

Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes

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SUMMARY

Mathematical models are developed to aid in the investigation of the implications of heterogeneity in contact with infection within a community, on the design of mass vaccination programmes for the control of childhood viral and bacterial infections in developed countries. Analyses are focused on age-dependency in the rate at which individuals acquire infection, the question of 'who acquires infection from whom', and the implications of genetic variability in susceptibility to infection. Throughout, theoretical predictions are based on parameter estimates obtained from epidemiological studies and are compared with observed temporal trends in disease incidence and age-stratified serological profiles.

Analysis of case notification records and serological data suggest that the rate at which individuals acquire many common infections changes from medium to high and then to low levels in the infant, child and teenage plus adult age groups respectively. Such apparent age-dependency in attack rate acts to reduce slightly the predicted levels of herd immunity required for the eradication of infections such as measles, when compared with the predictions of models based on age-independent transmission. The action of maternally derived immunity in prohibiting vaccination in infants, and the broad span of age classes over which vaccination currently takes place in the U.K., however, argue that levels of herd immunity of between 90 and 94 % would be required to eliminate measles.

Problems surrounding the interpretation of apparent age-related trends in the acquisition of infection and their relevance to the design of vaccination programmes, are discussed in relation to the possible role of genetically based variation in susceptibility to infection and observations on epidemics in 'virgin' populations. Heterogeneous mixing models provide predictions of changes in serology and disease incidence under the impact of mass vaccination which well mirror observed trends in England and Wales.

INTRODUCTION

Much progress has been made in recent years in the development and use of mathematical models to aid in the design of vaccination programmes for the control of directly transmitted viral and bacterial infections (Dietz, 1975, 1976; Hethcote, 1983; Anderson & May, 1982, 1983). Such research has produced predictions concerning, for example, the level of vaccination coverage required to eradicate specific infections (i.e. measles, pertussis and rubella) in developed countries, and the relative merits of different vaccination policies for the control of infections such as rubella where the risk of serious disease arising from infection is age-dependent (Anderson & May, 1983; Knox, 1980). An encouraging trend in such work has been the growing attention given to the critical evaluation of predictions in light of observed trends, and the estimation of relevant epidemiological parameters from empirical information. The qualitative agreement between observations and model predictions has, in certain circumstances, been surprisingly good given the comparative simplicity of model structures. This feature of the research has strengthened the belief that mathematical models can be valuable tools in the design of public health policy, provided they are used sensibly.

In a recent publication (Anderson & May, 1983) we argued that the next generation of models should incorporate certain refinements that would give a better representation of known epidemiological detail. In particular, we stressed two refinements, namely the need to take account of apparent age-related changes in the force or rate of infection of susceptible individuals, and the desirability of relaxing the widely made assumption that populations mix in a homogeneous manner (the so called 'mass action' principle). In this present paper we examine these issues and modify the theoretical basis of current models for recurrent epidemic behaviour, to encompass age-dependent heterogeneity in contact with, and susceptibility to infection. The predictions of this 'heterogeneous mixing' model are examined with respect to the epidemiology of measles in England and Wales. Future publications will consider the relevance of such refinements to the epidemiology and control of pertussis, rubella and mumps. Analysis of a further form of heterogeneity, namely that induced by spatial inhomogeneity in population density and rates of contact between individuals, is described in separate publications (May & Anderson, 1984; Anderson & May, 1985).

The practical relevance of apparent age-dependent transmission to the design of vaccination programmes may not be immediately obvious to those public health workers unfamiliar with the development and use of mathematical models in epidemiological study. We therefore now briefly summarize the principal conceptual issues involved, before turning to the details of analysis and interpretation in the main body of this paper. Current theory predicts a series of important properties concerning the transmission and persistence of infectious disease agents within communities of people subject to mass immunization. Most importantly, it suggests that while the infection is endemic, the density of susceptibles within the total population will remain approximately constant from year to year, irrespective of the level of vaccination coverage. As such, the critical level of herd immunity (measured as a proportion of the community) required to eradicate an infection

is simply one minus the proportion of susceptibles in the population prior to mass immunization (Dietz, 1976; Anderson & May, 1982, 1983). The prediction that roughly 94–96 % herd immunity is required to eradicate measles and pertussis in the United Kingdom and the United States is based upon arguments of this nature. Mass vaccination is also predicted to reduce the effective reproductive rate of the infection within a community (the average number of secondary cases generated by one primary case of infection) and hence to raise the average age at infection amongst those who experience the disease. Both these predictions are based, in part, upon the assumptions of homogeneity in mixing and age-independent rates of transmission. If, however, the rate or force of infection changes with age, the tendency of mass immunization to increase the average age at infection may mean that the *per capita* rate of exposure of susceptibles to infection in the older age classes may well differ from the rates acting in the age classes in which those susceptibles would have typically acquired infection prior to immunization. For example, if the *per capita* rate of infection is high in the 5- to 10-year-old age class and low in the 10 to 15-year-old age class, then an increase in the average age at infection as a result of control measures, from the young age class to the older age class, will substantially alter the probability that those still susceptible acquire the infection. The potential consequence of such a change is to reduce the predicted level of vaccination coverage required to eradicate the infection below that suggested by models which assume that the *per capita* rate of infection is constant and independent of age.

Empirical evidence of age-related changes in the *per capita* rate of infection has been documented by Collins (1929), Griffiths (1974) and Anderson & May (1982). Past mathematical studies of the impact of age-dependency on epidemic behaviour include those of Hoppensteadt (1974), Enderle (1980) and Knolle (1983). More recently, the arguments outlined above have been developed by Schenzle (1985) and Dietz & Schenzle (1984). These authors have emphasized the dependency of the observed rate of infection, within a given age class, on the relative degrees of contact that susceptibles of that age have with infecteds in their own and other age classes. This observation is important, since it focuses attention on the likely heterogeneity of transmission within and between age classes. Inhomogeneity may arise as a consequence of differing rates of contact or mixing within and between age classes, and/or as a result of age-related changes in inherent susceptibility to infection or degrees of infectiousness once infected. The net effect of both factors is to create heterogeneity in transmission within a population. A central question in such considerations is 'who acquires infection from whom'?

This paper examines these issues by the use of mathematical models and by the analysis of available empirical data. The paper is organised as follows. The first section deals with methods and general concepts and employs a simple two-age class model to illustrate (by numerical and analytical methods) the principal consequences of age-dependent heterogeneity in transmission. Mathematical details are, where possible, relegated to appendices. The following section describes the details of our analyses and is divided into three major parts. The first considers the empirical evidence (derived from case notification records and serological surveys) for age-dependency in the rate of infection, and places special emphasis on the epidemiology of measles in developed countries. Attention is also focused

on epidemics of disease in 'virgin' populations who have not previously (or, at least not in the past few decades) experienced the infection; and the implication of genetic, social or behavioural factors in generating heterogeneity in susceptibility to infection is examined. These latter factors may have important implications for the interpretation of apparent age-related changes in transmission. The second part considers the long term consequences of mass immunization (the equilibrium or steady state results) for the control of measles, and assesses the practical relevance of age-dependent variation in transmission. The third part examines short term temporal changes in the incidence of measles with respect to differing levels of vaccination coverage. Emphasis is placed on the comparison of predictions with observed trends. The final discussion and summary section considers the implications of the research for the design of vaccination programmes, discusses various problems in data interpretation and outlines some future research needs.

GENERAL CONCEPTS AND METHODS

We begin by describing briefly various general concepts which have arisen from the analysis of models which assume that the force of infection is independent of age, before moving on to consider the complexities arising from age-dependent infection processes.

Following earlier studies (e.g. Dietz, 1975; Anderson & May, 1983), we employ compartmental mathematical models to study both the dynamics of infection within communities of people and the impact of various vaccination policies. These models represent the human population by a series of compartments containing, for example, susceptible, infected but not infectious (i.e. latent), infectious and immune individuals.

Basic model and theoretical background

We first outline the structure of a 'basic model' which serves as the template for further elaboration and analysis. The numbers of individuals of age a , at time t , who are susceptible, infected but not infectious, infectious, and immune are defined by the variables $X(a, t)$, $H(a, t)$, $Y(a, t)$ and $Z(a, t)$, respectively. The rates of change of these variables with respect to both age a , and to time t , can be described as follows (see Anderson & May, 1983):

$$\frac{\partial X(a, t)}{\partial t} + \frac{\partial X(a, t)}{\partial a} = -[\mu(a) + \lambda(t)] X(a, t), \quad (1)$$

$$\frac{\partial H(a, t)}{\partial t} + \frac{\partial H(a, t)}{\partial a} = \lambda(t) X(a, t) - [\mu(a) + \sigma] H(a, t), \quad (2)$$

$$\frac{\partial Y(a, t)}{\partial t} + \frac{\partial Y(a, t)}{\partial a} = \sigma H(a, t) - [\mu(a) + \gamma] Y(a, t), \quad (3)$$

$$\frac{\partial Z(a, t)}{\partial t} + \frac{\partial Z(a, t)}{\partial a} = \gamma Y(a, t) - \mu(a) Z(a, t). \quad (4)$$

It is here assumed that the rate or force of infection, $\lambda(t)$, is some function of the total number of infectious people in the community ($\bar{Y}(t)$ where $\bar{Y}(t) = \int_0^\infty Y(a, t) da$), but *independent* of age. Individuals are subject to an age-dependent mortality rate $\mu(a)$. For simplicity we assume that $\mu(a)$ is a step function in which

the mortality rate is assumed to be zero up to life expectancy, L , and infinite thereafter (L is taken to be equal to 75 years; the validity of the step function assumption in models of disease dynamics in developed countries is discussed more fully in Anderson & May (1983)). Individuals pass from the latent to the infectious class ($H \rightarrow Y$) and from the infectious to the immune class ($Y \rightarrow Z$) at *per capita* rates σ and γ respectively, where $1/\sigma$ is the average latent period and $1/\gamma$ is the average infectious period. On recovery immunity is assumed to be lifelong. Under the 'mass action' assumption of disease spread (i.e. the net rate of spread is assumed to be directly proportional to the density of susceptibles times the density of infectives) the force of infection, $\lambda(t)$, may be defined as

$$\lambda(t) = \beta \int_0^L Y(a, t) da, \quad (5)$$

where L is life expectancy and β is a composite transmission coefficient measuring both the rate at which 'contacts' occur between susceptible and infectious people and the rate at which such contacts give rise to new cases of infection. Note that β is assumed to be independent of either the age of the susceptible or the age of the infective in the 'contact' which generates a new case. The properties of the model defined by equations (1)–(4), hereafter referred to as the *basic model*, are well documented in the literature (see Dietz, 1975; Anderson & May, 1983) and in what follows we simply focus on a few general concepts relevant to later developments.

At equilibrium

$$(\partial X(a, t)/\partial t = \partial H(a, t)/\partial t = \partial Y(a, t)/\partial t = \partial Z(a, t)/\partial t = 0),$$

the fraction of people susceptible at age a , $x(a)$ is simply

$$x(a) = \exp(-\lambda a). \quad (6)$$

We can therefore deduce the force of infection, λ , from information (serological or age specific case notification records) about age-specific susceptibility patterns (see Appendix 2 in Anderson & May, 1983). The average age at first infection, A , is defined as

$$\begin{aligned} A &= \left[\int_0^L \lambda a x(a) da \right] / \left[\int_0^L \lambda x(a) da \right], \\ &= \frac{1}{\lambda} \left\{ \frac{1 - [1 + \lambda L] e^{-\lambda L}}{1 - e^{-\lambda L}} \right\}. \end{aligned} \quad (7)$$

The *basic reproductive rate*, R_0 , defined as the average number of secondary cases produced by one infectious person in a population of susceptible people, is related to the average age at infection, A . Clearly if R_0 is high, A is likely to be low, and vice versa. More precisely, for most childhood infections where A is much less than human life expectancy, L ,

$$R_0 \simeq L/A. \quad (8)$$

If maternally derived antibodies provide a newborn child with protection against infection for D years then a more accurate definition of the relationship between R_0 and A is given by

$$R_0 \simeq L/(A - D). \quad (9)$$

At equilibrium R_0 is also related to the total fraction susceptible in the population, \hat{x} , where

$$R_0 \hat{x} = 1. \quad (10)$$

Hence R_0 may be estimated either from a knowledge of A and L (via equation (8)) or from a knowledge of the total number of susceptibles in a given population (via equation (10)). All the relationships defined by equations (8)–(10) can be derived directly from the equilibrium version of the model expressed by equations (1)–(4), (see Dietz, 1975; Anderson & May 1982, 1983).

Two further properties of the basic model are of general interest. To eradicate an infection by mass immunization it is clearly necessary to create a level of herd immunity such that the effective reproductive rate R must be reduced to less than unity in value (note that the basic reproduce R_0 , records the generation of secondary cases in a population where everyone is susceptible – the effective reproductive rate denotes the generation of secondary cases in a population where a proportion are immune). In other words, each primary case must on average generate less than one secondary case. Under the ‘mass action’ assumption of transmission the effective reproductive rate R is related to R_0 ;

$$R = R_0 x, \quad (11)$$

where x is the fraction susceptible. Alternatively equation (11) may be expressed in terms of the proportion immune p , such that

$$R = R_0(1 - p). \quad (12)$$

To reduce R to less than unity in value we therefore require that the proportion immune in the population exceed a critical value p_c where

$$p_c = [1 - 1/R_0]. \quad (13)$$

This may be achieved by immunizing a proportion greater than p_c of each new cohort of children at or near to birth, or, by immunizing a proportion at age V . In the latter case the critical value of p_c is given by (see Anderson & May, 1982);

$$p_c = [1 + V/L]/[1 + A/L], \quad (14a)$$

if Type II survivorship (constant death rate) is assumed. For the mortality function assumed throughout this paper ($\mu = 0$ up to age L), the corresponding expression is

$$p_c = [1 - 1/R_0]/[1 - V/L]. \quad (14b)$$

These two expressions are essentially equivalent when V/L and A/L are small, as they usually are. The basic model generates weakly damped oscillations in disease incidence to a stable endemic state. The oscillatory behaviour may be perpetuated indefinitely by stochastic (= chance) effects in the growth and decay of susceptible or infectious populations and/or seasonality in transmission (see Bartlett, 1957; Dietz, 1976; Anderson & May, 1979; Yorke *et al.* 1979). Irrespective of the mechanisms which perpetuate the oscillations, however, simple deterministic theory predicts that the oscillations will have an inter-epidemic period, T , approximately given by

$$T = 2\pi(A\kappa)^{\frac{1}{2}}, \quad (15)$$

where A is the average age at infection and κ is the generation time of an infection (the sum of the latent plus infectious periods; $\kappa = 1/\sigma + 1/\gamma$). The estimates provided by equation (15) closely mirror observed oscillatory periods for many common viral and bacterial infections (see Anderson & May, 1982; Anderson, Grenfell & May, 1984).

Mass immunization acts to reduce the net rate of transmission within a population by decreasing the *per capita* force of infection. As such, vaccination will tend to increase the average age at infection over that pertaining prior to control. Interestingly, simple mathematical models suggest that the manner in which mass immunization acts to reduce the force of infection is by decreasing the density of infectious individuals and *not* by reducing the number of susceptibles within a community. The basic model, therefore, predicts that the overall density of susceptibles within a population (in which the infection persists) will remain approximately constant, irrespective of the level of vaccination coverage. Empirical evidence supports this prediction (Fine & Clarkson, 1982*a*, 1984).

Many of the concepts outlined above have important practical implications for the design of disease control programmes based on mass immunization. It is therefore important to remember that, to a large extent, they have been derived from theoretical work based on models which assume that the force of infection within a population is independent of age. This assumption does not in general appear to be correct; a number of studies have provided empirical evidence of apparent age-dependency in transmission rates (Collins, 1929; Griffiths, 1974; Anderson & May, 1982, 1983). We now proceed to assess the sensitivity of the relationships and concepts discussed above to age-related changes in contact with infection.

Age-dependent rates of infection

Age dependency in transmission can be mirrored by one simple modification to the basic model; namely, the replacement of the $\lambda(t)$ term in equations (1) and (2) by a more general function $\lambda(a, t)$. We again assume a 'mass action' form of transmission such that (see May & Anderson, (1984), Schenzle (1985));

$$\lambda(a, t) = \int_0^L \beta(a', a) Y(a', t) da'. \quad (16)$$

Here the term $\beta(a', a)$ denotes the transmission coefficient arising from the contact of susceptibles of age a , with infectious individuals of age a' . The *per capita* force of infection, $\lambda(a, t)$, acting on susceptibles of age a at time t , ($X(a, t)$), is therefore the integral over all age classes of the product of the transmission coefficient, $\beta(a', a)$, times the number of infectious individuals, $Y(a', t)$. In other words, the force of infection is a composite parameter denoting the summed rates of contact of susceptibles within a given age class with infectious people of all age classes within the population. Any given value of the transmission coefficient $\beta(a', a)$ represents two components; namely, contact between two age classes and the likelihood that such contact (if it is between susceptible and infectious persons) will give rise to a new case of infection. It is possible that both components will be functionally related to age in very different ways. For example, the 'susceptibility' of a susceptible or the 'infectiousness' of an infected may vary with age

in a very different manner to that of the degree of contact or mixing between age groups. We suspect, although we are not certain, that age-related changes in contact are of greater importance than age-related changes in inherent susceptibility or infectiousness. For simplicity, we ignore these separate components of the transmission parameters and just consider a composite measure $\beta(a', a)$. In essence, therefore, the term $\beta(a', a)$ may be regarded as denoting 'who acquires infection from whom'. In other words, if the age span from birth to life expectancy, L , is divided into a series of discrete age classes within which the values of $\beta(a', a)$ are constant, for each pair of age classes the transmission coefficients, the β_{ij} 's, form a 'who acquires infection from whom' matrix of values ('WAIFW' matrix). The term β_{ij} simply denotes the transmission rate arising for susceptibles in age class i as a consequence of contact with infectious individuals in age class j .

Formal details of the 'modified basic model', which includes the term $\lambda(a, t)$ as defined in equation (16), and an analysis of its equilibrium properties are given in Appendix A. In what follows in this section we illustrate the principal theoretical conclusions to emerge from model analysis by reference to a series of very simple illustrative samples. We turn to the more complicated patterns relevant to the real world in the results section, and consider their interpretation in light of theoretical analysis by reference to the epidemiologies of specific childhood viral and bacterial infections.

A two-age-class model

By way of illustration, consider a population divided into two age classes; the first containing individuals in the age range 0 to a_1 , and the second containing people of age a_1 to L , where L is life expectancy (as discussed earlier we assume a step function survival curve where mortality is zero up to age L and infinite thereafter). We consider the equilibrium state and focus on age-related changes in the density of susceptibles where

$$\frac{dX(a)}{da} = -X(a) \int_0^L \beta(a, a') Y(a') da', \quad (17)$$

$$\frac{dH(a)}{da} = X(a) \int_0^L \beta(a, a') Y(a') da' - \sigma H(a), \quad (18)$$

$$\frac{dY(a)}{da} = \sigma H(a) - \gamma Y(a), \quad (19)$$

$$\frac{dZ(a)}{da} = \gamma Y(a). \quad (20)$$

The total density of the population, N , is given by

$$N = \int_0^L [X(a) + H(a) + Y(a) + Z(a)] da,$$

and the initial conditions are $H(0) = Y(0) = Z(0) = 0$ and $X(0) = N/L$ (i.e. total population size N constant, where the net birth rate exactly balances the net death rate). The 'who acquires infection from whom' matrix, M , containing the age-specific transmission coefficients, is defined as follows

$$M = \begin{pmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{pmatrix}, \quad (21)$$

where β_{ij} denotes the rate of transmission to susceptibles in age class i arising from contact with infecteds in age class j . The age-specific forces of infection, λ_1 and λ_2 for the two-age-class model are thus

$$\lambda_1 = \int_0^L \beta(1, a') Y(a') da = \beta_{11} \bar{Y}_1 + \beta_{12} \bar{Y}_2, \quad (22)$$

$$\lambda_2 = \int_0^L \beta(2, a') Y(a') da = \beta_{21} \bar{Y}_1 + \beta_{22} \bar{Y}_2, \quad (23)$$

where \bar{Y}_1 and \bar{Y}_2 are the total number of infectious people in age classes 1 and 2 respectively. Thus equation (17) can be solved to yield

$$a_1 \geq a \geq 0, \quad X(a) = X(0) e^{-\lambda_1 a}, \quad (24)$$

$$L \geq a > a_1, \quad X(a) = X(0) e^{-\lambda_1 a_1 - \lambda_2 (a - a_1)}. \quad (25)$$

The total numbers of susceptibles in age classes 1 and 2, \bar{X}_1 and \bar{X}_2 , are easily derived from equations (24) and (25);

$$\bar{X}_1 = \frac{X(0)}{\lambda_1} [1 - e^{-\lambda_1 a_1}], \quad (26)$$

$$\bar{X}_2 = \frac{X(0)}{\lambda_2} e^{-\lambda_1 a_1} [1 - e^{-\lambda_2 (L - a_1)}]. \quad (27)$$

For most childhood infections where $\sigma \gg \lambda_i$ and $\gamma \gg \lambda_i$ (e.g. the average latent ($1/\sigma$) and infectious ($1/\gamma$) periods are a matter of days while the average time stay in a susceptible age class before contracting the infection ($1/\lambda_i$) is a matter of years) it can be shown (see Appendix A) that

$$\bar{Y}_i \approx (X_i \lambda_i) / \gamma. \quad (28)$$

Hence equations (26) and (27) may be expressed in the form

$$\lambda_1 = \beta_{11} \frac{\bar{X}_1 \lambda_1}{\gamma} + \beta_{12} \frac{\bar{X}_2 \lambda_2}{\gamma}, \quad (29)$$

$$\lambda_2 = \beta_{21} \frac{\bar{X}_1 \lambda_1}{\gamma} + \beta_{22} \frac{\bar{X}_2 \lambda_2}{\gamma}. \quad (30)$$

If estimates of λ_1 and λ_2 can be obtained from serological data (or age-stratified case notification records) and γ and X_0 are known, then the only unknown parameter values in equations (29) and (30) are the transmission coefficients, the β_{ij} 's. Unfortunately, however, we have *two* equations in *four* unknowns. Before proceeding to discuss this problem further, various other properties of the model are of relevance.

The total proportion susceptible, x , in the total proportion, N , is

$$x = \sum_{i=1}^2 \bar{X}_i / N, \quad (31)$$

and the average age at first infection, A , is given by

$$A = \frac{\int_0^L a \lambda(a) X(a) da}{\int_0^L \lambda(a) X(a) da}. \quad (32)$$

Hence from equations (26) and (27)

$$A = \frac{[1 - (\lambda_1 a_1 + 1) e^{-\lambda_1 a_1}] / \lambda_1 + e^{-\lambda_1 a_1} [(\lambda_2 a_1 + 1) - (\lambda_2 L + 1) e^{-\lambda_2 (L - a_1)}] / \lambda_2}{[1 - e^{-\lambda_1 a_1 - \lambda_2 (L - a_1)}]}. \quad (33)$$

The concept of a basic reproductive rate needs some modification when the rate of transmission depends on varying degrees of contact between different age classes. It is necessary to define an age-specific basic reproductive rate, R_{0i} , which records the average number of secondary cases (in *all* age classes) generated by one primary case in age class i during the average duration of infectiousness, $1/\gamma$, of the primary case. Hence

$$R_{0i} = 1/\gamma \int_0^L \beta(a, i) N(a) da, \quad (34)$$

where $N(a)$ is the total number of individuals of age a . For a step function survival curve, $N(a) = N/L$ for all age classes, and thus

$$R_{0i} = \frac{N}{\gamma L} \int_0^L \beta(a, i) da. \quad (35)$$

For the two-age-class model

$$R_{01} = \frac{N}{\gamma L} [\beta_{11} a_1 + \beta_{21} (L - a_1)], \quad (36)$$

$$R_{02} = \frac{N}{\gamma L} [\beta_{12} a_1 + \beta_{22} (L - a_1)]. \quad (37)$$

Turning to the question of the eradication of the infection by mass immunization, we can derive a general criterion for the critical proportion to be immunized, p_c , as follows. If a proportion, p , are immunized at, or close to birth, such that q are still susceptible (where $q = 1 - p$), and the new forces of infection under the immunization programme are denoted as λ'_i 's, then the equation for changes in the density of susceptibles with age are:

$$a_1 \geq a \geq 0, \quad X(a) = X(0) q e^{-\lambda'_1 a_1}, \quad (38)$$

$$L \geq a \geq a_1, \quad X(a) = X(0) q e^{-\lambda'_1 a_1 - \lambda'_2 (a - a_1)}, \quad (39)$$

and the total densities of susceptibles in each age class are

$$\bar{X}_1 = \frac{X(0) q}{\lambda'_1} [1 - e^{-\lambda'_1 a_1}], \quad (40)$$

$$\bar{X}_2 = \frac{X(0) q}{\lambda'_1} e^{-\lambda'_1 a_1} [1 - e^{-\lambda'_2 (L - a_1)}]. \quad (41)$$

As the point of eradication is approached all the λ'_i 's must simultaneously tend to zero. Under such circumstances equations (40) to (41) may be simplified such that

$$\bar{X}_1 = \frac{X(0) q}{\lambda'_1} \lambda'_1 a_1, \quad (42)$$

$$\bar{X}_2 = \frac{X(0) q}{\lambda'_1} \lambda'_2 (L - a_1). \quad (43)$$

Hence from equations (29) and (30)

$$\lambda'_1 = \beta_{11} \frac{X(0)q}{\gamma} \lambda'_1 a_1 + \beta_{12} \frac{X(0)q}{\gamma} \lambda'_2 (L - a_1), \tag{44}$$

$$\lambda'_2 = \beta_{21} \frac{X(0)q}{\gamma} \lambda'_1 a_1 + \beta_{22} \frac{X(0)q}{\gamma} \lambda'_2 (L - a_1). \tag{45}$$

By arrangement, and defining $\bar{\beta}_{ij} = \beta_{ij} \frac{X(0)}{\gamma}$

$$0 = \lambda'_1 \left[\bar{\beta}_{11} a_1 - \frac{1}{q} \right] + \lambda'_2 \bar{\beta}_{12} (L - a_1), \tag{46}$$

$$0 = \lambda'_1 \bar{\beta}_{21} a_1 + \lambda'_2 \left[\bar{\beta}_{22} (L - a_1) - \frac{1}{q} \right]. \tag{47}$$

In matrix notation equations (46) and (47) may be expressed as

$$(W - QI)A = 0 \tag{48}$$

where

$$W = \begin{pmatrix} \bar{\beta}_{11} a_1, & \bar{\beta}_{12} (L - a_1) \\ \bar{\beta}_{21} a_1, & \bar{\beta}_{22} (L - a_1) \end{pmatrix}, \tag{49}$$

$$A = \begin{pmatrix} \lambda'_1 \\ \lambda'_2 \end{pmatrix}, \quad Q = 1/q, \quad \text{and}$$

I is the identity matrix.

Besides the trivial solution for equation (49) of $A = 0$, non-trivial solutions will exist if

$$W - QI = 0. \tag{50}$$

Equation (50) is a characteristic equation and the two roots, Q_1 and Q_2 are the eigenvalues of W . In other words, the two roots represent solutions for Q (and hence for the critical level of vaccination p_c required to reduce all the λ_i 's simultaneously to zero since $p_c = (1 - 1/q)$). The largest root in the range 0-1 represents the solution we require. The determinant of equation (50) is simply

$$Q^2 - Q[\bar{\beta}_{11} + \bar{\beta}_{22}(L - a_1)] + a_1(L - a_1) [\bar{\beta}_{11} \bar{\beta}_{22} - \bar{\beta}_{12} \bar{\beta}_{21}] = 0. \tag{51}$$

Given estimates of the $\bar{\beta}_{ij}$'s we can calculate the critical level of vaccination coverage, p_c , to eradicate the infection by solving equation (51) for Q , since $p_c = (1 - 1/Q)$.

All the quantities of epidemiological interest (e.g. A , the R_{0i} 's, and the age profiles of the proportion susceptible to infection) and the criteria of relevance to control by mass vaccination may therefore be calculated for models with age-dependent transmission in a manner similar to that outlined earlier for the basic model. In practical terms, however, a problem arises in connection with the estimation of the β_{ij} 's. The availability of serological data or age-stratified case notification records provides a means for estimating the age-specific forces of infection (the λ_i 's). Each λ_i , however, is a composite measure consisting of the summed products of each β_{ij} times the density of infectious individuals in class j , Y_j . Thus, as illustrated earlier by equations (29) and (30) for a two age class model,

we arrive at a set of n equations in n^2 unknown parameters. On the sole basis of a knowledge of the λ_i 's (all we can expect to estimate in practical terms), it is not possible to calculate a set of unique solutions for the transmission coefficients (the β_{ij} 's). Each age-dependent force of infection represents various degrees of contact with different densities of infecteds in the whole range of age classes within the population. For example, a λ_i value of 0.2 may arise in the case of a two age class population, with 10 infectious individuals in each age class, by zero contact with age class 2 given a β_{ij} coefficient of 0.02 for age class 1, or alternatively, by β_{ij} values of 0.01 for each of the age classes 1 and 2 (see equations (22) and (23)). In short, a knowledge of the age-dependent forces of infection tell us nothing about the various contributions, to a specific λ_i value, arising from varying degrees of contact between the different age classes.

In practice, however, it appears likely that the $n \times n$ matrix ($n =$ the number of age classes) will contain far less than n^2 different β_{ij} values. In other words, many of the coefficients may have identical values. To gain an understanding of the significance of age-dependent transmission we consider the special case in which there are only n different β_{ij} values in the 'who acquires infection from whom' matrix (Schenzle, 1985). In our simple two age model we consider the following 3 β_{ij} matrices, labelled configurations A, B and C.

	Configuration A		Configuration B		Configuration C	
	Age class		Age class		Age class	
	1	2	1	2	1	2
Age class 1	β_1	β_2	β_1	β_1	β_1	β_1
Age class 2	β_2	β_2	β_1	β_2	β_2	β_2

In configuration A, susceptibles in age class 1 have a unique transmission rate, β_1 , arising from contact with infecteds in their own age class and a different transmission rate, β_2 , arising from contact with infecteds in age class 2. Susceptibles in age class 2 have the same transmission rate, β_2 , as susceptibles in age class 1 arising from contact with infecteds in age class 2, for contacts both with infecteds in their own age class and infecteds in age class 1. As such, the age-specific forces of infection, λ_1 and λ_2 are given by

$$\lambda_1 = \beta_1 \bar{Y}_1 + \beta_2 \bar{Y}_2, \tag{52}$$

$$\lambda_2 = \beta_1 (\bar{Y}_1 + \bar{Y}_2). \tag{53}$$

Given information on the density (or proportion) of susceptibles in each age class (from which we can estimate the densities of infecteds - see equation (28)) and

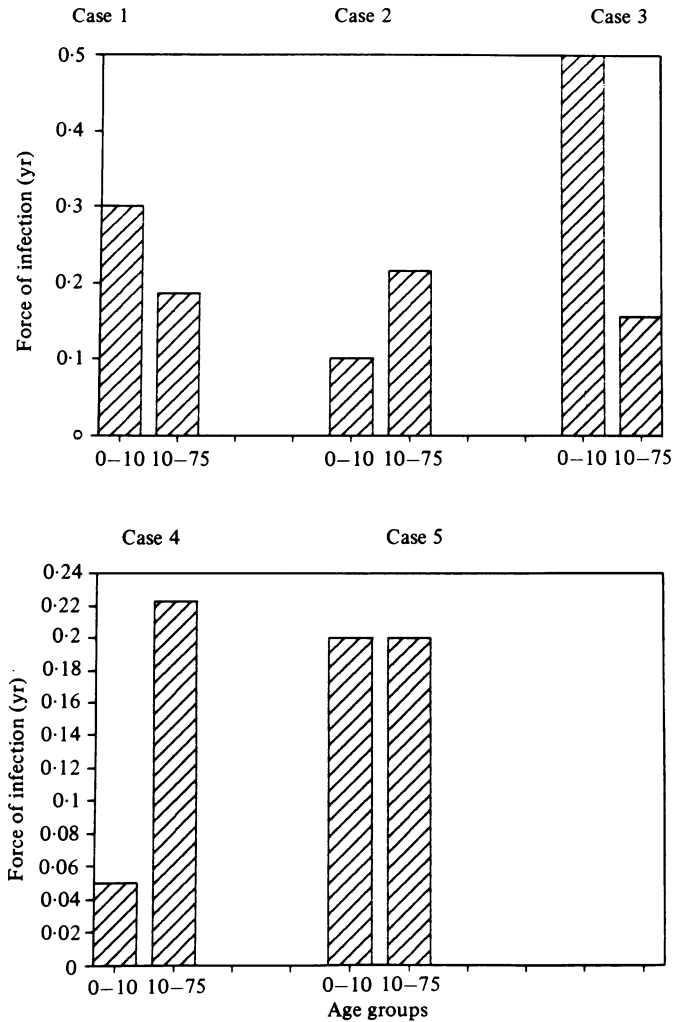


Fig. 1. Two age-class model: the magnitudes of the *per capita* forces of infection λ_1 and λ_2 in age class 1 (0-10 years of age) and age class 2 (10-75 years of age) for cases 1 to 5 (defined as year⁻¹).

estimates of λ_1 and λ_2 (from serological data) we are therefore able to solve equations (52) and (53) to arrive at estimates of β_1 and β_2 . In configuration B susceptibles in age class 1 have identical transmission rates (β_1) arising from contacts with infecteds in age class 1 and age class 2. Susceptibles in age class 2 have the same transmission rate as those in age class 1 (β_1) arising from contacts with infecteds in age class 1 but have a different rate, β_2 , as a consequence of contact with infecteds in their own age class. The two linear simultaneous equations for λ_1 and λ_2 are therefore

$$\lambda_1 = \beta_1(\bar{Y}_1 + \bar{Y}_2), \quad (54)$$

$$\lambda_2 = \beta_1 \bar{Y}_1 + \beta_2 \bar{Y}_2. \quad (55)$$

Table 1. Two age class model (0-10 years, 10-75 years); the values of A , \bar{p} , p_c , A_c , R_{01} and R_{02} for three configurations of the 'who acquires infection from whom' matrix and five different cases of different age-dependent forces of infection

Case	λ_1	λ_2	Average age at infection (A) (in years)	Proportion immune (\bar{p})	Coverage for eradication (p_c)	Average age of infection at eradication (A_c)	R_{01}	R_{02}
Configuration A								
1	0.3	0.185	3.46	0.95	0.93	37.1	15.1	13.9
2	0.1	0.215	8.06	0.89	0.94	37.9	14.3	16.1
3	0.5	0.154	2.06	0.97	0.92	35.8	15.0	11.5
4	0.05	0.223				Negative transmission coefficients		
5	0.2	0.200	5.00	0.93	0.93	69.7	15.0	15.0
Configuration B								
1	0.3	0.185				Negative transmission coefficients		
2	0.1	0.215	8.06	0.89	0.96	41.1	7.5	27.7
3	0.5	0.154				Negative transmission coefficients		
4	0.05	0.223	10.61	0.86	0.95	41.6	3.7	22.2
5	0.2	0.2	5.00	0.93	0.93	69.7	15.0	15.0
Configuration C								
1	0.3	0.185	3.46	0.95	0.93	35.0	22.5	13.9
2	0.1	0.215	8.06	0.89	0.93	40.0	7.5	16.1
3	0.5	0.154	2.06	0.97	0.93	30.0	37.5	11.5
4	0.05	0.223	10.61	0.86	0.93	41.2	3.7	16.72
5	0.2	0.2	5.0	0.93	0.93	69.7	15.0	15.0

Configuration C represents the simplest form of age-dependency in transmission. Susceptibles in any given age class have identical transmission rates arising from contacts with infecteds in all other age classes. The rate of transmission within a susceptible age class is therefore independent of the age class of the infecteds who transmit the infection. However, the transmission rates differ for susceptibles in each age class. In these circumstances the forces of infection are defined as

$$\lambda_1 = \beta_1(\bar{Y}_1 + \bar{Y}_2), \quad (56)$$

$$\lambda_2 = \beta_2(\bar{Y}_1 + \bar{Y}_2). \quad (57)$$

We examine the relevance of these three different configurations in the 'who acquires infection from whom' matrix by means of a series of simple numerical examples. We choose five cases for examination, each case representing a different combination of λ_1 and λ_2 values. These are presented in Fig. 1. A constraint is placed on the forces of infection such that the weighted average value (weighted by the numbers of people in each age class) over all ages, $\bar{\lambda}$, is held constant irrespective of the different age-specific λ_i values. In the simple two age class model where age class 1 contains individuals in the range 0 – a_1 , and age class 2 contains individuals in the range a_1 – L , and assuming a step function survival curve (equal numbers of individuals in each age class), then $\bar{\lambda} = [\lambda_1 a_1 + \lambda_2 (L - a_1)]/L = \text{constant}$. For each case we calculate six equilibrium quantities of epidemiological interest, namely, the average age at infection, A , in the unvaccinated population, the equilibrium proportion of immunes in the unvaccinated population, \bar{p} , the critical proportion of the population, p_c , that must be immunised to eradicate the infection, the average age at infection at the point of eradication of the disease agent, A_c , and the age-specific basic reproductive rates R_{01} and R_{02} (see equations (31), (33), (36), (37), (51) and Appendix A). For the purpose of illustration we consider an infection such as measles in England and Wales where $\bar{\lambda} = 0.2 \text{ year}^{-1}$ (in the absence of age-dependency in transmission, $A = 5$ years), $1/\sigma = 1/\gamma = 7$ days (one-week latent and infectious periods) and $a_1 = 10$ years and $L = 75$ years. For simplicity we assume that the duration of protection provided by maternal antibodies is negligible with respect to the typical age at which the infection is acquired. The results are summarized in Table 1 and age-dependent serological profiles are presented in Figure 2 for two specific cases (case 3 and case 4 – note that the serological profile simply depends on the values of λ_1 and λ_2 and is independent of the configuration of the 'who acquires infection from whom' matrix). A number of important points are illustrated by the results in Table 1.

(1) In three of the 15 numerical examples, the solution of the simultaneous equations for λ_1 and λ_2 (see equations (52)–(57)) gave rise to negative values for either β_1 or β_2 . Quite simply, this implies that for a given pair of λ_i values calculated from serological data, the configuration of 'who acquires infection from whom' specified in the model is not, in practice, possible. For example, with respect to case 3 of configuration B, the low force of infection in age class 2, λ_2 , cannot arise in practice if susceptibles in age class 2 have a high rate of contact with infecteds in age class 1. *In other words, only certain configurations (of all the possible ones) of contact and transmission within and between age classes can generate an observed set of age-dependent forces of infection.*

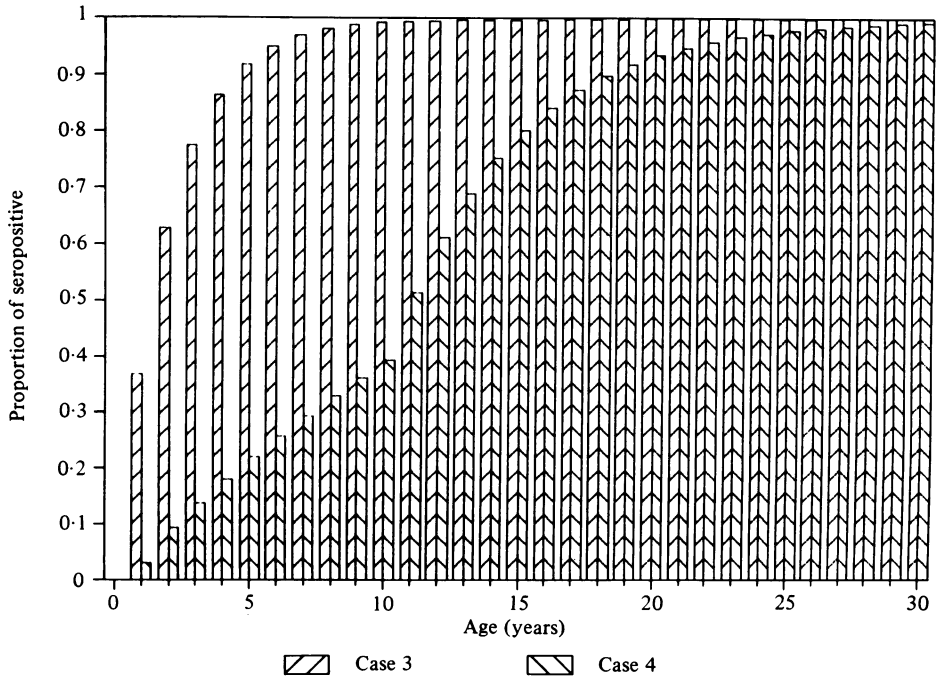


Fig. 2. The age serological profiles (cross-sectional projections) for the proportions seropositive at various ages generated by the forces of infection defined by cases 3 and 4 (see Fig. 1).

(2) When λ is constant and independent of age the proportion immune in the population at equilibrium in the absence of vaccination is equal to the critical level of vaccination coverage required to eradicate the infection (i.e. $\bar{p} = p_c$). Models with constant λ 's predict that the proportion immune (or conversely, the proportion susceptible) remains constant and independent of the level of vaccination coverage (see Anderson & May, 1983). This is not the case, however, if the force of infection changes with age (Table 1). If λ is high in the young age class and low in the old age class (cases 1 and 3 in Table 1) the critical proportion to be immunized to eradicate the infection, p_c , is *less* than the proportion of immunes at equilibrium in the unvaccinated population, \bar{p} . Conversely if λ is low in the young-age class and high in the old-age class, the proportion p_c is *greater* than \bar{p} . This result was first noted by Schenzle (1984) and, as illustrated in Table 1, is independent of the configuration of the β_{ij} matrix for a two age class model. The intuitive explanation of this phenomenon is straightforward. Vaccination acts to reduce the effective reproductive rate of the infection within the community and, as such, acts to increase the average age of infection in the vaccinated community when compared with the unvaccinated population. In the vaccinated population, therefore, as the level of vaccination coverage increases, more and more susceptible individuals are on average of older age when they first experience the infection. Thus if λ is high in the young age classes and low in the old age classes, those who contract the infection do so in an age class with a lower transmission coefficient than was the case before immunization. Under these circumstances the density of susceptibles

in the vaccinated community (at equilibrium) will be *greater* than the density of susceptibles prior to vaccination. This result clearly has very important implications both for the design of immunization programmes and for the interpretations of the impact of an ongoing control programme. Most importantly, estimates of the critical level of vaccination coverage for eradication using models which assume age-independent transmission and based on the weighted average force on infection, $\bar{\lambda}$, overall age classes (the procedure adopted in past research; see Anderson & May, 1983) will *exceed in value* the true level of coverage required in practice given high forces of infection in young age classes and low forces of infection in old age classes. Clearly, the converse situation arises if λ is low in the young-age classes and high in the old-age classes. In this case, calculations of the level of vaccination coverage required for eradication, based on models which assume constant age-independent λ s, will produce an *underestimate* of the true value. The accurate determination of age-related changes in the force of infection is therefore of considerable relevance to the design of immunization programmes.

(3) The average age at infection, A , is independent of the configuration of the 'who acquires infection from whom' matrix since the age serological profile (i.e. age-related changes in the proportions susceptible and immune) is simply determined by the age-specific forces of infection.

(4) The average age at infection A_c , just before the point of eradication of the infection from the community (as the level of vaccination coverage approaches the critical level, p_c) is predicted to be somewhat younger when the rates of infection are age-dependent than is the case if λ is independent of age. The relationship between A_c and the level of vaccination coverage, \bar{p} , is non-linear such that initially A_c increases slowly as p rises. This pattern changes, however, as \bar{p} increases and a rapid rise in the average age at infection is predicted as \bar{p} approaches the critical eradication level, p_c .

The preceding analysis of a simple two age class model well illustrates the significance of age-related changes in transmission for the interpretation of epidemiological data and the design of vaccination programmes. The real situation within human populations, however, is obviously more complicated than that outlined above, since the rates of infection may change with age in more subtle ways than can be mirrored by a two age class structure. For example, λ may change in value from low to high to medium in child, adolescent and adult age groups respectively. In such circumstances, the precise numerical details of these changes will determine whether or not calculations based on a constant age-independent force of infection, overestimate or underestimate the level of vaccination coverage required to eradicate an infection. Similarly, such fine numerical details will also determine the manner in which a vaccination programme influences the average age at infection. This aspect is of particular importance to the study of disease agents in which the chance of serious disease resulting from infection increases with age (e.g. Congenital Rubella Syndrome (C.R.S.) arising from rubella infection in women during their first trimester of pregnancy). In the results section of this paper we turn to these issues. First, we critically assess the empirical evidence for age-dependent patterns in the rate of infection and consider the practical interpretation of such information. Next we analyse the implications of model predictions for the control and epidemiological study of a specific

childhood viral infection, namely, measles. Throughout we place special emphasis on the interpretation of model predictions in light of available epidemiological data.

RESULTS

Age-dependent rates of infection and their interpretation

Four different aspects of the analysis and interpretation of age-dependent rates are examined in this section; namely, (1) information from case reports, (2) epidemics in 'virgin' populations which have not previously been exposed to a given infection, (3) serological data, and (4) the likely impact of other forms of heterogeneity in susceptibility to infection.

(1) *Case reports*

Public health statistics from government authorities in developed countries often provide information on the reported number of cases of various viral and bacterial infections over specified time intervals (i.e. weekly, monthly or by year). In many instances these reports are stratified according to the age of the individuals infected. As described in previous publications (see Griffiths, 1974; Anderson & May, 1983) such information can provide the basis for the estimation of age-dependent rates, or forces, of infection (the λ_i 's). Two major assumptions, however, underpin such estimation procedures. First, it is assumed that horizontal information (i.e. case reports over a short time interval such as one year) represents longitudinal trends. In other words, the cumulative sum of cases up to age i (summed from age 0 to i) divided by the total number of reported cases summed over all age classes, C , is assumed to represent the proportion of individuals of age i , p_i , who have experienced the infection throughout their i years of life. By age L (life expectancy), therefore, all individuals within the population are assumed to have experienced the infection. The graph of p_i versus age i thus represents a constructed 'age-serological' profile (see Anderson & May, 1983, Appendix 2). The questionable point of this procedure concerns the assumption that *all individuals experience the infection* at some point in their life span. Second, implicit in the use of age-stratified case records is the assumption that cases are equally likely to be reported, irrespective of the age of the afflicted individual. This seems highly unlikely.

If we accept these limitations, however, the constructed horizontal profile of those who have experienced the infection by a given age yields information on age-related rates of infection. The *per capita* force of infection, λ_i , over the age interval i to $i+1$ years is simply

$$\lambda_i = -\ln [(1-p_{i+1})/(1-p_i)], \quad (58)$$

where p_i is the proportion who have experienced the infection by age i and, conversely, $(1-p_i)$ is the proportion who are still susceptible by age i (see Anderson & May, 1983). We have employed this technique to analyse a large number of data sets for measles reports in Europe and North America. The results are presented in Figs. 3, 4, 5 and 6. Three histograms are portrayed in each figure representing age-related trends in (a) the number of reported cases, (b) the

proportion who have experienced the infection, and (c) the forces of infection (the λ_i 's). Fig. 3 records such trends for measles in England and Wales for a pre-vaccination year, 1966, and a post-vaccination year, 1980. It is interesting to note in Fig. 3*a*, that a vaccination coverage of approximately 50% of each cohort of children (vaccinated around 2 years of age) from 1967 to 1980, has tended to increase the proportion of cases occurring in older age classes over that pertaining prior to mass immunization (see in particular the 10–15 year age class) (Sutherland & Fayers, 1971). This trend is further illustrated in Fig. 3(*b, c*). The weighted average force of infection, $\bar{\lambda}$ (over the age range 0–25 years), has decreased from approximately 0.233 year⁻¹ in 1966 to approximately 0.192 year⁻¹ in 1980. Most importantly, however, the data presented in Fig. 2(*c*) depicts a clear relationship between the force of infection λ_i and age. The rate of infection increases approximately linearly up to the 5- to 10-year-old age class (see Anderson & May, 1982) and then declines in the 10- to 15- and 15- to 25-year-old age classes. The pattern is similar in both the pre- and post-vaccination years.

Analyses of more extensive data sets, all collected prior to wide-scale immunization are presented in Figs. 4, 5 and 6. The data are for measles cases reported in Baltimore, U.S.A. in the period 1908–17 (Fig. 4), Aberdeen, Scotland in the period 1803–1902 (Fig. 5) and Massachusetts, U.S.A. in the period 1930–40 (Fig. 6). Similar patterns are apparent in all three sets of data. The force of infection again rises approximately linearly in early childhood, peaks in the 5- to 10-year-old age group, and declines thereafter.

Age-related changes are also apparent in case report data for other common childhood viral and bacterial infections. Fig. 7, for example, is similar to Fig. 3, but records age-related trends for pertussis in England and Wales in the years 1956 (before very widescale immunization) and 1980 (the vaccination era). Note that the pattern depicted in Fig. 7(*c*) for pertussis is very similar to that for measles presented in Fig. 3(*c*). Similarly, Fig. 8 presents an analysis of case reports for scarlet fever in England and Wales during 1977. For these data, it is interesting to note that the force of infection remains high in the 10- to 15-year-old age group before declining in the older age classes. A detailed comparison of four infections (measles, mumps, chicken pox and rubella), generated from case reports in Baltimore, U.S.A. during 1963, is presented in Fig. 9. Note the differing forces of infection for the four diseases. Measles has the highest overall transmission rate, chicken pox the next highest, rubella the next, and mumps the lowest overall rate of transmission. This trend is also mirrored by other epidemiological variables such as the mean age of infection, A (lowest for measles, highest for mumps and rubella) and the interepidemic period, T (2–3 years for measles and chicken pox, 3–4 years for mumps, and 3–5 years for rubella). Most importantly, however, age-related changes in the force of infection are broadly similar for all four infections. The peak rate, however, may occur in either the 5- to 10-year-old age class (measles) or the 10- to 15-year-old age class (mumps, chicken pox and rubella). Unfortunately, detailed data are not available for the older age class. We suspect, however, that the rate would decline, as portrayed for measles in Figs. 3–6.

The analyses presented in Figs. 3–9 depict broadly similar patterns. The force of infection appears to be highly dependent on age varying in value from low to high back to low via the 0 to 5, 5 to 10 and 10- to 20-year-old age classes. A

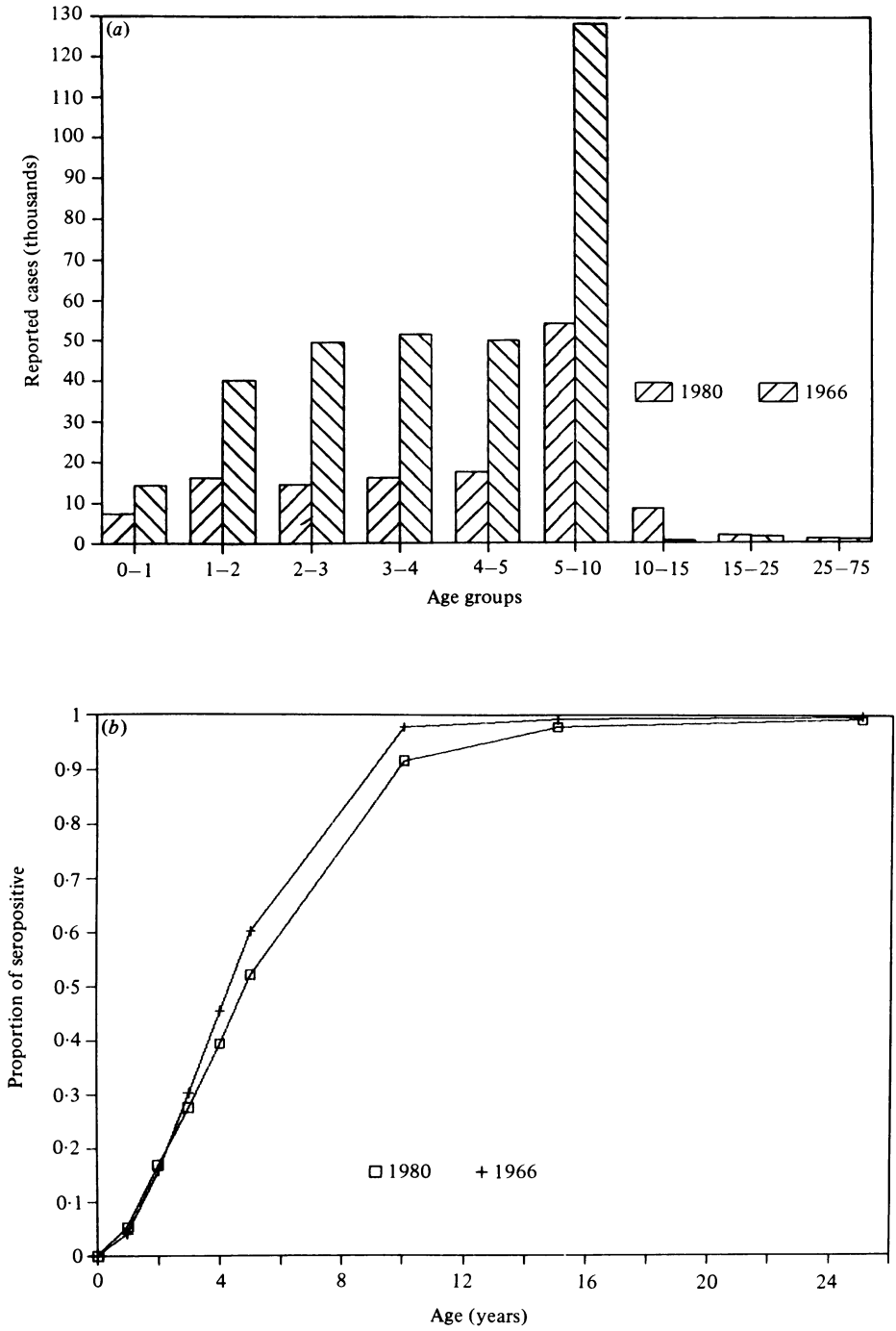


Fig. 3a-b. For description see opposite.

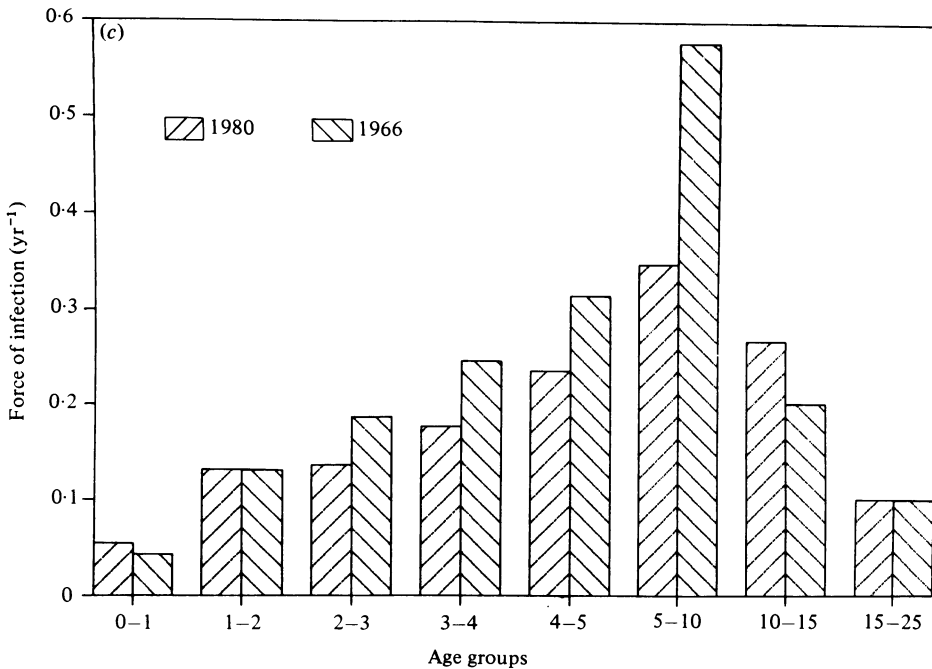


Fig. 3. (a) Reported cases of measles in England and Wales for 1966 and 1980. (b) estimated age-serological profiles (calculated from age-specific case reports) for measles infection in England and Wales during 1966 (prevaccination era) and 1980 (vaccination era) (data source: Annual Review of the Registrar General of England and Wales (1966) and Office of Population Censuses and Surveys (1980)). (c) The age-specific forces of infection, the λ_i 's, calculated from the predicted serological profiles recorded in (b) for measles infection in 1966 and 1980 (defined as year⁻¹).

summary of a range of data sets is presented in Table 2. Some caution is necessary, however, in the interpretation of these patterns. First, it could be argued that the similarity in the trends for measles in different geographical localities and at different times, plus the broadly similar trends for other infections such as pertussis, mumps, chicken pox, rubella and scarlet fever, reflect underlying differences in contact rates within and between different age groups. In other words, the explanation of such trends could be based solely on behavioural and social factors. However, the patterns could equally well represent consistencies in an age-related bias in the reporting of cases of infection. Without additional information we are unable to discriminate between these two alternative explanations of observed trends in case reports. The second problem concerns the number of reported cases relative to the total numbers of individuals in each class of the population. Our method of analysis assumes an approximately uniform age distribution in the population from birth to life expectancy. This is a reasonable assumption for many developed countries in the past decade or so but is less good for the earlier periods. Since the net rate of transmission is in part dependent on population density, certain of the case report data sets may be somewhat biased by uneven age distribution. Ideally, age-stratified case reports should be stan-

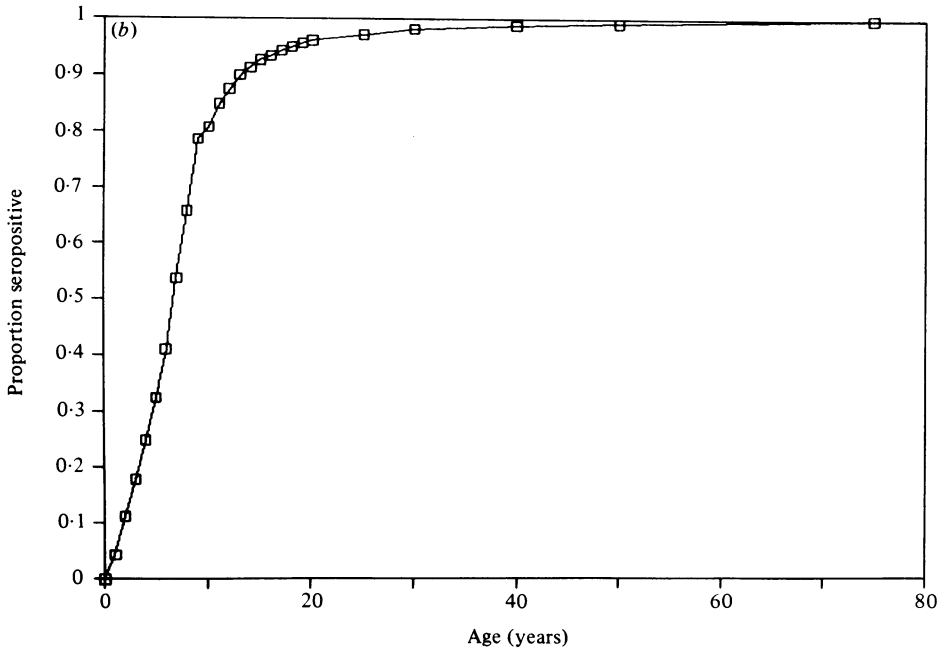
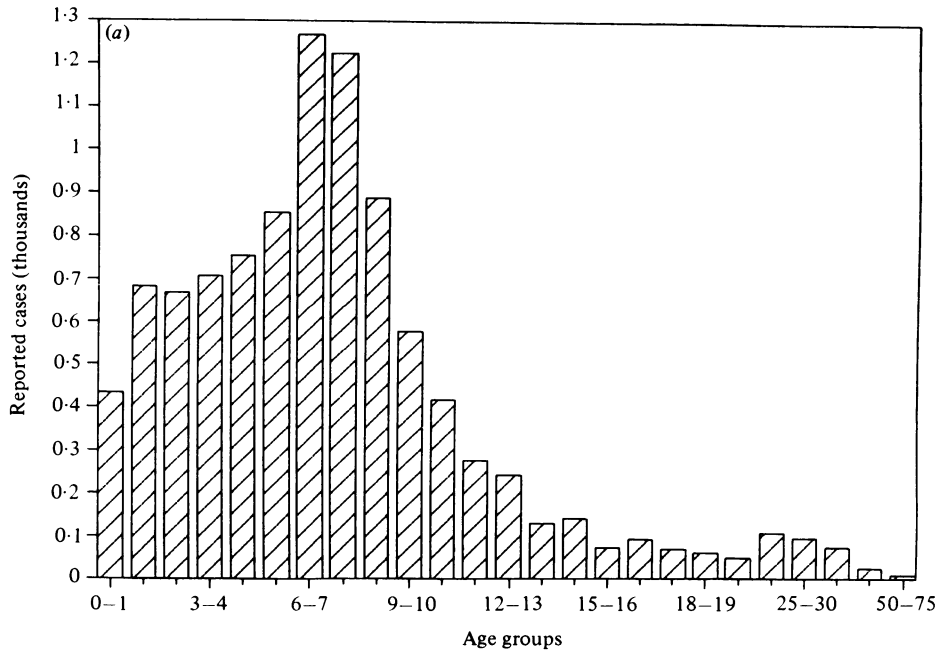


Fig. 4a-b. For description see opposite.

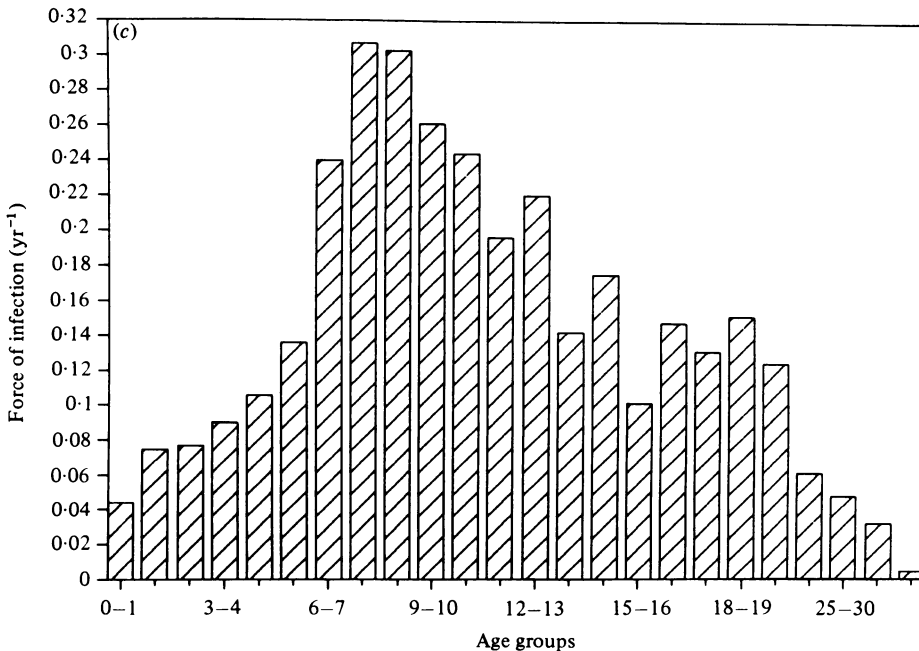


Fig. 4. Similar to Fig. 3 but representing case reports of measles in Baltimore, U.S.A. during the period 1908-17 (data source; Fales, 1928). (a) Case reports; (c) predicted serological profile; (c) age-specific forces of infection (year⁻¹).

standardized according to the total number of individuals in each age class. This is not always possible in the absence of detailed demographic data.

(2) Case reports from epidemics in 'virgin' populations

Outbreaks, or epidemics, of infection in populations who have never previously been exposed to a specific disease agent (or not been exposed for a long period of time (i.e. a period of decades)), can provide valuable information on age-specific attack rates. The course of such epidemics are of course unhindered by herd immunity arising from previous exposure. We consider three sets of data. The first represents an epidemic of measles in the Shetlands in 1977-8 (Fig. 10). Some exposure to infection had occurred in the past and a proportion of the population had been immunized. However, the population had an unusually high proportion of susceptible individuals prior to the epidemic (Macgregor *et al.* 1981). The second concerns an epidemic of measles in Southern Greenland in a totally susceptible population in 1951 (Fig. 11) (Christensen *et al.* 1953). The final example deals with an epidemic of rubella in Alaska in 1963 (Fig. 12) within a largely susceptible population (Broady *et al.* 1965).

For the measles epidemic in the Shetlands we present in Fig. 10 the case reports (standardized per 1000 head of population), the constructed horizontal profile of the proportion who have experienced the infection in relation to age, and the age-dependent forces of infection. We have treated the case reports in a similar manner to that outlined in the previous section in order to estimate the λ_i 's for

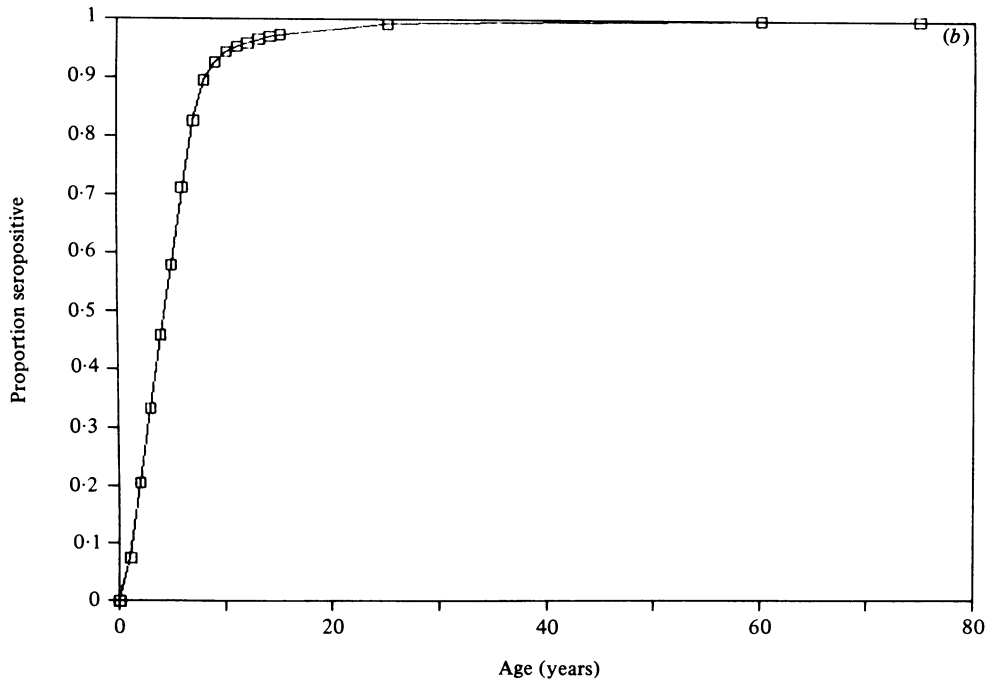
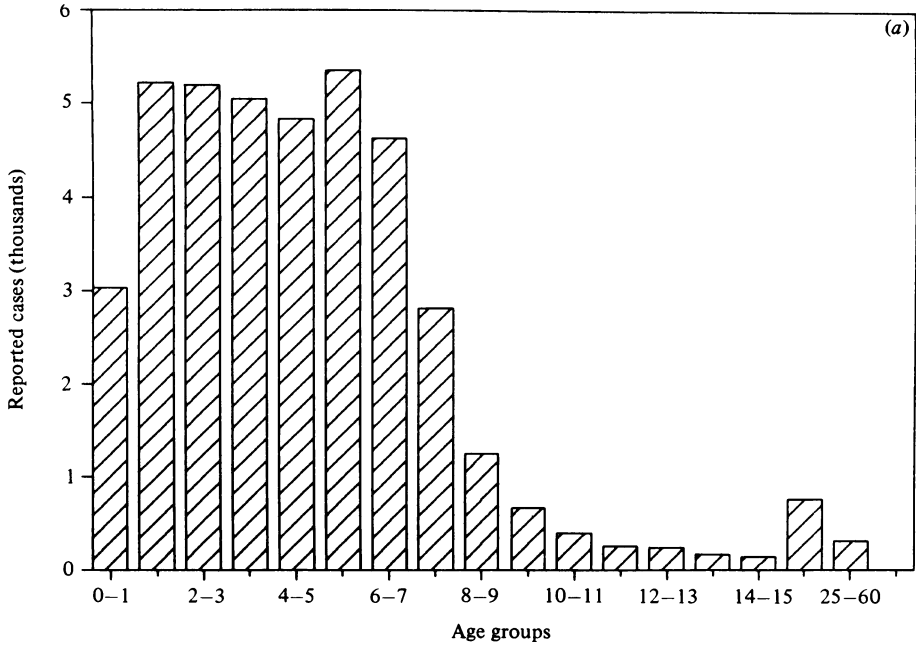


Fig. 5a-b. For description see opposite.

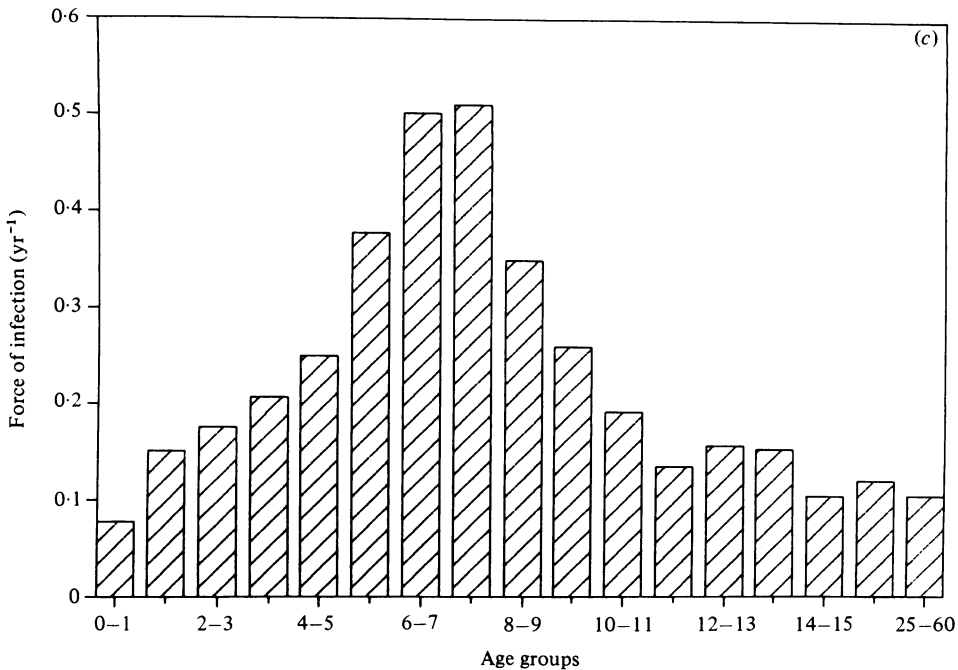


Fig. 5. Similar to Fig. 3 but representing case reports of measles in Aberdeen, Scotland during the period 1803-1902 (data source: Wilson, 1904). (a) Case reports; (b) predicted serological profile; (c) age-specific forces of infection (year^{-1}).

each age class. As can be seen in Fig. 10(c), the forces of infection do vary with age but much less dramatically than was the case in the communities with endemic measles infection. In particular, the rate of infection remains relatively high (relative to its peak value in the 15-25 age group) in the adult age classes. Also note that the force of infection attains its maximum value in the 15-25 age span.

The second example is of greater relevance since prior to the epidemic of measles the population in Greenland was essentially 100% susceptible to the infection. The proportion of each age class who experienced measles infection are presented in fig. 11. The attack rate is uniformly high although there is a minor trend for lower rates of infection in the very young (0-1 age group) and the very old (55-75 age group).

The third and final example of a rubella epidemic in Alaska is again within a highly susceptible population. A previous epidemic had occurred 20 years before the 1963 outbreak. The proportion sero-positive for rubella antibodies, both prior and post epidemic, are presented in Fig. 12. As for the measles epidemic in Greenland, the attack rate is uniformly high across all age groups.

These three examples suggest that, within 'virgin' (or 'semi-virgin') populations, age-related trends in the force of infection are less dramatic than those discussed in the previous section for populations with endemic infection. Most importantly, they reveal a much less marked decline in λ within the adult age classes when compared with the child age groups. It should be remembered, however, that social

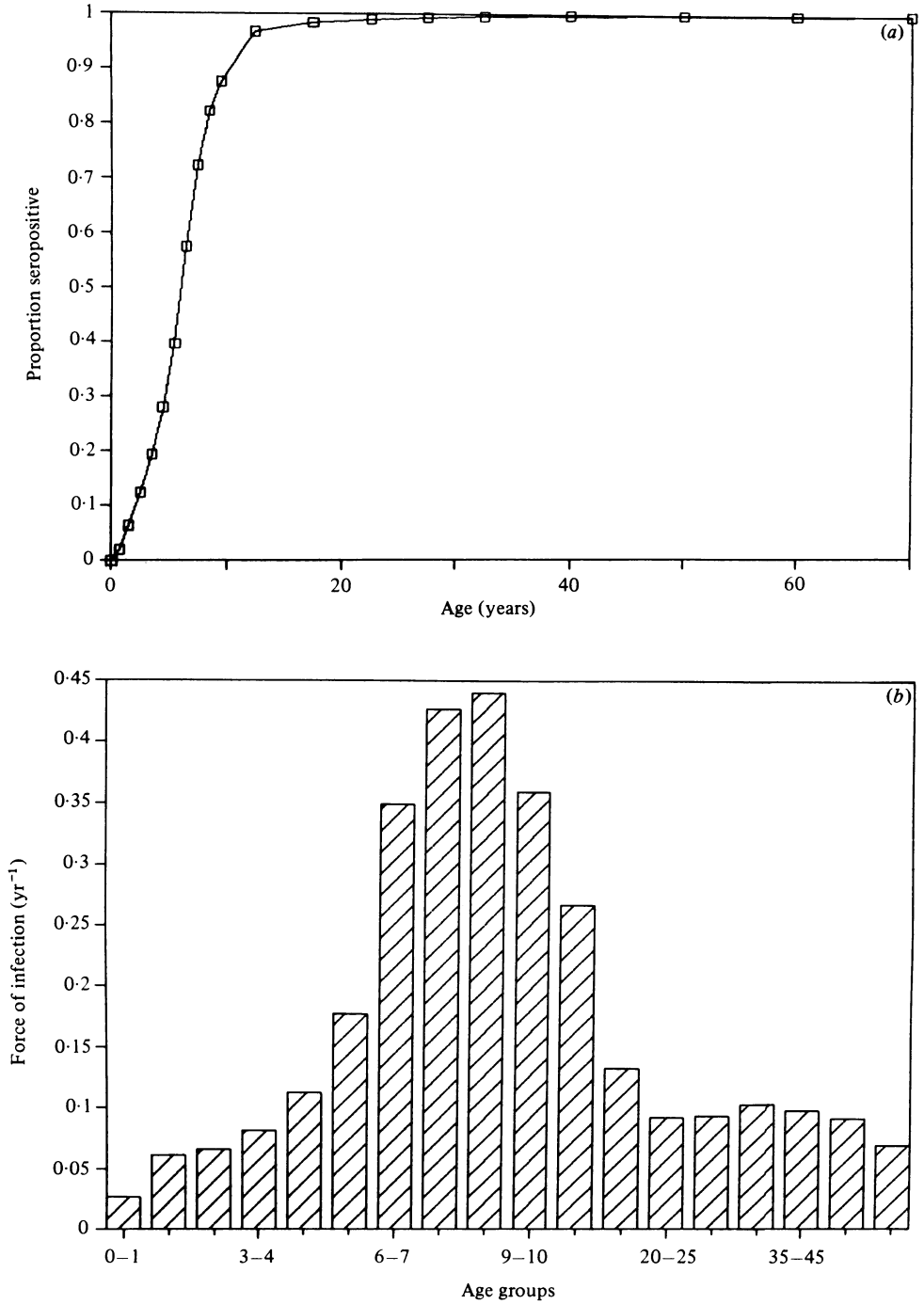


Fig. 6. Similar to Fig. 3 but representing case reports of measles in Massachusetts, U.S.A. during the period 1930-40 (data source: Wilson & Worcester, 1941). (a) Predicted serological profile; (b) age-specific forces on infection (year^{-1}).

and behavioural factors within such isolated communities may influence these observations. For example, given the prevailing climatic conditions in the Shetlands, Greenland and Alaska, it is likely that individuals spend greater periods of time in close contact within dwellings than would be the case in England and Wales. Furthermore the lower economic status of small island communities implies larger family sizes and fewer rooms per person in the average household than is the case in more affluent mainland communities. Such factors may conspire to maintain the rate of infection at a relatively high level amongst adult age groups.

(3) *Serological data*

The most reliable information for estimating age-dependent rates of infection is undoubtedly provided by serological survey. Unfortunately, however, few such studies have been carried out on a sufficient scale, and with adequate age stratification in the sampling programme, to provide the required information prior to the introduction of mass immunization. Post-immunization studies are of little relevance since age-related rates of vaccination confound the interpretation of the data.

We examine information from one pre-vaccination study in the United States (Black, 1959) and one post-vaccination study in England and Wales, in Figs. 13 and 14 respectively (Dr C. Miller, PHLS, personal communication). The survey of Black in New Haven, Connecticut, involving the testing of 302 sera shows clearly the decay in maternal antibody in early life followed by a rapid rise in positive scores during childhood before the attainment of a plateau at around 96% in the early adult age groups (Fig. 13*a*). Thereafter the proportion positive decays slightly to around 86% in the plus 50-year-old age class (Fig. 13*a*). The age-related forces of infection calculated from this information are presented in Table 2.

The geometric mean neutralizing antibody titres rise during childhood to reach a peak value in the 10- to 15-year-old age group before exhibiting a significant decay during adult life (Fig. 13*b*). Black (1959) notes that a definite positive correlation was found between the presence of measles antibodies and a positive history of the disease, but this relationship did not hold in all instances. This point raises doubts concerning the reliability of case notification records. The intriguing question surrounding these serological results, however, concerns 4–5% of individuals in the 15- to 30-year-old age class who appeared not to have experienced the infection. The presence of such individuals is largely responsible for the low forces of infection recorded for the older age groups.

Black (1959) concluded that negative sera in the older age groups probably came from individuals who had experienced measles infection but whose antibody titres had since decayed to undetectable levels. Genetic factors, for example, undoubtedly play a role in determining the level of antibody production following infection. Evidence for a decay in antibody titre through time is provided by the age-related trend of the geometric mean titres depicted in Fig. 13*b*). This argument, however, is but one of a number of plausible explanations. Undoubtedly, the sensitivity of the serological test employed (particularly in the detection of very low antibody titres) and the duration of antibody life and production following infection are important factors in determining the patterns of age-dependent rates of infection

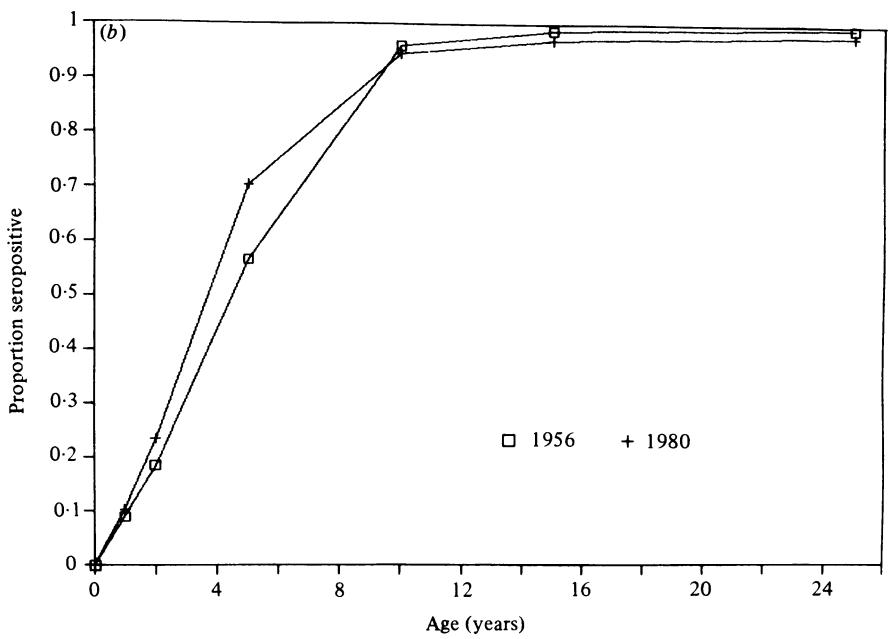
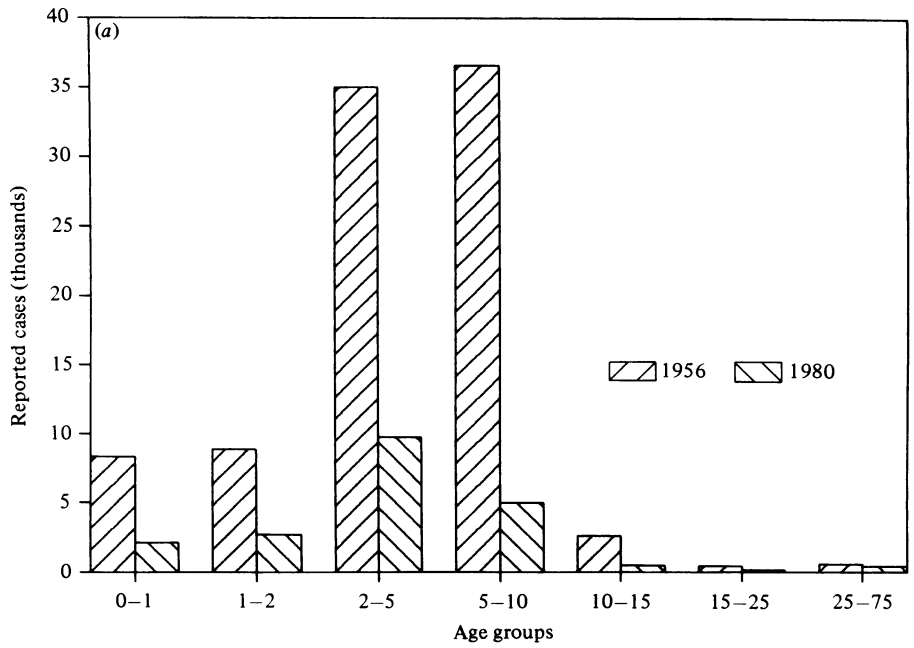


Fig. 7 a-b. For description see opposite.

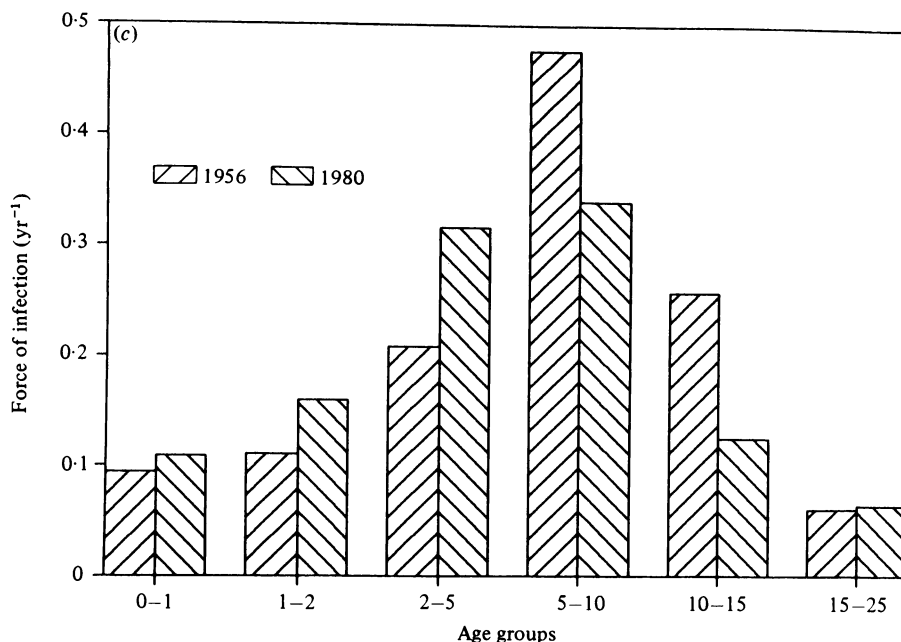


Fig. 7. Similar to Fig. 3 but representing case reports of whooping cough in England and Wales during 1956 (before very widescale vaccination) and 1980 (the vaccination era) (data source: as defined in the legend to Fig. 3). (a) Case reports; (b) predicted serological profile; (c) age-specific forces of infection (year⁻¹).

resulting from analysis of horizontal serological surveys. It is possible, however, that certain individuals within a population are not susceptible to infection, either as a consequence of social or behavioural factors (e.g. people living in very isolated locations with little contact with other children or adults in the community) or as a result of genetic factors determining specific or non-specific host responses to viral infection. Genetic factors may determine both the level of antibody production following infection, the degree of contact with infectious individuals required to induce infection and the degree to which an individual 'infected' is infectious to others. At present, however, little is understood concerning these issues. If the serological data is assumed to accurately reflect the proportions who have experienced the infection at different ages, then the calculated rates of infection exhibit a marked dependency on age (see Table 2). In a manner similar to that portrayed by the analyses of the case notification records, the force of infection appears to vary from a low value in young children to a high value in the 5- to 15-year-old age group and back to a low value in the 15- to 20-year-old age class. Under such circumstances, those individuals who escaped infection during childhood will have a very low probability of contracting the infection in adult life and hence may remain susceptible until death.

Further evidence for the existence of a small proportion of individuals in the adult age groups who appear, on the basis of serological test, not to have experienced the infection is provided by a small unpublished serological survey carried out in England and Wales during 1979-83 (Dr D. Miller, PHLS). The

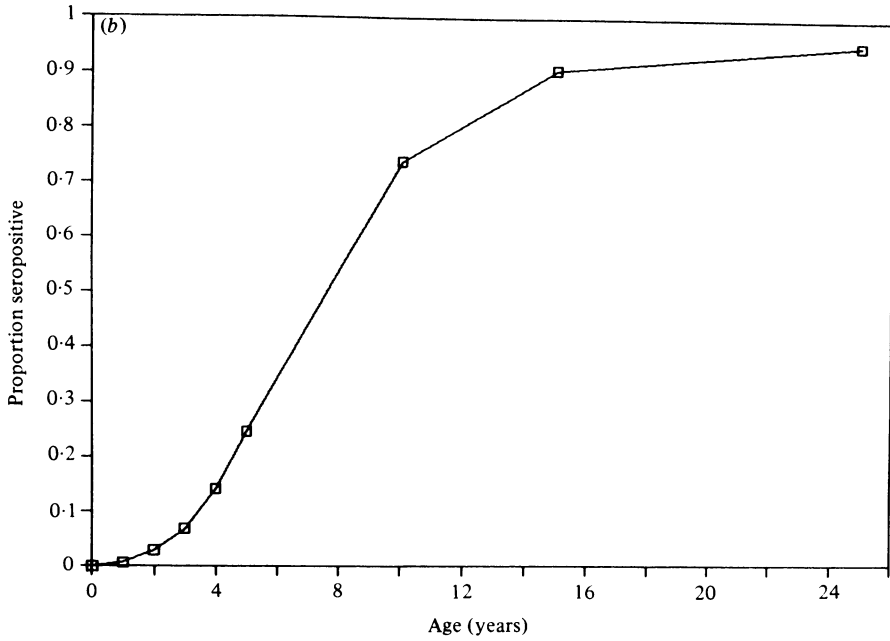
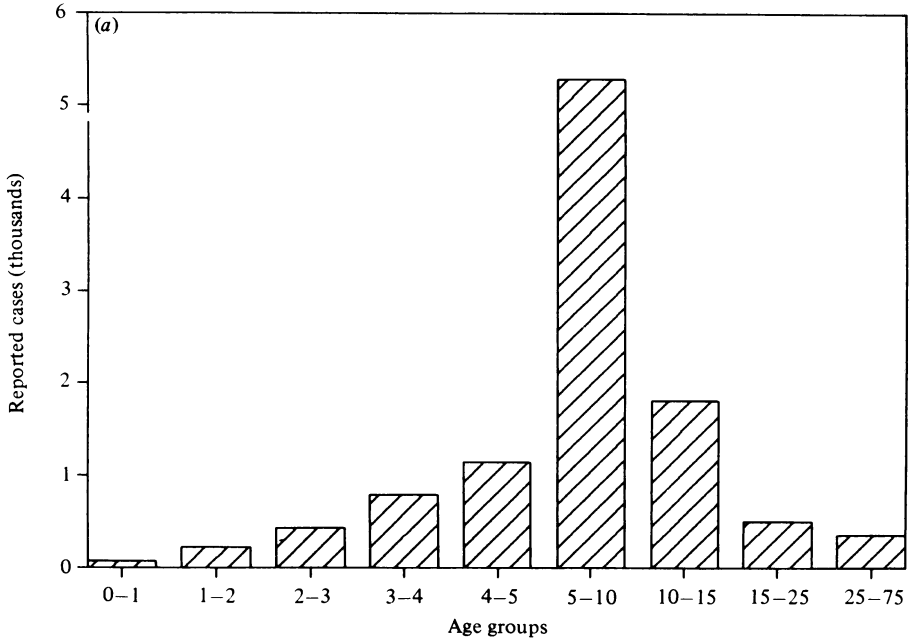


Fig. 8a-b. For description see opposite.

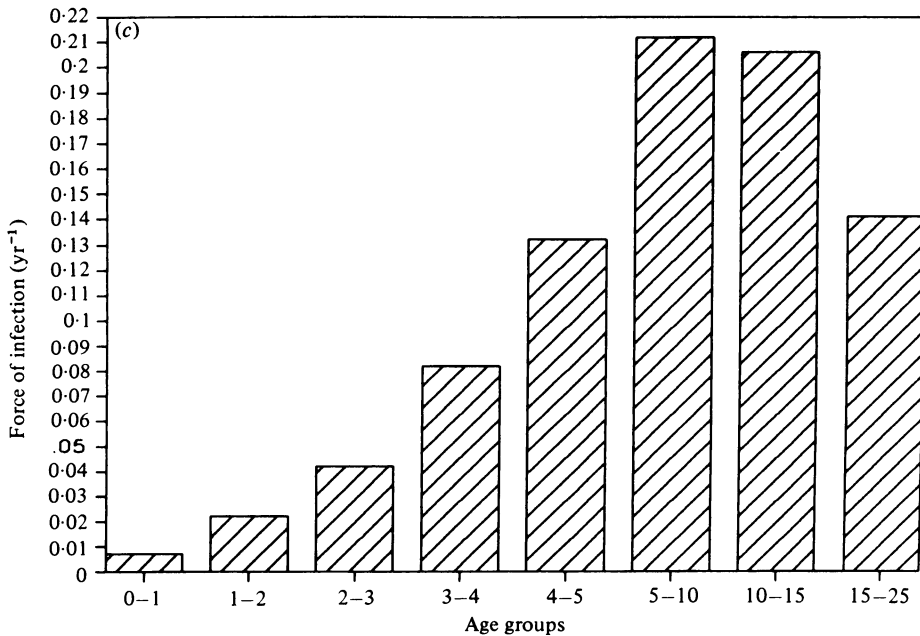


Fig. 8. Similar to Fig. 3 but representing case reports of scarlet fever in England and Wales during 1977 (data source: Annual Review of the Registrar General of England and Wales, 1977). (a) Case reports; (b) predicted serological profile; (c) age-specific forces of infection (year⁻¹).

results are portrayed in Fig. 14, from which it can be seen that 3-4% of adults (18- to 30-year-old age class) appear to remain seronegative for measles antibody. The rapid rise in seropositive individuals during early childhood is a simple consequence of the mass vaccination of 2- to 3-year-old children (roughly 50% of each cohort of children) from 1967 to the present day in England and Wales. The interpretation of these results, however, is made complicated by the impact of vaccination on the prevailing rates of infection.

(4) *Heterogeneity in susceptibility/exposure to infection*

To further our understanding of the various factors that may generate patterns of apparent age-dependency in the rates of infection we consider in this section the consequences of *age-independent* heterogeneity in susceptibility or exposure to infection. We are concerned specifically with the impact of such factors on age-serological profiles and the net rates of infection in each age class that generate the profiles.

Consider a population consisting of two groups of individuals (groups I and II) who differ in their innate susceptibility to infection for either genetic, social or behavioural reasons. It is assumed that susceptibility is unrelated to the age of the individuals in either group. A fraction $(1-f)$, of new births are assumed to belong to group I and the remaining fraction, f , to group II. If the forces of infection acting on susceptibles in group I and group II are defined as λ_1 and λ_2

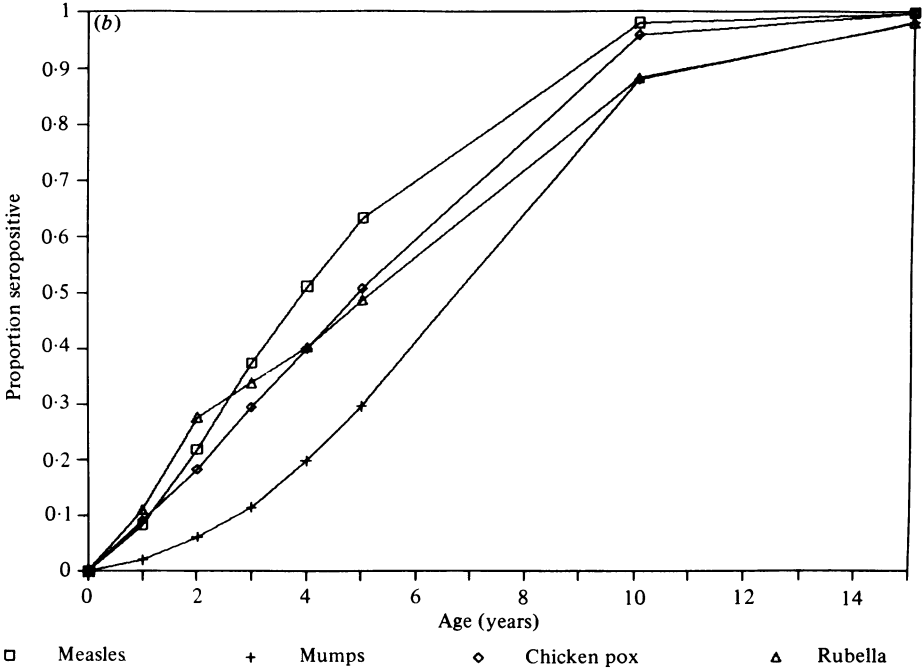
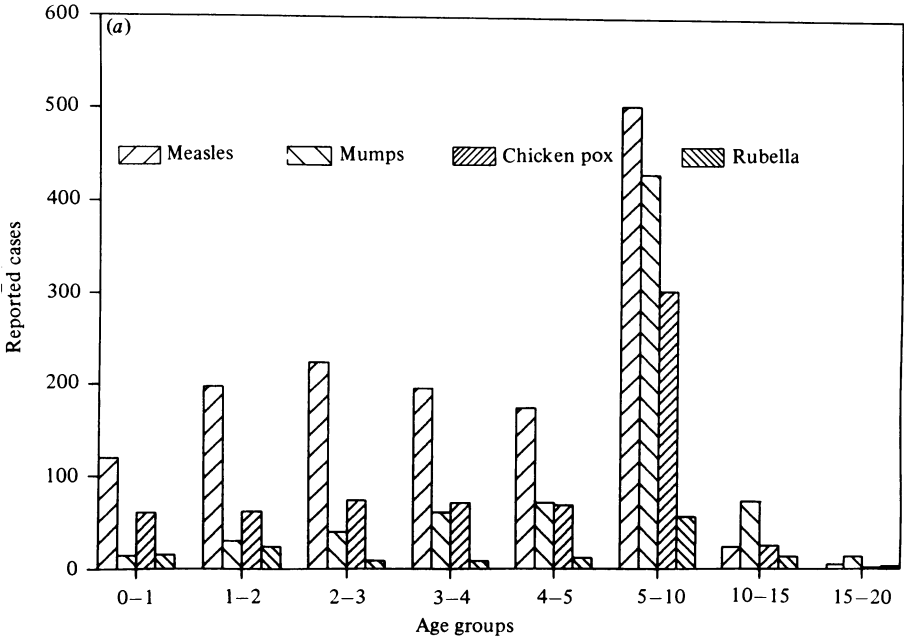


Fig. 9a-b. For description see opposite.

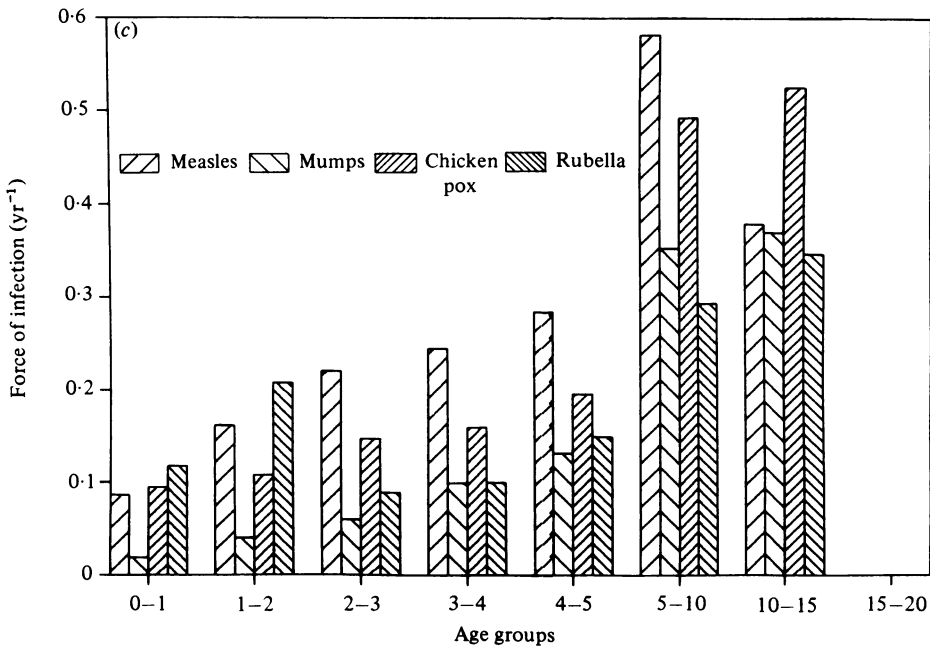


Fig. 9. A comparison of the number of reported cases of measles, mumps, chicken pox and rubella in Baltimore, U.S.A. during 1963 (data source: Baltimore Public Health Reports, 1963). (a) Case reports; (b) predicted serological profile; (c) age-specific forces of infection (year^{-1}).

respectively, then at equilibrium the proportion of susceptibles in the total population (groups I and II combined) of age a , $x(a)$, is given by

$$x(a) = (1-f) e^{-\lambda_1 a} + f e^{-\lambda_2 a}. \quad (59)$$

The forces of infection are defined as

$$\begin{aligned} \lambda_1 &= \beta_1(\bar{Y}_1 + \bar{Y}_2), \\ \lambda_2 &= \beta_2(\bar{Y}_1 + \bar{Y}_2) \end{aligned} \quad (60)$$

where β_1 and β_2 are the respective transmission coefficients of the two groups (which define the rate of contact between susceptible and infected individuals and the likelihood that a contact gives rise to infection) and \bar{Y}_1 and \bar{Y}_2 are the total densities of infectious individuals at equilibrium in each group. The properties of this model are fully defined in Appendix B.

Two serological profiles generated by equation (59) are displayed in Fig. 15(a) (the proportion immune at age a , $y(a)$, is simply $1-x(a)$). In both examples the forces of infection λ_1 and λ_2 were held constant, and independent of age, at values of 0.2 year^{-1} and 0.04 year^{-1} for groups I and II respectively. In one example, the value of f was set at 0.05 and in the other case the value was set at 0.15 (5 or 15% of the new births belonging to group II). As is clear from Figure 15a, in both examples a small proportion of individuals remain susceptible in the adult age classes. The explanation is straightforward. Individuals in group I who are highly

Table 2. Measles: age-dependent forces of infection (λ_i 's year⁻¹)

Geographical location and data	Age classes ... λ_i 's						$\bar{\lambda}$	Type	Reference
	0-5	5-10	10-15	15-20	20-75	75+			
Aberdeen, Scotland, 1883-1902	0.172	0.400	0.149	0.121	0.105	0.133	0.133	Case notifications	Wilson (1904)
Willesden, London, England, 1913	0.089	0.340	0.143	—	—	—	—	Case notifications	Butler (1913)
Maryland, U.S.A., 1908-17	0.078	0.250	0.195	0.131	0.030	0.065	0.065	Case notifications	Fales (1928)
Massachusetts, U.S.A., 1930-40	0.074	0.370	0.150	0.150	0.0914	0.117	0.117	Case notifications	Wilson & Worcester (1941)
Shetlands, U.K., 1977-8	0.049	0.100	0.100	0.109	0.045	0.057	0.057	Case notifications	Macgregor <i>et al.</i> (1981)
Baltimore, U.S.A., 1963	0.200	0.582	0.379	—	—	—	—	Case notifications	Baltimore Public Health Reports
London, Ontario, Canada, 1912-13	0.088	0.240	0.220	—	—	—	—	Case notifications	Henderson (1916)
Baltimore, U.S.A., 1900-31	0.124	0.320	0.176	—	—	—	—	Case notifications	Hedrich (1933)
Providence, R.I., U.S.A., 1917-24	0.190	0.440	0.114	—	—	—	—	Case notifications	Chapin (1926)
England and Wales, 1966	0.184	0.579	0.202	0.100	—	—	—	Case notifications	Registrar General Annual Reports
England and Wales, 1980	0.148	0.348	0.268	0.101	—	—	—	Case notifications	Registrar General Annual Reports
Denmark, 1971-72	0.171	0.278	0.155	—	—	—	—	Case notifications	Horwitz <i>et al.</i> (1974)
New Haven, Conn., U.S.A., 1955-8	0.100	0.240	0.362	0.086	—	—	—	Serology	Black (1959)
Average values	0.121	0.345	0.201	0.114	0.068	—	—	—	—

'susceptible' to infection ($\lambda_1 = 0.2 \text{ year}^{-1}$) rapidly acquire the disease in early childhood and become immune to further infection. In the teenage and adult age classes the remaining susceptibles are predominantly individuals from group II. These have a low 'susceptibility' ($\lambda_2 = 0.04 \text{ year}^{-1}$) and thus many remain uninfected throughout adult life. As illustrated in Fig. 15(b), the net force of infection appears to decline with age. If we were ignorant of the presence of the two groups of individuals with differing innate susceptibilities, the information recorded in Fig. 15(b) would suggest strong age-dependency in contact with infection. In reality, however, this 'apparent age-dependency' is generated by varying proportions of the two susceptibility groups remaining in the susceptible class at different ages. In early childhood most susceptibles belong to group I, while in the adult age classes most belong to group II. This simple example of the impact of *age-independent* heterogeneity in susceptibility raises obvious problems in the interpretation of observed age-related patterns in transmission. In the absence of additional information it is not possible to ascertain whether or not these patterns are a consequence of real variation in the *per capita* rate of infection with age. This problem is of great practical significance with respect to the design of vaccination programmes. As illustrated earlier, in the section describing the properties of a two age class model, the precise numerical detail of actual (as opposed to apparent) age-dependent contact with infection is an important determinant of the level of vaccination coverage required to eradicate an infection (the value of the parameter p_c). For example, in our *two 'susceptibility' class model*, λ values of 0.2 year^{-1} and 0.4 year^{-1} in groups I and II, concomitant with an f value of 0.05 , suggest a vaccination coverage of 93.3% for eradication of a disease such as measles (i.e. incubation and infection periods each of 7 days). If we now estimate the 'apparent age-dependent infection rates' for two age classes, 0–10 years of age and 10–75 years of age, from the serological profile (see Fig. 15(a)) generated by the two susceptibility class model, we arrive at values of $\lambda_1 = 0.182 \text{ year}^{-1}$ for age class 1 and $\lambda_2 = 0.061 \text{ year}^{-1}$ for age class 2. If these values are then employed in a *two age class model* (with a 'who contracts infection from whom' matrix of configuration A) we arrive at a predicted vaccination coverage of 79% for eradication. These results (and other relevant epidemiological statistics) are summarized in Table 3. The importance of the point made by this simple numerical example hardly needs stressing. If we assume that susceptibility to infection is heterogeneous, *independent* of age, we predict a critical vaccination significantly greater than that predicted if we assume that heterogeneity in susceptibility is a consequence of *age-dependent* changes in contact with infection. There is no simple solution to the dilemma since in practical terms the only data likely to be available are the forces of infection derived from case notifications or serological survey. We return to these issues in the discussion and summary sections of the paper. In the following section we consider the significance of age-related heterogeneity in the rate of infection for the design of vaccination programmes for measles. Our analyses assume that the observed trends are indeed a consequence of age-dependent changes in contact with infection, and not apparent age-dependency generated by other sources of heterogeneity.

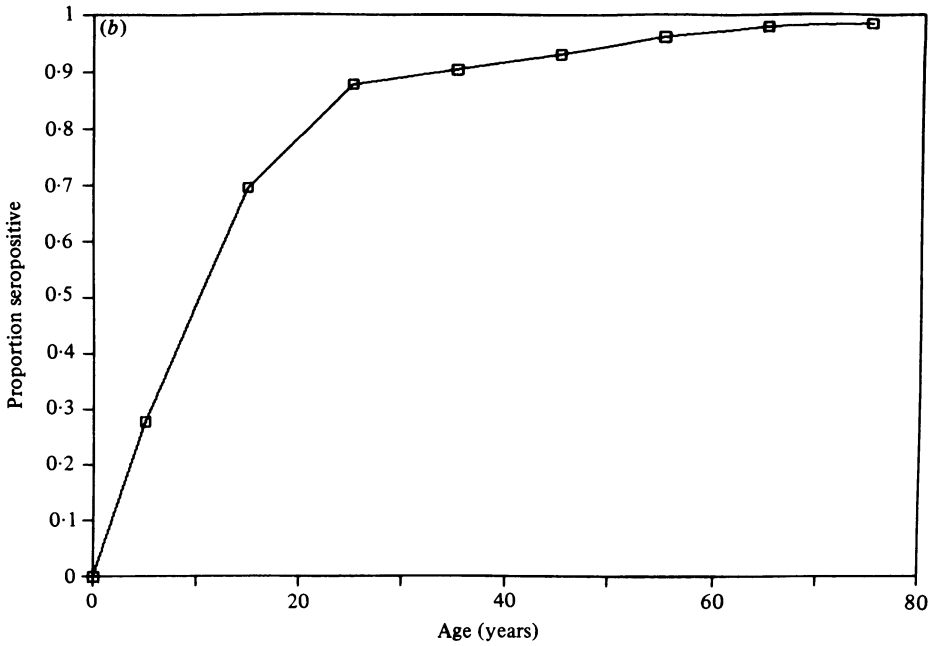
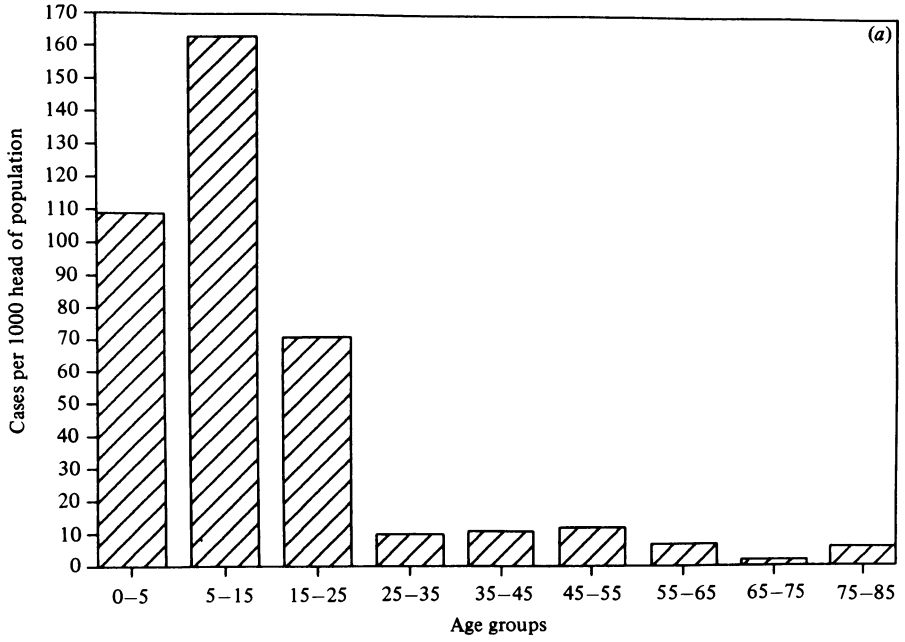


Fig. 10a-b. For description see opposite.

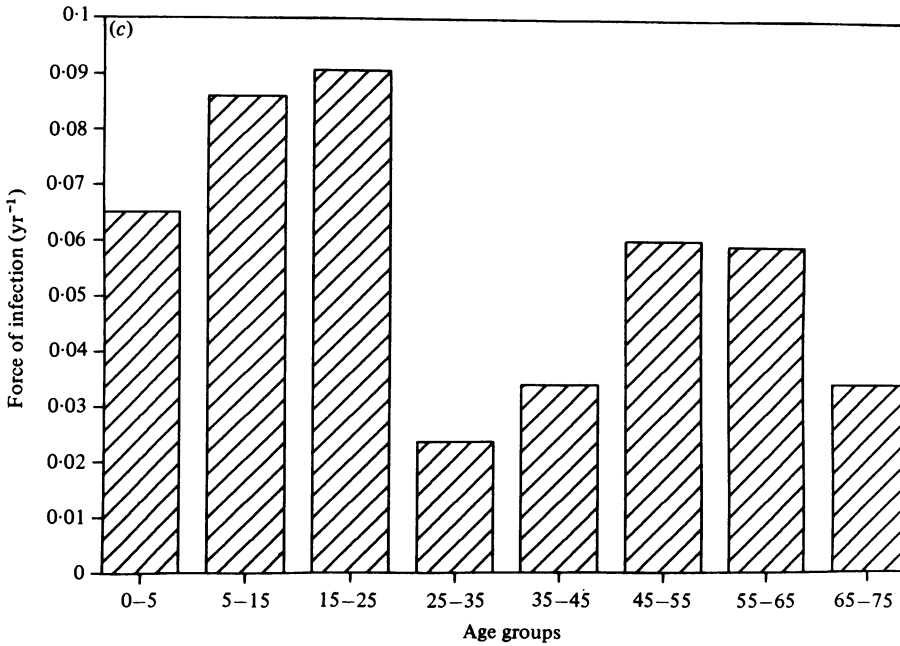


Fig. 10. Epidemics in 'virgin' populations. An epidemic of measles in the Shetlands, U.K. during the period 1977-8 (data source; Macgregor *et al.* 1981). (a) Case reports; (b) predicted serological profile after the epidemic; (c) age-specific forces of infection (year^{-1}).

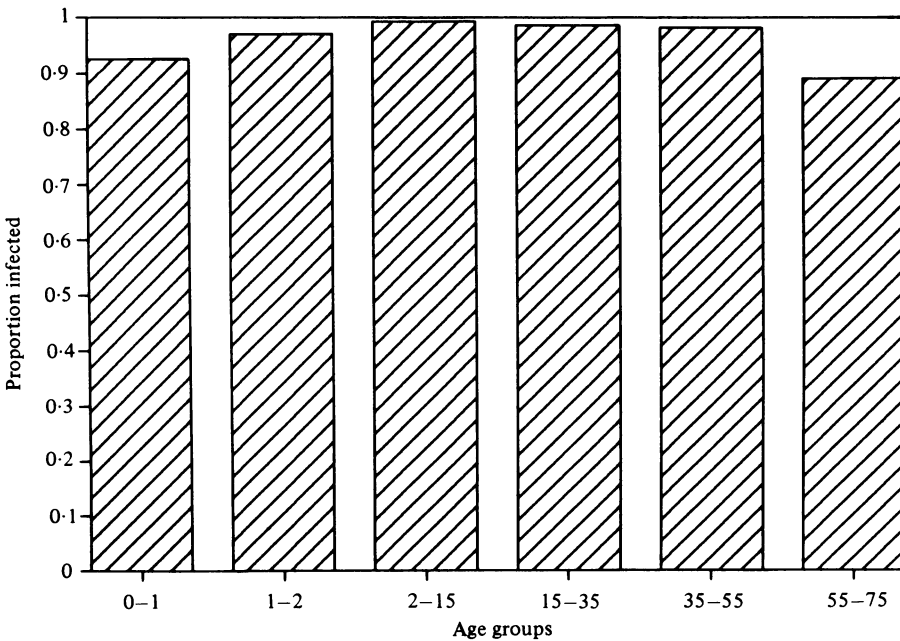


Fig. 11. Epidemics in 'virgin' populations. An epidemic of measles in Southern Greenland during 1951 (data source: Christensen *et al.* 1954). Proportions in each age class who experienced an attack of measles during the epidemic.

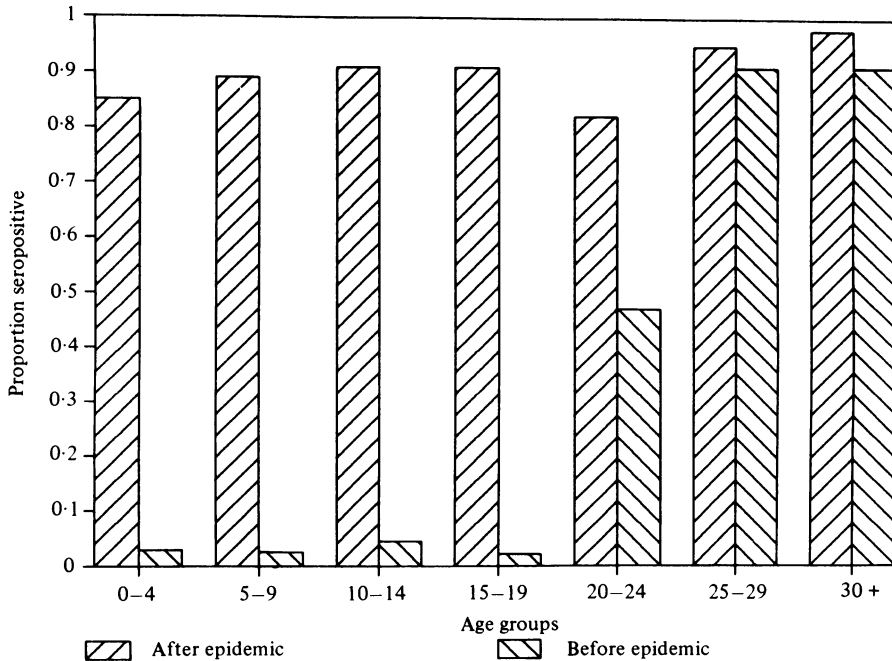


Fig. 12. Epidemics in 'virgin' populations. An epidemic of rubella in Alaska, U.S.A. during 1963 (data source; Broady *et al.* 1965). Proportion serologically positive for rubella antibodies prior to the epidemic and post epidemic.

Vaccination programmes for measles: model predictions and observed trends

The preceding section focused on the problems surrounding the estimation and interpretation of age-dependent rates of infection. In this section we assume that observed patterns (see Table 2) do indeed reflect age-related changes in contact with infection and employ an age-structured model to examine the impact of vaccination on various epidemiological variables. The model is detailed in Appendix A and is a simple extension of the two age class model outlined earlier in the main text. We consider *five* age classes which encompass the age ranges 0-5 years, 5-10 years, 10-15 years, 15-20 years and 20-75 years (Table 2). We focus in particular on the epidemiology of measles in England and Wales. The relevant parameter values are summarized in Table 4, which includes descriptions of total population size, net annual birth rate, durations of maternal antibody protection, latency and infectiousness. We explore the consequences of various combinations of λ_i values for the five age classes and various configurations of the 'who acquires infection from whom' matrix. Two aspects of the impact of vaccination are examined. First, we examine the steady state or *equilibrium conditions*. This is the state towards which a population may converge, in the long term, under the influence of a particular vaccination programme. The second aspect concerns the *short-term temporal dynamics* of the infection within a population, as it begins the passage to a new steady state following the initiation of mass immunization.

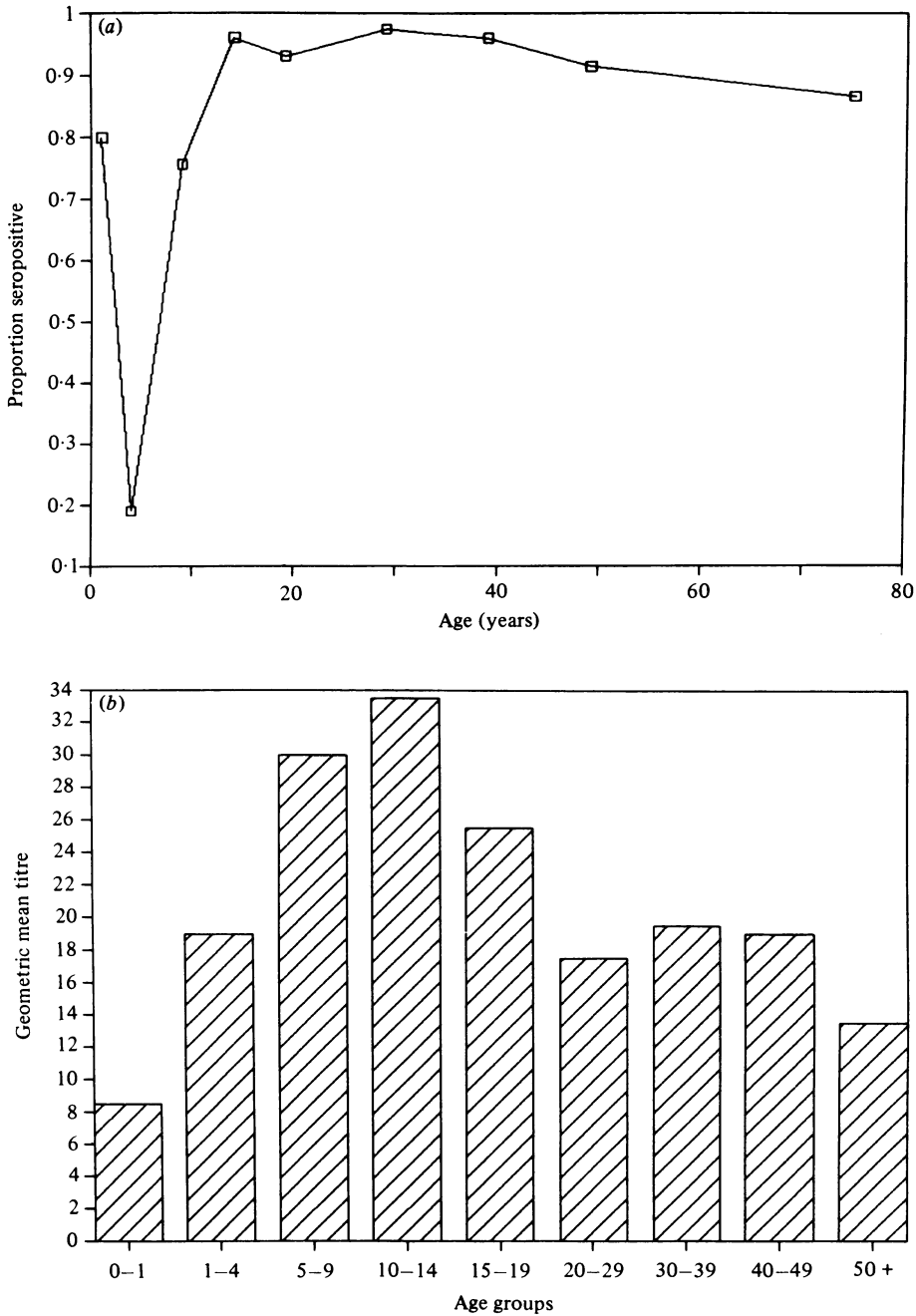


Fig. 13. Cross-sectional survey for the prevalence of measles antibodies in the population of New Haven, Connecticut, U.S.A. during 1957 (data source; Black, 1959) (sample size = 302) (a) Proportion serologically positive by age; (b) geometric mean neutralizing antibody titres by age.

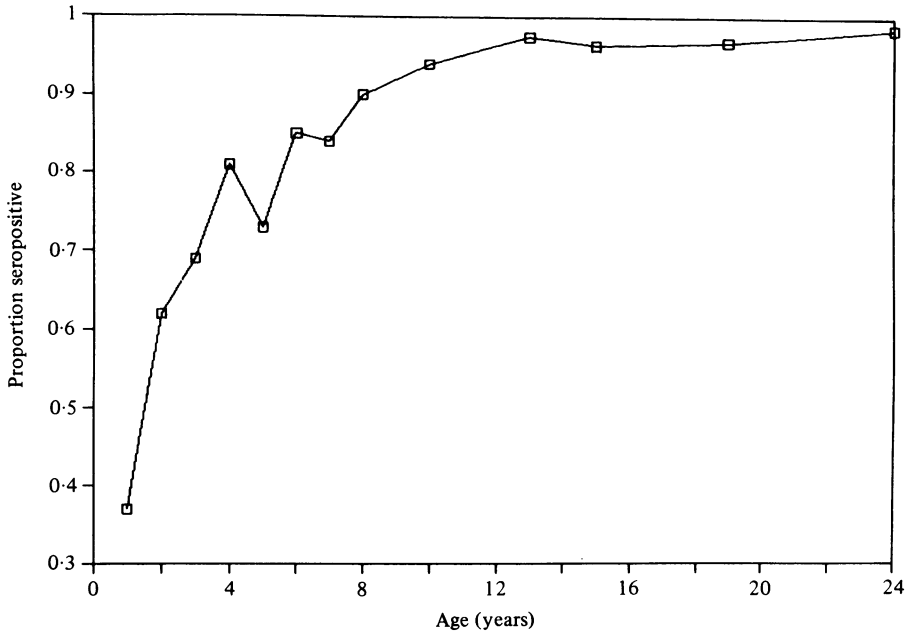


Fig. 14. Cross-sectional survey for the prevalence of measles antibodies in samples collected during the period 1979–83 in Oxford, Leeds, Bristol, Portsmouth, Liverpool, Leicester, Edgware, Manchester and Nottingham (unpublished data: Dr C. L. Miller, Epidemiological Research Laboratory, Public Health Laboratory Service, Colindale) (sample size = 4385).

Long-term steady state predictions

Three problems are considered with respect to the control of measles in England and Wales by mass immunization: (1) the significance of different patterns of age-specific forces of infection (as defined in Table 2); (2) the relevance of changes in the force of infection in the 20- to 75-year-old age group (the estimates of λ_5 are the least reliable as a consequence of the small number of cases involved and the problems surrounding the detection of low antibody titres) and (3) the significance of different configurations of the 'who acquires infection from whom' matrix. In each case we examine the impact of the different factors with reference to the average age at infection, A , prior to immunization and the critical level of vaccination coverage required to eradicate the infection, p_c (assuming that vaccination occurs soon after birth – this assumption will be relaxed in the section on short-term temporal trends).

(1) Three sets of λ_i values are examined; those derived from the case reports in England and Wales in 1966 (prior to mass immunization), those derived from the serological data collected by Black (1959) in the United States in 1955–8 and the average age-specific values obtained by averaging over all the data recorded for each age group in Table 2. In the absence of data from the older age classes we assume that the value of λ_5 for the 20- to 75-year-old age class is equal to that of the 15- to 20-year-old age group (Table 2). The configuration of the 'who

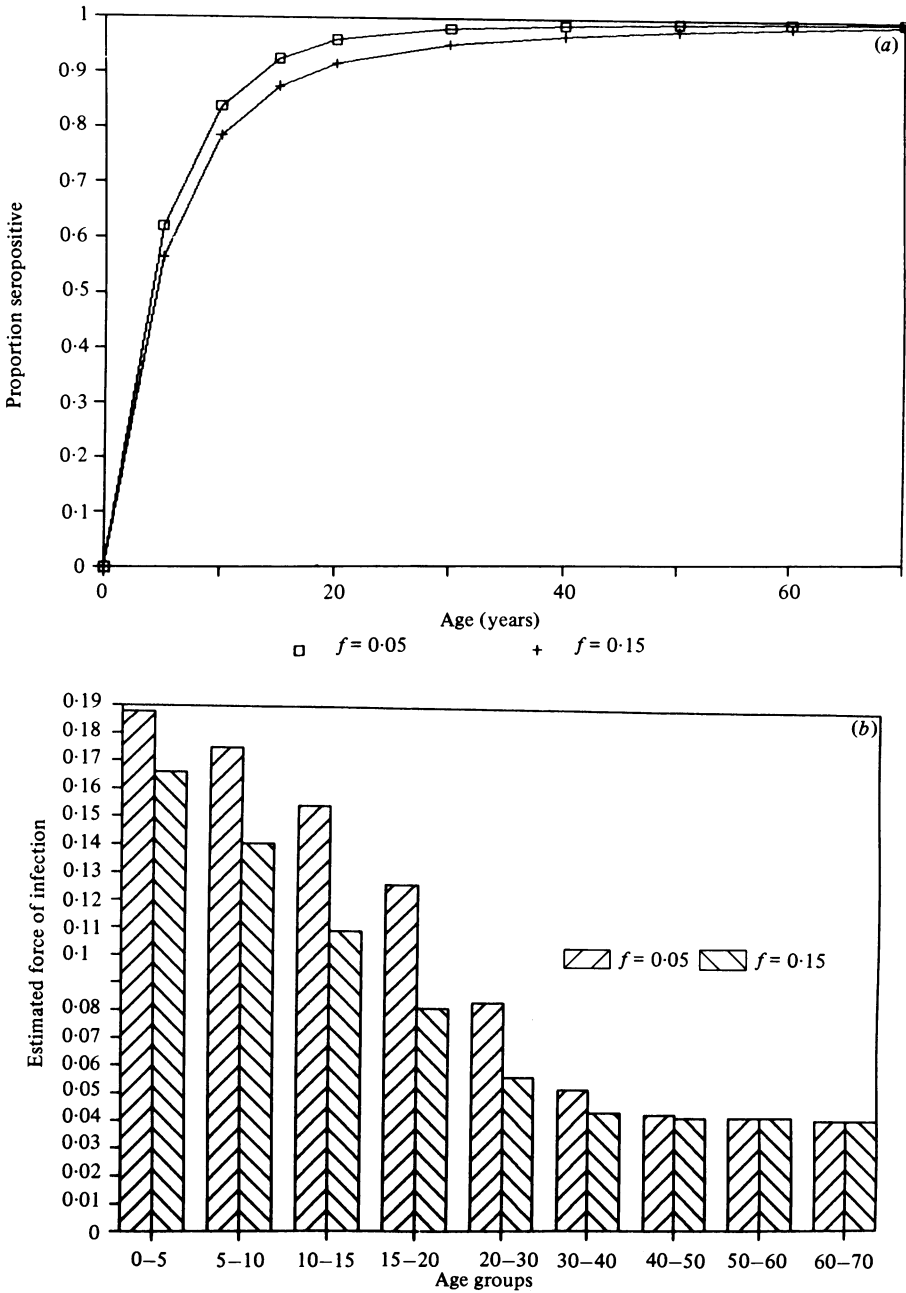


Fig. 15. 'Apparent' age-dependency in transmission generated by genetic variation in susceptibility to infection. (a) Two serological profiles generated by equation (59) in the main text. In both instances the forces of infection λ_1 and λ_2 were held constant and independent of age, at values of 0.2 year^{-1} and 0.04 year^{-1} for groups I and II respectively. In one example (the squares) the fraction 'resistant' to infection, f , was 5% and in the other example $f = 15\%$ (see text for further details). (c) The 'apparent' age-specific forces of infection calculated from the serological profiles portrayed in (a).

where the β_i 's are the transmission coefficients and the \bar{Y}_i 's are the total number of infectious people in each of the age classes at equilibrium. The principal feature of configuration A 1 is a unique *per capita* acquisition rate for susceptibles in the 5- to 10-year-old age group and a relatively unique *per capita* acquisition rate for the 0- to 5-year-old age group. In the remaining age groups, susceptibles have fairly uniform *per capita* acquisition rates irrespective of the age class from which the infection is acquired (in age group 5 the rate is uniform over all age classes).

The results of the equilibrium analyses are summarized in Table 5. In the assessment of these results note that in the absence of age-specific variation in the force of infection, the critical level of vaccination coverage (p_c) (as a proportion) is equal to the equilibrium proportion of immunes in the population (p) prior to the start of immunization (the predictions of the basic model). The results of our analysis suggest that with the observed trend of age-specific variation (low in the very young, high in the child population and low in the adult age groups) the actual level of vaccination coverage required is somewhat less than that predicted by the basic model (constant λ 's). In England and Wales, for example, on the basis of the λ estimates from case notifications, the basic model predicts that 94% of each cohort should be immunized near to birth, while the age-specific force of infection model predicts a level of 89%. The difference is of similar magnitude for the two other data sets of age-specific rates of infection (derived from serology and by averaging overall the values recorded in Table 2). Fortunately, the difference in the two estimates is on average small, being of the order of 5%. In practical terms, therefore, it appears prudent to recommend the adoption of the higher figure as a guide to the design of vaccination programmes and as the target immunization coverage required to eradicate measles in England and Wales. Further predictions of the age-dependent transmission model are presented in Figs. 16 and 17, which record the predicted age-serological profiles generated by the forces of infection estimated from the serological data and the case notification records. The good agreement between predictions and observed values is also recorded in Figs. 16 and 17. Note that the observations derived from case notification data do not provide information on the duration of protection in young children provided by maternally derived antibodies. This accounts for the discrepancies between observed and predicted values in the young age classes. The model assumes such protection lasts on average for a period of three months (Table 4).

(2) The estimate of the force of infection within the 20- to 75-year-old age class is, in practice, less reliable than those for the other age classes. When dealing with case notification data this is in part a consequence of the relatively few cases reported in this class when compared with the child age groups. In addition we suspect that the degree of under-reporting is greatest in the adult age group. In the case of serological data, very large samples are required in the adult age classes to accurately detect the small changes in the proportion seropositive occurring from relatively large increments in age. As illustrated in Fig. 16, the proportion seropositive attains a level of 0.95 by the age of 15 years and hence the maximum possible increase than can occur from age 15 to 75 years is only 0.05. In addition there is the concomitant complication introduced by the possibility that the ability to detect positive antibody titres decreases as the length of the interval increases between infection and serological diagnosis.

Table 5. Steady state model predictions (configuration A 1) for various estimates of the age specific forces of infection

Data source (see Table 2)	Age groups					Average age at infection A (years)	Proportion immune prior to immunization p	Critical vaccination coverage for eradication p_c
	0-5	5-10	10-15	15-20	20-75			
(1)	λ_1 (2)	λ_2 (3)	λ_3 (4)	λ_4 (5)	λ_5 (6)	(7)	(8)	(9)
Case Reports, England and Wales, 1966	0.184	0.579	0.202	0.100	0.100	4.3	0.94	0.89
Serology, U.S.A., 1955-8	0.100	0.240	0.362	0.086	0.086	6.6	0.91	0.86
Average values - Table 2	0.121	0.345	0.201	0.144	0.068	5.9	0.92	0.83

Table 6. Steady state model predictions (configuration A 1) for various values of the age-specific force of infection in the 20-75-year-old age group (λ_5). (λ_1 to λ_4 are set at the values derived from the England and Wales case reports in 1966: see Table 2)

Age-specific forces of infection (year ⁻¹)	Average age at infection, A (years)	Proportion immune prior to immunization, p	Critical vaccination coverage for eradication, p_c	
				λ_1
0.184	4.25	0.94	0.92	
0.184	4.27	0.94	0.89	
0.184	4.28	0.94	0.87	
0.184	4.29	0.94	0.85	
0.184	4.22	0.94	0.84	
0.184	4.15	0.94	0.84	

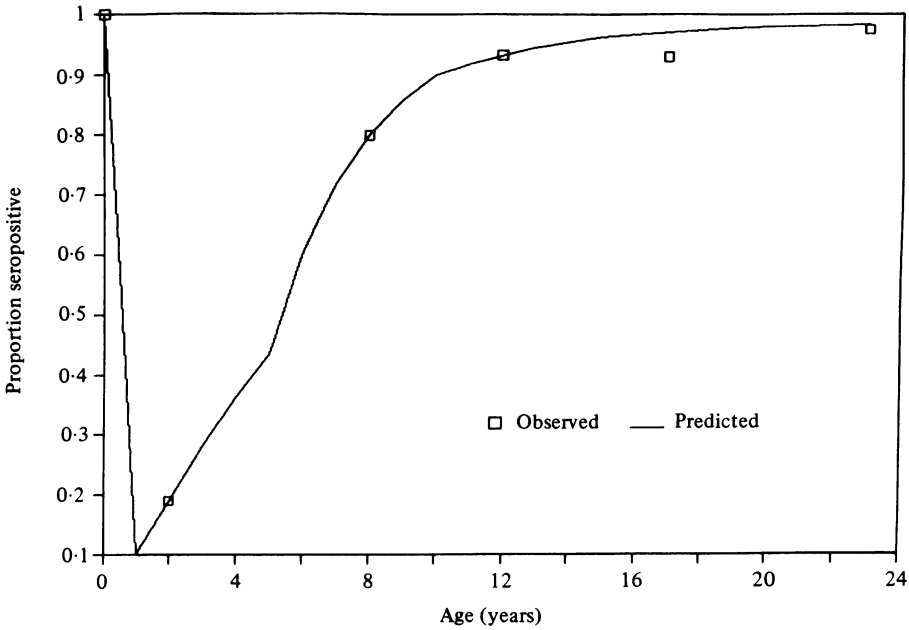


Fig. 16. Five age class model. Predicted age serological profile (solid line) compared with the serological data for measles antibodies collected by Black (1959) in Connecticut, U.S.A. (square points).

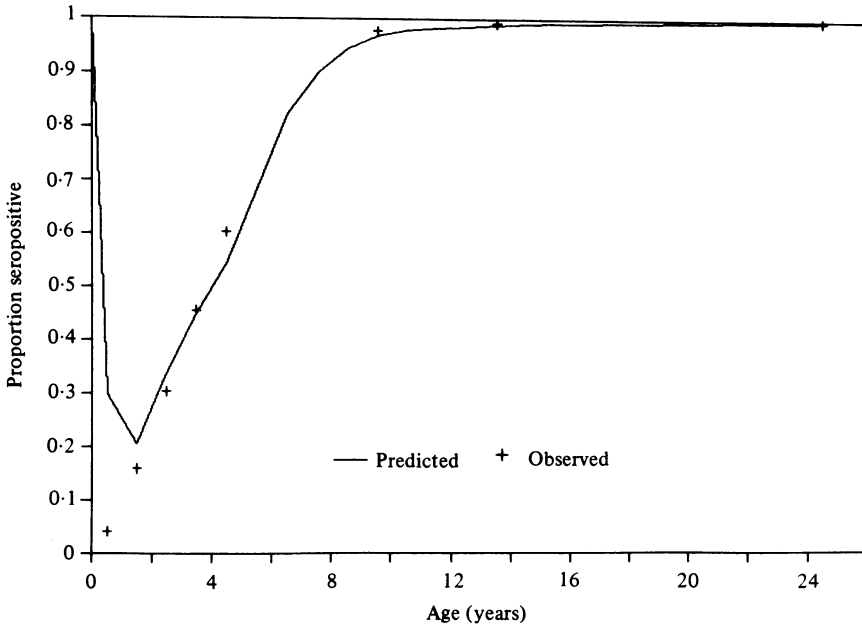


Fig. 17. Five age class model. Predicted age serological profile (solid line) compared with the serological profile calculated from case notification records for measles infection in England and Wales during 1966.

Age class	D 1					E 1				
	1	2	3	4	5	1	2	3	4	5
1	β_1	β_2	β_3	β_4	β_5	β_1	β_1	β_1	β_4	β_5
2	β_2	β_2	β_3	β_4	β_5	β_1	β_2	β_2	β_4	β_5
3	β_3	β_3	β_3	β_4	β_5	β_1	β_2	β_3	β_4	β_5
4	β_4	β_4	β_4	β_4	β_5	β_4	β_4	β_4	β_4	β_5
5	β_5	β_5	β_5	β_5	β_5	β_5	β_5	β_5	β_5	β_5

Age class	F 1					G 1				
	1	2	3	4	5	1	2	3	4	5
1	β_1	β_2	β_3	β_4	β_5	β_1	β_1	β_3	β_4	β_1
2	β_1	β_2	β_3	β_4	β_5	β_1	β_2	β_3	β_4	β_5
3	β_1	β_2	β_3	β_4	β_5	β_3	β_3	β_3	β_4	β_5
4	β_1	β_2	β_3	β_4	β_5	β_4	β_4	β_4	β_4	β_5
5	β_1	β_2	β_3	β_4	β_5	β_1	β_5	β_5	β_5	β_5

Of the seven configurations (including A 1) only three are feasible, in the sense that given the estimated age-dependent forces of infection, all the five transmission coefficients (the β_i 's) have positive and hence realistic values (see section on the two age class model). The feasible configurations are A 1, B 1 and C 1. This result enables us to eliminate from the analysis a high proportion of the possible configurations (admittedly certain of those defined above are unlikely to arise in practice). Of the feasible structures, matrix B 1 defines a configuration in which the probability that a susceptible contracts infection is simply dependent on the age of the individual and is independent of the age of the infectious person from whom the infection is acquired. This appears unlikely in practice since young children undoubtedly have a much greater degree of close contact with others of their own age class than they do, for example, with teenagers or very elderly people. The structure of matrix C 1 is somewhat similar to that already discussed for configuration A 1 and simply represents a slight variation of the theme of unique rates of acquisition of infection within child age groups and cosmopolitan acquisition rates for adults between all age groups.

The equilibrium analyses for the feasible configurations are summarized in Table 7. Encouragingly, there is no substantial difference between the predictions based on the three different configurations. We suggest that configurations A 1 and

Table 7. *Steady state model predictions: the impact of changing the configuration of the 'who acquires infection from whom' matrix*

(The configuration A 1 to C 1 are defined in the main text; the forces of infection are as estimated from the case reports for England and Wales 1966: see Table 2.)

Configuration of matrix	Average age at infection, A (years)	Average age at infection at the point of eradication, A_c (years)	Critical vaccination coverage for eradication, p_c
A 1	4.3	33.1	0.89
B 1	4.3	28.3	0.91
C 1	4.3	33.0	0.89

C 1 are a reasonable approximation of current beliefs concerning the transmission of the common viral and bacterial infections of children. There is little to choose between either of these structures in the absence of additional information concerning detailed case to case studies or behavioural data on within and between age class contact. This result is somewhat fortunate since, in practical terms, we do not believe that it will be feasible to acquire detailed data on 'who acquires infection from whom' (Schenzle, 1984). In theory, of course, such information could be obtained but it would require very elaborate and detailed case to case epidemiological studies.

On the basis of these results we now proceed to explore the short-term dynamics of measles incidence, under the impact of mass vaccination, on the basis of configuration A 1 for the 'who acquires infection from whom' matrix.

Short-term predictions of temporal changes in incidence

The steady state results discussed in the previous section indicate what may happen (under the assumptions of our model) in the long term, for a given vaccination policy. The phrase 'long term' implies, however, many decades after the instigation of the type of vaccination programme employed in developed countries. Eradication of the infection would only occur rapidly if every age group in a community were immediately vaccinated, upon the instigation of control measures, in such a manner that the required level of herd immunity, p_c , was equal throughout all the age classes. In practice, vaccination programmes usually focus on selected age classes of a population, such as young children in the case of measles. This point is well illustrated by the history of measles immunization in England and Wales over the period 1967–81 as recorded in Table 8. Vaccination is predominantly focused on the 1- to 2-year-old and 2- to 3-year-old age classes. Over this 14 year period, roughly 45–50% of each cohort, are immunized by their seventh year of life (Table 8). In such circumstances, many decades pass before the full effects of herd immunity (generated by the level of vaccination coverage) are realized within the community.

We examine the short-term dynamics predicted by the age-dependent transmission model and employ standard methods of numerical analysis to generate time-dependent solutions of the model defined by equations (1) to (4) (where $\lambda(t, a)$ is as defined in equation (16)). To ensure numerical accuracy, simulation step lengths of less than one week are required. For the majority of the analysis we work

Table 8. Proportions of susceptibles in different age classes vaccinated against measles in England and Wales during the years 1967-1981

(source D.H.S.S.; the values recorded for the 4-7-year-old age classes are approximate estimates.)

Year	Age class						
	0-1	1-2	2-3	3-4	4-5	5-6	6-7
1968	0.003	0.120	0.128	0.110	0.100	0.100	0.100
1969	0.001	0.096	0.143	0.086	0.033	0.033	0.033
1970	0.002	0.260	0.250	0.112	0.041	0.041	0.041
1971	0.002	0.290	0.260	0.100	0.025	0.025	0.025
1972	0.002	0.330	0.280	0.065	0.020	0.020	0.020
1973	0.002	0.320	0.290	0.067	0.020	0.020	0.020
1974	0.0025	0.26	0.260	0.040	0.020	0.020	0.020
1975	0.0025	0.260	0.230	0.040	0.020	0.020	0.020
1976	0.001	0.280	0.290	0.050	0.010	0.010	0.010
1977	0.001	0.260	0.310	0.058	0.010	0.010	0.010
1978	0.001	0.270	0.310	0.053	0.011	0.010	0.010
1979	0.001	0.310	0.320	0.053	0.012	0.011	0.010
1980	0.001	0.330	0.320	0.056	0.010	0.010	0.011
1981	0.001	0.350	0.320	0.050	0.010	0.012	0.010
1982	0.001	0.360	0.360	0.060	0.010	0.010	0.012
Cohort	Total proportion vaccinated by 7 years of age						
1968	0.44						
1972	0.53						
1976	0.54						

with configuration A 1 of the 'who acquires infection from whom' matrix and the set of λ_i values derived from the case notification records in England and Wales in 1966 (see Table 2). The impact of vaccination is mirrored by the subtraction of a term $C(a)X(a, t)$ from equation (1) and the addition of an identical term to equation (4) where $C(a)$ records the age-dependent rate of vaccination of susceptible individuals.

For each numerical simulation, the system is started at the equilibrium, or steady state (see Table 4 for a list of parameter values) and total population size and net birth rate are set to mirror average conditions in England and Wales over the past decade. We assume that maternal antibodies provide protection for a period of approximately three months (see Anderson & May, 1983). The system is perturbed from the equilibrium state (by reducing the equilibrium proportion of susceptibles in each age class by a constant fraction, z , at the start of each run (usually set at $z = 0.8$)) in order to monitor the oscillatory behaviour of the system as it returns to the steady state.

Numerical studies are employed to examine three problems; (1) the impact of different configurations of the 'who acquires infection from whom' matrix on short-term temporal behaviour (2) the predicted behaviour of the system under past and current levels of vaccination in England and Wales, and (3) future behaviour under different levels of vaccination coverage. In each case we examined temporal changes in both the incidence of infection and the age serological profile. Throughout, an attempt is made to compare predictions with observed trends.

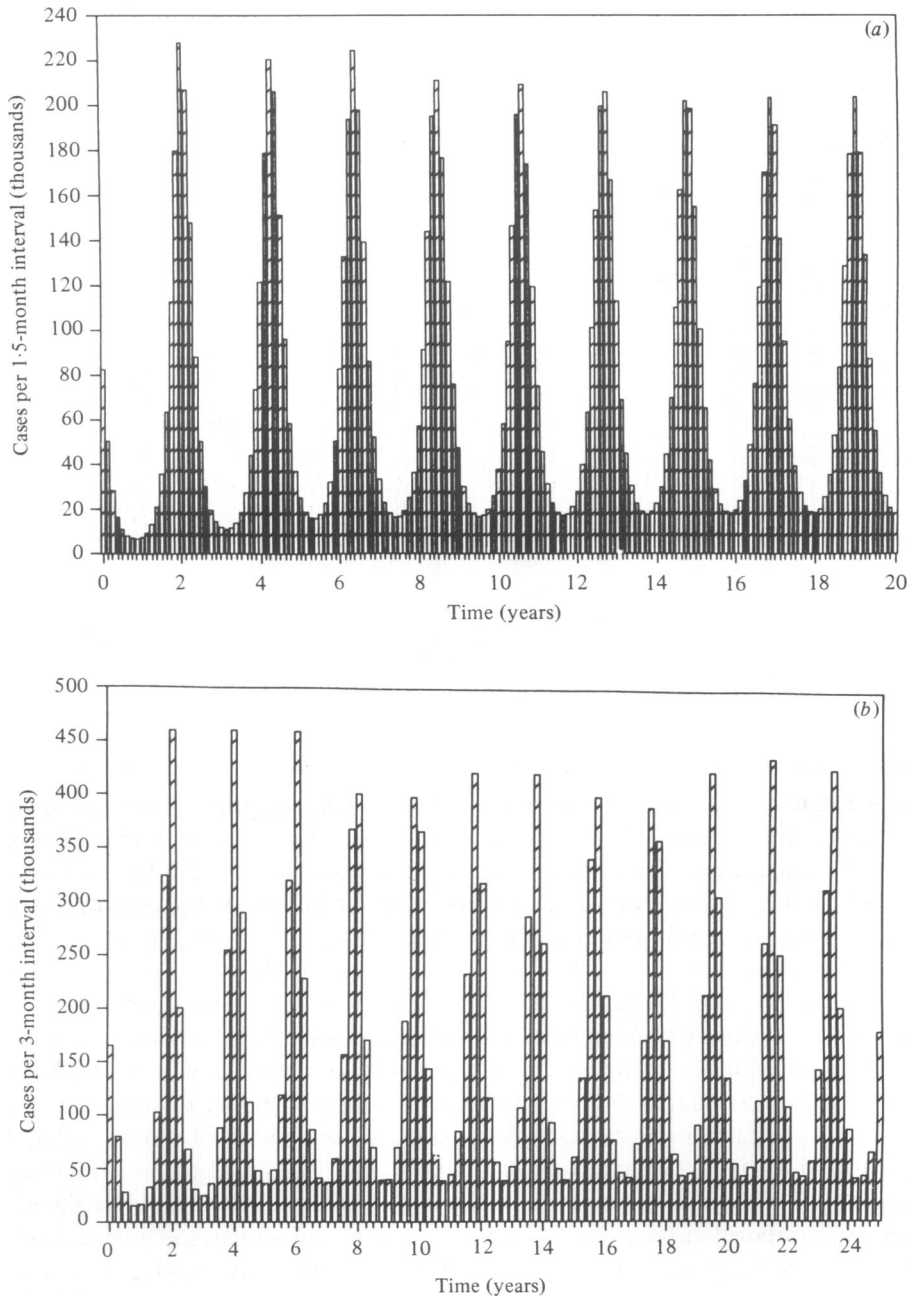


Fig. 18. (a) Predicted temporal changes in the number of reported cases of measles infection over 1.5 monthly intervals following perturbation of the five age class model from its equilibrium state (perturbation induced by reducing the fractions susceptible in each age class by a factor of 0.8) (see Table 4 for simulation parameter values). The A 1 configuration of the 'WAIWF' matrix (see main text) and the 1966 England and Wales forces of infection (derived from case reports) were employed in the simulation. (b) Identical to (a) but with a 3-month interval for the accumulation of new cases of infection.

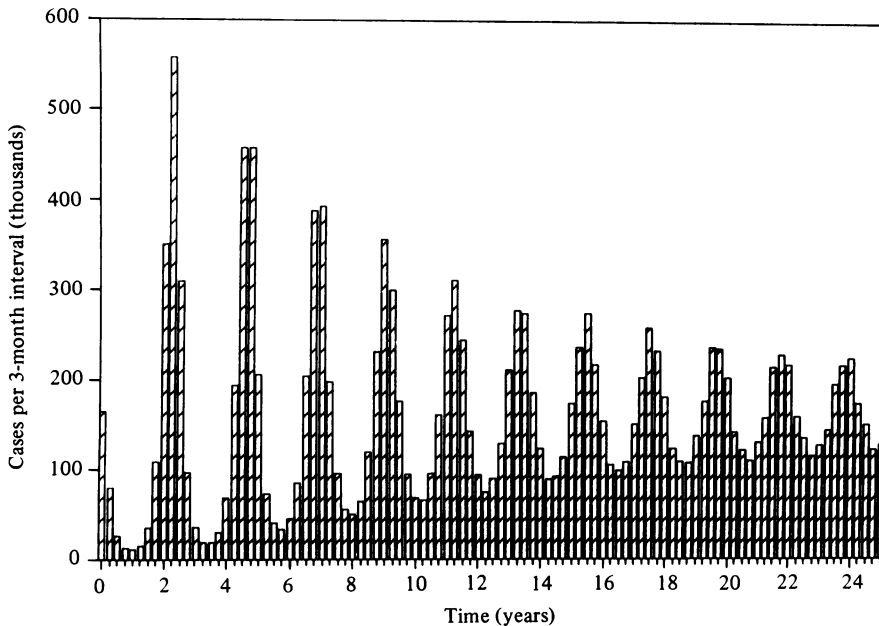


Fig. 19. Similar to Fig. 18*b* but employing the B 1 configuration of the 'who acquires infection from whom' matrix.

(1) *Matrix configuration and temporal dynamics in the absence of vaccination*

Three configurations, A 1, B 1 and C 1, of the 'who acquires infection from whom' matrix are considered. For each matrix, the 1966 case report forces of infection for England and Wales (Table 2) were used to calculate the transmission coefficients (the β_i 's). The results are compared with the homogeneous case in which λ was held constant and independent of age (fixed at $\lambda = 0.2 \text{ year}^{-1}$). The simulation results are presented in Figs. 18 (configuration A 1), 19 (configuration B 1), 20 (configuration C 1) and 21 (homogeneous case) over periods of 25 years. The histograms record the accumulated number of new cases (incidence) arising over intervals of 1.5 and 3 months. Note that the time interval over which cases are reported or accumulated (the temporal unit of incidence) will influence the apparent pattern of epidemic cycles. The inter-epidemic period of most viral and bacterial infections is rarely an exact integer of yearly units. As such, fractions of one year (such as weeks, months or 3-month periods) will not exactly coincide with uniform temporal subdivisions of one complete epidemic cycle (for example a 3-month interval may incorporate segments of two consecutive epidemic cycles). This point is illustrated in Fig. 19*a, b*. In histogram (*a*) the interval was set at 1.5 months and the epidemics (occurring at approximately, but not precisely, two year intervals) appear fairly uniform in character. It is clear from histogram (*a*) that the amplitude of the cycles is slowly damping as time increases from the point of perturbation (time $t = 0$). In contrast, the *identical* simulation record in histogram (*b*), but presented as cases per 3 monthly interval, shows a degree of irregularity in the epidemic pattern, and it is not at all clear that the amplitude of the cycles is decreasing through time.

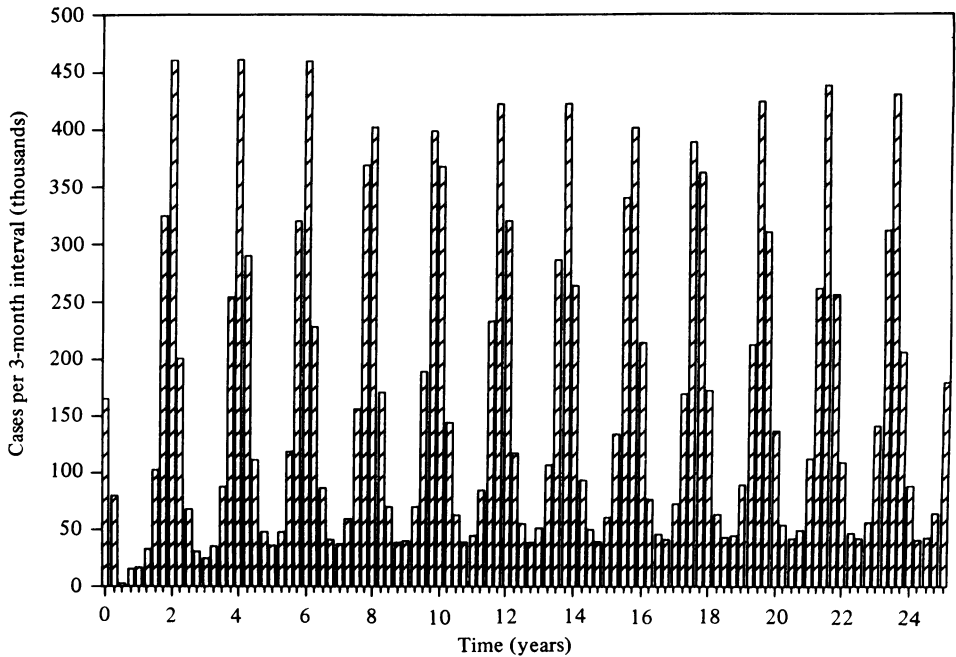


Fig. 20. Similar to Fig. 18*b* but employing the C 1 configuration of the 'who acquires infection from whom' matrix.

The point of major interest in Figs. 19 to 21 concerns the impact of the configuration of the 'WAIFW' matrix on the oscillatory behaviour of the system following perturbation. In all cases the system is stable (if the simulation are run for very long time periods a steady non-oscillatory state is obtained). However, certain configurations, such as A 1 and C 1 (which are very similar in structure), accentuate the oscillatory patterns (very long damping periods). In these instances seasonal fluctuation in transmission, or stochastic effects, will tend to perpetuate the oscillations indefinitely. The configuration in which the forces of infection simply depend on age and are independent of differing degrees of contact between age classes, damps most rapidly. The homogeneous case in which λ is held constant (Fig. 21) has a damping time intermediate between configurations A 1 and C 1 (slow damping) and configuration B 1 (fast damping). With λ fixed at 0.2 year^{-1} in the homogeneous case the inter-epidemic period is approximately 3 years. Most interestingly the 2 year inter-epidemic period generated by configurations A 1, B 1 and C 1 (with the 1966 case report λ_i values) *exactly* mirrors that observed for measles in England and Wales prior to mass vaccination (Fig. 22). This is a very encouraging result.

The configuration (A 1 and C 1), which are potentially the most accurate mirror of within and between age class transmission, provide a precise description of temporal changes in incidence in real communities (compare Fig. 18*a* and Fig. 22 (the 1948–68 segment prior to mass vaccination)). Quantitative comparisons, however, are made complicated by two factors. First, our model takes no account of seasonal changes in transmission (see Bliss & Blevins, 1959; Fine & Clarkson,

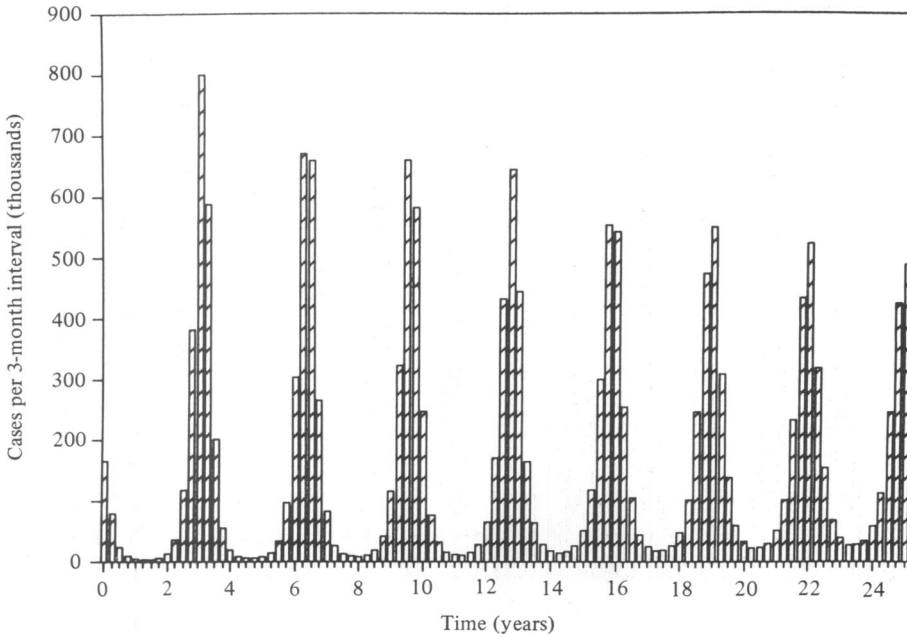


Fig. 21. Similar to Fig. 18*b* but the forces of infection were held constant and independent of age where $\lambda = 0.2 \text{ year}^{-1}$ for all age classes.

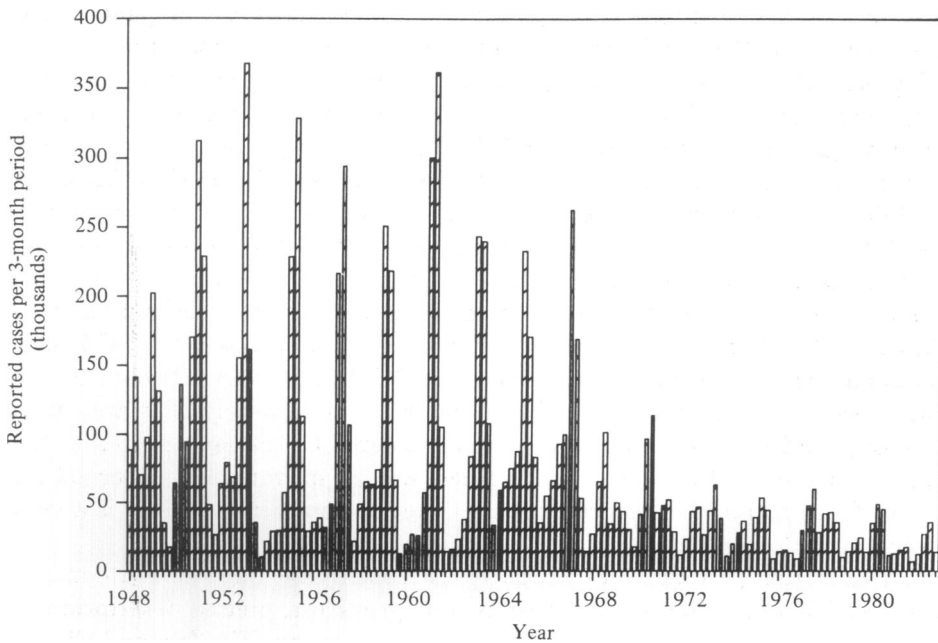


Fig. 22. Reported cases of measles over 3-month intervals in England and Wales for the period 1948 to 1982 (data source: Annual Review of the Registrar General of England and Wales (Registrar General 1948–1973) and the Office of Population Censuses and Surveys, 1974–1982). Mass immunization was initiated during 1967–8.

1982*a*; Yorke & London, 1973) arising primarily as a consequence of the aggregation and dispersal of children during school term time and holiday periods, respectively. In this paper we restrict our attention to models with no seasonal component. It is important to note, however, that the introduction of appropriate seasonal variation in heterogeneous mixing models can generate oscillations with an annual component and a longer term two-year cycle. We exclude such considerations from the present analysis due to difficulties arising in the precise estimation of seasonal transmission coefficients from observed incidence pattern. The second factor is of greater immediate importance and concerns the problems of the efficiency of case reporting in England and Wales. As recently discussed by Fine & Clarkson (1982*b*), incompleteness of notification records can confuse quantitative comparisons between predicted and observed trends. These authors estimated that, prior to widescale immunization (1948–68), the degree of under-reporting was of the order of 37–44 % (63–56 % notification efficiency). They also point out that notification efficiency is probably inversely correlated with disease incidence (reporting efficiency high in years of high measles incidence and vice versa). A comparison of our model predictions and observed trends substantially supports their conclusions. In England and Wales, with a population of around 49·6 million people, we estimate (on the basis of a direct comparison between the reported cases and our model predictions) that on average over a full two-year epidemic cycle the degree of under-reporting is of the order of 39–40 % in the pre-vaccination era. A final point of interest concerns the predicted age-serological profiles in epidemic and non-epidemic years. For configuration A 1, differences do occur from year to year but these are of insufficient magnitude to be detected by either current serological survey techniques or the case reporting system in England and Wales (Fig. 23).

In summary, age-related heterogeneity may or not accentuate oscillatory behaviour, depending on the precise configuration of the 'who acquires infection from whom' matrix. The most appropriate configuration (A 1) with high transmission and mixing within child age classes enhances oscillatory behaviour over that generated by homogeneous transmission models. Furthermore, the recurrent epidemic patterns generated by this configuration closely mirror observed trends both with respect to the inter-epidemic period and the amplitude of the cycles (the difference in incidence between high and low years).

(2) *The impact of vaccination*

To assess model behaviour under the impact of vaccination we focus on configuration A 1 and employ the recorded vaccination rates for England over the period 1968–82 (a 15 year period) (see Table 8 for a compilation of the proportional vaccination coverages of 7 age classes (0–1 years to 6–7 years)). In all the simulations discussed in this section the system was started at equilibrium, perturbed from this state (by reducing the equilibrium numbers of susceptible individuals in each age class by a factor of 0·8) and allowed to oscillate for a specified period before initiating vaccination. The coverage for the first year of mass immunization was taken to be that reported for 1968 in England and the coverages for the years thereafter followed the sequence of events in England from 1968 to 1982 (Table 8). The vaccine was assumed to have an efficiency of 100 % (all those vaccinated were assumed to be immune to infection).

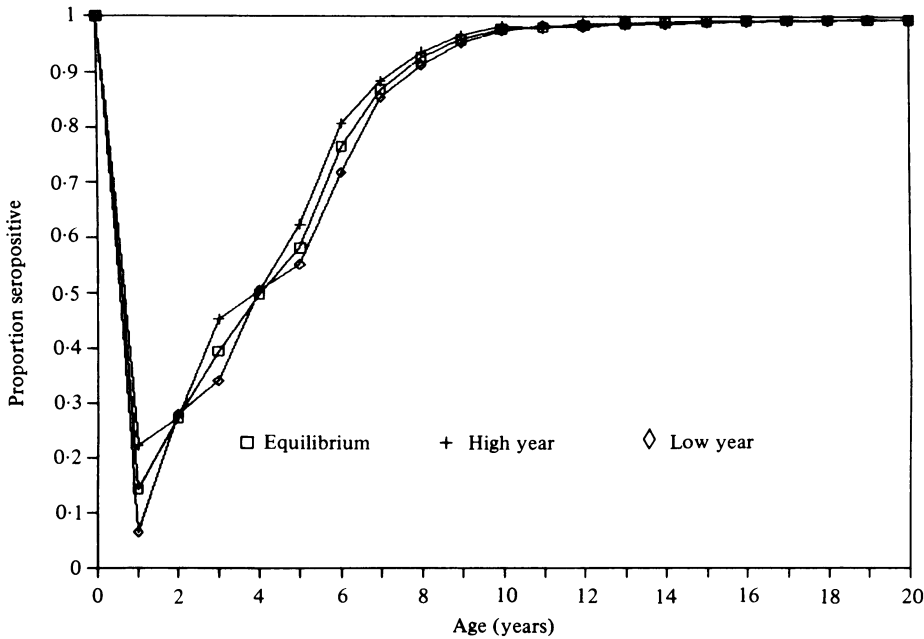


Fig. 23. Differences in the predicted age serological profiles for measles in epidemic and inter-epidemic years. These profiles are compared with the predictions at equilibrium.

The principal simulation results are presented in Figs. 24 and 25. In Fig. 24, vaccination was initiated in year 10 during a major epidemic (high incidence). In Fig. 25, immunization was started in year 9 which, by contrast, was a year of low incidence in our simulation (an inter-epidemic year). In both cases the forces of infection prior to immunization were set at the 1966 case report estimates for England and Wales. It is interesting to note that the greatest benefit (in terms of the rapidity with which incidence declines through time) is achieved by initiating vaccination in an inter-epidemic year when the total density of susceptibles is low following the previous epidemics. More generally, the predicted patterns broadly mirror the qualitative trends in England and Wales following the introduction of mass immunization against measles infection. In quantitative terms, however, model predictions underestimate the observed impact of immunization. This could be due to a variety of factors, not least of which is the comparative simplicity of the assumptions incorporated in our model. Other factors include case-reporting efficiency (we have already suggested that such efficiency is inversely correlated with measles incidence in line with Fine & Clarkson's comments (Fine & Clarkson, 1982*b*)), seasonal changes in the rate of infection and vaccination reporting efficiency. The latter aspect is difficult to assess although it is highly probable that some vaccinations performed are not reported. To counterbalance this, however, is the question of vaccine efficacy. We assumed it to be around 100%, but in practice current evidence suggests an efficiency of between 90 and 95% (Marks, Halpin & Orenstein, 1978; Shelton *et al.* 1978). Seasonal changes are of undoubted importance as illustrated by a number of recent studies (Fine & Clarkson, 1982*a*; Anderson *et al.* 1984; Schenzle, 1984).

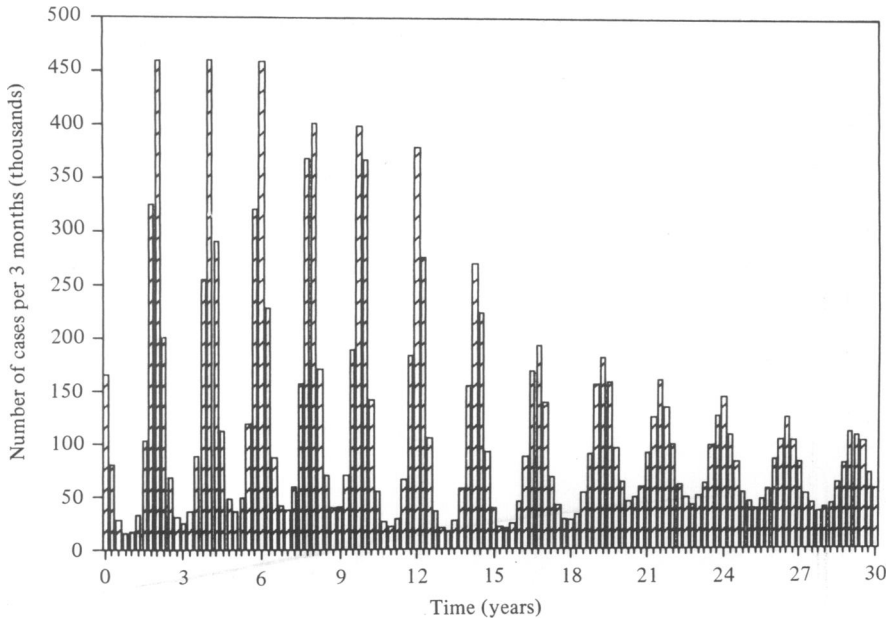


Fig. 24. Similar to Fig. 18*b*, but mass vaccination was initiated in year 10 of the simulation. For the next 15 years the age-specific rates of vaccination were set at the recorded values for England over the period 1968–82 (see Table 8). For the last five years of the simulation the levels of vaccination were held constant at the 1982 figures for England.

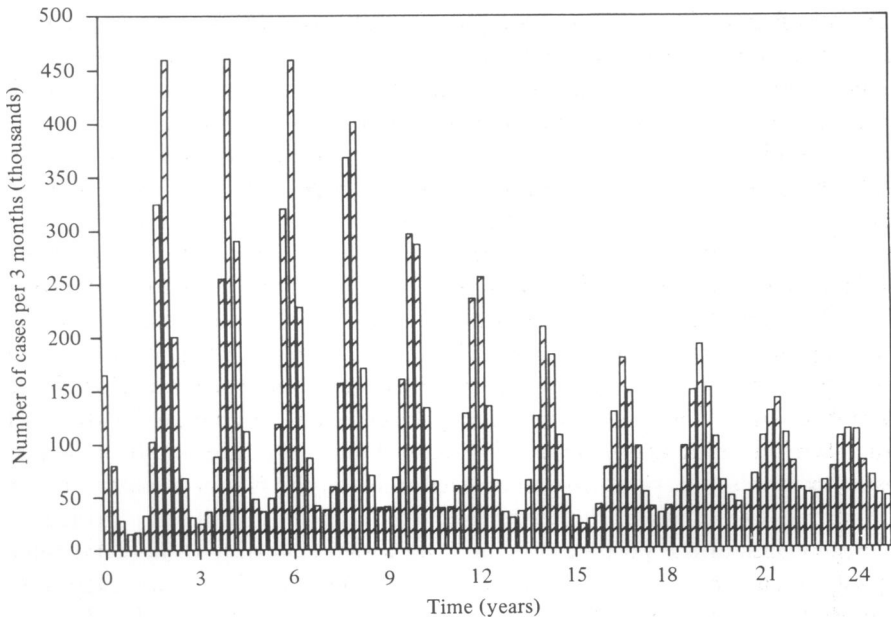


Fig. 25. Identical to Fig. 24, but vaccination was started in year 9 of the simulation. The next 15 years of vaccination was as defined in Table 8 for England over the period 1968–82. The last year of vaccination was held constant at the 1982 level reported for England.

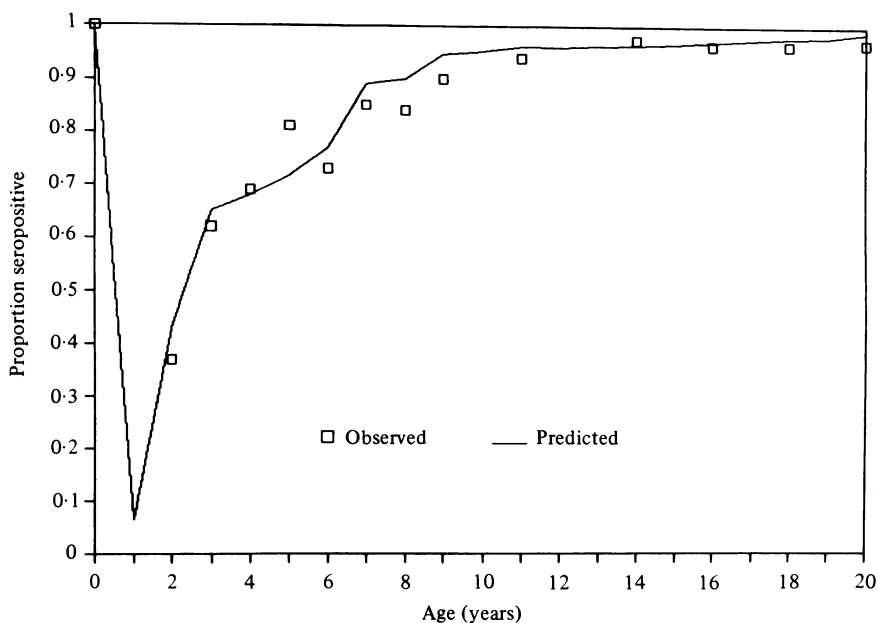


Fig. 26. Predicted and observed serological profiles for measles antibody after 12 years of mass vaccination. The levels of vaccination coverage were set as reported in England (see Table 8) for the years 1968–79. The observed data are as reported in the legend to Fig. 14.

We are especially puzzled by our underestimation of the *apparent* effect of vaccination in England and Wales (compare Figs. 23 and 25) on measles incidence as a result of the accuracy of the model in predicting changes in the age-serological profile arising from periods of mass immunization. For example, the serological data collected from a variety of locations in England over the period 1979–83 (Dr C. Miller, unpublished data) is well mirrored by model predictions. As portrayed in Fig. 26, the agreement between observation and prediction is striking. This result leads us to tentatively suggest that the failure of the model to accurately mirror quantitative trends in incidence, is in part a consequence of under-reporting of cases and numbers vaccinated. If we assume the discrepancy is entirely due to case reporting efficiency, then our results indicate that the degree of under-reporting in the post-vaccination era is of the order of 60%. This discrepancy could also result from our failure to incorporate seasonal transmission within the model. The impact of mass immunization may be enhanced by large seasonal changes in the degree of contact within child age groups. We suspect that all three factors, seasonal changes in transmission, poor case reporting efficiency in the vaccination era and under-reporting of vaccination play a role.

Further features of the predicted behaviour which accord with observation are the impact of vaccination on the inter-epidemic period, T , the average age at infection, and the amplitude of the epidemics. The cycle period has lengthened in the simulation (Fig. 25) from 2 years to 2.5 years after 15 years of mass immunization. This is in precise agreement with observed trends (see Anderson, Grenfell & May, 1984). The average age at infection, A , has increased from 4.3 years

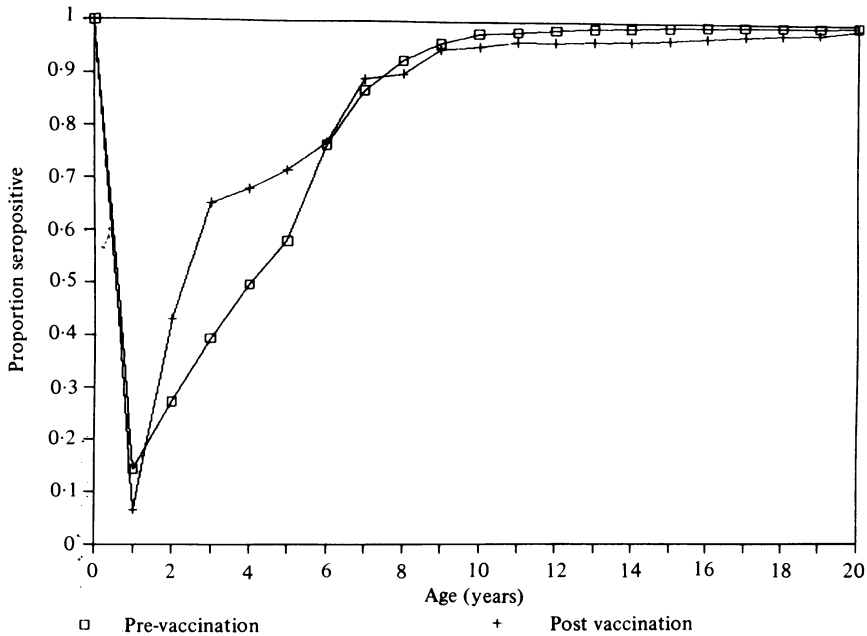


Fig. 27. Predicted serological profiles for the simulation presented in Fig. 26 in year 0 (pre-vaccination) and year 25 (after 15 years of vaccination at the levels reported for England from 1968–82).

of age to 5.3 years of age over the same period. This again exactly mirrors observed trends (A was 4.4 years in 1968 and between 5.2 and 5.5 years in the period 1980–2; see Anderson & May, 1982). The accuracy of the age-dependent transmission model's predictions is in marked contrast to the poor predictive power of a homogeneous, constant force of infection model. The latter predicts substantial changes in A and T under current levels of vaccination coverage (Anderson & May, 1983).

A more careful examination of predicted age-serological profiles before and after 15 years of immunization reveals some interesting points. As portrayed in Fig. 27, the proportion seropositive in the 1- to 6-year-old age classes is substantially raised as a consequence of immunization. *Those who are not immunized, however, are exposed to a reduced force of infection (as a consequence of the decreased incidence of measles) and hence have a greater chance of remaining seronegative during their teenage and adult years, than was the case prior to mass vaccination.* This predicted pattern is in close agreement with the observations of Roden & Heath (1977) who concluded that by 1975 the measles immunization programme in England and Wales had reduced the proportion immune among 11-year-old children. Similar patterns have also been observed in the United States (Rand, Emmons & Merigan, 1976). This observation has disturbing public health implications if the risk of serious complications arising from infection (measles encephalitis) increases with age. The risk of such complications does appear to increase with age (see Miller, 1963; Anderson & May, 1983) but not so rapidly as to cause a serious problem. Under a 50% vaccination coverage by the age of 3 years, the *proportion* of all cases

occurring in the older age groups will increase, but the actual *number* of cases will decrease with respect to that pertaining prior to vaccination (see Anderson & May, 1983). The model also captures the tendency of vaccination to suppress the relative difference between incidence in epidemic and non-epidemic years over that apparent in unvaccinated populations (Fig. 25).

The refinement of age-dependent contact and transmission, appears to considerably enhance the predictive power of models of recurrent epidemics. It generates a series of important epidemiological features which closely mirror observed trends. These include age-serological profiles under the impact of mass vaccination, the inter-epidemic period (both before and after immunization) and the average age at infection (both before and after immunization). With respect to temporal patterns in measles incidence, the agreement between prediction and observation is less satisfactory. Taking into account reporting efficiency in England and Wales, the predictions in the pre-vaccination era are in broad agreement with observed trends. Post-vaccination comparisons are less good although we suspect this is a result of a series of factors including the failure of our model to mirror seasonal changes in transmission, plus under-reporting of cases and vaccinations.

(3) *Future trends and vaccination policies*

As mentioned earlier the current level of vaccination coverage against measles in England and Wales is very poor in comparison to other European countries and North America. A question of considerable public health significance concerns what level of coverage we should aim to attain in this country to eradicate measles (cases of indigenous origin) (Hinman *et al.* 1980). Past estimates have been in the region of 94–96% (see Anderson & May, 1982). The revised estimates presented in earlier sections of this paper suggest a figure of approximately 89% (see Table 7). Even a figure of this level would be difficult to attain given that its derivation is based upon the assumption that vaccination takes place in the first year of life. Three factors complicate this issue. First, immunization during very early life, while maternally derived antibodies provide a degree of resistance to infection, often fails to adequately protect the child in later life. As such immunization is normally recommended for infants of greater than one year of age. Second, the efficacy of the vaccine (as mentioned earlier) is not 100%; current vaccines probably protect 95% of those immunized. Thus a 96% vaccination coverage would only create 91% herd immunity. Third, vaccination ideally should be encouraged as soon as possible after maternally derived antibody protection has waned. In Britain, however, vaccination takes place predominantly in the second and third year of a child's life, but a significant number of children are immunized in their fourth and fifth years of life. Thus of an overall 50–55% coverage of a cohort of children by the age of 7 years some will be vaccinated after the average age at which the infection would have been typically acquired prior to mass vaccination. All these factors conspire to suggest that eradication of measles in England and Wales may well be an extremely difficult task. Our model, however, can provide some helpful information on the likely effects of increasing our level of coverage.

We consider one particular case, namely an 80% 'effective' level of coverage (implying an 84% immunization rate given a 95% efficacy of the vaccine) administered in total between the ages of one to two years. The predicted trends

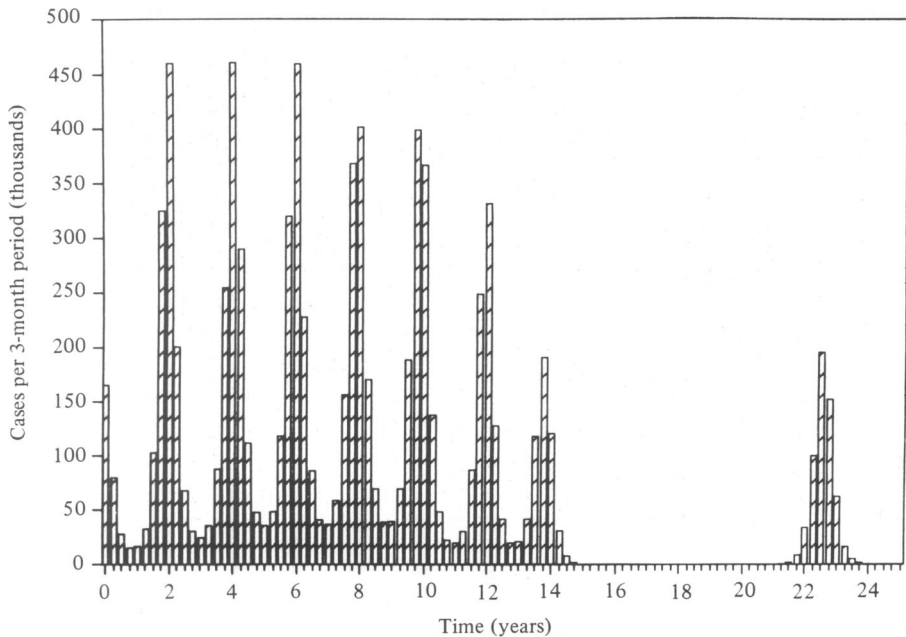


Fig. 28. Similar to Fig. 18*b* but mass vaccination was initiated in year 10 of the simulation. The level of vaccination was held constant for 15 years at 80% of 1-2-year-old children.

in incidence are displayed in Fig. 28. In this numerical example vaccination at an 84% coverage level was initiated in year 10 (starting at the worst possible time – during an epidemic year). This level of coverage has a dramatic impact; the number of cases in years 15–21 are reduced to an average of about 50–100 per year. Note that the impact is slow to materialize as a consequence of focusing immunization on a single cohort of children each year. The number of susceptibles eventually builds up to a sufficient level to trigger an epidemic in year 22–23. During the long inter-epidemic period (roughly 7 years) the low incidence would probably imply local extinctions as a consequence of stochastic or chance effects in transmission (see Bartlett, 1956). The predicted age-serological profile under this immunization scheme 15 years after the start of vaccination is presented in Fig. 29. Note the dramatic impact of an 80% coverage on the proportion seronegative in the teenage and young adult age classes. The cohort in which immunization was initiated 16 years earlier is easily discernible from the serological profile. These predicted changes in incidence can be compared with data from Oxford city in England, which is presented in Fig. 30 (personal communication, Dr C. Miller). Since 1967 this region had an atypically high level of vaccination coverage (for England) of greater than 80% of 1- to 3-year-old children. A decline in vaccine uptake in the early 1980's explains the resurgence in 1983. Note how the inter-epidemic period has lengthened from a 2-year cycle prior to 1966 to a 6-year cycle in the 1970s. The persistence of measles in this locality during the inter-epidemic periods of 1972–5 and 1979–81 can probably be explained in part by immigration of infected individuals into this area from surrounding regions with lower levels of vaccination and concomitantly higher incidence of infections.

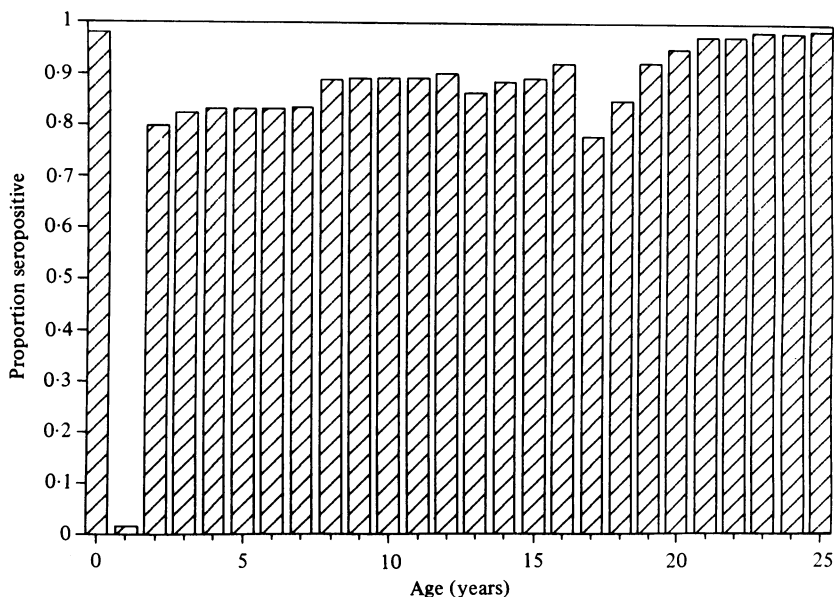


Fig. 29. The predicted serological profile in year 25 of the simulation recorded in Fig. 28.

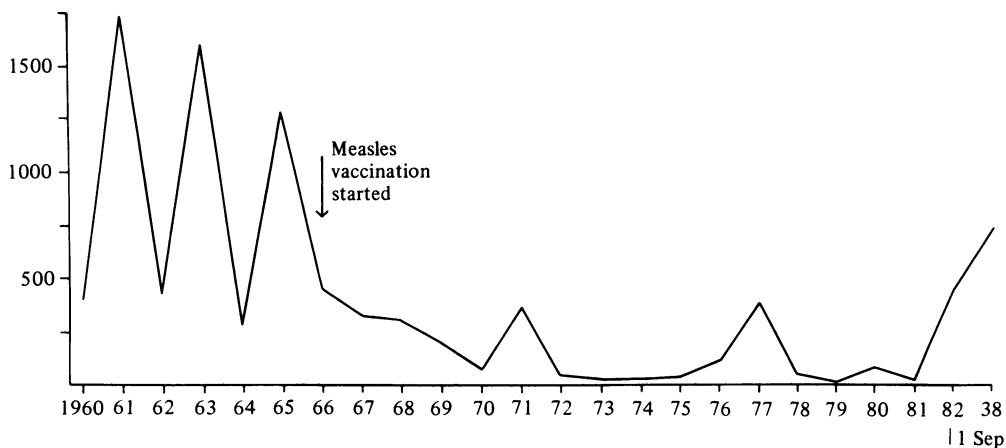


Fig. 30. Annual measles notifications in Oxford city, England over the period 1960–83 (see text for further details).

DISCUSSION AND CONCLUSIONS

Theoretical predictions suggest that an *effective* level of immunization of 89% or more, spread uniformly over the whole of England, Scotland and Wales, could virtually eradicate measles. *Note, however, to achieve such an effective level of herd immunity greater than 94% of children must be immunized as close to their first birthday as is practically possible* (due to the problems of vaccine efficacy). If vaccination is spread over the second, third and fourth years of life a coverage of greater than 94% would be required. The desirability of vaccination as close to

the first birthday as possible is clearly apparent from such predictions. Unfortunately however, in practical terms, children of this age are at their least accessible with respect to contact with doctors and nurses in the primary health care system. At a younger age, post-natal clinics provide an opportunity for contact with parents (particularly mothers) but maternally derived antibody protection prohibits vaccination. Attendance at playschool or primary schools at a later age provides a further opportunity but this is too late (age 4–5 years) to effectively create the desired level of immunity. Clearly, there is no easy solution to this problem aside from repeated publicity, aimed at parents, urging vaccination of their children in the early part of the child's second year of life. Past attempts in this direction have failed in England and Wales. Legislation, along the lines operating in the United States, requiring vaccination certificates for school attendance has proved successful in certain countries. Measles eradication, however, is unlikely to result from such compulsion unless the majority of children are vaccinated well before the age of first attendance at school.

Turning to technical matters, the refinement of age-related heterogeneity in transmission as a component of models of recurrent epidemic behaviour greatly enhances the accuracy of their predictive power. The five age-class model, discussed in the results section of this paper, produces predictions which are (in general) in reasonable agreement with observed trends. Particularly good argument is provided with respect to oscillatory behaviour, age-serological profiles and the average age at infection both with respect to populations subject to mass immunization and unvaccinated communities. This aspect of the research helps to remove some of the doubts raised earlier in this paper concerning the validity of apparent age-related changes in the force of infection. We raised a series of important queries concerning the likelihood that decreased rates of infection in adult age groups arise either as a consequence of genetically based heterogeneity in susceptibility to infection, or as a consequence of the failure of current serological techniques to detect low antibody titres in those individuals who experienced the infection many years previously. These complications are of importance and should not be ignored, particularly when viewed in light of the likely role of genetic factors and the apparent constancy of the force of infection in different age groups within 'virgin' populations who are predominantly susceptible to a specific infection (see Figs. 11 and 12). We therefore suggest that great caution must be exercised in accepting recent estimates (Schenzle, 1985; Dietz & Schenzle, 1984) which suggest much lower levels of vaccination for measles eradication than indicated by earlier work (Anderson & May, 1982, 1985). It appears prudent at present to work on the basis of the higher predictions (as outlined in this paper) until the complications of age-related changes in transmission and the potential role of genetic heterogeneity in susceptibility to infection are more fully understood. If the force of infection is higher in adult age groups than suggested by the data presented in Table 2, our caution over the practical feasibility of measles eradication in England and Wales is of greater significance. Higher true rates of infection in adult age groups would necessitate slightly higher levels of vaccination coverage than those suggested earlier.

With respect to future research needs we can identify two broad areas, one concerned with the mathematical models themselves, and the other involving the

collection of epidemiological data (a more important need). Turning to the theory itself, there is clearly a need to explore the consequences of seasonal fluctuation in transmission within models incorporating age-related changes in contact with infection (Schenzle, 1985). In addition, more theoretical work is required to examine the stability properties of such models, particularly in light of the question of whether or not age-related changes themselves (in the absence of seasonal or stochastic factors) can create sufficient instability to generate limit cycle behaviour. Our numerical studies suggest that certain configurations of the 'who acquires infections from whom' matrix, concomitant with specific ranges of parameter values, generate undamped oscillatory behaviour. This aspect needs thorough investigation by analytical techniques. We also see some advantage arising from a more detailed analysis of the properties of models which capture genetically based variation in susceptibility and resistance to infection (both related and unrelated to age).

In the context of epidemiological research four major requirements are apparent. The first concerns serological data. The overall paucity of such information prior to widescale immunization is not surprising given that the methodology to accurately detect and quantify specific antibodies has evolved relatively recently. Less understandable, however, is the almost complete absence of information in recent years for communities in England and Wales. Age-stratified cross-sectional studies would provide valuable information on a variety of important issues, including the efficiency of the case reporting system, the level of herd immunity generated by current immunization programmes, the relative rise in the proportion of seronegative individuals in the young adult age classes following the introduction of mass immunization, and the rate of decay in antibody titres over time post infection. In addition, carefully designed studies could throw some light on the possible involvement of genetic factors in determining antibody production post infection (and hence the detectability of a past infection). Serological data is also of great value in testing the accuracy of model predictions and epidemiological assumptions, as indicated in the previous section of this paper.

A further need concerns the configuration of the 'who acquires infection from whom' matrix. We are not optimistic that precise quantitative data are obtainable from behavioural studies of intermixing and 'contact' within and between child and adult groups. Qualitative behavioural indicators, however, could be of great value. More importantly, detailed case to case, and household to household studies could in theory provide estimates of the age-specific transmission coefficients. In practice, however, we envisage many difficulties in such research.

Finally, we wish to stress the belief that the substantial advances made in mathematical epidemiology over the past decade have practical relevance for the design of public health policy and, in particular, for disease control by mass immunization. We hope it is apparent from this paper that the current generation of models, when closely linked to epidemiological data, generate predictions which broadly mirror observed trends. They therefore provide many insights of practical relevance to the design of immunization programmes and the interpretation of observed epidemiological trends. Recent advances, however, should not detract from the need to further improve and refine both the mathematical framework and the epidemiological data base.

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APPENDIX A

The main text aims to make clear the biological basis of our mathematical models, and to present the essentials of the mathematical results. This appendix fleshes out the technical details. Unlike the main text, the appendix assumes a fair level of mathematical literacy; the presentation in places is telegraphic, directed to those who may be likely to retrace or extend the calculations.

Equations for epidemiological dynamics

The basic model describing changes with age, a , and time, t , in the numbers of susceptibles, latents, infectives and immunes (X , H , Y , Z , respectively) are set out in equations (A 1)–(A 4), which are discussed more fully elsewhere (Anderson & May, 1983). The essential new feature of the present paper is that the force of infection, λ , now can depend on both age and time, as described by equation (16):

$$\lambda(a, t) = \int_0^{\infty} \beta(a, a') Y(a', t) da'. \quad (\text{A } 1)$$

As discussed in more detail by May (1985), equations (A 1)–(A 4) constitute a set of linear partial differential equations in the variables X , H , Y and Z , provided $\lambda(a, t)$ is initially treated as a given parameter. The equations can be integrated, using the method of characteristics (Hoppensteadt, 1974), which is essentially a mathematical consequence of the biological fact that as time t passes each individual's age advances from a to $a+t$. The force of infection, $\lambda(a, t)$, can then be determined by substituting the solution for Y as a function of λ into equation (A 1).

In practice, it is simplest to integrate the partial differential equations numerically, advancing a step at a time from the specified initial values (as discussed more fully in Anderson & May, 1983), to get explicit solutions in particular cases. This is how Figs. 19–22 and 25–30 are obtained. The details of the computer programme are available on request.

Age-dependent effects at equilibrium

If the above system of equations has settled to its equilibrium state, the age-dependent quantities $X(a)$, $H(a)$, $Y(a)$, $Z(a)$ may be obtained by dropping all time dependence in equations (1)–(4):

$$dX/da = -[\lambda(a) + \mu(a)] X(a), \quad (\text{A } 2)$$

$$dH/da = \lambda(a) X(a) - [\sigma + \mu(a)] H(a), \quad (\text{A } 3)$$

$$dY/da = \sigma H(a) - [\gamma + \mu(a)] Y(a), \quad (\text{A } 4)$$

$$dZ/da = \gamma Y(a) - \mu(a) Z(a). \quad (\text{A } 5)$$

These equations, which are linear if λ is treated as a parameter, can be integrated explicitly to give:

$$X(a) = X(0) e^{-\phi(a) - m(a)}, \quad (\text{A } 6)$$

$$H(a) = X(0) e^{-m(a)} \int_0^a \lambda(a') e^{-\sigma(a-a') - \phi(a')} da', \quad (\text{A } 7)$$

$$Y(a) = \sigma e^{-m(a)} \int_0^a H(a') e^{m(a') - \gamma(a-a')} da'. \quad (\text{A } 8)$$

Here we have defined

$$\phi(a) = \int_0^a \lambda(a') \delta a', \quad (\text{A } 9)$$

$$m(a) = \int_0^a \mu(a') da'. \quad (\text{A } 10)$$

By substituting equation (A 8) into equation (A 1), it can be seen that $\lambda(a)$ is given as the solution of the integral equation

$$\lambda(a) = \sigma X(0) \int_0^\infty B(a, a') \lambda(a') e^{-\phi(a')} da'. \quad (\text{A } 11)$$

Here $\phi(a)$ is given by equation (A 9) and the kernel, $B(a, a')$, is defined as

$$B(a, a') = \int_t^\infty ds \int_{a'}^\infty dt \beta(a, s) e^{-\gamma(s-t) - \sigma(t-a') - m(s)}. \quad (\text{A } 12)$$

Once the function $\beta(a, a')$ and the parameters σ , γ , $\mu(a)$ and $X(0)$ are specified, equation (A 11) can be solved to find $\lambda(a)$, and thence the complete solution follows from equations (A 6)–(A 8).

Approximate solutions at equilibrium

For most childhood infections, the latent and infectious periods ($1/\sigma$ and $1/\gamma$) are around a week or so, whereas the average age at infection ($A \sim 1/\lambda$) is at least several years. This is the case for measles, mumps, pertussis, rubella and many other such infections. If we make use of this biological fact to put

$$\sigma, \gamma \gg \lambda, \quad (\text{A } 13)$$

in equations (A 2)–(A 5), we obtain the approximate result quoted in equation (28):

$$Y(a) \simeq \lambda(a) X(a)/\gamma. \quad (\text{A } 14)$$

This result is obtained by evaluating the integrals in equations (A 7) and (A 8) approximately by noting that the functions $\phi(a')$ and $m(a')$ in general change more slowly than either $\sigma(a-a')$ or $\gamma(a-a')$ in the exponents in (A 7) and (A 8), respectively. As an explicit example, the integral in equation (A 8) may be evaluated in detail for constant λ , whereupon equation (A 14) is seen to be correct up to terms of relative order λ/σ , λ/γ , $\exp[-(\sigma-\lambda)a]$ and $\exp[-(\gamma-\lambda)a]$. For a more full discussion, see May (1985).

Under the approximation of equation (A 14), the relationship between $\lambda(a)$ and $\beta(a, a')$ simplifies from equations (A 11) and (A 12) to:

$$\lambda(a) = [X(0)/\gamma] \int_0^\infty \beta(a, a') \lambda(a') e^{-m(a') - \phi(a')} da'. \quad (\text{A } 15)$$

Finite age classes: the β_{ij} matrix

In practical situations, it makes sense to group individuals into some finite set of age classes, as discussed in the main text. We define 'age class i ' to embrace those individuals in the range from age a_{i-1} to age a_i ; the force of infection is constant, λ_i , within the age class. The previous analysis of continuous functions is now largely reduced to matrix algebra.

At the same time, we take the mortality function to be $\mu = 0$ for $a < L$, $\mu = \infty$ for $a > L$, as discussed in the main text. Under these circumstances, $X(0) = N/L$ prior to vaccination.

The equilibrium expression (A 6) for the number of susceptibles of age a , in the age class i , may now conveniently be written

$$X_i(a) = X(0) \exp[-\psi_{i-1} - \lambda_i(a - a_{i-1})]. \quad (\text{A } 16)$$

Here ψ_i is defined as the constant

$$\psi_i = \sum_{j=1}^i \lambda_j(a_j - a_{j-1}). \quad (\text{A } 17)$$

The index i runs over the n age classes, $i = 1, 2, \dots, n$ (and $\psi_0 \equiv 0$). The total number of susceptibles in the age class i , \bar{X}_i , is obtained directly by integrating equation (A 16) to get

$$\bar{X}_i = X(0) [\exp(-\psi_{i-1}) - \exp(-\psi_i)] / \lambda_i. \quad (\text{A } 18)$$

From equation (A 14) we can write

$$\bar{Y}_i = \lambda_i \bar{X}_i / \gamma. \quad (\text{A } 19)$$

Finally, substituting equation (A 19) into equation (A 1), we have an explicit algebraic relationship between the forces of infection, λ_i , and the WAIFW matrix β_{ij} :

$$\lambda_i = \sum_{j=1}^n \beta_{ij} \bar{Y}_j. \quad (\text{A } 20)$$

The set of equations on page 45 give an explicit example of this general relationship (A 20), for a specified shape of the β_{ij} matrix. Alternatively, it proves convenient to use equations (A 18) and (A 19) to rewrite equation (A 20) as

$$\lambda_i = \sum_{j=1}^n \bar{\beta}_{ij} \Psi_j, \quad (\text{A } 21)$$

Here $\bar{\beta}_{ij}$ is a constant multiple of β_{ij} ,

$$\bar{\beta}_{ij} \equiv (N/\gamma L) \beta_{ij}, \quad (\text{A } 22)$$

and Ψ_j is defined as

$$\Psi_j \equiv \exp(-\psi_{j-1}) - \exp(-\psi_j). \quad (\text{A } 23)$$

Were the WAIFW matrix, β_{ij} , determinable, we could use equation (A 21) to determine the λ_i , and hence all else would follow. As discussed more fully in the main text, the usual situation is that we know the set of n quantities λ_i before vaccination and seek to estimate β_{ij} ; the special structures imposed on the β_{ij} matrix by Schenzle and by us are chosen to give only n independent elements in the matrix, which then can be estimated from the λ_i . Specifically, once the n quantities λ_i are given, we first calculate ψ_j from equation (A 17), then calculate Ψ_j from equation (A 23), and in this way compute the n distinct elements of $\bar{\beta}_{ij}$ from equation (A 21).

Other relevant quantities are computed as follows.

The total fraction of the population remaining susceptible at equilibrium is given from equation (31) as

$$x = \sum_{i=1}^n \bar{X}_i / N. \quad (\text{A } 24)$$

That is,
$$x = \sum_{i=1}^n \Psi_i / (\lambda_i L), \quad (\text{A } 25)$$

with Ψ_i defined by equation (A 23).

The average age at infection, A , is given by the definition (7); substituting equation (A 16) into this definition, and performing the integrals, we eventually obtain the result

$$A = \sum_{i=1}^n [(1 + \lambda_i a_{i-1}) \exp(-\psi_{i-1}) - (1 + \lambda_i a_i) \exp(-\psi_i)] / [\lambda_i (1 - \exp\{-\psi_n\})]. \quad (\text{A } 26)$$

This gives the explicit expression of equation (33) for the 2-age class example discussed in the main text.

The age-specific basic reproductive rate, R_{0i} , for an infective in age class i follows from the definition given in equation (34), and is

$$R_{0i} = \sum_{j=1}^n \bar{\beta}_{ji} (a_j - a_{j-1}). \quad (\text{A } 27)$$

Here the matrix $\bar{\beta}$ is as defined in equation (A 22).

Criterion for eradication of infection by vaccination

If a proportion, p , are vaccinated effectively at birth, the initial number of susceptibles is essentially

$$X(0) = (N/L) (1 - p). \quad (\text{A } 28)$$

The new force of infection in the age class i is now written λ'_i , and may be obtained by altering the above analysis to include the factor $(1 - p)$.

In the limit as eradication is just approached, we have $\lambda'_i \rightarrow 0$ for all i . This corresponds to the quantities Ψ_i of equations (A 23) and (A 17) reducing to $\Psi_i \rightarrow \lambda'_i (a_i - a_{i-1})$. Thus at the margin of eradication, equation (A 21) for λ'_i reduces to the set of n simultaneous equations

$$\lambda'_i = (1 - p) \sum_{j=1}^n \bar{\beta}_{ij} (a_j - a_{j-1}) \lambda'_j. \quad (\text{A } 29)$$

Here the elements $\bar{\beta}_{ij}$ are defined by equation (A 22), and in general will be evaluated from the pre-vaccination forces of infection, λ_i , by the procedure described above. The set of homogeneous equations (A 29) will be satisfied if

$$\det \|\bar{\beta}_{ij} (a_j - a_{j-1}) (1 - p) - \delta_{ij}\| = 0. \quad (\text{A } 30)$$

That is, the critical level of vaccination, p_c , is given by

$$p_c = 1 - 1/A, \quad (\text{A } 31)$$

where A is the dominant eigenvalue of the matrix whose elements are $\bar{\beta}_{ij} (a_j - a_{j-1})$.

Notice, incidentally, that the β matrices chosen by Schenzle and ourselves are usually symmetric ($\beta_{ij} = \beta_{ji}$), whence Λ is the dominant eigenvalue of the matrix whose elements are given by the R_{0i} of equation (A 27). It immediately follows that, if all R_{0i} are the same ($R_{0i} = R_0 = \text{constant}$), then $\Lambda = R_0$ and $p_c = 1 - 1/R_0$; this is the familiar result for a homogeneously mixed population.

Notice also that, in this limit $\lambda'_i \simeq 0$, the average age at infection, A' , is given by the appropriate limiting form of equation (A 26):

$$A' = \frac{1}{2} \sum_{i=1}^n (a_i^2 - a_{i-1}^2) \lambda'_i \bigg/ \sum_{i=1}^n (a_i - a_{i-1}) \lambda'_i. \quad (\text{A } 32)$$

The λ'_i are to be computed from equation (A 29); they are the eigenvectors of the matrix of equation (A 30).

Further refinements

Suppose, instead of vaccinating effectively at age zero, we assume a fraction p of all individuals are vaccinated at age V . We take V to lie in the age class k : $a_k > V > a_{k-1}$. The line of argument that led to equation (A 30) as the eradication criterion for p now takes the form

$$\det \|\bar{\beta}_{ij} \theta_j - \delta_{ij}\| = 0. \quad (\text{A } 33)$$

Here $\bar{\beta}_{ij}$ is still given by equation (A 22), with the elements of $\bar{\beta}_{ij}$ computed from the pre-vaccination λ_i as discussed earlier. The quantities θ_j are defined to be

$$\theta_j = a_j - a_{j-1}, \quad \text{if } j < k; \quad (\text{A } 34a)$$

$$\theta_j = (1-p)(a_k - V) + (V - a_{k-1}), \quad \text{if } j = k; \quad (\text{A } 34b)$$

$$\theta_j = (1-p)(a_j - a_{j-1}), \quad \text{if } j > k. \quad (\text{A } 34c)$$

Computation of the critical value of p is a straightforward, if tedious, task.

The presence of maternal antibodies is another realistic complication for many childhood infections. Suppose maternal antibodies protect newborn infants until exactly age D . This corresponds to the existence of an additional age class '0', which cannot be infected and cannot transmit infection: $\beta(a, a') = 0$ if either a or $a' < D$. Such complications can be included by adding a 'zeroth' age class, with $\beta_{0i} = \beta_{i0} = 0$ for all i . The calculations go forward as above, except now the entering age is not zero but D ($a_0 = D$ and $\psi_1 = \lambda_1(a_1 - D)$) rather than $\psi_1 = \lambda_1 a_1$.

Clearly the realistic refinements of protection by maternal antibodies up to age D and vaccination at age V ($V > D$) can be combined.

APPENDIX B

This appendix sketches briefly the analysis of an epidemiological model for a population comprising several distinct genotypes. The presentation follows closely that given for age-related (as opposed to genetic) heterogeneity in Appendix A.

A genetically heterogeneous epidemiological model

Suppose the total population N is divided into n genetically distinct subpopulations, with the total numbers of the i th genotype being $N_i = f_i N$ ($i = 1, 2, \dots, n$).

We assume not only that N remains constant over time, but also that the population of each genotype remains similarly constant. Within the population of genotype i , we define the number of susceptible, latent, infectious and immune individuals to be X_i , H_i , Y_i and Z_i , as before; notice that the subscript i now labels genotypes (in distinction to Appendix 1, where it labelled discrete age classes).

At equilibrium, the equations describing the transitions among the epidemiological categories $X_i(a)$ etc., for the subpopulation of genotype i , are given again by equations (A 2)–(A 5) of Appendix A. For individuals of genotype i , the force of infection, λ_i , is taken to be the same at all ages; thus we now have genetic heterogeneity, but not age-related heterogeneity, in the force of infection. We further assume that there is homogeneous mixing among genotypes, and that all genotypes are equally infectious. The different genotypes differ only in their susceptibility or resistance to acquiring infection. Under these assumptions

$$\lambda_i = \beta_i \bar{Y}. \quad (\text{B } 1)$$

Here \bar{Y} is simply the total number of infectious individuals at equilibrium,

$$\bar{Y} = \sum_{i=1}^n \bar{Y}_i. \quad (\text{B } 2)$$

Assuming $\mu(a) = 0$ up to age L , as elsewhere in this paper, we can integrate equation (A 2) to obtain the number of susceptibles of genotype i at age a :

$$X_i(a) = X_i(0) \exp(-\lambda_i a). \quad (\text{B } 3)$$

Here $X_i(0) = N_i/L = f_i N/L$, whence the fraction of the overall population who are susceptible at age a is

$$x(a) = \sum_{i=1}^n f_i \exp(-\lambda_i a). \quad (\text{B } 4)$$

This gives equation (59) for the 2-genotype model discussed in the main text. The total number of susceptibles of genotype i is obtained by integrating equation (B 3) to get

$$\bar{X}_i = X_i(0) [1 - \exp(-\lambda_i L)] / \lambda_i. \quad (\text{B } 5)$$

The total number of infectious individuals of genotype i now follows from the approximate equation (28), whose justification was discussed in Appendix A:

$$\bar{Y}_i = X_i(0) [1 - \exp(-\lambda_i L)] / \gamma. \quad (\text{B } 6)$$

If the transmission coefficients β_i are given, we can now calculate the quantities λ_i from the nonlinear algebraic equations (B 1), (B 2) and (B 6). More usually, however, we know the pre-vaccination values of the forces of infection, λ_i , and these to compute the underlying quantities β_i : the explicit computational recipe is

$$\beta_i = \lambda_i Y, \quad (\text{B } 7)$$

$$\bar{Y} = (N/\gamma L) \sum_{j=1}^n f_j [1 - \exp(-\lambda_j L)]. \quad (\text{B } 8)$$

Criterion for eradication of infection by vaccination

Suppose, as before, that a fraction p of each genotype are vaccinated, essentially at birth. The initial number susceptible then becomes effectively

$X_i(0) = (N_i/L)(1-p)$, and the new (diminished) forces of infection, λ'_i , are obtained from the appropriate modifications of the equations given above.

As ever, the marginal eradication criterion ($p = p_c$) is obtained from the limit $\lambda'_i \rightarrow 0$, whence equation (B 1) reduces to

$$\lambda'_i = (\beta_i N/\gamma)(1-p_c) \sum_{j=1}^n f_j \lambda'_j. \quad (\text{B } 9)$$

Clearly these solutions are of the form $\lambda'_i = \beta_i C$, where C is some constant (independent of i); substituting this into equation (B 9) gives

$$1 = (N/\gamma)(1-p_c) \sum_{j=1}^n f_j \beta_j. \quad (\text{B } 10)$$

That is, the critical fraction to be vaccinated for eradication is

$$p_c = 1 - 1 / \left[\sum_{j=1}^n f_j \beta_j N/\gamma \right]. \quad (\text{B } 11)$$

If the pre-vaccination forces of infection λ_i are known, the quantities $\beta_j N/\gamma$ can be determined directly from equations (B 7) and (B 8). This result gives Figures 15*a* and 15*b* for the 2-genotype model specified in the main text.

Notice that in equation (B 11), if the bulk of the population are of the most susceptible genotype ($f_1 \simeq 1$, $\beta_i \ll \beta_1$ for $i \neq 1$), p_c has essentially the value that would be estimated by assuming the population is wholly of the genotype 1. At the same time, however, the total fraction susceptible will relatively rapidly saturate to the fraction f_1 , and thereafter will climb relatively slowly toward 100% in later years. As discussed in the main text, if this genetically determined pattern in $x(a)$ is (incorrectly) interpreted as arising from age-related changes in the transmission coefficients within a genetically homogeneous population, then serious underestimates of p_c can be produced.

Finally, we observe that additional complications – such as vaccination at age V rather than essentially at birth, and/or the effects of protection by maternal antibodies up to age D – can be grafted onto the above analysis, as indicated at the end of Appendix A. Specifically, the addition of both these complications changes the eradication criterion of equation (B 11) to

$$p_c = [1 - (1/R) - (D/L)] / [1 - (V/L)]. \quad (\text{B } 12)$$

Here R is the expression inside square brackets in equation (B 11):

$$R = \sum_{j=1}^n f_j \beta_j N/\gamma. \quad (\text{B } 13)$$

Equation (B 12) reduces to equation (14) of the main text when the population is genetically homogeneous and $D = 0$.