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# Measles vaccination policy

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## SUMMARY

Where immunization campaigns locally eliminate measles, it will be important to identify the vaccination policy most likely to prevent future epidemics. The optimum age for vaccination depends on the rate of decline of maternal antibody, because the presence of antibody reduces vaccine efficacy. The first part of this paper contains a quantitative reappraisal of the data on antibody decline and seroconversion rates by age. The decline in maternal antibody protection follows delayed exponentials, with delays of 2–4 months, and subsequent half-lives of 1–2 months. Using this result in an analytical mathematical model we find that the optimal age to administer a single dose of vaccine to children, which is independent of vaccine coverage, lies within the range 11–19 months. We also show that, where the optimal age cannot be met, it is better to err towards late rather than early vaccination. There are therefore two reasons why developing countries, which presently vaccinate during infancy because measles transmission rates are high should eventually switch to the second year of life. The possible gains from two-dose vaccination schedules are explored with respect to both coverage and efficacy. A two-dose schedule will be beneficial, in principle, only when there is a need to increase net vaccine efficacy, after coverage has been maximized with a one-dose schedule.

## INTRODUCTION

Substantial efforts are being made to control measles by vaccination worldwide, and in some countries measles incidence has been reduced to levels that are close to elimination. The most recent example is Finland, where indigenous measles has been eliminated by vaccinating over 96% of children at 14–18 months, and again at 6 years [1]. In other areas, such as the English-speaking Caribbean, Brazil, Chile and central America, and England and Wales, measles has been almost eliminated by high coverage of infants or young children, plus supplementary mass vaccination across a wide range of age groups. Mass vaccination aims to increase coverage by immunizing those children who were missed at younger ages, and those who did not respond to the first dose [2]. The policy questions that arise in countries that are close to, or which have succeeded in, eliminating measles include: At what age should measles vaccine be

administered post-elimination? Is a single dose of vaccine sufficient? If two or more doses are needed, at what ages should they be administered?

The optimal age for measles vaccination has been debated since vaccine was introduced [3–5]. Previous studies have considered this question in the context of endemic measles infection. The optimal age is that which minimizes the number of susceptibles, and it lies at the point at which antibody prevalence is at a minimum: vaccinating before this age increases the number of vaccine failures arising from the presence of maternal antibody (greater risk of infection after vaccination), whilst vaccinating after this age leaves more children exposed to natural infection (greater risk of infection before vaccination).

In developed countries, the half-life of maternal antibody is a few months, but the average age of infection is around 5–6 years [6–8]. The window of opportunity to protect children against measles is therefore wide, and vaccine is not routinely administered until 12–23 months of age. In developing countries, however, where transmission rates in pre-school children are usually higher, vaccination cannot be delayed until most children have lost maternal antibody because many will by then have been infected by wild measles virus. Using data on the age-specific incidence of measles and age-specific seroconversion rates to measles vaccine in developing countries, the World Health Organization Expanded Programme on Immunization calculated that cases and deaths would be minimized by vaccinating at age 8–9 months, and consequently recommends vaccination at age 9 months in developing countries [9].

Effective vaccination programmes lower the incidence of infection, and widen the 'trough' in age-prevalence curves. Vaccination should continue to minimize the number of susceptibles as incidence declines, if necessary by changing the age of vaccination. In principle, vaccine could be offered to children in one age-group (single-dose strategy), or divided among two (two-dose strategy) or more age groups. Under a two-dose strategy, the second dose might be administered randomly, in which case children in the population could receive zero, one or two doses. Or it might be administered systematically, in which case the number of doses received is either zero or two. Under a random two-dose strategy, benefits may arise from the extra coverage gained (vaccine delivered to a larger number of people in total), or from an increase in net efficacy (some vaccine failures at round one protected at round two), and it will be desirable to distinguish the effects of these processes.

In this paper, we tackle these questions by bringing together theory and data. The first part contains a quantitative reappraisal of the data from major studies on maternal antibody decline and seroconversion rates with age. It leads to an improved model of the way in which vaccine immunogenicity changes with age. In the second part, we use this model to calculate the optimal ages at which one to two doses of vaccine should be administered under random and systematic coverage. By making the simplifying (equilibrium) assumption that measles has been eliminated, it is possible to find, analytically, the optimal ages at which to give one or two doses with random or systematic coverage. Whilst analytical tractability is a benefit of simplification, it carries a cost in diminished realism. We therefore compare the 'general' results from our simple model with the specific results obtained from simulations with more detailed models [10–11].

## VACCINE IMMUNOGENICITY WITH AGE: A REAPPRAISAL OF THE DATA

We want to know what proportion of vaccinated children seroconvert as a function of age, but there are few data on seroconversion by month of age to standard-titre measles vaccines, particularly among infants under 6 months of age. Since seroconversion rates in young children who have not contracted measles depend on the level of maternal antibody, these may be used to estimate seroconversion rates, assuming that there is a critical antibody level below which children will seroconvert.

Unpublished data from a study in Tanzania suggest that the percentage of children with maternal antibody levels below 55 mIU by plaque inhibition assay correlated well with the percentage that seroconvert [12]. A study in Mexico showed that seroconversion rates after giving standard titre Schwarz vaccine fell sharply from 76% when maternal antibody levels (plaque neutralization assay, PN) were less than 40 mIU, to 40% at levels of 40–990 mIU, and to zero at over 200 mIU [13]. Thus high seroconversion may be expected at levels below 40–50 mIU and low seroconversion at levels over 100 mIU. Unfortunately, many studies of maternal antibody in infants have used less sensitive assays, such as haemagglutination inhibition (HI), and have expressed results in titres or concentrations rather than international units. Seronegativity by those assays may therefore not precisely reflect the ability to seroconvert after vaccination. Nonetheless, data on levels of maternal antibody by age can be used to derive a functional form for the dependence of seroconversion rates on age.

### *Decay of maternal antibody*

The most comprehensive set of longitudinal data on maternal antibody by age of the infant is shown in Figure 1 [14], where the frequency distribution of children is plotted against HI titre for children of different ages measured in 4-week periods (FWPs).

In Figure 1 the lowest measured HI titre corresponds to a serial dilution of 3 ($\ln(\text{HI titre}) \approx 1$). These data can be fitted to normal distributions but, because of the cut-off at a dilution of 3, it is necessary to fit the cumulative data to cumulative normal distributions. A method for doing this is given in Appendix 1 and the means and standard deviations of the fitted normal distributions are shown in Figure 2.

The data in Figure 2 can be fitted to second order polynomials in age. The fitted lines and the coefficients of the fitted lines are given in Table 1. Because the decline in the mean and standard deviation of the ln (HI dilution titre) is not quite linear, the decline in antibody levels is not precisely exponential. From the fits given in Figure 2, we can determine the number of children that would seroconvert as a function of age assuming different critical values for the antibody level at which seroconversion occurs. To do this we calculate

$$p = \int_{x^*}^{\infty} N(m, s)\, dx, \tag{1}$$

where $p$, the proportion of children that will seroconvert, is the integral from, $x^*$,

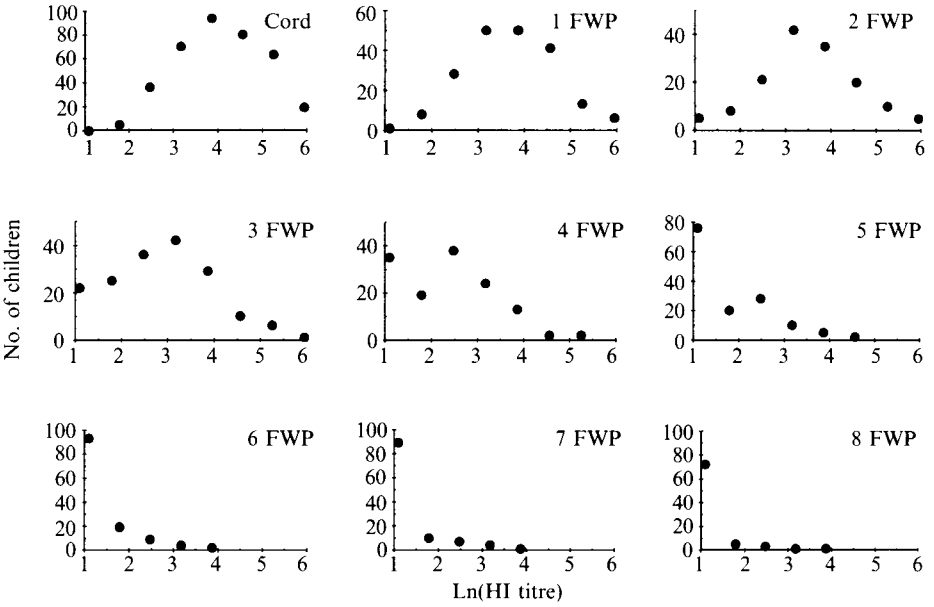


Fig. 1. Frequency distributions of ln (HI titres) in cord blood and for children aged 1–8 FWPs (4-week periods). Note that the left most point on each plot corresponds to the lowest recorded antibody level.

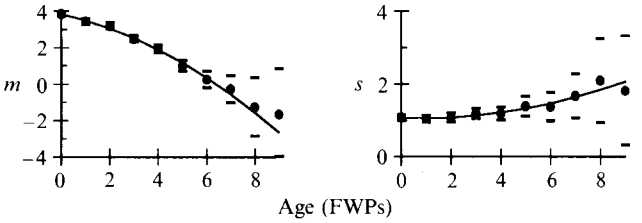


Fig. 2. The means ($m$) and standard deviations ($s$) of the ln (HI titre) obtained by fitting normal distributions to the data shown in Figure 1. The error bars indicate $\pm 1$ standard deviation.

Table 1. *Coefficients of the fitted lines shown in Figure 2*

| Coefficient | $m$ | S.D. | $s$ | S.D. |
|---|---|---|---|---|
| Constant | 3·830 | 0·052 | 1·070 | 0·039 |
| Age | −0·294 | 0·052 | −0·022 | 0·039 |
| Age$^2$ | −0·048 | 0·010 | 0·015 | 0·007 |

the critical HI titre for seroconversion, to infinity of a normal distribution with mean $m$ and standard deviation $s$ calculated using the coefficients in Table 1.

Figure 3*a* shows $1-p$, the proportion of children that are protected by maternal antibody as a function of age assuming that the critical value of the HI titre is either 1, 2, 4 or 8 serial dilutions. Figure 3*b* shows a plot of $\ln(1-p)$ and within the precision of the data we can fit the curves to delayed exponentials. Fitting the

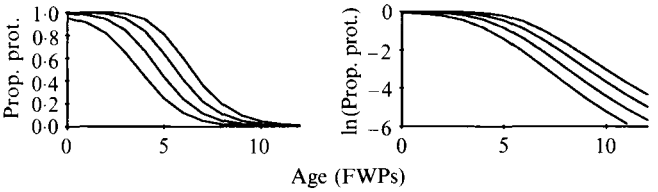


Fig. 3. (*a*) $1-p$, the proportion of children that are protected by maternal antibody plotted as a function of age for various values of the critical HI titre. The lines, from right to left, are obtained by assuming that the critical titres are 1, 2, 4 and 8. (*b*) As for (*a*) but the vertical axis is now $\ln(1-p)$.

Table 2. *The delay and decay rate of maternal antibody protection for a range of critical levels of the HI dilution titre obtained by fitting each curve shown in Figure 3 to a delayed exponential*

| Critical HI dilution | Delay (FWPs) | Decay rate (FWPs) | Half-life (FWPs) |
|---|---|---|---|
| 1 | 4·02 | −0·67 | 1·03 |
| 2 | 3·54 | −0·72 | 0·96 |
| 4 | 2·85 | −0·76 | 0·92 |
| 8 | 1·88 | −0·77 | 0·90 |

data in Figure 3*b* to delayed exponentials, so that we assume that the proportion of people who are protected by maternal antibody is one up to the age corresponding to the delay and falls exponentially thereafter, gives the results shown in Table 2. Table 2 shows that the delay before protection begins to wane ranges from 2–4 FWPs, depending on the critical HI dilution titre for protection. After the initial delay the number of protected halves about once in each FWP. If the critical HI dilution titre is 4, for example, all children are protected up to just less than 3 FWPs, at about 4 FWPs half are protected at 5 FWPs one-quarter are protected, and so on.

We may compare these results with those from other studies in developed and developing countries. Dabis and colleagues [15] determined the number of children that were seropositive by age in a cross-sectional study in Brazzaville. Fitting their data to a delayed exponential gives a delay of about 2 months and a half-life thereafter of about 1·4 months. In Peru, Vaisberg and colleagues [16] obtained a half-life of about 50 days. In the pre-vaccination era, measles antibody levels persisted longer in infants in high income than low income countries [17]. In the USA, Sato and colleagues, [18] showed that the antibody level in the child decays exponentially from birth to 0·1% of the cord value at age 11 months, which is consistent with our results (Table 2) if the critical HI dilution titre is 8. Mother and cord blood antibody levels tend to be lower in vaccinated mothers than mothers who had natural measles [19–21]; consequently, in highly vaccinated populations, the age at which most infants become susceptible may often be closer to that in developing countries. Chui and colleagues [22] present data from a small study in Alberta, Canada, showing that after 6 months, 93% of the children of vaccinated mothers were without detectable neutralizing antibody (NT titre $\leqslant 10$), which would also be consistent with results from the Kenyan study if the critical HI dilution titre is 8.

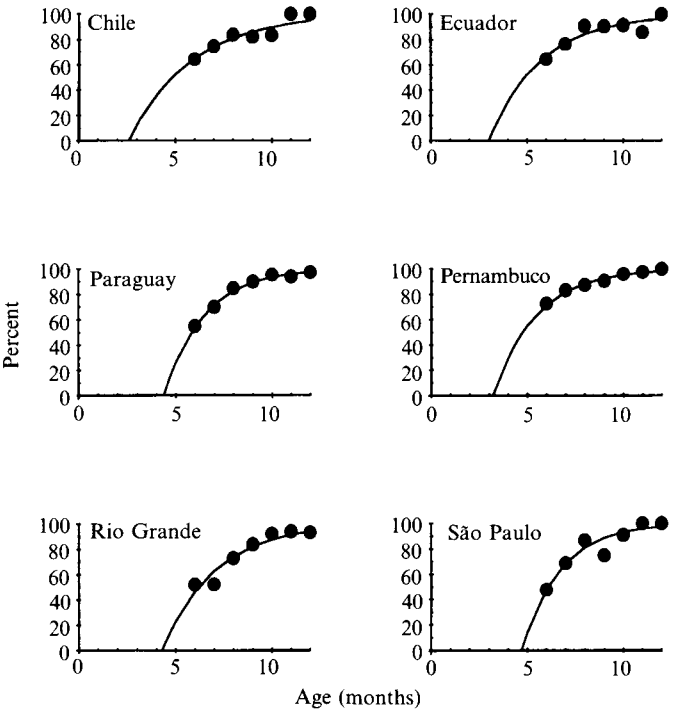


Fig. 4. Seroconversion rates as a function of age for six sites in Latin America. The fitted lines are delayed exponentials and the coefficients of the fits are given in Table 3.

Table 3. *Parameters for the fit of delayed exponentials to the data in Figure 4*

| Location | Delay (months) | S.D. (months) | Decay rate (month$^{-1}$) | S.D. (months$^{-1}$) | Corr. coeff. | Half-life (months) | S.D. (months) |
|---|---|---|---|---|---|---|---|
| Chile | 2·58 | 1·77 | 0·31 | 0·12 | 0·973 | 2·26 | 0·89 |
| Ecuador | 3·01 | 1·33 | 0·37 | 0·11 | 0·944 | 1·86 | 0·54 |
| Paraguay | 4·37 | 0·50 | 0·49 | 0·08 | 0·891 | 1·43 | 0·25 |
| Pernambuco | 3·22 | 0·90 | 0·45 | 0·10 | 0·942 | 1·53 | 0·32 |
| Rio Grande | 4·29 | 0·44 | 0·36 | 0·05 | 0·884 | 1·91 | 0·28 |
| São Paulo | 4·70 | 0·51 | 0·51 | 0·12 | 0·906 | 1·37 | 0·32 |
| Wtd mean | 4·24 | 0·26 | 0·43 | 0·04 | | 1·60 | 0·14 |

*Seroconversion rates*

The Ministries of Health [23] for a number of Latin American countries have provided age-specific seroconversion rates following vaccination for six sites in Latin America. Figure 4 and Table 3 show the maximum likelihood fits [24] to their data using delayed exponentials. The delay varies from 2·5–5 months and the half-life of the maternal antibody is about 1·5–2 months. The weighted mean value ($\pm$S.E.) of the delay is $4{\cdot}24 \pm 0{\cdot}26$ months, of the decay rate is $0{\cdot}43 \pm 0{\cdot}04$/month and the mean half-life of the decay is $1{\cdot}60 \pm 0{\cdot}14$ months. None of the individual measurements differs significantly from the weighted mean values ($P > 0{\cdot}1$).

In a review of six studies comparing the response of infants 4–6 or 9–10 months of age to Edmonston–Zagreb (EZ) and Schwarz measles vaccines of varying titres, McLean and colleagues [25] fitted seroconversion rates to a delayed exponential model for both strains. For the EZ vaccine the delay is only 0·75 months while the decay rate is 0·433/month giving a half-life after the delay of 1·6 months. For the Schwarz vaccine the delay was about 3 months with a similar half-life after the delay.

In summary, the available evidence is that sero-conversion rates generally follow delayed exponentials with delays of between 2 and 4 months and half-lives for the decay of maternal antibody protection thereafter of between 1 and 2 months.

## CALCULATION OF OPTIMAL VACCINATION AGES

### *Single-dose strategy*

Figure 5 is a schematic diagram of the number of people that are immune as a function of age, either because of maternal antibody or vaccination. We are aiming to minimize the number of susceptibles in the population (minimize the area above the heavy line), assuming (i) that the proportion protected follows a delayed exponential, (ii) that human survivorship is Type-I, in which everyone lives to age $L$ and then dies, (iii) that protection by maternal antibody declines exponentially with age at a rate $\mu$ starting from 1 at age $D$ (where $D$ is the delay), and (iv) vaccine efficacy depends only on the presence of maternal antibody and not on genetic, nutritional, logistic or other factors. Children are vaccinated at age $\tau$. after the initial delay $D$, and the proportion that are vaccinated is $\nu$. We show in Appendix 2 that $\tilde{\tau}$, the optimal age for vaccination is then

$$\tilde{\tau} = M \ln\left(\frac{(L-\tilde{\tau})+M}{M}\right) \approx M \ln\left(\frac{L}{M}\right) \tag{2}$$

to which we must add the delay. In Equation 2, $M = 1/\mu$ and the half-life for the decay is $t_{1/2} = \ln(2)/\mu$. We note, from Equation 2, that the optimal vaccination age is independent of the vaccine coverage. Figure 6 shows that the way in which the optimal age of vaccination changes with the mean duration of maternal antibody and life expectancy. If maternal antibody decays with a half-life of 1 month the optimal age for vaccination is about 9 months plus the delay time giving an optimal age of 11–13 months. If antibody decays with a half-life of 2 months the corresponding ages are 17–19 months.

Having determined the optimal age for vaccination, we can now find the corresponding proportion susceptible, $\tilde{s}$, in the population and Appendix 2 shows that this is

$$\tilde{s} \approx \frac{\nu\tilde{\tau}}{L} + (1-\nu). \tag{3}$$

Note that the proportion of susceptibles, unlike the optimal vaccination age, will depend on the form of the entire curve from age 0 upwards, so that $\tilde{s}$ will be more sensitive than $\tilde{\tau}$ to the assumption that the maternal antibody decay can be represented by a delayed exponential.

Figure 7 shows the proportion susceptible as a function of the half-life of the

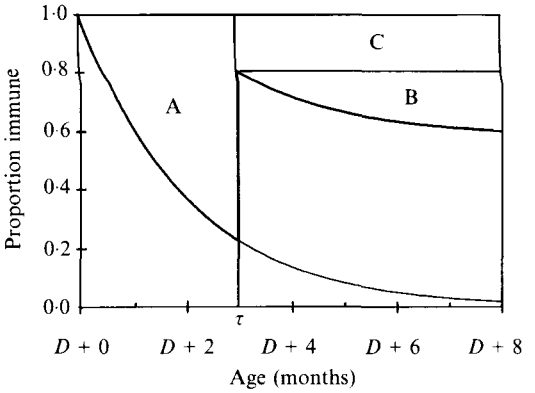


Fig. 5. Schematic diagram of the proportion of children that are immune as a function of age either due to maternal antibody or to vaccination. It is assumed that a proportion $\nu$ of people are vaccinated. $D$ is the age at which maternal antibody protection begins to wane. The vaccination age is $D+\tau$.

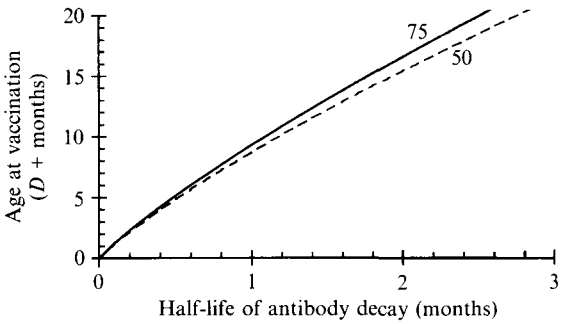


Fig. 6. Optimal age of vaccination as a function of mean duration of maternal antibody. Solid line $L = 75$ yr, dashed line $L = 50$ years. $D$ is the age at which maternal antibody protection begins to wane.

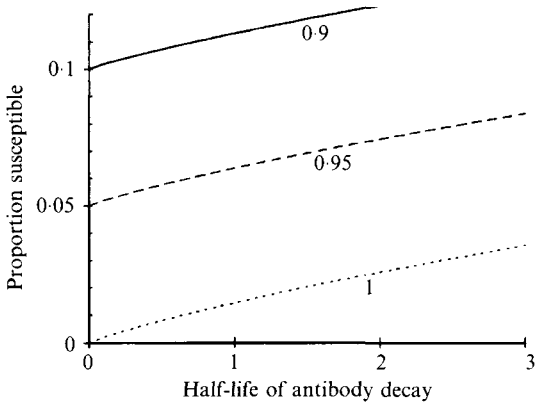


Fig. 7. Proportion susceptible as a function of the mean duration of maternal antibody. Vaccination coverage: solid line $\nu = 0{\cdot}9$, dashed line $\nu = 0{\cdot}95$, dotted line $\nu = 1$. Life expectancy = 50 years.

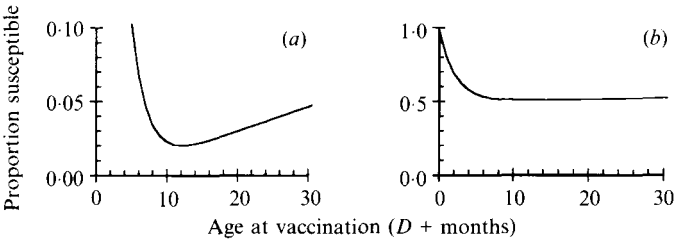


Fig. 8. Proportion of the population that are susceptible against age of vaccination. Half-life of antibody decay = 1·5 months, life-expectancy = 50 years. Vaccination coverage (*a*) $\nu = 1$, (*b*) $\nu = 0{\cdot}5$. $D$ is the age at which maternal antibody protection begins to wane.

decay of maternal antibody if vaccine is delivered at the optimal age. If the half-life is 2 months, say, then the proportion protected will be about 88% with 90% coverage: 95% protection requires about 97% coverage.

Figure 8 shows the asymmetrical effect of failing to vaccinate at the optimal age. With 100% coverage (Figure 8*a*), a half-life for maternal antibody decay of 1·5 months and a life-expectancy of 50 years, vaccinating at the optimal age of about $D+12$ months (where $D$ is the initial delay) leaves 2% of the population susceptible. Vaccinating as late as $D+30$ months only increases this to 4·6%, but vaccination before about $D+7$ months is highly undesirable because the proportion of susceptibles rises steeply. Qualitatively, the same result is obtained when coverage is lower (Figure 8*b*), though with lesser penalties for early or late vaccination.

All these results have been obtained assuming (Type-I survivorship). For Type-II survivorship, in which the mortality rate does not depend on age and the life expectancy is $L$, the results are the same to first order. This is to be expected since we are only concerned with what happens in the first 1 or 2 years of life. Over this time, Type-II survivorship gives a mortality that is still much less than the rate of loss of maternal antibody.

*Random two-dose strategy*

When individuals in a population are vaccinated more than once at random, we must distinguish between the different effects on coverage and efficacy. Coverage will be increased because some individuals will receive their first dose of vaccine at round two. Net efficacy will increase because some vaccine failures from round one (who had maternal antibody) will be protected at round two.

Figure 9, like Figure 5, is a schematic diagram of the proportion of immunes as a function of age under a random two-dose schedule. The easiest way to determine the effect of two doses is to calculate the additional number of people who are protected by the second round, the area marked $E$ in Figure 9. From Appendix 3, the reduction in the number of susceptibles due to the second vaccination is

$$Ls_2 = (\nu(1-e^{-\mu\tau_2}) - \nu^2(1-e^{-\mu\tau_1}))\,(L-\tau_2) \tag{4}$$

and the optimal ages for delivering the first ($\tau_1$) and second doses ($\tau_2$) are given by

$$e^{\mu\tau_1} = 1+\mu(L-\tau_1)-\mu\nu(L-\tau_2) \tag{5}$$

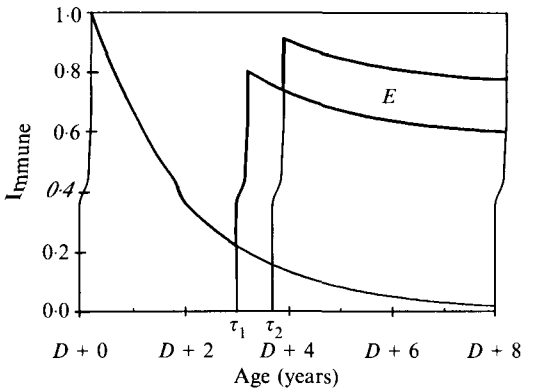


Fig. 9. The proportion of people that are immune as a function of age either due to maternal antibody or to vaccination. The vaccination ages are $D+\tau_1$ and $D+\tau_2$. The area marked $E$ indicates the additional proportion of people that are protected by the second round.

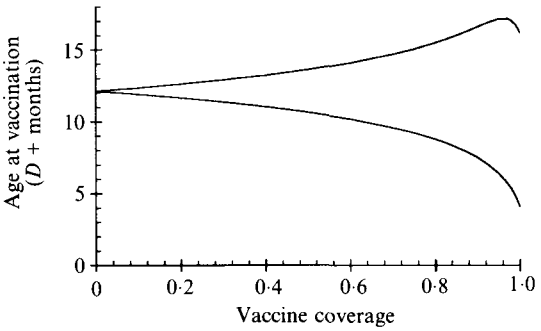


Fig. 10. Optimal ages for giving two vaccines against vaccine coverage. $L = 50$ years, half-life of maternal antibody decay = 1·5 months.

and

$$e^{\mu\tau_2}(1-\nu+\nu^2 e^{-\mu\tau_1}) = 1+\mu(L-\tau_2). \quad (6)$$

Figure 10 sketches these optimal ages, revealing that a split schedule is worth adopting only when coverage is high. At low vaccine coverage most of the susceptibles are children who have not been vaccinated, rather than vaccine failures. The emphasis is on increasing coverage by vaccinating more children, at the single optimal age. As coverage increases, there is more to be gained by adopting a split schedule: at 100% coverage, the optimal ages are $D+4$ and $D+16$ months, whereas the optimal age for one dose was $D+12$ months (Fig. 8).

The reason why it is worth vaccinating at two ages when coverage is high can be found in Figure 11. Figure 11*a* shows a comparison of one- and two-dose schedules if the half-life of the maternal antibody is 1·5 months. (Note that this comparison is independent of the delay.) With 90% random coverage on each of two occasions, and hence different net coverage under the two schedules, the proportion susceptible is reduced from about 12% for one dose to 2·5% for two

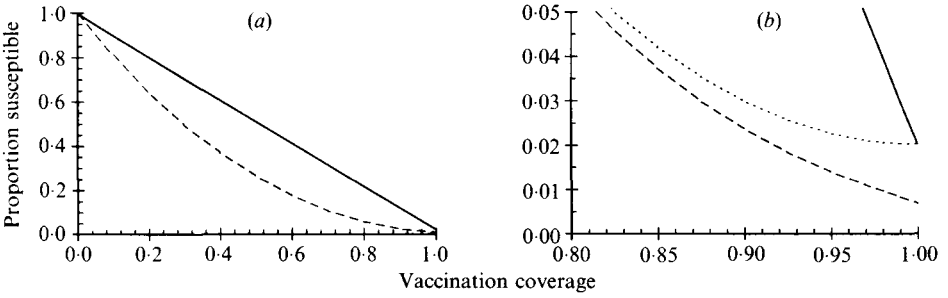


Fig. 11. Proportion susceptible as a function of vaccination coverage. The mean duration of maternal antibody is 1·5 months, the life-expectancy is 50 years. The solid line gives the proportion remaining susceptible for a one-dose schedule, the dashed line the proportion remaining susceptible for a two-dose schedule with random coverage. In (*b*) the right hand part of (*a*) is plotted on an expanded scale. The dotted line is for a one-dose schedule but at a coverage corresponding to the effective coverage for a two-dose schedule.

doses. From Figure 11*b*, it is clear that most of this improvement is due to the increase in effective coverage (compare dotted and solid lines), rather than to the increase in net efficacy (compare broken lines). In other words, we might as well improve coverage, where possible, with a single dose. This is true except when coverage approaches 100%, in which case we are concerned primarily with increasing efficacy, and hence with administering a second dose to those in whom vaccine failed at round one.

It should be noted (Equation 52, Appendix 3) that if the age at which the first dose is given is fixed, the second dose should be given at $M \ln (L/M)$ months later, provided the vaccination coverage is high. For $M = 1/\mu \approx 2$ months and $L \approx 50$ years, the second dose should be given about 1 year after the first. Babad and colleagues [11] consider two-dose schedules with the first dose given in the second year of life and the second dose given in either the fourth or eleventh year. They conclude that it is better to give the second dose at the younger age, in agreement with the results presented here although our results indicate that a spacing of 1 year would be better than a spacing of 2 years.

*Systematic two-dose strategy*

Under a completely systematic two-dose strategy, there is no gain from extra coverage, only from extra efficacy: children either receive two doses or none. The small advantage to be gained from giving two doses systematically, according to our model, is illustrated again by the difference between the two broken lines in Figure 11*b*.

## DISCUSSION

Many measles epidemiologists would guess that, post-elimination in developed countries, a single dose of vaccine should be given during the second year of life. The incorrect assumption behind the guess is that maternal antibody is non-existent by year two. Here we have obtained the expected result with a model

which reflects the best available data in assuming that antibody decays at a constant rate after a time delay following birth. We have also shown that, when the optimum cannot be met, it will be better to err on the side of late rather than early vaccination. This may be relevant when children cannot be vaccinated within a narrow age range, as is the case when immunization is carried out infrequently by mobile teams.

In developing countries, where transmission is high and vaccination is currently focused on infants, our results support intuition in suggesting that vaccine should eventually be delivered in year two. However, those considering the switch should be aware of the hazard of doing so prematurely: the simulation results of McLean and Anderson [10] show how switching to older age groups before elimination can lead to an increase in measles incidence rather than a decrease.

According to our model, the benefits of giving two doses of vaccine randomly at different ages arise mostly from the increased effective coverage, over a wide range of coverage, rather than from increased efficacy. Coverage can be increased, in principle, simply by improving a one-dose schedule, but we need to ask whether there are circumstances, in practice, under which coverage can be more effectively increased with two doses. Data for districts in Wales suggest that if a second dose of MMR vaccine were offered at the time of the DT booster (age 4 years), there would be an uptake of less than one third by those who had not previously received MMR vaccine [11]. Periodic mass vaccination across a wide age range, timed according to results from serological screening, may be preferable if this leads to higher participation rates by previously unvaccinated people. More information is needed on the implementation of two-dose strategies and mass campaigns to determine attendance at the second age of opportunity among children who did and did not receive the first dose.

Currently, two-dose strategies are promoted as a means of immunizing children who did not respond to the first dose of vaccine (primary vaccine failures) [26] and we agree, in principle, that this should be their primary purpose. High levels of coverage (approaching 100%) indicate that the delivery problem has essentially been solved, and the major concern is to improve on efficacy. Given a half-life of maternal antibody of 1·5 years, we find that the maximum benefit is to reduce the proportion remaining susceptible from 2% to about 0·7%, independent of the delay. In the absence of precise information on the herd immunity threshold required to prevent measles outbreaks, we cannot say whether this marginal benefit has any public health importance.

The estimated reduction in the proportion of the population remaining susceptible under a two-dose schedule is lower than commonly assumed. Based on epidemiological evaluations of vaccine efficacy, measles vaccine has been assumed to be 90–95% effective when administered after 12 months of age [11], leading to a predicated 5–10% increase in the proportion immune of all individuals revaccinated. However, not all studies evaluated efficacy by precise age at vaccination, and those that did so found that the efficacy was lower when administered at 12–14 months than 15 months or above [5]. In addition, the tendency to evaluate vaccine efficacy during outbreaks, which may represent exceptional situations, leads to potential biases that underestimate efficacy [27]. Furthermore, epidemiological studies do not distinguish between primary and

secondary vaccine failures. Thus the 'true' efficacy when vaccine is administered at the optimal age is difficult to determine from published studies, but is probably greater than 95%.

One should also consider the possible benefits of boosting antibody under a two-dose strategy. Most children who respond to measles vaccination will have long-term or lifelong immunity, although studies have documented measles among some who seroconverted after vaccination (secondary vaccine failures; [28, 29]). Revaccination of persons in whom antibody has waned to low or undetectable levels appears to offer only transient benefit. In a large fraction of such persons, although antibody levels boost after revaccination, they subsequently fall to previous levels [30, 31]. Therefore, administering a second dose to children who responded to the first dose appears unlikely to affect the proportion of susceptibles in the population in the longer term.

At the heart of our analysis is a quantitative description of the way in which vaccine immunogenicity changes with age. Although this comes from a reappraisal of the most comprehensive published data on maternal antibody decline and seroconversion rates, many of these data pertain to the pre-vaccine era and maternal antibody is likely to be lost at progressively earlier ages as we enter an era when most mothers have vaccine-acquired immunity that is less and less likely to be boosted by exposure to wild virus. In our model, the optimum age for administration of a single dose of vaccine varied from around 12–18 months, according to whether a half-life of 1 or 2 months was assumed. However, the qualitative results obtained with our model are independent of the absolute half-life.

In conclusion, the results of this formal analysis largely conform with current belief. A single dose of vaccine is best given during the second year of life in areas where there is little or no measles transmission. The main reason, in principle, for giving two doses at different ages is to improve on efficacy rather than coverage but, with measles vaccine, the question of efficacy predominates only when coverage approaches 100%.

## APPENDIX 1

We wish to fit normal distributions to the data given in Figure 1. Because the HI test is insensitive to low antibody levels, we can determine the cumulative distributions but not the frequency distributions and we have to fit these to cumulative normal distributions. In order to do this we start from the result given by Kendall and Stuart [32] for fitting data to order statistics.

Let $y_i$ be the $i$-th order statistic so that if $y_i$ is the ln (HI titre), $i$ is the number of children whose ln (HI titre) is less than $y$. We wish to fit the data to a normal distribution with mean $\mu$ and variance $\sigma^2$. Then we let

$$\hat{z}_i = (y_i - \mu)/\sigma \quad i = 1, 2, \ldots, n \tag{7}$$

and define the following parameters:

$$E(\hat{\mathbf{z}}) = \mathbf{z} \tag{8}$$

$$V(\mathbf{z}) = \mathbf{V}. \tag{9}$$

In the large number approximation the order statistics are normally distributed so that [32]

$$z_i = F^{-1}\left(\frac{i}{n}\right), \tag{10}$$

where $F^{-1}$ is the inverse standard normal cumulative distribution function. and

$$V_{i,j} = \frac{i}{n}\left(1-\frac{j}{n}\right)\Big/ nf(x)^2,\ i<j \tag{11}$$

where $f$ is the standard normal probability density function. Defining

$$\Delta = \{(\mathbf{1}'\mathbf{V}^{-1}\mathbf{1})(\mathbf{z}'\mathbf{V}^{-1}\mathbf{z})-(\mathbf{1}'\mathbf{V}^{-1}\mathbf{z})^2\}, \tag{12}$$

it follows (32) that

$$\hat{\mu} = -\hat{\mathbf{z}}\mathbf{V}^{-1}(\mathbf{1}\hat{\mathbf{z}}-\hat{\mathbf{z}}\mathbf{1}')\mathbf{V}^{-1}\mathbf{y}/\Delta \tag{13}$$

$$\hat{\sigma} = 1'\mathbf{V}^{-1}(\mathbf{1}\mathbf{z}'-\mathbf{z}'\mathbf{1}')\mathbf{V}^{-1}\mathbf{y}/\Delta \tag{14}$$

$$V(\hat{\mu}) = \sigma^2\mathbf{z}'\mathbf{V}^{-1}\mathbf{z}'/\Delta \tag{15}$$

$$V(\hat{\sigma}) = \sigma^2 1'\mathbf{V}^{-1}1/\Delta \tag{16}$$

$$Cov(\hat{\sigma},\hat{\mu}) = -\sigma^2 1'\mathbf{V}^{-1}\mathbf{z}/\Delta. \tag{17}$$

In the particular case of order statistics the covariance matrix has the following structure (illustrating the result for four points):

$$\mathbf{V} = \begin{pmatrix} a_1b_1 & a_1b_2 & a_1b_3 & a_1b_4 \\ a_1b_2 & a_2b_2 & a_2b_3 & a_2b_4 \\ a_1b_3 & a_2b_3 & a_3b_3 & a_3b_4 \\ a_1b_4 & a_2b_4 & a_3b_4 & a_4b_4 \end{pmatrix}, \tag{18}$$

where

$$a_i = \frac{i}{n}\Big/\sqrt{nf(x)} \tag{19}$$

$$b_i = \left(1-\frac{i}{n}\right)\Big/\sqrt{nf(x)}. \tag{20}$$

The matrix V can be inverted analytically to obtain $\mathbf{U} = \mathbf{V}^{-1}$. $\mathbf{U}$ is tridiagonal so that we may write

$$\mathbf{U} = \mathbf{V}^{-1} = \begin{pmatrix} \alpha_1 & \beta_1 & 0 & 0 \\ \beta_1 & \alpha_2 & \beta_2 & 0 \\ 0 & \beta_2 & \alpha_3 & \beta_3 \\ 0 & 0 & \beta_3 & \alpha_4 \end{pmatrix}, \tag{21}$$

and it is straightforward to show that

$$\alpha_n = \frac{b_{n-1}a_{n+1}-a_{n-1}b_{n+1}}{(b_{n-1}a_n-a_{n-1}b_n)(b_n a_{n+1}-a_n b_{n+1})}. \tag{22}$$

and

$$\beta_n = \frac{-1}{(b_n a_{n+1} - a_n b_{n+1})}. \tag{23}$$

(Note that in these two equations we set $b_0 = 1$ and $a_0 = 0$.) We can now evaluate the various matrix combinations in Equations 13–17 analytically. First of all

$$\mathbf{Uy} = \begin{pmatrix} \alpha_1 & \beta_1 & . & . \\ \beta_1 & \alpha_2 & \beta_2 & . \\ . & \beta_2 & \alpha_3 & \beta_3 \\ . & . & \beta_3 & \alpha_4 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{pmatrix} = \begin{pmatrix} \alpha_1 y_1 + \beta_1 y_2 \\ \beta_1 y_1 + \alpha_2 y_2 + \beta_2 y_3 \\ \beta_2 y_2 + \alpha_3 y_3 + \beta_3 y_4 \\ \beta_3 y_3 + \alpha_4 y_4 \end{pmatrix} \tag{24}$$

so that

$$h_2 \equiv \mathbf{z'Uy} = \Sigma\, \alpha_i z_i y_i + \beta_i (z_i y_{i+1} + z_{i+1} y_i) \tag{25}$$

from which it follows that

$$k_1 \equiv \mathbf{1'U1} = \Sigma\, (\alpha_i + 2\beta_i) \tag{26}$$

$$k_2 \equiv \mathbf{1'Uz} = \Sigma\, (\alpha_i z_i + \beta_i (z_i + z_{i+1})) \tag{27}$$

$$\mathbf{z'U1} = (\mathbf{1'Uz})' = k_2 \tag{28}$$

$$k_3 \equiv \mathbf{z'Uz} = \Sigma\, \alpha_i z_i^2 + 2\beta_i z_i z_{i+1} \tag{29}$$

$$h_1 \equiv \mathbf{1'Uy} = \Sigma\, (\alpha_i y_i + \beta_i (y_i + y_{i+1})), \tag{30}$$

where the sums on $\alpha_i$ are from $i = 1$ to $n$ and on $\beta_i$ from $i = 1$ to $n-1$. Finally, we get the required analytical solutions for the parameter values:

$$\Delta = k_1 k_3 - k_2^2 \tag{31}$$

$$\hat{\mu} = \frac{k_3 h_1 - k_2 h_2}{k_1 k_3 - k_2^2} \tag{32}$$

$$\hat{\sigma} = \frac{k_1 h_2 - k_2 h_1}{k_1 k_3 - k_2^2} \tag{33}$$

$$V(\mu) = \sigma^2 k_3 / \Delta \tag{34}$$

$$V(\sigma) = \sigma^2 k_1 / \Delta \tag{35}$$

$$Cov\,(\mu, \sigma) = -\sigma^2 k_2 / \Delta. \tag{36}$$

Unfortunately, the large number approximations break down when the numbers are small. Numerical simulations show, however, that good parameter estimates may be obtained, even for small numbers, if we replace Equations 10 and 11 by

$$z_r = F^{-1}\left(\frac{3r-1}{3n+1}\right) \tag{37}$$

and

$$V_{r,s} = \frac{3r-1}{3n+1}\left(1 - \frac{3s-1}{3n+1}\right) \Big/ (nf(x)^2) \tag{38}$$

so that Equations 19 and 20 become

$$a_i = \frac{3i-1}{3n+1}\Big/\sqrt{nf(x)} \tag{39}$$

$$b_i = \left(1-\frac{3i-1}{3n+1}\right)\Big/\sqrt{nf(x)}. \tag{40}$$

To test Equations 39 and 40, a series of simulations were carried out in which 4, 8, 16, 32, 64 or 128 points were chosen from a pseudo-random normal distribution. For each of these between 2 and the total number of points were then chosen from the cumulative distribution function and used to calculate the mean and standard deviation of the distribution. Estimates of the mean never differed significantly from zero and were unbiased. Estimates of the scale parameter, $\sigma$, were biased but the bias was always less than 1·5% of the true value and less than 12% of the estimate of the standard error in the parameter.

Although these expressions seem complicated they are straightforward to implement. First of all calculate $z_i$, $a_i$ and $b_i$ using Equations 37, 39 and 40 with $F^{-1}$ the inverse standard normal cumulative distribution function and $f$ the standard normal probability density function. Then calculate $\alpha_i$ and $\beta_i$ using Equations 22 and 23 and the $h$s and $k$s using Equations 25–30. Equations 31–36 then give the co-efficients and their variances.

## APPENDIX 2

For a one-dose schedule the number of susceptibles is equal to the area above the line in Figure 1 where

$$\mathrm{A} = \int_0^{\tau}(1-\mathrm{e}^{-\mu t})\,dt, \quad \mathrm{B} = \mathrm{e}^{-\mu\tau}\int_0^{L-\tau}(1-\mathrm{e}^{-\mu t})\,dt, \quad \mathrm{C} = (1-\nu)(1-\mathrm{e}^{-\mu\tau})(L-\tau) \tag{41}$$

so that the number of susceptibles is

$$\begin{aligned} Ls &= \int_0^{\tau}(1-\mathrm{e}^{-\mu t})\,dt + \mathrm{e}^{-\mu\tau}\int_0^{L-\tau}(1-\mathrm{e}^{-\mu t})\,dt + (1-\nu)(1-\mathrm{e}^{-\mu\tau})(L-\tau) \\ &= \nu\tau + L(1-\nu) - \frac{1}{\mu} + \mathrm{e}^{-\mu\tau}\left(\frac{1}{\mu}\mathrm{e}^{-\mu(L-\tau)} + (L-\tau)\nu\right). \end{aligned} \tag{42}$$

We shall see that $\tau \approx 12$ months, $\mu \approx 0{\cdot}5$ months$^{-1}$, $L \approx 25$–$75$ years, $\mathrm{e}^{-\mu L} \approx 10^{-11}$, so that

$$Ls \approx \nu\tau + L(1-\nu) - \frac{1}{\mu} + (L-\tau)\nu\,\mathrm{e}^{-\mu\tau}. \tag{43}$$

From Equation 43

$$L\frac{ds}{dt} = \nu(1-\mathrm{e}^{-\mu\tau}(1+\mu(L-\tau))). \tag{44}$$

Setting $L\,ds/dt = 0$ gives $\tilde{\tau}$, the age at vaccination for which the number of susceptibles in the population is a minimum, $\tilde{s}$:

$$e^{\mu\tilde{\tau}} = \mu(L-\tilde{\tau})+1 \approx \mu(L-\tilde{\tau}) \tag{45}$$

$$\tilde{\tau} \approx M \ln\left(\frac{L}{M}\right), \tag{46}$$

where $M = 1/\mu$ is the mean life-time of maternal antibody. When $\tau = \tilde{\tau}$

$$L\tilde{s} \approx \nu\tilde{\tau} + L(1-\nu) - M(1-\nu) \tag{47}$$

so that the minimum number of susceptibles is

$$\tilde{s} \approx \frac{\nu\tilde{\tau}}{L} + (1-\nu). \tag{48}$$

Note that as $\nu \to 0$ we need to keep the last term in Equation 47 and $\tilde{s} \to 1 - M/L$. If the vaccine coverage is 1, then the minimum number of susceptibles is simply the age at vaccination divided by the mean life expectancy.

## APPENDIX 3

The decrease in the number of susceptibles as a result of giving the second dose, the area marked $E$ in Figure 10, is

$$Ls_2 = (\nu(1-e^{-\mu\tau_2}) - \nu^2(1-e^{-\mu\tau_1}))(L-\tau_2) \tag{49}$$

and the derivative with respect to $\tau_2$ gives the optimal time for giving the second dose as

$$e^{\mu\tau_2}(1-\nu+\nu^2 e^{-\mu\tau_1}) = 1+\mu(L-\tau_2) \tag{50}$$

so that if vaccine coverage is 1,

$$e^{\mu(\tau_2-\tau_1)} = 1+\mu(L-\tau_2) \tag{51}$$

and

$$\tau_2 \approx \tau_1 + M \ln\left(\frac{L}{M}\right) \tag{52}$$

the same result as for one dose but with the time at which the first dose is administered added on to the time at which the second dose is administered.

If the vaccine coverage is very low, $\nu \to 0$ and

$$e^{\mu\tau_2} = 1+\mu(L-\tau_2) \tag{53}$$

so that the second dose should be given at the time at which a single dose would be given.

The optimal time for giving the first dose is obtained by differentiating with respect to $\tau_1$ from which

$$e^{\mu\tau_1} = 1+\mu(L-\tau_1) - \mu\nu(L-\tau_2) \tag{54}$$

so that if $\nu = 1$,

$$e^{\mu\tau_1} = 1+\mu(\tau_2-\tau_1) \tag{55}$$

as expected since once the second dose is fixed the first dose problem is the same as the one dose problem with $L$ replaced by $\tau_2$. As $\nu \to 0$

$$e^{\mu\tau_1} = 1 + \mu(L - \tau_1) \tag{56}$$

so that the first dose, like the second dose, should be given at the time at which a single dose would have been given. In other words, assuming random coverage, if the vaccine coverage is low, the only thing that one can do is to increase it. Only when the vaccine coverage is reasonably high is it worth splitting the ages.

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