively low infectiousness, when compared with other infections, reflected in the basic reproduction number, a composite parameter relating to probability of contact, and the probability that those contacts result in new infections.

This paper intends to present the design of a vaccination strategy against rubella in the State of São Paulo, Brazil. The design is based on serological data and, through mathematical techniques, a mixed strategy consisting of a pulse and a routine vaccination schedule is proposed. The risk of shifting the average age of first infection to reproductive ages is minimized and the reduction of the force of infection is maximized. This paper is organized as follows: after the introduction we present the deduction of an optimal interval to vaccinate children in a pulse schedule and the optimal age to vaccinate in a routine scheme; the third section presents the predictable outcomes of the strategy proposed, as related to the proportion of remaining susceptible, the risk of Congenital Rubella Syndrome (CRS) and the impact on the force of infection; the next section presents the real data upon which the calculations were performed. Conclusions comment on the strategies proposed and describe the campaign adopted in the State of São Paulo.

A MIXED VACCINATION STRATEGY AGAINST RUBELLA

Brazil has a long tradition of mass vaccination campaigns, since the mid-seventies, started with vaccination against meningitis. This strategy has proved to be highly successful and encouraged health authorities to adopt such a programme against other childhood infections. In Brazil there was no official vaccination programme against rubella up to 1992. As a consequence of a successful mass vaccination campaign against measles in São Paulo in 1987, the Ministry of Health decided, in 1992, to carry out a major countrywide vaccination campaign against measles, intended to reach all children aged between 9 months and 15 years old. The State of São Paulo decided to take the opportunity of this Federal campaign to introduce rubella and mumps vaccination along with measles. Immediately after the pulse campaign, the measles–rubella–mumps vaccine was introduced in the routine immunization programme of the State of São Paulo. In this section we describe this mixed vaccination strategy, designed to control rubella in the State of São Paulo, Brazil.

The pulse vaccination design

The pulse vaccination strategy design assumed a constant contact rate β, and a steady-state situation for rubella. It was also assumed that a fraction p of the target population would be vaccinated with a rate ν, between the ages a_1 and a_2,

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in the shortest period of time as possible. The proportion of children vaccinated between ages a_1 and a_2, p, is given by:

$$p = 1 - \frac{\int_{a_1}^{a_2} N(a, \nu)\, \mathrm{da}}{\int_{a_1}^{a_2} N(a, \nu = 0)\, da}, \tag{1}$$

where $N(a)$ is the number of children aged a, and ν is the vaccination rate. The vaccination rate, ν, and the proportion of children vaccinated, p, are related by:

$$\nu = \mu \left[\frac{1 - \exp[-(\mu+\nu)(a_2 - a_1)]}{1 - \exp[-\mu(a_2 - a_1)]} \frac{1}{1-p} - 1 \right], \tag{2}$$

where μ is the natural mortality rate.

Under the steady-state assumption, the equation for the remaining fraction of susceptibles, $X(a)$, has the form:

$$X(a) = \begin{cases} X_0 \mathrm{e}^{-(\mu+\lambda)a} & \text{for} \quad 0 \leqslant a \leqslant a_1 \\ (1-p) X_0 \mathrm{e}^{-(\mu+\lambda)a} + p X_0 \mathrm{e}^{\nu a_1} \mathrm{e}^{-(\mu+\lambda+\nu)a} & \text{for} \quad a_1 \leqslant a \leqslant a_2 \\ [(1-p) + p \mathrm{e}^{-\nu(a_2 - a_1)}] X_0 \mathrm{e}^{-(\mu+\lambda)a} & \text{for} \quad a > a_2, \end{cases} \tag{3}$$

where λ is the so called force of infection [5].

The solution of the equations for the latent, $H(a)$, and infections, $Y(a)$, states are given by:

$$H(a) = \exp[-(\mu+\sigma)a] \lambda \int_0^a \exp[(\mu+\sigma)a'] X(a')\, da', \tag{4}$$

where σ is the inverse of the incubation period, and

$$Y(a) = \exp[-(\mu+\gamma)a] \sigma \int_0^a \exp[(\mu+\gamma)a'] H(a')\, da', \tag{5}$$

where γ is the recovery rate.

From the classical definition of the force of infection

$$\lambda = \beta \int_0^\infty Y(a)\, da \tag{6}$$

it is possible to calculate its value before the introduction of a vaccination scheme, by setting $\nu = 0$, in equation 3, which takes the form:

$$\lambda_0 = \mu \left[\frac{X_0}{\mu} \left(\frac{\sigma\beta}{(\mu+\sigma)(\mu+\gamma)} \right) - 1 \right]. \tag{7}$$

From equations (2–7) it is possible to relate the average force of infection before, λ_0. and after, λ, the pulse vaccination, by the following:

$$\lambda_0 + \mu = \frac{\lambda + \mu}{1 - p \dfrac{\nu \exp[-(\lambda+\mu)a_1]}{\mu+\lambda+\nu} [1 - \exp[-(\mu+\lambda+\nu)(a_2 - a_1)]]}. \tag{8}$$

Details on the derivation of equation 8 can be seen in the appendix.

Fig. 1 shows the numerical simulations of equation 8 for a set of age intervals

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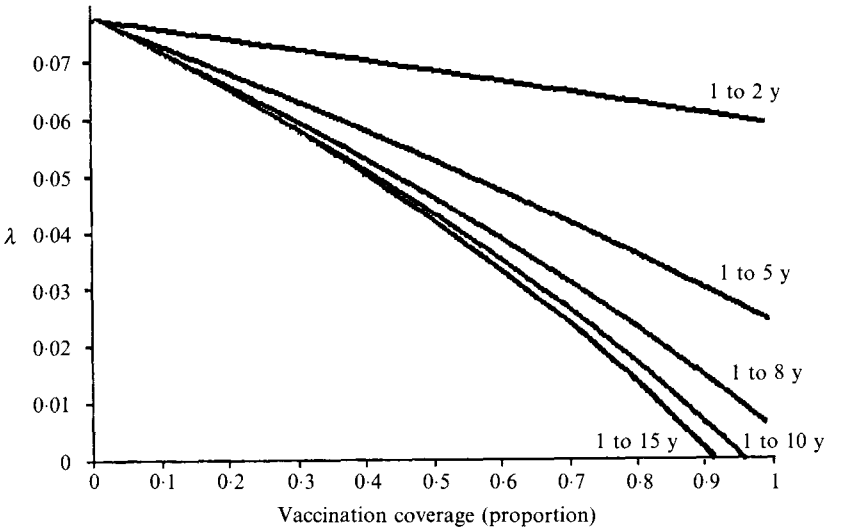

Fig. 1. Numerical simulations of the force of infection, λ, estimated from equation 9 for different age intervals ranging from 1–2 to 1–15 years, as a function of the proportion of children covered by the pulse vaccination. The vaccination rate, ν, and the natural mortality rate, μ, were set as 0·25 and 0·017, respectively.

Table 1. *Rubella serological data from the city of Caieiras, State of São Paulo, Brazil, from [14]*

Age class	Proportion of seropositives
< 1 month	1·00
1 month	0·875
2 months	0·636
3 months	0·545
4 months	0·455
5 months	0·154
6 months	0·067
7 months	0·077
8 months	0·000
9 months	0·000
10 months	0·000
11 months	0·087
1 year	0·051
2 years	0·160
3 years	0·068
4 years	0·353
5–9 years	0·520
10–14 years	0·778
15–19 years	0·833
20–24 years	1·00
25–29 years	0·899
30–34 years	1·00
35–39 years	1·00

and the proportion of children covered by the pulse vaccination. The force of infection before the pulse vaccination was estimated from the serological data described by Azevedo Neto and colleagues [14]. Table 1 shows a summary of the serological data.

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The vaccination rate, ν, and the natural mortality rate, μ, were set as 0·25 and 0·017, respectively [13].

It can be seen from Fig. 1 that the expected reduction in the average force of infection as a result of vaccinating children between 1–10 and 1–15 years old is practically the same. Therefore considering the probability of pregnancy in girls above 10 years, and the additional costs and logistic difficulties of vaccinating a wider age interval, it was recommended to local health authorities that the pulse vaccination campaign should be restricted to the age interval between 1 and 10 years.

The routine vaccination design

In order to estimate the optimum age to vaccinate children routinely against rubella in São Paulo, we applied Hethcote's formulations [9] with β assumed as a constant (i.e. an age-independent λ), and a new formulation for $\beta(a, a')$ to the epidemiological setting described in [1].

A model with β constant

For this we need an additional variable corresponding to seroconversion function, $C(a)$, which describes the age-dependent proportion of children responsive to vaccination. This function has been described for the region by Azevedo Neto and colleagues [14]. Consider the system of equations:

$$\left.\begin{aligned}
\frac{dX(a)}{da} &= -[\lambda C(a) + \nu(a) + \mu] X(a), \\
\frac{dH(a)}{da} &= \lambda C(a) X(a) - [\sigma + \mu] H(a), \\
\frac{dY(a)}{da} &= \sigma H(a) - [\gamma + \mu] Y(a), \\
\frac{dZ(a)}{da} &= \gamma Y(a) + \nu(a) X(a) - \mu Z(a).
\end{aligned}\right\} \tag{9}$$

The vaccination rate is now given by:

$$\nu(a) = p\delta(a - a_v), \tag{10}$$

where p is the proportion of children vaccinated, a_v is the age at which those children are vaccinated and δ is the Dirac's Delta function [15].

Under the steady-state assumption, the equation for the remaining fraction of susceptibles, $X(a)$, has the form [9]:

$$X(a) = \begin{cases} \exp\left[-\lambda \int_0^a C(a')\, da'\right] & \text{for} \quad 0 \leqslant a \leqslant a_v \\ [1 - pC(a_v)] \exp\left[-\lambda \int_0^a C(a')\, da'\right] & \text{for} \quad a > a_v. \end{cases} \tag{11}$$

Solving the equation for $H(a)$ in system 9 with $X(a)$ given by 11, and integrating equation for $Y(a)$ in system 9, we get (for $\lambda \neq 0$):

$$\frac{\beta\sigma X_0}{(\mu + \gamma)(\mu + \sigma)} \int_0^\infty C(a) X(a) \exp[-\mu a]\, da = 1. \tag{12}$$

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Fig. 2. Women reproductive function, $R(a)$, as fitted by equation 16 to demographic data from the State of São Paulo, Brazil.

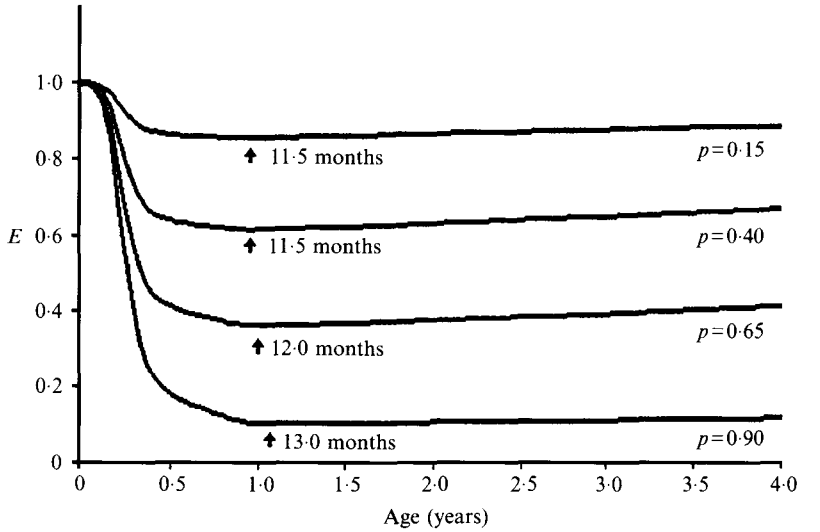

Fig. 3. *Lifetime Expected Risk* of acquisition of rubella, E, as a function of the age of vaccination and proportion of coverage in the routine vaccination scheme chosen.

From equation 12, we can estimate the value of β, by setting $p = 0$, that is, in the absence of vaccination. This value is not supposed to change with vaccination, so for a given p, it is possible to estimate λ for each age, a_v, to vaccinate children. Finally, we can calculate the *Lifetime Expected Risk* [9] of acquisition of rubella by:

$$E = \lambda \int_0^{\infty} C(a)\, R(a) \exp\left[-\lambda \int_0^{a} C(a')\, da' \right] da \qquad (13)$$

where $R(a)$ is a function that describes the 'undesirability' of acquiring rubella at certain ages. This function can be understood either as a constant risk for all ages, or a function which is near zero for low ages, increasing to a maximum value at the fertile age interval, and dropping after menopause. In the case of rubella, $R(a)$

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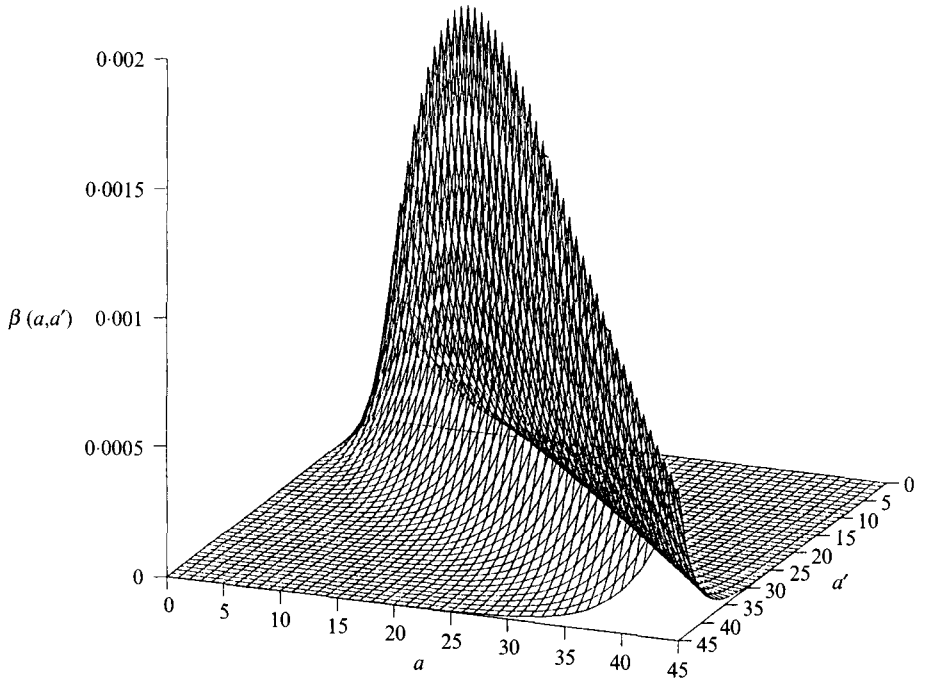

Fig. 4. Age-dependent contact function $\beta(a, a')$ as estimated by equation (15).

can be assumed as identical to the fertility function for a given population. From reproductive data, it is possible to fit a continuous function with form:

$$R(a) = \begin{cases} 0 & \text{for} \quad a < a_r \\ \phi_1(a - a_r)\exp[-\phi_2(a - a_r)] & \text{for} \quad a \leqslant a_r \end{cases} \tag{14}$$

where a_r is the beginning of the reproductive age, and ϕ_i $(i = 1, 2)$ are fitting parameters. Fig. 2 shows the result of fitting equation 14 to female fertility data from the state of São Paulo.

Solving equation 13 with $R(a)$ as in equation 14 we get the optimum ages to vaccinate children against rubella for several coverage data. The results of this procedure are shown in Fig. 3. It can be noted that, for 90% of vaccination coverage, for this specific community, the best age to vaccinate in order to minimize the risk of infection is 13 months. As the immunization programme for the state of São Paulo includes a second dose for the measles vaccine at 15 months of age, and, as shown in Fig. 3 there is no significant difference between this and the optimum age to vaccinate, it was recommended to the local health authorities to include the rubella vaccine at that age.

A model with an age-dependent β

In order to check the approximated solutions provided by Hethcote's formulations we designed a continuous function for the age-dependent contact rate $\beta(a, a')$. As mentioned above, this is a composite function describing the probability of potentially infective contacts between susceptible individuals of age a with infective individuals of age a'. The function proposed is a continuous equivalent to the 'Who-Acquired-the-Infection-from-Whom' matrix described by Anderson and May [6].

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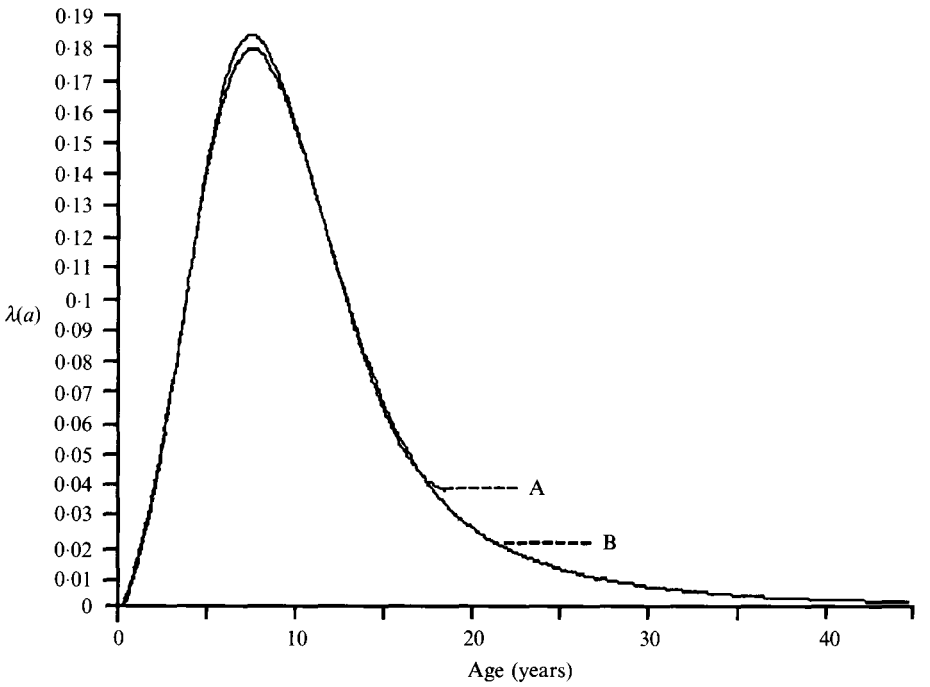

Fig. 5. Age-dependent force of infection, $\lambda(a)$, estimated by catalytic methods (curve A) through the equation, described in [11], [17]:

$$\lambda(a) = \frac{[-dS^{+}(a)]/da}{[1-S^{+}(a)]}$$

where $S^{+}(a)$ is the age-dependent proportion of seropositives, as compared with that estimated by applying equation (15) (curve B).

The age-dependent contact function can be theoretically described by an infinity of continuous probability distributions. The heuristic discussion on how contacts between individuals occur led us to test an *ad hoc* distribution composed by a Laplace and a Gamma distribution [16], with form:

$$\beta(a,a') = \frac{b_0 b_3}{b_2 \Gamma(b_1+1)} \frac{(a/b_2)^{b_1} e^{-a/b_2}}{(2-e^{-b_3 a})} e^{-b_3|a-a'|} \tag{15}$$

where b_i $(i = 0, 1, 2, 3)$ are parameters and $\Gamma(b_1+1)$ is the gamma function. Fig. 4 shows the shape of the function chosen for $\beta(a,a')$, with the parameters fitted to data from the community which our calculations were based upon. It can be noted from the figure that, under our assumptions, individuals of age a have more potentially infective contacts with individuals of the same age. The number of those contacts among individuals of the same age group increases with growing ages, reaching its maximum by the teens, and then decays.

The performance of equation 15 in recovering the actual force of infection for the region is demonstrated in Fig. 5, where we show the force of infection of the community studied estimated by catalytical methods [17] (curve A) as compared with that obtained by using equation 15 (curve B).

Fig. 6 shows the reduction in the force of infection as a result of vaccinating

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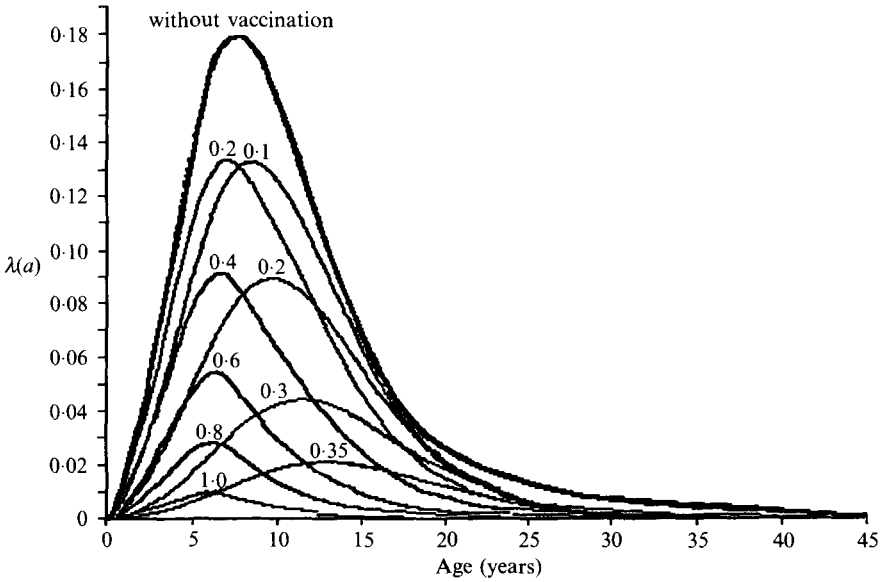

Fig. 6. Impact of two alternative vaccination strategies on the force of infection. The set of curves under that without vaccination represents the force of infection after the vaccination between 1 and 2 years of age (right curves labelled with coverage proportions 0·1–0·35), and between 7 and 8 years of age (left curves labelled with coverage proportions 0·2–1·0).

children between 1 and 2 years (curves with coverage proportions of 0·1 to 0·35), as compared with vaccination of children between 7 and 8 years old (curves with coverage proportions of 0·2 to 1·0). As can be noted, the former strategy is by far more effective in reducing the force of infection. Therefore, the optimum age to vaccinate children routinely proposed in the previous section is adequate. Also noteworthy in Fig. 6 is the effect in shifting the average age of the first infection to the right in case of vaccination between 1 and 2 years of age, and to the left in case of vaccination between 7 and 8 years of age. This difference is probably due to the fact that the average age of the first infection in this community, before vaccination, was 6 years [14]. So, vaccinating children at an age interval above that comprising the average age of first infection is not only less effective in reducing the force of infection, but also causes a leftwards shift in the average age of the first infection.

Theoretical threshold conditions for eradication as a function of the vaccination coverage can be estimated by applying the results of equation 15 on system 9. The result of this calculation is presented in the paper by Coutinho and colleagues [1], where it is demonstrated that vaccination of children between 1 and 2 years of age is, in fact, a very effective way of controlling the infection.

PREDICTABLE OUTCOMES OF THE STRATEGY PROPOSED

In this section we briefly describe the results of the numerical simulations of the basic model, in order to have an insight on what is expected to occur as a result of the vaccination strategy proposed.

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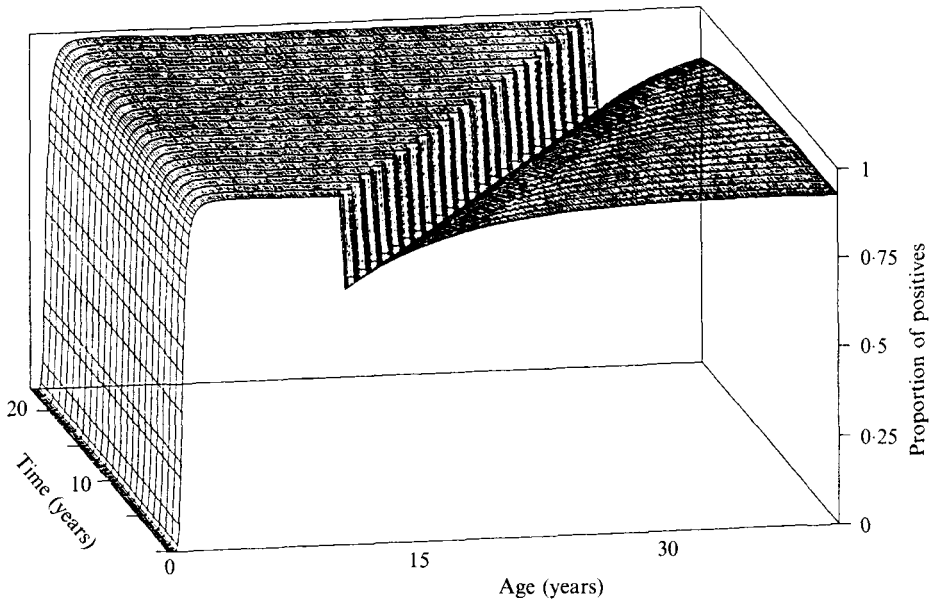

Fig. 7. Time evolution of the proportion of seropositives, stratified by age. It can be seen that the figures have a valley beginning at 10 years of age in time 0, which travels upwardly in age with time. This corresponds to a susceptibility 'window' and it divides the population into those who are positive due to natural infection (plane right to the window) and those who are positive due to vaccination (plane left to the window).

First, we describe the results of the numerical simulation of the model described by the partial differential equations (2.1–2.3) described in the paper by Coutinho and colleagues [1]. Fig. 7 shows the time evolution of the age-dependent proportion of seropositives to rubella virus after the introduction of vaccination, assuming that the routine scheme is as effective as the pulse vaccination, and that the force of infection after the campaign is reduced to negligible values. In addition, it is assumed that vaccination against rubella provides lifelong immunity. It can be noted that there is a sharp increase in the proportion of seropositives from ages 1 to 10, dropping to pre-campaign values for ages greater than 10 years, creating a susceptibility 'window' that drifts up in age with time.

Next, we describe the estimation of the expected ratio, $\rho(a_1, a_2)$, of new cases of congenital rubella syndrome (CRS), at equilibrium, as related to the endemic levels before the intervention proposed. For this we applied the following relationship [5]:

$$\rho(a_1, a_2) = \frac{\int_{a_1}^{a_2} r(a)\,\lambda^*(a)\,X^*(a)\,da}{\int_{a_1}^{a_2} r(a)\,\lambda_0^*(a)\,X_0^*(a)\,da} \tag{16}$$

where a_1, and a_2 are the extremes of the age interval over which the prevalence is calculated, $r(a)$ is the function that describes the risk of developing CRS, and the underscript 0 represents the variables before the intervention. Fig. 8 shows the

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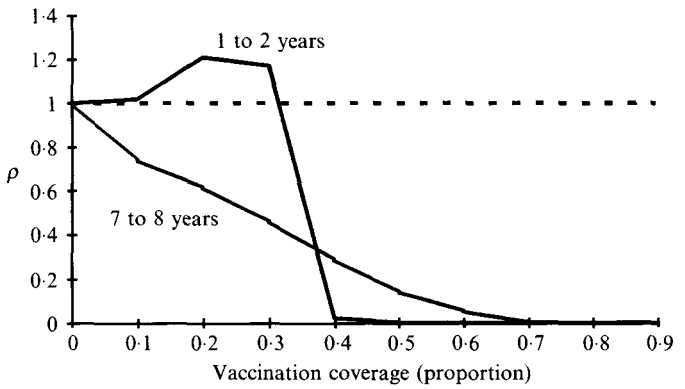

Fig. 8. Relative number of cases of CRS after vaccination as compared with before vaccination as a function of coverage proportions. Broken line denoting 1 indicates no effect of intervention, whilst continuous lines represent the impact of vaccination between 1 and 2 years of age, as compared with vaccination between 7 and 8 years of age. It can be noted that, for low coverages, the latter strategy is more effective. On the other hand, for high coverages, the former strategy has a greater impact on the CRS incidence.

results of the calculation of equation 16 when routinely vaccinating children between 1 and 2 as compared with 7 and 8 years of age. The calculations were performed considering the ages 14 and 45 years ($\rho(14, 45)$) as the extremes of the age interval for which the prevalence was calculated (thus representing the female fertile period) and for several vaccination coverage levels. It can be seen that, for low coverage levels, there is a relative increase in the incidence of CRS, which is attributable to the expected shift upwards in the average age of first infection observed when considering vaccination between 1 and 2 years of age. On the other hand, with coverages above 40% there is a remarkable decrease in the relative incidence of CRS in case of vaccinating between 1 and 2 years. In case of vaccinating between 7 and 8 years, this reduction is seen for any vaccination coverage, but it is much less intense. This implies that for areas in which vaccination coverages above 37% can be expected the former scheme is clearly more effective in reducing the incidence of CRS.

CONCLUSIONS

The present work is a natural corollary of previous developments in the area of childhood infections control. It combines theoretical developments with real data drawn from the same community which the proposed strategy is based upon and aimed to.

Since the strategy proposed by Macdonald in the late sixties for introducing measles vaccination as early as possible in life [18], very rarely have model-based propositions on control strategies been accepted and implemented by health authorities. Certainly this is the first time that it happened in Brazil.

The proposed strategy is a mixed one, in the sense that it combines a mass vaccination pulse aimed to a well defined age interval (1–10 years) with a routine

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vaccination at a single age (15 months), introduced immediately after the mass campaign. So, during the period between 25 April and 5 June 1992, 6850000 children were vaccinated against measles, rubella and mumps in the State of São Paulo, representing 96% of the target population. In addition, a mopping up operation, consisting of vaccinating all contacts of suspected cases of infection, was assembled. We are presently carrying out a field study, in order to evaluate the efficacy of the proposed strategy and to assess its impact on the intensity of transmission of rubella. The results will be presented in a future paper.

Some consequences and some assumed oversimplifications in the design deserve further comments.

The most important of the immediate consequences of the strategy proposed, which causes some comprehensible, although not entirely justified uneasiness among the public health authorities, is the accumulation of remaining susceptibles at the reproductive ages. This phenomenon is a direct consequence of the dropping in the force of infection and it is expected to be most accentuated the more intense is the reduction in the force of infection. However the accumulation of susceptibles in this age interval does not imply an increased risk of infection (except those related to imported cases) due to herd immunity provided by the high vaccination coverages attained. The mopping up operation and a surveillance system at the border of the State of São Paulo (the only one which adopted the strategy) are measures which we believe are able to prevent outbreaks caused by imported cases.

With the pulse vaccination campaign we expect the equilibrium to be reached in a much shorter period of time. In addition, by providing high seroprevalence levels in the age interval covered by the campaign we guarantee that those children are protected until the equilibrium due to the routine is achieved. The temporal dynamics caused by the pulse strategy is a theoretical problem distinct from that addressed by this paper and will be subject of a future study.

An important oversimplification initially assumed in the design of vaccination strategies was the constancy of the force of infection, which has been overcome in this paper. To include age-dependence in that parameter severely complicates the analysis. In addition, the estimation of the real contact patterns in a population may be a very cumbersome task. So, as a first approximation, we decided to estimate the impact of competing strategies on the force of infection based on average values over all ages of the force of infection, for the pulse vaccination strategy designed. As mentioned above the majority of papers dealing with the transmission dynamics of childhood infections assume an age-independent force of infection. We think that, for the design of the pulse strategy, this approximation is justified since it simplifies the calculations. Furthermore, the intensity of transmission at the equilibrium is determined by the routine scheme and the mass campaign has the objective of reducing the time taken for the system to attain the new equilibrium.

Finally, in spite of the estimation of the optimum age for routine vaccination being based on an age-independent force of infection, following well established formulations [9], the use of an age-dependent contact function, as proposed in this paper, although still lacking experimental support (for the determination of $\beta(a, a')$), confirmed that approach as appropriate.

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APPENDIX

In this appendix we provide a detailed calculation of equation 8 from the main text.

The solution of the integration of equation 3 in equation 4 results in:

$$H(a) = X_0 \frac{\lambda}{\sigma - \lambda} [e^{-(\mu+\lambda)a} - e^{-(\mu+\sigma)a}] \tag{17}$$

for $0 \leqslant a < a_1$:

$$H(a) = \lambda X_0 \left\{ \frac{1-p}{\sigma-\lambda} e^{-(\mu+\lambda)a} + p \frac{e^{va_1}}{\sigma-\lambda-v} e^{-(\mu+\sigma+v)a} - \left[\frac{\lambda}{\sigma-\lambda} + \frac{pv e^{-(\sigma-\lambda)a_1}}{(\sigma-\lambda)(\sigma-\lambda-v)} \right] e^{-(\mu+\sigma)a} \right\} \tag{18}$$

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for $a_1 \leqslant a \leqslant a_2$, and

$$H(a) = \lambda X_0 \left\{ \left[\frac{(1-p) + p\,e^{-v(a_2-a_1)}}{\sigma-\lambda} \right] e^{-(\mu+\lambda)a} - \left(\frac{1}{\sigma-\lambda} + \frac{pv\,e^{-(\sigma-\lambda)a_1}}{(\sigma-\lambda)(\sigma-\lambda-v)} + e^{(\sigma-\lambda)a_2} \frac{pv}{\sigma-\lambda-v} e^{-v(a_2-a_1)} \right) e^{-(\mu+\sigma)a} \right\}, \quad (19)$$

for $a > a_2$.

Substituting equations 17 or 18 or 19 into equation 5 we get:

$$Y(a) = \lambda\sigma \frac{X_0}{\sigma-\lambda} \left[\frac{e^{-(\mu+\sigma)a}}{\gamma-\lambda} - \frac{e^{-(\mu+\sigma)a}}{\gamma-\sigma} + \frac{\sigma-\lambda}{(\gamma-\lambda)(\gamma-\sigma)} e^{-(\mu+\gamma)a} \right], \quad (20)$$

for $0 \leqslant a < a_1$;

$$Y(a) = \frac{(1-p)(X_0/\sigma-\lambda)}{\gamma-\lambda} e^{-(\mu+\lambda)a} + \frac{p[X_0/(\sigma-\lambda-v)]\,e^{-(\mu+\lambda+v)a}}{\gamma-\lambda-v} - \frac{\frac{X_0}{\sigma-\lambda} + p[X_0 v/(\sigma-\lambda)(\sigma-\lambda-v)]\,e^{(\sigma-\lambda)a_1}}{\gamma-\sigma} e^{-(\mu+\sigma)a} + \left[\frac{X_0}{\sigma-\lambda} \frac{\sigma-\lambda}{(\gamma-\lambda)(\gamma-\sigma)} + pX_0\,e^{-(\gamma-\lambda)a_1} \times \left(\frac{v}{(\sigma-\lambda)(\sigma-\lambda-v)(\gamma-\sigma)} + \frac{1}{(\sigma-\lambda)(\gamma-\lambda)} - \frac{1}{(\sigma-\lambda-v)(\gamma-\lambda-v)} \right) \right] e^{-(\gamma+\mu)a} \quad (21)$$

for $a_1 \leqslant a \leqslant a_2$, and

$$Y(a) = \lambda\sigma \left\{ \begin{array}{l} \frac{X_0[(1-p) + p[e^{-v(a_2-a_1)}/\sigma-\lambda]]}{(\gamma-\lambda)} e^{-(\mu+\lambda)a} \\ - \frac{(X_0/\sigma-\lambda) + p\frac{X_0 v}{(\sigma-\lambda)(\sigma-\lambda-v)} e^{(\sigma-\lambda)a_1}}{\gamma-\sigma} e^{-(\mu+\sigma)a} \\ + \frac{p\frac{X_0 v}{(\sigma-\lambda)(\sigma-\lambda-v)} e^{(\sigma-\lambda)a_1} e^{-v(a_2-a_1)}}{\gamma-\sigma} e^{-(\mu+\sigma)a} + \left[\frac{X_0}{(\gamma-\lambda)(\gamma-\sigma)} \right. \\ + pX_0\,e^{-(\gamma-\lambda)a_1} \left(\frac{v}{(\sigma-\lambda)(\sigma-\lambda-v)(\gamma-\sigma)} + \frac{1}{(\sigma-\lambda)(\gamma-\lambda)} \right. \\ \left. \left. - \frac{1}{(\sigma-\lambda-v)(\gamma-\lambda-v)} \right) + pX_0\,e^{(\gamma-\lambda)a_2} e^{-v(a_2-a_1)} \right. \\ \times \left(\frac{v}{(\sigma-\lambda)(\sigma-\lambda-v)(\gamma-\sigma)} + \frac{1}{(\sigma-\lambda)(\gamma-\lambda)} \right. \\ \left. \left. + \frac{1}{(\sigma-\lambda-v)(\gamma-\lambda-v)} \right) \right] e^{-(\mu+\gamma)a} \end{array} \right. \quad (22)$$

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for $a > a_2$.

From the classical definition of the force of infection

$$\lambda = \beta \int_0^\infty Y(a)\, da \tag{23}$$

it is possible to calculate its value before the introduction of a vaccination scheme, by setting $\nu = 0$, in equations 20, 21, or 22, which takes the form:

$$\lambda_0 = \mu \left[\frac{X_0}{m} \left(\frac{\sigma\beta}{(\mu+\sigma)(\mu+\gamma)} \right) - 1 \right]. \tag{24}$$

We can now integrate equations 20, 21, or 22 for all ages, resulting in a transcendental equation for λ given by:

$$\begin{aligned}
\frac{1}{\sigma\beta X_0} = {} & \frac{1}{\gamma-\lambda} \left\{ \frac{1}{\sigma-\lambda} \left[\frac{(\gamma-\lambda)}{(\gamma-\sigma)} \frac{e^{-(\mu+\sigma)a_1}}{(\mu+\sigma)} - \frac{e^{-(\mu+\lambda)a_1}}{(\mu+\lambda)} \right] - \frac{1}{(\gamma-\sigma)} \frac{e^{-(\mu+\gamma)a_1}}{(\mu+\gamma)} \right. \\
& \left. + \frac{(\lambda+\sigma+\mu-\gamma)}{(\gamma-\sigma)(\mu+\sigma)(\mu+\lambda)} + \frac{1}{(\gamma-\sigma)(\mu+\gamma)} \right\} \\
& + \frac{(1-p)}{(\sigma-\lambda)(\gamma-\lambda)} \left[\frac{e^{-(\mu+\lambda)a_1} - e^{-(\mu+\lambda)a_2}}{(\mu+\lambda)} \right] + \frac{p}{(\sigma-\lambda-\upsilon)(\gamma-\lambda-\upsilon)} e^{\nu a_1} \\
& \times \left[\frac{e^{-(\mu+\lambda+\upsilon)a_1}}{\mu+\lambda+\upsilon} + \frac{e^{-(\mu+\lambda+\upsilon)a_2}}{\mu+\lambda+\upsilon} \right] + \frac{p\upsilon}{(\sigma-\lambda)(\gamma-\sigma)(\sigma-\lambda-\upsilon)} e^{(\sigma-\lambda)} \\
& \times \left[\frac{1}{(\sigma-\lambda)(\gamma-\sigma)} \right] \left[\frac{e^{-(\mu+\sigma)a_1}}{\mu+\sigma} + \frac{e^{-(\mu+\lambda)a_2}}{\mu+\sigma} \right] \\
& + \left\{ \frac{1}{(\sigma-\lambda)(\gamma-\sigma)} + p\, e^{(\gamma-\lambda)a_1} \left[\frac{\upsilon}{(\sigma-\lambda)(\gamma-\sigma)(\sigma-\lambda-\upsilon)} + \frac{1}{(\sigma-\lambda)(\gamma-\lambda)} \right. \right. \\
& \left. \left. + \frac{1}{(\sigma-\lambda-\upsilon)(\gamma-\lambda-\upsilon)} \right] \right\} \frac{e^{-(\mu+\gamma)a_1} - e^{-(\mu+\gamma)a_2}}{\mu+\sigma} + \left[\frac{(1-p)+p\, e^{-\upsilon(a_2-a_1)}}{(\sigma-\lambda)(\gamma-\lambda)} \right] \\
& \times \frac{e^{-(\mu+\lambda)a_2}}{\mu+\lambda} - \left\{ \frac{1}{(\sigma-\lambda)(\gamma-\sigma)} + p\upsilon [e^{(\sigma-\lambda)a_1} - e^{-\upsilon(a_2-a_1)+(\sigma-\lambda)a_2}] \right. \\
& \left. \times \frac{1}{(\sigma-\lambda)(\gamma-\sigma)(\sigma-\lambda-\upsilon)} \right\} \frac{e^{-(\mu+\sigma)a_2}}{\mu+\sigma} \\
& + \left\{ \frac{1}{(\gamma-\lambda)(\gamma-\sigma)} + \pi [e^{(\gamma-\lambda)a_1} - e^{-\upsilon(a_2-a_1)+(\gamma-\lambda)a_2}] \right\} \\
& \times \left[\frac{\upsilon}{(\sigma-\lambda)(\gamma-\sigma)(\sigma-\lambda-\upsilon)} + \frac{1}{(\sigma-\lambda)(\gamma-\lambda)} - \frac{1}{(\sigma-\lambda-\upsilon)(\gamma-\lambda-\upsilon)} \right] \\
& \times \frac{e^{-(\mu+\gamma)a_2}}{\mu+\gamma}.
\end{aligned} \tag{25}$$

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From equations 7 and 25, it is possible to relate λ_0 with λ due to the fact that the product $\sigma\beta X_0$ has the same value before and after the introduction of vaccination. Therefore we get

$$\lambda_0+\mu=\frac{\lambda+\mu}{1-p\{\nu\exp[-(\lambda+\mu)a_1]/\mu+\lambda+\nu\}[1-\exp[-(\mu+\lambda+\nu)(a_2-a_1)]]}, \tag{26}$$

which is equation 8 from the main text.

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