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Rubella seroepidemiology in a non-immunized population of São Paulo State, Brazil

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SUMMARY

A rubella serological survey of 476 individuals selected by cluster sampling technique from Caieiras, a small town located in the outskirts of São Paulo city, southeastern Brazil, was carried out over the period November 1990–January 1991. The aim of the study was to characterize rubella epidemiology in a representative non-immunized community in south east Brazil. The survey comprised a seroprevalence study, stratified by age (0–40 years) and a seroconversion study of rubella vaccine in non-infected children below 2 years of age. Mathematical techniques were applied to resultant data sets to determine the age dependent rates of decay in the proportion of individuals with maternally derived antibodies, vaccine seroconversion, and infection of susceptibles, termed the force of infection, and to estimate the average age at first infection.

INTRODUCTION

Rubella is considered to be a worldwide public health problem due to the risk of foetal infection and subsequent congenital defects [1]. In spite of this, rubella is not a notifiable disease in most countries. This is especially true for the developing world, where little has been done to determine the magnitude of the problem of rubella infection as a cause of embryonic and foetal damage [2].

Rubella is not a notifiable disease in Brazil. The epidemiological data available are restricted to some urban areas such as the states of São Paulo and Rio de Janeiro, where major outbreaks of rubella were observed in 1968, 1974 and 1981 [2]. Highest incidence occurs in the spring (September–November), a seasonality that coincides with that of measles and mumps. Past serological studies [2, 3]

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show that about 80% of the Brazilian population have antibodies to rubella by the age of 20 years. The infection occurs through early childhood, and about 70% of individuals are seropositive by the age of 9 years [2]. Amongst pregnant women there is an average seroprevalence of 82%. These serological data are consistent with observations in different parts of the world before the large-scale introduction of the rubella vaccine [4].

Information on the occurrence of Congenital Rubella Syndrome (CRS) in Brazil is anecdotal. No official figures are available and studies attempting to establish data on the incidence of CRS have not been successful. According to a recent report [2], fragmentary data are available from paediatric pathology services, neurological institutions, paediatric clinics in general and laboratories of clinical pathology. There is a clear increase in the number of cases of CRS observed in these institutions after peaks of epidemics. Data from an otorhinolaryngology clinic in a large university hospital in São Paulo have shown that about 12·5% of deafness cases is due to CRS [5]. However, these data are not sufficient to base a critical evaluation of the incidence of congenital rubella infection and CRS.

Although available commercially in Brazil since early 1970s rubella vaccine is not included in the government immunization programme, although a major campaign followed by a routine immunization programme of measles, mumps and rubella was introduced in the State of São Paulo in 1992 (Secretary of Health São Paulo State, personal communication). In the initial campaign, vaccine was given to a wide age group (1–10 years). According to official reports about 7 million children were vaccinated. The age interval for this pulse vaccination strategy, and the optimal age for routine vaccination thereafter were estimated from the results of this paper and a companion paper [6]. Before 1992, rubella vaccine was used on a private physician's recommendation or at request of the parents [2]. This *ad hoc* process of immunization is unlikely to have had a significant impact on herd immunity to rubella virus.

In Brazil as a whole, where funding for public health problems compete for priority in the allocation of meagre resources, rubella vaccination is not considered a priority at present. In addition past work has highlighted potential hazardous effect of mass vaccination, like the increased incidence of CRS with low vaccination coverage [7–9]. However, strategies of rubella vaccination must be considered for future immunization programmes of nationwide scale, when more precise data on the public health impact of CRS is established, and resources become available. Furthermore, the vaccination programme implemented in the State of São Paulo is expected to serve as a model to other poorer states, where epidemiological, as well as clinical data are practically nil.

This study aims to quantify rubella transmission in a community in which there was no programme of immunization prior to the time of this survey. As recommended by expert committees of the World Health Organization [9, 10] and others [11–13], the use of serological surveys is an important adjunct to other means of defining the immunization status of a community. We therefore decided to carry out a serological investigation of a random sample from the city of Caieiras, a small town localized in the outskirts of São Paulo City, Brazil. This survey comprised a seroprevalence study and a seroconversion study in children < 2 years old, both stratified by age. Mathematical techniques were utilized to

determine central parameters relating the epidemiology and control of rubella infection, namely, age-dependent forces of infection, the average age of the first infection, and age-specific vaccine seroconversion rates.

MATERIAL AND METHODS

The community sampled

The community chosen was the population of Caieiras, a small town located in the northern part of São Paulo City, crossed by the Tropic of Capricorn. The town's population (about 30000 inhabitants in 1990) is distributed over an area of 104 km^2, most of them (> 90%) in the urban area. This city has grown from 1980–90 at a rate of 4·3% per year, which characterizes a fairly rapidly growing community. About 47% of the community is < 20 years of age.

Caieiras is typical of industrialized towns in SE Brazil. Its economy is based on one major factory and 75 smaller industries. The social structure is highly heterogeneous, a characteristic shared by many southern Brazilian cities. The average family size is five individuals per dwelling. Infant mortality (per 100000 inhabitants) for 1980 was 59·75 falling to 40·65 in 1990. This should be compared with the extreme values found in the State of São Paulo, with, in 1990, an average value of 30·92, the highest rate being 156·72 and the lowest 17·61 [14].

Population sampling

The community was initially stratified into 23 age classes (Table 1) to take account of expected rates of changes in seroprevalence, with increasing age. Hence age class sizes were monthly over the first year of life, yearly up to age 4 and 5 yearly thereafter to age 40 years. The number of individuals sampled within an age class, $n_0(a)$, was estimated using standard theory [15]

$$n_0(a) = \frac{1-P(a)}{\epsilon^2 P(a)} \tag{1}$$

where $P(a)$ is the *a priori* estimate of seroprevalence and ϵ is set for the desired level of precision (0·2). In the absence of suitable finely age-stratified rubella serology in Brazil, expected proportions seropositive by age were assumed from typical values in published data [4]. Since the community studied was small, a finite population correction factor was applied to sample sizes [16] as follows

$$n'(a) = \frac{n_0(a)}{(1+[n_0(a)-1]/N(a))}. \tag{2}$$

The sampling could be described succinctly as a 2-level cluster sample: individuals were sampled within families within randomly selected administrative regions [15]. The number of dwellings required to be visited within the community such that by chance the desired sample size for each age class would be achieved, $D(a)$, was calculated by

$$D(a) = \frac{n'(a)D_t}{N(a)} \tag{3}$$

where D_t is the total number of dwellings in the town, $n'(a)$ is the number of

Table 1. *Rubella seroprevalence in Caieiras, São Paulo State, Brazil*

Age* class	Sample size	Sero-positive	Sero-negative	Proportion seropositive	Confidence interval (0·95)
< 1 m	8	8	0	1·000	0·63–1·00
1–2 m	8	7	1	0·875	0·47–1·00
2–3 m	11	7	4	0·636	0·31–0·89
3–4 m	11	6	5	0·545	0·23–0·83
4–5 m	11	5	6	0·455	0·16–0·75
5–6 m	13	2	11	0·154	0·00–0·35
6–7 m	15	1	14	0·067	0·00–0·19
7–8 m	26	2	24	0·077	0·00–0·17
8–9 m	22	0	22	0·000	0·00–0·15
9–10 m	14	0	14	0·000	0·00–0·23
10–11 m	23	0	23	0·000	0·00–0·15
11–12 m	23	2	21	0·087	0·00–0·20
1–2 y	59	3	56	0·051	0·00–0·11
2–3 y	50	8	42	0·160	0·06–0·26
3–4 y	44	3	41	0·068	0·00–0·14
4–5 y	34	12	22	0·353	0·19–0·51
5–9 y	50	26	24	0·520	0·38–0·66
10–14 y	9	7	2	0·778	0·40–0·97
15–19 y	12	10	2	0·833	0·52–0·98
20–24 y	11	11	0	1·000	0·71–1·00
25–29 y	9	8	1	0·889	0·52–1·00
30–34 y	10	10	0	1·000	0·69–1·00
35–39 y	3	3	0	1·000	0·29–1·00

* Age in months (m) or years (y).

individuals within age class corrected to a finite population, and $N(a)$ is the number of individuals of age a known from census records [14]. Of the 62 administrative regions in Caieiras with around 150 dwellings each, 32 were randomly selected. These regions were enumerated, addresses recorded and the houses, totalling 4072, numbered in consecutive order (there was no stratification by social class, location in the town, etc.). Finally, using intervals determined by $D(a)$ from equation 3 for each age group, houses were selected for visiting.

Survey team and protocol

Home visiting was carried out by eight individuals experienced in nursing practice, supervised by two researchers. Visitors were instructed to check the age(s) selected in a certain address. When they happened to find some of the selected elements they presented the purposes of the project. After a verbal consent the visitor entered the house and made an interview about the vaccination history of the chosen person. Children with a recent (last month) history of measles, mumps, rubella or polio vaccination were excluded from the sero-conversion study in order to avoid non-specific reaction interference, entering only into the seroprevalence study. It should be mentioned that no child has received rubella vaccine prior to this study. A blood sample was then drawn. Children below 2 years of age were vaccinated against rubella (Rudivax, Pasteur-Merrieux), subsequent to taking a blood sample, and another visit was booked for the collection of a second sample 1 month later, for the assessment of seroconversion.

The survey team worked in the area from the 19 November 1990 to 18 January 1991, spending the first 30 days interviewing, drawing blood samples and vaccinating, and a further month to collect blood from the children who were immunized against rubella on the first visit.

Blood collection

Blood was collected by vacuum containing system or by 'butterfly needle' venipuncture for children below 2 years of age. The sera obtained after centrifugation of clotted samples were stored at −20 °C.

Laboratory tests

A quantitative enzyme immunoassay (ELISA) kit was used to measure antibodies of IgG class against rubella (ETI-Rubek-G, Sorin Biomedica, Diagnostici, Saluggia, Vercelli, Italy). The cut-off of 10 IU/ml, as recommended by the manufacturer, was used to distinguish seropositive (assumed immune) from seronegative (assumed susceptible) individuals. Seroconversion following vaccination was defined as a change from seronegative to seropositive, or a fourfold rise in the IgG concentration from the first to the second sample [17].

Data management

After establishing the proportion of seropositive for each age class, data were fitted to two continuous functions by Maximum Likelihood technique [18], one for the maternally derived antibodies decay phase, $M(a)$, and another for the naturally acquired infection phase, $S^{+}(a)$. From these continuous functions the rate of decay in the proportion with maternally derived antibody protection, $\delta(a)$, and the rate at which susceptibles are infected (force of infection), $\lambda(a)$, were derived. The proportion of children who seroconverted, $C(a)$, after vaccination was also fitted to a continuous function. The general shape of the functions describing $M(a)$ and $C(a)$ is

$$\frac{1}{1+\exp\left(\sum_{i=0}^{n} \kappa_i a^i\right)} \tag{4}$$

where κ_i are the fitting parameters.

The rate of decay in the proportion with maternally derived antibody protection, $\delta(a)$, was calculated according to the equation

$$\delta(a) = -\frac{dM(a)}{da} M(a)^{-1} \tag{5}$$

where $M(a)$ is the proportion of individuals with maternally derived antibodies at age a.

As defined in catalytic models of epidemic spread [19–22] we can relate the proportion of susceptible at age a, $x(a)$, taken from serological data, to the *per capita* force of infection by

$$x(a) = \exp\left(-\int_0^a \lambda(a')\,da'\right). \tag{6}$$

Table 2. *Fitting parameters obtained from serological data by Maximum Likelihood and respective standard errors (SE)*

	Function					
	$M(a)$*		$C(a)$†		$S^+(a)$‡	
Parameter		SE		SE		SE
κ_0§	**−4·2**	0·56	**3·7**	0·46	—	—
κ_1	**27·7**	5·94	**−18·1**	3·67	**0·061**	0·0062
κ_2	**−58·2**	18·77	**16·4**	8·52	**0·005**	0·0055
κ_3	**54·7**	17·85	**−7·6**	5·70	**0·135**	0·0235

* $M(a)$, decay of maternal IgG.
† $C(a)$, proportion seroconverting after vaccination.
‡ $S^+(a)$, naturally-acquired infection.
§ κ, parameters fitted to the seropositive function (equations 4, 8, 9).

Through differentiation of equation (6) we can estimate the age-dependent force of infection, $\lambda(a)$, from serological data by

$$\lambda(a) = \frac{dS^+(a)/da}{1-S^+(a)} \tag{7}$$

where $S^+(a)$ is the function relating the proportion of seropositive to age, due to naturally acquired infection. In some cases, $S^+(a)$ can be fitted to a sigmoidal curve like that described in equation (4). However, this approach is not always consistent with the properties of forces of infection. It may produce negative values, or increase steeply in the older age groups. Therefore, we decided to apply the method proposed by Farrington [23] for estimating the force of infection, $\lambda(a)$, by setting

$$\lambda(a) = (\kappa_1 a - \kappa_2)\, e^{-\kappa_3 a} + \kappa_2 \tag{8}$$

where κ_i are parameters fitted to the seropositive function

$$S^+(a) = 1 - \exp\left[\frac{\kappa_1}{\kappa_3} a\, e^{-\kappa_3 a} + \frac{1}{\kappa_3}\left(\frac{\kappa_1}{\kappa_3} - \kappa_2\right)(e^{-\kappa_3 a} - 1) - \kappa_2 a\right]. \tag{9}$$

The average age of the first infection, A, in persons eventually infected, is defined by the equation [24]

$$A = \frac{\int_0^\infty a\lambda X(a)da}{\int_0^\infty \lambda X(a)da} \tag{10}$$

which, in the case of an age-dependent force of infection, $\lambda(a)$, and considering the proportion of remaining susceptibles, $x(a) = X(a)/N(a)$, simplifies to

$$A = \frac{\int_0^\infty x(a)\, da}{\int_0^\infty \lambda x(a)\, da} \tag{11}$$

where $x(a)$ can be approximated by $[1-S^+(a)]$.

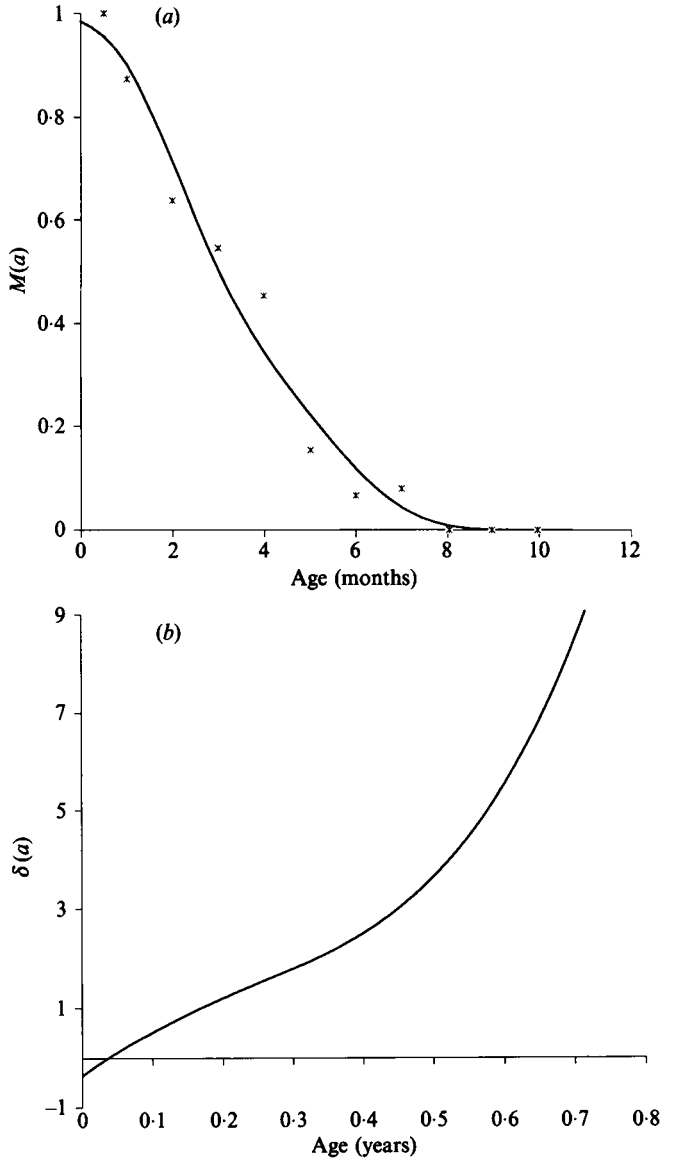

Fig. 1. (*a*) Fitting of declining phase of maternally derived antibodies, $M(a)$. Continuous line, fitted function; stars, proportion of seropositivity obtained from survey. (*b*) Age-dependent rate of declining in the maternally derived antibodies, $\delta(a)$ (equation 5).

RESULTS

Serological profile

During the first month of field work 476 samples were collected covering all age classes (Table 1), of whom 228 children below 2 years of age were vaccinated against rubella, in order to determine the seroconversion rate to the vaccine.

The age-seroprevalence data are recorded in Table 1, reveal a descending phase of seropositivity in the first 8 months of life, with no individuals of age 8–10

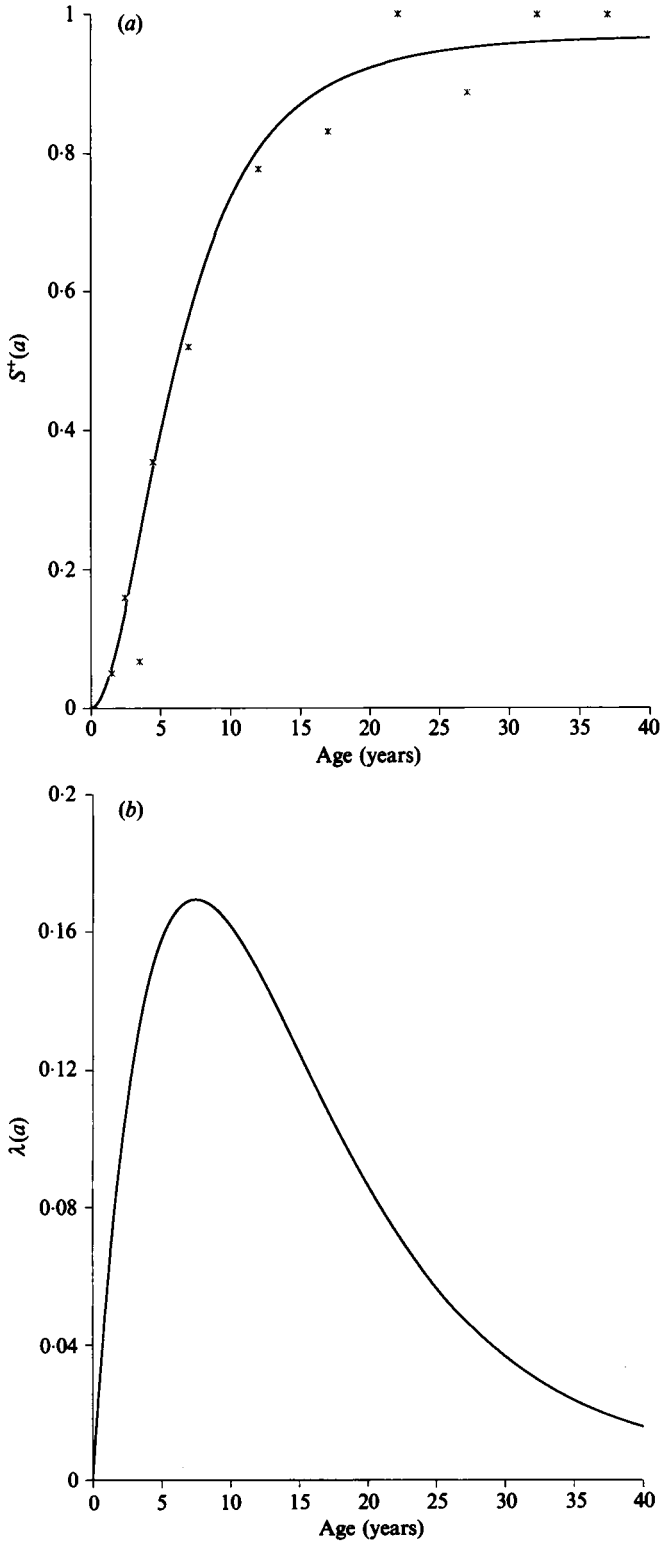

Fig. 2. For legend see opposite.

Table 3. *Seroconversion study*

Age (months)	Sample size	Number of seroconverters	Proportion of seroconversion
< 1	7	0	0·000
1–2	8	1	0·125
2–3	6	3	0·500
3–4	11	4	0·364
4–5	7	3	0·429
5–6	11	10	0·909
6–7	13	13	1·000
7–8	22	21	0·954
8–9	19	19	1·000
9–10	9	7	0·778
10–11	17	17	1·000
11–12	19	19	1·000
12–24	47	47	1·000

months rubella seropositive. Following this, the proportion serologically positive increases with age to a plateau of between 90 and 100% over the age range 20–24 to 35–39 years.

Table 2 shows the fitting parameters to equation 4 for $M(a)$ and $C(a)$, and equation 9 for $S^+(a)$. Fig. 1 (a) shows the fitted $M(a)$ curve through the field data. The rate of decay in the proportion of individuals with maternally derived antibodies, $\delta(a)$, resulting from equation 5 is shown in Fig. 1 (b).

Fig. 2 (a) illustrates the function $S^+(a)$ obtained through the observed profile.

The force of infection $\lambda(a)$ resulting from the estimation of parameters κ_i as applied to equation 8 is shown in Fig. 2 (b).

It can be noted in Fig. 2 (b) a pronounced age-dependence in rubella force of infection for this community, raising steeply from 1–8 years, and a smoother decline thereafter. We can also note a residual level of $\lambda(a)$ in reproductive ages. However, the small number of individuals surveyed in these age classes does not allow any definitive conclusion related to the risk of congenital rubella infection.

The average age of the first infection calculated by equation 11 for this community with the upper limit of integration assumed as the life expectancy (65 years) resulted in 6 years.

Seroconversion study

From the 228 children vaccinated against rubella during the first visit, it was possible to get a second blood sample from 196 individuals. As shown in Table 3, the ability of vaccine to seroconvert or generate a fourfold rise in antibody concentration increases with age, being null in infants under 1 month, rising to around 40% by age 4 months and then rapidly increasing to around 90–100% in the age range 5–12 months.

Fig. 2. (a) Fitting of ascending phase of seroprevalence. Continuous line, fitted function; stars, proportion of seropositivity obtained from survey. (b) Age-dependent force of infection calculated according to equation 8.

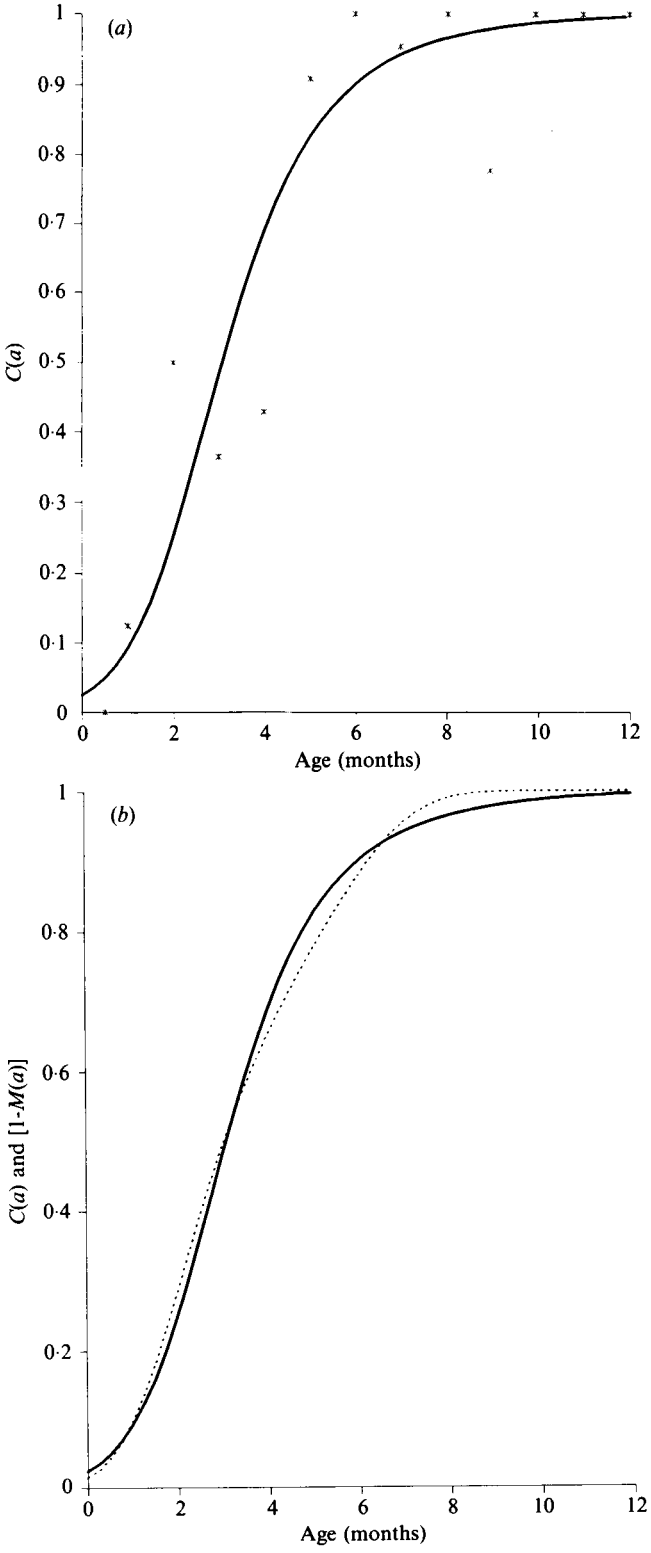

Fig. 3. For legend see opposite.

Fig. 3(*a*) illustrates the seroconversion function obtained for children below 2 years old of Caieiras. In Fig. 3(*b*) this function is superimposed to the function $1-M(a)$ in order to emphasize the correlation between maternally derived antibodies and the immunological capacity to respond to the vaccination stimuli.

DISCUSSION

This rubella serological survey of a household sample of Caieiras residents was carried out to gain baseline data on which control and immunization needs might be identified and optimum strategies planned. It combined a field study with mathematical techniques seldom applied by public health authorities and a seroconversion study which is original in having a wide age range vaccinated. Several important results were obtained during the current survey which indicated the need for public health action. The antibody determination reflects persistence of passively transferred maternal antibodies up to age 8 months, and cumulative prevalence, indicating the lifetime experience of the population sampled with rubella, from 10 months of age upward. Incidence rates were estimated from prevalence data by applying mathematical techniques described above. In addition, the seroconversion study and the incidence rates estimation could be used for the design of control strategies in order to minimize the risk of CRS.

Some of the results obtained confirm concepts established before. Maternally derived antibodies are found in high proportion at delivery, due to the high prevalence found among adults, and there is a decrease of this proportion during the first 8 months of the infancy [25–27]. The rate of decay in the proportion of individuals with maternally derived antibodies showed an age-dependence, contrasting with the established concept of a constant rate of decay [8].

When we compare the continuous function that represents the decay of the proportion of individuals which have maternally derived antibodies, $M(a)$, with the seroconversion function, $C(a)$, we realize that there is a strong correlation between them. These results suggest that the seroconversion doesn't take place when there are antibodies against rubella virus detectable. This is more evident when one plots $1-M(a)$ and $C(a)$ together (Fig. 3(*b*)). As the seroconversion function, for operational reasons, is a more difficult parameter to estimate in a population than $M(a)$, it could be possible to use $1-M(a)$ to represent $C(a)$ when studying a given immunization strategy by mathematical techniques, to be applied to a particular population.

The serological profile of this community also indicates that rubella infection rates have low intensities before the age of 5 years ($< 35\%$ seropositive). This could be explained by the supposedly low rate of contacts between susceptible and infectious individuals in these age classes. When we look at the pre-school and school ages, the proportion of individuals with detectable antibodies to rubella increases rapidly, slowing down again from 15 years old upward, leaving enough

Fig. 3. (*a*) Fitting of seroconversion after vaccination. Continuous line, fitted function; stars, proportion of seroconversion obtained. (*b*) Seroconversion function, $C(a)$ (continuous line), superimposed to the complement of the maternally derived antibodies function, $1-M(a)$ (dashed line).

susceptible on the reproductive phase of this community. However, it is clearly the case that too few samples were collected in the adult age range to give any significance to the force of infection estimates. This makes it very difficult to say anything useful about the force of infection in women at child bearing age and the possible risk of maternal infection. Clearly this is an age range that future research should consider. In addition, it should be mentioned that one or more individuals from each family were selected. This could introduce some bias as seroprevalence in family members would tend to be correlated.

In order to take into account age-dependence in the force of infection for the estimation of control strategies it should be necessary to provide a function for the contact rates, $\beta(a,a')$, representing individuals with age a who acquired the infection from individuals of age a'. In another paper [6] we show how to design control strategies taking account of those age-dependencies. This is done by providing a continuous function for the 'Who-Acquire-Infection-From-Whom' matrix of Anderson and May [24].

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