Measles in developing countries

Part I. Epidemiological parameters and patterns

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SUMMARY

This paper presents a review of published data concerning the epidemiology of measles in developing countries. Simple mathematical models provide a framework for data analysis and interpretation. The analyses highlight differences and similarities in the patterns of transmission of the measles virus in developed and developing countries. Whilst the rate of loss of maternally derived immunity to measles is broadly similar, the average age at infection is much lower, and case fatality rates are much higher in developing countries. Data analysis also serves to illustrate inter-relationships between different kinds of epidemiological data. Thus, for example, in order to correctly interpret an age stratified serological profile from a developing country it is necessary to have information on the rate of decay of maternal antibodies and age specific case fatality rates. To determine the probable impact of a given vaccination programme, information on the birth rate in the community concerned is also required. A discussion is given of the epidemiological data required in order to effectively design a community based vaccination programme aimed at the eradication of measles.

INTRODUCTION

Throughout much of the developing world measles remains a major disease particularly in young children. Walsh & Warren (1979) estimate that of the order of 900 000 deaths from measles occur each year in developing nations. The viral infection induces serious complications such as acute diarrhoea, encephalitis, otitis media, pneumonia and exacerbation of protein energy malnutrition. (Krugman & Katz, 1981). Mortality arising from measles infection is closely associated with malnourishment in children (Morley, Woodland & Martin, 1963).

The epidemiology of the infection in many developing countries is somewhat analogous to that of measles in England prior to the 20th century. The average age at infection, for example, is typically low at around 1–3 years of age. This is to be compared with the equivalent statistic of 4–6 years that pertained in most industrialized countries just prior to the introduction of mass immunization in the mid 1960s (Morley, 1969*a, b*; Anderson & May, 1982; Walsh, 1983). The high rates of transmission in developing countries are a consequence of behavioural and

Fig. 1. Schematic illustration of the window problem. (a) Hypothetical serological profile that might be drawn from a community in the industrialised world. (b) Serological profile that might be drawn from a community in a developing country. ▨, Maternal antibody protection. ▤, Immunity following infection.

demographic factors (May & Anderson, 1984; Anderson & May, 1985*a*). One implication of high transmission is that virtually all women of child-bearing age have experienced the infection and so most children are born with maternally derived antibodies to measles virus antigens. These protect from infection and disease for roughly 3–12 months, but they also prevent successful immunization via the use of the current generation of vaccines for a similar period of time (Albrecht *et al.* 1977; Halsey, 1983). These two factors; high transmission rates and the inhibitory effect of maternally derived antibodies, combine to cause what can be termed the 'window' problem. A substantial proportion of a cohort will

have had measles already by the age at which maternally derived protection has waned for almost all children. The problem is illustrated using two schematic serological profiles in Fig. 1. The first graph of Fig. 1 represents the situation in a community where the average age at infection is about six years and there are very few cases in children below 2 years of age. This leaves a 'window' during the second year of life when virtually no children are immune and most of a cohort can be successfully vaccinated. Fig. 1(b) represents a serological profile that would be drawn from a community where the average age at infection was 2·5 years and there were many cases in children below 2 years of age. This leaves no 'window' when a large proportion of a cohort would be expected to seroconvert following vaccination. An important consequence of this issue is uncertainty concerning what is the best or optimal age at which to vaccinate in communities in developing countries with high transmission rates (Heymann *et al.* 1983; Walsh, 1983). Such uncertainty is of special importance at present given the implementation of the World Health Organisation's (W.H.O.) Expanded Programme for Immunisation (E.P.I.) which aims to make measles vaccine available to all children by the end of the decade (E.P.I., 1986).

The problems of vaccination programme design are well suited to the methods of analysis provided by mathematical descriptions of the transmission of infectious disease agents (Anderson & May, 1985*a*; May & Anderson, 1984). To that end we have constructed an age-structured, partial differential equation model of measles transmission in developing countries where population growth rates tend to be high (as compared with developed countries) and where case fatality rates are significant. The model can be used to compare the outcomes of a number of vaccination programmes with different levels of coverage and ages at immunization.

In this paper we summarize the existing quantitative data on the epidemiology of measles in developing countries. We also take the opportunity to employ some of this data for the estimation of epidemiological parameters that will be used to generate model predictions. The research on data interpretation and analysis is employed to illustrate the inter-dependence of epidemiological and demographic variables as determinants of measles transmission and the choice of an optimal vaccination programme.

MATERIALS AND METHODS

Published data concerning the epidemiology of measles in developing regions of the world has been reviewed and data selected for analysis on the basis of quantitative detail and study design. To assess the dynamics of transmission, we consider data on the duration of protection provided by maternally derived antibodies, the age distribution of cases of infection, age stratified serological profiles, age-related measles case fatality rates, and age-specific fertility and mortality schedules. The majority of the data is derived from horizontal as opposed to longitudinal studies.

Parameter definitions for the different types of data are derived from the mathematical model of measles transmission (May & Anderson, 1984; Anderson & May, 1983, 1985*a, b*). The model is compartmental in structure and defines rates of

movement of individuals between a series of states, namely, protected by maternally derived antibodies, susceptible, infected but not infectious (latent), infectious and immune. The steady state or equilibrium version of the model defines age distributions of individuals within these various states in terms of parameters such as the rate of decay of maternally derived protection, the latent and infectious periods, age specific mortality broken into background mortality and case fatalities, the age specific force or rate of infection and the net birth rate of the community. We first derive estimates of these model parameters from published data and then define algebraic expressions for a number of key summary epidemiological statistics, such as the average age at infection, in terms of the parameters. These two exercises highlight the inter-relationships between different types of epidemiological statistics and their dependencies on demographic parameters such as the net birth rate and age-specific mortality rates.

RESULTS

Epidemiological and demographic data

Maternally derived antibodies. Children of immune mothers are born protected from measles infection by the presence of transplacentally derived antibodies. Over the course of the first year of life these antibodies wane in abundance and the rate at which infants lose their maternally derived protection from infection can be estimated from age-stratified serological profiles which focus on the youngest age classes. The age stratification should be fine – ideally in age bands of one month. In the collection of such data care should be taken to exclude all infants who have experienced infection over the first year of life. This requirement is difficult to fulfil as infection, when it occurs during the first year of life, is usually subclinical (Krugman *et al.* 1965). So in practice all *known* cases are excluded. Figure 2 shows the results of estimating the rate of loss of protection from maternal antibodies from eight such surveys, along with 95% confidence intervals for the estimated value of the rate. The most important point illustrated in the figure is that there is no significant difference in the rate of loss of protection by maternal antibodies between children in developed and developing countries. The parameter for exponential decay shown in Fig. 2(f) (data from the USA) is not significantly different from any of the other estimates in Fig. 2 (which are from a variety of developing countries). Thus although the rate of loss of protection by maternal antibodies varies between communities, there is no clear pattern of longer duration of protection in industrialized countries.

Once protection by maternal antibodies has waned, the child becomes susceptible to measles infection. The average duration of this susceptibility amongst the children of a community is a measure of the rate of disease transmission in that community. This rate has been dubbed ‘the force of infection’ and is generally denoted by the symbol λ (Griffiths, 1974; Grenfell & Anderson, 1985). It can be estimated from data on the age distribution of cases of infection in a community, or, more precisely, from serological profiles finely stratified by age.

Cases of infection. Figure 3 illustrates the results from a series of studies of the age distribution of measles cases expressed in terms of the cumulative case

Fig. 2. The rate of loss of protection by maternal antibodies. Best estimates of the rate of decay, δ , of maternal antibody protection assuming that the duration of protection is exponentially distributed. The parameter δ is measured in units of per protected infant per year. Places and dates of surveys are as follows; when known, sample sizes are given in parentheses. (a) Guadelupe, Mexico 1982 (125) (Sabin *et al.* 1983). (b) Tanzania, 1977 (649) (E.P.I. 1981). (c) Nairobi, Kenya 1976 (1764) (Ministry of Health, Kenya, 1977). (d) Hyderabad City, India 1985 (199) (Bhaskaram *et al.* 1986). (e) Nigeria (108) (Abdurrahman *et al.* 1982). (f) New York, USA early 1960s (107) (Krugman *et al.* 1965). (g) Bulawayo, 1975 (87) (Burrowes & Cruickshank 1976). (h) Nigeria, 1979 (455) (Harry & Ogunmekan, 1981).

Fig. 3. Age stratified case reports of measles infection. (When known sample sizes are given in parentheses.) $\square$, S.W. Somalia 1978 (910) (E.P.I. 1980); +, W. Bengal India 1976-8 (862) (Garai & Chakraborty, 1980); $\diamond$, New Haven 1955-8 (Black, 1959).

distribution by age. Comparing the curves (a) and (b) (from Somalia and India respectively) with (c) (from the USA) illustrates the fact that many cases of measles occur at a younger age in the developing areas of the world. In industrialized countries like the UK and the USA there are virtually no cases below the age of 1 year. Thus almost all the members of a cohort have lost the protection provided by maternal antibodies and have entered the susceptible state before any are infected by the measles virus. This makes the estimation of the force of infection from such data quite simple as one can reasonably assume that 100% of a cohort are susceptible at 9 months and then estimate the force of infection as the parameter of the exponential decay of the percentage susceptible in subsequent age classes (Anderson & May 1983, Grenfell & Anderson, 1985).

In developing countries where infection is often acquired at a much younger age such simplifying assumptions cannot be made. A technique must therefore be developed to allow for the overlap in age classes when some children are still protected by maternal antibodies, but some have already experienced measles infection. An ordinary differential equation model is used. Two subdivisions of the population are considered; the proportion protected by maternal antibodies (denoted by $M'(a)$) and the proportion susceptible at age a ($X'(a)$). The decay of maternal antibody protection in the community is assumed to follow an exponential curve so the age distribution of the proportion of the population in the maternal antibody-protected class can be described by

$$\frac{dM'}{da} = -\delta M'(a); \quad M'(0) = 1 \quad (\text{all newborns are protected})$$

with solution

$$M'(a) = \exp(-\delta a).$$

The infants who leave the maternal-antibody-protected class go directly into the susceptible class which they leave at the *per capita* rate $\lambda(a)$ as a result of infection ($\lambda(a)$ is the age-dependent force of infection). So the age distribution of the proportion in the susceptible class is given by the solution of

$$\frac{dX'}{da}(a) = \delta M'(a) - \lambda(a) X'(a).$$

The area under the curve that we construct when we draw a graph of cumulative cases by age represents all the people who have left the susceptible class through measles infection, so the area above the curve represents the people protected by maternal antibodies or susceptible, (i.e. $M'(a) + X'(a)$). For age-independent forces of infection (i.e. $\lambda(a)$ equal to a constant λ for all a)

$$M'(a) + X'(a) = \frac{\lambda \exp(-\delta a)}{(\lambda - \delta)} - \frac{\delta \exp(-\lambda a)}{(\lambda - \delta)}.$$

Because of the algebraic form of this equation, estimates of λ must be obtained via numerical algorithms that search for zeros of the function

$$F(\lambda) = \frac{[M'(a) + X'(a)](\lambda - \delta)}{[\lambda \exp(-\delta a) - \delta \exp(-\lambda a)]}.$$

The quantity $M'(a) + X'(a)$ is obtained from the data.

If an age-prevalence study of cases of infection is to provide a good reflection of the rate of disease transmission in a community it must satisfy a number of criteria which are as follows. First it should be drawn from a representative sample of the total population. Second, the period of time over which it is gathered should encompass one complete epidemic cycle of 1 or 2 years. Finally an ideal survey would be finely stratified by age and would record the age of the oldest case recorded. The reason for this last requirement is that in order to calculate the force of infection from case reports one must assume that there are no cases in individuals older than the upper limit of the top age class. If the top age class is simply labelled '15+' it is impossible to estimate the age of the oldest case. The consequence of making an inappropriate estimate of the age above which there are no cases can be illustrated using the data in Fig. 3*b*. This figure is based on results presented by Garai & Chakrabourty (1980) and illustrates a survey covering an unusually broad range of ages which was carried out in a rural community in India over the years 1976–8.

The survey covered all age groups including five cases in people over the age of 40 years. We based our analysis on the difference in the susceptible population at the age 3 years and at age 15 years, (starting at age 3 years allows us to ignore the complication presented by maternal antibodies discussed above). Taking the data as they are presented, we are told that 36·8% of cases occurred in children aged 2 years or less, 90% of cases were in those aged below 15 years, and 93·7% were in those aged below 20 years. From this information we estimate that the force of infection in the 3–15 years age group is $\lambda = 0\cdot15$ per susceptible per year. Now suppose that the study had ignored the 54 people aged 20 or over who had measles during the course of the 2 year study, and hence assumed that 100% of cases were in those aged below 20 years. The new cumulative age distribution has 39·2% of cases occurring in those aged 2 or below, and 96% in those aged less than 15 years. The new estimate of the force of infection for the 3–15 years age group is $\lambda = 0\cdot23$ per person per year. This example well illustrates the importance of studies covering all age classes.

Serological data. A more reliable source of information on measles age-prevalence in unvaccinated communities is provided by serological surveys that measure the proportion in different age groups in a community that have antibodies to measles virus antigens at a level sufficient to indicate probable protection from infection. Figure 4 shows serological profiles drawn from communities in a number of developing countries, and, for comparison, a serological profile from the USA. All the profiles shown are from communities with little or no vaccination against measles infection. Therefore most people are registered as seropositive either because they are protected by maternal antibodies or because they have experienced the infection. The studies which have a fine 'grain' of age stratification, Fig. 4(*a*) and (*b*), show the usual pattern of a sharp drop in the percent seropositive during the first year of life as maternally derived antibodies wane, followed by a rebound as immunity acquired through natural infection begins to rise in the population. This pattern is not revealed in Fig. 4(*c*) and (*d*) because they are based upon studies which did not cover infants. Figure 4(*a*) illustrates how immunity acquired through infection is exhibited before immunity from maternally derived antibodies has been completely lost by all individuals. In other words there is no

Fig. 4. Age-stratified horizontal surveys of the presence of antibodies to the antigens of the measles virus. (When known, sample sizes are given in parentheses.) (a) Dakar, Senegal 1957 (151) (Boue, 1964). (b) Bangkok, Thailand 1967 (367) (Ueda *et al.* 1967). (c) Paraguay 1971 (408) (Golubjanikov *et al.* 1971). (d) New Haven, Connecticut (308) (Black, 1959).

Fig. 5. Schematic illustration of the effect of case fatalities upon the serological profile. The figure shows serological profiles drawn from two hypothetical communities which have the same rate of measles transmission and average ages at infection but different case fatality rates (cfr). One community has high (50%) case fatalities from measles (□) and one has no measles case fatalities (+). The unrealistically high case fatality rate of 50% is used in this schematic figure to give a clear illustration of the impact of case fatalities.

age at which all individuals in a cohort are susceptible. In contrast, for the profile from the USA almost every member of the cohort has lost his or her maternally derived antibodies before any member acquires antibodies through natural infection.

Although the available data from developing countries are mostly based on surveys with fairly small sample sizes, age-dependent forces of infection can be estimated from these serological profiles. However, in addition to the technical problems with the interpretation of cumulative age distributions which were mentioned above, there is an additional difficulty to be overcome when using serological profiles to estimate forces of infection. The curves showing cumulative age distributions of cases give a record of all those who have had measles, regardless of the outcome of the infection. The serological profile is a record only of those who have survived measles infection. It thus becomes necessary to take account of case fatality rates when estimating transmission rates from serological profiles. A description of the way in which this can be done is given in the appendix; suffice it to say here that the method depends upon the consideration of a subset of the population which we call 'excess deaths' which represents those people who have died of measles who we would not yet expect to have died from some other cause. Figure 5 gives a schematic representation of this problem showing serological profiles from two hypothetical communities with the same rate of measles transmission but differing case fatality rates. Because the children who die as a result of their measles infection are not present to have their sera

Table 1. *The dependence of the estimated force of infection upon the assumed rate of decay of maternal antibody protection and the case fatality rate*

Annual <i>per capita</i> rate of loss of maternal antibody (yr ⁻¹)	Average duration of maternally derived protection (months)	Case fatality rate	Age-dependent forces of infection λ (<i>a</i>) (yr ⁻¹)							
			Age classes (years)							
			0-1	1-2	2-4	4-6	6-8	8-10	10-50	
2	6	Low	0.059	0.121	0.455	0.581	0.241	0.225	0.167	
2.5	4.8	Low	0.149	0.068	0.446	0.580	0.241	0.225	0.167	
2	6	High	0.118	0.141	0.485	0.584	0.241	0.225	0.167	
2	6	Medium	0.069	0.135	0.473	0.591	0.241	0.225	0.167	
2	6	Zero	0.056	0.108	0.442	0.574	0.241	0.225	0.167	

collected, the serological profile from the community with a high case fatality rate has a less steep slope than the serological profile from the community with no case fatalities. This could be misinterpreted as implying a higher average age at infection in the high case-fatality-rate community if case fatalities were not taken into account. It is therefore important to have information on the prevailing case fatality rate and rate of loss of protection of maternal antibodies in a community when interpreting a serological profile from that community. Table 1 shows the dependence of the estimated force of infection upon the assumed rate of decay of maternal antibody protection and the case fatality rate. The forces of infection were estimated from Ueda *et al.* Bangkok serology (Fig. 4*b*; Ueda *et al.* 1967). In the 0–1 years age group the estimated force of infection increases as the rate of loss of maternal antibodies rises. This is because the proportion immune through the possession of maternal antibody is assumed smaller and therefore the proportion assumed to have experienced measles is greater. In the 1–2 and 2–4 years age groups the estimated force of infection decreases as the rate of loss of maternal antibodies increases. This is because the *differences* between the proportions immune through infection at the beginnings and ends of these age ranges are diminished. The high case fatality rates are from The Gambia (Fig. 6*a*; Hull *et al.* 1983). The medium case fatality rates are from rural south India (Fig. 6*c*; John *et al.* 1980) and the low case fatality rates are from rural Kenya (Fig. 6*b*; Muller *et al.* 1977). Increasing the assumed case fatality rates increases the estimates of the force of infection. This is because a greater case fatality rate implies more immunes ‘absent’ from the serological profile because they have died as a result of infection.

Case fatality rates. The case fatality rates used in drawing up Table 1 are shown in Fig. 6. These results are from a selection of surveys which have studied case fatality rates in developing countries. There is some difficulty over the definition of a case fatality in communities where general levels of health are poor. It is often difficult to be specific about the cause of an individual’s death since a number of factors are often responsible. In practice, a common definition for a case fatality is any death occurring within 1 month of the onset of measles symptoms (Aaby, 1983*a*; Kasongo Project, 1981). For case fatality data to be reliable, one needs to be confident that the denominator (total number of cases) counts all individuals who have experienced measles infection, no matter how mild their symptoms have been. For this reason hospital and dispensary studies are rather unsatisfactory since they generally record the most severe cases. Community based studies are therefore of greater value when trying to ascertain the case fatality rate. The Machakos studies in rural Kenya are firmly based in the community and yield good data on case fatality rates (Muller *et al.* 1977). An extensive series of papers presenting work carried out in Guinea Bissau (Aaby *et al.* 1983*a–c*, 1984*a–c*) are also based on studies carried out in the community. Even community based studies can be misleading when sample sizes are small. In Figure 6(*a*) the point on the graph which gives a case fatality rate of 100% for 6- to 8-month-old infants represents only two children. This gives an example of the importance of large sample sizes in such studies.

Demographic data. It is well known that there are great differences in demographic patterns between developed and developing countries. It is the

Fig. 6. Age-stratified case fatality rates from measles infection. (When known sample sizes are given in parentheses.) (a) Mortality at 9 months follow up, The Gambia (Hull *et al.* 1983). (b) Machakos, Kenya 1976-7 (Muller *et al.* 1977). (c) Vellore, India 1979 (1281) (John *et al.* 1980). (d) 3 Guatemalan villages 1959-63 (449) (Gordon *et al.* 1965).

Table 2. *Demographic data from developing and developed countries. Data are from the U.N. Demographic Yearbook for 1982*

Country	Crude birth rate per 1000 per year	B (years)	Female expectation of life at birth (years)	Population growth rate (per 1000 per year)
Malawi	48.5	20.6	44.2	23.4
Ecuador	41.6	24.0	61.8	31.2
Thailand	32.3	31.0	58.7	23.4
UK	12.8	78.1	76.6	1.1

purpose of this section to give a few illustrative examples of these differences and to illustrate their relevance to the interpretation of epidemiological data. These examples will be used in the next section, in conjunction with some of the epidemiological data shown above, to show how epidemiological and demographic parameters interact to determine observed trends in infection.

Figure 7 shows birth rates, death rates and age distributions from Malawi and from the United Kingdom. Comparing birth rates one sees much higher birth rates in the Malawian population with a peak of 280.3 live births per 1000 women in the 20–24 years age group, contrasting with a peak of only 129.9 live births per 1000 women in the 25–29 years age group in the UK. Another difference is in the infant mortality rates; 151.3 per 1000 per year in Malawi, but only 12.7 per 1000 per year in the UK. These two differences combine to generate the different age distributions shown in Figures 7(e) and (f). For Malawi the age distribution of the population follows a curve close in shape to an exponential decay with children under 5 years of age making up a large part of the population. In contrast the age distribution of the population of the UK is almost uniform over the age range 0–70 years.

These curves showing age-dependent demographic rates, give a detailed view of demographic patterns in different countries. It is helpful to find ways of summarizing the information represented by these graphs in single parameters, such as the crude birth rate and the overall population growth rate. In the next section reference will be made to a demographic parameter B which is defined as the reciprocal of the average, *per capita* (defined per head of the total female and male population) birth rate. Thus if CBR is the crude birth rate (expressed per 1000 of the male and female population)

$$B = 1000/\text{CBR},$$

Table 2 shows crude birth rates, population growth rates, female expectation of life at birth and values of the parameter B for the two countries of Fig. 7 and also for Ecuador and Thailand. The most important observation to be made is that a higher birth rate leads to a lower value of B . It may also be noticed that in countries with rapidly growing populations B has a much lower value than L , (female expectation of life at birth), whilst in populations of fixed size the two quantities assume similar values.

Fig. 7. For legend see opposite.

Fig. 7. Demographic patterns in Malawi and the UK. (a) and (b) Age-specific fertility rates; live births per 1000 women per year. (c) and (d) Age-specific death rates; deaths per 1000 per year. (e) and (f) Age distribution of the population. (a), (c), (e) Malawi. (b), (d), (f) UK (England and Wales). All data are from the United Nations *Demographic Yearbook* for 1982.

Summary epidemiological parameters

This section draws together results from the previous two sections and uses them in the estimation of summary epidemiological parameters. Three parameters are considered; the average age at infection, A , the basic reproductive rate, R_0 , and the critical vaccination proportion for the eradication of the infection p_c . The average age at infection is a self-explanatory parameter and represents a good measure of the overall rate of transmission in a community. The basic reproductive rate R_0 is defined as the average number of new cases that would be generated if one infectious individual were introduced into a wholly susceptible population (MacDonald, 1952; Anderson & May 1982, 1985*a*). The critical vaccination proportion for eradication p_c is the proportion of the population that must be successfully vaccinated in order to eradicate the infection (Anderson & May, 1982, 1983, 1985*a*).

In models that assume that the age distribution of the population is uniform, and the size of the population is constant, it can be shown that

$$A \simeq 1/\lambda + 1/\delta, \quad (1)$$

where λ is the *per capita* infection rate of susceptibles and δ is the rate of decay of protection by maternally derived antibodies (Anderson & May, 1983). This result can be trivially extended to cover populations where the age distribution is not uniform and the total population is not of fixed size. If μ represents the age-independent *per capita* death rate and r the *per capita* population growth rate it can be shown that

$$A \simeq 1/(r + \mu + \lambda) + 1/(r + \mu + \delta). \quad (2)$$

This result is based on the assumption that the force of infection λ and the death rate μ are the same for all members of the populations, regardless of their age. It is possible to derive a similar result based on the assumption that these rates change with age (i.e. $\lambda(a)$ and $\mu(a)$), but the result is algebraically too clumsy to be enlightening. However it does give a better estimate of the average age at infection than the age independent algorithm. The estimated average age at infection can be affected by differing assumptions about a community's demographic and epidemiological characteristics, and in Table 3 we use the age-dependent algorithm to generate examples of the dependence of the average age at infection on parameters other than the forces of infection. The references for case fatality rates are as in Table 1. The table is presented in four sections. These show the effects of variation in: the serological profile, case fatality rate, rate of loss of protection by maternal antibodies and population growth rate. The last part of the table shows the importance of the interplay between demography and epidemiology when interpreting age-prevalence data.

The second summary parameter presented in Table 3 is the basic reproductive rate R_0 . This represents the average number of new cases that would be generated by the introduction of one infectious individual into a wholly susceptible population. In a homogeneously mixing population it can be shown that

$$R_0 \simeq B/(A - D), \quad (3)$$

Table 3. *Sensitivity of the average age at infection A and the basic reproductive rate R_0 to parameter variation*

B (years)	r (per 1000 yr ⁻¹)	Case fatality rate (yr ⁻¹)	δ (yr ⁻¹)	D (years)	A (years)	R_0
19.1	41.9	Zero Low Medium High	2	0.5	3.62 3.55	6.12 6.26
					3.46 3.34	6.45 6.73
19.1	41.9	Low			3.55 3.52 3.50	6.26 6.32 6.37
19.1 25.9 34.2	41.9 25.4 11.0	Low	2	0.5	3.55 3.67 3.78	6.26 8.17 10.43

where B is the reciprocal of the average birth rate (discussed in section 3), A is the average age at infection and D is the average duration of maternal antibodies (Anderson & May, 1985*a*). The most important conclusion to be drawn from Table 3 is in the comparison of two populations which exhibit the same serology but have differing birth rates. In the population with the higher birth rate (thus lower B) the infection has a lower basic reproductive rate.

The parameter R_0 is of great interest because of its role in determining the level of herd immunity required to eradicate an infection. Herd immunity can be considered as the indirect protection of unvaccinated susceptibles by high levels of vaccination amongst the remaining segments of the population. This protection is a consequence of the reduction in virus transmission brought about by the removal of vaccinated individuals from the susceptible class. It is through the effects of herd immunity that it is possible to eradicate a disease without vaccinating every single susceptible (Fox *et al.* 1971). The connection between the basic reproductive rate and the proportion of the population that must be vaccinated for eradication is as follows:

$$p_c = 1 - 1/R_0. \quad (4)$$

(Anderson & May, 1983) This expression reveals that the larger R_0 is, the more difficult it will be to eradicate the infection. Again it is interesting to consider two communities with similar serology (identical average age at infection prior to control) but different birth rates. The one with the greater birth rate will have a lower R_0 and therefore eradication will be more easily achieved. This does not imply that an increase in the birth rate leads to a decrease in the critical vaccination proportion for eradication. Rather it should be interpreted that a community with a low average age at infection because of a high birth rate will be more easily rid of measles infection than a community where the low average age at infection is a consequence of behavioural patterns that enhance transmission leading to a high R_0 .

DISCUSSION

Many factors interact to determine the rate of transmission of the measles virus within human communities. The measurement of this overall rate or force of transmission is central to the design of optimal vaccination programmes in the context of determining both the optimal age at which to vaccinate and the level of vaccination coverage required to eradicate the infection (Anderson & May, 1985*a*). Field studies of measles transmission in developing countries should therefore be designed to acquire the necessary data for the estimation of this rate as encapsulated in the summary epidemiological parameter, the basic reproductive rate of infection R_0 .

Our review of the available data on measles transmission interpreted with the aid of simple mathematical models of the dynamics of transmission highlights a series of data requirements for the determination of R_0 . Serological data, finely stratified by age is of major importance since the rise in seropositivity with age in children reflects the force of transmission. Precise interpretation of observed patterns, however, depends on the availability of other information. Of particular importance are the rate of decay of maternally derived antibodies, age-specific mortality and case fatality rates and the net birth rate of the community. Many different combinations of parameter values for these major factors can generate similar profiles of the change with age in the proportion of individuals with antibodies specific to measles virus antigens. In the absence of detailed data on the decay in maternally derived protection, case fatality rates and net birth rates it is not possible to derive precise estimates of the overall rate of transmission of the virus within a community. Since this latter factor is the primary determinant of control variables such as the optimum age at which to vaccinate, future studies of measles transmission should attempt to acquire more precise epidemiological and demographic data. A clear illustration of this point is provided in Table 3. The last three rows of the table record estimates of the basic reproductive rate, R_0 , in three hypothetical communities with similar average ages at infection between 3.5 and 3.7 years of age (i.e. similar serological profiles) but with very different net birth rates. In the absence of information on the birth rates it might be assumed that similar levels of cohort vaccination coverage (given the similarities in the serological profiles of the three communities) would result in the eradication of infection. This is not the case, however, since constancy in the average age at infection implies that in the high birth rate community, the effective rate of contact between susceptible and infective children is much lower than in the low birth rate community. So lower levels of cohort vaccination would be required to interrupt transmission in the high birth rate community when compared with the low birth rate population. This example well illustrates the subtle interplay between demographic and transmission related parameters determining observed epidemiological patterns (e.g. serology).

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APPENDIX

This appendix is used to give a brief presentation of the mathematical model on which our analyses are based, and to describe two methods of data interpretation: the interpretation of serological profiles and the interpretation of case fatality rates. The basic model consists of a set of five differential equations describing the rates at which individuals progress through the following five states; protected by maternally derived antibodies, susceptible, infected but not yet infectious, infectious and immune. These five classes, or compartments are represented by the five letters, M , X , H , Y and Z and the rates at which people progress from one to the next are described by the following partial differential equations.

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

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

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

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

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

An additional quantity describing total population size, N , is useful, and since,

$$N(a, t) = M(a, t) + X(a, t) + H(a, t) + Y(a, t) + Z(a, t),$$

the dynamics of this total population are described by;

$$\frac{\partial N}{\partial a} + \frac{\partial N}{\partial t} = -\mu(a) N(a, t) - \alpha(a) Y(a, t). \quad (\text{A } 6)$$

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

$$M(0, t) = \int_0^\infty m(a) N(a, t) da, \quad (\text{A } 7)$$

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

That is, all newborns are protected by maternal antibody. In addition, the quantities

$$M(a, t_0), X(a, t_0), H(a, t_0), Y(a, t_0) \quad \text{and} \quad Z(a, t_0)$$

are all assumed to be known for some time t_0 , thus providing the necessary initial conditions for the equations.

The interpretation of the model's parameters should be as follows. δ is the rate of decay of maternal antibody 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 (A 8). $1/\sigma$ and $1/\gamma$ 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 rate is described below. $m(a)$ is the age-dependent fertility rate.

The following definition of the force of infection $\lambda(a, t)$ is used:

$$\lambda(a, t) = \frac{\int_0^\infty \beta(a, a') Y(a', t) da'}{\int_0^\infty N(a', t) da'}. \quad (\text{A } 8)$$

In order to be able to estimate age-specific, equilibrium values of the force of infection from serological data we require an algebraic description of the proportion of the community that are susceptible at any given age. We name this proportion $X^0(a, t) = X(a, t)/N(a, t)$. As the rate of change of the total population $N(a, t)$ is governed not only by population size, but also by the number of

individuals in the infectious state (A 6), straightforward division of (A 2) will give an equation for X^0 whose right-hand side contains terms involving products of $Y^0(a, t)$ and $X^0(a, t)$. This seems to make the problem much more difficult. However the introduction of a sixth state, 'excess deaths' allows the definition of an alternative set of proportions which serve to clarify the problem. Conceptually this sixth class represents those individuals who have died as a result of contracting the disease and who *would not have died from some other cause*. The numbers in this class of age a at time t , $E(a, t)$, are therefore described by the equation

$$\frac{\partial E}{\partial a} + \frac{\partial E}{\partial t} = \alpha(a) Y(a, t) - \mu(a) E(a, t). \quad (\text{A } 9)$$

It is now possible to define a new 'would-be' total population:

$$W(a, t) = N(a, t) + E(a, t),$$

that is, the total living population plus those who have died prematurely as a result of having had the disease. This total population $W(a, t)$ obeys the following differential equation:

$$\frac{\partial W}{\partial a} + \frac{\partial W}{\partial t} = -\mu(a) W(a, t). \quad (\text{A } 10)$$

Having defined this new type of total population $W(a, t)$ it is in turn used in the definition of a third set of variables; $X'(a, t) = X(a, t)/W(a, t)$ and so on for the other five classes M' , H' , Y' , Z' and E' . The partial differential equations governing their dynamics are identical to (A 1)–(A 5) and (A 9) except they lack the term $-\mu(a), M(a, t)$, etc. The boundary conditions are as follows:

$$\begin{aligned} M'(0, t) &= 1, \\ X'(0, t) &= H'(0, t) = Y'(0, t) = Z'(0, t) = E'(0, t) = 0. \end{aligned}$$

and the initial conditions are trivially derived from the initial conditions specified for (A 1)–(A 5) with the additional specification of $E(a, t_0)$.

Under the assumption that $\lambda(a, t)$ and $\alpha(a)$ are constant over given age ranges and that $\partial \lambda(a, t)/\partial t = 0$, the equilibrium values of this set of variables are easily found by solving the piecewise-linear ordinary differential equations which are obtained when the time derivatives for the equations describing their dynamics are set at zero. This then gives expressions for the equilibrium age distributions of individuals in each of the states in terms of the model's parameters.

It then remains to clarify the relationship between these 'd variables and the quantities which are of epidemiological interest, the '0d variables. Since

$$N(a, t) = W(a, t) - E(a, t)$$

and

$$E(a, t) = W(a, t) E'(a),$$

$$\begin{aligned} X^0(a, t) &= \frac{X(a, t)}{W(a, t) - E(a, t)} \\ &= \frac{X(a, t)}{W(a, t)(1 - E'(a))} \\ &= \frac{X'(a)}{(1 - E'(a))}. \end{aligned}$$

From the serological profile the proportion susceptible at each age $X^\circ(a)$ is known. If all parameters other than the force of infection are known, having derived an algebraic expression for $X^\circ(a)$ in terms of the model's parameters, it takes only an application of a root-finding algorithm to the function

$$F(\lambda) = X^\circ(a)(1 - E'(a)) - X'(a)$$

to obtain the age-specific values for the force of infection.

Clearly the magnitude of $E'(a)$ governs the extent by which this estimated value of the force of infection differs from the value that would be obtained using a method that does not take account of case fatalities. Since

$$E'(a) = \int_0^a \alpha(a') Y'(a') da',$$

this in turn depends upon the magnitude of $\alpha(a)$, which is determined by the case fatality rate. Given a set of age-specific case fatality rates,

$$p_1, p_2, \dots, p_n \text{ for age classes } 0-a_1, a_1-a_2, \dots, a_{n-1}-a_n$$

a set of disease-related death rates for these same age classes are derived as follows: the parameter p_j represents the proportion of those people aged between a_{j-1} and a_j leaving the infectious state, who go into the excess deaths state. Expressed algebraically,

$$p_j = \frac{\int_{a_{j-1}}^{a_j} \alpha_j Y(a) da}{\int_{a_{j-1}}^{a_j} (\gamma + \alpha_j) Y(a) da} = \frac{\alpha_j}{(\gamma + \alpha_j)},$$

$$\alpha_j = \frac{\gamma p_j}{(1 - p_j)}. \quad (\text{A } 11)$$

For the younger age classes, where the case fatality rate can be as high as 26% (Aaby, 1983*a*), taking account of death from disease can increase the estimated force of infection by as much as 17% when compared with estimates that are derived using methods which ignore disease-related deaths. When studying the dynamics of measles in less-developed countries much of the interest lies in the first few years of life. Therefore such an underestimation of the force of infection at these young ages is of considerable practical relevance.