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Measles in developing countries. Part II. The predicted impact of mass vaccination

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SUMMARY

A mathematical model is developed to mimic the transmission dynamics of the measles virus in communities in the developing world with high population growth rates and high case fatality rates. The model is used to compare the impacts of different mass vaccination programmes upon morbidity and mortality arising from infection by measles virus. Analyses identify three conclusions of practical significance to the design of optimal vaccination programmes. First, there is no single optimum age at which to vaccinate children for all urban and rural communities in developing countries. For a given community the best age at which to vaccinate depends critically on the age distribution of cases of infection prior to the introduction of control measures. Second, numerical studies predict that the introduction of mass vaccination will induce a temporary phase of very low incidence of infection before the system settles to a new pattern of recurrent epidemics. Mass vaccination acts to lengthen the inter-epidemic period in the post-vaccination period when compared with that prevailing prior to control. Third, numerical simulations suggest that two-phase and two-stage vaccination programmes are of less benefit than one-stage programmes (achieving comparable coverage) aimed at young children. The paper ends with a discussion of the needs for: improved programmes of data collection; monitoring of the impact of current vaccination programmes; and the development of models that take account of viral transmission dynamics, host demography and economic factors.

INTRODUCTION

The design of vaccination programmes against measles in developing countries poses a range of practical and conceptual problems. Some of these are related to the rapid rate of acquisition of infection in young children as reflected in age stratified sero-epidemiological studies of antibody to measles virus antigens (Walsh, 1983; McLean & Anderson, 1987). One of the central practical problems is what is the optimal age to vaccinate children in order to have the maximum impact on the incidence of measles related morbidity and mortality for a given rate of vaccination coverage.

Mathematical models that accurately mirror the transmission dynamics of the measles virus can help to resolve such problems by providing a framework within which to explore the potential impact of different types of vaccination programmes. They have been extensively used to explore the problems of control

of viral and bacterial childhood infections in developed countries (e.g. Anderson & May, 1985*a*, *b*; Anderson & Grenfell, 1985; Grenfell & Anderson, 1985; Schenzle, 1984). However, a number of the assumptions embodied in these models do not hold for infectious disease transmission in developing countries. Specifically, most of the models assume that case fatalities are negligible and that the population is of fixed size (although subject to the recruitment and loss of individuals). In developing countries measles case fatalities are often of great significance in the child age classes. In addition the high birth rate of many communities in the developing world, have a significant impact on the overall rate of virus transmission (May & Anderson, 1985; McLean, 1986) via their influence on the rate of replenishment of susceptibles in the population.

In a previous paper we discussed these problems and reviewed the available data on the epidemiology of measles in the developing world and the significance of demographic patterns for viral transmission. We also attempted to estimate the key epidemiological parameters that determine observed trends in the incidence of measles and discussed the interrelationships between these parameters (McLean & Anderson, 1987). In this paper we build on these analyses and explore the impacts of various vaccination programmes by means of a mathematical model of viral transmission and the demography of the human community. The principal aims of this research are to improve understanding of the impact of mass vaccination in high birth rate communities and to determine the optimal way in which to design mass vaccination programmes with respect to vaccination coverage and the age at which vaccine is administered.

METHODS

The model that is investigated consists of a set of five partial differential equations describing the rates at which individuals of age a progress through five different states through time t. The five states are: protected by maternally derived antibodies ($M(a,t)$), susceptible ($X(a,t)$), infected but not yet infectious ($H(a,t)$), infectious ($Y(a,t)$) and recovered and immune ($Z(a,t)$). We make the simplifying assumption that infants progress from the protected state (in which vaccination always fails) straight into the susceptible state (in which vaccination is always successful). The model follows standard lines (see McLean, 1986; Anderson & May, 1985*a*) and is as follows:

$$\frac{\partial M}{\partial a}+\frac{\partial M}{\partial t}=-(\mu(a)+\delta)\,M(a,t), \tag{1}$$

$$\frac{\partial X}{\partial a}+\frac{\partial X}{\partial t}=\delta M(a,t)-(\mu(a)+\lambda(a,t))\,X(a,t), \tag{2}$$

$$\frac{\partial H}{\partial a}+\frac{\partial H}{\partial t}=\lambda(a,t)\,X(a,t)-(\mu(a)+\sigma)\,H(a,t), \tag{3}$$

$$\frac{\partial Y}{\partial a}+\frac{\partial Y}{\partial t}=\sigma H(a,t)-(\mu(a)+\alpha(a)+\gamma)\,Y(a,t), \tag{4}$$

$$\frac{\partial Z}{\partial a}+\frac{\partial Z}{\partial t}=\gamma Y(a,t)-\mu(a)\,Z(a,t). \tag{5}$$

The boundary conditions for M, X, H, Y and Z are as follows:

$$M(0,t) = \int_0^\infty m(a)N(a,t)\,da, \tag{6}$$

$$X(0,t) = H(0,t) = Y(0,t) = Z(0,t) = 0,$$

where $N(a,t)$ denotes the total population of age a at time t, and $m(a)$ is the age specific, per capita fertility rate. So equation 6 states that all newborns are protected by maternal antibody. Once a vaccination programme has been running for some time, some young women will reach child-bearing age whilst still susceptible, and their children would clearly be born into the susceptible class. In the following numerical analyses we only consider events in the 16 years following the introduction of mass vaccination, so do not include this extra complication. Initial conditions are defined as described below. The interpretation of the model's parameters is as follows. δ is the rate of decay of maternal antibody protection (so $1/\delta$ is the average duration of protection) and $\mu(a)$ is the age-dependent background death rate which (being independent of status with regard to infection) applies equally to every class. $\lambda(a,t)$ is the per capita rate at which susceptibles become infected and is described in detail in equation (7). $1/\sigma$ and $1/(\gamma+\alpha)$ are, respectively, the average duration of the latent period and the average duration of infectiousness. $\alpha(a)$ is the disease-related death rate whose relationship to the case fatality is described in a previous paper (McLean & Anderson, 1987). Briefly the relationship is that if f is the proportion of cases that are fatal, α is the rate (per unit time) at which infectious people die from measles and $1/(\gamma+\alpha)$ is the average duration of infectiousness, $f = \alpha/(\alpha+\gamma)$. The age dependent force of infection $\lambda(a,t)$ is defined as follows:

$$\lambda(a,t) = \frac{\int_0^\infty \beta(a,a')\,Y(a',t)\,da'}{\int_0^\infty N(a',t)\,da'}. \tag{7}$$

The function $\beta(a,a')$ determines the importance attributed to the number of infectious people in age class a' when determining the per capita force of infection for susceptibles of age a. The functional form of β is restricted to being a two dimensional step function, i.e. a function that can be represented by a matrix of constants. This matrix is called the 'who acquires infection from whom' (WAIFW) matrix (Anderson & May, 1985*a*). This form of function is used because the elements of the matrix it defines can (under defined assumptions) be calculated from data on the age prevalence of infection (see Schenzle, 1984; Anderson & May, 1985*a*; Grenfell & Anderson, 1985).

This model differs from other age-structured models of the transmission dynamics of childhood infectious diseases in three respects. First, the removal of infectious individuals at per capita rate $\alpha(a)$ represents measles case fatalities – a phenomenon that most published models ignore. Second the number of newborns is calculated as a function of total population size (eqn 6). In most past work the number of newborns entering the system is fixed at a constant which exactly matches losses from the system through deaths. The lifting of this restriction allows the investigation of the impact of population growth on viral

transmission. The third difference is the inclusion of total population in the denominator of the definition of the force of infection (eqn 7). This represents the assumption that the per capita force of infection is not affected by population growth. This assumption is difficult to test as to do so requires long term data on age-prevalence of infection from communities whose population growth has been carefully monitored. For developing countries such information does not exist. The consequences of relaxing this assumption have been discussed elsewhere (McLean, 1987).

All parameter values of the model are estimated from published epidemiological and demographic data relating to developing countries. Methods of estimation are described in the first of this pair of papers (McLean & Anderson, 1987).

Using a step length of 3 days, Euler's method is used to solve the equations 1–5 along the characteristic lines $t = a + \text{constant}$ (Burden *et al.* 1978). The initial conditions are set by:

(i) solving the ordinary differential equations obtained by dropping time derivatives (i.e. setting $\partial M/\partial t = \partial X/\partial t = \ldots = \partial Z/\partial t = 0$);

(ii) transforming these solutions so that they conform to the stable age distribution determined by the age-specific birth and death rates, and then;

(iii) perturbing the whole system by shifting 20% of the susceptible class into the immune class. The perturbation allows the investigation of the dynamics of the system as it returns to equiiibrium. A range of different sized perturbations (from 10 to 40%) have been investigated, the only difference between them being the size of the initial epidemic.

The initial conditions are calculated using the age-dependent forces of infection that are defined by a given parameter set. After the equilibrium solutions have been found (i), and transformed so as to conform to the requisite stable age distribution (ii), the elements of the WAIFW matrix are calculated using the method described by Anderson & May (1985*a*). After the WAIFW matrix has been calculated, it is used to calculate the forces of infection at all subsequent time steps. This is achieved with the use of equation (7), given a knowledge of the number of cases by age at the previous time step. The population size is initially set at 200000 in all numerical studies.

These numerical calculations produce five large two-dimensional arrays describing the numbers of people in each model compartment by age, through time. We present summaries of the quantitative information in these arrays as figures showing total cases through time, age-stratified serology at a given time, age distribution of cases at a given time or total mortality from infection over a number of years.

RESULTS

We present four sets of results concerning the predicted impact of different types of mass vaccination programmes against measles in developing countries. The first of these compares the impact of vaccination programmes targeted at different age groups. The second describes a long period of low incidence that immediately follows the initiation of a mass vaccination programme – we term this low incidence phase the 'honeymoon period'. The third set of results consider the impact of programmes which start with one target age group and then switch

to another, these we call '*two-phase*' policies. The final set considers the impact of vaccination at two different ages, one in early and one in late childhood; we denote this a '*two-stage*' policy. The population-specific parameters used in these numerical studies are based on demographic statistics that reflect a population with high fertility rates and a high rate of population growth.

(1) *The optimum age at which to vaccinate*

The impact of vaccination programmes that target different age groups are compared using parameter sets based on serological profiles drawn from two different communities. The serological profiles are illustrated in Fig. 1. Two different serological profiles have been chosen to illustrate different patterns of measles transmission in the developing world. The first serological profile, (Fig. 1*a*) is from a community with rapid loss of passive immunity and a young average age at infection. This serological profile gives a good illustration of the window problem at its worst with 100% of 2-year olds, seropositive. The sera were collected in Dakar, Senegal in 1957 (Boue, 1964). (In this parameter set the mean duration of protection by maternal antibodies is set at 3 months and a set of age specific forces of infection, estimated from the serological profile, is used which predict a mean age at infection of 1·09 years.) The second serological profile (Fig. 1*b*) is from a community where the duration of protection by maternal antibodies is longer (perhaps because of better nutrition) and the average age at infection is older, hence the window problem is less severe. These sera were collected in Bangkok, Thailand in 1967 (Ueda *et al.* 1967). (In this parameter set the mean duration of protection by maternal antibodies is set at 6 months and a set of age-specific forces of infection, estimated from the serological profile, is used which predict a mean age at infection of 3·20 years.) In the following explanations we refer to the parameter set based on Fig. 1(*a*) as the Dakar parameter set, and the other as the Bangkok parameter set.

Figure 2(*a*) shows the predicted total number of cases under four different regimens of vaccination using the Dakar parameter set. In each case 50% of each cohort are vaccinated, but the age at which vaccine is administered is varied. A measles vaccine uptake rate of 50% is now being achieved by a number of developing countries (EPI, 1987). The youngest age at which vaccine is administered is 3 months and the oldest age is 1 year. The greatest reduction in morbidity (as reflected by the longitudinal trend in cases of infection) is predicted to occur when the vaccination campaign is targeted at those aged 6–9 months. At younger than 6 months too much vaccine is wasted on individuals still protected by maternal antibody, and at older than 9 months too many children have already experienced measles. The Bangkok parameter set, representing a lower rate of transmission prior to control and a longer duration of maternally derived protection (see Fig. 1*b*), gives rise to different predictions as illustrated in Fig. 2(*b*). The combination of long lasting protection from maternal antibodies, and a relatively low risk of infection at a young age make vaccination at age 1 year 6 months the best choice for reducing the number of cases and also for the reduction of mortality arising from infection. A summary of the impact of vaccination at different ages on mortality is presented in Fig. 3. All vaccination programmes act to reduce total mortality but the age distribution of disease induced deaths can be

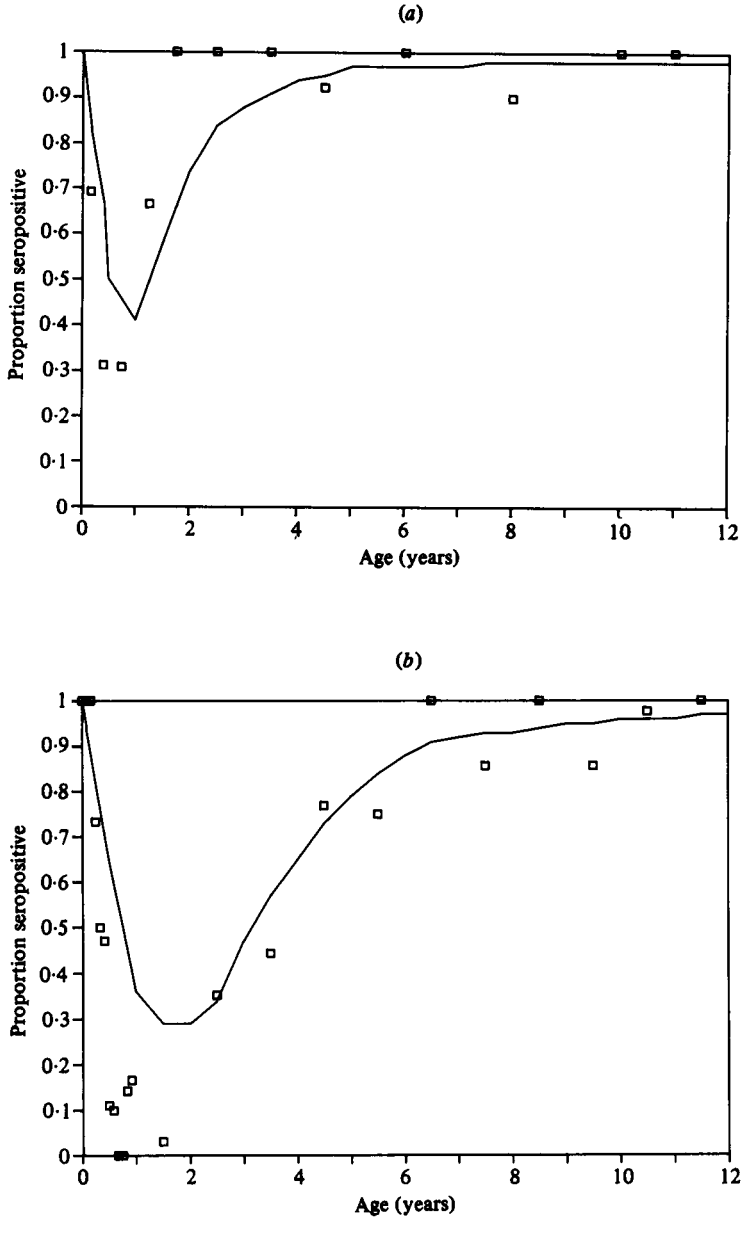


Fig. 1. Serological profiles used in finding optimal ages at vaccination. The figures show raw data (□) and (—) typical serological profiles from model solutions. (a) Serology drawn in Dakar, Senegal in 1957 (Boue, 1964). (b) Serology drawn from Bangkok, Thailand in 1967 (Ueda *et al.* 1967).

changed. The best results are obtained by vaccinating between 6 and 9 months for a community with very high transmission and rapid decay of maternally derived protection (Fig. 3*a*) and at around 1·5 years of age in a community with a lower transmission rate and longer maternally derived protection (Fig. 3*b*). The principal conclusion to emerge from these numerical studies is that the optimum

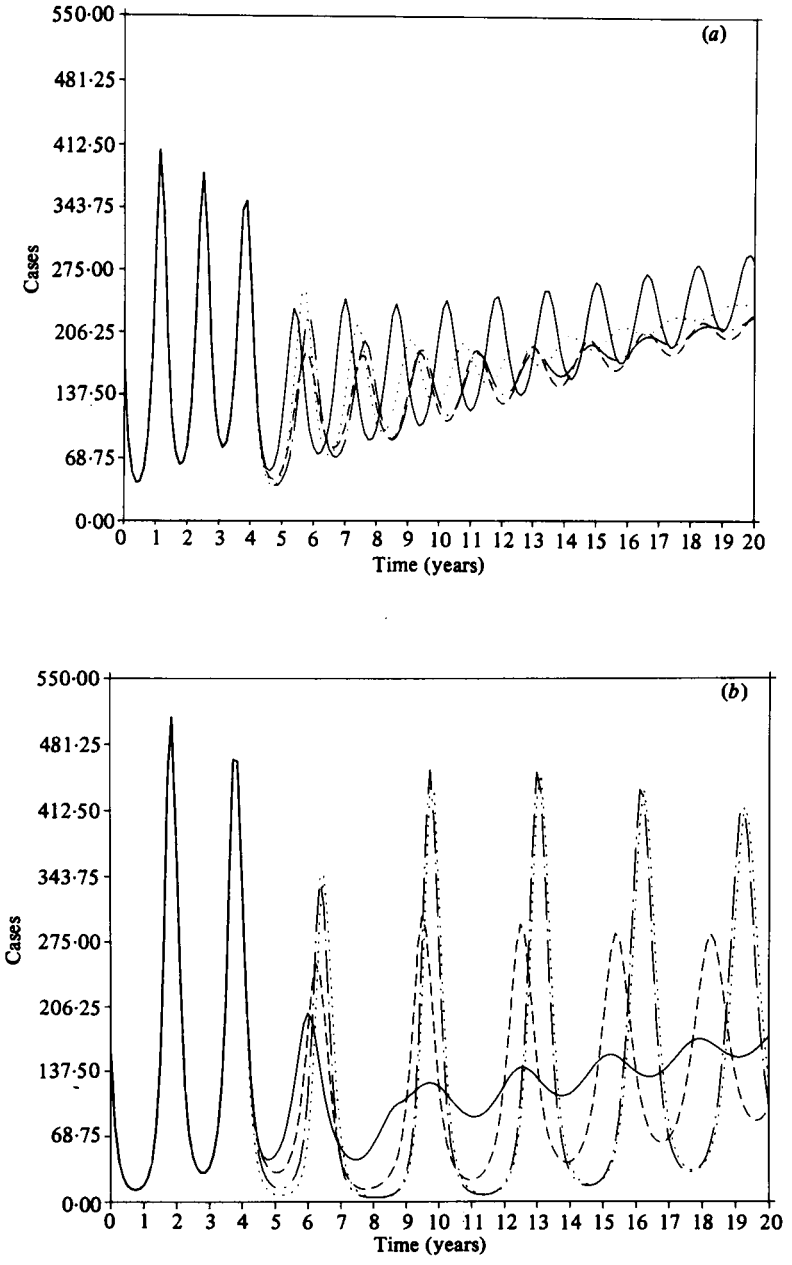


Fig. 2. Optimal age at vaccination in different communities: morbidity. These figures illustrate the predicted impact on morbidity of vaccination programmes targeted at different age groups. In (*a*), based on the Dakar parameter set (Boue, 1964), four regimens of vaccination are compared with target 3-month-old (—), 6-month-olds (- - - -), 9-month-olds (— — —) and 1-year-olds (· · · · · · · · ·). In (*b*), based on the Bangkok parameter set (i.e. older average age at infection) (Ueda *et al.* 1967), the four regimens compared with 1 year 3 months old, 1 year 6 months old, 1 year 9 months old and 2 years old. All vaccination campaigns achieve coverage of 50% of their target age group.

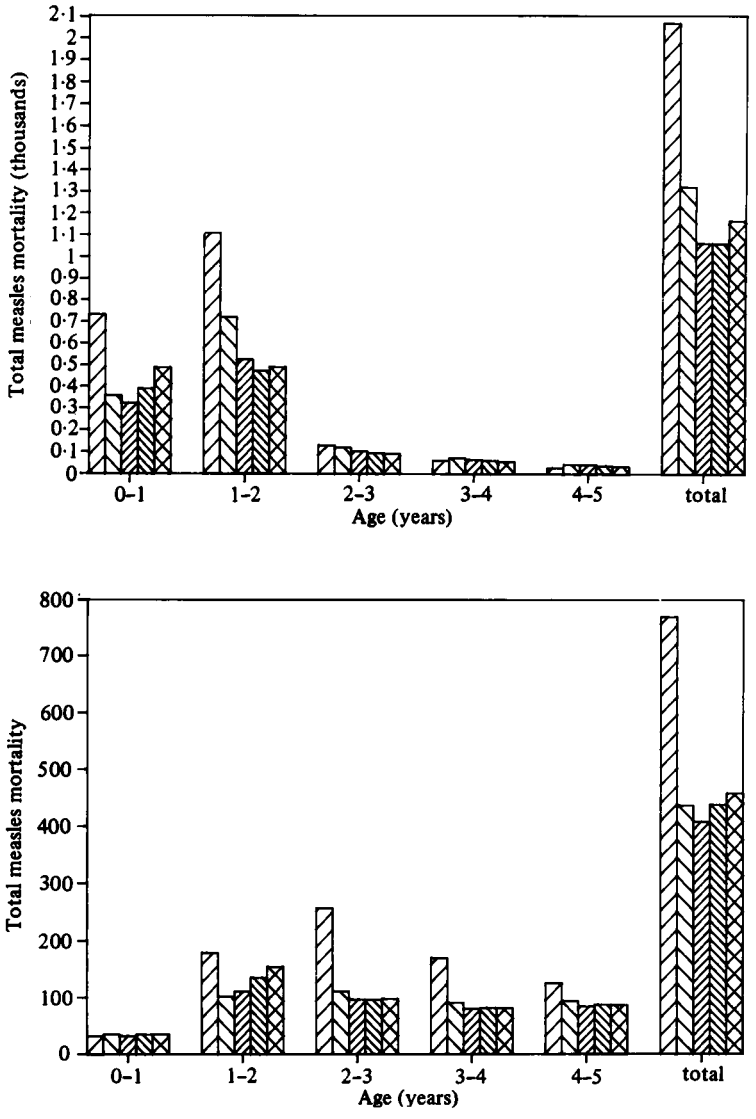


Fig. 3. Optimal age at vaccination in different communities. Mortality over 10 years in the post-vaccination era by age group and totalled across all age groups. (a) Predicted mortality in a community with very high disease transmission (Boue, 1964). The five possibilities compared are; no vaccination (▨), and the four vaccination regimens discussed in Fig. 2*a*, i.e. vaccination of 50% age 3 months (▧), 6 months (▩), 9 months (■) and 1 year (⊠). (b) Predicted mortality in a community with lower disease transmission rates (Ueda *et al.* 1967). The possibilities compared are: no vaccination (▨) and 50% coverage of four target age groups; 1 year 3 months old (▧), 1 year 6 months old (▩), 1 year 9 months old (■), and 2 years old (⊠).

age at which to immunize is is critically dependent on the age distribution of cases prior to the introduction of mass vaccination.

(2) *Temporal trends in incidence following the introduction of vaccination: the 'honeymoon period'*

In this, and all the following results sections numerical studies are based upon the Dakar parameter set which well illustrates the window problem. Figure 4(*a*) compares the predicted temporal trends in measles cases in three communities subjected to different levels of vaccination and a community with no control. It illustrates the predicted pattern of the incidence of infection immediately following the introduction of a mass vaccination programme. In particular, it highlights the extension of the inter-epidemic period following the introduction of control measures. In order to understand these predictions it is necessary to refer to the concept of herd immunity. Theoretical and empirical studies suggest that there is a threshold density of susceptible people in a defined population below which viral transmission cannot be maintained (Anderson & May, 1982; Fine & Clarkson, 1982). When the force of infection depends upon the age of susceptible individuals this threshold is formed from the sum of the susceptible population in each age class, weighted by age. In the absence of vaccination the susceptible population oscillates about this threshold (as a consequence of epidemics of measles) with an age distribution determined by the rate of loss of protection by maternal antibody and the age-dependent forces of infection. After the introduction of mass vaccination the susceptible population oscillates about an equilibrium determined by the rate of loss of protection by maternal antibody, the forces of infection and the age-specific vaccination regimen. The weighted sum of this post-vaccination susceptible population is the same as the weighted sum of the pre-vaccination susceptible population, but the age distribution that generates the sum is different. The period of low incidence after the introduction of control, the 'honeymoon period', is generated during the shift from the pre-vaccination to the post-vaccination age distribution of susceptibles. A clearer picture of this change is provided in Fig. 4(*b*) in which the predicted age and time dependent pattern of the proportion susceptible in the population is shown over a period of time which includes the introduction of mass vaccination. The figure illustrates events following the introduction of a campaign with 50% coverage, with lower or higher coverage rates the picture would be qualitatively the same, but, as shown in Fig. 4(*a*), the higher the coverage rate, the longer it will take for the susceptible pool to rebuild to its critical size. A gradual introduction of the vaccination programme, where small proportions are immunized in the early years, would lessen the magnitude of the perturbation to the age distribution of the susceptible population. The rapid and widespread introduction of vaccination against measles that has been spurred by the WHO's Expanded Programme for Immunization should induce a period of low incidence following the introduction of control similar to that recorded in Fig. 4(*a*). The important practical point to note is that a dramatic short-term reduction in measles incidence after the start of mass vaccination is not an accurate reflection of the longer term impact of the control programme. After the initial period of very low incidence, the system will settle to a higher level of incidence with an inter-epidemic period slightly

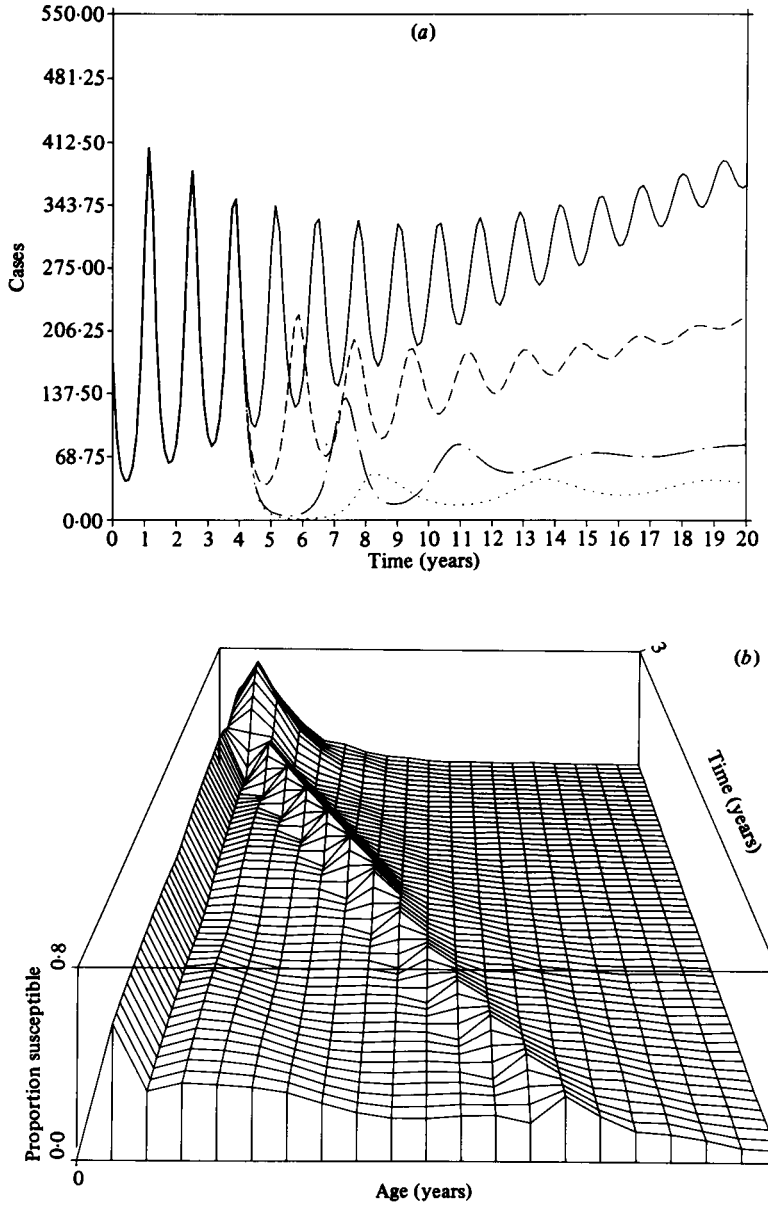


Fig. 4. The 'honeymoon period'. (a) Total cases through time for three different levels of vaccination and no vaccination. (—) no vaccination; (----), 50%; (– – –) 75%; (·····) 80%. All vaccination regimens target 9-month-old susceptibles and are introduced at time 4 years. (b) The shift in the age distribution of the susceptible population that follows the introduction of mass vaccination, illustrated here in a figure showing the changing age distribution of the susceptible population of a community over the course of 7 years. At time 4 years, vaccination of 50% of 9 month olds is introduced.

longer than that pertaining prior to control. As illustrated in Fig. 4(*a*) the degree to which the inter-epidemic period is increased over that pertaining prior to control depends upon the level of vaccination coverage. The impact of mass vaccination on the inter-epidemic period has been discussed in previous publications (Anderson & May, 1982, 1985*a*; McLean, 1986, 1987).

(3) *Two-phase vaccination policies*

One of the central problems in the design of vaccination programmes in developing countries is to achieve high rates of seroconversion by vaccination at an age at which the greatest proportion of children have neither maternal antibodies nor antibodies acquired through natural infection (i.e. the 'window problem', McLean & Anderson, 1987). It has been suggested (Black, 1982) that the window problem might be overcome by adopting a two-phase vaccination programme in which vaccination is initially targeted at very young children, and then after a few years switched to older age classes. The rationale behind this suggestion is that the initial phase of mass vaccination at an early age will raise the average age at infection and hence widen the window of susceptibility over which children can be successfully immunized. Once the age window is increased, the programme can be targeted at older children all of whom have lost their maternally derived protection. A clear example of the impact of mass vaccination in altering the age distribution of cases of measles is given in Fig. 5.

In this section we examine the efficacy of this approach via numerical solution of the model of viral transmission under the impact of a two-phase programme. In the first of a series of simulations we compare the outcome of an unchanging one-stage strategy targeted at 9-month-old infants and reaching 75% of them, with strategies with the same levels of coverage that switch 2 years after the introduction of immunization to either 1-year-old or 1·5-year-old children (Fig. 6). The high coverage rate of 75% was used in these studies because higher coverage rates have a greater chance of success with a two-phase programme (because of their greater impact on post-vaccination age distributions of case) and 75% is a coverage rate that some developing countries are already achieving (EPI, 1987). Interestingly, our predictions suggest that neither of the two-phase options result in any improvement over the unchanging, one-stage strategy. In fact both led to substantially greater levels of morbidity and mortality. An inspection of the predicted age distribution of cases *after* the two-phase programmes have been implemented (Fig. 7) shows that there are substantial numbers of cases in those below the second target age for vaccination in both the two-phase programmes. Extensive numerical studies, employing longer time periods between the switch from one phase to the second, higher levels of vaccination coverage or different age groups for the targeting of the two phases lead us to believe that this conclusion is very robust to changes in practical details. In illustration of this point, Fig. 8 records a selection of these numerical simulations in which the details of the implementation of the two-phase programmes are altered. In every case the unchanging strategy achieves lower total numbers of cases.

Our conclusion is that contrary to Black's suggestion (Black, 1982), two-phase programmes do not offer any improvement over one-stage programmes that achieve the same overall level of vaccination coverage. In essence, the notion that

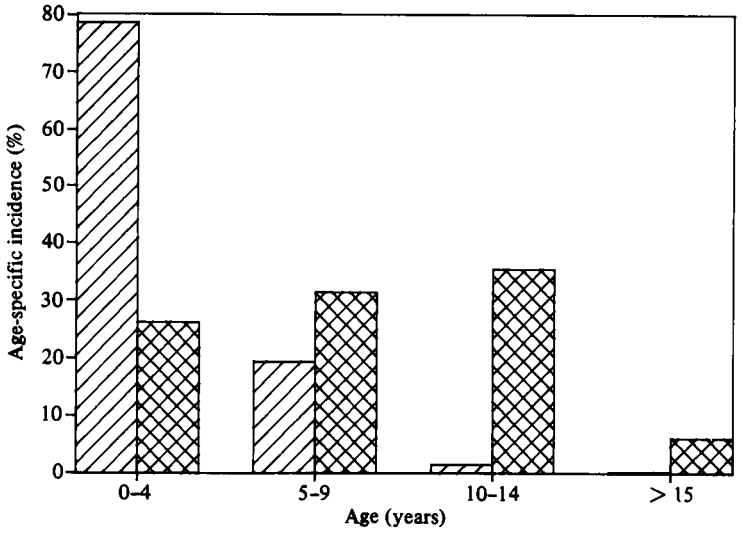


Fig. 5. Change in age distribution following vaccination. ▨, Age distribution of cases before vaccination. ⊠, Age distribution of cases after vaccination. Data are from China (Yihao & Wannian, 1983).

two-phase vaccination programmes might work arises because after several years of low levels of vaccination the age-incidence of infection profile will begin to resemble that observed in developed countries in the pre-vaccine era. Thus, one might argue, regimens of vaccination like those in developed countries (i.e. targeted at 1–2 year olds) should produce similar benefits to those observed in industralized societies. A schematic representation of these ideas is given in Fig. 9 which compares schematic curves showing cumulative cases by age for an industrialized country before vaccination and a developing country before and after vaccination. The shape of the 'after' curve in the developing country is very similar to the shape of the 'before' curve in the industrialized country. This leads to the idea that a vaccination strategy that is appropriate in a developed country, will eventually also be appropriate in a developing country. However, the patterns of age prevalence observed in developed countries are a consequence of low intrinsic rates of transmission and low birth rates. In contrast, in developing countries after several years of vaccination the patterns of age prevalence are a consequence of the artificial reduction of the susceptible pool by immunization. As soon as immunization is shifted towards older age group and the susceptible pool is once more allowed to surpass its critical level, epidemics occur, and reach the youngest, unprotected children just as they did in the pre-vaccination era. A clear picture of this chain of events is given in Fig. 7 where the age distribution of cases predicted by the model are recorded through time for a one-stage programme and the two two-phase programme.

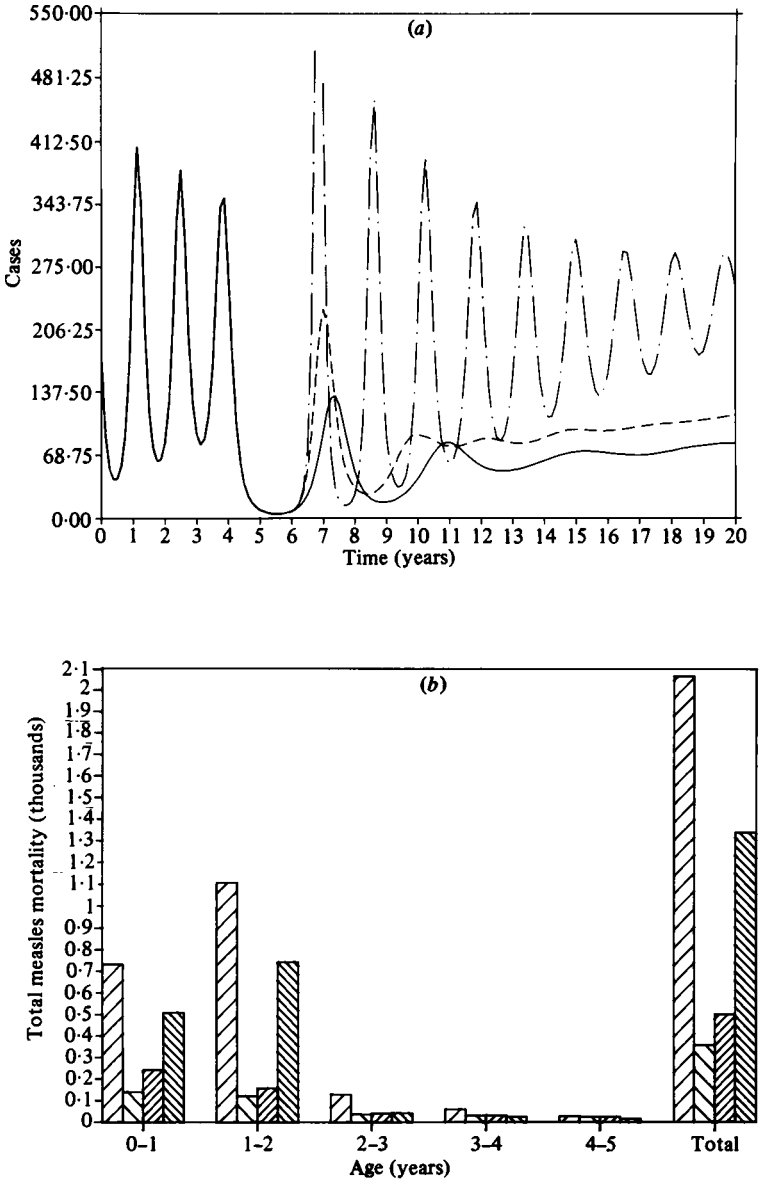


Fig. 6. Failure of two-phase policies. (a) Total cases through time for: (—) an unchanging policy reaching 75% of 9-month-old susceptibles; (-----) a two-phase policy which after vaccinating 75% of 9 month olds for 2 years, switches to target 1 year olds; and (– – –) a two-phase policy which after vaccinating 75% of 9 month olds for 2 years, swtiches to target 1·5 year olds. Both two-phase policies lead to an increase in morbidity when compared with the unchanging policy. (b) Comparing total mortality for years 10–20 for an unvaccinated community (▨), and the same three regimens of vaccination; (▧), one-stage, (▩), two-phase (2nd target age 1 year) and (■), two-phase (2nd target age 1·5 years). The graph shows that the one-stage policy leads to the greatest reduction in mortality.

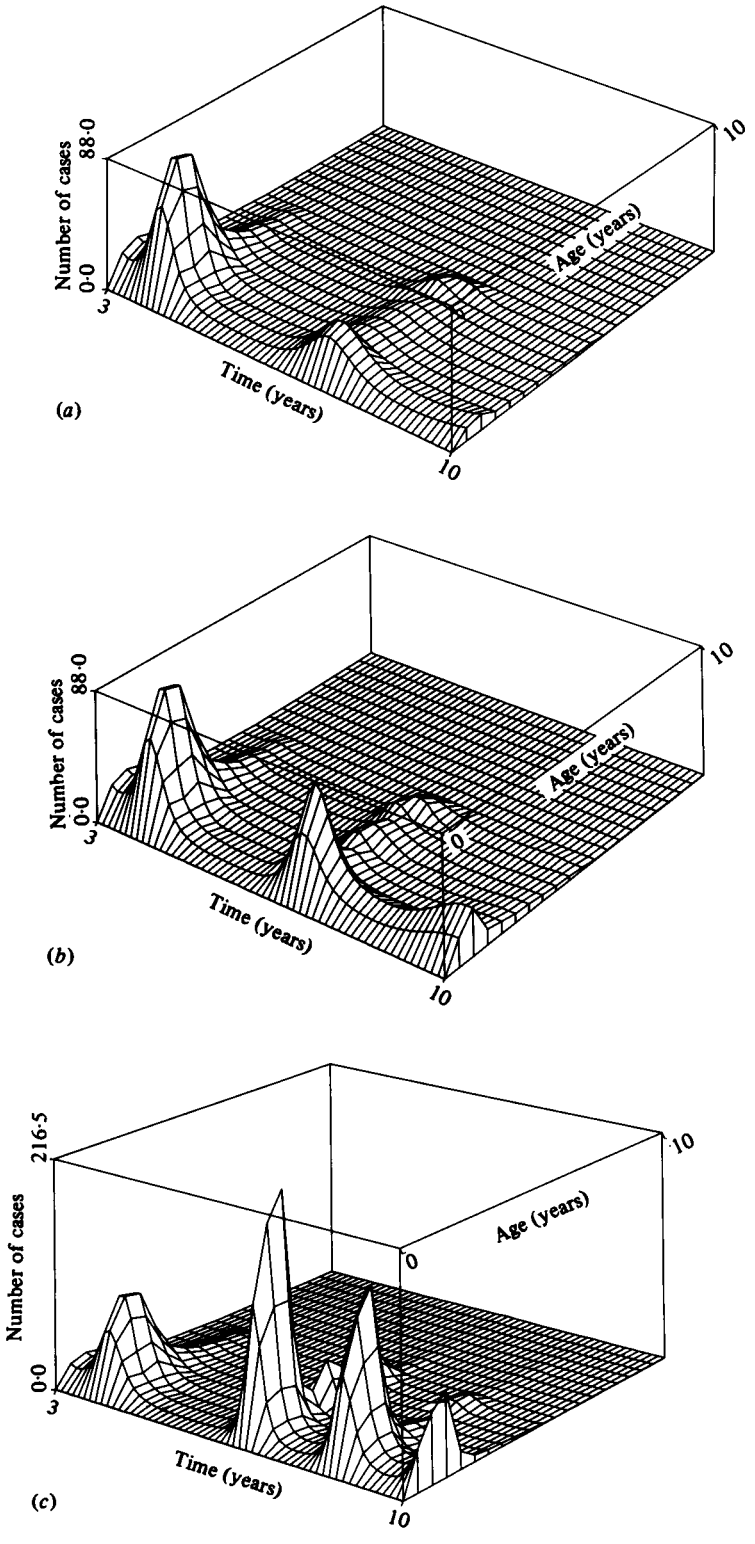


Fig. 7. For legend, see opposite

(4) *Two-stage vaccination programmes*

An alternative strategy to the outlined in the previous section, is to adopt two stages of vaccination targeted simultaneously at two different age classes. This type of approach has been adopted recently in Finland, where children are targeted for vaccination at 4–18 months of age and at 6 years of age (Peltola *et al.* 1986).

We investigate this approach in a similar manner to that described in the previous section, namely, via numerical simulation exploring different combinations of target ages for the two stages of this form of programme. We again compared predicted changes in measles incidence under different two-stage programmes with a one stage programme with the same overall coverage. Thus the one stage programme targets 75% of 9 months olds and the two-stage programmes target 50% of the youngest children and 50% of the remaining unvaccinated children at the older age giving a total coverage of 75%. Assuming that no child is vaccinated twice, these two regimens represent similiar commitments in terms of numbers of doses delivered. As illustrated in Fig. 10, we arrive at a similar conclusion to that described for the two-phase programmes detailed in the previous section. Extensive numerical simulations suggest that no advantage is to be gained by a two-stage programme. Indeed, in all cases examined the two-stage programmes resulted in an increase in morbidity (as measured by incidence – Fig. 10*a*) and mortality arising from infection – Fig. 10(*b*). The reasons underlying this observation are similar to those described above. Where transmission rates are high prior to the introduction of control (and the average age at infection is therefore low), the maximum benefit is obtained by high vaccination coverage in a one stage programme aimed at the narrow age window in which the proportion susceptible is at its greatest prior to the introduction of control.

CONCLUSION

Our numerical studies of the properties of a mathematical model of measles virus transmission in developing countries and the impact of different programmes of mass vaccination have identified three major results of practical significance, Before turning to these, however, we first reiterate the major demographic and epidemiological differences between developed and developing countries that are relevant to viral transmission and mass vaccination. These differences are summarized in Fig. 11. In brief, in developing countries birth, mortality, case fatality and disease transmission rates are all high by comparison with developed

Fig. 7. Age distribution of cases for one-stage and two-phase policies. Three-dimensional views of cases by age and time for the two-phase programmes as compared with an unchanging regime. (*a*) Unchanging regime reaching 75% of 9-month-old susceptibles. (*b*) At time $t = 4$ years, a regime reaching 75% of 9-month-old susceptibles is introduced, and at time $t = 6$ years, this is changed to 75% of 1-year-old susceptibles. (*c*) At time $t = 4$ years, a regime reaching 75% of 9-month-old susceptibles is introduced, and at time $t = 6$ years, this is changed to 75% of 1·5-year-old susceptibles.

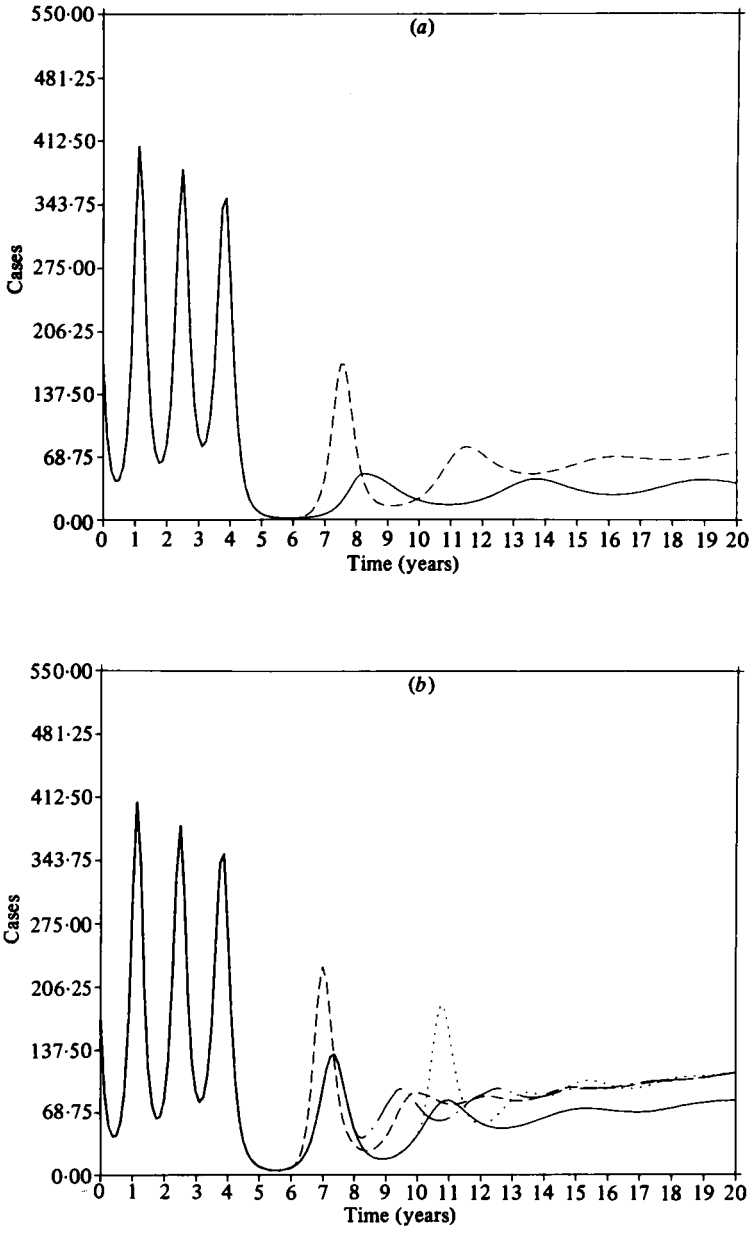
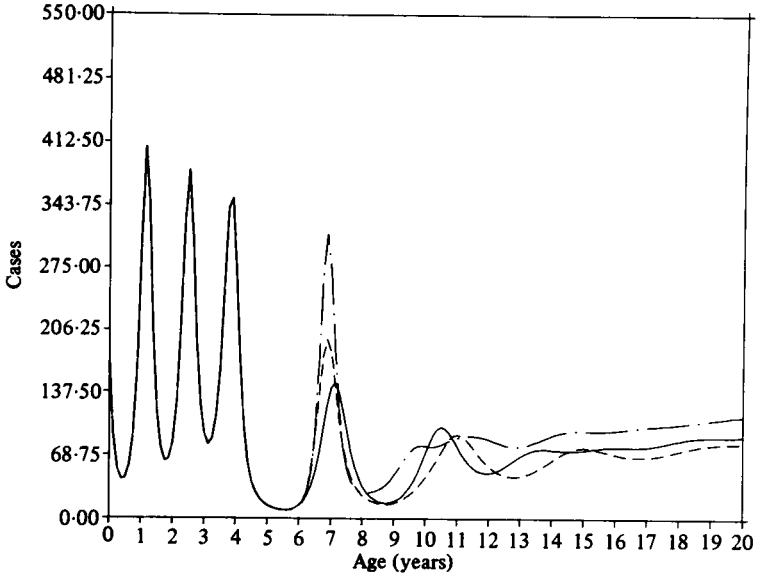
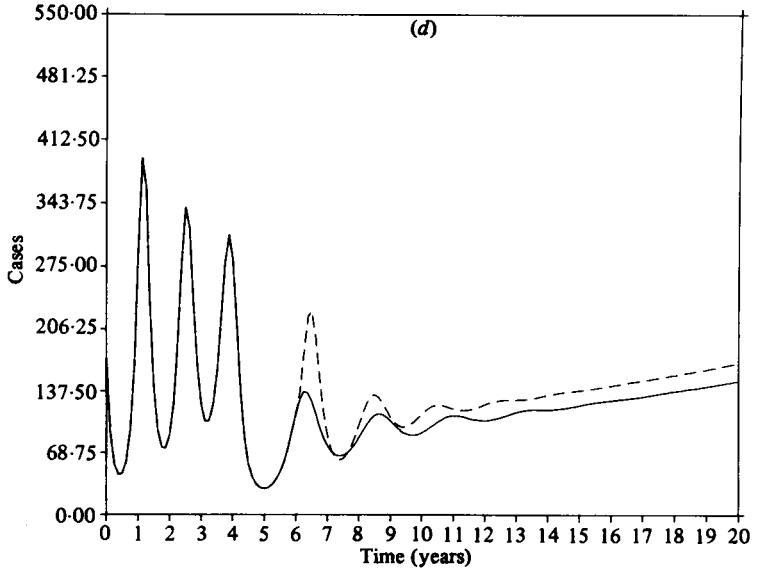


Fig. 8. Alternative two-phase policies. The failure of two-phase programmes is robust to changes in the vaccination regimens, coverage levels, and model assumptions regarding age-dependent mixing. (a) Higher levels of vaccination. Total cases through time for an unchanging strategy reaching 80% of 9-month-old susceptibles (—), compared with a two-phase policy which after vaccinating 80% of 9-month-old susceptibles for 2 years, switches to target 1 year olds (----). (b) Switch the strategy later. Total cases through time for an unchanging strategy reaching 75% if 9-month-old susceptibles (—), compared with three two-phase programmes that switch to target 1 year olds at times 6 years (----), 8 years (– – –), and 10 years (·····). (c) Initially target a younger age group. Total cases through time for an unchanging





strategy reaching 75% of 6-month-old susceptibles (—), compared with a two-phase policy which after vaccinating 75% of 6-month-old susceptibles for 2 years, switches to target 9 month olds (-----) and, a two-phase policy which after vaccinating 75% of 6-month-old susceptibles for 2 years, switches to target 1 year olds (– – –). (d) A homogenously mixing population. Total cases through time for an unchanging strategy reaching 75% of 9-month-old susceptibles (—), compared with a two-phase policy which after vaccinating 75% of 9-month-old susceptibles for 2 years, switches to target 1 year olds (- - -). The parameter set used assumes no age-dependent mixing, i.e. that the population mixes homogenously.

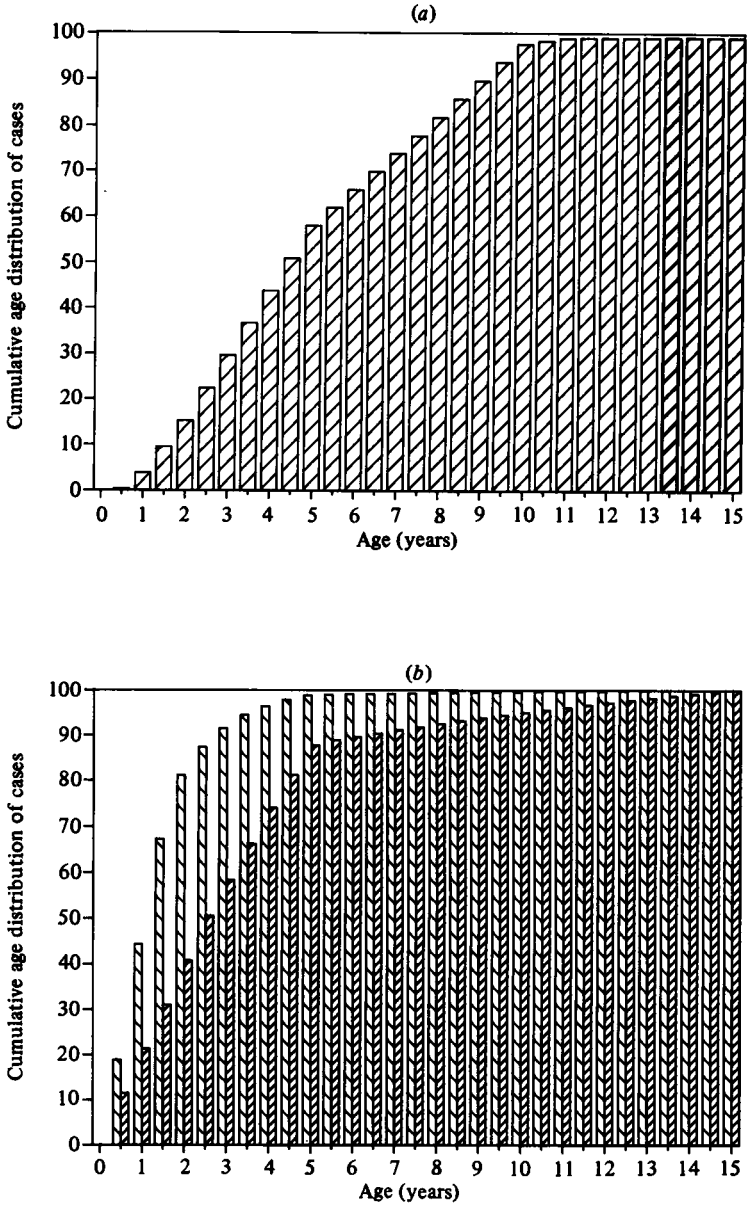


Fig. 9. Why two-phase programmes should work. (a) Schematic representation of the cumulative age distribution of cases in developed country *before* the introduction of mass vaccination. (b) Schematic representation of the cumulative age distribution of cases in a developing country before (▨), and after (■) the introduction of mass vaccination.

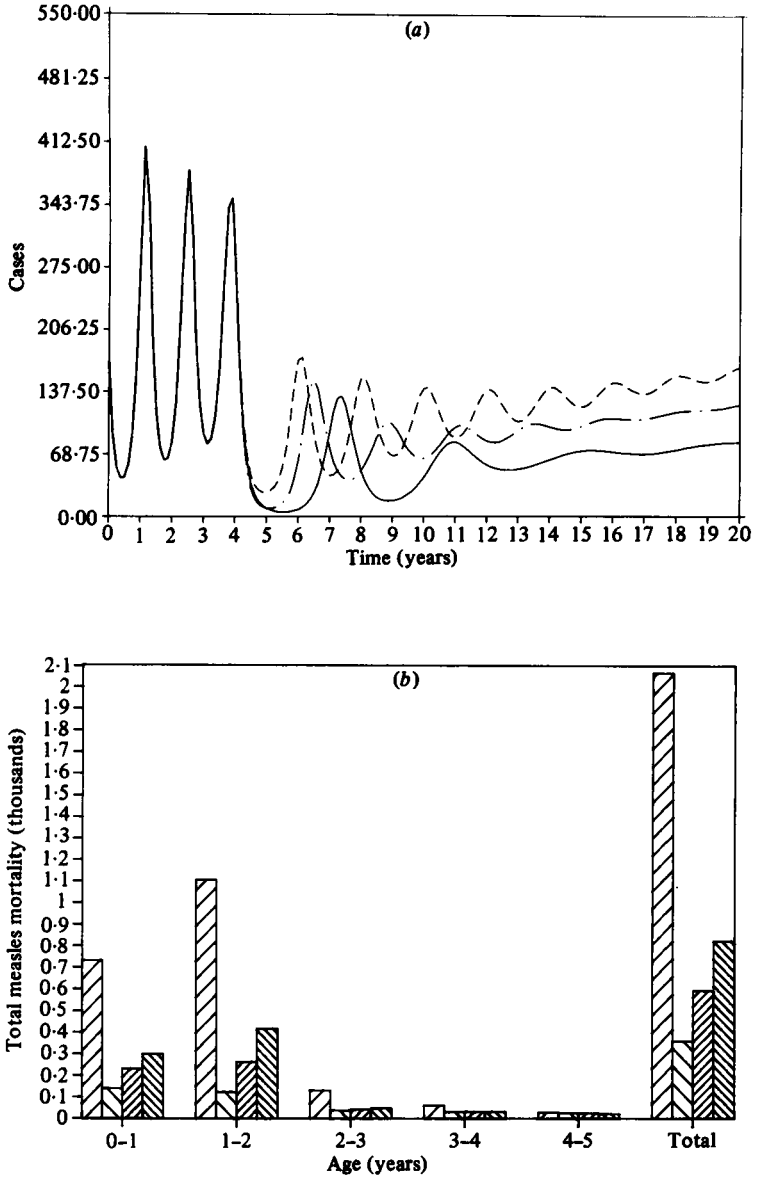


Fig. 10. Failure of two-stage policies. (a) Greater reductions in levels of incidence are achieved by one-stage programmes which vaccinate 75% of 9-month-old susceptibles (—) when compared with two two-stage programmes which vaccinate 50% of 9 month olds *and* 50% of; 1·5 year olds (----), 2 year olds (– – –). (b) Mortality over the 10-year time period $t = 10$ years to $t = 20$ years for an unvaccinated community (▨), a community subject to the one-stage vaccination programme described above (▧), and the two two-stage programmes with 2nd target age group 1·5 years (■), and 2 years (■) as in 10(a).

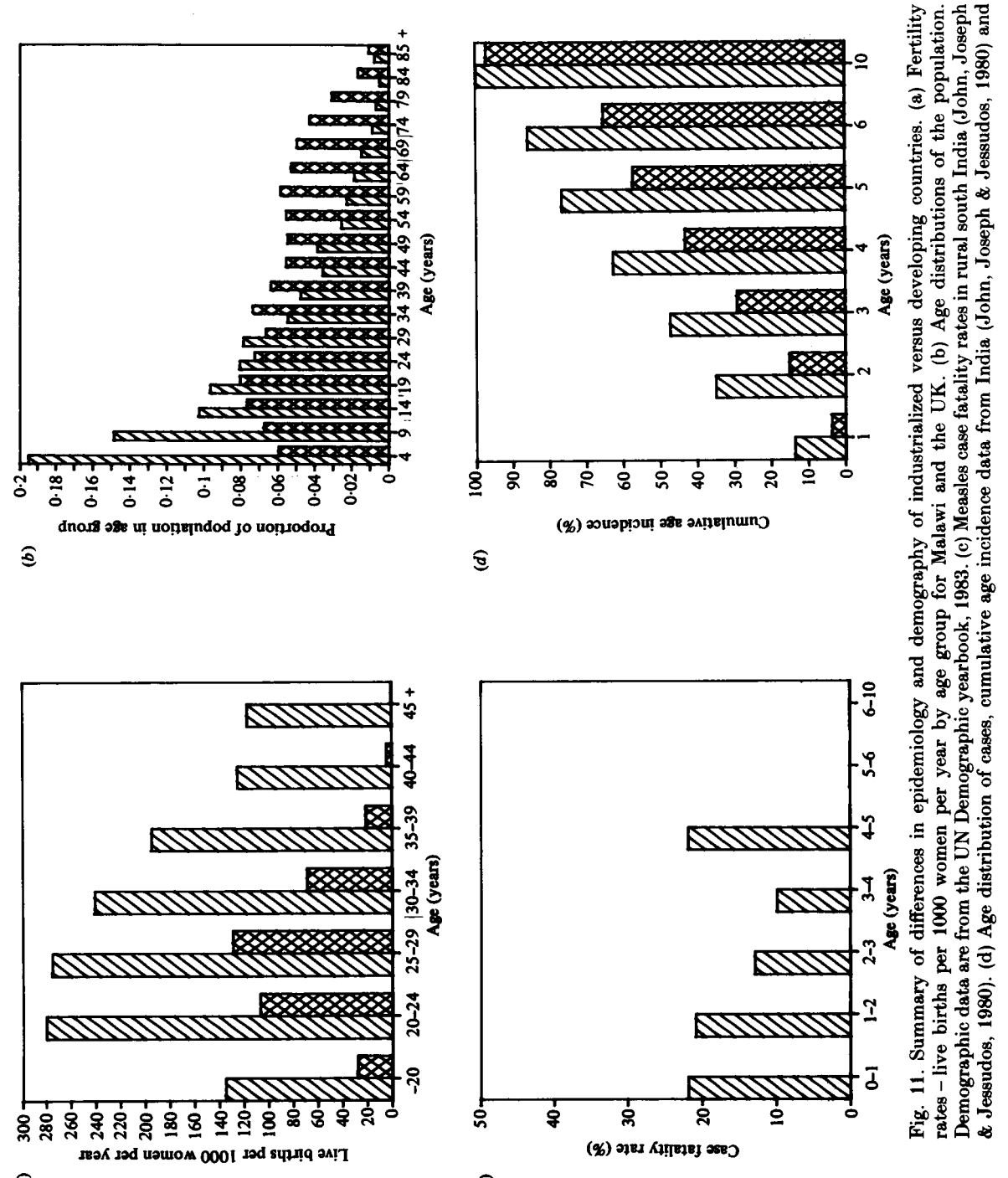


Fig. 11. Summary of differences in epidemiology and demography of industrialized versus developing countries. (a) Fertility rates – live births per 1000 women per year by age group for Malawi and the UK. (b) Age distributions of the population. Demographic data are from the UN Demographic yearbook, 1983. (c) Measles case fatality rates in rural south India (John, Joseph & Jessudos, 1980). (d) Age distribution of cases, cumulative age incidence data from India (John, Joseph & Jessudos, 1980) and

countries. As shown in Fig. 11, in every age group the fertility rate in Malawi is twice that of the UK, and nearly 20% of the population of Malawi is under 5 years of age. In comparison the population of the UK is fairly evenly distributed. In contrast to the high case fatality rates shown in Fig. 11(*c*) a study undertaken in the UK just before the introduction of vaccination found 12 deaths in 50000 cases (Miller, 1964).

The first result of practical significance is that there is no one age at which vaccination will in any sense be 'optimal' for all communities in the developing world. As described in the first section of this paper, the optimal age at which to vaccinate depends critically on the pattern of age incidence of measles that prevails in a given community prior to the introduction of mass vaccination. The age at which the peak in susceptibility to measles occurs (i.e. the trough in the age-serological profile) differs greatly between communities as described by us in a previous publication (McLean & Anderson, 1987). Ideally, therefore, a profile of changes in seropositivity with age should be obtained prior to the introduction of control in a given locality.

The second result is that a long period of low incidence of infection is to be expected following the introduction of a mass vaccination programme. These immediate gains in terms of reduction in morbidity and mortality should be interpreted with caution since following the initial perturbation to the age distribution of the susceptible population induced by vaccination, the system will settle to a level of incidence higher than that observed in the early stages of the programme (Fig. 3*a*) (for a non-eradicating programme with a fixed level of cohort vaccination). Community health planners should therefore be aware that the apparent initial success of a vaccination campaign may be followed by a major epidemic. This is not necessarily a sign of a decline in vaccine uptake but simply a reflection of the perturbed system settling to a new pattern of recurrent epidemics (with a lengthened inter-epidemic period) under the impact of mass vaccination.

The third and major result of practical relevance to planners of primary health programmes in the developing world concerns the predicted impacts of different vaccination strategies. We have considered one-stage, two-stage and two-phase programmes. A diagrammatic summary of the designs we have examined is presented in Fig. 12. One-stage strategies find an optimal age at vaccination and target all immunization efforts at that age group. Two-phase strategies start by targeting one age group and then switch to targeting an older age group. Two-stage strategies divide their attention between different age groups. The principal conclusion of our extensive numerical studies is that no benefit is to be gained by adopting either two-phase or two-stage programmes over that obtained by a one-stage programme with the same overall coverage rate. Our analyses suggest that the optimum approach is to obtain as high a level of coverage as is practically possible at the age at which the proportion susceptible to infection prior to the introduction of mass vaccination is at its highest. The primary factor that underlies this conclusion is the high rate of transmission of measles in communities in developing countries when compared with those which existed in developed countries prior to the introduction of mass vaccination. Any two-phase or two-stage programme that involves targeting a second phase or stage of vaccination at

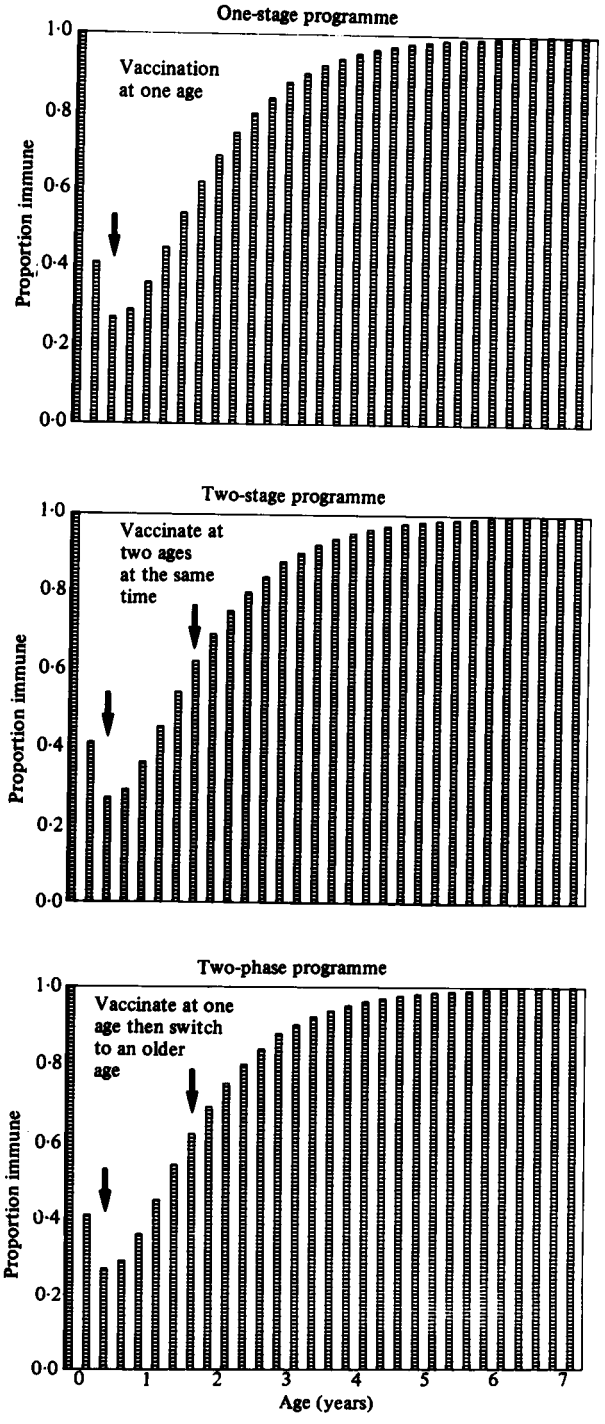


Fig. 12. Schematic representation of different vaccination strategies.

children in age classes older than the average age at which infection was typically acquired prior to the introduction of mass vaccination is *less* beneficial than a single-stage programme aimed at children younger than the average age at infection. In assessing the practical relevance of this conclusion we stress that our analyses have focused simply on epidemiological issues and have not taken into account economic considerations. In future work in this area, it would be desirable to introduce some form of cost-benefit analysis by means of grafting economic parameters into models of viral transmission.

In conclusion, we return to an issue discussed by us in a previous publication. Namely the demographic and epidemiological data ideally required to effectively design mass vaccination programmes. It is again clear from the analyses presented in this paper that effective programme design is greatly enhanced by the collection of detailed serological, demographic and case fatality information prior to the introduction of control measures. Linked to this suggestion is the obvious need in future work for more careful monitoring of the impacts of current vaccination programmes in developing countries by carefully designed longitudinal and horizontal epidemiological studies. Such information, in conjunction with mathematical models that mirror viral transmission and host demographic process, can greatly enhance our ability to determine the likely impact of a given programme of vaccination. They can also help in the choice of an optimal strategy to minimize morbidity and mortality arising from infection with the measles virus.

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