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Optimal Ages of Vaccination for Measles

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ABSTRACT

A mathematical modeling approach is used to theoretically estimate ages of vaccination which minimize the lifetime expected risk due to measles in a population. In developing countries where there are limited resources for measles vaccination, the calculations show that vaccination of a large fraction at one optimal age is much better than vaccination of half as many children at two ages. Optimal ages of vaccination are calculated from approximate measles seroconversion rate curves and estimated parameter values for Kenya, parts of South America, and the USA.

1. INTRODUCTION

A major issue at the 1982 International Symposium on Measles Immunization was the determination of suitable measles vaccination strategies for developing and developed countries [1]. Although some differences in the vaccination strategies used in the world could be justified because the epidemiological and environmental conditions vary between countries, it is clear that not all of the diverse strategies used can be optimal or even nearly optimal.

The vaccination model formulated here includes an expression for the lifetime expected risk due to measles in a population. This model incorporates vaccine efficacy rates which increase with age and protective passive immunity rates which decrease with age. The calculations using this model yield some general and specific suggestions regarding measles vaccination strategies. These results are summarized in the discussion section.

2. CURRENTLY RECOMMENDED AGES OF VACCINATION

Although vaccination as early as 6 months has been used in parts of Africa, the consensus now seems to be that vaccination for measles in

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tropical Africa should be given at age 9 months [2]. This recommendation is based partly on experience and partly on computer simulations to determine the optimal month of vaccination to minimize morbidity or mortality. These calculations did not use an explicit model, but they were based on morbidity and mortality data and on seroconversion rate data [3–6]. Percentages vaccinated in Africa are usually less than the 61% achieved in Gambia and the 82% achieved in Tanzania [7]. Mortality rates from measles are often high in tropical Africa because of malnutrition, concurrent infection, and inadequate case management. Mortality rates of 5% to 10% are common, and rates of 20% have been reported [2].

Countries such as Brazil and Chile now recommend vaccination at 9 months. Vaccination coverage is increasing in South America; for example, about 58% of the population is now vaccinated in Brazil and 88% in Chile [8, 9]. Costa Rica recommends vaccination for measles at age 6–11 months and again at 12 months. Approximately 70% of the susceptible populations have been vaccinated for measles in Mexico and Costa Rica [10, 11].

The recommended age of measles vaccination in the United States of America (USA) is now 15 months [12]. In 1985 about 98% of children entering school were vaccinated for measles. The incidence of measles in the USA decreased to 1497 reported cases in 1983, but increased to 2534 in 1984, 2813 in 1985 and 6273 in 1986 [13]. In developed countries the complication and mortality rates from measles have been decreasing and are now very low [14]. Canada recommends measles vaccination at age 12 months, and 80% to 98% of school entry children are vaccinated [15].

In some western European countries, measles is regarded as a mild disease and vaccination rates are very low. For example, less than 25% are vaccinated in France, and about 50% are vaccinated for measles in the United Kingdom [16, 17]. In contrast, over 90% are vaccinated in Yugoslavia, and 98–99% are vaccinated in Czechoslovakia [18, 19]. The incidence in these countries is very low. Yugoslavia now recommends vaccination at 12 months, while Czechoslovakia recommends one dose at 14 months and a second dose 6 to 10 months later. Poland recommends measles vaccination at 9 to 12 months [20]. Sweden now recommends vaccination at 18 months and again at 12 years [21].

Iran recommends measles vaccination at 6 to 9 months and again at 12–15 months [22]. The USSR recommends vaccination at 15 to 18 months [23]. In most parts of China, 8 months is considered to be the optimal age of vaccination; however, vaccination at 12 months is used in areas where measles is thought to be under control [24]. Three different measles vaccination strategies are used in parts of China: the first type involves doses at 9 to 12 months with booster doses at 5 or 9 years, the second type has one dose within the first two years and one booster dose at 7 years, and the third is one dose given at 12 months.

3. SEROCONVERSION RATES AS A FUNCTION OF AGE

When a mother is immune to measles, maternal antibodies are transferred across the placenta to the fetus. Most of these maternal antibodies dissipate during the first year of the child's life. These maternal antibodies provide the child with protection against measles infection during the first several months of life. At the same time these antibodies interfere with the development of immunity following vaccination.

Serologic methods are used to measure the level in the blood of antibodies to measles. When hemagglutination inhibition titration is used to measure

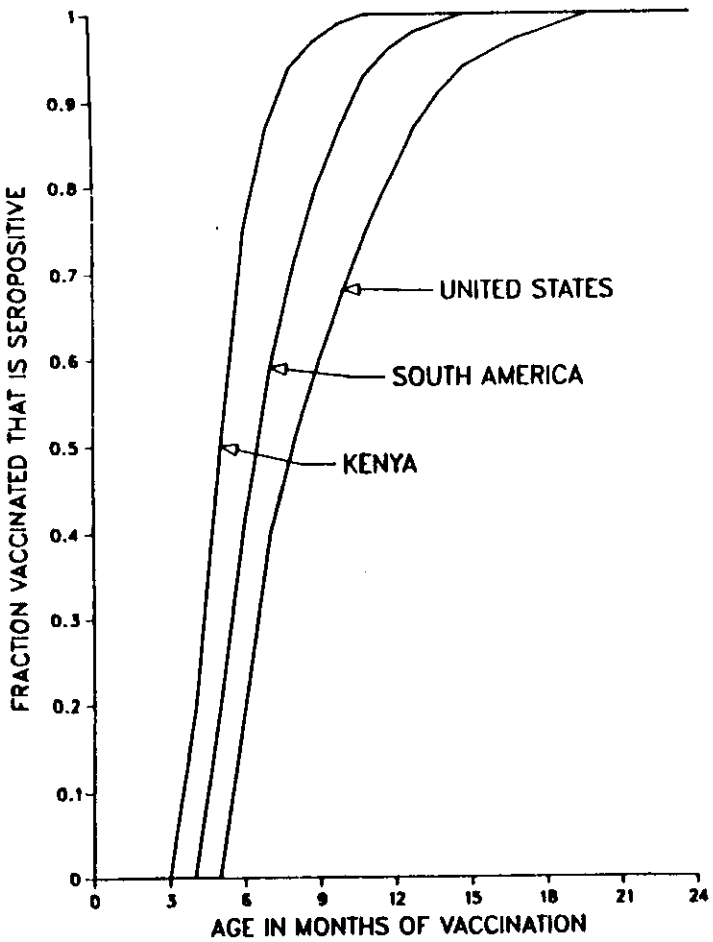

FIG. 1. Seroconversion rate curves on three continents.

the level of antibodies, the results are reported as positive or negative response to a certain dilution of the blood sample. The level of maternal antibody necessary to prevent measles infection seems to correspond to positive response to dilutions of from 1:3 to 1:6 [25]. Moreover, that study found that maternal antibodies must be at a titre of 1:6 to hamper the take of the vaccine. Thus the levels of antibodies which prevent measles infection and which prevent successful vaccination seem to be about the same. Another study [26] found that some levels of maternal antibodies may not be able to prevent natural infection, but may still prevent successful vaccination with live measles vaccine given subcutaneously. Thus loss of passive immunity might occur at an age slightly earlier than the age of successful vaccination.

Seroconversion after vaccination means that the vaccination appears to be successful, i.e., a blood sample of the vaccinated individual has yielded a positive response at a dilution which indicates immunity that protects against measles infection. The seroconversion rate is the fraction of individuals vaccinated who have a seropositive response. Since maternal antibodies wane in the first year of life, seroconversion rates increase as a function of age in the first year. Premature infants seroconvert at younger ages than full-term infants, presumably because they received less maternal antibody before birth [27].

Figure 1 shows that the graphs of seroconversion rates as a function of age are different in different parts of the world. Although the seroconversion data in the three geographic regions are not good enough to justify the use of a statistical fitting procedure, the approximate seroconversion rate curves are justified by the data below. These curves are also consistent with the raw data shown in Figure 4 in Black [28]. Black states that the early loss of passive immunity among children in a developing country occurs because their mothers have less antibody. A study of Haitian children confirms that infants seroconvert earlier if they are born to mothers with lower antibody titres [29].

KENYA

The Kenya seroconversion curve in Figure 1 is based on a study by the Ministry of Health in Kenya and the World Health Organization [25]. This curve is for normal birthweight children: in this study the few low birthweight and premature children seemed to have approximately the same seroconversion rates. The Kenya curve is based on the following data in the paper: the distribution of HI antibody titres according to age in Table 2, the postvaccination HI titres according to age of vaccination in Table 6, and the interpretation of the results in the discussion section. The seropositive fractions are 0 from 1 to 3 months, are 0.20, 0.50, 0.75, 0.87, 0.94, 0.97, and 0.99 for 4 through 10 months, respectively, and are 1.0 for ages beyond 10

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months. These values have been chosen so that they are consistent with the data and so that the seroconversion curve is reasonably smooth. This seroconversion curve is only an approximation; the nature of the data does not justify using a statistical fitting procedure. This seroconversion curve is consistent with seroconversion rates of 0.50, 0.76, and 0.90 at ages 5, 6 and 7 months, respectively, measured in the Upper Volta [30]. It is also consistent with a seroconversion rate of 0.92 for children vaccinated between 6 and 9 months of age in Nairobi [31]. Seroconversion curves similar to the Kenya curve were also reported in Pernambuco, Brazil and in Taipei, Taiwan [32].

Another study in Kenya led to a "smoothed" seroconversion curve with seroconversion rates of 0.52, 0.72, 0.86, and 0.95 occurring at 6.4, 7.4, 8.3, and 9.2 months, respectively [3]. This seroconversion curve is similar to our Kenya curve, but is shifted approximately one month later. This difference may occur because in this study seropositive was defined as response at 1:12 dilution while the earlier Kenya study used 1:3 dilution.

A study in Tanzania found seroconversion rates of 0.44 at 6–7 months, 0.63 at 8–9 months, 0.83 at 12–13 months, 0.88 at 14–15 months, 0.91 at 16–21 months, and about 0.80 after 21 months [4]. Seropositive was defined as having antibody titre of 1:6 or more. Although these results are not consistent with our Kenya curve, there are possible explanations. Since the seroconversion rate was only about 0.80 after 21 months, many children might have had natural measles infections between the time they were first tested and the time of vaccination. There is some evidence that previous measles infection or vaccination does alter the serologic response to vaccination [33]. In the article [4] some doubt was expressed about the potency of the vaccine and about the threshold titres used.

SOUTH AMERICA

The South America seroconversion curve in Figure 1 corresponds to a seroconversion curve for Chile, Ecuador, and the cities of Pará and São Paulo in Brazil [32, Figure 4]. The seropositive fractions are 0 from 1 to 4 months, are 0.20, 0.42, 0.59, 0.71, 0.80, 0.87, 0.93, 0.96, 0.98, and 0.99 at ages 5 through 14 months, respectively, and are 1.0 beyond 14 months. This curve is for normal weight-for-age children. Seropositive is defined as reaching a titre of at least 1:10. The fraction of underweight children (probably due to malnutrition) who seroconverted was higher at many age groups than the fraction of normal weight children. Seroconversion for Haitian infants [29] is about one month earlier than the South America curve in Figure 1.

THE UNITED STATES OF AMERICA

The USA seroconversion curve in Figure 1 is based on several sets of data. One study [34] reported seroconversion rates with response at 1:10 dilution as seropositive of 0.286, 0.565, 0.722, and about 0.80 for ages 6–7 months, 8–9 months, 10–12 months, and 12 months, respectively. The data from several seropositivity studies in the USA are collected and summarized in [35]. In an earlier study [27] seroconversion rates of 0, 0, 0, 375, 0.5, 0.5, 0.815, and 0.80 were found for ages 6 through 12 months, respectively. The seropositive fractions on the USA approximate curve in Figure 1 are 0 for 1 to 5 months, are 0.20, 0.40, 0.51, 0.60, 0.68, 0.75, 0.81, 0.91, 0.94, 0.955, 0.97, 0.98, and 0.99 for ages 6 through 19 months, and are 1.0 beyond 19 months.

Some studies in the USA have found seroconversion rates that are higher for a given age than those given in Figure 1. In the most recent Measles Surveillance Report [14], the seroconversion rates in 12-month old children from various studies given in Tables 15 and 16 are 0.86, 0.80, 0.79, 0.83, 0.89, 0.79, 0.79, 1.0, and 0.826. Thus the USA curve in figure 1 can be regarded as a conservative (i.e., late) estimate of the seroconversion curve in the USA.

4. THE VACCINATION MODEL

Here we obtain an expression for the lifetime expected risk due to measles by using discrete analogs of results for a continuous vaccination model [36]. In later sections we use seroconversion curves and parameter estimates to find the ages of vaccination which are optimal in the sense that the lifetime expected risk of measles is minimized for people in the three geographic areas. Initially successful measles vaccination appears to confer permanent lifetime immunity even though the level of measles antibodies may become so low that they are undetectable by titration tests [34].

THE CONTINUOUS VACCINATION MODEL

Let $C(a)$ be the seroconversion rate at age a expressed as the fraction seroconverting. Vaccine efficacy is the fraction of susceptibles vaccinated who become immune and is equal to one minus the fraction that are primary vaccination failures. We assume that the vaccine efficacy at each age a is the same as the seroconversion rate $C(a)$. We also assume that the loss of protective passive immunity corresponds to the seroconversion rate, so that the probability of being susceptible at age a due to loss of passive immunity is $C(a)$.

Consider a population of constant size in which the birth and death rates are equal to μ. The constant death rate is equivalent to a negative exponential survival curve, which is more realistic in developing countries than in developed countries. All newborns become susceptible when they lose their passive immunity. People in the population pass sequentially through the four states: passively immune due to maternal antibodies, susceptible, infectious, and removed with permanent immunity due to natural infection or vaccination. Let $[1-C(a)]x(a,t)$, $C(a)x(a,t)$, $y(a,t)$, and $z(a,t)$ be the

age density functions of the population at age a and time t that are passively immune, susceptible, infectious, and removed, respectively. The contact rate β is the average number of adequate contacts of an infective per day. The infection rate or incidence is determined by mass action with a force of infection λ which is the product of the contact rate β and the total number of infectives. Assume that a fraction V_1 of the population is vaccinated at age A_1 months and a fraction V_2 of the population is vaccinated at aged A_2 months. Since people are randomly chosen for vaccination at each age, it follows that V_j is also the probability of being vaccinated at age A_j, and $V_jC(A_j)$ is the probability of a susceptible of age A_j becoming immune due to vaccination. Note that the fractions V_1 and V_2 of the population are chosen independently at the ages A_1 and A_2.

The dynamics of disease transmission are described by partial integrodifferential equations for the age density functions. On the intervals $[0, A_1]$, $[A_1, A_2]$, and $[A_2, \infty)$ the model is

$$\begin{aligned}
&\frac{\partial x}{\partial a} + \frac{\partial x}{\partial t} = -\lambda(t)C(a)x(a,t) - \mu x(a,t),\\
&\frac{\partial y}{\partial a} + \frac{\partial y}{\partial t} = \lambda(t)C(a)x(a,t) - (\gamma+\mu)y(a,t),\\
&\frac{\partial z}{\partial a} + \frac{\partial z}{\partial t} = \gamma y(a,t) - \mu z(a,t),\\
&\qquad \lambda(t) = \beta\int_0^\infty y(s,t)\,ds.
\end{aligned} \tag{4.1}$$

The initial conditions at $t = 0$ and the matching conditions at ages 0, A_1, and A_2 are

$$\begin{aligned}
&x(a,0) = x_0(a), \quad y(a,0) = y_0(a), \quad z(a,0) = z_0(a),\\
&x(0,t) = \mu, \quad y(0,t) = 0, \quad z(0,t) = 0,\\
&\qquad x(A_1+0,t) = [1 - V_1C(A_1)]\,x(A_1-0,t),\\
&\qquad x(A_2+0,t) = [1 - V_2C(A_2)]\,x(A_2-0,t).
\end{aligned} \tag{4.2}$$

The conditions on the left and right limits of the susceptible fractions at ages A_1 and A_2 correspond to jump decreases caused by vaccination. Since the death and recovery rates are equivalent to waiting times with negative exponential distributions, the average lifetime is $L = 1/\mu$ and the average infectious period is $1/(\gamma+\mu)$. The contact number σ, which is the average number of adequate contacts of an infective during the infectious period, satisfies $\sigma = \beta/(\gamma+\mu)$.

For large time the solutions of the model above approach steady state age distributions which are found by setting the time derivatives equal to zero.

The total population of age a, $\kappa(a) = x + y + z$, satisfies $\kappa(a) = \mu e^{-\mu a}$. The fractions of those of age a who are in class x, in class y (infectious), and class z (removed) are $u = x/\kappa$, $v = y/\kappa$, and $w = 1 - u - v$, respectively. The differential equations on the intervals $[0, A_1]$, $[A_1, A_2]$, and $[A_2, \infty)$ and conditions for the stable age distributions are

$$\begin{aligned}
&\frac{du}{da} = -\lambda C(a)u, \qquad u(0) = 1,\\
&\frac{dv}{da} = \lambda C(a)u - \gamma v, \qquad v(0) = 0,\\
&\qquad \lambda = \int_0^\infty v(s)\mu e^{-\mu s}\,ds,\\
&u(A_1+0) = [1 - V_1C(A_1)]\,u(A_1-0),\\
&u(A_2+0) = [1 - V_2C(A_2)]\,u(A_2-0).
\end{aligned} \tag{4.3}$$

When the disease dies out, the force of infection λ is 0, the infective fraction $v(a)$ is 0, and the fraction that is either passively immune or susceptible is

$$u(a) = \begin{cases} 1, & 0 \leq a \leq A_1,\\ 1 - V_1C(A_1), & A_1 < a \leq A_2,\\ [1 - V_1C(A_1)][1 - V_2C(A_2)], & A_2 < a < \infty. \end{cases} \tag{4.4}$$

If the inequality

$$\sigma\int_0^\infty C(a)u(a)\mu e^{-\mu a}\,da \leq 1 \tag{4.5}$$

is satisfied, where $u(a)$ is given by (4.4), then for large time all solutions approach the stable age distribution above, corresponding to permanent fade-out of the disease. Intuitively, if the contact number times the largest possible average susceptible fraction is not greater than one, then the average infective cannot replace itself with at least one new infective during the infectious period, and consequently the disease dies out.

If the inequality is not satisfied, then [except when $y_0(a) = 0$] the fraction $u(a)$ (passively immunes and susceptibles) approaches a steady state age

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distribution given by

$$u(a) = \begin{cases} \exp\left(-\lambda\int_0^a C(s)\,ds\right), & 0 \leqslant a \leqslant A_1, \\ [1 - V_1C(A_1)]\exp\left(-\lambda\int_0^a C(s)\,ds\right), & A_1 < a \leqslant A_2, \\ [1 - V_1C(A_1)][1 - V_2C(A_2)]\exp\left(-\lambda\int_0^a C(s)\,ds\right), & A_2 < a < \infty, \end{cases} \tag{4.6}$$

where λ is a positive constant. At this endemic steady state age distribution, the average infective must infect (or reproduce) exactly one new infective [37, 38] so that $\sigma\overline{Cu} = 1$, where $\overline{Cu}$ is the average susceptible fraction. Thus the force of infection λ satisfies

$$1 = \sigma\int_0^\infty C(a)u(a)\mu e^{-\mu a}\,da \tag{4.7}$$

where $u(a)$ is given by Equation (4.6).

The inequality (4.5) and the equality (4.7) reduce to those in Hethcote [38] when $C(a) = 1$ for all ages a. When $C(a) = 1$, the contact number σ can be estimated using $\sigma = 1 + L/Av$, where $L = 1/\mu$ is the average lifetime and Av is the average age at which individuals are infected in the population at a time before there was any vaccination [37, 38]. There is no corresponding simple formula for the model considered here; however, if B is the average age for the loss of passive immunity, then an approximation to the contact number is given by

$$\sigma = 1 + \frac{L - B}{Av - B}. \tag{4.8}$$

An expression for the average age of attack was obtained in Hethcote [38] and it was observed there that vaccination before the average age of attack causes it to increase, and vaccination after the average age of attack causes it to decrease.

THE LIFETIME EXPECTED RISK

Let $R(a)$ be some measure of the risk associated with infection by the disease at age a. Various choices of the measure of risk are possible. If infection is equally undesirable at all ages, then we could set $R(a) = 1$ for all ages a. On the other hand, the risk $R(a)$ could be taken to be the probability of death due to infection at age a or to be any composite measure of the undesirability of infection at age a. The seroconversion rate

$C(a)$ is assumed to be the probability of being susceptible at age a due to loss of passive immunity, and $C(a)$ is also assumed to be the vaccine efficacy at age a.

At a steady-state age distribution, the probability $P(a)$ of infection at age a is given by $-u'(a)$, where $u(a)$ is the age distribution of passively immunes and susceptibles. At the endemic steady state age distribution given by Equation (4.6), the probability $P(a)$ is $\lambda C(a)u(a)$, which corresponds to the infection rate in the equation (4.3). The lifetime expected risk E to people in the population due to the disease is given by

$$E = \int_0^\infty R(a)P(a)\,da = \lambda\int_0^\infty R(a)C(a)u(a)\,da. \tag{4.9}$$

If the risk factor $R(a)$ is always 1, then the lifetime expected risk is

$$E = 1 - V_1C(A_1)\exp\left(-\lambda\int_0^{A_1} C(s)\,ds\right) - [1 - V_1C(A_1)]V_2C(A_2)\exp\left[-\lambda\int_0^{A_2} C(s)\,ds\right]. \tag{4.10}$$

The fractions V_1 and V_2 can be interpreted as the probabilities of being vaccinated at ages A_1 and A_2, respectively, for an individual born into the population, so that E is the lifetime probability of infection for a person in the population. Note that E is not the same as the expected risk for a person vaccinated twice. The expression (4.10) could also be obtained by adding the products of the risks and probabilities corresponding to being unvaccinated, vaccinated only at age A_1, vaccinated only at age A_2, and vaccinated at both ages.

DISCRETIZATION OF THE MODEL

A discrete age structure is achieved by dividing the population into age groups; let the integer i be the age in months of a group. Let

$$D(i) = \sum_{j=1}^{i} C(j) \tag{4.11}$$

where $C(j)$ is the seroconversion rate at age j months. The discrete version of the inequality (4.5) which determines whether the disease dies out is

$$\sigma\left[\sum_{i=1}^{A_1} C(i)\mu e^{-\mu i} + [1 - V_1C(A_1)]\sum_{i=A_1+1}^{A_2} C(i)\mu e^{-\mu i} + [1 - V_1C(A_1)][1 - V_2C(A_2)]\sum_{i=A_2+1}^{1200} C(i)\mu e^{-\mu i}\right] \leqslant 1. \tag{4.12}$$

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If the equality (4.12) is satisfied, then the disease dies out; otherwise, the disease remains endemic. The maximum age in this population is 1200 months (i.e., 100 years).

The discretized stable age distribution for the class of those who are either passively immune or susceptible is

$$u(i) = \begin{cases} e^{-\lambda D(i)}, & 0 \leqslant i \leqslant A_1, \\ [1 - V_1 C(A_1)]\, e^{-\lambda D(i)}, & A_1 < i \leqslant A_2, \\ [1 - V_1 C(A_1)][1 - V_2 C(A_2)]\, e^{-\lambda D(i)}, & A_2 < i < 1200, \end{cases} \tag{4.13}$$

which is analogous to (4.6). When the disease dies out, the force of infection λ is zero. When the disease remains endemic, the force of infection λ is a positive constant which satisfies an equation like (4.7) given by

$$\sigma \sum_{i=1}^{1200} C(i)\, u(i)\, \mu e^{-\mu i} = 1, \tag{4.14}$$

where $u(i)$ is given by Equation (4.13). The equation (4.14) is based on the observation that at an endemic stable age distribution, the average infective must infect (or reproduce) exactly one new infective [36–38].

THE LIFETIME EXPECTED RISK

Let $R(i)$ be a measure of the risk due to measles infection at age i months. If infection by measles were equally hazardous at all ages, then we could set $R(i) = 1$ for all ages i. The risk $R(i)$ could also be taken to be the probability of death due to measles infection at age i or to be any composite measure of the undesirability of measles infection at age i.

Let $P(i)$ be the probability that a susceptible becomes infected during the ith month of life. For the discretized model $P(i)$ is given by

$$P(i) = C(i)\, u(i) - C(i+1)\, u(i+1), \tag{4.15}$$

where $u(i)$ is given by Equation (4.13). $P(i)$ is the difference between the probabilities of being susceptible at ages i and $i+1$.

The lifetime expected risk E or expected value of a loss due to measles for people in the population is analogous to (4.9) and is given by

$$E = \sum_{i=1}^{1200} R(i)\, P(i), \tag{4.16}$$

where $P(i)$ is given by Equation (4.15). Note that this is the lifetime

expected risk for all people in the population, including those who were unvaccinated, those who were vaccinated once at age A_1 or age A_2, and those who were vaccinated at both ages.

In order to compute E, one first needs to approximate the contact number σ using Equation (4.8) and then solve Equation (4.14) iteratively for the force of infection λ. Using this λ and the values of $D(i)$ calculated from Equation (4.11), the stable age distribution can be found from Equation (4.13) and the lifetime expected risk found from Equations (4.15) and (4.16). The calculations are all carried out with the aid of a computer program which presents as output the lifetime expected risk for all combinations of vaccination ages.

The continuous vaccination model and its discrete analog incorporate all of the essential features necessary to calculate optimal ages of vaccination. However, these models do not consider different groups with different contact rates and do not incorporate the known seasonality of measles. More refined models could be used, but parameter estimation becomes more difficult as the models become more complex. It has been suggested that models with larger contact rates among school children might be more realistic in developed countries. Since the model, the seroconversion rate curves, and the parameter values used here are approximations to reality, the optimal ages of vaccination calculated are also approximations. Since the optimal ages of vaccination are particularly sensitive to changes in the seroconversion rate data, their reliability is limited by the quality of the data currently available. Better seroconversion data will lead to improved estimates.

The model (4.1)–(4.2) differs from the models in Dietz [37], Hethcote [38], and Anderson and May [39] in that $C(a)$ is included as the loss of passive immunity in the differential equations and as the vaccine efficacy in the matching conditions. Cvjetanovic, Grab, and Dixon [40] use a computer simulation model in which a fraction of the newborns have passive immunity for 6 months. Their simulation calculations for measles show that elimination can be obtained if 70% of the 12-month olds are immunized; we are skeptical of this result, since measles has persisted in the USA, where vaccination levels are much higher. The model here is similar to the models of Katzmann and Dietz [41] and of Anderson and May [39], in which the passive immunity decays exponentially. They compute the optimum age of vaccination for various proportions being vaccinated and observe that their optimum age for measles vaccination in Kenya agrees with the recommendation of WHO. The model here differs from their model in that it uses approximate seroconversion rate curves based on data instead of assuming exponential decay of passive immunity. Black [28] uses data to determine the best ages of vaccination for measles in various parts of the world without using a mathematical model. Halsey et al. [29] conclude from the data on Haitian children that the best age of vaccination is 9 months.

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5. ESTIMATING CONTACT NUMBERS

Recall that the contact number for a disease in a population is the average number of adequate contacts of an infectious person during the infectious period. Thus the contact number is a measure of the transmissibility of the disease in the population [42]. Measles has high contact numbers and seems to be the most easily spread of the directly transmitted diseases [43]. The contact numbers estimated in this section using Equation (4.8) are only crude approximations, but as we note in the next section, our results are insensitive to these choices of parameter values.

The average ages for loss of passive immunity for the seroconversion rate curves in Figure 1 are $B = 4.78$ months for the Kenya curve, $B = 6.55$ months for the South America curve, and $B = 8.435$ months for the USA curve. The average lifetimes L for Kenya, South America, and the USA in the prevaccine era were approximately 50, 60, and 70 years, respectively.

Various average ages of infection in tropical Africa have been reported. A relevant quotation [44] is, "In the developing countries the highest incidence of the disease is seen in the second year of life. The majority of children are infected by the time they are three years old." Some reported median ages in months of measles infection are 24.7 in Ghana, 16.5 in W. Nigeria, 21.5 in E. Nigeria, 18.5 in Uganda, Kenya, and Malawi, and 29.7 in Tanazania, Zambia, and Rhodesia [45]. One report [46] states that "The average age of infection ranges from 14 months in densely populated areas of Africa, where children are on their mother's back most of the time, to 24-60 months in low density areas." The Machakos project found that the median age of measles cases in rural Kenya was 2.5 years [3]. We will assume that the average age of infection in Kenya is 2 years. If $L = 50$ years, $B = 4.78$ months, and $Av = 2$ years, then the contact number found from Equation (4.8) is $\sigma = 32.0$.

Data on the average age of infection in South America were not found. However, the average age of infection in Mexico in a partially vaccinated population in 1974-1981 was approximately 4 years [11]. Since vaccination in early childhood tends to increase the average age of infection [38], the average age of infection in the prevaccine era was probably 3 or 3.5 years. We assume that the average age of infection in the population in South America corresponding to the seroconversion curve in Figure 1 is 3.5 years. If $L = 60$ years, $B = 6.55$ months, and $Av = 3.5$ years, then the estimate of the contact number found from Equation (4.8) is $\sigma = 21.1$.

The average age of infection for measles in the prevaccine era in the USA is thought to be approximately 5 years [38, 43]. If $L = 70$ years, $B = 8.435$ months, and $Av = 5$ years, then the contact number estimate is $\sigma = 17.1$.

6. RESULTS WHEN THE RISK IS INFECTION

Here we determine optimal ages of vaccination for one-dose vaccination strategies by setting $V_2 = 0$ in the vaccination model. The risk factor $R(i)$ is

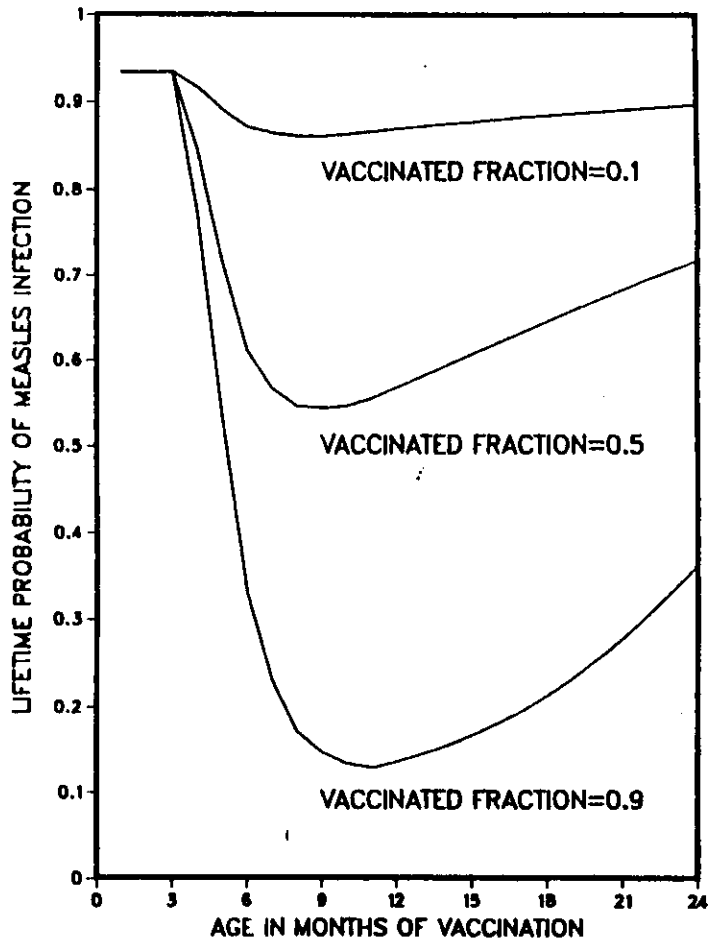

FIG. 2. Theoretical lifetime risk of measles infection in Kenya for the given vaccinated fraction.

taken to be 1.0 for all ages, so that the lifetime expected risk E is the probability for people in the population of being infected with measles during their lifetime when a fixed fraction V_1 of the population is vaccinated at age A_1. Ages of vaccination which minimize the lifetime expected risk of measles are calculated for the three geographic locations.

Figure 2 shows the results using the seroconversion rate curve and parameter value estimates for Kenya. When 10% of the population is vaccinated, the minimum lifetime probability of measles infection in the population occurs when the age of vaccination is 8 months, but the expected

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risk curve is fairly flat, so that it is nearly optimal to vaccinate anywhere between 7 and 12 months. When 50% of the population is vaccinated, the optimal age of vaccination is at 9 months, and it is nearly optimal to vaccinate anywhere between 8 and 11 months. When 90% of the population is vaccinated, the optimal age is 11 months, and it is nearly optimal to vaccinate between 10 and 12 months.

The theoretical optimal age is insensitive to changes in the values chosen for the average lifetime L and the average age Av of infection which determine the contact number σ. That is, when L is changed from 50 years

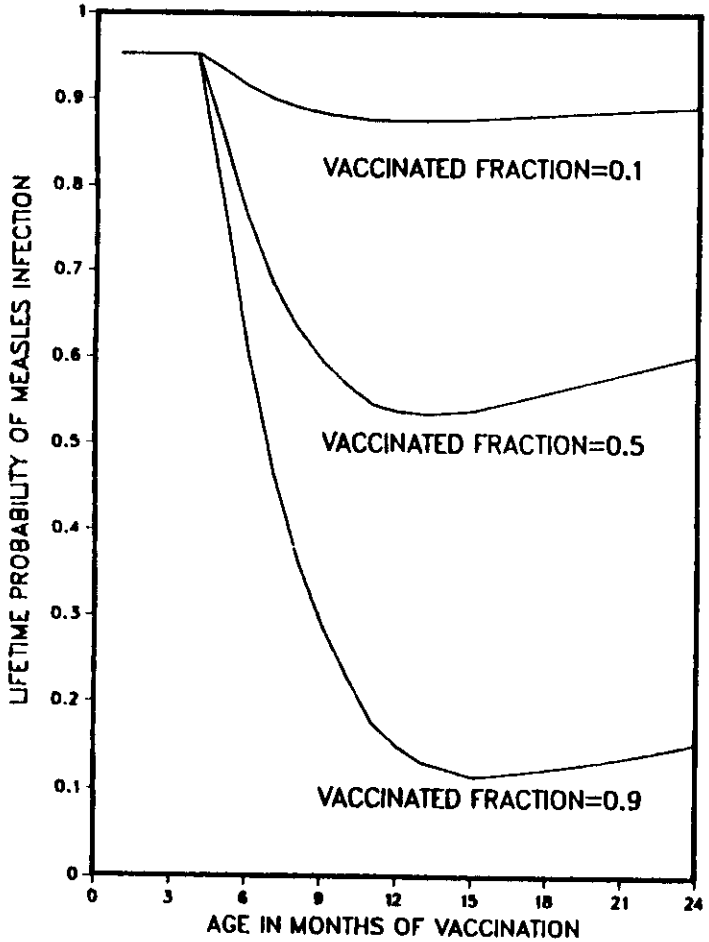

FIG. 3. Theoretical lifetime risk of measles infection in South America for the given vaccinated fraction.

to 40 or 60 and Av is changed from 2 years to 1.5 or 2.5, there is no perceptible change in the curves in Figure 2, and the optimal age of vaccination does not change by more than one month. However, when the Kenya seroconversion curve is shifted so that it is 1, 2, and 3 months later, the curves in Figure 2 and the optimal ages of vaccination are also shifted so they are 1, 2, and 3 months later. This strong dependence of the theoretical optimal age of vaccination on the seroconversion rate curve is also observed for the other seroconversion rate curves in Figure 1.

Figure 3 shows the results of calculations using the seroconversion rate curve and the parameter values for South America. The optimal ages of

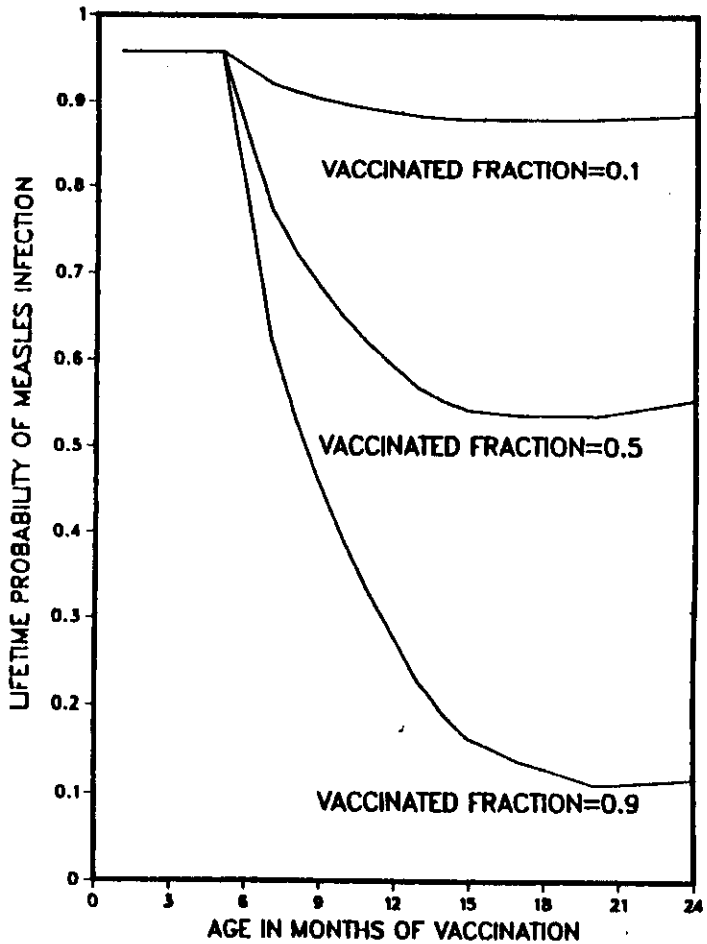

FIG. 4. Theoretical lifetime risk of measles infection in the United States for the given vaccinated fraction.

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vaccination when 10%, 50%, and 90% of the population is vaccinated are 12, 13, and 15 months, respectively. It can be seen from Figure 3 that vaccination ages within a few months of these ages are nearly optimal. Again, these results are only slightly dependent on the values chosen for the parameters L and Av, but are strongly dependent on the position of the seroconversion rate curve.

Figure 4 shows the results of calculations using the seroconversion rate curve and the parameter values for the USA. The optimal ages of vaccination when 10%, 50%, and 90% of the population is vaccinated are 15, 19, and 20 months, respectively. Since the curves in Figure 4 are fairly flat near their minimum points, the lifetime expected risks are near the minimum value when the ages of vaccination are within a few months of the optimal age of vaccination.

7. RESULTS WHEN THE RISK IS DEATH

Here we also consider one-dose vaccination strategies. The risk of mortality when individuals are infected by measles depends on their ages and on the population being considered. In developing countries the risk of mortality is much higher. In tropical Africa the percentage of measles cases that lead to death range from 5% to 25% [44]. In evaluating the results below, it is important to remember that case fatality rate data are sometimes unreliable due to underreporting of measles cases.

In the Machakos study in Kenya, the case fatality rates found from 1056 cases were 6.4% from ages 1 to 12 months, 11.8% from 12 to 24 months, 6.4% from 24 to 36 months, and 5.2% beyond 36 months [4]. The case fatality rate is higher from 12 to 24 months because malnutrition is more common at these ages and measles is more severe in a malnourished child. There is also some evidence that malnourished children spread measles up to three times longer than other children [45]. In the Gambia the case fatality rates determined from 135 cases were 100% for ages 6 to 8 months, 71.4% for ages 9 to 11 months, 22.2% for 1 year olds, 17.6% for 2 year olds, 13% for 3 and 4 year olds, 5.6% for 5 and 6 year olds, and 0% for those beyond 6 years of age [46]. A study in Bangladesh showed that the case fatality rates found from 896 cases were about 4.3% from children from 1 to 23 months, from 25 to 47 months, and from 48 to 71 months, and 1.6% for children 6 to 10 years of age [47].

Although these three studies are not completely consistent, they do suggest that the case fatality rates in developing countries are higher for younger children. We assume mortality risk factors of 40, 20, 10, and 5 for individuals with ages <1, 1, 2–4, and >5 years, respectively. Using these values for $R(i)$ together with the seroconversion rate curve and parameter values for Kenya, the optimal ages of vaccination are approximately one month earlier than those obtained when the risk was measles infection.

When 10%, 50%, and 90% of the population is vaccinated, the risk of mortality due to measles is minimized at ages 7, 8, and 9 months, respectively. Again, the optimal ages are strongly dependent on the seroconversion rate curve.

Data on the case fatality rate for measles in South America were not found: however, the age specific measles mortality is higher for younger children. In temperate South America the age specific measles mortality for age groups <1, 1–4, 5–9, 10–14, 15–19, and ≥ 20 years are 31.1, 7.9, 1.0, 0.4, 0.2, and 0.04 per 100,000 population, respectively [9]. Because there is no death per case information on South America, we will use the same mortality risk factors used in the Kenya calculations. The risk of mortality when 10%, 50%, and 90% of the population is vaccinated is minimized at ages 11, 12 and 15 months, respectively. These ages are about one month earlier than the optimal ages found when the risk factor was measles infection.

In the USA the reported case fatality rates are higher for infants and for adults. The death to case ratios in 1973–75 were 3.32, 1.50, 0.44, 0.49, 0.52, and 2.00 per thousand cases for ages <1, 1–4, 5–9, 10–14, 15–19, and ≥ 20 years, respectively. In 1976–78 the death to case ratios for these same age groups were 0.72, 0.42, 0.09, 0.30, 0.12, and 2.37 per thousand cases, respectively [14]. Based on the 1976–78 data, we assume mortality risk factors of 0.72, 0.42, 0.17, and 2.37 for ages <1, 1–4, 5–19, and ≥ 20 years, respectively.

Using the mortality risk factors above together with the seroconversion rate curve and parameter values for the USA, we find a surprise when we calculate the expected risks for vaccination at various ages. When the percentages of the population vaccinated are 10%, 20%, 30%, ..., 90%, the risk of mortality is minimized for all people in the population when the vaccination ages are 15, 15, 15, 20, 23, 31, 38, 43, and 45 months, respectively. For the higher percentages vaccinated, these optimal ages of vaccination are significantly larger than those found in the previous section where the risk was measles infection. However, the risk of mortality is minimized *for a vaccinated person* at the vaccination age of 15 months when 10% of the population is vaccinated, at age 16 months for 20% vaccinated, at age 17 months for 30% vaccinated, and at age 20 months for 40% to 90% vaccinated.

These surprising results have the following explanation. When a small fraction of the population is vaccinated, those who are vaccinated should be vaccinated reasonably early so that they avoid as much as possible the high death per case rate at ages 1–4, and those who are unvaccinated will probably acquire natural infection at a young age, so they will avoid the very high death per case rate for those over 20 years of age. When 90% of the population is vaccinated, there is a clear conflict between what is best for the vaccinated people and what is best for the population as a whole. Although

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it is better for vaccinated people to be vaccinated at age 20 months, it is better for the entire population if vaccination is done at age 45 months. The entire population benefits from this late vaccination because it allows more natural infection in the population and increases the probability that unvaccinated people will acquire immunity through natural infection and thus avoid measles infection when they are older than 20 years. Calculations using the model, seroconversion curve, and contact number for the USA show that measles dies out if 94% of the population is vaccinated successfully at age 20 months. Consequently, we do not recommend that the age of vaccination be increased to 45 months; instead, we recommend that lower vaccination ages be used and that great effort be exerted to achieve a very high level of immunity in the population through vaccination.

8. TWO-DOSE VACCINATION STRATEGIES

Our calculations for two-dose strategies when the risk is infection or death show that the optimal two-dose strategy always occurs when the two doses are given at ages as close as possible to each other. In the calculations for Kenya and South America, the optimal ages for the two doses are always within two months of the optimal ages for the one-dose vaccination strategies. For example, in Kenya when the risk is infection (respectively, death), the optimal ages are 7 and 8 months (7 and 8) when 10% of the population is vaccinated at each age, and are 9 and 10 months (8 and 9) when 50% of the population is vaccinated at each age.

In the USA when the risk is measles infection (respectively, death), the optimal ages of vaccination are 16 and 17 months (15 and 16) when 10% of the population is vaccinated at each age, and are 19 and 20 months (40 and 42) when 50% of the population is vaccinated at each age so that 75% of the population is eventually vaccinated. These optimal vaccination ages are similar to those that occur for the corresponding one-dose strategies.

The single-dose vaccination strategies in which all of the vaccine doses are given at the same age are always significantly better than the two-dose vaccination strategies in which half of the doses are given at one age and the other half are given at a later age. Consequently, from a theoretical point of view, no two-dose vaccination strategy should be called optimal. The model here assumes that a first unsuccessful dose will leave the child fully responsive to a second dose; however, there is evidence that after a first dose some children are susceptible to measles, but are less likely to be immunized by a second dose [28]. This consideration also makes a two dose vaccination strategy undesirable.

9. DISCUSSION

The calculations of the lifetime expected risks for infection and for death using the approximate seroconversion rate curve and parameter estimates for

Kenya lead to optimal ages of vaccination of 9 and 8 months when 50% of the population is vaccinated. The currently recommended vaccination age of 9 months in Kenya and tropical Africa is consistent with these results. If the seroconversion rate curve labeled South America in Figure 1 accurately reflects seroconversion rates in some countries of South America, then the calculations here suggest that a recommended vaccination age of 12 or 15 months would be better for these countries than the currently recommended vaccination age of 9 months.

Calculations of the lifetime expected risks using the seroconversion curve and parameter values for the USA suggest that the optimal vaccination age for measles in the USA is later than the currently recommended vaccination age of 15 months. Although there were only 1497 measles cases reported in the USA in 1983, the incidence increased to 2587 in 1984, 2822 in 1985, and 6255 in 1986 [3]. Measles could continue at low levels for many years before nationwide herd immunity and eradication are achieved [38]. Since there are now none or very few measles cases in many states, it would not be imprudent to vaccinate children for measles in these states at age 18 months or at age 24 months. The risk of getting measles between ages 15 and 18 months or between 15 and 24 months is probably much lower in these areas of the USA than the risk of not becoming immune when vaccinated at age 15 months and then getting measles later.

In the USA, the death per case rate for people over age 20 years is over 5 times the rate for children between 1 and 4 years of age and is approximately 14 times the rate for people between 5 and 19 years, so that it is clearly riskier to get measles as an adult. When 90% of the population is vaccinated, calculations using the USA data show that the risk of mortality due to measles is minimized for vaccinated people if vaccination occurs at age 20 months, but the risk of mortality is minimized for the entire population if vaccination occurs at age 45 months. We do not recommend that the age of vaccination be increased to 45 months, but we do recommend that the age of vaccination be increased above 15 months in some areas of the USA and that efforts to increase the percentage vaccinated be continued. Calculations using the model here with USA data suggest that uniform successful vaccination of 94% of the population at age 20 months causes measles to die out.

No vaccination strategy which recommends two doses is optimal. That is, for every seroconversion rate curve and set of parameter values, there seems to be one theoretically optimal age of vaccination so that vaccinations before or after that age are not given at the optimal age. If one uses computer simulation to search for the optimal two-dose strategy, then the optimal strategy occurs when the doses are both given very near the optimal age for a single dose. Although there is no such thing as an optimal two-dose vaccination strategy, there could be practical reasons for giving two doses. The advantage of a second dose is that it will provide immunity for many of

those who did not receive a first dose or did not become immune after the first dose.

Previous calculations [38] revealed that it is very difficult to eliminate measles by herd immunity using a single-dose vaccination strategy. In that model, herd immunity required that over 94% of the 15 month old children become immune, which in turn required that over 99% be vaccinated, since the primary vaccination failure rate was 5%. Vaccination coverage greater than 99% is very hard to achieve. However, these calculations are consistent with the experience of epidemiologists in Czechoslovakia [19], who state, "It is evident that the permanent elimination of measles requires a level of herd immunity of $\geqslant 95\%$, a level that is impossible to achieve even with a vaccination coverage of almost 100%."

Herd immunity is much easier to achieve using a two-dose vaccination strategy. Previous calculations [38] showed that herd immunity can be achieved if over 80% of all children are vaccinated at age 15 months and over 77% of all children are vaccinated at age 5 years when they enter school. A two-dose strategy such as this might be useful in areas of the USA where measles cases are still occurring because some children are not vaccinated for measles when they are young.

If vaccine-acquired immunity to measles is actually lifelong as assumed in our model, then the use of booster doses at 7, 9, and 12 years in China and Sweden is not necessary. It would be very desirable if the question about the duration of vaccine-acquired immunity to measles could be completely resolved by careful studies.

The two-dose strategies used in Costa Rica, Czechoslovakia, and Iran consist of an early first dose (6 to 14 months) and a second dose approximately 6 months later. These strategies seem to be based on the desire to protect a fraction of the vaccinated population with the first dose and then to protect a larger fraction of the population with a second dose when the seroconversion rate is higher. These strategies do provide more protection for a twice-vaccinated person than a single-dose strategy, but the cost per person is twice that of the single-dose strategy. The two-dose strategy has clearly been effective in Czechoslovakia, where there are very few measles cases.

Two-dose vaccination strategies have sometimes been advocated for developing countries [48–50]. In developing countries where there are limited resources for measles vaccination, it is clearly better to vaccinate a large fraction of the population once at a nearly optimal age then to vaccinate half as many children at two ages. For example, using the Kenya seroconversion curve and parameter values, vaccinating 90% at the optimal age of 11 months gives an expected risk of measles infection in the population of $E = 0.13$, while vaccinating 45% of the population at age 6 months and 45% of the population at age 12 months gives $E = 0.40$. Thus our calculations are

consistent with the recommendation that developing countries should concentrate on delivering one dose of measles vaccine to a large fraction of the population instead of giving two doses to smaller fractions [5,51]. Another reason for not using a two-dose strategy is that a failed early vaccination has a negative effect on the mother's attitude and willingness to cooperate. A two-dose measles vaccination strategy should be considered in a country only after a large fraction of the population is receiving one dose of measles vaccine.

When there is an outbreak of measles, vaccinations are sometimes given to children as young as 6 months of age. For example, this has been done among some Indian populations in Canada [52]. Infants vaccinated at a very young age should be revaccinated, since a significant fraction of them will not become immune after the first dose. This revaccination should occur at the optimal vaccination age for a single dose, provided that a sufficient time period has elapsed so that the first dose does not interfere with seroconversion after the second dose.

The calculations here illustrate how seroconversion rates and other data can be used to estimate optimal ages of vaccination. Of course, the seroconversion rate curves in Figure 1 are approximations, and the model used is an approximation to reality. Since the optimal ages of vaccination depend strongly on the seroconversion rates, it would be desirable to obtain more accurate information about seroconversion rates at different ages in various countries by means of careful studies. Better approximations of the optimal ages of vaccination will be possible as better data become available.

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