MATHEMATICAL MODELS OF THE EPIDEMIOLOGY OF MEASLES IN DEVELOPING COUNTRIES.

by

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An investigation is made into the equilibrium and dynamic properties of a mathematical model that seeks to describe the epidemiology of measles in developing countries. Advances in the sophistication of mathematical models of recurrent epidemics have led to the application of such models to help in the design of optimal immunisation policies in developed countries. However most of these models do not take account of case fatalities nor of positive population growth rates. They are therefore of limited use to aid in the design of control policies in developing areas. A deterministic, compartmental, age-structured model which allows for age-dependent case fatality rates and for population growth is presented and used to compare the impact of different control policies.

Methods of data interpretation are described which allow the estimation of the model's parameters from published epidemiological data. From such data a baseline parameter set is established. This is then used as a template in the investigation of the sensitivity of the model's equilibrium and dynamic properties to parameter variation.

The study goes on to investigate the predicted impact of a number of different vaccination regimes and concludes that it is not possible to select a vaccination regime that will be optimal in all regions of the developing world. Comparisons are made between control programmes that vaccinate once only, programmes that vaccinate twice, and programmes that start off with one policy and then switch to another.

The final set of results consider the effect of differences in the assumptions incorporated in the model on its predictions under different regimes of population growth. Particular attention is paid to changes, through time, in age prevalence of disease that come about as a result of population growth.

Throughout the thesis, reference is made to the epidemiology of measles in tropical regions, and where possible results are interpreted in terms of their implications for the design of public health policy in developing countries.

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Chapter 1

Introduction

There are a number of childhood infectious diseases for which there exist safe and effective vaccines, but which continue to cause significant morbidity and mortality, especially in developing countries. Three such diseases - measles, neonatal tetanus and whooping cough - were the cause of 5 million childhood deaths in 1984. Within the context of gross mortality, measles is the most damaging of these diseases (Henderson, 1984). In this study measles has been used as an example of a directly transmitted childhood infectious disease for which there exists an effective vaccine. Existing vaccination programmes have had limited impact on disease incidence, and the reasons for this are complex. A study undertaken in The Cameroons in 1975 (McBean, 1976) identified 4 areas of vaccine wastage resulting in only 17% of doses being effective. Two areas of wastage were related to age. Either the recipient was too old and had had the disease already, or the child was too young and so was protected by maternally derived antibody, and therefore could not be successfully immunised. The other two areas of vaccine wastage were heat inactivation, or simply that the doses were thrown away. These first two problems (vaccine given to children still protected by maternal antibody, and vaccine given to children already immune after having had measles) are manifestations of what is called the 'window problem'. Children of immune mothers (virtually all children) are born with transplacentally derived antibody. Maternally derived antibodies wane during the course of the first year of life, but

whilst a child has these antibodies they are protected (partially or completely) from infection by the measles virus, and cannot be successfully immunised (Albrecht et al 1977, Halsey 1983). In developed countries there is little risk of infection during these early years, and almost all infants have lost their protection by maternal antibody before any have acquired their own antibodies through infection (Collins 1929, Black 1959). It is therefore practical to wait until all children are susceptible and to vaccinate during the second year of life. In contrast, in developing countries the average age at infection is much lower (Morley 1969a & b, Walsh 1983). Therefore a substantial proportion of a cohort will have had measles already by the age at which every child could be successfully immunised (i.e. by the age at which maternally derived protection has waned for almost all children). It is thus much more difficult to determine the optimal age for vaccination. The work described in this thesis centres upon the formulation of a mathematical model of disease transmission that can be applied to the assessment of the impact of different policies of mass vaccination in a developing country.

The type of model presented is a deterministic compartmental model which describes the changes in age prevalence of disease that take place over the course of time. Such models have already been extensively studied, and have been usefully applied to questions about optimal vaccination policy in developed countries (see, for example, Anderson & May 1985a and Schenzle 1984b). However, existing models make two assumptions that, although quite reasonable when modelling events in developed countries, are harder to defend when trying to mimic events in the developing world. These two assumptions are (1) that there are negligible disease related deaths,

and (2) that the population is of fixed size. There is ample evidence that case fatality rates are far from negligible in developing countries. Two examples are given in the findings of Williams (1983), and John (1980). Williams found a case fatality rate of 64% amongst Gambian infants, falling to a rate of 4% amongst 6 - 8 year olds. John (1980), whose data was collected in India, found a lower case fatality rate of 22% amongst infants falling to 2% amongst 6 - 8 year olds. In both cases the case fatality rate was strongly dependent upon age, being at its highest amongst infants, and falling to zero for those over 8 years old. Turning to consider population growth rates, United Nations data (United Nations, 1983) shows that in Kenya the population is currently growing at an annual rate of 39 per 1000, and in Thailand the rate is 32 per 1000. These contrast sharply with an annual growth rate in the United Kingdom of 1.1 per 1000. Thus whilst it may be reasonable to assume that the population of the U.K. is of fixed size, the same cannot be said of Kenya, Thailand or many other developing countries.

The work presented here is the result of expressing in mathematical terms what are believed to be the major biological processes that determine the epidemiology of measles in a developing country. These combine characteristics of infection within individual hosts (the latent and infectious periods, the rate of exposure to infection, the case fatality rate) with characteristics of the whole human population (the fertility and death rates). The objectives of the study can be divided into two groups; those for which the underlying motivation is the better understanding of some process or interaction, and those where the hope is to be able to make some objective choice between alternative courses of action.

The first group contains the following aims:

1) To understand more clearly the way in which demographic and epidemiological processes interact to give rise to observed patterns of morbidity.

2) To formally describe the rôle played by the case fatality rate in giving rise to these observed patterns. In particular to understand the effect of case fatalities upon the shape of the serological profile.

A large part of the work in solving these problems lies in the development of methods of data analysis. These allow the interpretation of available epidemiological and demographic information in order to derive parameter estimates for inclusion in the model. Once a full set of model parameters has been chosen the second set of objectives can be tackled, namely the comparison of different regimes of mass vaccination.

The layout of the thesis is along the following lines. These introductory remarks are followed by two chapters reviewing published literature of particular relevance to the project. Chapter two reviews theoretical work which examines deterministic mathematical models of directly transmitted infectious diseases. Chapter three deals with papers that contain data about the epidemiology of measles in developing countries. In chapter four the model is introduced and its parameters described. Chapter five presents equilibrium results and methods of data interpretation that allow the estimation of the model's parameters. These methods are applied in chapter six which covers the presentation of data and its interpretation. Chapters seven eight and nine then present results obtained through numerical solution of the full model. In chapter seven the

properties of the model are investigated without introducing the extra complications of immunisation measures. Attention concentrates on the analysis of the sensitivity of the model's predictions to parameter variation. Chapter eight is devoted to comparing different vaccination regimes, and chapter nine considers the implications of slight changes in the way in which the model is formulated. The penultimate chapter extracts results from preceding chapters to draw some conclusions pertinent to public health policy in developing countries. Chapter eleven consists of a discussion of the whole project, its failures and successes and implications for the direction of future research.

Chapter 2

Literature Review I.
Mathematical Models of the Epidemiology of
Directly Transmitted Human Diseases.

2.1 Aims of chapter 2.

The literature concerning mathematical models of epidemiological processes is very large (see Bailey, 1975) and has expanded rapidly in recent years. In this chapter the relevant subset of the existing literature - those papers that concern themselves with directly transmitted diseases of humans - has been singled out for attention. Because comprehensive reviews of the subject already exist, attention focuses upon recent developments (since 1975) with occasional reference to older papers that are of particular relevance to current work. The aim, then, is to review current trends in research on the modelling of the spread of directly transmitted infectious diseases within human communities and the control of such diseases by immunisation. Attention is primarily focused on deterministic as opposed to stochastic models.

2.2 Chapter layout.

The main body of the chapter commences with some introductory remarks which consider the attractions of epidemic modelling. This is followed by a brief section concerning models for the spread of infection

within households. Attention then turns to models which consider the dynamics of the spread of infection amongst larger communities. Consideration is firstly given to the simplest ordinary differential equation models. The successes and shortcomings of these models are discussed. The rest of the chapter consists of a sequential consideration of the various refinements that have been made to the simple models to try and redress their shortcomings. A discussion of difference equation models is followed by consideration of models which employ delay differential equations. Models of age-structured communities with homogenous and heterogenous mixing are then considered, followed by stochastic models, models with seasonally varying contact rates and finally models with a variety of types of heterogeneity other than age-dependent heterogeneity.

2.3 Introductory remarks.

Childhood infectious diseases have a number of observed properties that have made their epidemiology attractive to mathematical treatment. First of all there is the very fact that they do occur mostly amongst children. To quote Fales (1928);

> Specific infectious diseases are, in general, selective in their incidence, and in the distribution of many diseases this selection is strikingly exhibited by an unequal frequency of occurrence in different age groups ... so characteristic as to have given these infections the group designation "infectious diseases of childhood".

More recently, Fine and Clarkson (1982b) have pointed out that in the U.K. there is a sharp peak in the age distribution of measles amongst five and six year olds. Recurrent oscillations made up of seasonal patterns and occasional large outbreaks have been another source of interest. Anderson, Grenfell and May (1984) have performed time series analyses upon long term

data for a number of infectious diseases and have found evidence of annual, biennial and longer term cycles. These interesting properties, the importance of infectious diseases in terms of public health and the apparent simplicity of the interactions that give rise to the observations have combined to attract much mathematical attention to the modelling of childhood infectious diseases. Much of the research has been aimed at understanding why infectious diseases should often be restricted to certain subgroups of the population (e.g. children), why there should be occasional large outbreaks, and why there are seasonal cycles. Another motive has been the assessment of the impact of different control measures. This latter motivation lay behind the earliest application of calculus to questions of infectious disease transmission - Daniel Bernoulli's work on the impact of innoculation on the epidemiology of smallpox presented to the Academie Royale des Sciences in 1760.

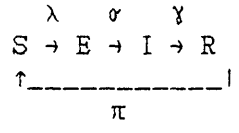
2.4 Household models.

When considering the spread of disease amongst very small populations such as households, chance effects are of great importance. Stochastic models are therefore better able to mimic observed trends. Particular attention has focused on models which use chains of binomial distributions to describe the numbers of cases in successive generations of the disease. Reed and Frost used such a model in lectures from the 1930's onwards but their work was not published until after their deaths (Frost (1976), Sartwell(1976), Fine(1977)). Greenwood (1931) and McKendrick (1926) considered similiar models. More recently interest has again be aroused in such models (Griffiths (1973), Becker(1980) & (1981a)) and advances have

been made in extending such models to allow for heterogeneity of the infectiousness of individuals, (Becker 1981b) and heterogeneity of contact rates within and between households (Becker and Angulo 1981, Becker and Hopper 1983, Ball 1985). Dietz (1985) reviews some of these developments and compares their predictions with data on chains of cases of the common cold in households (Brimblecombe et al 1958). These models are useful in the estimation of the length of the incubation and infectious periods and can be used to estimate transmission rates (see Bailey 1975, chapter 15), but they are of limited applicability in the broader context of large communities.

2.5 Simple ordinary differential equation models.

The underlying framework of all models lies in the description of the transition from the susceptible state to the infectious state. In deterministic models a description is given of the **number** of new cases per unit time, whilst in stochastic models the description given is of the **probability** of a new case. Models that describe the spread of infection within large communities are mostly compartmental in structure, and their general framework can be summarised by the following flow diagram:



The population under consideration is split into a number of non-overlapping compartments for example S - susceptibles, E - exposed (i.e. infected but not yet infectious), I - infectious and R - removed (i.e. dead or immune to reinfection). The model then consists of a set of differential

equations describing the rates at which individuals progress from one group to the next. In the example illustrated λ is the infection rate, σ is the rate at which individulas leave the incubating (exposed) class, γ is the rate of loss of infectiousness, and π is the rate of loss of immunity. the type of differential equations used and the exact configuration of the progression from class to class depend upon the natural history of the disease under consideration, and the aims of the model. For diseases with no immunity (e.g. gonnorhea) S-I-S models are appropriate, people becoming susceptible again immediately after they have recovered. If there is immunity upon recovery an S-I-R model can be used and for diseases for which acquired immunity only exists temporarily the configuration S-I-R-S is appropriate. When there is an appreciable time lapse between the moment of infection and the onset of infectiousness the exposed class can also be included giving S-E-I-R models (where E denotes the exposed or incubating class). In this section ordinary differential equation models are discussed leaving the consideration of models with partial derivatives, stochasticity and delay differential equations to subsequent sections.

The simplest S-I-R model (Kermack and McKendrick (1927)) is as follows

$$\frac{dS}{dt} = -\beta S I \tag{2.1}$$

$$\frac{dI}{dt} = \beta S I - \gamma I \tag{2.2}$$

$$\frac{dR}{dt} = \gamma I \tag{2.3}$$

In this model the infection rate is defined as $\lambda = \beta I$. Thus in time Δt there are $\beta S I \Delta t$ new cases and $\gamma I \Delta t$ removals, β is the transmission

rate and γ the recovery rate. The term β S I is known as the mass action term. It represents the assumption that a community of people mix like an ideal gas and that the rate of disease transmission is directly proportional to the number of meetings between individuals. As it stands this model contains no demographic rates so can only be used for the consideration of single epidemics in closed populations. However the addition of birth and death terms is easily achieved and allows the modelling of recurrent epidemics in populations subject to the input of new susceptibles.

The set of differential equations have two equilibrium points, one with no cases called the zero equilibrium and one with a positive number of cases - known as the endemic equilibrium. The stability properties of these two equilibrium points can be thought of as depending upon the value of one summary parameter, R_o, the basic reproductive rate (Macdonald 1952). The basic reproductive rate represents the number of new cases that would be generated if one infectious individual were introduced into a wholly susceptible population. When R_o is greater than 1 the endemic equilibrium is stable and the model with renewal of susceptibles exhibits weakly damped oscillations of a period in broad agreement with the longer term oscillations visible in case reports. When R_o is less than 1 the zero equilibrium is stable. Intervention in the transmission of disease (e.g. immunisation) to such an extent that the value of R_o falls below unity will therefore lead to disease eradication. It is from this observation that the idea of the critical vaccination proportion for eradication (p_c) has arisen, p_c being the proportion that must be immunised in order to reduce the value of R_o below 1.

This model and a number of models derived from it have been extensively applied to a large number of problems concerning viral (Anderson & May 1982, Millar 1970, Dietz 1975), bacterial (Hethcote & Yorke 1984), and vector borne (MacDonald 1973, Dietz 1980) diseases. The books by Bailey (1975) and Anderson (1982a) give reviews of some of these applications and Wickwire (1977) reviews applications of mathematical optimisation theory to models for the control of infectious diseases.

Analytic treatments of this model and closely related models are presented by Hethcote (1976) and by Waltman (1974). The qualitative behaviour of these ordinary differental equation models is well understood (Hethcote 1973) and Hethcote et al (1981b) present a review of analytic results for autonomous models in which they conjecture that 'a single population, constant parameter epidemic model can support periodic solutions if and only if the model is cyclic and involves temporary immunity'. In this context the term cyclic is used in the sense that the structure of the model is cyclic with individuals passing from the susceptible class to the immune class and back again. Recently studies have been made of models where the transmission term $\beta S I$ is replaced by a term $\beta S^p I^q$ (Liu et al 1986) and it has been shown that such a model has qualitively different behaviour from those with a simple product term, however no biological justification is given for the use of this transmission term.

The threshold theorems derived from the simple models have given useful insights into the epidemiology of directly transmitted infectious diseases. However there are many observed properties that these simple

models fail to mimic. First of all, because they describe total numbers of cases, they can give no insight into the age distribution of cases. Also the values for the critical vaccination proportion p_c that they predict tend to be lower than actual experience would suggest (see Fine & Clarkson 1983 for a critique). They predict damped oscillations towards a stable equilibrium when perpetuated oscillations are observed. The period of these oscillations agrees broadly with the longer term observed oscillations but the observed annual cycles are not mimicked. Although they give a fair description of reccurrent epidemics in large communities they fail to account for the fade-out of diseases in smaller communities. Finally, the assumption of homogenous mixing ignores the many heterogeneities acting to divide communities up into sub-units. The following sections deal with models which, through some refinement of these basic models, attempt to improve upon one or more of these shortcomings.

2.6 Difference equation models.

Soper (1929) noted the marked periodicity of measles and presented a difference equation model with no losses from the infectious class which exhibited oscillatory behaviour. However it was pointed out by Wilson and Worcester (1945) that the inclusion of a finite removal rate on the infectious class or of a death rate would push the model into damped oscillatory behaviour. May (1986) discusses the model in some detail and shows that the period of its oscillations is the geometric mean of the generation time of the infection and the average age at infection.

2.7 Delay differential equations.

The analysis of observational data on the time taken for case-to-case transmission implies that neither the duration of the incubation period (i.e. infected but not yet infectious) nor the duration of infectiousness are exponentially distributed (Bailey 1975, chapter 15). Investigations have therefore been made into models which allow these durations to be distributed in ways other than the exponential distribution implied by the term $-\gamma Y$ in equation 2.2 (Hethcote & Tudor, 1980; Hethcote et al 1981a & b; London & Yorke 1973, Yorke and London 1973, Smith 1983a & b, Grossman 1980). On the whole these modifications do not qualitatively change the solutions of the models, but it has been shown that for a model with temporary immunity (i.e. of the SIRS type) a large constant time in the immune class can induce limit cycle behaviour in the model - that is the model may mimic recurrent epidemics (Green, 1978).

2.8 Partial differential equation models which assume homogenous mixing.

Motivated by a desire to model the age distribution of infection as it changes through time, a number of recent studies have extended the S-E-I-R model so that there is an age structure. These models keep track, not only of the passing of time, but also of the ageing of individuals. Equations 2.1 to 2.3 are therefore replaced by a similiar set of partial differential equations. However the models described here still assume homogenous mixing across the whole population. Particular interest has been generated by questions concerning the optimal vaccination policies to control the rubella virus given that the most detrimental effect of the infection occurs when

it is contracted by women during the first trimester of pregnancy (Knox 1980, Anderson & May 1983, Hethcote 1983, Dietz 1981). These studies consider the effect of different vaccination programmes on the number of cases of congenital rubella syndrome (C.R.S.) - the disease of unborn infants whose mothers contract rubella which can result in severe disabilities. Similiar models have also been applied to the modelling of influenza (Longini et al, 1978); acute bacterial diseases (Cvjetanovich et al 1978) and poliomyelitis and measles (Cvjetanovich et al 1982, Fine and Clarkson 1982b). Katzmann and Dietz (1984) have used such a model for the consideration of the optimal age for vaccination in a situation where maternal antibodies prohibit immunisation of newborns. The solutions of these models with age-structure have an age distribution in broad agreement with those that are observed, but the sharp peaks in incidence at age 5 and 6 years pointed out by Fine and Clarkson (1982b) are not mimicked.

All of the models discussed so far assume that the population (though experiencing turnover through births and deaths) is of fixed total size. This assumption is dropped in a paper by May and Anderson (1985) which investigates disease dynamics in exponentially growing populations.

Work is progressing to extend existing asymptotic stability results to models that have an age structure. Greenhalgh (1986) has shown the stability of the endemic equilibrium of a model with age structure and homogenous mixing.

2.9 Models with age-dependent heterogeneity.

A natural extension to a model for an age-structured population is to consider the effects of age-dependent transmission. A very general model was proposed in 1974 (Hoppensteadt 1974) and some early approaches to the problem considered the case where the per capita rate of acquisition of infection increased linearly with age (Griffith 1974, Anderson and May 1982). This approach proved satisfactory for describing the acquisition of infection in the child and young teenage classes but was considered to imply too large a rate of infection for adults. A model was then proposed where the transmission rate from an infectious individual to a susceptible depended only on the difference in their ages (Knolle 1983). The most fruitful approach so far, however, seems to have been the division, by age, of the population into a number of homogenously mixing subgroups followed by the definition of a transmission matrix $\beta_{i,j}$ for transmission from infectives in the jth age class to susceptibles in the ith age class. The estimation of age-dependent forces of infection from which the elements of such a transmission matrix could be calculated is discussed by Grenfell and Anderson (1985) and the methods of data interpretation which have been developed allow a close relationship between theory and observation. Studies of such models have shown that age dependent mixing may reduce the critical vaccination proportion for eradication when compared with predictions based on models which assume homogenous mixing across all age classes (Schenzle 1984a, Tudor 1985), but may, under other assumptions about the details of the configuration of the matrix $\beta_{i,j}$, act to increase it (Anderson & May 1984). Models with age dependent mixing have been used to investigate the effects of different vaccination strategies upon the

incidence of measles (Anderson and May 1985a, Schenzle 1984b, Tudor 1985) and rubella (Anderson and Grenfell (1985). Dietz and Schenzle (1985) propose a model with heterogeneity according to age and a rate of loss of infectiousness that is a function of time spent in the infectious class.

These models predict age distributions of cases much closer to observed age distributions than those predicted by earlier models with homogenous mixing, and the oscillatory behaviour of their solutions is only very weakly damped.

2.10 Stochasticity.

In a classic series of papers Bartlett (1956, 1957, 1960) showed that the inclusion of a stochastic element in the transmission function could serve to perpetuate oscillations indefinitely. However these outbreaks do not occur with any strict periodicity. This work also gave rise to the important threshold theorems about the size of town that could support measles without the disease fading out. Similiar models have been studied more recently by Stirzaker (1975) who investigates periodic solutions of stochastic models with seasonality. Stochastic epidemic models were recently reviewed by Neyman and Price (1984)

2.11 Seasonality.

Seasonality in the transmission of disease has attracted much interest. Fine and Clarkson (1982a) consider that seasonality is more important than the build up of susceptibles in determining the timing of

epidemics. Anderson, Grenfell and May (1984) performed time series analyses on long term data for childhood infectious diseases and found evidence of annual, biennial and longer term cycles. London and Yorke (1973, Yorke and London 1973) inferred that contact rates are seasonal from an analysis of data from New York and Baltimore. In a later paper (Yorke et al 1979) they show that seasonality in transmissability can greatly increase the minimum population size for perpetuation of diseases. A paper by Dietz (1976) presenting a set of ordinary differential equations with a seasonally varying contact rate provoked a series of analytic studies of the model's periodic solutions (Grossman et al 1977, Grossman 1980, Gumowski et al 1980, Smith 1983a & b), and a series of papers considering the possibility of the co-existence of periodic solutions of both large and small amplitude (Schwartz and Smith 1983, Aron and Schwartz 1984, Schwartz 1985). Analytic studies of the effect of including seasonality in the contact rate have been one of the major preoccupations of theoreticians in recent years. However some of these studies have become somewhat divorced from the original problems that the models were intended to consider.

2.12 Heterogeneity.

There are a number of types of heterogeneity that can be incorporated into epidemic models. Anderson and May (1984b & 1985b) identify four types of heterogeneity; temporal (i.e. heterogeneous mixing according to age), spatial, genetic and behavioural. Models with age-dependent heterogeneity have already been considered.

Little attention has been paid to the effects of the genetic heterogeneity of the host population on the observed patterns of epidemics. Anderson and May (1984 and 1985a) have described how genetic heterogeneity might give rise to patterns of age prevalence that resemble those induced by age-dependent susceptibility to infection.

Models that consider spatially heterogenous populations can be divided into two groups; those that use diffusion processes to model the dissemination of disease along a line or in the plane, and those that consider networks of subpopulations that mix homogenously within and heterogenously between groups. Diffusion models were reviewed in 1977 by Mollison (1977). Their applications to human diseases is limited by the fact that human transportation networks dominate the spread of disease. They have, however, been successfully applied to the spread of animal diseases, particularly rabies (Murray et al 1986).

Of the second type of model with spatial heterogeneity the Soviet simulation models of the spread of influenza (Baryon et al 1977) have recently attracted renewed attention (Rvachev & Longini 1985, Longini et al 1986) and summaries of their results are now available in English (Fine 1982). Monte Carlo simulation techniques have been used in a series of papers based on measles data from around Bristol (Cliff et al 1975, Murray & Cliff 1977). Stability properties of multisite models have been studied by Hethcote and others (Hethcote 1976, 1978, Nold 1980, Hethcote et al 1981, Hethcote & Thieme 1985, Post et al 1983). Dietz (1980) shows that spatial heterogeneity can act to raise the basic reproductive rate R_0 when compared with estimates derived from models with homogenous spatial mixing. Models

which consider the immunisation of spatially heterogenous populations have also been studied (Hethcote 1978) and it has been suggested that immunisation efforts should be concentrated on the larger population centres (May & Anderson 1984) as opp osed to the smaller centres. Arita et al (1986) present an observational study of the effect of population density upon the impact of the smallpox immunisation programme.

Many of the models described above as being for spatially heterogenous populations are general enough to be applicable to populations whose heterogeneity is generated by behavioural differences. Such studies are of particular relevance to the modelling of sexually transmitted diseases where it has been shown that disease can be perpetuated by a core group of highly active individuals (Kemper 1980, Hethcote & Yorke 1984). Lajmanovich & Yorke (1976) have shown the global asymptotic stability of an ordinary differential equation S-I-S model with n subpopulations which they apply to the modelling of gonorrhea transmission. Hethcote and Thieme (1985) have extended asymptotic stability results to include models of heterogenously mixing populations which include immunisation or where the rate of loss of infectiousness depends upon class age.

2.7 Summary.

The behaviour of simple ordinary differential equation models for epidemics is now well understood. Progress is being made in various directions, all aimed at making the models a better mirror of reality. These include the introduction of various types of heterogeneity, the study of delay differential equation models, and the further analysis of stochastic

models. A lot of attention has recently been paid to somewhat abstract models with seasonal contact rates, and in some cases these studies have not made any attempt to link the model to published data, nor to seek a biological interpretation for the mathematical results. However, other areas of research are moving more towards the construction of mathematical models that make direct use of epidemiological data and whose results are aimed at being of use in the planning of public health programmes.

Chapter 3

Literature Review II.

Observed Patterns of Measles Epidemiology in Developing Countries.

3.1 Aims of the Chapter.

The aim of this chapter is to review existing publications concerned with the epidemiology of measles in developing countries.

3.2 Organisation of Information

The first set of papers reviewed are those which themselves present reviews of the subject. A number of topics concerned with the epidemiology of measles are then considered in turn. Part of this review considers age specific rates of seroconversion and the rate of loss of protection by maternal antibodies. This is followed by a section devoted to papers on age prevalence. Attention then turns to studies that have measured case fatality and mortality rates. Studies of the impact of existing programmes are then assessed.

3.3 Existing Literature Reviews.

An excellent general overview of the current status of measles in developing countries has been published by Walsh (1983), whose article also

considers the problems inherent in administering measles vaccine in developing countries. Similiar topics are covered in briefer format by Abdurrahman and Taqi (1981) and a leading article in the British Medical Journal (Anonymous, 1976). Ofosu-Amaah (1983) combines a presentation of current logistic problems with a historical perspective of measles in Africa. His paper is presented in a volume containing the proceedings of a conference on measles and measles immunisation which contains a great many articles on measles epidemiology and on the impact of existing programmes. Cutting (1983) and Foege (1982) both combine reviews of existing problems with presentation of economic arguments for the eradication of measles, but both admit that eradication is still a long term goal.

One of the barriers to the eradication of measles is a problem generated by the comparatively short interval between loss of protection by maternal antibodies and natural infection. This difficulty has been called the 'window problem'. A very full and careful bibliographic review of the window problem has been prepared by Halsey (1983) with particular attention paid to data on age specific rates of sero-conversion. Black (1982) puts particular emphasis on changes in age prevalence that can be expected as a result of large scale immunisation programmes, and discusses some of the implications of such changes. In particular he puts forward the idea that it may be possible to increase the age of administration of vaccine after the average age at infection has risen. This rise in the average age at infection is expected as a result of mass vaccination - even at fairly low levels. In a paper that emphasises the differences between the epidemiology of measles in urban, rural and insular populations Davis (1982) gives a stimulating summary of areas requiring more research. A

clinician's perspective is presented by Guillozet (1979) who considers clinical complications of contemporary measles in tropical Africa. Morley's classic description of severe measles can be read in his 1969 papers in the Lancet (Morley, 1969a & b) along with an interesting review of the status of measles right across the developing world at that time. He also provides a review of some beliefs and proverbs about measles including the chilling Arabic comment; 'count your children after the measles has passed'.

3.4 Seroconversion rates.

One purpose of studies of age specific rates of seroconversion is to provide information that will help in choosing an ideal age for administration of measles vaccine given the problem of low vaccine efficacy in children with high titres of maternally derived antibody. The procedure adopted is to select a number of children with no history of measles or of measles vaccination and perform serological tests on blood samples taken from each child before and after immunisation. Some studies (but not all) exclude older children with high antibody titres for measles at the first screening. This is based on the assumption that they have experienced a sub-clinical measles infection. There is no consensus on the criterion that should be adopted to represent seroconversion. Some studies demand a four fold rise in the dilution of serum that will inhibit agglutination (Ghosh et al, 1977; Hendrickse et al, 1966; Ministries of Health of Brazil et. al., 1983), others a ten fold rise (Wood et al, 1980). A different approach is to choose a particular level of dilution at which to screen, and to call samples positive or negative according to whether or not they inhibit agglutination at this level of dilution. The levels of dilution used are:

1:3 (Ministry of Health of Kenya, 1977; E.P.I., 1979) 1:4 (Job et al, 1984), 1:6 (E.P.I., 1981) 1:8 (Mhere et al, 1984; Burrowes & Cruickshank, 1976; Dick et al, 1975 - although Dick uses the complement fixation test as opposed to the haemagglutination inhibition test), or 1:10 (Lee et al, 1983; Breman et al, 1975). Some studies do not specify the criterion for seropositivity that they have set (King, 1978; Ogunmekan et al, 1981). A number of studies (Breman et al, 1975; King, 1978; Hendrickse et al, 1965; Ghosh et al, 1977; Ogunmekan et al, 1981; Burrowes & Cruickshank 1976) clump children into such broad age bands that very little information is gained on changes in the rate of seroconversion with respect to age. Amongst those studies that stratify their subjects by month of age there is great variation in the age specific seroconversion rates. (See table 3.1.) This can partly be explained by small sample sizes, but is also an illustration of the wide variation between communities in different geographical locations.

The question of what happens to children who fail to seroconvert after immunisation has been addressed by Black and co-workers in a project based in Brazil (Black et al 1984). In a longitudinal study of 79 children who failed to seroconvert after measles vaccination they found that only 60% of those remaining susceptible could be successfully revaccinated 1½ years after the first immunisation. These results confirm observations made in the United States (Linnemann, 1983; Wilkins & Wehrle, 1979), but in the context of a developing country.

Some studies of rates of seroconversion (Job et al, 1984; Hendrickse et al, 1966; Ministry of Health of Kenya, 1977; Burrowes & Cruickshank, 1975; E.P.I., 1981; E.P.I., 1979) describe the pre-vaccination age-stratified

Reference	Criterion	% +ve 6 months	% +ve 12 months
Lee, 1983	1 : 10	82% (17)	100% (12)
Ministries of Health of Brazil et al 1983	1 : 10 & × 4	59% (319)	97% (139)
Mhere, 1984	1 : 8	15% (35)	76% (21)
Dick, 1975	1 : 8	23% (13)	80% (5)
Job, 1984	1 : 4	74% (32)	95% (20)
Wood, 1980	× 10	57% (46)	89% (9)
Ministry of Health of Kenya, 1977	1 : 3	90% (31)	100% (38)

Table 3.1
Summary of data on age specific seroconversion rates from studies that stratify age in months. Figures in parentheses show sample sizes.

serological profiles as well as the seroconversion rates. This information can be used to determine the rate of loss of protection by maternal antibody. The illustration of the neonatal antibody profile is the primary objective of other studies (Harry & Ogunmekan, 1979; Bottiger et al, 1981; Bhaskaram et al, 1986; Abdurrahman et al, 1982). An analysis of the data presented in a series of such papers is presented in chapter 6 section 4. As with rates of seroconversion, there is a broad spectrum of results with the estimated average duration of protection by maternal antibody ranging from 3 months (Ministry of Health of Kenya, 1977) to 5 months (Burrowes & Cruickshank, 1975).

Great hopes have been raised by the success of trials of Edmonston-Zagreb vaccine administered by inhaling an aerosol of measles antigen. Sabin et al (1983) found a seroconversion rate of 100% of 4-6 month olds with and without maternal antibodies. This success prompted Morley (1983) to suggest that eradication of measles this century might be a possibility. However, further trials in The Gambia (Whittle et al 1983 & 1984) have been less successful, and the method of aerosol vaccination is not yet in widespread use.

3.5 Age prevalence studies.

Studies of age prevalence levels of measles fall into three groups. First, and most reliable, are serological surveys which measure the proportion by age in the community that have measles antibodies at a level sufficient to protect them from infection. In the absence of such information community based surveys of age incidence can also give a good

indication of the degree of transmission within different age groups in the community. If even this information is not available, hospital and dispensary records can give a 'quick and dirty' overview of age prevalence. However they must be treated with suspicion in the light of the fact that they are bound to be biased towards cases in the younger age classes where measles infection is more likely to lead to severe disease (Morley & MacWilliam, 1961)

A number of serological surveys were carried out in French West Africa in the sixties (Cantrelle, 1965; Cantrelle, 1969; Baylet, 1969; Boue, 1964) . The study by Boue (1964) is of particular interest as it contrasts serology from an urban and a rural community, finding that 100% of 1½ - 2 year olds in Dakar had antibodies to measles, whilst in Popenguine (a small fishing village) only 33% of the same age group were measles seropositive. Since the French West African series of studies were performed there have been very few serological surveys in Africa. Stanfield & Bracken (1971) performed a small survey on children under 6 years old in the area around Kampala. Although such a study can give useful information about the rate of acquisition of infection amongst the very young, when planning an immunisation programme it is desirable to have information on transmission rates across all age classes. Details of data requirement are discussed in chapters 6 & 10. India has been better covered by serological surveys (Mehta et al, 1972; Dave, 1983; Bhau et al, 1979; Broor et al, 1976; John & Jesudoss, 1973). The study performed by Broor et al (1976) includes a large number (568) of individuals of ages ranging from new-borns to 35 years and over. Mehta's (1972) study includes a group of 'adults' but their ages are unspecified, and all the other Indian studies only consider children below

10 or 12 years of age. Other Asian countries where such studies have been carried out are Thailand (Ueda et al, 1967), Burma (Chin & Thaung, 1985) and Nepal and Sri Lanka (Brink & Nakano, 1978). The Brink and Nakano study, like Boue's Senegalese study, compares serology from regions of different population densities. They found that 27% of hill dwelling children in the age group 12 -23 months were measles seropositive whilst 59% of the same age group living in the flatter, more densely populated areas had antibodies to measles. Kenny et al (1976) and Golubjatnikov et al (1971) have studied age prevalence of measles antibodies using serology in Central America. Data from these surveys is presented, analysed and interpreted in chapter 6.

A subset of published serological profiles - those drawn from isolated communities - are of particular interest. To quote from one paper on measles in isolated communities (Van Mazijk et al, 1982): 'Epidemics in isolated populations commonly affect all ages and the relative susceptibility of the very young, the young, and the elderly can be compared in a way not at present possible in larger societies.' F.L. Black has been particularly active in the collection of serological profiles from isolated communities (Black, 1962 & 1975). Willis and Warburton (1974) have studied measles susceptibility on Pacific islands, and Adels & Gajdusek (1963) have made a similiar study in New Guinea and Micronesia.

India is well represented by papers presenting community based surveys of age incidence (Garai & Chakraborty, 1980; Siddiqi et al, 1974; Mathews et al, 1971; Dhanoa & Cowan, 1982; John et al, 1980; Sinha, 1977; Agarwal et al, 1976; Pereira & Benjamin, 1972; Shah et al, 1972). The information contained

in these papers is not analysed in this thesis, but they undoubtedly contain a rich source of information on age prevalence of measles in India in the pre-vaccination era. An important community based age incidence survey from Asia was collected by Koster and co-workers in Bangladesh (Koster et al, 1981). In Africa a whole series of excellent studies have been carried out as part of the Machakos project including two papers on age incidence of measles (Voorhoeve et al, 1977; Muller et al 1977). Another survey of age incidence in a rural setting is presented by E.P.I. (1980b) in an account of measles epidemiology in rural Somalia. Finally, two studies from rural Guatemala represent Central America in this list of community based age prevalence studies (Gordon et al, 1965; Scrimshaw et al, 1966).

The final set of papers to be reviewed in this section present age prevalence data based on hospital and dispensary records and case reports. Although these are not the best ways to gain an accurate impression of the patterns of age incidence in a community, they have the advantage of being readily available. Morley & MacWilliam (1961) and Gans et al (1961) brought attention to the severity of measles in tropical Africa using hospital in and out-patient data. In a later paper Morley and others present further hospital based evidence of the severity of measles in West Africa (Morley et al, 1967). Other African countries from which such information is available are Kenya (O'Donovan, 1971; Hayden, 1974), Senegal (Helmholz & Seck, 1975), South Africa (Loening & Coovadia, 1983), Ethiopia (Kaartinen, 1984), Tanzania (Gupta & Singh, 1975), Botswana (E.P.I., 1980a) and Ghana (Blankson, 1975). In India it is well known that people are reluctant to take a child sick with measles to see a doctor, and it is probably for this reason that most of the age incidence studies have been community based.

There are two studies based on case notifications from Central and South America; one is from Mexico (de Castro, 1983) and the other is from Chile (Ristori et al, 1962).

3.6 Case fatality rates and mortality rates.

Data on age specific case fatality rates are fairly abundant in Africa. In their 1961 paper Morley & MacWilliam showed case fatality rates amongst outpatients and admissions to Ilesha general hospital. For case fatality data to be really reliable, one needs to be confident that the denominator (total number of cases) counts all individuals who have experienced measles infection, no matter how mild their symptoms have been. For this reason hospital and dispensary studies are rather unsatisfactory as they are bound to see only the worse cases. Community based studies are therefore of great value when trying to ascertain the case fatality rate. The Machakos studies in rural Kenya are firmly based in the community and have produced data on case fatality rates (Muller et al, 1977). An extensive series of papers presenting work carried out in Guinea Bissau (Aaby et al, 1983a b & c 1984a b & c) are also based on studies carried out in the community. In these papers Aaby challenges the notion that children die of measles because they are malnourished, and instead suggests that overcrowding is a much better indicator of high risk groups than low weight for age. These results are supported by work carried out in Bangladesh (Koster et al 1981). In India there are many religous beliefs associated with measles infection, and children with measles are often hidden in the home. This makes the collection of data on case fatality rates particularly difficult and helps to explain why there have been very few published studies on measles case

fatality rates in India. However John et al (1980) carried out a small study in rural south India where they overcame the problem of children being kept inside by performing house-to-house visits specifically looking for cases. In chapter 6 these data are reviewed in more detail. Some studies present data as mortality rates, i.e. death rates per 1000 population (Gordon et al, 1965; Borgono, 1983) but such information is much more difficult to interpret than case fatality rates in the absence of data on the age distribution of the population.

3.7 Impact of vaccination campaigns.

A number of studies have examined the impact of vaccination campaigns upon the incidence of measles. Two of these are from Yaounde, Cameroun (McBean et al, 1976; Heymann et al 1983). The first of these records the depressing statistic that only 17% of measles vaccine doses brought into the country resulted in the seroconversion of a child following administration. The later paper presents more optimistic results and reports a 44% fall in measles incidence between 1974 and 1979. A report on the campaign in West and Central Africa which aimed to eradicate smallpox and control measles (Foster & Pifer, 1971) points to the need for continual control measures. An interesting approach is taken in a paper based on a study in Zaire (Kasongo project team, 1981). The project questioned the influence of measles vaccination on survival patterns and concluded that the gain in survival probability endowed by measles vaccination, tended to diminish over the course of time. A review of the epidemiology of measles in China (Yihao & Wannian, 1983) reports that following a successful

immunization campaign the age distribution of cases has shifted upwards and the case fatality rate dropped.

3.8 Summary.

There is a large amount of data available which describes the epidemiology of measles in developing countries, but much of the published work contains little quantitative detail. A brief overview of what quantitative information exists has been given; a more detailed review of the data itself is presented in chapter 6.

Chapter 4

Introduction to the Model.

4.1 Aims of chapter 4.

In this chapter the aim is to give a general introduction to the model. This is to be achieved by: defining the different compartments of the model; setting down the partial differential equations describing the flows between these compartments; and then giving a verbal explanation of the reasoning behind these equations. Details of the meanings of the parameters and the types of data from which they could be estimated are shown in a table. The restrictions that have been imposed upon the model for the purposes of this study are then explained.

4.2 Chapter layout.

The chapter commences with a brief description of the type of model used. This is followed by definitions of the model's five compartments. The partial differential equations, initial conditions, and boundary conditions that constitute the substance of the model are then set down and a verbal explanation of the biological assumptions they represent is given. This is accompanied by a diagram representing the model in a schematic way. A table summarising information on the parameters will follow. Next, attention will focus upon the most important of the parameters, the force of infection, and an associated idea, the 'who acquires infection from whom' matrix. This leads on to a description of the specific type of age

dependency that has been imposed upon all the age dependent parameters of the model. A section follows explaining the notational conventions used, and the chapter concludes with a summary of the material presented.

4.3 Model Description

The model used throughout this study is age structured, compartmental and deterministic and is derived from the model described by Anderson and May in their studies of the design of vaccination programmes in developed countries (Anderson & May 1983, Anderson & May 1985a). The model investigated in this study, differs from that used by Anderson and May in the following two ways. The assumption that the total population is constant has been dropped and the possibility that there may be appreciable case fatalities has been allowed. These extra complications have been included to allow for certain special features of the epidemiology and demography of developing countries. The model consists, in essence, of a set of partial differential equations describing the flows between subsets of the population, and initial and boundary conditions for these equations. The population is divided into five groups: maternal antibody protected, those infants who still have transplacentally derived antibodies and are therefore protected from disease; susceptibles, those who have lost their protection by maternal antibody and have not yet had any experience of the infection in question; incubators, those who have caught the disease but are not yet capable of infecting others; infectives, people at that stage of the disease when they can pass infection on to others; and immunes, people who have recovered from the disease and by virtue of their immunity are

protected from contracting it again - this immunity is assumed to be lifelong.

These five classes, or compartments are represented by the five letters; M, X, H, Y & Z. The following are the partial differential equations describing the rates at which people pass from one class to another.

$$\frac{\partial M}{\partial a} + \frac{\partial M}{\partial t} = -(\mu(a) + \delta)\, M(a,t) \tag{4.1}$$

$$\frac{\partial X}{\partial a} + \frac{\partial X}{\partial t} = \delta\, M(a,t) - (\mu(a) + \lambda(a,t))\, X(a,t) \tag{4.2}$$

$$\frac{\partial H}{\partial a} + \frac{\partial H}{\partial t} = \lambda(a,t)\, X(a,t) - (\mu(a) + \sigma)\, H(a,t) \tag{4.3}$$

$$\frac{\partial Y}{\partial a} + \frac{\partial Y}{\partial t} = \sigma\, H(a,t) - (\mu(a) + \alpha(a) + \gamma)\, Y(a,t) \tag{4.4}$$

$$\frac{\partial Z}{\partial a} + \frac{\partial Z}{\partial t} = \gamma\, Y(a,t) - \mu(a)\, Z(a,t) \tag{4.5}$$

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

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

the dynamics of this total population are described by;

$$\frac{\partial N}{\partial a} + \frac{\partial N}{\partial t} = -\mu(a)\, N(a,t) - \alpha(a)\, Y(a,t) \tag{4.6}$$

The boundary conditions for M, X, H, Y & Z are as follows;

$$M(0,t) = \int_0^\infty m(a)\, N(a,t)\, da \tag{4.7}$$

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

That is, all newborns are protected by maternal antibody.

In addition, the quantities

$M(a,t_o)$, $X(a,t_o)$, $H(a,t_o)$, $Y(a,t_o)$ & $Z(a,t_o)$

are all assumed to be known for some time t_o, thus providing the necessary initial conditions for the equations. The manner in which these initial conditions are set when finding numerical solutions to the set of equations is described in chapter 7.

There now follows an explanation of the biological interpretation of equations 4.1 to 4.5.

All individuals are born protected by maternal antibodies. Although these infants have protection from measles, they are still at risk from other sources, and the group is therefore subject to losses at an age specific rate $\mu(a)$ representing deaths by any cause other than measles. This is referred to as the background death rate. Infants who survive this period leave the maternal antibody protected group at a constant per capita rate δ to join the susceptible class. Hence the average length of time spent in the maternal antibody protected group is approximately equal to $1/\delta$.

Once in the susceptible class, individuals are at risk of contracting measles. This they do at a per capita rate $\lambda(a,t)$. This rate, $\lambda(a,t)$, is called the force of infection. However, some susceptible individuals will die as a result of other causes, and therefore the background death rate $\mu(a)$ also applies to this class.

Upon becoming infected individuals enter the incubator class, where they stay, on average, for time $1/\sigma$ before becoming infectious. Once again they may die from other causes during this time.

Once an individual has become infectious, he is deemed to be at heightened risk due to having the disease. There is, therefore, an

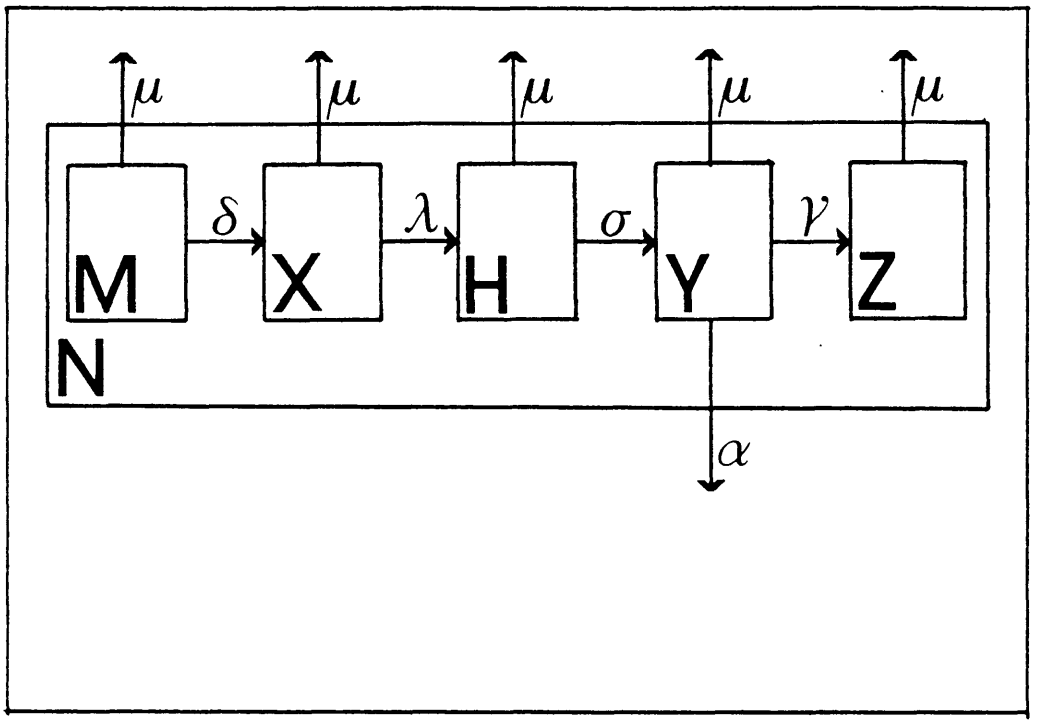


Figure 4.1
Scheme of flows between compartments in the model. Note in particular that the total population (N) loses individuals at a higher rate from the infectious (Y) compartment than from the others.

additional death term $\alpha(a)$ representing disease related deaths. Other risk factors don't disappear just because an individual has measles, so the background death rate is still present.

Those individuals who survive the disease enter the immune class at a constant per capita rate γ, where they stay until they die at an age specific per capita rate $\mu(a)$. Figure 4.1 summarises the possible transitions between model compartments.

4.4 The model's parameters

Parameter values are estimated from epidemiological data. The magnitude of the parameters determines the speeds with which the transitions between groups take place. Thus parameter estimation forms the bridge between observed patterns and the model's behaviour. All the work presented in this study has been performed using parameter values measured from field data. Table 4.1 summarises information about the parameters, and gives a guide to the range of values that they may take.

The force of infection $\lambda(a,t)$ plays a central rôle in disease dynamics because it governs the speed at which new cases are generated. Its definition is as follows:

> the force of infection is the per capita rate at which susceptibles become infected.

The relationship between the force of infection and the size of the infectious population is perhaps the most important distinguishing feature between different models of the dynamics of directly transmitted diseases. The relationship that has been used in this study is the following;

Parameter	Biological Interpretation	Age Dependent / Independent	Type of Data Measured From	Approx. Range of Values(yr^{-1})
δ	rate of loss of maternal antibodies	independent	serological surveys of young age classes excluding known cases	2 - 5
$\mu(a)$	background death rate	dependent	demographic tables	0 - ,15
$\lambda(a,t)$	per capita rate of acquisition of infection	dependent	serological surveys	0 - 1,8
σ	$1/\sigma$ is the mean incubation time	independent	clinical observations	73 - 45 so $1/\sigma$ is 5 - 8 days
γ	$1/\gamma$ is the mean infectious time	independent	clinical observations	91 - 60 so $1/\gamma$ is 4 - 6 days
$\alpha(a)$	disease related death rates	dependent	case fatality rates	0 - 90
$m(a)$	fertility rate	dependent	demographic tables	0 - 0,35

Table 4.1
Summary of information about the model's parameters and per capita rates

$$\lambda(a,t) = \frac{\int_0^\infty \beta(a,a')\ Y(a',t)\ da'}{\int_0^\infty N(a',t)\ da'} \qquad (4.8)$$

In classical non-age-structured deterministic models, (Kermack & McKendrick 1927, Bailey 1975) X, Y and N represent the densities of the susceptible, infectious and total populations respectively. Individuals move from the susceptible to the infected state at rate β X Y, that is at a rate proportional to the product of the density of susceptible and the density of infectious individuals. This is the so called 'mass action' assumption. The age-independent version of equation 4.8 would state that individuals move from the susceptible to the infected state at rate β X (Y / N). Here X and Y represent the total numbers of susceptible and infectious people in a community and N represents the size of that community. Therefore the rate of transmission is proportional to the number of susceptibles and the fraction of the community that are infectious. Under the assumption that neither the area occupied by the community, nor the number of people in the community are changing the two definitions differ only by the constant 1 / N. In chapter 9 consideration will be given to alternative definitions that might be appropriate for studies of the dynamics of disease transmission in communities that are growing.

The constant of proportionality β represents the combination of two biological quantities; firstly the degree of contact between infectious and susceptible individuals, and secondly the probability that contact between an infectious and a susceptible individual will result in infection. The function $\beta(a,a')$ is exactly analogous to the constant β, with the extension that the two components mentioned above are deemed to be dependent on the

ages of the infectious and susceptible individuals. So $\beta(a,a')$ combines the following two factors; the degree of close contact between susceptible people of age a and infectious people of age a', and the propensity for a susceptible person aged a to develop the infection after exposure to an infectious person aged a'.

This study follows previous work on age structured epidemic models (Schenzle 1984a, Anderson & May 1985a) in dividing a lifetime into n discrete age classes and assuming that for susceptible individuals in the ith age class and infectious individuals in the jth age class, $\beta(a,a')$ is a constant with value β_{ij}. Thus $\beta(a,a')$ is a step function which can be represented by an n by n matrix of constants. This matrix $[\beta_{ij}]$ is called the 'who acquires infection from whom' (WAIFW) matrix. The two components of $\beta(a,a')$ are too complex to measure directly, but using the definition of the force of infection it is possible to find values for the β_{ij} by an indirect method. Restricting the function $\beta(a,a')$ in the manner mentioned above has the following immediate consequence. For any fixed time τ, $\lambda(a,\tau)$ is a step function, constant over the age ranges determined in the definition of $\beta(a,a')$. Figure 4.2 illustrates the kind of surface that would represent $\beta(a,a')$.

Let $\lambda_i(t)$ be defined,

$$\lambda_i(t) = \lambda(a,t) \Big|_{(a_{i-1},a_i)}$$

then by definition

$$\lambda_i(t) = \frac{\sum_{j=1}^{n} \beta_{ij} \bar{Y}_j(t)}{\bar{N}(t)} \qquad (4.9)$$

where

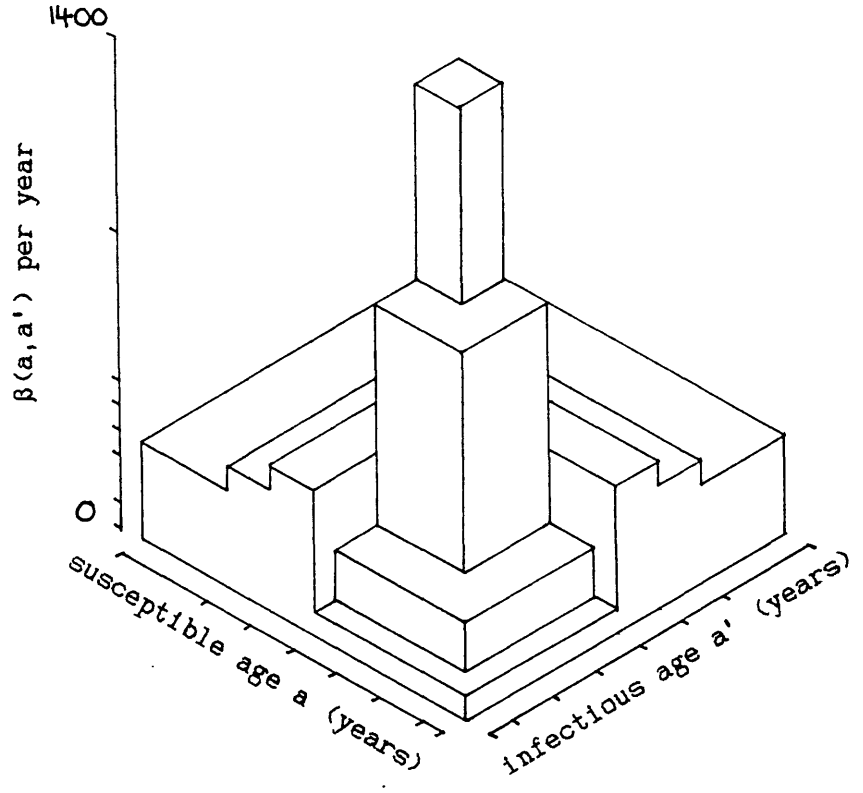


Figure 4.2
The 'who acquires infection from whom matrix', β_{ij}. In this study the transmission function $\beta(a,a')$ is restricted so that it can be represented by an n × n matrix of constants. This matrix is further restricted so that it only has n different elements. This further restriction is necessary to allow the calculation of the β_{ij}'s from the estimated λ_i's.

$$\bar{Y}_j(t) = \int_{a_{j-1}}^{a_j} Y(a',t)da'$$

and as before $\bar{N}(t)$ represents the total number of people in the community. Under the additional assumption that $\partial\lambda(a,t)/\partial t = 0$ (i.e. that each $\lambda_i(t)$ is equal to a constant λ_i), it is possible to estimate the λ_i from age prevalence data. Having measured the λ_i from a data set, still assuming that $\partial\lambda(a,t)/\partial t = 0$, a set of $\bar{Y}_j$ can be calculated from the equilibrium age distribution for $Y(a)$. If the β_{ij} matrix is then restricted to having only n elements, these $\beta_1,\ldots,\beta_n$ are trivially derived from the set of linear equations represented by equation 4.9.

There are two important facts about this matrix $[\beta_{ij}]$. Firstly, a given set of λ_is measured from a serological profile does not define a unique WAIFW matrix. Fortunately those configurations that give rise to negative values for one or more of the $\beta_1,\ldots,\beta_n$ can be rejected as being biologically unacceptable and this eliminates a number of the possibilities. However it does become necessary to investigate the effect of adopting a variety of different configurations for the WAIFW matrix. This work is presented in chapter 7. The second important point to be borne in mind is that the elements of the matrix do not change with time. They represent sociological and biological quantities that are assumed to be constant over long periods of time.

The distillation of the force of infection into n functions $\lambda_i(t)$ is extended to all the age dependent parameters. So a lifetime is divided up into the same n age classes as for the β matrix;

$a_0 - a_1$, $a_1 - a_2,\ldots,$ $a_{n-1} - a_n$.

The parameters $\mu(a)$, $\alpha(a)$ and $m(a)$ are then defined as step functions constant over these age classes;

$$\mu(a) = \begin{cases} \mu_1 \\ \vdots \\ \mu_j \\ \vdots \\ \mu_n \end{cases} \quad \alpha(a) = \begin{cases} \alpha_1 \\ \vdots \\ \alpha_j \\ \vdots \\ \alpha_n \end{cases} \quad m(a) = \begin{cases} m_1 \\ \vdots \\ m_j \\ \vdots \\ m_n \end{cases} \quad \text{for} \quad \begin{array}{l} 0 \leq a < a_1 \\ \vdots \\ a_{j-1} \leq a < a_j \\ \vdots \\ a_{n-1} \leq a < a_n \end{array}$$

The ways in which these are estimated, and full details of the process for finding the $\beta_{i,j}$s are described in chapter 6.

4.5 Notational conventions

The majority of the notational conventions that will be used in the text have already been mentioned. The purpose of this section is to draw them all together in one place.

$M(a,t)$	the number of people protected by maternal antibodies of age a at time t.
$X(a,t)$	the number of susceptible people of age a at time t
$H(a,t)$	the number of people who are infected but not yet infectious of age a at time t
$Y(a,t)$	the number of infectious people of age a at time t
$Z(a,t)$	the number of immune people of age a at time t
$N(a,t)$	the number of people of age a at time t
$\bar{Y}(t)$	the total number of infectious people at time t

$\bar{Y}_j(t)$ the total number of infectious people in the jth age class at time t
(and similiarly for all other groups)

a_{i-1} the lower limit of the ith age class

a_i the upper limit of the ith age class

4.6 Summary

The set of partial differential equations, boundary conditions and initial conditions that constitute the model have been presented and their biological interpretations given. The model is different from that from which it is derived because it allows case fatalities and population growth. All the age dependent parameters of the model are restricted to being step functions, and one set of age classes serves all the parameters.

Chapter 5

Equilibrium Results and Methods of Data Interpretation

5.1 Aims of chapter 5.

The purpose of this chapter is to present results gained by studying the equilibrium properties of the model defined in chapter 4. These results fall into two categories, those that are generated to enable the interpretation of epidemiological data, and those that express certain epidemiological properties of a community in terms of the model's parameters. Discussion will focus first upon methods of data interpretation, and then upon the derivation of expressions for three epidemiological measures namely; the average age at infection (A), the basic reproductive rate (R_o) and the critical vaccination proportion (p_c).

5.2 Chapter layout.

The text commences with a list of the reasons for studying equilibrium properties. This is followed by an outline of the assumptions that are inherent in such studies, and a defence of their applicability to this model. The derivation of a method for interpreting serological profiles starts with the addition of a new class to the model, this class is called '*excess deaths*'. Using this extra class, a method is derived whereby values of the force of infection can be measured from serological profiles drawn

from communities that have suffered significant case fatalities. A second method of data interpretation is then described. This demonstrates how to measure disease related death rates from case fatality rates. The second part of the chapter is devoted to finding expressions for the three epidemiological measures; the average age at infection (A), the basic reproductive rate (R_0) and the critical vaccination proportion (p_c). Before this can be done a reduced version of the model is introduced, which does not allow for the protection by maternal antibody. The quotation of pertinent results from mathematical demography completes the preliminary work necessary for this section of the chapter. The first set of results derived and discussed considers the special case when the model has only one age class. Expressions are derived for the average age at infection, the basic reproductive rate and critical vaccination proportion. This exercise is then repeated for the general case when the model has many age classes. The chapter concludes with a summary of the results.

5.3 Introductory remarks.

The full model, represented by equations 4.1 to 4.5 and their initial and boundary conditions, is too complex to be treated analytically. For this reason its solution is investigated using numerical methods. However computer simulated solutions of the equations can only yield limited insights into the model's behaviour. The analytical treatment of a greatly simplified version of the model can give a complimentary set of results. These are useful because they embody certain properties of the model's behaviour in easily understood formulae. The following simplification is made when equilibrium properties are studied: rather than making the force

of infection vary with the number of infective people, it is assumed that the force of infection is equal to a constant. (Or when transmission is assumed to be age dependent a vector of constants). Under these assumptions the age distribution of individuals in each class does not change with time, and the problem becomes one of the consideration of a set of ordinary differential equations describing these age distributions. The connection between this simple problem and the full model is the assumption that over a long period of time the force of infection as defined in the full model does tend to a constant value as time tends to infinity. This has not been proven analytically, but results of numerical analysis do not disagree with this assumption.

5.4 Methods of data interpretation.

The principle objective of this area of study is to be able to measure the force of infection from available age prevalence data. Such data takes the form of serological profiles which represent the proportion of the population seropositive by age. The proportion of the community of age a at time t in each class is represented by a "d variable. Thus;

$$M^{\circ}(a,t) = \frac{M(a,t)}{N(a,t)} \qquad X^{\circ}(a,t) = \frac{X(a,t)}{N(a,t)} \qquad H^{\circ}(a,t) = \frac{H(a,t)}{N(a,t)}$$

$$Y^{\circ}(a,t) = \frac{Y(a,t)}{N(a,t)} \qquad Z^{\circ}(a,t) = \frac{Z(a,t)}{N(a,t)} \tag{5.1}$$

As the rate of change of the total population N(a,t) is governed not only by population size, but also by the number of individuals in the infectious state (equn. 4.6), straightforward division of equations 4.1 through 4.5 will give a set of equations for M° to Z° whose right hand sides all contain terms involving products of $Y^{\circ}(a,t)$ and whichever variable is under

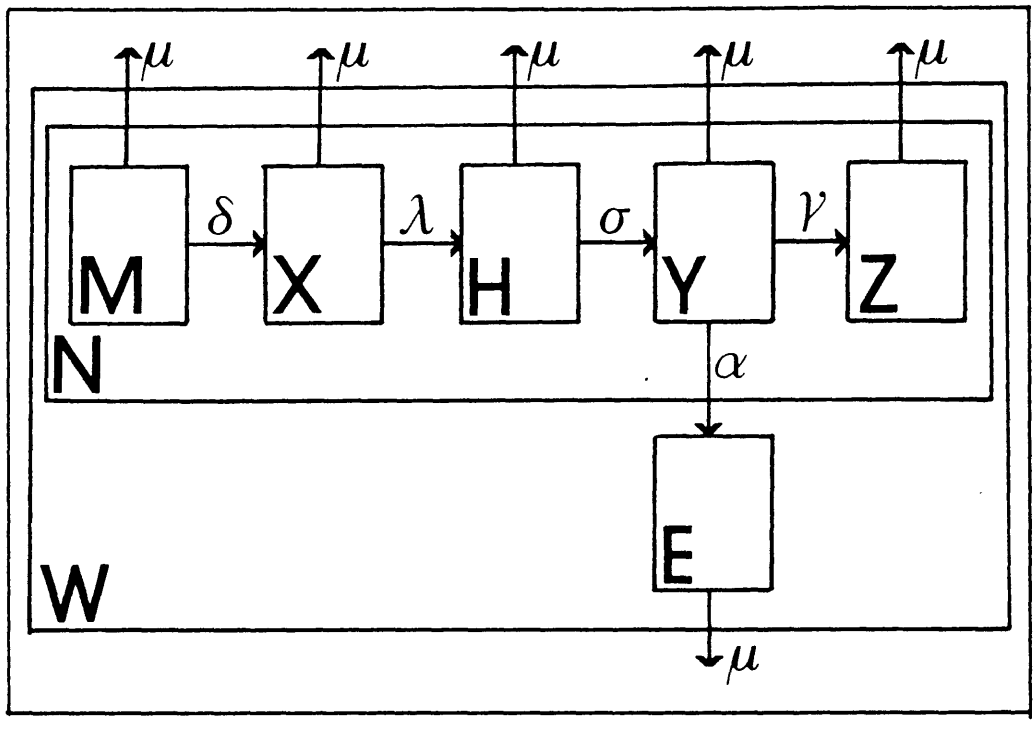


Figure 5.1
Scheme of flows between compartments in the extended model. By defining a new compartment E, and an alternative total population W, a situation is achieved where losses from the 'would-be total' population W are at a uniform rate from each compartment.

consideration. This seems to make the problem much more difficult. However the introduction of a sixth state, 'excess deaths' allows the definition of an alternative set of proportions which serve to clarify the problem. Conceptually this sixth class represents those individuals who have died as a result of contracting the disease and who would not have died from some other cause. The numbers in this class of age a at time t, E(a,t), are therefore described by the equation

$$\frac{\partial E}{\partial a} + \frac{\partial E}{\partial t} = \alpha(a)\, Y(a,t) - \mu(a)\, E(a,t) \qquad (5.2)$$

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

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

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

$$\frac{\partial W}{\partial a} + \frac{\partial W}{\partial t} = - \mu(a)\, W(a,t) \qquad (5.3)$$

This extended system is summarised in figure 5.1.

Having defined this new type of total population W(a,t), it is in turn used in the definition of a third set of variables;

$$M'(a,t) = \frac{M(a,t)}{W(a,t)} \quad X'(a,t) = \frac{X(a,t)}{W(a,t)} \quad H'(a,t) = \frac{H(a,t)}{W(a,t)}$$
$$Y'(a,t) = \frac{Y(a,t)}{W(a,t)} \quad Z'(a,t) = \frac{Z(a,t)}{W(a,t)} \quad E'(a,t) = \frac{E(a,t)}{W(a,t)} \qquad (5.4)$$

The partial differential equations governing their dynamics are as follows.

$$\frac{\partial M'}{\partial a} + \frac{\partial M'}{\partial t} = - \delta\, M'(a,t) \qquad (5.5)$$

$$\frac{\partial X'}{\partial a} + \frac{\partial X'}{\partial t} = \delta\, M'(a,t) - \lambda(a,t)\, X'(a,t) \qquad (5.6)$$

$$\frac{\partial H'}{\partial a} + \frac{\partial H'}{\partial t} = \lambda(a,t)\, X'(a,t) - \sigma\, H'(a,t) \qquad (5.7)$$

$$\frac{\partial Y'}{\partial a} + \frac{\partial Y'}{\partial t} = \sigma H'(a,t) - (\alpha(a) + \gamma) Y'(a,t) \qquad (5.8)$$

$$\frac{\partial Z'}{\partial a} + \frac{\partial Z'}{\partial t} = \gamma Y'(a,t) \qquad (5.9)$$

$$\frac{\partial E'}{\partial a} + \frac{\partial E'}{\partial t} = \alpha(a) E'(a,t) \qquad (5.10)$$

The boundary conditions are as follows:

$M'(0,t) = 1$

$X'(0,t) = H'(0,t) = Y'(0,t) = Z'(0,t) = E'(0,t) = 0$

and the initial conditions are trivially derived from the initial conditions specified for equations 4.1 to 4.5 with the additional specification of $E(a,t_0)$.

Under the assumption that $\lambda(a,t)$ and $\alpha(a)$ are constant over given age ranges and that $\partial\lambda(a,t)/\partial t = 0$, the equilibrium values of this set of variables are easily found by solving the piecewise-linear ordinary differential equations which are obtained when the time derivatives for equations 5.5 to 5.10 are set to zero. This then gives expressions for the equilibrium age distributions of individuals in each of the states in terms of the model's parameters.

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

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

and

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

$$M^{\circ}(a,t) = \frac{M(a,t)}{W(a,t) - E(a,t)}$$

$$= \frac{M(a,t)}{W(a,t)\ (1 - E'(a))}$$

$$= \frac{M'(a)}{(1 - E'(a))}$$

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

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

to obtain the age-specific values for the force of infection, the λ_i. In chapter 6 some illustrative examples of serological profiles and the forces of infection estimated from them are shown.

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

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

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

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

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

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

so

$$\alpha_j = \frac{\gamma \, p_j}{(1 - p_j)} \qquad (5.11)$$

For the younger age classes, where the case fatality rate can be as high as 26% (Aaby, 1983a), taking account of death from disease can increase the estimated force of infection by as much as 17% when compared with estimates that are derived using methods which ignore disease related deaths. When studying the dynamics of measles in less developed countries much of the interest lies in the first few years of life. Therefore such an underestimation of the force of infection at these young ages is of considerable practical relevance. In chapter 6 some numerical examples of disease related death rates are shown, and the dependence of the force of infection upon the disease related death rate is illustrated with examples.

5.5 Epidemiological constants.

In the following analysis a reduced system is considered for the sake of clarity. The maternal antibody protected class is dropped and the boundary condition altered to

$$X(0,t) = \int_0^L m(a)\, N(a,t)\, da$$

to accommodate this change.

Before deriving expressions for the epidemiological constants, the following two definitions, additional to those mentioned at the end of chapter 4, are made.

$$B = \frac{\bar{N}(t)}{N(0,t)}$$

that is, B is the reciprocal of the average birth rate.
And,

$$l(a) = \exp\left[-\int_0^a \mu(a')\, da' \right] .$$

In order to investigate epidemiological constants such as the average age at infection it is necessary to note a few pertinent results from the theory of mathematical demography (Pollard, 1973). The 'would be' population, W(a,t), whose dynamics obey equation 5.3 can be thought of as undergoing an age structured birth-death process if the following alteration is made to the fertility function.

$$N(0,t) = \int_0^L m(a)\, N(a,t)da = \int_0^L m(a)\, (1 - E'(a))\, W(a,t)\, da$$

If the following definition,

$$\omega(a) = m(a)\, (1- E'(a))$$

is made, then,

$$N(0,t) = \int_0^L \omega(a)\, W(a,t)\, da$$

but since

$$W(0,t) = N(0,t)$$

this yields

$$W(0,t) = \int_0^L \omega(a)\, W(a,t)\, da \qquad (5.12)$$

It is well known (Pollard, 1973) that under the conditions defined by equations 5.3 and 5.12 the 'would be' population W(a,t) settles to a stable age distribution with overall growth at rate r, where r satisfies the Euler relation

$$\int_0^L \omega(a)\, e^{-ra}\, l(a)\, da = 1$$

and the stable age distribution is given by

$$W(a,t) = W(0,t)\, e^{-ra}\, l(a) \qquad (5.13)$$

The total population $\bar{N}(t)$ also grows at rate r, since

$$N(a,t) = W(a,t)\,(1 - E'(a))$$

$$\frac{d\bar{N}(t)}{dt} = \int_0^L \frac{\partial N(a,t)}{\partial t}\, da = r\,\bar{N}(t)$$

Hence

$$\bar{N}(t) = \bar{N}(0)\, e^{rt} \qquad (5.14)$$

In what follows it is assumed that there is only one age class. As discussed above these results are derived because they can give insights into some of the properties of the model. They are also useful when trying to understand the more complex formulae derived when the case with many age classes is studied.

A further piece of preliminary work is necessary before continuing. This is to find an expression for the total susceptible population $\bar{X}(t)$, and an approximation to the value of the total infectious population $\bar{Y}(t)$. Bearing in mind that

$$X(a,t) = W(0,t)\, e^{-ra}\, l(a)\, X'(a) \qquad (5.15)$$

and that when there is only one age class;

$$l(a) = e^{-\mu a}, \qquad (5.16)$$

and

$$X'(a) = e^{-\lambda a}, \tag{5.17}$$

it is easily shown that

$$\bar{X}(t) = W(0,t)\, X'(0)\, \frac{1 - e^{-(r + \mu + \lambda)L}}{(r + \mu + \lambda)} \tag{5.18}$$

If L is large, this simplifies to;

$$\bar{X}(t) = \frac{W(0,t)}{(r + \mu + \lambda)} \tag{5.19}$$

At equilibrium,

$$Y'(a) = \frac{\sigma \lambda}{(\sigma - \lambda)} \left\{ \frac{e^{-\lambda a} - e^{-(\gamma + \alpha) a}}{(\gamma + \alpha - \lambda)} - \frac{e^{-\gamma a} - e^{-(\gamma + \alpha) a}}{(\gamma + \alpha - \sigma)} \right\}$$

dropping terms of order of magnitude $e^{-\sigma a}$ and $e^{-\gamma a}$ this simplifies to

$$Y'(a) \simeq \frac{\lambda X'(a)}{(\gamma + \alpha)}$$

and therefore

$$\bar{Y}(t) = \frac{\lambda \bar{X}(t)}{(\gamma + \alpha)} \tag{5.20}$$

The necessary tools are now available to derive expressions for the equilibrium values of three important epidemiological quantities, namely, the average at infection A, the basic reproductive rate R_o, and the critical proportion to be vaccinated for eradication p_c.

The average age at infection is defined as follows;

$$A = \frac{\int_0^L a\, \lambda(a)\, X(a,t)\, da}{\int_0^L \lambda(a)\, X(a,t)\, da} \tag{5.21}$$

and for one age class, without vaccination

$$X(a,t) = W(0,t)\, e^{-(r + \mu + \lambda)a}$$

so

$$A = \frac{\lambda\, W(0,t) \int_0^L a\, e^{-(r + \mu + \lambda) a}\, da}{\lambda\, W(0,t) \int_0^L e^{-(r + \mu + \lambda) a}\, da}$$

hence

$$A = \frac{1 - e^{-(r + \mu + \lambda)L}((r + \mu + \lambda)L + 1)}{(r + \mu + \lambda)\ (1 - e^{-(r + \mu + \lambda)L})}$$

If L is large

$$A = \frac{1}{(r + \mu + \lambda)} \qquad (5.22)$$

Consideration of the relative sizes of r, μ and λ gives

$$A \simeq \frac{1}{\lambda}$$

This relationship (noted in previous works on age structured epidemic models (Anderson & May 1985a)) is of interest because of its implications for the outcome of vaccination programmes. When the force of infection is lowered as a result of vaccination, the average age at infection will rise. In a situation where the risk of serious disease resulting from infection is at its highest in the younger age groups, this effect of immunisation is obviously beneficial.

The basic reproductive rate R_0 represents the number of new cases that will arise if a single infectious individual is introduced into a totally susceptible population (Macdonald, 1952). The effective reproductive rate R is the number of new cases that will arise as a result of the introduction of one more infectious individual into a population containing susceptible and immune individuals. The quantities are related in the following way;

$$R = R_0 \frac{\bar{X}}{\bar{N}}$$

In a situation where the total human population is static, at equilibrium the reproductive rate R is equal to 1. In this model, however, where the force of infection, $\lambda(a,t)$, is a function of the proportion of the population that are infectious and the total population is growing this definition no

longer holds. In order for the disease to remain at equilibrium the number of infected individuals must increase at the same rate as the total population. An individual is on average infectious for time $1/(\gamma + \alpha)$. So at the start of his infectious period the total population is (equation 5.14)

$$\bar{N}(0)\, e^{rt}$$

and at the end it is

$$\bar{N}(0)\, e^{r(t + 1/(\gamma + \alpha))}$$

i.e. the population increases by a factor of $e^{r/(\gamma + \alpha)}$ so

$$R = e^{r/(\gamma + \alpha)}$$

Therefore, at equilibrium

$$R_0 = \frac{\bar{N}(t)\, e^{r/(\gamma + \alpha)}}{\bar{X}(t)}$$

$$= \frac{\bar{N}(t)\, e^{r/(\gamma + \alpha)}(r + \mu + \lambda)}{\dot{W}(0,t)\,(1 - e^{-(r + \mu + \lambda)L})}.$$

If L is large

$$R_0 = \frac{\bar{N}(t)\, e^{r/(\gamma + \alpha)}(r + \mu + \lambda)}{W(0,t)}$$

and equation 5.22 for $\dot{A}$ holds.

Also

$$W(0,t) = N(0,t)$$

and

$$\frac{\bar{N}(t)}{N(0,t)} = B$$

hence for large L,

$$R_0 = \frac{B}{A} e^{r/(\gamma + \alpha)} \qquad (5.23)$$

Since r is small and γ is large $e^{r/(\gamma+\alpha)} \simeq 1$ and equation 5.23 therefore agrees with the expression for R_0 derived in May and Anderson (1985), even though that study uses a different definition of the force of infection. The interest in this result lies in comparing values of R_0 for

Country	Year	A	B	R_o	Reference for value of A
Chile	1962	3.4	42.5	12.5	Ristori et al, 1962
U.S.	1965	5	68.3	13.7	Collins, 1929
Ghana	1960-68	2.5	30.6	12.2	Morley, 1969a
Kenya	1974	3.5	26.1	7.5	W.H.O., 1979
India	1976	3	35.3	11.8	Bhau et al, 1976
Senegal	1964	1.8	31.1	17.3	Boue, 1964

Table 5.1
Sample values of R_o from around the world. All values for B are estimated from, U.S. Agency for International Development, 1977.

developed and developing countries. In developing countries the average age at infection is low, but the high birth rate and and consequent low value of B balance this, yielding the surprising result that R_0 is no greater in developing countries than in developed ones. Some numerical values for R_0 are shown in table 5.1 to illustrate this point. In calculating these values the term $e^{r/(\gamma + \alpha)}$ has been ignored as its value is approximately 1. (For example, realistic values of r, γ and α might be; r = 0.02, γ = 52 and α = 10, yielding $e^{r/(\gamma + \alpha)} = 1.00032$.)

To conclude this section concerned with the model with one age class, attention is centred upon the critical vaccination proportion: the proportion of the population that needs to be vaccinated in order to achieve eradication.

When there is only one age class the definition of the force of infection is

$$\lambda = \frac{\beta \bar{Y}(t)}{\bar{N}(t)}$$

where β is a constant determined by factors that are unchanged by vaccination

$$\beta = \frac{\lambda \bar{N}(t)}{\bar{Y}(t)}$$

$$= \frac{\bar{N}(t) (\gamma + \alpha) (r + \mu + \lambda)}{W(0,t) X'(0) (1 - e^{-(r + \mu + \lambda)L})}$$

and if L is large

$$\beta = \frac{B (\gamma + \alpha)}{A_0} \qquad (5.24)$$

Where equation 5.24 is derived using equations 5.18, 5.21 & 5.22, and A_0 represents the average age at infection before vaccination is introduced.

Now suppose that a fraction p of each cohort is successfully vaccinated at birth. The force of infection under these circumstances is still defined as

$$\lambda = \frac{\beta \bar{Y}(t)}{\bar{N}(t)}$$

substituting equation 5.18 for $\bar{Y}(t)$ and using the definition of $\bar{X}(t)$

$$\bar{X}(t) = \int_0^L W(0,t)\ X'(0)\ e^{-(r + \mu + \lambda)\ a}\ da$$

yields

$$\lambda = \frac{\beta\ W(0,t)\ [\int_0^L e^{-(r + \mu + \lambda)\ a}\ da\ ]\ X'(0)}{\bar{N}(t)\ (\gamma + \alpha)}$$

but the initial condition is now $X'(0) = (1 - p)$, so

$$(1 - p) = \frac{\bar{N}(t)\ (\gamma + \alpha)}{W(0,t)\ [\int_0^L e^{-(r + \mu + \lambda)\ a} da\ ]\ \beta}$$

at eradication $p \to p_c$, $\lambda \to 0$, and $\bar{N}(t) \to \bar{W}(t) = W(0,t)\ [\int_0^L e^{-(r + \mu)a} da]$

so

$$1 - p_c = \frac{(\gamma + \alpha)}{\beta} \qquad (5.25)$$

and using equation 5.24 for β gives;

$$p_c = 1 - \frac{A_0}{B} \qquad (5.26)$$

As discussed when considering R_o, B / A_o is approximately constant. This has the very important implication that the proportion of each cohort that needs to be immunized to eradicate measles in developing countries is the same as that necessary for eradication in developed countries.

Having found expressions for A, R_o and p_c in the special case where there is only one age class, the general case is now investigated. As in the previous section a few definitions and preliminary results are discussed first.

Defining

$$\psi_i = \sum_{j=1}^{i} \lambda_j\ (a_j - a_{j-1})$$

and

$$\psi_0 = 0$$

yields, when $a_{i-1} \leq a < a_i$,

$$X'(a) = X'(0) \exp[-\psi_{i-1} - \lambda_i (a - a_{i-1})]. \qquad (5.27)$$

Furthermore, if

$$\phi_i = \sum_{j=1}^{i} \mu_j (a_j - a_{j-1})$$

and

$$\phi_0 = 0$$

then for $a_{i-1} \leq a < a_i$

$$l(a) = \exp[-\phi_{i-1} - \mu_i (a - a_{i-1})] \qquad (5.29)$$

The definition of $\bar{X}_j(t)$ is;

$$\bar{X}_j(t) = \int_{a_{j-1}}^{a_j} X(a,t)da$$

$$= \int_{a_{j-1}}^{a_j} W(a,t)\, X'(a)\, da$$

using equations 5.27 and 5.29 for $X'(a)$ and $l(a)$,

$$\bar{X}_j(t) = W(0,t)\, X'(0) \int_{a_{j-1}}^{a_j} e^{[-\psi_{j-1} - \lambda_j (a_j - a_{j-1})]} e^{-ra} e^{[-\phi_{j-1} - \mu_j (a_j - a_{j-1})]} da$$

$$= W(0,t)\, X'(0)\, [1 - e^{-(r+\mu_j+\lambda_j)(a_j - a_{j-1})}]\, e^{-(ra_{j-1} + \phi_{j-1} + \psi_{j-1})} \qquad (5.30)$$

Using the analogous argument to that shown in the derivation of equation 5.20, it is easy to show that for $a_{j-1} \leq a < a_j$

$$Y'(a) \simeq \frac{\lambda_j X'(a)}{(\gamma + \alpha_j)}$$

And therefore that,

$$\bar{Y}_j(t) \simeq \frac{\lambda_j \bar{X}_j(t)}{(\gamma + \alpha_j)} \qquad (5.31)$$

For the details of this last approximation see Anderson and May (1985a). The necessary tools have now been assembled for the derivation of the many age class results: these start with the consideration of the average at infection, A.

Substituting the expression for X(a,t) (equation 5.15) into the definition of the average age at infection (equation 5.21), and exploiting the fact that $\lambda(a,t)$ has been restricted to being a step function, yields;

$$A = \frac{\sum_{i=1}^{n} \lambda_i \int_{a_{i-1}}^{a_i} a\, e^{-ra}\, l(a)\, X'(a)\, da}{\sum_{i=1}^{n} \lambda_i \int_{a_{i-1}}^{a_i} e^{-ra}\, l(a)\, X'(a)\, da}$$

Substitution of equations 5.27 and 5.29 for $X'(a)$ and $l(a)$ gives

$$A = \frac{\sum_{i=1}^{n} \lambda_i \int_{a_{i-1}}^{a_i} a\, e^{-(r+\mu_i+\lambda_i)(a-a_{i-1})}\, e^{-(\phi_{i-1}+\psi_{i-1}+ra_{i-1})}\, da}{\sum_{i=1}^{n} \lambda_i \int_{a_{i-1}}^{a_i} e^{-(r+\mu_i+\lambda_i)(a-a_{i-1})}\, e^{-(\phi_{i-1}+\psi_{i-1}+ra_{i-1})}\, da}$$

which after integration becomes;

$$A = \frac{\sum_{i=1}^{n} \frac{\lambda_i}{(r+\mu_i+\lambda_i)^2} \left[(r+\mu_i+\lambda_i)a_{i-1} + 1\right] e^{-(\phi_{i-1}+\psi_{i-1}+ra_{i-1})} - \left[(r+\mu_i+\lambda_i)a_i + 1\right] e^{-(\phi_i+\psi_i+ra_i)}}{\sum_{i=1}^{n} \frac{\lambda_i}{(r+\mu_i+\lambda_i)} \left[e^{-(\phi_{i-1}+\psi_{i-1}+ra_{i-1})} - e^{-(\phi_i+\psi_i+ra_i)}\right]} \quad (5.32)$$

Although this equation clearly fails to endow any further insight as it stands, it is helpful for showing how the numerical value of the average age at infection depends upon the age dependant case fatality rate and the configuration of the WAIFW matrix. Tables are shown in chapter 6 depicting this relationship.

For the many age class model the basic reproductive rate is redefined in the following way; R_{oi} is the average number of secondary cases (in all age classes) generated by one case in age class i if the population is wholly susceptible. An individual in age class i is susceptible for time $1/(\gamma + \alpha_i)$. The per capita rate at which susceptible people in the jth age class become infected is λ_j, and in the definition of R_{oi} it is stated that

the whole population should be susceptible. Thus the number of new cases generated in the jth age class by an infectious individual in the ith age class is equal to

$$\frac{\lambda_j \bar{N}_j}{(\gamma + \alpha_i)}$$

and therefore

$$R_{0i} = \frac{\sum_{j=1}^{n} \lambda_j \bar{N}_j}{(\gamma + \alpha_i)}$$

By definition

$$\lambda_j = \frac{\sum_{k=1}^{n} \beta_{jk} \bar{Y}_k}{\bar{N}}$$

but in this case $\bar{Y}_i = 1$ and $\bar{Y}_j = 0$ for $j \neq i$ so

$$\lambda_j = \frac{\beta_{ji}}{\bar{N}}$$

so

$$R_{0i} = \frac{\sum_{j=1}^{n} \beta_{ji} \bar{N}_j}{(\gamma + \alpha_i)\bar{N}} \qquad (5.33)$$

Once again this formula is somewhat unenlightening as it stands, but is useful for comparing changes in the numerical values of the age specific basic reproductive rates under different assumptions about the case fatality rate and WAIFW matrix configuration. These are studied in chapter 6.

The argument used in order to find the critical vaccination proportion when there are many age classes is rather more complex than the others, so before embarking upon the derivation a brief summary is given.

The aim is to obtain an expression of the form

$$\underline{\lambda}^T = (1 - p_c)\, G\, \underline{\lambda}^T$$

where $\underline{\lambda}$ is the vector $(\lambda_1, \lambda_2, \ldots, \lambda_n)$ and G is a matrix of constants that are found under the assumption that each λ_i is very small. The argument will then continue,

$$|(1 - p_c)G - I| = 0$$

for nontrivial solution for $\underline{\lambda}$. And therefore,

$$p_c = 1 - \frac{1}{\epsilon}$$

where ϵ is the dominant eigenvalue of G.

By definition

$$\lambda_i = \frac{1}{\bar{N}(t)} \sum_{j=1}^{n} \beta_{ij} \bar{Y}_j(t)$$

using equation 5.31 for $\bar{Y}_j(t)$ yields

$$\lambda_i = \frac{1}{\bar{N}(t)} \sum_{j=1}^{n} \frac{\beta_{ij}\, \lambda_j\, \bar{X}_j(t)}{(\gamma + \alpha_j)}$$

Substituting equation 5.30 for $\bar{X}_j(t)$

$$\lambda_i = \frac{1}{\bar{N}(t)} \sum_{j=1}^{n} \frac{\beta_{ij}\, \lambda_j}{(\gamma + \alpha_j)} \; W(0,t)\, X'(0) \left[1 - e^{-(r+\mu_j+\lambda_j)(a_j - a_{j-1})}\right] e^{-(ra_{j-1} + \phi_{j-1} + \psi_{j-1})} \Big/ (r + \mu_j + \lambda_j)$$

At the critical vaccination proportion $X'(0) = (1 - p_c)$ and the $\lambda_i \to 0$,

$$\lambda_i = \frac{1}{\bar{N}(t)} \sum_{j=1}^{n} \frac{\beta_{ij}\, \lambda_j}{(\gamma + \alpha_j)} \; W(0,t)\,(1 - p_c) \left[1 - e^{-(r+\mu_j)(a_j - a_{j-1})}\right] e^{-(ra_{j-1} + \phi_{j-1})} \Big/ (r + \mu_j + \lambda_j)$$

$$\underline{\lambda}^T = (1 - p_c)\, G\, \underline{\lambda}^T$$

has non-trivial solution if and only if

$$\left|G - \frac{1}{(1 - p_c)} I\right| = 0$$

So $\dfrac{1}{(1 - p_c)}$ must be an eigenvalue of G.

That is,

$$p_c = 1 - \frac{1}{\epsilon} \qquad (5.34)$$

where ϵ is the dominant eigenvalue of the matrix G whose elements g_{ij} are

$$g_{ij} = \beta_{ij} \frac{W(0,t)[\ 1 - e^{-(r+\mu_j)(a_j - a_{j-1})}\ ]\ e^{-(ra_{j-1} + \phi_{j-1})}}{\bar{N}(t)\ (\ \gamma + \alpha_j\ )\ (\ r + \mu_j\ )} \quad (5.35)$$

Some numerical values for p_c are shown and discussed in chapter 6.

5.6 Summary

The equilibrium properties of the model have been studied and have yielded two different types of results. The first type shows how to interpret case fatality rates and serological profiles in order to derive parameter sets for the model. The second type shows how certain epidemiological constants depend upon the model's parameters. For the special case where there is only one age class these relationships are as follows; the average age at infection is approximately equal to the reciprocal of the force of infection; the basic reproductive rate R_o is approximately equal to B/A where A is the average age at infection, and B is the reciprocal of the average birth rate; the critical vaccination proportion for eradication of disease p_c is equal to $1 - 1/R_o$.

These last two results yield the important conclusion that the proportion of each cohort that must be immunised in order to eradicate measles in developing countries is the same as that necessary in developed countries. When there are many age classes these relationships are not easily summarised because they are algebraically very clumsy. These results are useful for looking at numerical values of these epidemiological measures and these are considered in the next chapter.

Chapter 6.

Data Presentation and Interpretation.

6.1 Objectives of chapter 6.

This chapter has three objectives; (1) to present the available data concerning measles epidemiology in developing countries; (2) to prepare this data for input to the model using the methods of data interpretation discussed in the previous chapter; and (3) to use these parameter sets to investigate the numerical values of the three epidemiological constants also discussed in the previous chapter.

6.2 Chapter layout.

The chapter starts with a 'recipe' for a simulation run. That is, a list of all the parameters that must be provided in order to find a numerical solution to the full model. This list also indicates the form in which this information must be prepared. The main body of the chapter then goes on to discuss each item on the list in more detail; reviewing the types of data that can provide such information, discussing the methods of data interpretation necessary to extract parameter values from the raw data, and giving examples of estimated parameter values. The types of data fall into five groups; demographic data, data on the rate of loss of protection by maternal antibody, case fatality rates, serological profiles, and case reports through time. Having discussed the strengths and the

weaknesses of the available data, the idea of a baseline parameter set is introduced. This is a set of parameter values that is selected as a 'constant' from which the effects of parameter variation can be measured. The final section of the chapter uses the baseline parameter sets that have been prepared in order to investigate the effects of parameter variation on the numerical values of the average age at infection (A), the basic reproductive rate (R_0) and the critical vaccination proportion (p_c).

6.3 Recipe for a simulation run

As the model investigates the effect of population growth on measles epidemiology, data on age specific birth and death rates are essential components of the analysis. These are entered as vectors of live births per thousand women per year by age, and annual death rates by age. As discussed in chapter five section five, there is a stable age distribution associated with any such pair of vectors. This is the age distribution to which a population will settle if subjected to unchanging rates of births and deaths. These stable age distributions are calculated separately, and also read into the programme.

The epidemiological parameters that are required are the following: the rate of loss of protection by maternal antibody, (assumed to be a constant of value δ); the age specific disease related death rates, (a vector of constants denoted by α_i); and the age specific forces of infection (another vector of constants denoted by λ_i). The configuration of the WAIFW matrix, and the regime of vaccination to be examined must also be specified.

6.4 Data and parameter values

The first type of data presented concerns the differences between the demography of the developed versus the developing world. The first comparison is between the respective age distributions of populations in these regions. In figure 6.1 the age distributions of the populations of Ecuador, Iran, Kenya, Senegal, Thailand and the U.K. are compared. These graphs show the familiar pattern of a large proportion of the population in the 0-5 and 5-10 age bands in developing countries, contrasting with a much more homogenous distribution by age in the U.K. Indeed in the U.K. and the U.S.A. at present the age distribution is, to a good approximation, uniform. In figure 6.2 age specific fertility rates from the same six countries are compared. These graphs display a similiar gulf between developed and developing countries. In the U.K. the peak is at 25-29 years with a value of 135.8 births per thousand women per year, less than half the peak value of 338 in Kenya. These patterns of age distribution of population and fertility rate can be characterised by one constant; the overall, annual, per-capita birth rate. This is defined as the annual number of live births, divided by the total population. For a community which remains constant in size, births must just balance deaths and therefore the average per-capita birth rate must be equal to the reciprocal of the expectation of life. In communities where there is net growth in the size of the population, the annual per capita birth rate is greater than the reciprocal of the expectation of life. The constant B that has been used in chapter five is the reciprocal of this average birth rate. In table 6.1 crude demographic rates from a variety of countries are compared. In order to study the effect of different values for the age specific birth and death

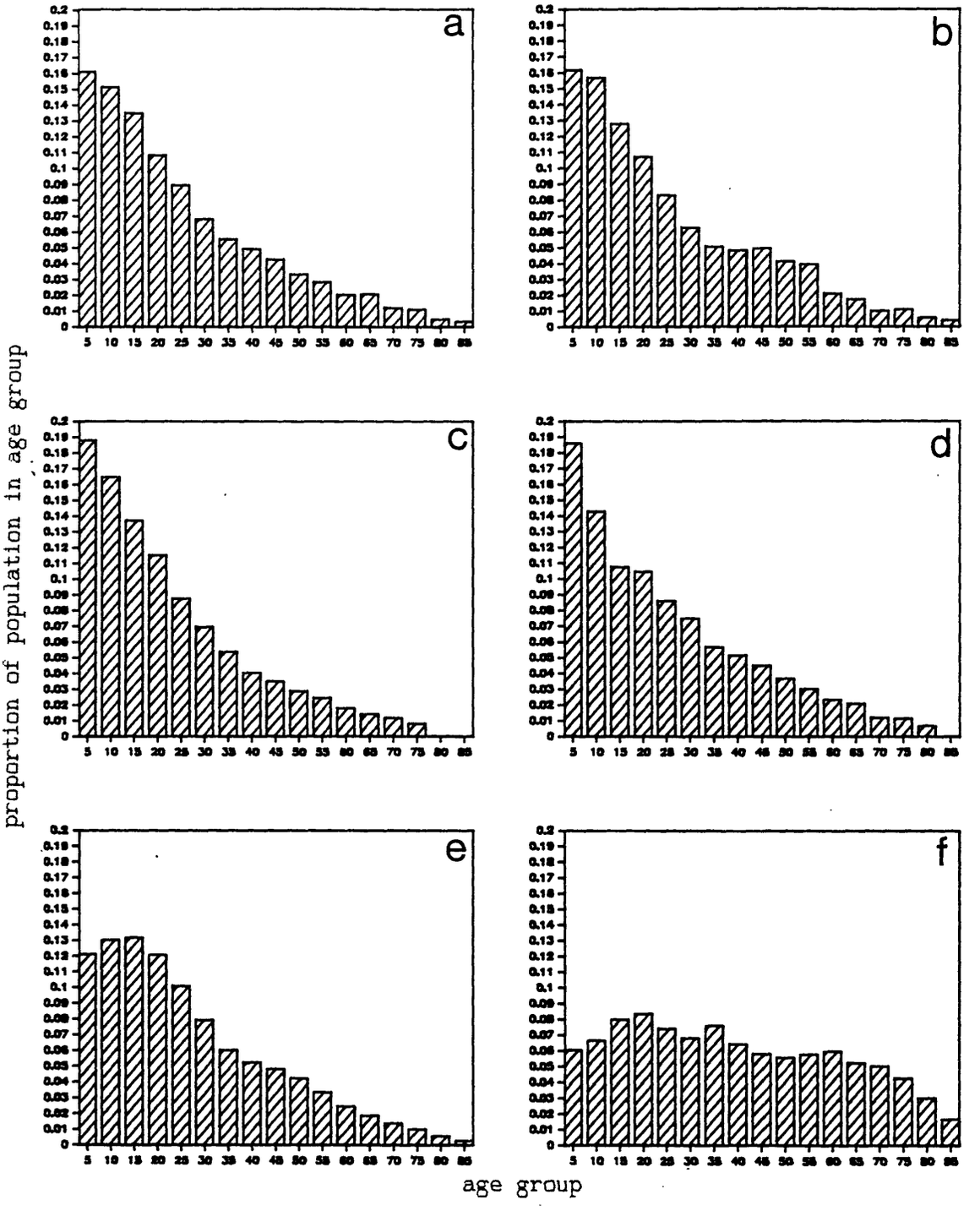


Figure 6.1
Age distribution of populations from a variety of developing and developed countries;
(a) Ecuador, (b) Iran, (c) Kenya, (d) Senegal, (e) Thailand, and (f) United Kingdom (England and Wales).
The graphs record the age distributions of populations, showing totals for five year age bands, expressed as a fraction of the whole population.
All data are from the United Nations Demographic Yearbook for 1983.

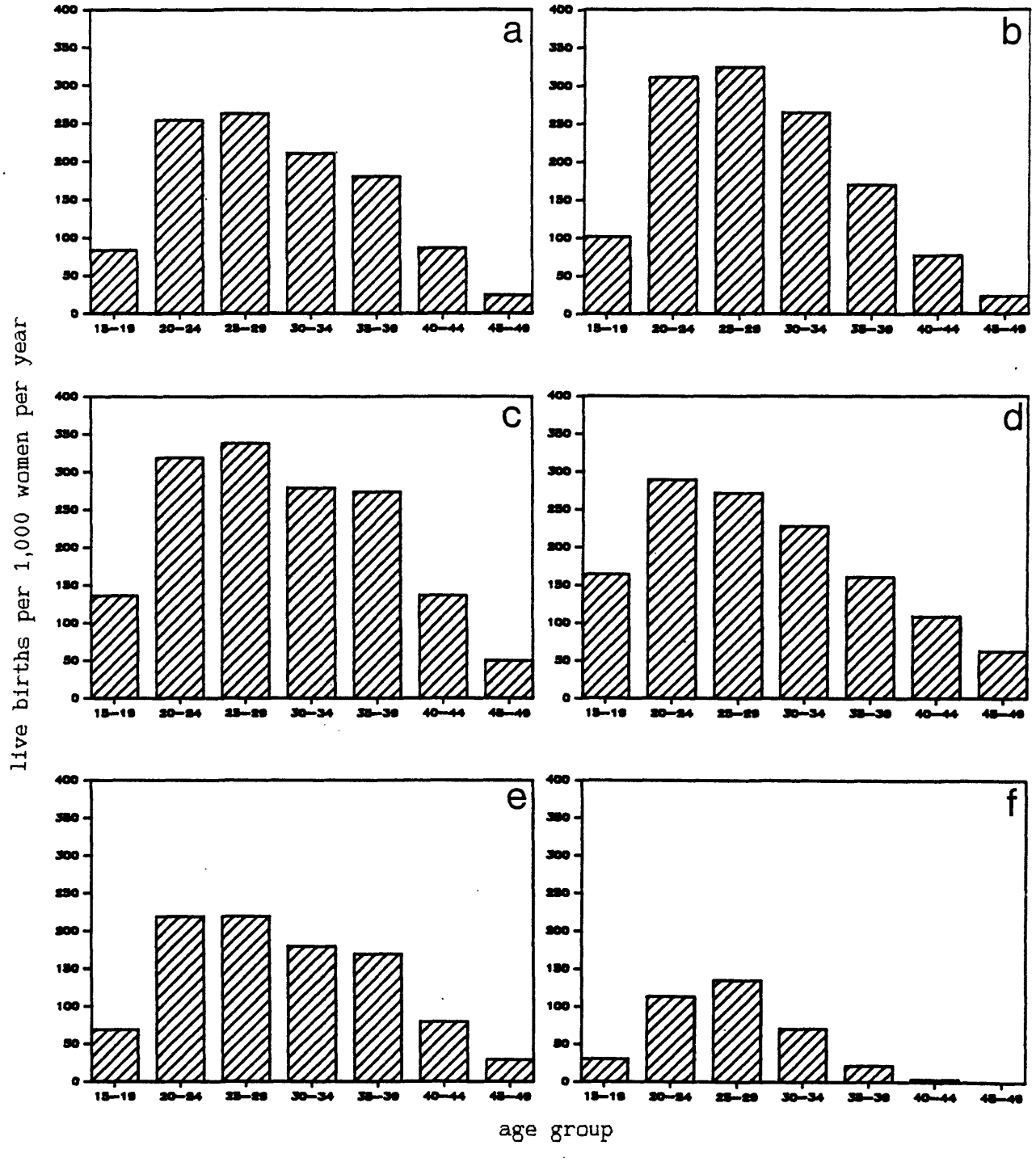


Figure 6.2
Age specific fertility rates from a variety of developed and developing countries;
(a) Ecuador, (b) Iran, (c) Kenya, (d) Senegal, (e) Thailand, and (f) United Kingdom (England and Wales).
The graphs record live births per 1,000 women per year.
All data are from the United Nations Demographic Yearbook for 1983.

Country	Year	(rates per 1000 yr^{-1})			(Average annual birth rate)$^{-1}$ B	Year	expectation of life at birth	
		Crude Birth Rate	Crude Death Rate	Popn Growth Rate r			Male	Female
Ecuador	1975-80	41,6	10,4	31,2	24,0	1974-79	59,5	61,8
Iran	1974-75	42,5	11,5	31,0	23,5	1973-78	57,6	57,4
Kenya	1975-80	53,8	14,4	39,4	18,6	1969	46,9	51,2
Senegal	1975-80	47,8	22,1	25,7	20,9	1975-80	40,6	43,8
Thailand	1975-80	32,3	8,9	23,4	31,0	1960	53,6	58,7
India	1979	33,2	12,8	20,4	30,1	1961-70	46,4	44,7
UK (E+W)	1981	12,8	11,7	1,1	78,1	1978-80	70,4	76,6
USA	1982	16,0	8,6	7,4	62,5	1979	69,9	77,8

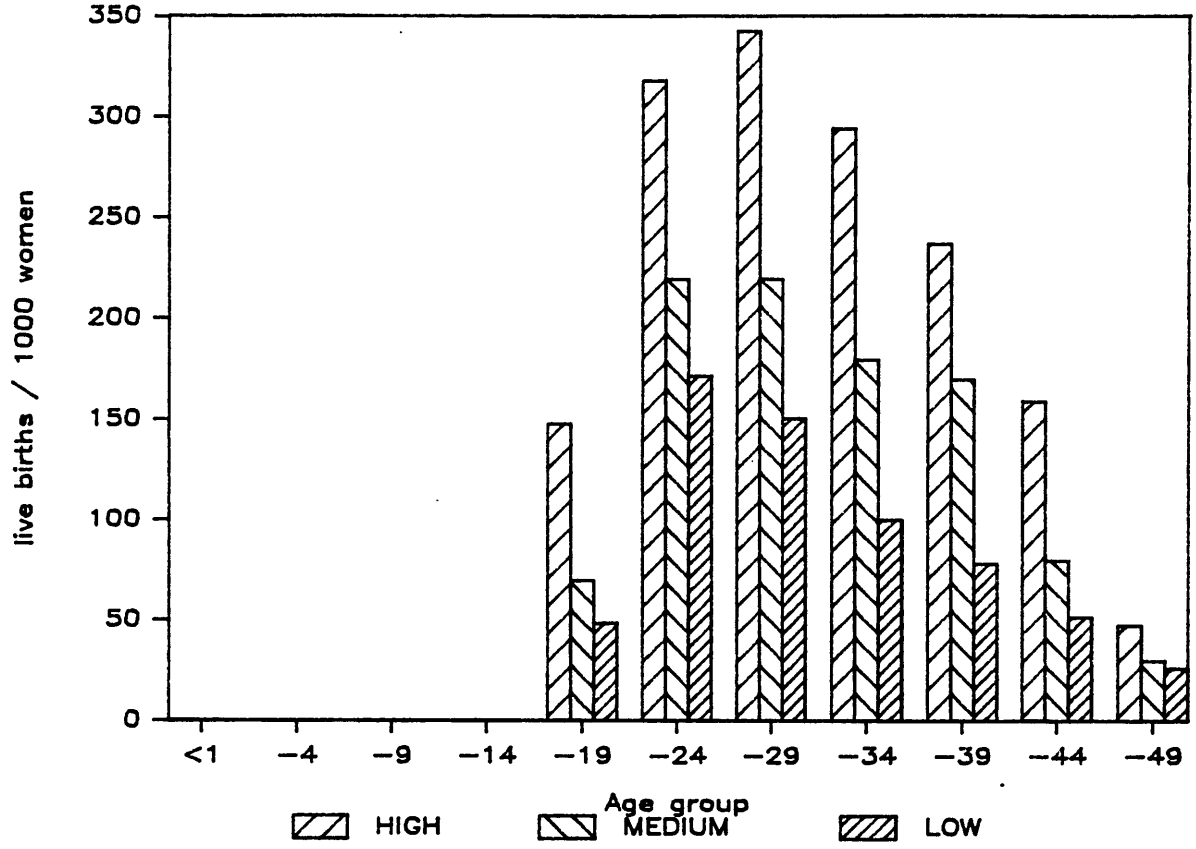
Table 6.1
Crude demographic data from a selection of developed and developing countries. The average annual birth rate is calculated as crude birth rate / 1000 so B is an inverse measure of the birth rate. Notice that in the UK and USA B is approximately equal to the expectation of life at birth, whilst in all other countries B is substantially the lesser of the two.

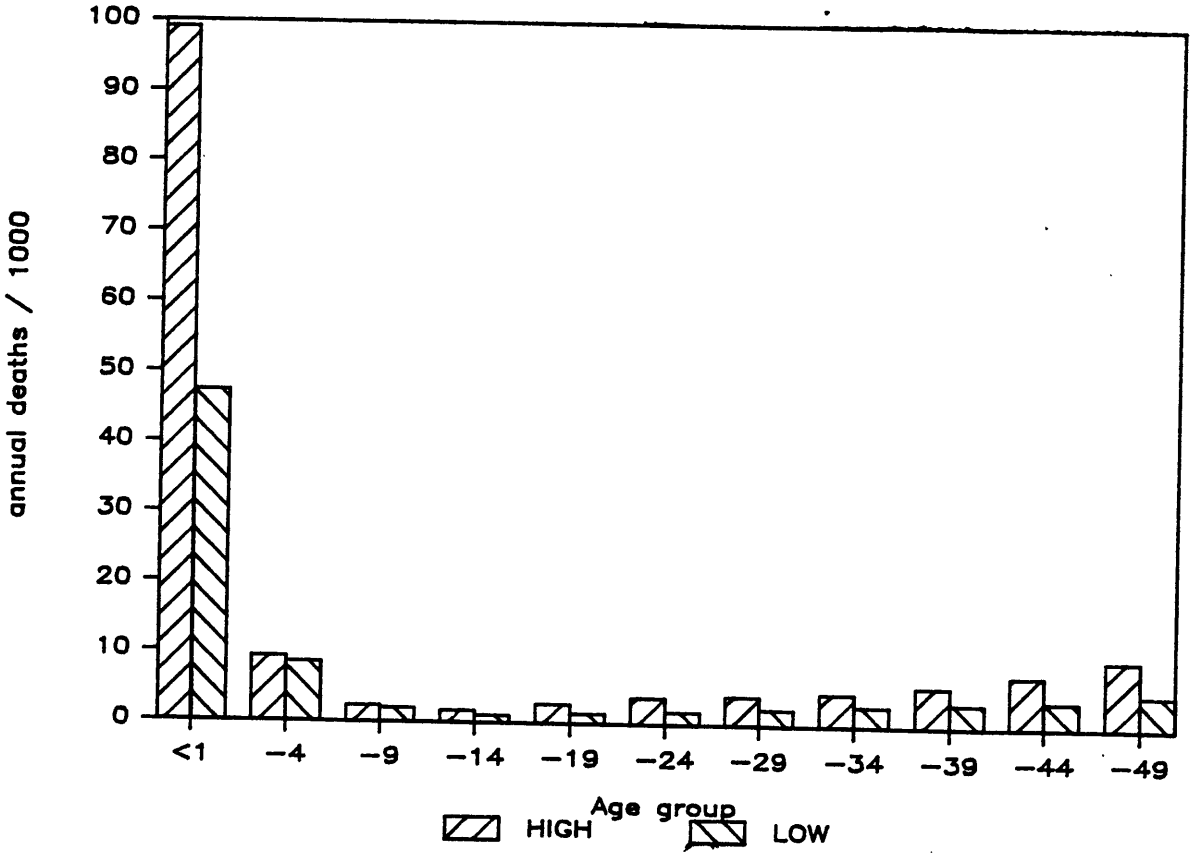
rates, the following approach was adopted. High, medium and low birth rates and high and low death rates were selected. The six possible combinations of these were then studied. Figures 6.3 and 6.4 show the birth and death rates that were used, and figure 6.5 shows the stable age distributions associated with each of the six possible combinations. Table 6.2 summarises the other important demographic constants, namely overall population growth rate and average birth rate, associated with each of the combinations.

The first of the three types of epidemiological data that need to be specified is the rate of loss of protection by maternal antibody. Built into the model is the assumption that there is an exponential decay in the proportion of each cohort protected by transplacentally derived antibodies. That is, by age **a** a fraction $\exp(-\delta \mathbf{a})$ of each cohort is still protected. (See equation 4.1) The quantity that needs to be estimated is therefore the decay coefficient δ. A special type of serological profile is needed in order to estimate δ. A normal serological profile records the proportion, by age, of a community which displays a level of measles antibody that could be assumed to offer protection from measles infection. A serological profile designed to measure δ must have the following additional properties. Attention should focus on the youngest age classes, those aged less than 18 months. The age stratification must be very fine - ideally in age bands of one month. All measles cases should be excluded. This last requirement is very difficult to fulfil as subclinical infection is common amongst very young children. So in practice all known cases are excluded. Figure 6.6 shows the results from 4 surveys which meet these requirements, and figure 6.7 shows the values of the rate of loss of protection by maternal antibody

Figure 6.3
High, medium and low age specific fertility rates selected for use in studies of the effects of variations in demographic processes. The high fertility rates are from Kenya in the years 1966-70, the medium fertility rates are from Thailand in the years 1974-79, and the low fertility rates are from Thailand in the years 1970-74. The high and low data are from U.S. Agency for International Development (1977), and the medium data are from the United Nations demographic yearbook for 1982.

Figure 6.4
High and low age specific death rates selected for use in studies of the effects of variations in demographic processes. The high death rates are from Thailand in the year 1970, and the low death rates are from Sri Lanka in the years 1970-72. All data are from U.S. Department of Commerce, Bureau of Census, Country Demographic Profiles.


live births / 1000 women
350
300
250
200
150
100
50
0
<1
-4
-9
-14
-19
-24
-29
-34
-39
-44
-49
Age group
HIGH
MEDIUM
LOW


annual deaths / 1000
100
90
80
70
60
50
40
30
20
10
0
<1
-4
-9
-14
-19
-24
-29
-34
-39
-44
-49
Age group
HIGH
LOW

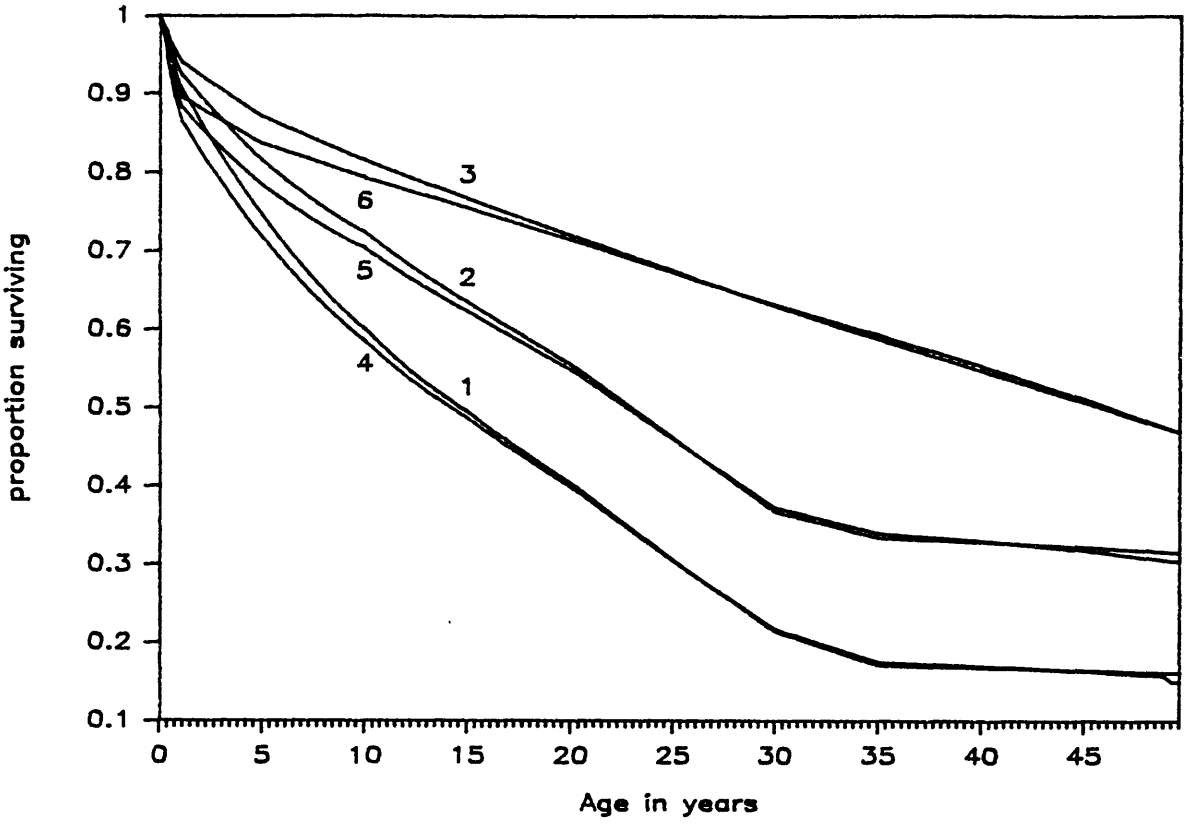


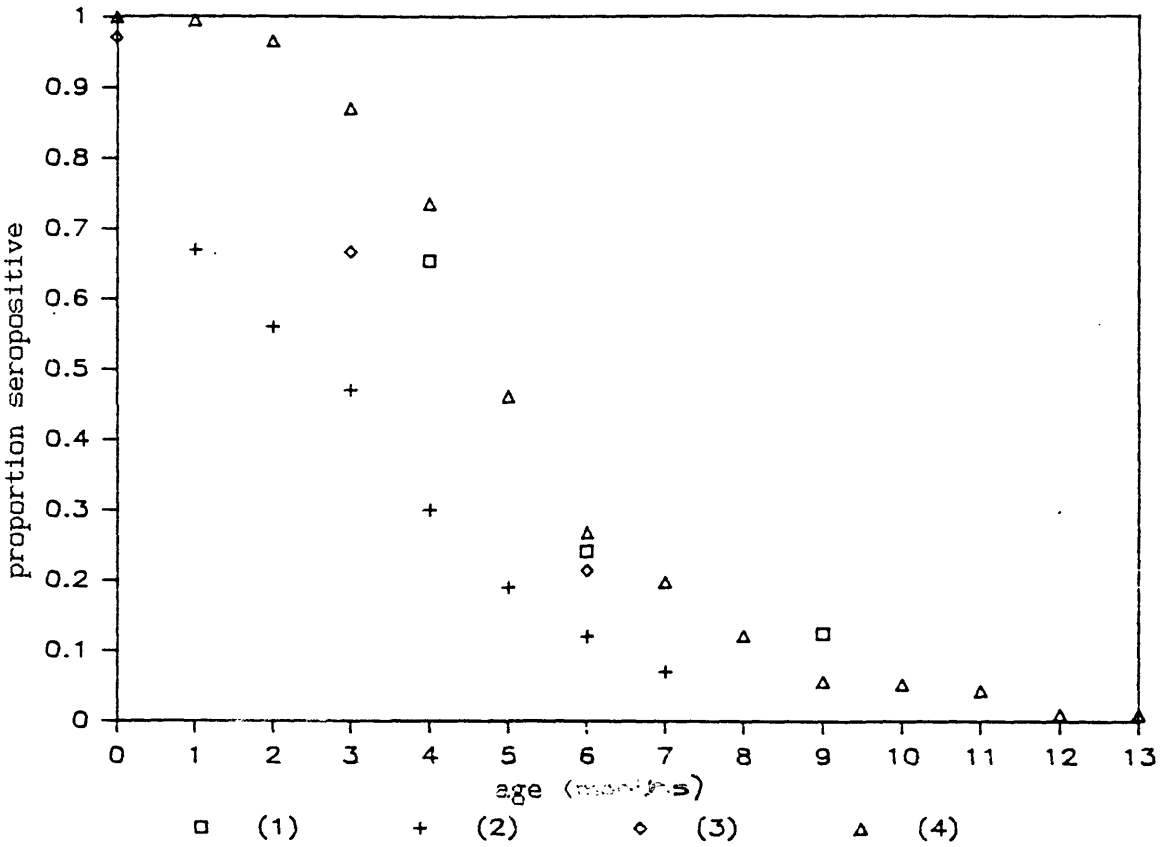
Figure 6.5
Stable age distributions associated with each of the six possible combinations of birth and death rates.
(1) High birth rate, Low death rate
(2) Medium birth rate, Low death rate
(3) Low birth rate, Low death rate
(4) High birth rate, High death rate
(5) Medium birth rate, High death rate
(6) Low birth rate, High death rate.

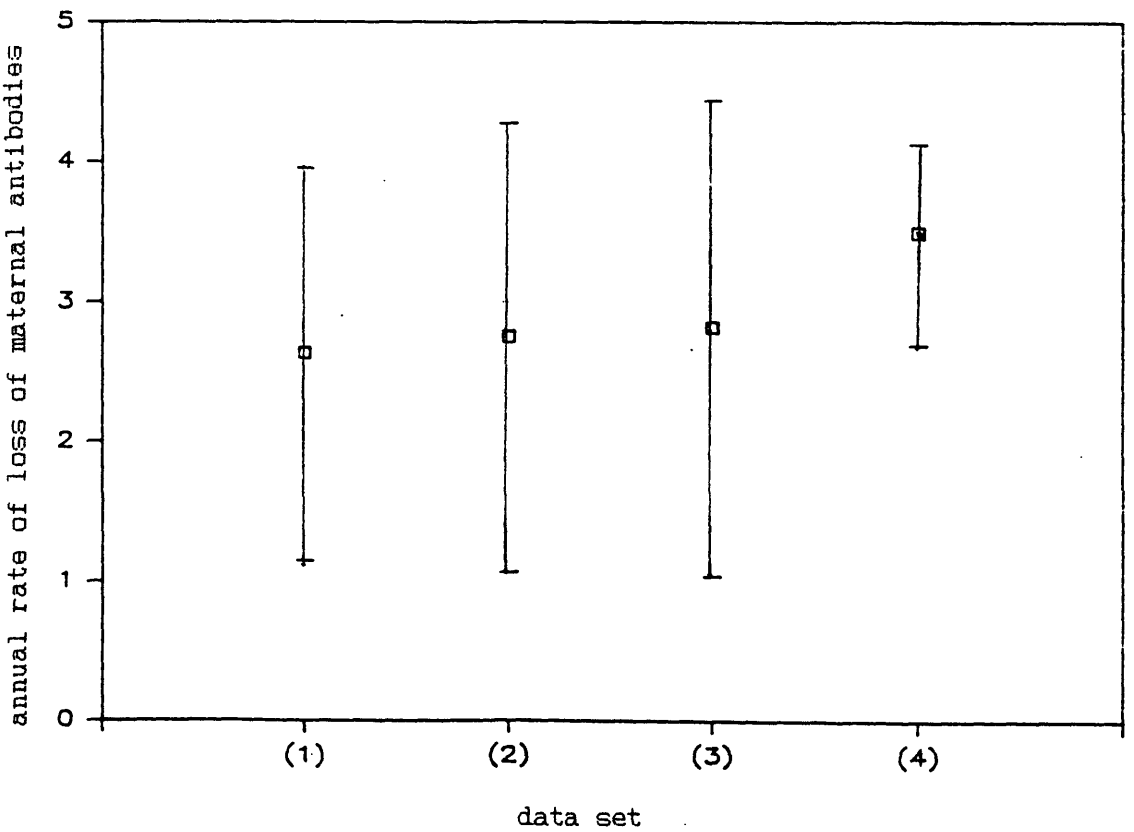
Birth Rate	Death Rate	Population Growth Rate (per 1000) $year^{-1}$ r	Population Doubling Time years	(Annual Birth Rate)$^{-1}$ years B
high	low	41.9	16.5	19.1
medium	low	25.4	27.3	25.9
low	low	11.02	62.9	34.2
high	high	38.9	17.8	18.8
medium	high	22.4	30.9	25.4
low	high	8.02	86.4	33.8

Table 6.2
Crude demographic rates from the six possible combinations of the selected high, medium and low birth and death rates. Notice that the values in cloumns 3 and 5 (that is the values of r and B respectively) are close to the values in the corresponding columns in table 6.1. This is taken as an indication that these combinations of demographic rates give a fair representation of the range of population processes seen in developing countries.

Figure 6.6
Serological profiles which exclude known cases. These are used to measure the rate of decay of maternal antibodies. When known, sample sizes are shown in parentheses.
(1) Bulawayo. (87) Burrowes and Cruickshank, 1975
(2) Tanzania. (649) E.P.I. 1981
(3) Nigeria. (108) Abdurrahman et al. 1982
(4) Nairobi, Kenya. (1764) Ministry of Health, Kenya 1977

Figure 6.7
Values for the rate of loss of maternal antibodies (δ) estimated from the serological profiles excluding known cases shown in figure 6.6. Error bars show 95% confidence intervals for the estimated values of δ. Data are from:
(1) Burrowes and Cruickshank, 1975
(2) E.P.I. 1981
(3) Abdurrahman et al. 1982
(4) Ministry of Health, Kenya 1977


proportion seropositive
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
age (months)
(1) (2) (3) (4)


annual rate of loss of maternal antibodies
5
4
3
2
1
0
(1) (2) (3) (4)
data set

that were estimated from them. The average duration of protection can be seen to lie somewhere between 3 and 12 months.

The second type of information required is the age specific disease related death rate. With the sort of age dependancy used in this study (described in chapter 4 section 4), this will consist of a vector of values, one for each age class. The raw data that is used for estimating disease related death rates is in the form of case fatality rates. There is some difficulty over the definition of a case fatality. In communities where general levels of health are poor it is often difficult to be specific about the cause of an individual's death. It is often the case that a number of factors are responsible. In practice a common definition for a case fatality is any death occurring within one month of the onset of measles symptoms. Figures 6.8 and 6.9 show some data on case fatality rates from Africa and from Asia, and table 6.3 shows some values of disease related death rates as measured from case fatality rates.

Figures 6.10 to 6.12 show serological profiles from a variety of developing countries, and 6.13 shows a serological profile from the U.S.A. As discussed above, they record the proportion of each age group that display a level of measles antibody (i.e. antibody titre) that would be expected to prevent measles infection. All the profiles shown are from studies which specifically exclude individuals known to have been vaccinated. Therefore people register as seropositive either because they are protected by maternal antibody, or because they have experienced the disease. For the African and Asian profiles (figures 6.10 and 6.11) there is the usual pattern of a sharp drop in the percent seropositive during the

Figure 6.8
Measles case fatality rates in Africa. Data are from community studies and studies of outpatients. When known, sample sizes are shown in parentheses.

1 Outpatients and addmissions. Ilesha Hospital December 1959 - May 1960 (2119) (Morley and MacWilliam, 1961)

2 & 3 An epidemic in two Gambian villages: 2, Keneba (230); 3, Jali (207) March - April 1961. (McGregor, 1964.)

4 & 5 Two epidemics in the Machakos study area in Kenya: 4, April 74 - March 76, (424); 5, April 76 - March 77 (665). (Muller et al, 1977.)

6 Bandim Guinea-Bissau March - April 1979 (98) (Aaby et al 1983a.)

7 & 8 Urban and Rural Guinea Bissau: 7, Rural (103); 8, Urban (83). 1979 - 1983. (Aaby et al 1983b)

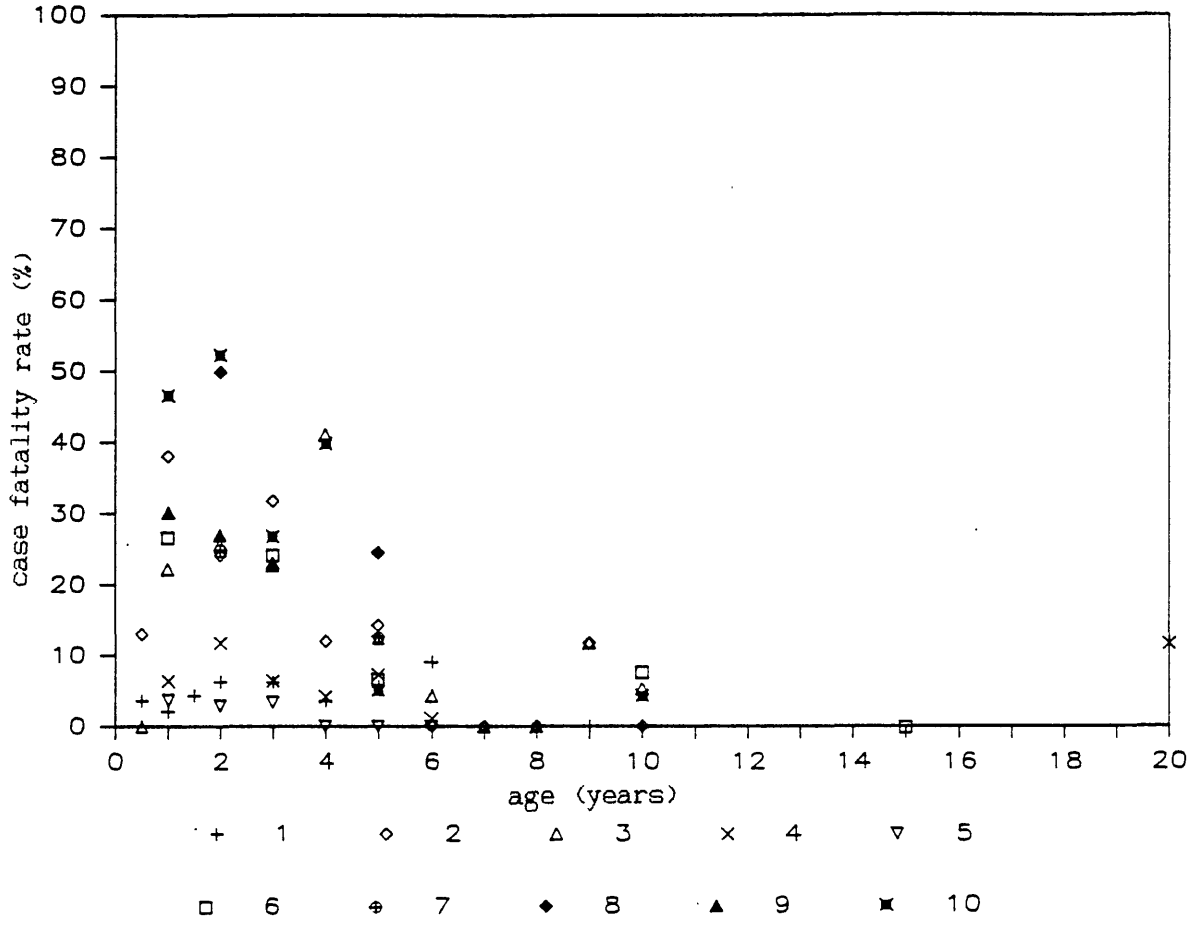
9 Bandim, Guinea Bissau1979 (170) (Aaby et al 1984a)

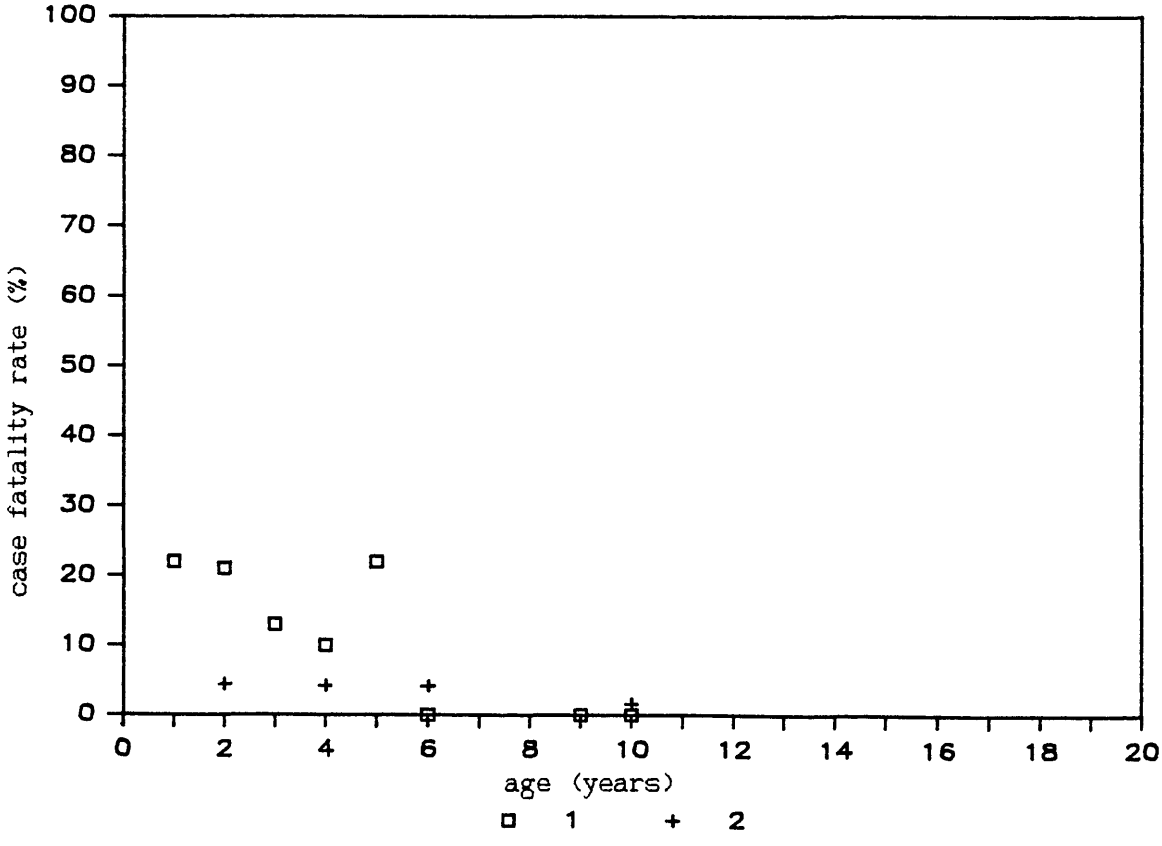
10 Quinhamel, Gunea Bissau 1979 - 1982 (162). (Aaby et al 1984b)

Figure 6.9
Measles case fatality rates in Asia. Data are from community studies and studies of outpatients. When known, sample sizes are shown in parentheses.

1 A village in rural south India October 1977 - March 1978 (65) (John et al 1980)

2 12 villages Matlab Bangladesh August 1975 - July 1976 (896) (Koster et al 1981)


case fatality rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
age (years)
1
2
3
4
5
6
7
8
9
10


case fatality rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
age (years)
1
2

Age Class (yrs)		0 - 1	1 - 2	2 - 4	4 - 6	6 - 8	8 - 10
High	case fatality rate (%)	63,64	22,22	15,00	7,69	4,00	0,00
	disease related death rate (yr^{-1})	91,01	14,86	9,18	4,33	2,17	0,00
Medium	case fatality rate (%)	22,22	21,43	11,11	13,33	0,00	0,00
	disease related death rate (yr^{-1})	14,86	14,18	6,50	8,00	0,00	0,00
Low	case fatality rate (%)	6,35	11,86	5,08	5,08	0,00	0,00
	disease related death rate (yr^{-1})	3,53	7,00	2,79	2,79	0,00	0,00

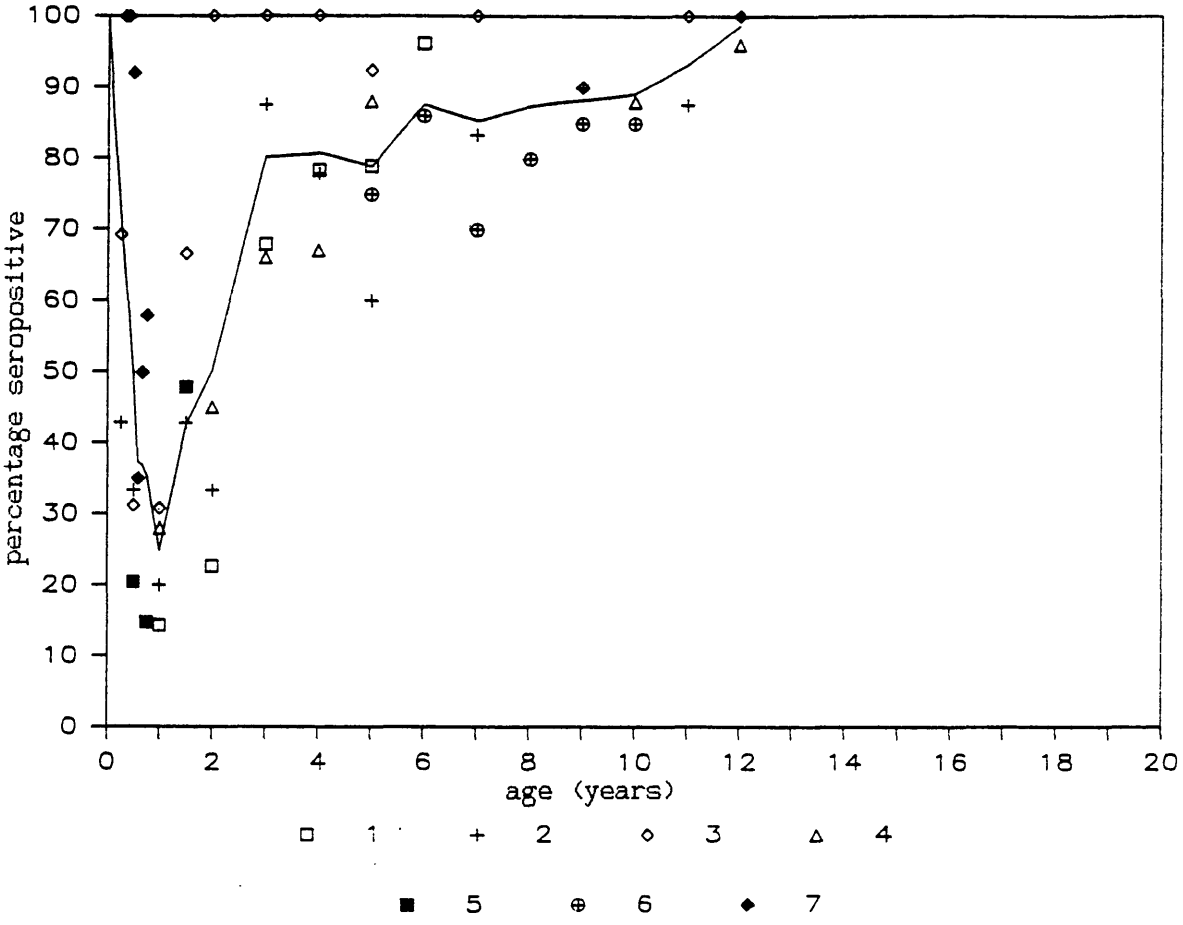
Table 6.3
Disease related death rates measured from case fatality rates. The formula derived in chapter 5 (equation 5.11) has been used for these calculations. The value of γ has been set at 52 (that is the infectious period is assumed to last, on average, for 1 week). The high case fatality rates are from a study in The Gambia (Williams, 1983), the medium case fatality rates are from a study in rural South India (John, 1980) and the low case fatality rates are from a study in rural Kenya (Muller, 1977)

first year of life as maternally derived antibodies wane, followed by a rebound as herd immunity acquired through natural infection begins to accumulate. This pattern does not show through in the data from Central America (figure 6.12) because the age specificity during the first year of life is not of a sufficiently fine grain. It is noticeable that in the African and Asian graphs a cohort begins to show immunity acquired through infection before immunity from maternally derived antibodies has been completely lost. So there is no age at which all individuals in a cohort are susceptible. In contrast, in the profile from the U.S.A. almost every member of the cohort has lost his or her maternally derived antibodies before any member acquires antibodies through infection. This illustrates the 'window problem' that was discussed in chapter 1. The absence of any age at which a whole cohort could be expected to seroconvert after vaccination makes it difficult to decide on the optimal age for immunization. If vaccine is given at too young an age many children will still be prevented from seroconverting by the presence of transplacentally derived antibodies. If the age at vaccination is raised much above one year a large percentage of each cohort will have already had measles. There is also the added complication that the case fatality rate is markedly greater amongst infants so they are arguably at greatest need of protection by immunisation.

The most interesting feature of these graphs is the rapidity of the rebound following loss of protection by maternal antibody, particularly in developing countries. A comparison of the solid lines (which simply pass through a set of points representing a crude average of all the data) shows that the percent of the population seropositive rises much more quickly in

Figure 6.10
Measles serology from Africa. When known, sample sizes are shown in parentheses.
1 Pikine, Senegal. July 1968 (144) (Cantrelle, 1969)
2 Popenguine, Senegal. 1957 (88) (Boue, 1964)
3 Dakar, Senegal. 1957 (151) (Boue 1964)
4 Dakar, Senegal. 1964. (Baylett,1969)
5 Lagos, Nigeria. 1979 (224) (Ogunmekan, 1981)
6 Niakhar, Senegal. 1964 (87) (Cantrelle, 1965)
7 Lagos, Nigeria. 1979 (152) (Harry & Ogunmekan, 1979)

Figure 6.11
Measles serology from Asia. When known, sample sizes are shown in parentheses.
1 Pondicherry, S. India. 1978 (350) (Bhau, 1979)
2 Bombay, India. 1971 (250) (Mehta, 1972)
3 Chandigarh, N. India 1975 (569) (Broor, 1976)
4 Rural villages, Maharashtra, India. 1971 (897) (Shah, 1972)
5 Vellore Town, India. 1972 (277) (John, 1973)
6 Bangkok, Thailand. 1967 (367) (Ueda, 1967)
7 Rural Nepal. 1977 (1145) (Brink, 1978)
8 Rural Sri Lanka. 1977 (1966) (Brink, 1978)


percentage seropositive
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
age (years)
1 2 3 4
5 6 7

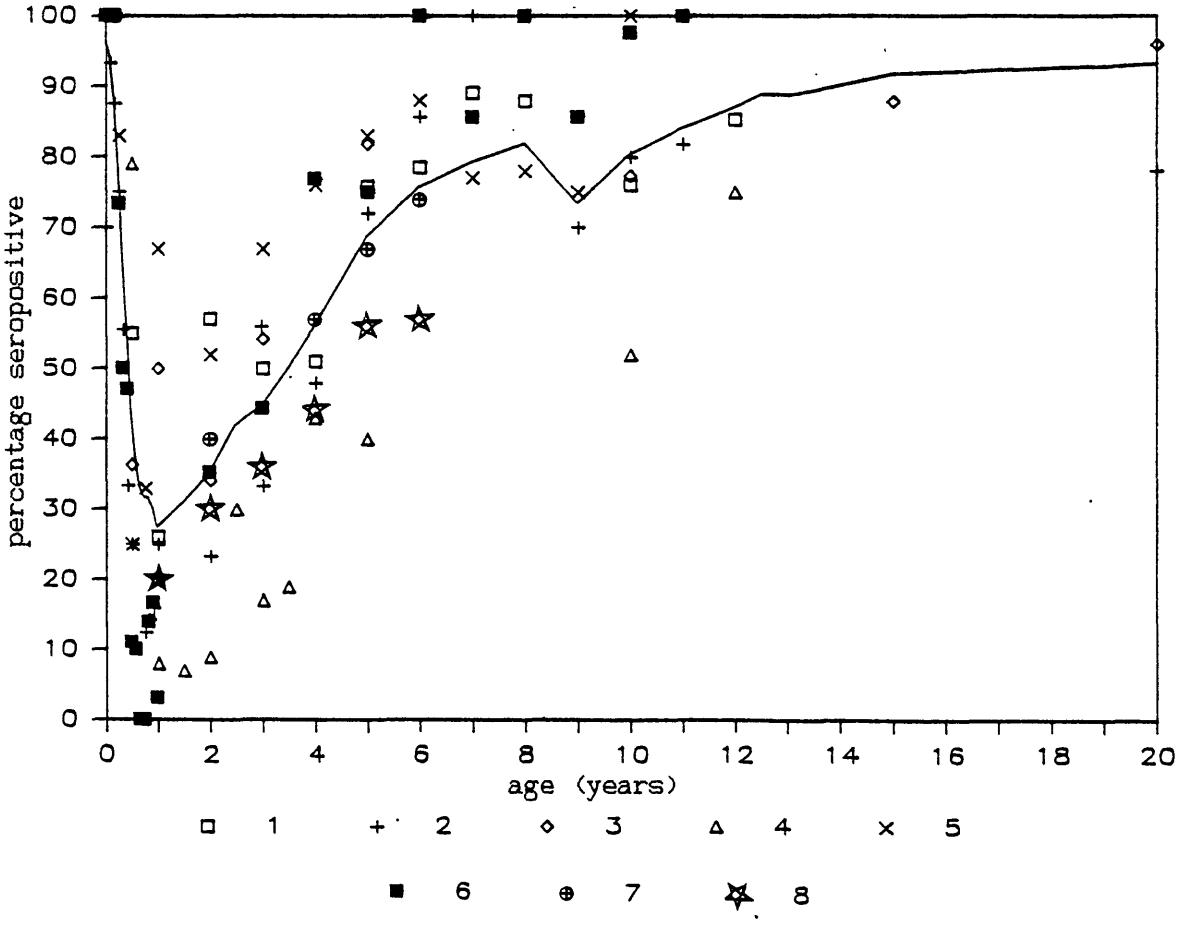
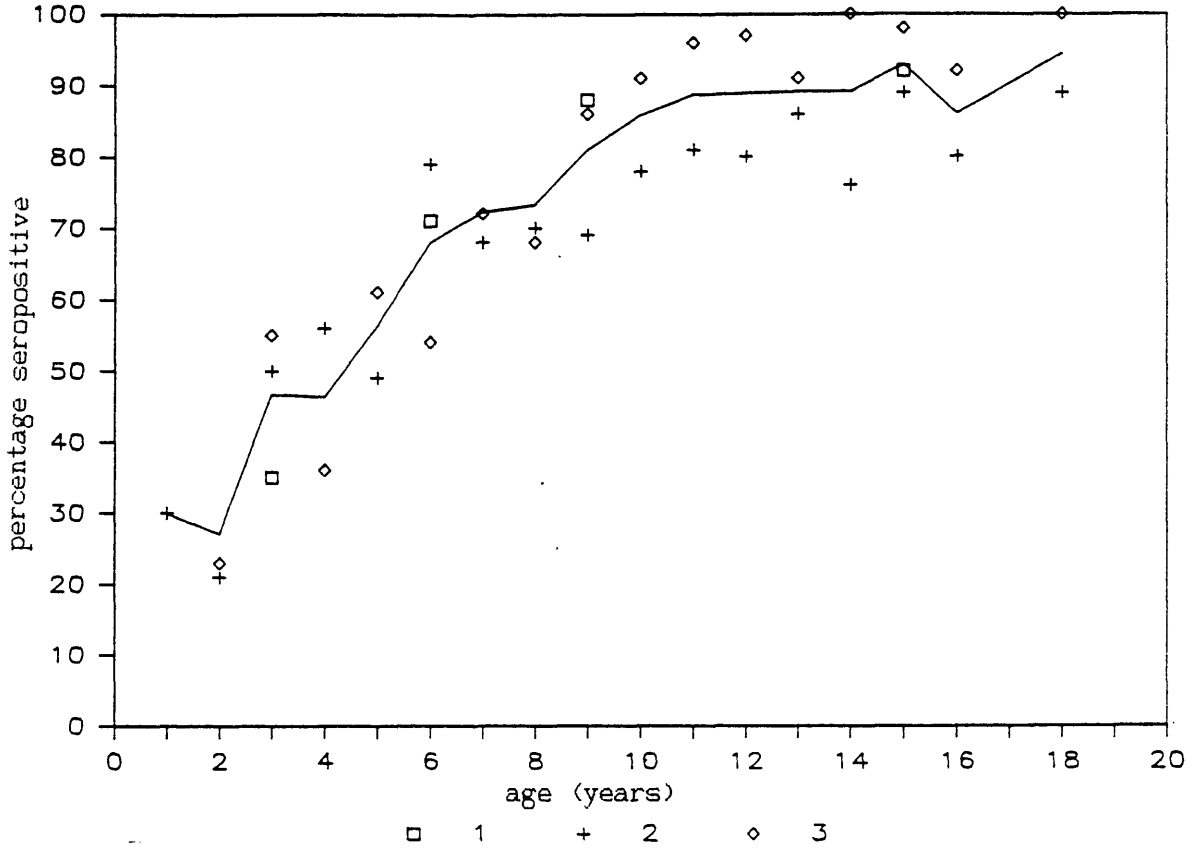
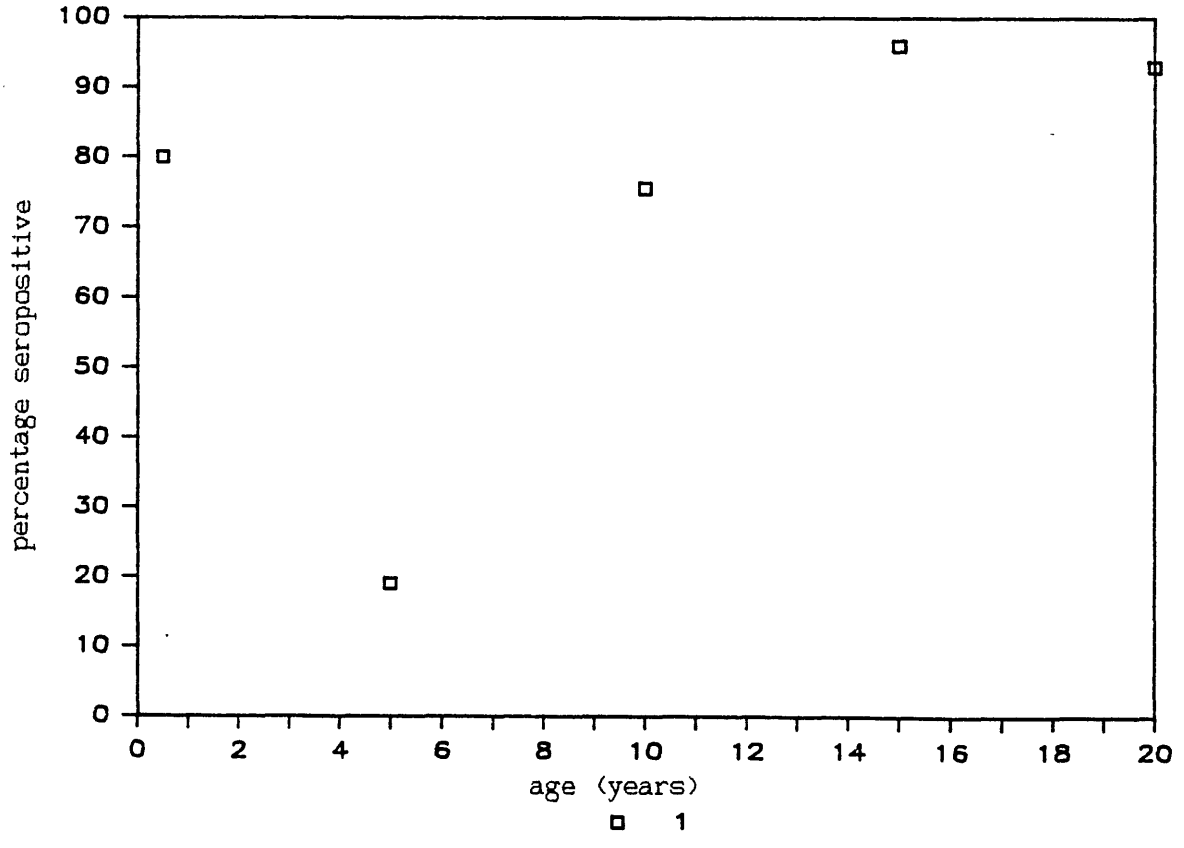

percentage seropositive
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
age (years)
1 2 3 4 5
6 7 8

Figure 6.12
Measles serology from Middle America. When known, sample sizes are shown in parentheses.
1 Middle America (i.e. Dominican Republic, Honduras, & Republic of Panama) 1974 (2970) (Kenny, 1976)
2 Huixquilucan, Mexico. 1971 (667) (Golubjatnikov, 1971)
3 Paraguay 1971 (408) (Golubjatnikov, 1971)

Figure 6.13
Measles serology from the U.S.A.
1 New Haven, Connecticut. (308) Black, 1959


percentage seropositive
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
age (years)
1
2
3


percentage seropositive
100
90
80
70
60
50
40
30
20
10
0
0
2
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8
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12
14
16
18
20
age (years)
1

the African and Asian graphs than in the graph from the U.S.A. The differences between the data from Central America and from the U.S.A. though less striking are still apparent. These differences in gradient can be formally interpreted through the estimation of forces of infection from these serological profiles. In figure 6.14 and table 6.4 the values for the force of infection, and the serological profiles they would predict are compared with raw data. The four serological profiles that have been used are amongst the best summarised in figures 6.10, 6.11 and 6.12. It is worth pointing out that the two profiles from Senegal are from an urban and a rural community, Popenguine being a small fishing village. The method for estimating values of the force of infection from serological profiles has been described in chapter 5. It is important to remember that from a given serological profile, the estimated values of the force of infection will depend upon the assumed values of the rate of loss of protection by maternal antibody and the disease related death rates. Table 6.5 shows the effect of variation in the disease related death rates and the rate of loss of protection by maternal antibody upon the estimated values of the force of infection. The values of the force of infection read into the program serve only as a starting point from which a set of values for the transmission (or WAIFW) matrix, $[\beta_{ij}]$ can be calculated. However it is also necessary to specify a configuration of the matrix which, as discussed in chapter 4, is restricted to having n elements. In table 6.6 two different WAIFW matrix configurations and the β_{ij}'s they generate are shown. These were calculated from the forces of infection which were estimated from the Ueda serological profile. The following method was used. The estimated λ's are used to generate equilibrium age distributions for each of the six age classes in the model. From the age distribution for the infectious (Y)

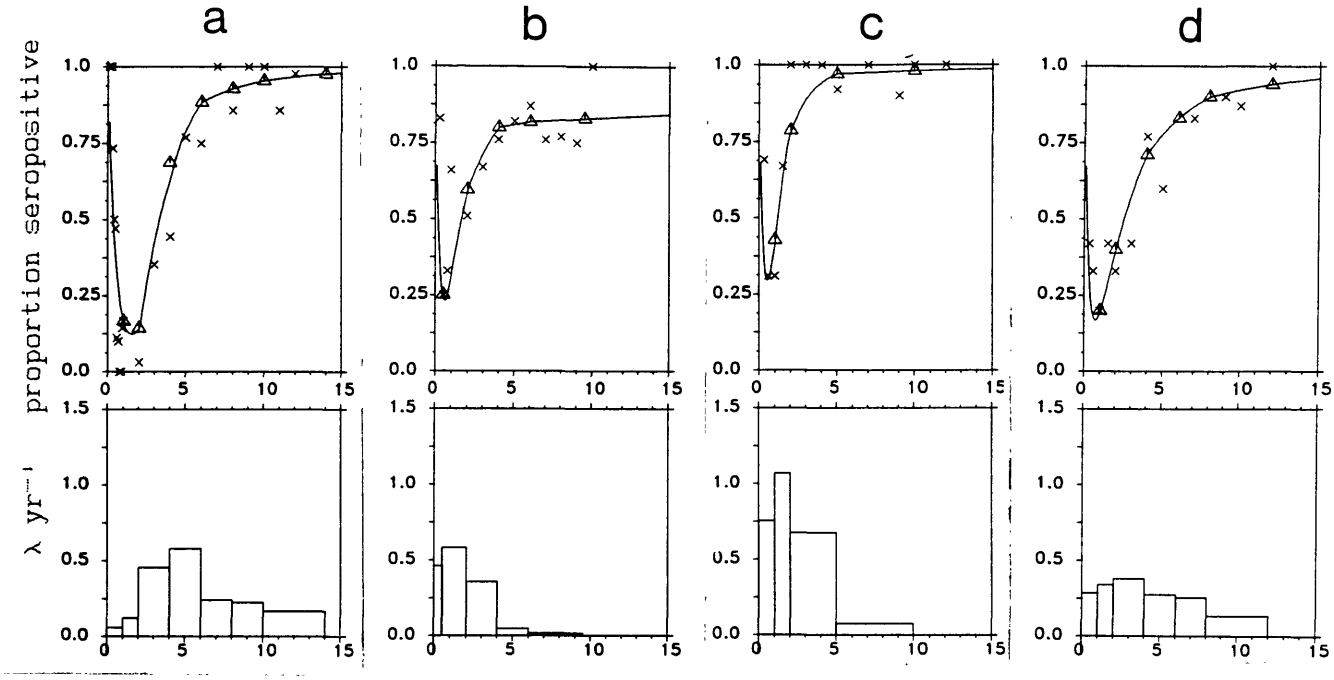


Figure 6.14
A selection of serological profiles and the forces of infection (λs) measured from them.
× raw data points
△ reblocked data points
— predicted serology from estimated λs
Data are from:
(a) Bangkok, Thailand. (Ueda, 1967)
(b) Vellore, India. (John, 1973)
(c) Dakar, Senegal. (Boue, 1964)
(d) Popenguine, Senegal (Boue, 1964)

Place	Date	Forces of infection (yr^{-1})						
Bangkok	1967	,0595	,1209	,4553	,5810	,2410	,2253	,1673
Dakar	1957	,7556	1,0701	,6755	,07558			
Popenguine	1957	,2838	,3405	,3796	,2725	,2555	,1328	
Vellore	1972	,4598	,5819	,3575	,0482	,0168		
Age (years)		0 0,5	1	2	3	4	5 6 7 8 9 10	50

Table 6.4
Forces of infection measured from serological profiles. These are the same results as those presented in graphical form in figure 6.14.

Case Fatality Rate	Rate of loss of maternal antibodies (yr^{-1})	Forces of infection (yr^{-1})						
		λ_1	λ_2	λ_3	λ_4	λ_5	λ_6	λ_7
High	2	,1179	,1415	,4852	,5844	,2410	,2253	,1673
Medium	2	,0688	,1347	,4727	,5914	,2410	,2253	,1673
Low	2	,0595	,1209	,4553	,5810	,2401	,2253	,1673
Zero	2	,0565	,1079	,4417	,5744	,2401	,2253	,1673
Low	2,25	,1117	,0919	,4497	,5805	,2401	,2253	,1673
Low	2,5	,1490	,0678	,4464	,5803	,2401	,2253	,1673
Low	3	,1945	,0317	,4433	,5803	,2401	,2253	,1673
Low	4	,2271	-,0084	,4418	,5803	,2400	,2253	,1673

Table 6.5
The dependance of the estimated values of the forces of infection upon the assumed values of the rate of loss of maternal antibodies, and the case fatality rates. High, medium and low case fatality rates refer to those shown in table 6.3. Notice that a higher case fatality rate used when estimating the λs leads to a higher value for λ. That is, methods that do not take case fatalities into account give underestimates of the true value of the force of infection. In general greater values of δ serve to increase λ_1 and decrease λ_2. Notice, also, that when the value of δ is set to 4 per year (i.e. average duration of maternal antibodies is 3 months), a negative value for λ_2 is estimated, hence the assumption that δ is equal to 4 is incompatible with this serological profile.

Configuration 1

56.7	56.7	56.7	56.7	311.0	291.1	214.5
56.7	146.7	146.7	146.7	311.0	291.1	214.5
56.7	146.7	703.0	703.0	311.0	291.1	214.5
56.7	146.7	703.0	1389.2	311.0	291.1	214.5
311.0	311.0	311.0	311.0	311.0	291.1	214.5
291.1	291.1	291.1	291.1	291.1	291.1	214.5
214.5	214.5	214.5	214.5	214.5	214.5	214.5

Configuration 2

76.3	76.3	76.3	76.3	76.3	76.3	76.3
155.0	155.0	155.0	155.0	155.0	155.0	155.0
583.8	583.8	583.8	583.8	583.8	583.8	583.8
745.0	745.0	745.0	745.0	745.0	745.0	745.0
307.9	307.9	307.9	307.9	307.9	307.9	307.9
288.9	288.9	288.9	288.9	288.9	288.9	288.9
214.5	214.5	214.5	214.5	214.5	214.5	214.5

Table 6.6
Who acquires infection from whom (WAIFW) matrix configurations. The arrangements of these numbers indicate the assumptions that are made about heterogeneity of transmission according to age. Configuration 1 implies the assumption that both the age of the infectious individual and the age of the susceptible individual influence the rate of disease transmission, and that the hihgest transmission takes place within the 4-6 year old age group. Configuration 2 implies the assumption that the transmission coefficient depends solely upon the age of the susceptible.

class, the total number of infectious individuals in each age class ($\bar{Y}_j$) is calculated. The total population $\bar{N}$ is also found from these equilibrium age distributions. Because the WAIFW matrix only contains n different β_{ij}'s the set of linear equations;

$$\lambda_i = \sum_{j=1}^{n} \beta_{ij} \bar{Y}_j / \bar{N}$$

can be solved for the n different β's.

There are, however, a number of properties of serological profiles drawn from developing countries which combine to cause problems with the estimation of the age dependent lambdas. These are illustrated in figure 6.15. In developing countries very high levels of immunity are reached at young ages. For example in the serological profile illustrated, 21 out of 22 people aged between 8 and 10, and 42 out 43 aged between 10 and 14, were seropositive. Sample sizes tend to be small - the whole survey illustrated involved 367 individuals. A third factor is that surveys tend to deal exclusively with young people - in the survey shown the oldest individuals were fourteen. These three factors combine to make it impossible to make a reliable estimate of λ_n - the force of infection that should apply to the top age class.

In table 6.7 this problem is illustrated with an example based upon the data in figure 6.15. In order to restrict the number of cases to be considered, two assumptions were made when drawing up this table. These were; (1) 21 seropositives out of every 22 people by the age of 10 is a correct representation of the situation in the community, and (2) the force of infection amongst adults is at least zero. In the terminology of the

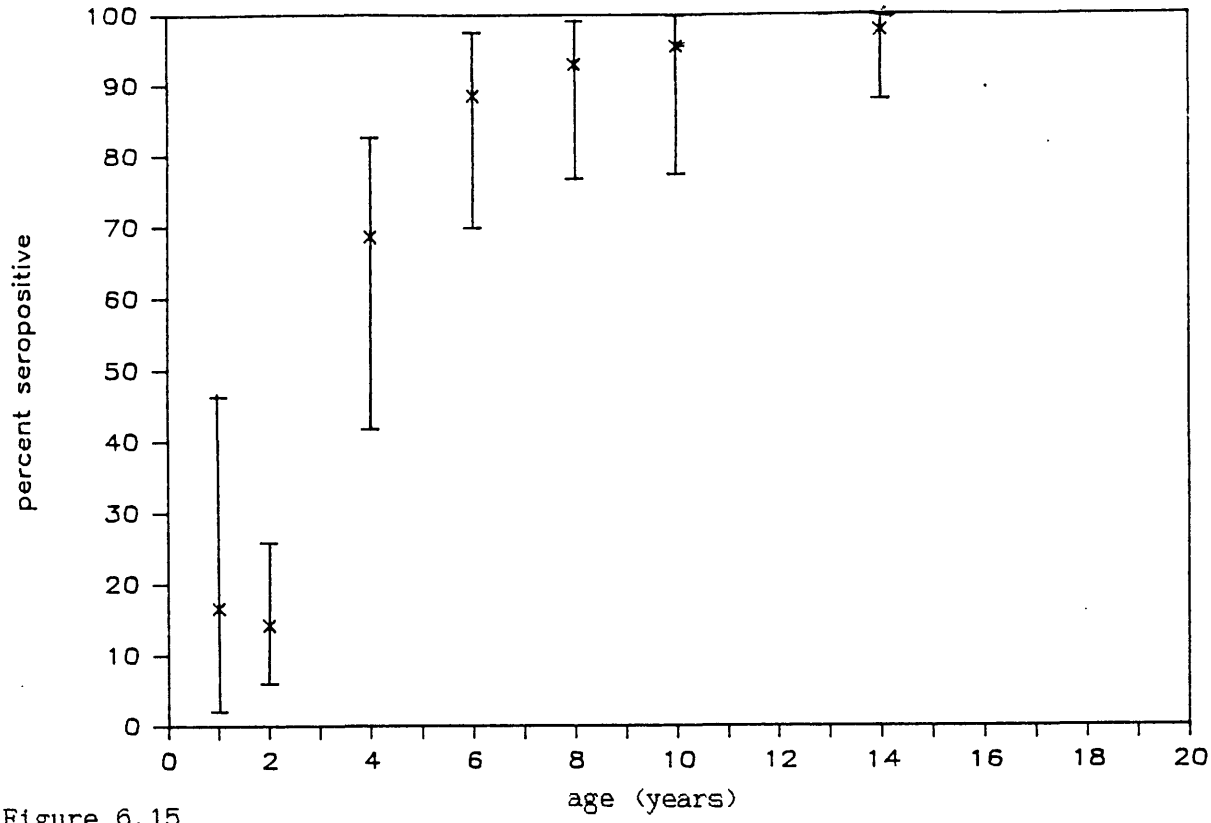


Figure 6.15
Ueda's serological profile with 95% confidence intervals for the percentages.

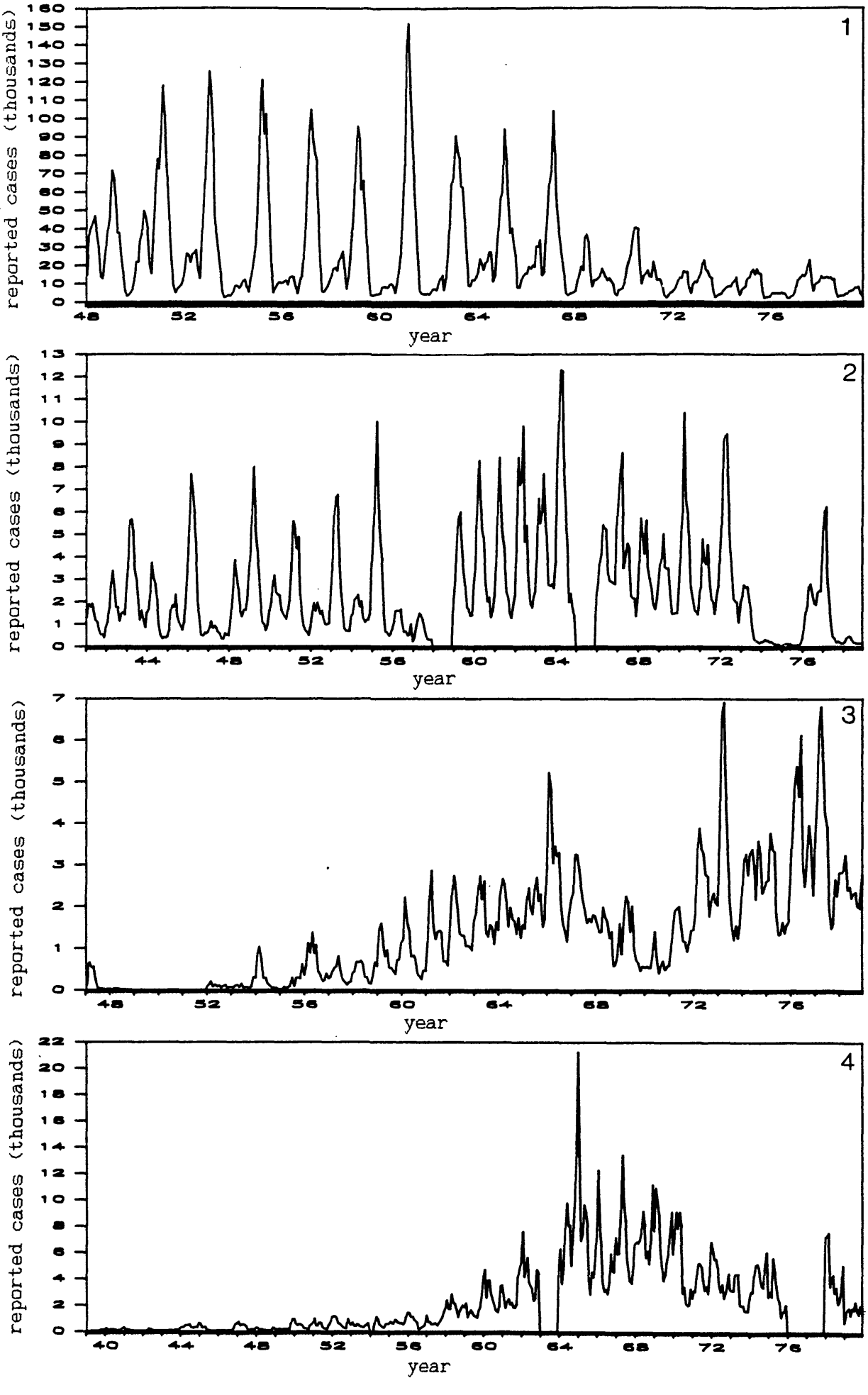
p_7	λ_7	β_1	β_2	β_3	β_4	β_5	β_6	β_7
95,45	0,0	62,99	152,96	709,22	1395,43	317,27	297,31	0,0
97,67	0,1673	56,74	146,71	702,97	1389,18	311,02	291,06	214,52
98,81	0,3353	49,09	139,06	695,32	1381,53	303,37	283,41	428,57
99,94	1,0821	14,74	104,71	66-,97	1347,18	269,02	249,06	1379,72

Table 6.7
The range of possible estimates for λ_7 and β_1 to β_7 given that p_6 is assumed to be 95.45, and λ_7 is assumed to be at least 0. (Here p_6 is the proportion seropositive between age 8 and 10.)

table these assumptions are interpreted to; (1) p_6 = 95.45, and (2) $p_7 \geq$ 95.45. From the calculation of 95% confidence intervals for p_7 an upper limit of 99.94 is set, and two intermediate values for p_7 are chosen. This gives a range of four plausible values of p_7 from which λ_7 can be estimated. The table shows that although the range of p_7 is only 5%, the corresponding range for λ_7 is much greater, and the effect upon the calculated values of the β_i's - particularly β_7 - is also great. To summarise, problems inherent to the study of measles in developing countries (high levels of immunity at young ages) and created by shortcomings of existing data (small sample sizes concentrating on young people) combine to make the reliable estimation of the force of infection for adults impossible. This in turn affects the calculated values of the age specific transmission coefficients.

The final sets of epidemiological data to be considered record reported cases of measles through time. (Figure 6.16). The series from the U.K. shows the familiar cycle of a year of high incidence followed by a year of low incidence, the pattern persisting until 1968 when it is disrupted by the introduction of widespread vaccination. The time series from Mexico has the same high year - low year cycle until 1956, then in the years 1959 to 1964 there are yearly epidemics of equal magnitude. It seems possible that this change may be as a result of increasing urbanisation (see chapter 9 for a further discussion of this point). This pattern of annual epidemics is disrupted in 1964, either by the introduction of vaccination, or through some change in reporting procedure. It is impossible to tell which. The series from Senegal shows annual cycles coupled with an underlying trend of increasing numbers of reported cases. This same trend

Figure 6.16
Long term measles case reports.
1 United Kingdom (England and Wales)
2 Mexico
3 Senegal
4 Iran
The U.K. data are from the Annual reviews of the Registrar General of England and Wales. The data for Mexico, Senegal and Iran are from W.H.O. annual statistical reviews for 1940 - 1980


1
reported cases (thousands)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
48 52 56 60 64 68 72 76
year
2
reported cases (thousands)
0 1 2 3 4 5 6 7 8 9 10 11 12 13
44 48 52 56 60 64 68 72 76
year
3
reported cases (thousands)
0 1 2 3 4 5 6 7
48 52 56 60 64 68 72 76
year
4
reported cases (thousands)
0 2 4 6 8 10 12 14 16 18 20 22
40 44 48 52 56 60 64 68 72 76
year

is apparent in the data from Iran. It must be stressed that this type of data is notoriously unreliable, to the extent that the W.H.O. no longer considers it worth publishing.

In order to investigate the effect of variation in parameter values, it is necessary to choose some baseline from which variation can be measured. To this end two baseline parameter sets have been established. The first of these uses forces of infection measured from the Ueda serological profile and the second uses forces of infection measured from the serology collected by Boue in Dakar (see figure 6.14 (a) and (c) for references). The Ueda data shows a comparitively low force of infection whilst the λs measured from the Boue data are much higher. High birth rate, low death rate (thus maximum population growth rate) and low case fatality rates are shared by both baseline parameter sets. For the Ueda baseline parameter set the value of δ is set to two per year, whilst for the Boue baseline parameter set, δ is four per year. Thus average ages of loss of protection by maternal antibody are six months and three months respectively. These baseline parameter sets are used extensively in the studies presented in the next section.

In the next three sections attention focuses upon numerical values of the average age at infection, A, the basic reproductive rate, R_0, and the critical vaccination proportion for eradication, p_c. Using the formulae derived in chapter 5, tables are drawn up that show the sensitivity of these numerical values to variations in the force of infection, demographic rates, case fatality rates and WAIFW matrix configuration. The discussion falls into three sections, each one focusing on the results presented in one

of the three tables; 6.8, 6.9 and 6.11. Table 6.8 shows the outcome of parameter variation upon the value of the average age at infection, and tables 6.9 and 6.11 deal in a similiar fashion with the basic reproductive rates and the critical vaccination proportion. In what follows, it is useful to bear in mind that it is the serological profile that is taken as a starting point. If changes are made to the assumed values of the case fatality rates, the values taken by the forces of infection must also change. In this way the serological profile predicted by the combination of case fatality rates, rate of loss of protection by maternal antibody and forces of infection remains constant in shape. Occasional reference is made to the one age class versions of the formulae for A, R_0 and p_c. Although these are not the formulae that were used in drawing up the tables, they are referred to because they can contain relevant information that is obscured by the algebraic detail of the many age class versions.

6.5 Sensitivity of the average age at infection, A, to parameter variation.

In table 6.8 comparisons are drawn between different values of the average age at infection. These were calculated using the formula presented in equation 5.32. When considering these results it should be remembered that equation 5.32 was derived under the assumption that all new-borns are susceptible. This is clearly not true, and would lead to underestimation of the average age at infection. In particular, the result from the Boue serological profile collected in Dakar (row 11) probably underestimates the true average age at infection by about six months.

As can be seen by comparing rows (1) and (2), alterations to the configuration of the WAIFW matrix have no effect upon the value of the average age at infection. This is to be expected because the formula in equation 5.32 is couched in terms of the λ_i's which determine the values of the $\beta_{i,j}$'s, while being independent of the configuration of the WAIFW matrix. Comparing rows (1), (3) and (4) shows that increases in the assumed level of case fatalities lead to decreases in the estimated average age at infection. This is essentially the same result as that shown in table 6.5. That is, increases in the assumed level of case fatalities lead to increased estimates of the forces of infection. These in turn lead to decreased estimated values for the average age at infection.

Turning now to the effects of variations in the demographic rates, birth rates are considered first. Rows (1), (5) and (6), and (7), (8) and (9) reveal that lower birth rates lead to slightly higher estimates of the average age at infection. Turning to the one age class result, $A = 1/(r + \mu + \lambda)$, makes it easier to see why this should be so. Lower birth rates lead to decreasing population growth rates r, and decreasing values of r lead to increasing values of A. Comparison of rows (1) and (7), (5) and (8), and (6) and (9) show that decreases in the death rate also serve to increase the average age at infection. Again use of the one age class formula helps to see why this occurs. It should be noted that both these effects (of variation in birth and death rates) are very small.

To compare the average ages at infection implied by different serological profiles, it is useful to refer back to figure 6.14 and table 6.4. These show the serological profiles referred to as 'Ueda', 'John', 'Boue

Serological Profile	Demography births - deaths	Case Fatality Rate	WAIFW Matrix Config	Average age at Infection	
Ueda	high-low	low	1	3.198	(1)
			2	3.198	(2)
		zero	1	3.260	(3)
		medium	1	3.111	(4)
	medium-low	low	1	3.247	(5)
	low-low	low	1	3.290	(6)
	high-high	low	1	3.200	(7)
	medium-high	low	1	3.249	(8)
	low-high	low	1	3.292	(9)
John	high-low	low	1	1.241	(10)
Boue (Dakar)	high-low	low	1	1.089	(11)
Boue (Popenguine)	high-low	low	1	2.207	(12)

Table 6.8
Sensitivity of the calculated value of the average age at infection to parameter variation. Calculations were performed using the formula for the average age at infection derived in chapter 5. Serological profiles are those shown in figure 6.14. High, medium and low birth rates are those shown in figure 6.3. High and low death rates are depicted in figure 6.4. Case fatality rates and WAIFW matrix configurations are shown in tables 6.3 and 6.6 respectively.

(Dakar)' and 'Boue (Popenguine)' in the table, and the forces of infection estimated from them. As would be expected, the steepest, earliest rebounds lead to the lowest average ages at infection.

6.6 Sensitivity of the basic reproductive rates, R_{0i}, to parameter variation.

Before looking in detail at the results in table 6.9, a brief recap is presented of the definition of the basic reproductive rate, and the formula for its calculation. The basic reproductive rate for the ith age class, R_{0i}, is the number of new cases that would be generated in a wholly susceptible population, if one infectious individual whose age lay in the ith age class was introduced. Equation 5.33 shows that R_{0i} is calculated as the product of the average time for which someone in the ith age class is infectious, $(1 / (\gamma + \alpha_i))$, and the average 'infectability' of the population when exposed to an infectious individual in the ith age class $(\Sigma \beta_{ji} N_j / N)$. Figure 6.17 shows three dimensional sketches of the function $\beta(a,a')$ for the four different serological profiles considered in table 6.8. It is hoped that reference to these graphs will be helpful in the following discussion. The first row of table 6.9 shows the R_{0i}'s that are calculated from the Ueda baseline parameter set, which includes the WAIFW matrix illustrated in figure 6.17(a). The comparatively large values of β_3 and β_4 are reflected in the large values of R_{03} and R_{04}. In row (2) the effect is shown of switching the WAIFW matrix configuration to configuration 2 (table 6.6). The only heterogeneity within this row is provided by the differences in the duration of infectiousness brought about by the age specific disease related death rates. So the values of the R_{0i}'s are approximately equal, and only vary where the disease related death rates vary.

The situation concerning the effects of variation in the disease related death rates is somewhat more complex. There are two ways in which changes in the α's may act to change the values of the R_{0i}'s. Firstly higher α's lead to shorter infectious periods and therefore smaller R_{0i}'s. Secondly higher α's result in higher estimated values for the λ's (forces of infection), hence greater β's, hence greater R_{0i}'s. Which of these two effects is the dominating influence depends upon the relative differences between the values of the disease related death rates. Thus when the differences are very large the first effect dominates and higher case fatality rates imply smaller R_{0i}'s: this is seen for R_{01} to R_{04}. When the differences are smaller the second effect is more important and greater case fatality rates lead to greater R_{0i}'s: this is illustrated by R_{05}, R_{06} and R_{07}.

Comparing rows (1), (5) and (6), and (7), (8) and (9) illustrates the fact that lower assumed birth rates lead to lower estimates for the R_{0i}. Consideration of the one age class result $R_0 = B / A$ helps to explain this. Lower birth rates imply greater values of B and hence greater R_0. In contrast higher death rates imply higher R_{0i}'s.

The last comparison to be made whilst considering basic reproductive rates is between different serological profiles. As there is only one basic reproductive rate for each age class, John's serological data only provides five R_{0i}'s, Boué's serological study from Dakar only generates four, and so on. The R_{0i}'s calculated using John's serological data are very low. This is because of the very low values of λ_4 and λ_5 that were estimated from that serological profile. As a result β_4 and β_5 are excessively small (as can be

Serological Profile	Demography births - deaths	Case Fatality Rate	WAIFW Matrix Config^{n}	Basic Reproductive Rates							
				R_{o1}	R_{o2}	R_{o3}	R_{o4}	R_{o5}	R_{o6}	R_{o7}	
Ueda	high-low	low	1	3,33	3,46	5,40	6,38	4,84	4,71	4,13	(1)
			2	5,34	4,91	5,29	5,29	5,57	5,57	5,57	(2)
		zero	1	3,47	3,77	5,47	6,52	4,74	4,61	4,04	(3)
		medium	1	2,64	3,26	5,33	6,10	4,99	4,86	4,26	(4)
	medium-low	low	1	4,38	4,45	6,48	7,46	5,95	5,82	5,23	(5)
	low-low	low	1	5,63	5,62	7,75	8,73	7,27	7,15	6,54	(6)
	high-high	low	1	3,42	3,54	5,49	6,47	4,94	4,81	4,22	(7)
	medium-high	low	1	4,50	4,56	6,60	7,58	6,08	5,95	5,35	(8)
	low-high	low	1	5,81	5,80	7,94	8,93	7,48	7,35	6,74	(9)
John	high-low	low	1	2,42	2,63	2,11	0,62	0,44	-	-	(10)
Boue (Dakar)	high-low	low	1	4,64	5,14	4,49	1,69	-	-	-	(11)
Boue (Popenguine)	high-low	low	1	4,16	4,20	4,76	4,16	3,12	-	-	(12)

Table 6.9
Sensitivity of the calculated value of the basic reproductive rates to parameter variation. Calculations were performed using the formula for the basic reproductive rates derived in chapter 5. Serological profiles are those shown in figure 6.14. High, medium and low birth rates are those shown in figure 6.3. High and low death rates are depicted in figure 6.4. Case fatality rates and WAIFW matrix configurations are shown in tables 6.3 and 6.6 respectively.

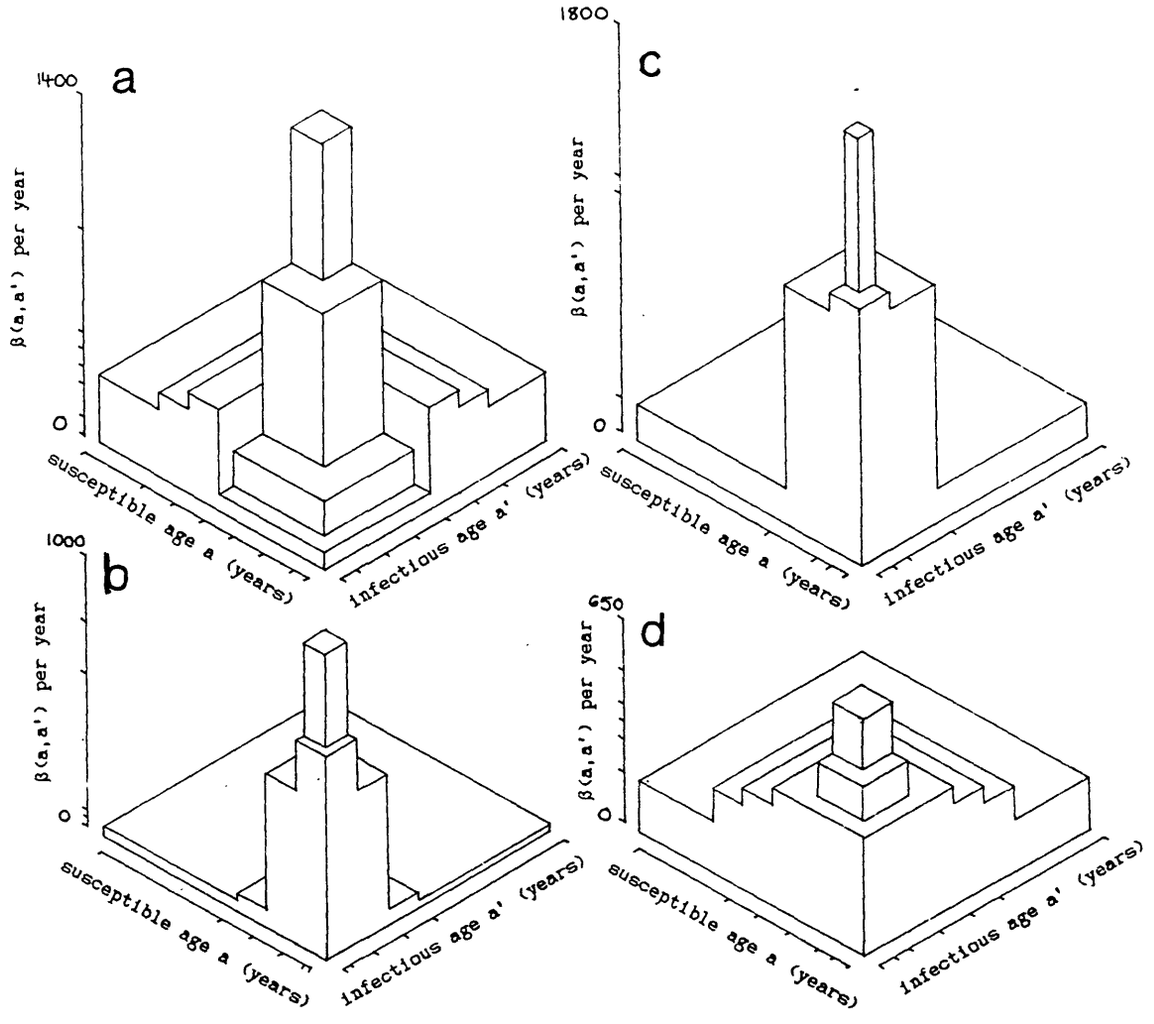


Figure 6.17
Diagrams of the four transmission functions (the $\beta(a,a')$s) generated by the four serological profiles in figure 6.14.
(a) Ueda
(b) John
(c) Boué (Dakar)
(d) Boué (Popenguine)
For references see legend to figure 6.14

seen in figure 6.16c). As these apply to all individuals over the age of 4, the averaging process in the calculation of the R_{oi}'s only inflates their influence. The problem here stems right back to specious estimates of the force of infection in older age classes. This serves to illustrate the great importance of obtaining good data on changes in proportion immune by age across the whole spectrum of ages. The R_{oi}'s for Boué's serology from Dakar and from Popenguine are surprisingly similiar in value given the disparity in the λ's and β's. This is simply a consequence of the averaging process that forms part of the calculation of the basic reproductive rate.

6.7 Sensitivity of the critical vaccination proportion for eradication, p_c.

In section 4 of this chapter attention was drawn to problems associated with the estimation of λ_m - the force of infection for adults - and an illustrative example of these problems was given. (figure 6.14 and table 6.7) As is shown in table 6.10 these problems with the estimation of λ_m have a great effect upon the estimated value of p_c. The values of p_c shown in table 6.10 were calculated using equation 5.34, for each of the four possible sets of β_i's generated by different assumed values of the proportion seropositive at age fourteen years. As can be seen an unacceptably broad range of values for p_c is calculated. The fact that p_c should be so sensitive to small variations in parameters about which there is little information effectively removes any confidence in its predictions. These problems notwithstanding, a sensitivity analysis of p_c to variation in other parameters has been performed, and the results are presented below.

In table 6.11 the effects of variation in model parameters upon p_c are shown. Changing the configuration of the WAIFW matrix has a substantial effect upon p_c. Because the choice of the matrix configuration cannot be fixed by reference to data, this is a disturbing result. Changes in the assumed level of case fatalities have virtually no effect upon the value of p_c. This is because the two counteracting effects discussed in section 6.6 balance each other out. As would be expected a lower assumed birth rate leads to higher vaccination levels required for eradication. The reason for this is most easily seen by considering the one age class result (equation 5.26)

$$p_c = 1 - A / B$$

where B is the reciprocal of the average birth rate and A is the average age at infection. Decreases in the assumed birth rate lead to increases in the value taken by B, and hence increases in p_c. This does not mean that increasing the birth rate in a community makes eradication of disease easier! The interpretation of this result should be as follows. The average age at infection in a community is determined by a combination of demographic and social factors. If a high rate of transmission (low average age at infection) is the result of a very high birth rate then eradication will be easier than if the same high transmission is the result of a greater degree of mixing. Comparing the values of B in tables 6.1 and 6.2 shows that only the low birth rate gives a value for B near to that which prevails in Thailand. As the Ueda data were taken in Bangkok, this can be interpreted as indicating that vaccination levels of 86% are nearer to the true eradication level than levels of 78%. This makes the useful point that it is vital to have good demographic data about the community under

consideration if reliable values for the critical vaccination proportion are to be found.

Turning to consider the rest of the results in the table, comparison between rows (1) and (6), (4) and (7), and (5) and (9) show that differences in the death rate have very little effect upon the critical vaccination proportion. The result from the John serological profile is quite untenable. As in the last section this is because of the very low levels estimated for R_{max}. Here again is an illustration of the importance of good data on age specific changes in immunity in the older age classes. The last two rows show surprisingly similiar results. Looking back at the average age at infection for the Dakar and the Popenguine data (1.089 and 2.207 respectively), and, again remembering the one age class result;

$$p_c = 1 - A / B$$

(equation 5.26) would suggest that the critical vaccination proportion would be lower in the fishing village Popenguine. However this is not the case, and this is another illustration of the importance of the influence of the force of infection in the older age classes.

There are three factors that undermine faith in these predictions of the critical vaccination proportion. First of all they are based upon a formula that is derived from a simplified model that ignores the period of infancy when children are protected by maternal antibodies. Secondly they are sensitive to small variations in the force of infection for adults; this quantity is hard to estimate with accuracy. Thirdly they are sensitive to variation in the configuration of the WAIFW matrix about which there is

p_7	λ_7	p_c (%)
95,45	0,0	67,84
97,67	0,1673	78,28
98,81	0,3353	87,24
99,94	1,0821	95,71

Table 6.10
Range of possible values for p_c given variation in the estimated value for λ_7 and β_1 to β_7. The selection of the range of values of λ_7 is documented in table 6.7.

Serological Profile	Demography births - deaths	Case Fatality Rate	WAIFW Matrix Config	Critical Vaccination Proportion	
Ueda	high-low	low	1	0.783	(1)
			2	0.815	(2)
		zero	1	0.782	(3)
		medium	1	0.783	(4)
	medium-low	low	1	0.819	(5)
	low-low	low	1	0.854	(6)
	high-high	low	1	0.787	(7)
	medium-high	low	1	0.823	(8)
	low-high	low	1	0.858	(9)
John	high-low	low	1	0.511	(10)
Boue (Dakar)	high-low	low	1	0.728	(11)
Boue (Popenguine)	high-low	low	1	0.729	(12)

Table 6.11
Sensitivity of the calculated value of the critical vaccination proportion to parameter variation. Calculations were performed using the formula for the critical vaccination proportion for eradication derived in chapter 5. Serological profiles are those shown in figure 6.14. High, medium and low birth rates are those shown in figure 6.3. High and low death rates are depicted in figure 6.4. Case fatality rates and WAIFW matrix configurations are shown in tables 6.3 and 6.6 respectively.

little information. These three factors combine to severely reduce the reliability of the predictions embodied in these estimates of p_a.

6.6 Summary

The overall message from this chapter is that the interrelationships between data sets are as important as the quality of any one data set. Thus a high quality serological profile with large sample sizes covering all age classes is of greatly diminished value if it is not backed up with information on the case fatality rates, birth rates and background death rates which prevail in the community from which the profile was drawn.

Chapter 7

Dynamics Results in the Absence of Control Measures. Sensitivity Analyses.

7.1 Aims of chapter 7.

The aim of this chapter is to investigate the effect of parameter variation on the dynamic behaviour of the full model. In much the same way as section 5 of chapter 6 investigated the sensitivity of A, R_0 and p_c to parameter variation, this chapter studies the outcome of deviation from the baseline parameter sets upon the model's full solution.

7.2 Chapter layout.

The chapter starts with a description of the numerical method by which an approximation to the model's full solution is sought. This is followed by a detailed description of the solution generated by the baseline parameter set. The main body of the chapter is then presented in four parts dealing, respectively, with the following four types of data; birth and death rates, case fatality rates, rate of loss of protection by maternal antibody, and WAIFW matrix configuration. The chapter concludes with a summary of the principal results.

7.3 Numerical methods.

Using a step length of three days, Euler's method is used to solve the equations 4.1 - 4.5 along the characteristic lines t = a + constant. The initial conditions are set by:

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

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

(iii) perturbing the whole system by shifting 20% of the susceptible class into the immune class. The perturbation allows the investigation of the dynamics of the system as it returns to equilibrium.

The initial conditions are calculated using the age-dependent forces of infection that are defined by a given parameter set. After the equilibrium solutions have been found (i), and transformed so as to conform to the requisite stable age distribution (ii), the elements of the WAIFW matrix are calculated using the method described in chapter 6 section 4. After the WAIFW matrix has been calculated, in all subsequent time steps it is used to calculate the forces of infection. This is done using definition 4.9 with the vector describing number of cases by age at the last time step.

7.4 The baseline parameter set.

In this chapter, only the baseline parameter set founded on the serology collected in Thailand (the Ueda baseline parameter set) is used

(Ueda et al 1967). In what follows the properties of this data set are summarised. The birth rates are high and death rates are low (see figs 6.3 and 6.4 for references) and therefore the rate of population growth is rapid. The disease related death rates are at a low level, measured from case fatality rates which have a maximum of 11% amongst 1 - 2 year olds (table 6.3 for values and references). The rate of loss of protection by maternal antibody is set at 2 per year; the average duration of protection by maternal antibody is six months. The WAIFW matrix configuration is that called configuration 1 in table 6.6. Thus heterogeneity in transmission is assumed to be the combination of differences in mixing amongst age groups, and changes in susceptibility according to age. Figure 7.1 shows the number of cases by age and time that are predicted by the model using this set of parameters. The figure shows the solution surface for the Y(a,t) class of the model. The number of cases cycles with a period of approximately two years. The oscillations can be seen to be damping fairly quickly towards an equilibrium age distribution of cases. As the number of new susceptibles is always increasing (due to the positive net population growth rate), there is an underlying trend of increasing numbers of cases each year. However, there are no gross changes in the age distribution of these cases, so a slice cut across the surface at time 20 years would have the same shape as a slice cut at time 1 year. The 'step' between ages 1½ and 2 is caused by the combination of the low estimated value of the force of infection for this age class (λ_2 = .1209) with the fact that by age 1½ practically all children have lost their protection by maternal antibody. Thus there is not the influx of new susceptibles that keeps the number of cases rising in the younger ages. (It seems unlikely that this is a realistic reflection of the true age distribution of cases.) Figure 7.2(a) shows the changing

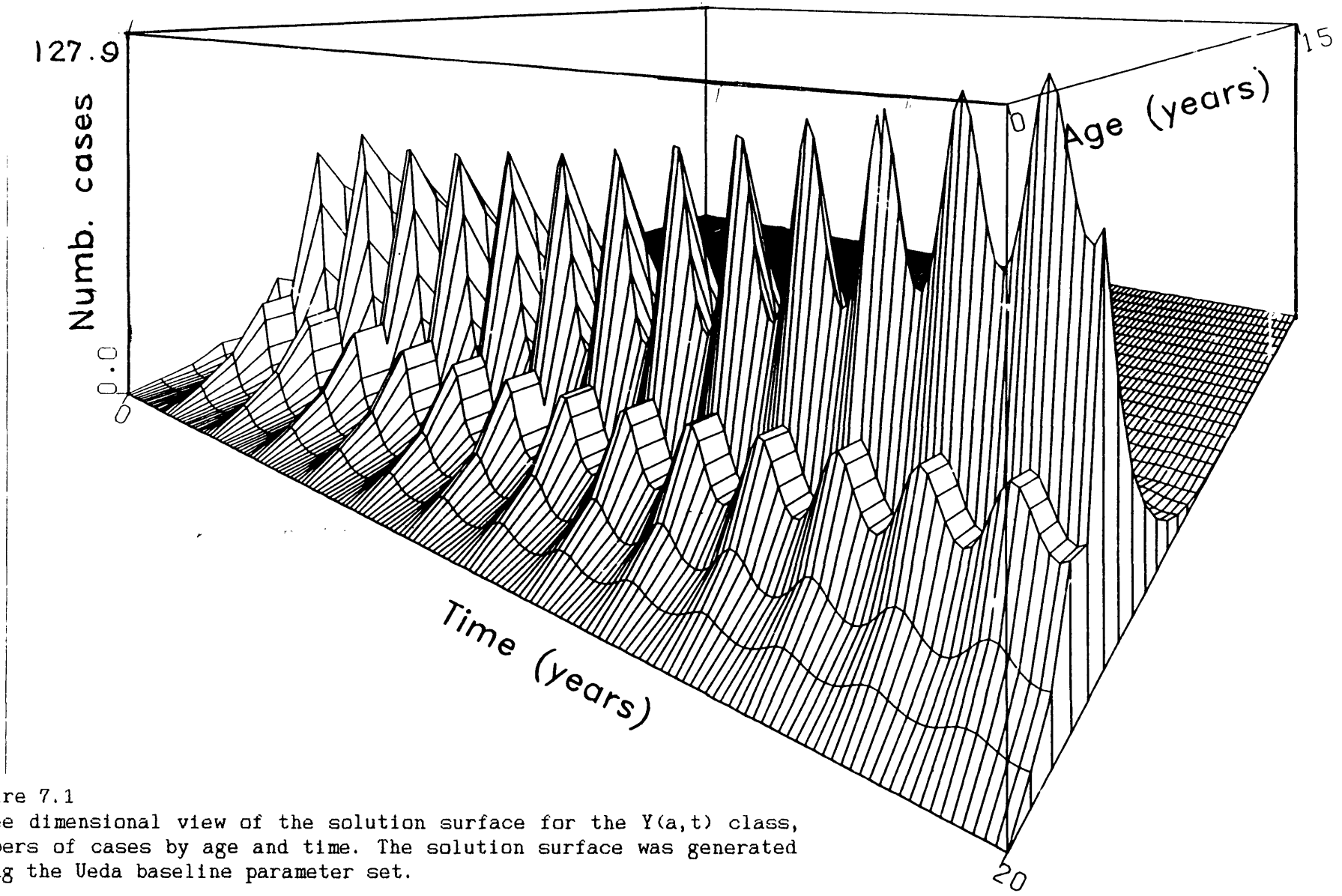


Figure 7.1
Three dimensional view of the solution surface for the Y(a,t) class, numbers of cases by age and time. The solution surface was generated using the Ueda baseline parameter set.

serological profile over the course of 20 years. In an unvaccinated community, people appear as seropositive either because they still have protection from maternal antibody, or because they have experienced measles. The serological profile records the proportion seropositive by age, so that each point on the surface in figure 7.2(a) is found by adding M(a,t) and Z(a,t) (maternal antibody protected and immunes) and dividing the sum by N(a,t) (total population). The oscillations that were so visible in figure 7.1 are still visible in the serological profile. In a year of high incidence people are, on average, infected at a younger age, therefore the serological profile has a steeper slope when compared with a year of low incidence. The third surface to be shown from the solution of the Ueda baseline parameter set (figure 7.2(b)) records the number of people of age a at time t in the excess deaths class. This class represents those who have died from measles who would not yet be expected to have died from some other cause. Individuals enter the class at a rate determined by the number of cases and the age specific case fatality rates, and leave it at an age specific, per capita rate equal to the background death rate as applied to the uninfected members of the community. In figure 7.2(b) there is a rise up to age seven years as a result of the large numbers of cases and high case fatality rate in the young age classes. The graph then falls off as mortality from other causes begins to dominate. Once again the oscillations in the number of cases per year can be seen. Note that the excess deaths class has the best 'memory' of the fluctuations in number and age of cases. Thus each epidemic peak is 'remembered' as a peak in the number of excess deaths amongst those who were case fatalities in that year. The only difference between a year of high incidence and a year of low incidence is whether you get it aged 2 or aged 4. In a year of high incidence, however, many more people

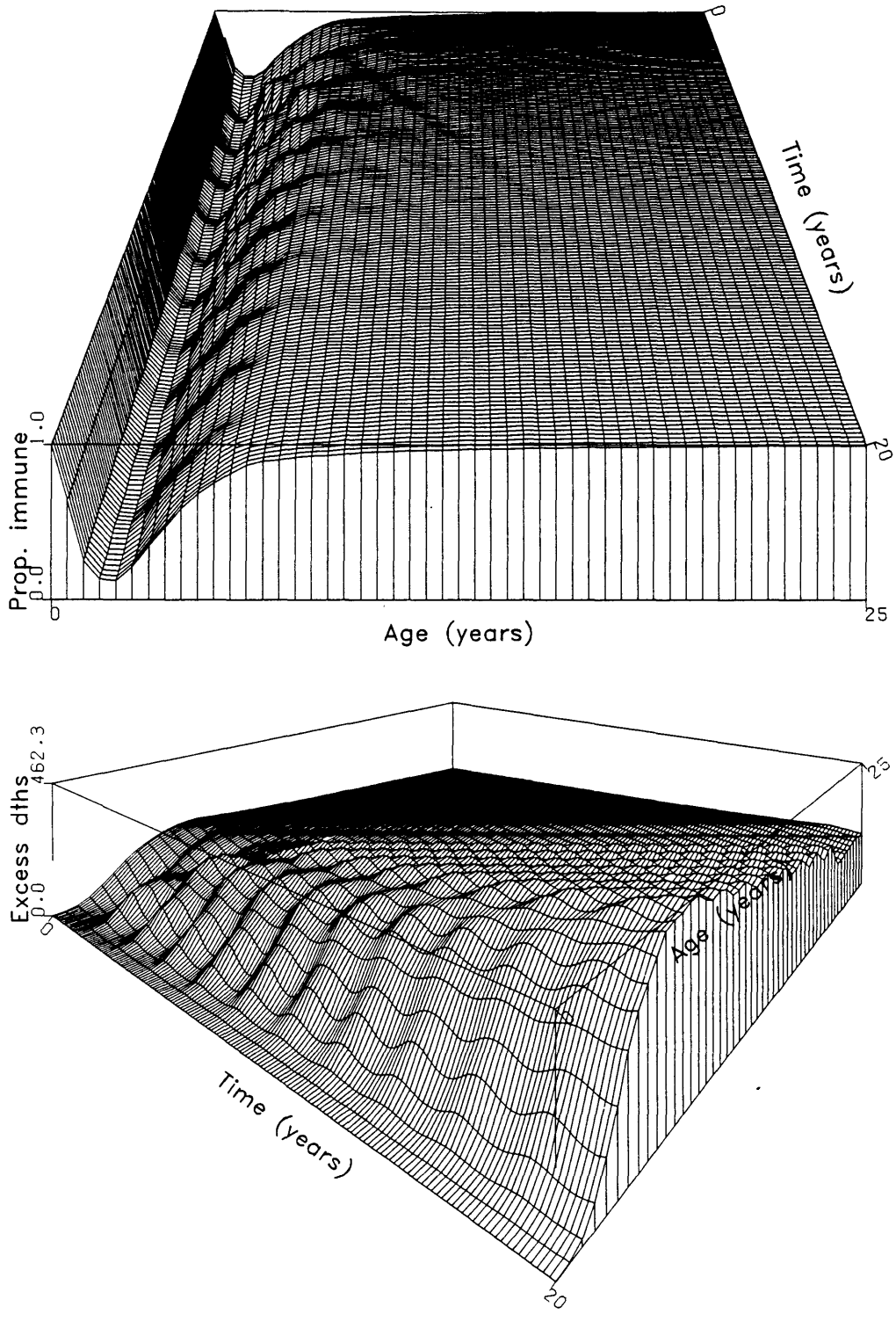


Figure 7.2
(a) Three dimensional view of the changing serological profile through time generated using the Ueda baseline parameter set. Each point on this surface is obtained by adding M(a,t) to Z(a,t) and dividing the sum by N(a,t).

(b) Three dimensional view of the solution surfaces for the E(a,t) class, numbers of excess deaths by age and time. Numbers in this class count individuals who have died of measles who one would not yet expect to have died from some other cause. The solution was generated using the Ueda baseline parameter set.

are killed by the disease than in a year of low incidence because of the much higher case fatality rate amongst young children. It is because of this good memory that there is a deep trough running diagonally across the surface. This represents the very low number of case fatalities generated during the year immediately after the initial perturbation. These surfaces help gain an overview of the solutions generated by the model. However for comparing solutions generated using different parameter sets it is more useful to look at slices through these surfaces and totals over all ages through the course of time.

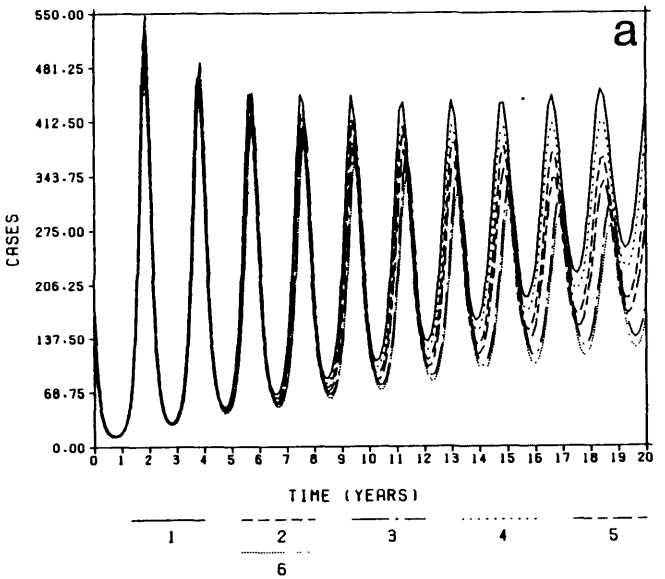
7.5 Demographic processes.

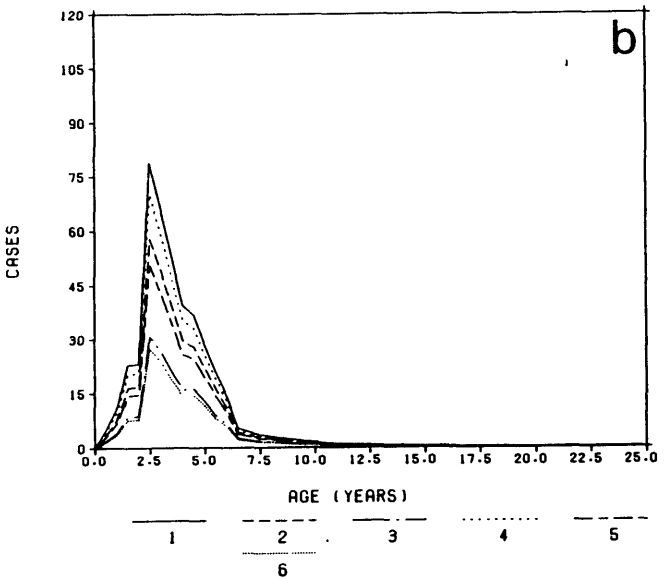
The first set of comparisons to be made considers the effect of changes in birth and death rate on model predictions. The parameters used are those discussed in chapter 6 and illustrated in figures 6.3 and 6.4. A selection of three birth rates and two death rates are combined in six combinations. Attention focuses first on the number of cases that are predicted by each of the six possibilities. Figure 7.3(a) shows the total number of cases over the course of twenty years. Comparing the relative positions of the six lines and the population growth rates associated with each of the six possible combinations, it is easy to see that greater rates of population growth lead to larger numbers of cases. Although the rate of damping is unaltered, the inter-epidemic period is slightly shortened. In figure 7.3(b) the number of cases, by age, at time 20 years is shown for each of the six possibilities. As before the greater the rate of population growth the more cases, but the age distribution of cases is independent of either birth or death rates. This can best be seen in figure 7.3(c) which

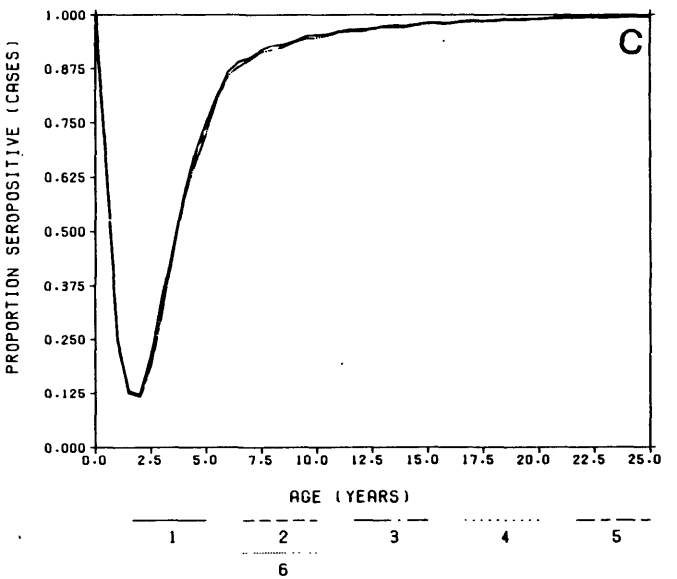
Figure 7.3
Sensitivity of the model's predictions under variation of the vital rates. Results generated using the Ueda baseline parameter set and deviations from it. Actual birth and death rates used are documented in chapter 6 figures 6.3 and 6.4.

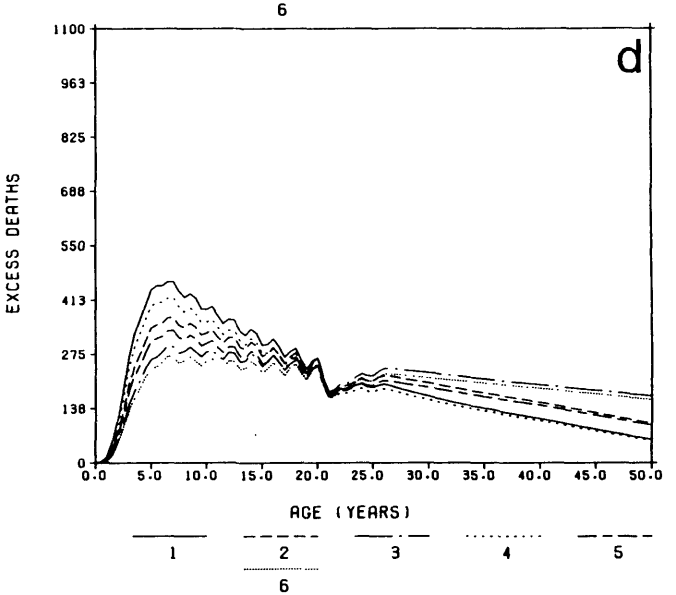
(a) Total cases through time.
(b) Age incidence of measles after twenty years.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection after twenty years.
(d) Numbers by age in the excess deaths class after twenty years.

1	High birth rate, low death rate, population growth rate is	41.9 per 1000 per year
2	Medium birth rate, low death rate, population growth rate is	25.4 per 1000 per year
3	Low birth rate, low death rate, population growth rate is	11.02 per 1000 per year
4	High birth rate, high death rate, population growth rate is	38.09 per 1000 per year
5	Medium birth rate, high death rate, population growth rate is	22.4 per 1000 per year
6	Low birth rate, high death rate, population growth rate is	8.02 per 1000 per year


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4 5 6


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5 6


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5 6


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4 5 6

shows the serological profiles for these same six possibilities. The age distribution of cases is independent of population growth rate because the definition of the force of infection used in generating these results (equation 4.9) assumes that the rate of transmission depends upon the proportion of the population that is infected. Figure 7.3(d) shows the numbers, by age, after 20 years, in the excess deaths class for each of the six possibilities. This class has the best memory of past events in the community. Again each epidemic peak is 'remembered' as a peak in the number of excess deaths amongst those who were case fatalities in that year. This graph also illustrates the process by which the initial conditions are set. At time 20 years there is a confluence of all six lines. Points to the right of this meeting place represent individuals who were in the excess deaths class at the time when initial conditions were set. Thus the order in which the six lines appear conform to the stable age distributions as shown in figure 6.5: from the top downwards the order is 3-6-2-5-1-4. To the left of the crossover lie points representing people who have entered the excess deaths class since the setting of the initial conditions. Here, numbers of excess deaths fall into the same order as the total number of cases, (1-4-2-5-3-6). That is, given identical age distributions a larger number of cases leads to a larger number of excess deaths.

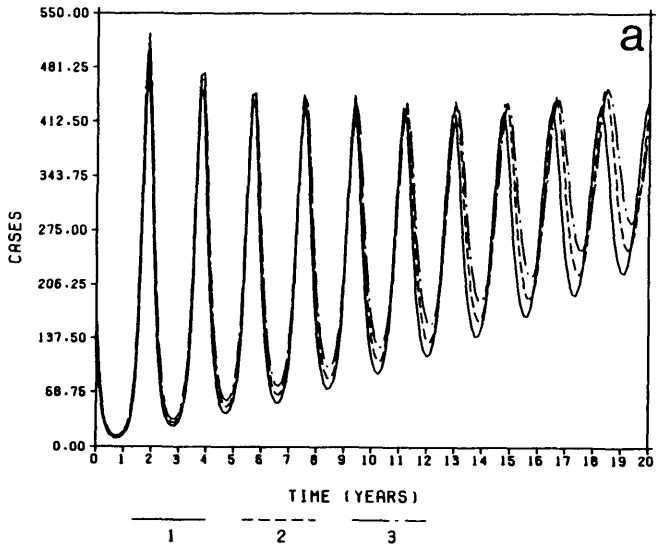
7.6 Case Fatality Rates

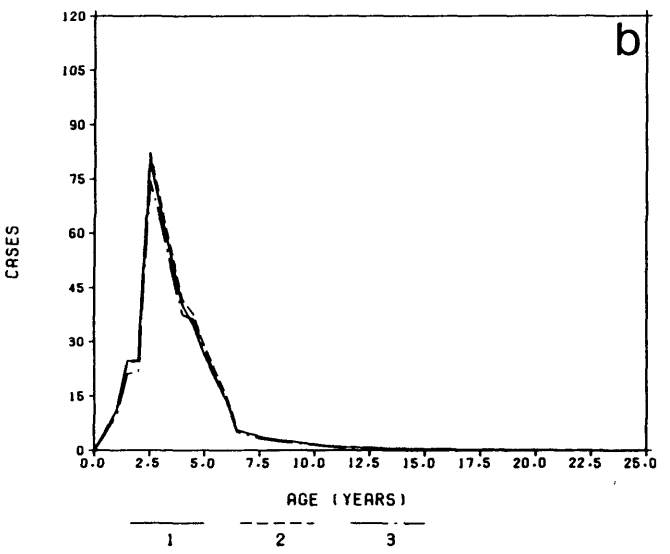
In table 6.3 three sets of case fatality rates and the disease related death rates associated with them are listed. For the dynamical studies of the model the highest of these three had to be omitted because its very high disease related death rate amongst infants (91.01 yr^{-1}) would have

Figure 7.4
Sensitivity of the model's predictions under variation of the case fatality rate. Results generated using the Ueda baseline parameter set and deviations from it. Actual case fatality rates and disease related death rates are documented in chapter 6 table 6.3.

(a) Total cases through time.
(b) Age incidence of measles after twenty years.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection after twenty years.
(d) Numbers by age in the excess deaths class after twenty years

1 Medium case fatality rate
2 Low case fatality rate
3 Zero case fatality rate


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3


b
CASES
120
105
90
75
60
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30
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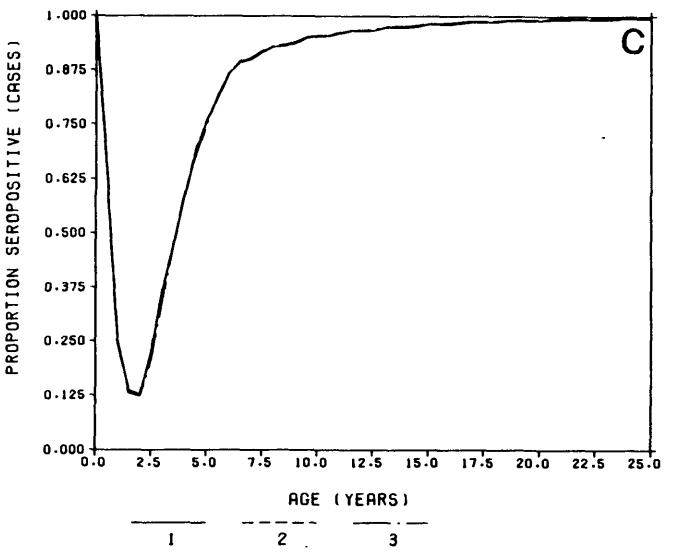
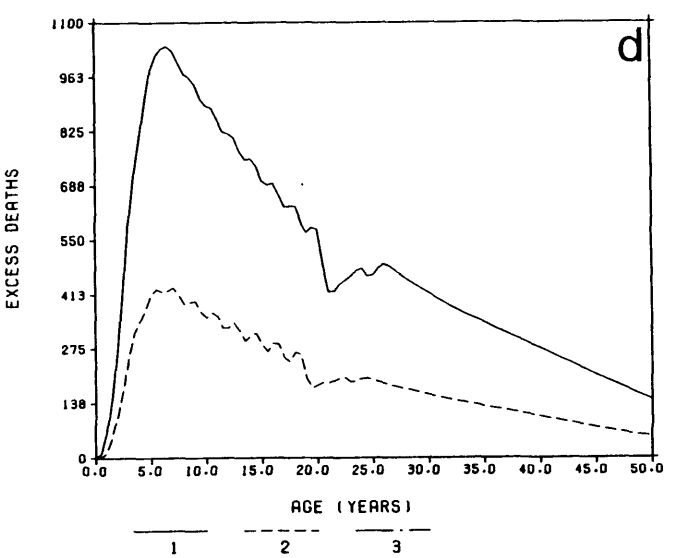
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3

caused severe numerical accuracy problems related to the step length. Thus in what follows three possibilities are considered: medium, low and zero case fatality rates. Here the serological profile is taken as the starting point. Therefore when changes are made to the values of the case fatality rates, the values taken by the forces of infection are also changed. Figure 7.4(a) shows total cases through time for the three cases; medium, low and zero case fatalities. In table 6.5 it was shown that a higher assumed case fatality rate leads to higher estimated values for the forces of infection. It is these slightly higher forces of infection that lead to the slightly larger numbers of cases, and shorter inter-epidemic periods associated with higher case fatality rates. The very slight differences in numbers of cases by age in figure 7.4(b) illustrate the fact that in order to keep a constant serological profile, the assumed force of infection must be changed to account for changes in the case fatality rates. Figure 7.4(c) illustrates the constancy of the serological profile under these restrictions. Figure 7.4(d) shows excess deaths by age after 20 years for the medium and low case fatality rates. The example where the case fatality rate is set to zero does not register on this graph. As would be expected there are many more excess deaths when the case fatality rate is assumed to be of medium severity, yet the overall shape of the curve is similiar for the low and medium examples.

7.7 Rate of loss of protection by maternal antibody.

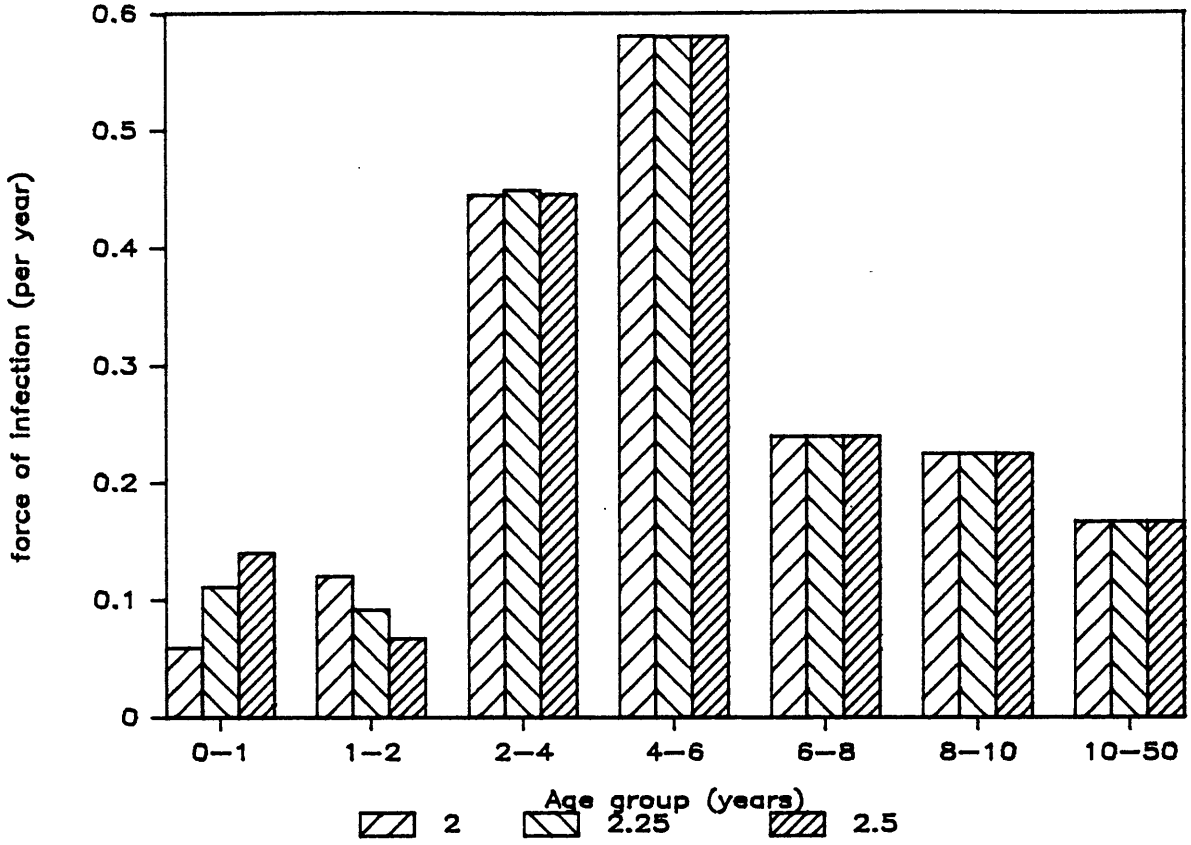
In this section the insistence on keeping a fixed serological profile as a starting point is relaxed. Two sets of experiments are shown: the first varies the rate of loss of protection by maternal antibody δ and the

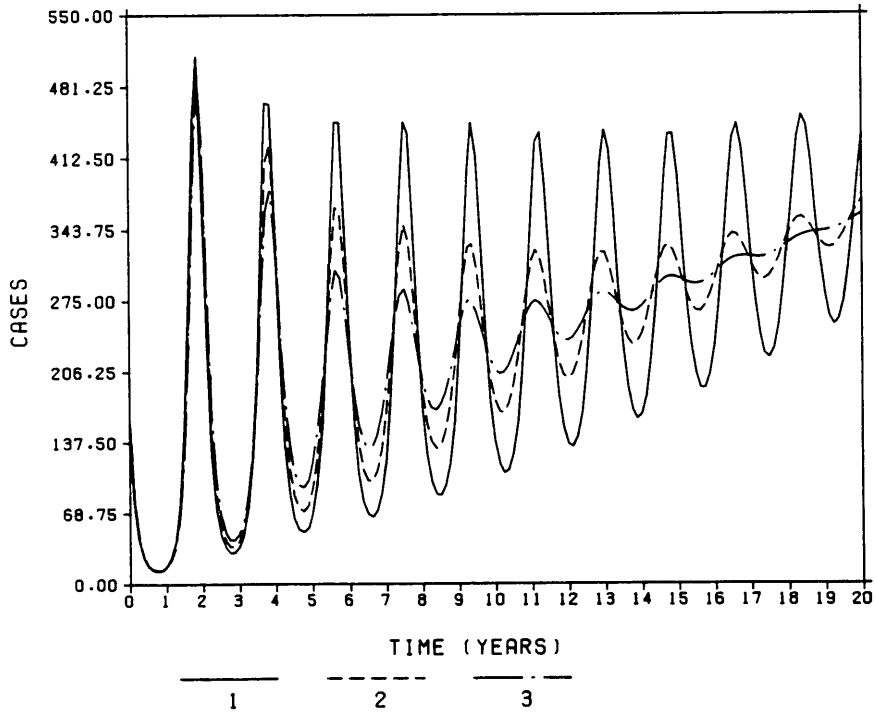
forces of infection λ so that the serological profile is of fixed shape; the second varies δ but not λ. This deviation from the normal procedure is allowed so that the underlying processes generating the numerical results can be better understood. Figures 7.5, 7.6 and 7.7(a) and (b) deal with the first experiment where, as previously, the serological profile is fixed at the starting point (t = 0). Three possible values for the rate of loss of maternal antibodies are investigated; δ=2, δ=2.25, and δ=2.5. These correspond to average durations of maternal antibody protection of 6 months, 5.3 months and 4.8 months respectively. A broader range of values for δ was not investigated because if δ is set to any greater value either negative λs or negative βs are generated. Figure 7.5 shows the three sets of forces of infection (estimated from the Ueda serology) associated with each of the three different values for the duration of maternal antibody protection. Note that for δ=2.25 and δ=2.5 the force of infection amongst infants is greater than amongst 1-2 year olds. Figure 7.6 shows total cases through time for each of these three cases. Notice also the dramatic increase in the rate of damping for the increased values of δ. Figure 7.7(a) shows cases by age at time 20 years and illustrates the strange age distributions of cases predicted when using the two larger values of δ. It is perhaps surprising that such 'lumpy' age distributions of cases should give rise to the smooth, uniform serological profiles shown in figure 7.7(b); However it is important to remember that the forces of infection were chosen specifically to keep a uniform serological profile. In order to try and understand the damping effect illustrated in figure 7.6, the experiment was repeated without altering the forces of infection. Figure 7.8(a) shows total cases through time as predicted by three separate runs of the programme, differing only in the value of the rate of loss of

Figure 7.5
Forces of infection estimated from Ueda's serological profile under three different assumptions about the rate of loss of protection by maternal antibodies.

Figure 7.6
Sensitivity of the model's predictions under variation of the rate of loss of protection by maternal antibodies, δ. In this example the usual procedure of keeping the serological profile as the fixed starting point is adhered to. Thus, when δ varies, the age dependent λs vary as illustrated in figure 7.4. Results generated using the Ueda baseline parameter set and deviations from it. Total cases through time.

1 δ =.2.0
2 δ = 2.25
3 δ = 2.5


force of infection (per year)
0.6
0.5
0.4
0.3
0.2
0.1
0
0–1
1–2
2–4
4–6
6–8
8–10
10–50
Age group (years)
2
2.25
2.5


CASES
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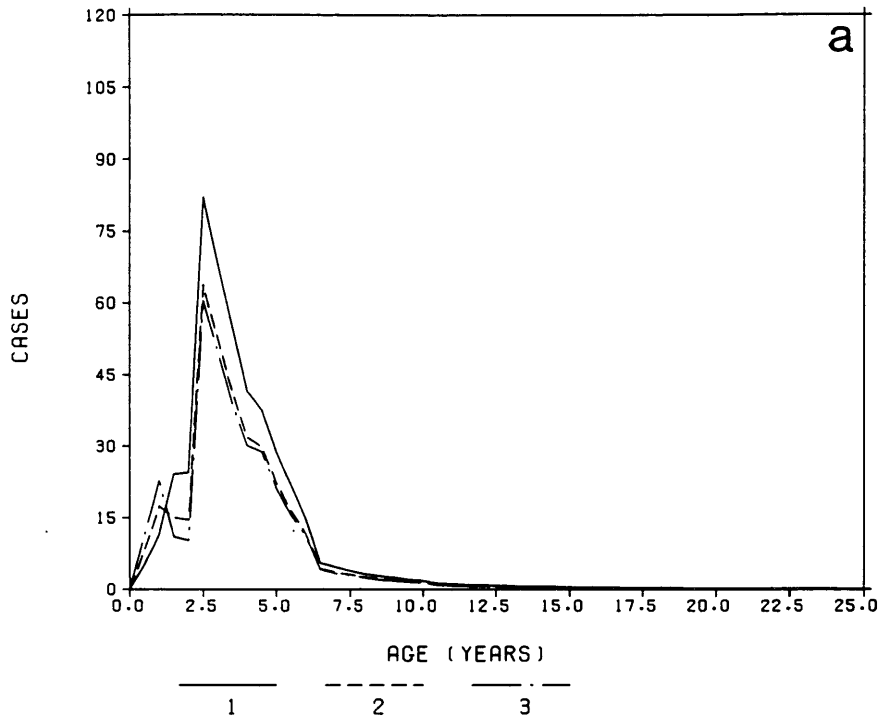
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1
2
3

Figure 7.7
Sensitivity of the model's predictions under variation of the rate of loss of protection by maternal antibodies, δ. In this example the usual procedure of keeping the serological profile as the fixed starting point is adhered to. Thus, when δ varies, the age dependent λs vary as illustrated in figure 7.4. Results generated using the Ueda baseline parameter set and deviations from it.

(a) Age incidence of measles after twenty years.
(b) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection after twenty years.

1 $\delta = 2.0$
2 $\delta = 2.25$
3 $\delta = 2.5$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7.5
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17.5
20.0
22.5
25.0
AGE (YEARS)
1
2
3

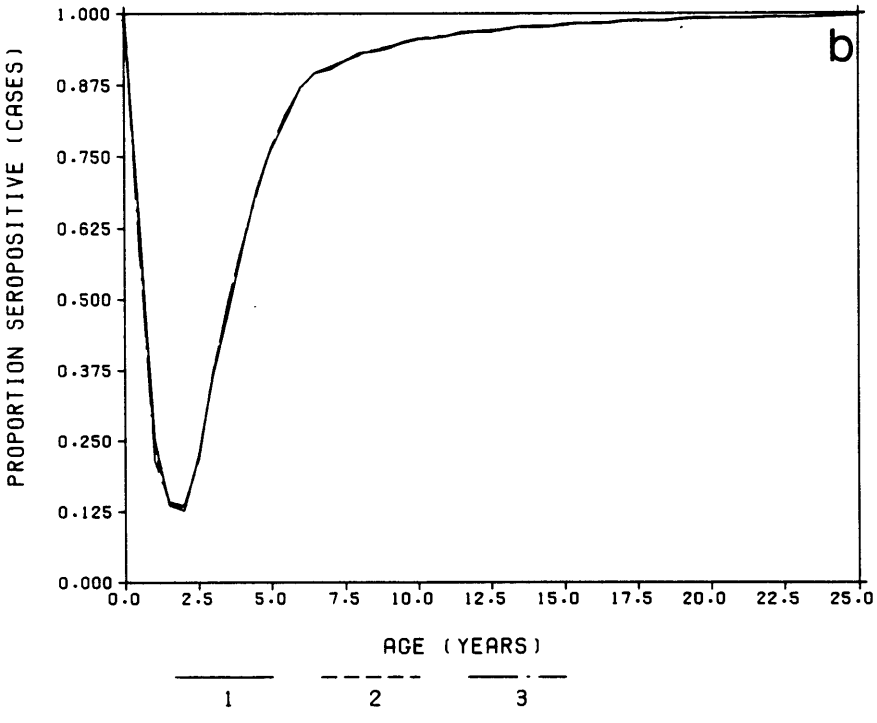
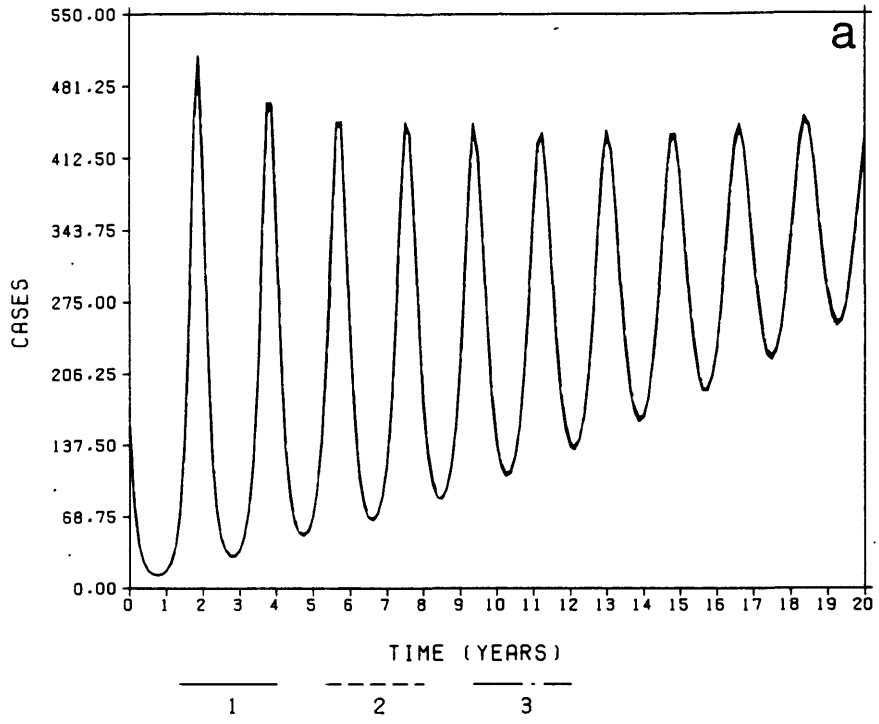
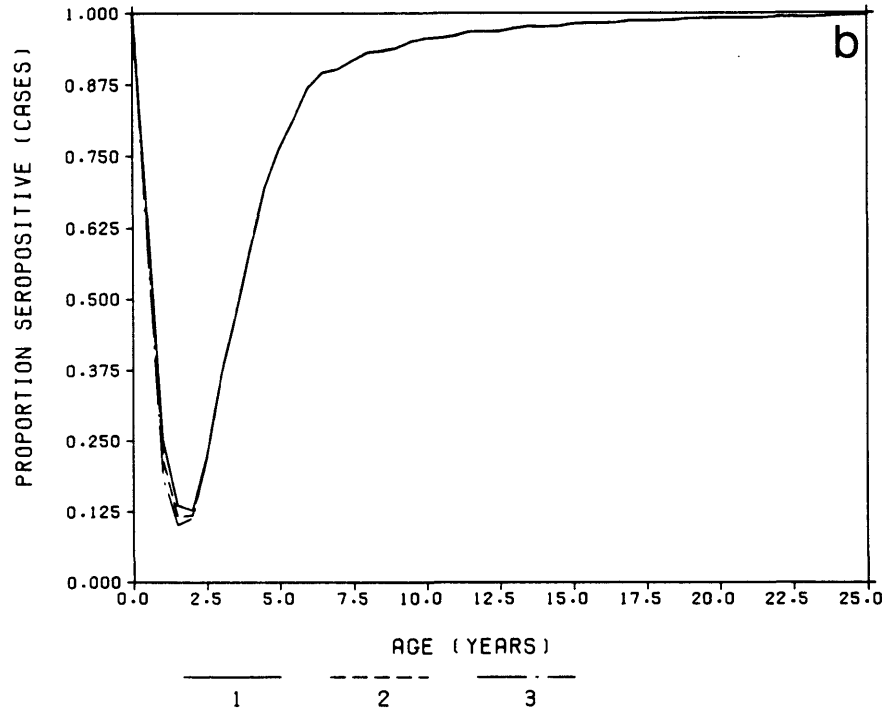

b
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
AGE (YEARS)
1
2
3

Figure 7.8
Sensitivity of the model's predictions under variation of the rate of loss of protection by maternal antibodies, δ, without changing the forces of infection. Thus, in this case **the serological profile is not fixed.** Results generated using the Ueda baseline parameter set and deviations from it.

(a) Total cases through time over the course of twenty years.
(b) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection after twenty years.

1 $\delta = 2.$
2 $\delta = 2.25$
3 $\delta = 2.5$


a
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
CASES
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1
2
3


b
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
PROPORTION SEROPOSITIVE (CASES)
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2
3

protection by maternal antibody. Again δ was varied from 2 to 2.5. This result shows that the damping illustrated in figure 7.6 is a result of the relative values of the forces of infection, and not caused by changes in δ. Figure 7.8(b) emphasises the fact that for this latest experiment the serological profile was not held constant.

7.9 Who Acquires Infection from Whom (WAIFW) matrix configuration.

In chapter 6 (table 6.6) two different configurations of the WAIFW matrix were shown. In this, the final section of this chapter, the impact of changing the WAIFW matrix configuration on the model's solution is considered. Figure 7.9(a) shows total cases through time for the two configurations under consideration. The second configuration (representing the assumption that all age heterogeneity is the result of age related changes in susceptibility) results in a longer inter-epidemic period. Figure 7.9(b) shows serological profiles at the peak of the last epidemic for each of the two configurations. The figure shows that the age distribution of cases is not affected by the WAIFW matrix configuration.

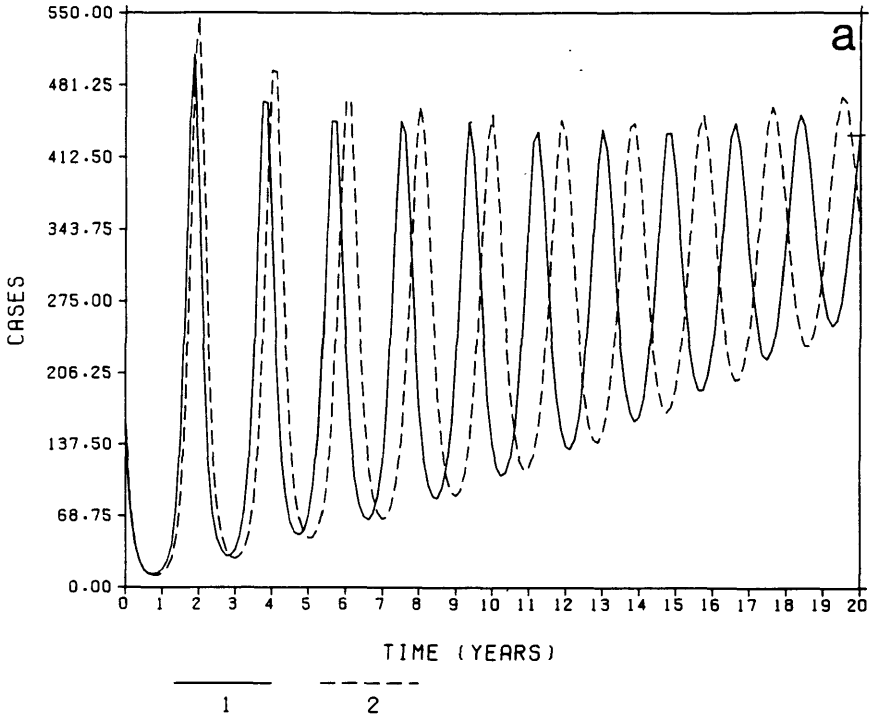
7.10 Summary

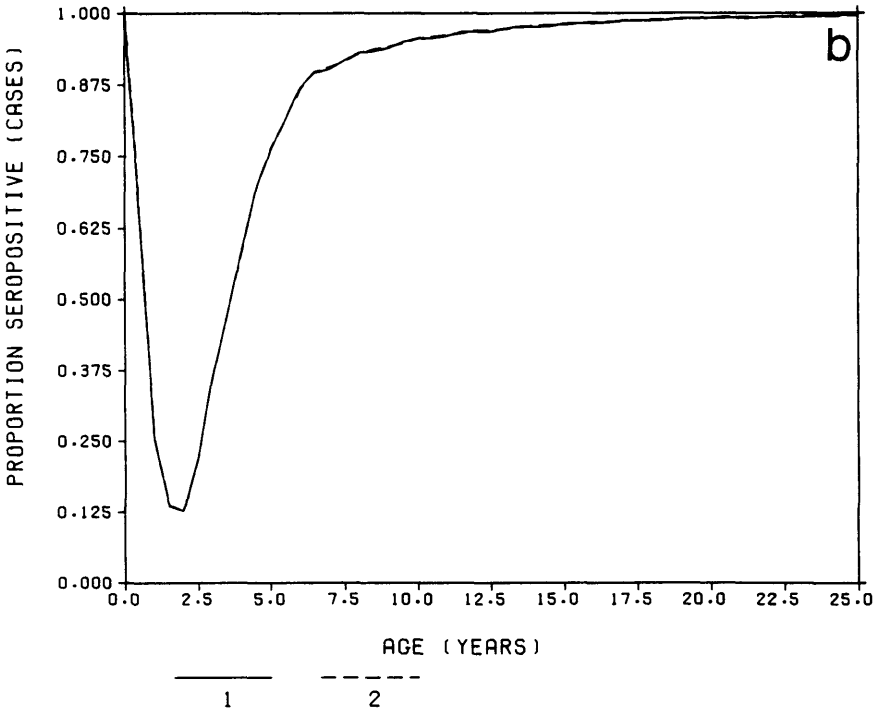
The chapter has studied the affect of parameter variation upon the solution of the full time- and age-dependent model. It has been shown that a higher population growth rate leads to a larger number of cases, but does not affect the age distribution of those cases. Changes in the case fatality rate only effect the model's dynamics slightly. These changes are brought about indirectly through the changes in the force of infection made

Figure 7.9
Sensitivity of the model's predictions under variation of the configuration of the WAIFW matrix. Results generated using the Ueda baseline parameter set and deviations from it. The matrix configurations considered are those shown in table 6.6

(a) Age incidence of measles after twenty years.
(b) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection after twenty years.

1 Configuration 1
2 Configuration 2


a
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
CASES
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1
2


b
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
PROPORTION SEROPOSITIVE (CASES)
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2

in order to keep a uniform serological profile. Similarly, changes in the rate of loss of protection by maternal antibody do not affect the model's dynamics. However the gross changes in the relative values of the forces of infection amongst the first few age classes (made so as to preserve the shape of the serological profile) have a marked effect upon the rate of damping of the oscillations. It is not clear why this should be so, but the assumption is that the relationship between the values of the force of infection is important. Equally unclear is the reason why two different WAIFW matrix configurations should lead to two very different inter-epidemic periods. These last two points require further investigation, (possibly analytic) perhaps in the context of a 'stripped down' model with less complexitity (e.g. population growth and case fatalities).

Chapter 8

Dynamics Results with Control Measures.

Assessment of Different Vaccination Strategies.

8.1 Aims of chapter 8.

The overall aim of this chapter is to study the impact of different mass vaccination strategies upon measles morbidity and mortality. This is attempted by comparing the model's behaviour when different regimes of control by vaccination are introduced. This objective is approached by two groups of experiments. The first of these continues the theme of the previous chapter, and considers the sensitivity of the model's predictions to changes in parameter values. The effects of variation in the rate of loss of protection by maternal antibody are studied with particular reference to the window problem. As before, the method used is to study the effects of deviations from a baseline parameter set. The second group of experiments compares the outcome of a range of different vaccination strategies. Throughout the chapter, special attention is paid to four ways of summarising model predictions, namely; total cases through time, cases by age, age-specific serology, and excess deaths by age. In order to study the effect of mass vaccination when applied to communities displaying different patterns of age specific exposure to infection, in this chapter two different baseline parameter sets with different age-specific forces of infection are used.

8.2 Chapter layout.

The chapter starts with an explanation of the way in which the protection of susceptibles by vaccination is included in the model. Then an overview of the results for the Boué baseline parameter set is presented. As in chapter 7 this is presented via the discussion of surfaces describing the full solution of the equations for a selection of the model's compartments. After a discussion of the actual levels of coverage currently being achieved in developing countries, attention focuses on the impact of vaccination upon the model's dynamics. Section 7 of the chapter then deals with model sensitivity to parameter variation. Comparisons are made between parameter sets based on the predicted impact of a vaccination regime of 50% of 9 month olds. Variation in the rate of loss of protection by maternal antibody is studied for both baseline parameter sets. Attention then turns to evaluation of different regimes of immunisation. These fall into three groups. The first, referred to as the 'one stage programmes', consists of vaccinating a certain proportion of individuals within a community at a given age once and once only. The second group, the 'two stage programmes', consists of vaccinating the community twice. The third group, the 'two-phase programmes', start off with a one stage programme for a given number of years and then switch to a different one stage programme.

8.3 The inclusion of vaccination in the model.

Anderson and May (1983) include vaccination in their model as a rate process. Thus when they say 'vaccinate 85% of 1 year olds' they do indeed

vaccinate 85% of children between 1 and 2 years old each year. This is included in the model by introducing an age specific instantaneous rate c(a) which describes the vaccination schedule, and acts to remove individuals from the susceptible class X to the immune class Z. Thus equations 4.2 and 4.5 become:

$$\frac{\partial X}{\partial a} + \frac{\partial X}{\partial t} = \delta\, M(a,t) - (\mu(a) + \lambda(a,t) + \mathbf{c(a)})\, X(a,t) \qquad (8.1)$$

$$\frac{\partial Z}{\partial a} + \frac{\partial Z}{\partial t} = \gamma\, Y(a,t) + \mathbf{c(a)}\, X(a,t) - \mu(a)\, Z(a,t) \qquad (8.2)$$

where for an annual vaccination proportion p

$$c(a) = \begin{cases} 0 & 0 \leq a < 1 \\ -\ln (1 - p) & 1 \leq a < 2 \\ 0 & 2 \leq a < L \end{cases}$$

However in this study it was desirable to be more precise about the exact age at which individuals were to be vaccinated so as to be able to assess the effect of slight shifts in the age at which vaccine is administered. For example, in section 5 the difference between vaccination at 6 months and at 9 months is studied. Therefore vaccination of 85% of 1 year olds is assumed to take place within 3 days of their 1st birthday. As the step length in the numerical procedure employed to solve the partial differential equations is set at three days, vaccination is very simply introduced into the simulation programme.

8.4 The Boué baseline parameter set.

It is most useful to describe the Boué baseline parameter set through comparison with the baseline parameter set used in the previous chapter - the Ueda baseline parameter set. The difference lies in the age-dependent forces of infection and the rate of loss of protection by maternal antibody.

The forces of infection are depicted in figure 6.14 (a) and (c), and tabulated in table 6.4. The Boué data show much higher forces of infection amongst children under 5 years old, but a low force of infection for everybody over 5. In comparison the Ueda data yield a more homogenous range of forces of infection. In the Boué baseline parameter set the rate of loss of protection by maternal antibody is assumed to be 4 yr^{-1} (i.e. average duration is 3 months), whilst for the Ueda baseline parameter set the parameter δ is set to 2 yr^{-1} implying an average duration of protection by maternal antibody of 6 months. Figures 8.1, 8.2 and 8.3 show three dimensional surfaces describing the number of cases, the proportion seropositive and the number of excess deaths through age and time for both baseline parameter sets. The high force of infection for the Boué data is reflected in the very steep rise in the number of cases by age, and the concentration of cases amongst young individuals. Epidemics are more frequent than with the Ueda data, and the oscillations damp more quickly towards the equilibrium age distribution of cases. This rapid damping can be seen when comparing the serological profiles through time for the two parameter sets. The Ueda serology has much more visible ripples than the Boué, and (as mentioned in the previous chapter) these reflect the fact that in epidemic years, individuals are, on average, infected at a younger age. The other point to note when comparing serological profiles is the much greater severity of the window problem in the Boué serology. The rise in the proportion seropositive is so rapid that a maximum of just over 50% of any cohort are susceptible simultaneously. This is to be compared with the Ueda serology where the 'trough' of susceptibility is much deeper. The third set of surfaces for comparison show excess deaths through time and age. In order to interpret the differences between these two surfaces it is

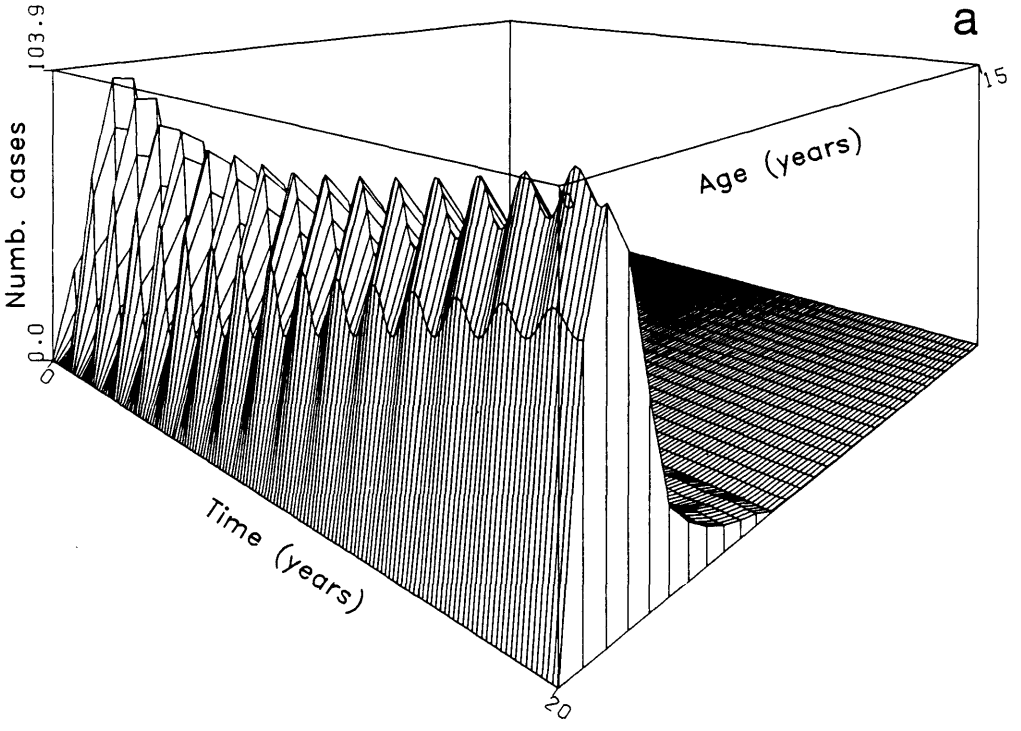
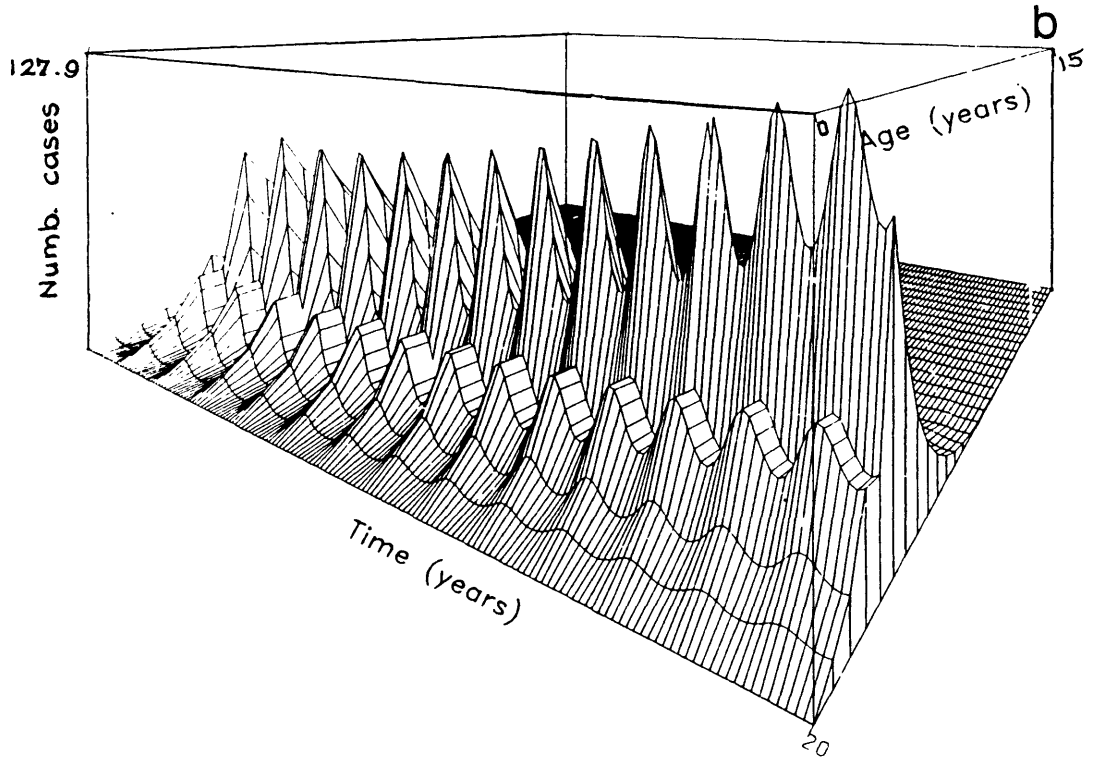


Figure 8.1
Three dimensional views of solution surfaces for the Y(a,t) class, numbers of cases by age and time. Solution surfaces are shown generated using both baseline parameter sets to allow comparison of the two.
(a) Solution for the Boué baseline parameter set.
(b) Solution for the Ueda baseline parameter set.
The solutions were generated using the numerical method described in section 7.3



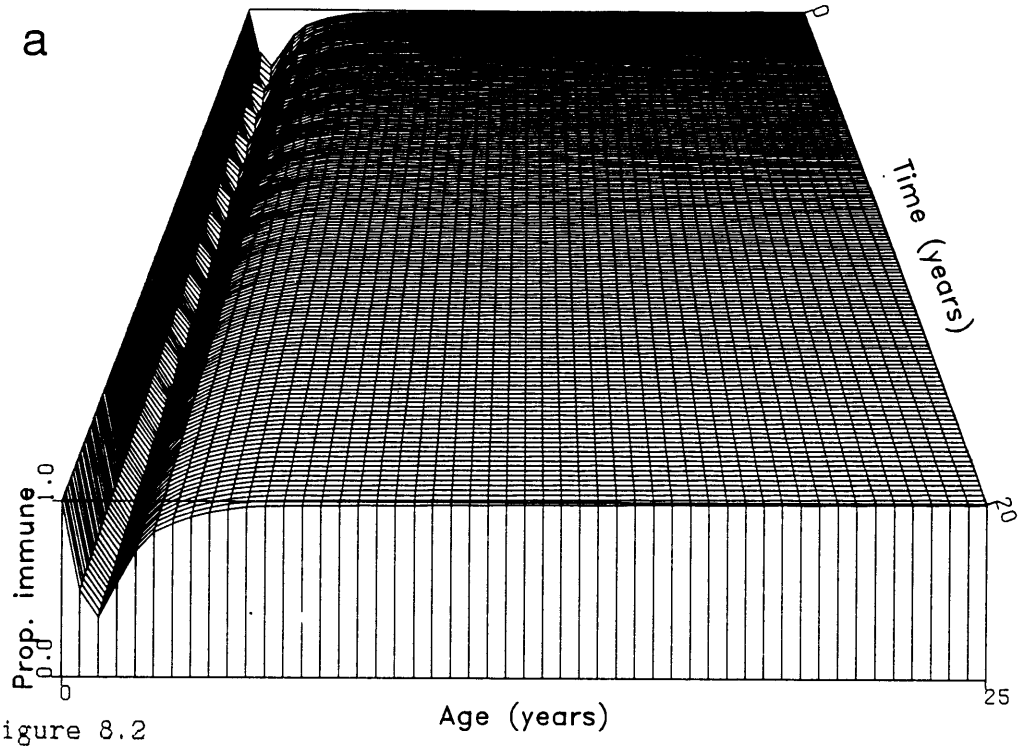
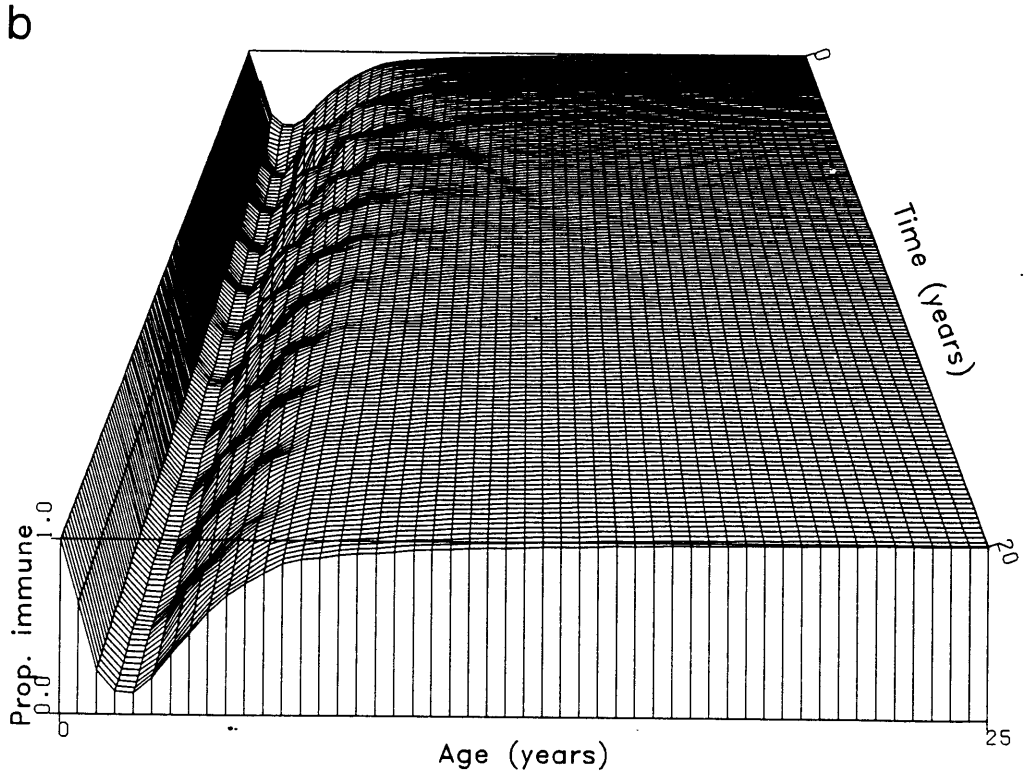


Figure 8.2
Three dimensional views of the changing serological profiles through time generated by the two baseline parameter sets. Each point on these surfaces is obtained by adding M(a,t) to Z(a,t) and dividing the sum by N(a,t).
(a) Solution for the Boué baseline parameter set.
(b) Solution for the Ueda baseline parameter set.



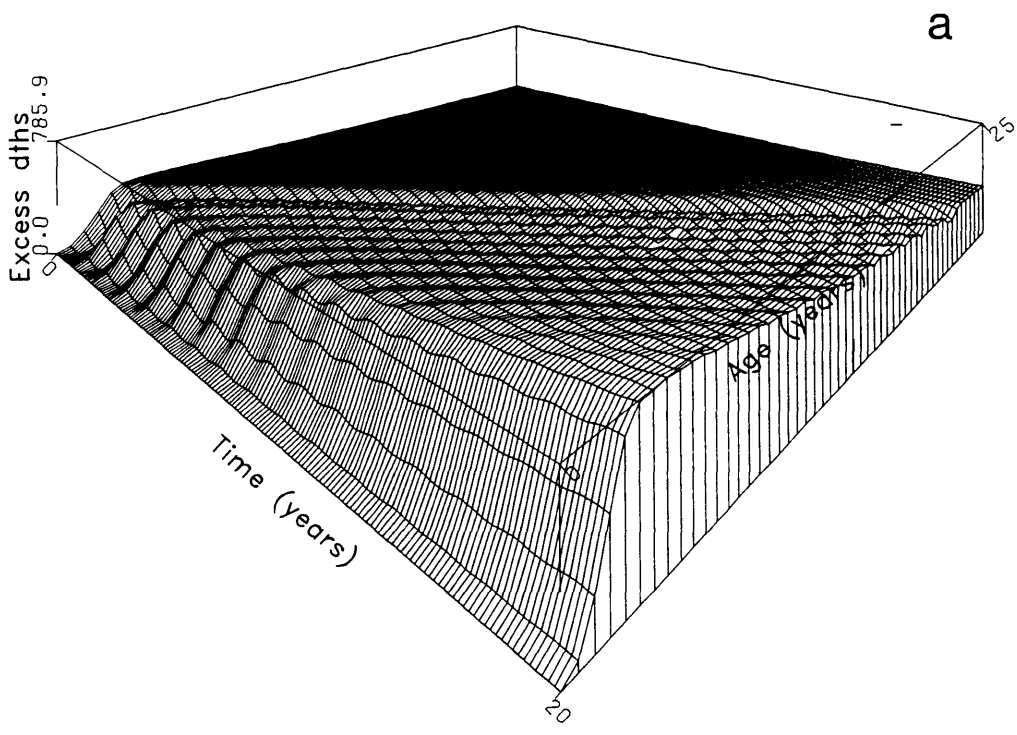
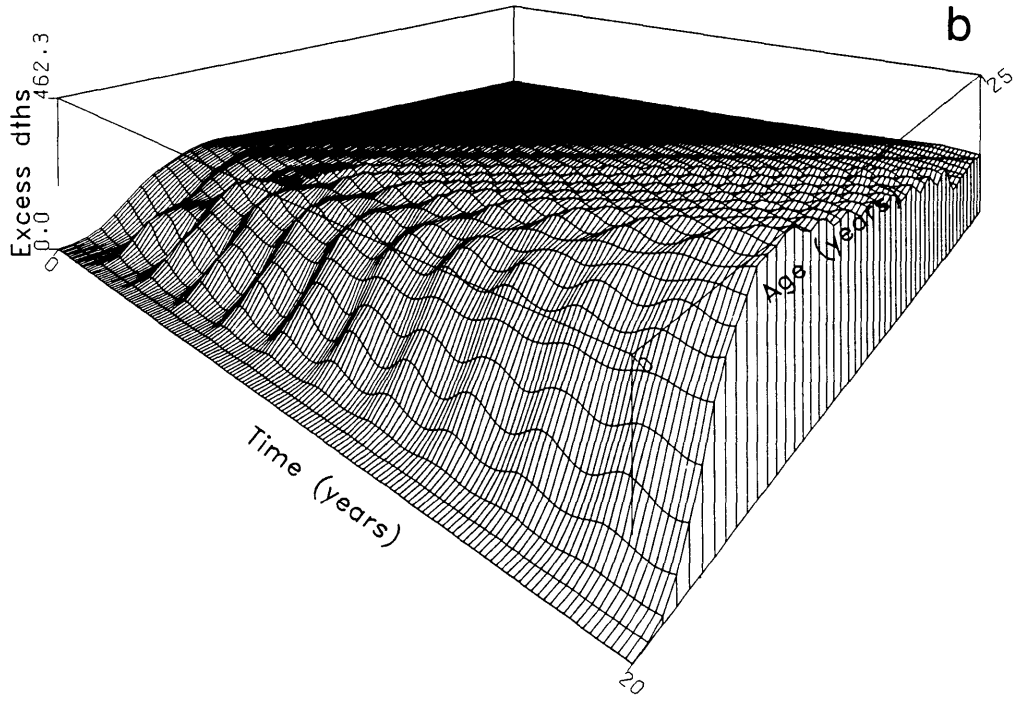


Figure 8.3
Three dimensional views of the solution surfaces for the E(a,t) class, nubers of excess deaths by age and time. Numbers in this class count individuals who have died of measles who one would not yet expect to have died from some other cause.
(a) Solution for the Boué baseline parameter set.
(b) Solution for the Ueda baseline parameter set.



necessary to note that the axis on figure 8.3(a) rises to a value of 758.9, and on figure 8.3(b) the maximum value is 462.3. Both baseline parameter sets assume the same (low) disease related death rates, so this difference in the numbers of excess deaths is solely the result of the difference in the age distributions of cases.

8.5 Vaccination coverage rates.

One of the beneficial achievements of the Expanded Programme for Immunisation at the W.H.O. has been the design and dissemination of a statistical protocol for the estimation of vaccine coverage, known as the EPI cluster sampling technique. The protocol has provided a standard technique for finding out what percentage of children in a target age group have received vaccine. Figure 8.4 shows the results of all the coverage surveys using this method that have been published by E.P.I. since January 1985. The figures would imply that, at the moment, certain developing countries can achieve coverage levels of between 50% and 75%. The W.H.O. recommended age for the administration of measles vaccine is 9 months.

8.6 The effect of vaccination.

Figures 8.5(a) to (e) and 8.6(a) to (e) show the effect of a vaccination campaign which successfully immunises 50% of susceptibles at the age of nine months. Figure 8.5 shows effects on a community where disease transmission is described by the Boué parameter set and figure 8.6 shows the predicted consequences for a community for whom the Ueda parameter set applies. Vaccination of 50% of those susceptibles aged nine months is

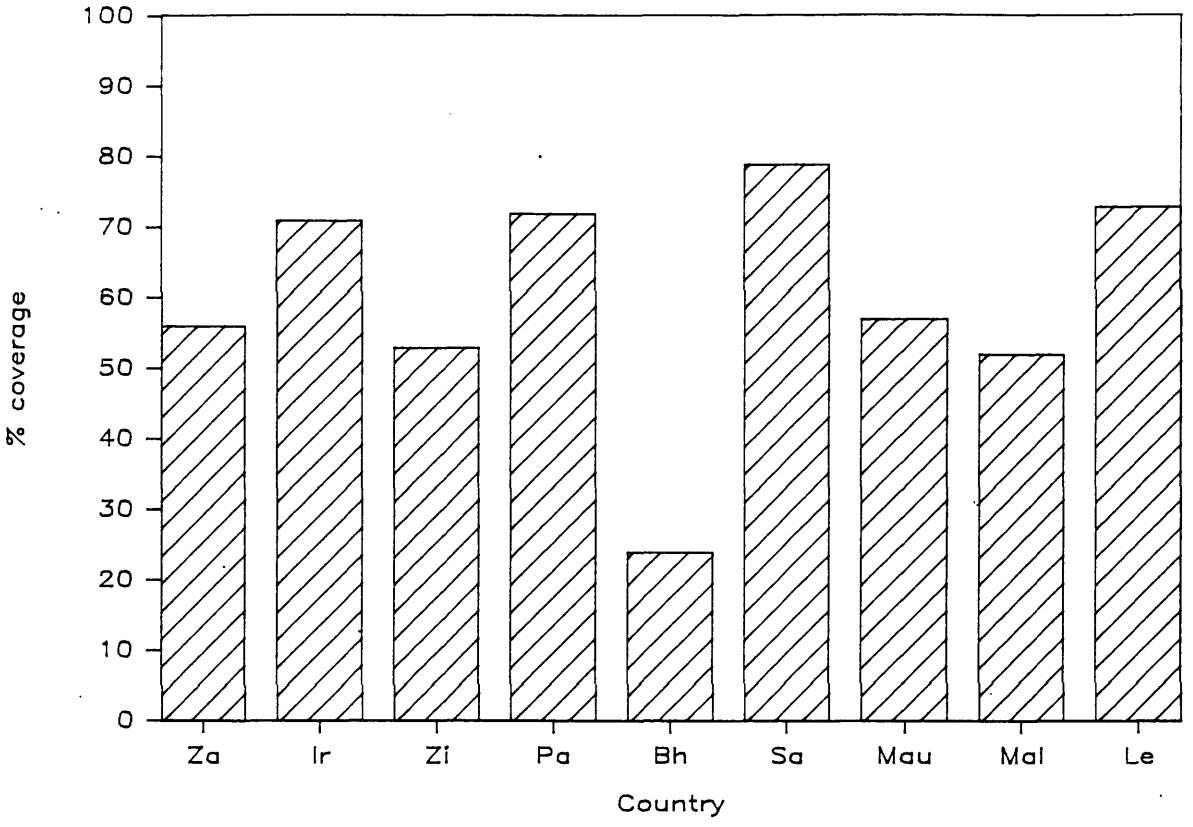


Figure 8.4
Coverage with measles vaccine in the 12-23 month age group. Data collected using the EPI cluster sampling technique, and reported by EPI Geneva since January 1985.

Za Zambia (E.P.I. 1985a)
Ir Islamic Republic of Iran (E.P.I. 1985b)
Zi Zimbabwe (E.P.I.1985c)
Pa Pakistan (E.P.I.1985d)
Bh Bhutan (E.P.I. 1986a)
Sa Saudi Arabia (E.P.I. 1986b)
Mau Mauritius (E.P.I. 1986c)
Mal Malawi (E.P.I. 1986d)
Le Lesotho (E.P.I. 1986e)

introduced after the simulation has been running for four years. Figure 8.5(a) shows that the vaccination campaign acts to reduce the number of cases, but not by as much as 50% because some children are still protected by maternal antibody at the age of nine months, and because some cases occur before the age of vaccination. The inter-epidemic period is also affected by mass immunisation in that it lengthens. Straight after the introduction of vaccination there is a particularly long period of low incidence: this is discussed in detail at a later stage in this chapter. Figure 8.5(b) shows the number of cases by age before and after the introduction of vaccination. The number of cases declines, and there is a shift in the age distribution towards the older ages. There is a slight increase in the number of cases in people over five years old. Figure 8.5(c) shows the proportion who are seropositive as a result of infection at the end of the simulation. The figure illustrates the easing of the window problem that is brought about by low-to-moderate levels of vaccination. The proportion serologically positive, either through successful vaccination or through having had the disease is shown in figure 8.5(d); the proportion still susceptible - the area above the line - remaining approximately the same after the introduction of vaccination, but with a different age distribution. The last graph in figure 8.5 shows the numbers in the excess deaths class. The numbers in this class are reduced by the introduction of mass immunisation. This is a consequence of the reduced number of cases, and the fact that these cases are occuring, on average, at an older age when the case fatality rate is lower. Turning to consider the same five graphs based on the results generated using the Ueda data, the same overall effects can be seen. However in figure 8.6(a) the immediate dynamic response to the introduction of mass vaccination is slightly different; this

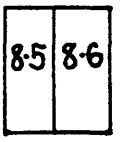
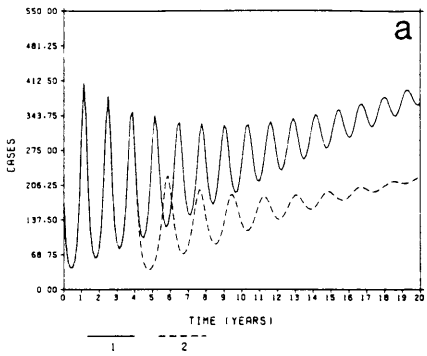


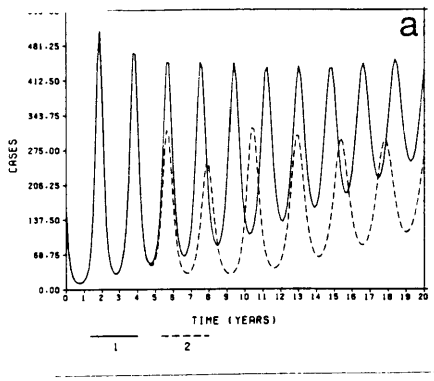
Figure 8.5
The effects of introducing vaccination upon the model's predictions when using the Boué baseline parameter set.
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Proportions seropositive through the presence of maternal antibodies, naturally acquired immunity infection or as a result of successful vaccination. Taken at the time of the peak of the last epidemic.
(e) Numbers by age in the excess deaths class at the peak of the last epidemic.

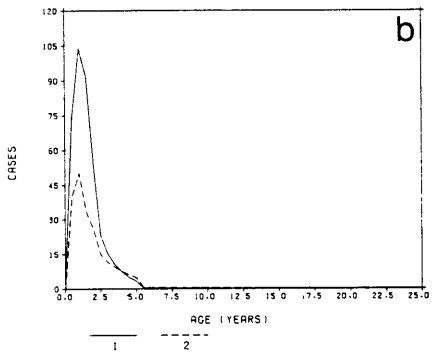
1 Without vaccination. The peak of the last epidemic is at time t = 19.25 years.
2 With vaccination of 50% of 9 month old susceptibles starting from time t = 4 years. The peak of the last epidemic is at time t = 18.5 years.

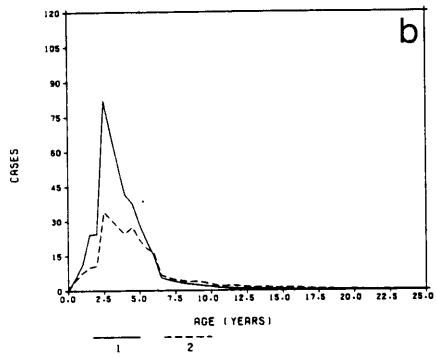
Figure 8.6
The effects of introducing vaccination upon the model's predictions when using the Ueda baseline parameter set.
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired through infection. Taken at the time of the peak of the last epidemic.
(d) Proportions seropositive through the presence of maternal antibodies, naturally acquired immunity through infection or as a result of successful vaccination. Taken at the time of the peak of the last epidemic.
(e) Numbers by age in the excess deaths class at the peak of the alst epidemic.

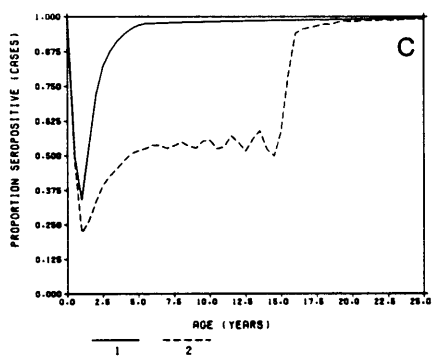
1 Without vaccination. The peak of the last epidemic is at time t = 18.75 years.
2 With vaccination of 50% of 9 month old susceptibles starting from time t = 4 years. The peak of the last epidemic is at time t = 18 years.

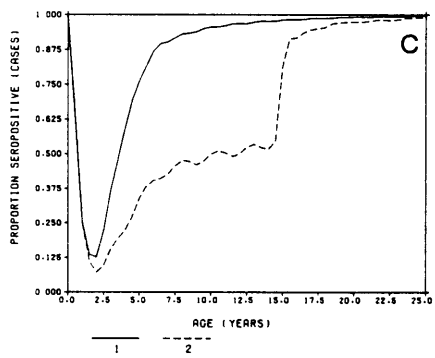

a
CASES
TIME (YEARS)
1
2

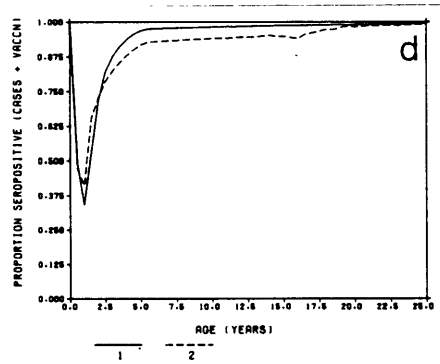

a
CASES
TIME (YEARS)
1
2

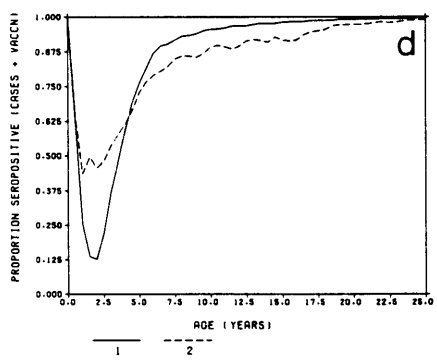

b
CASES
AGE (YEARS)
1
2

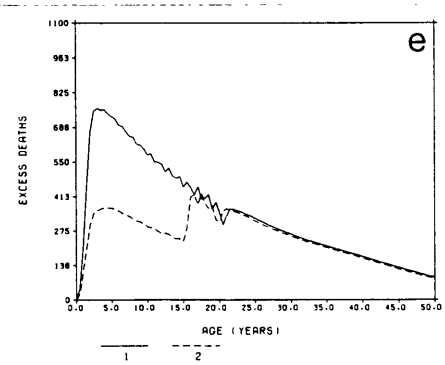

b
CASES
AGE (YEARS)
1
2

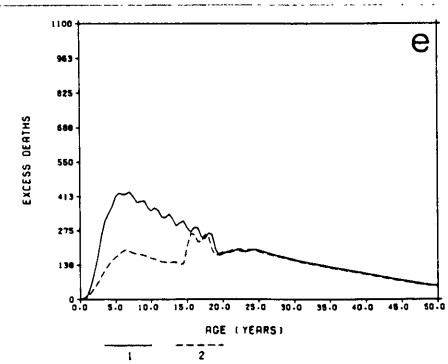

c
PROPORTION SEROPOSITIVE (CASES)
AGE (YEARS)
1
2


c
PROPORTION SEROPOSITIVE (CASES)
AGE (YEARS)
1
2


d
PROPORTION SEROPOSITIVE (CASES + VACCN)
AGE (YEARS)
1
2


d
PROPORTION SEROPOSITIVE (CASES + VACCN)
AGE (YEARS)
1
2


e
EXCESS DEATHS
AGE (YEARS)
1
2


e
EXCESS DEATHS
AGE (YEARS)
1
2

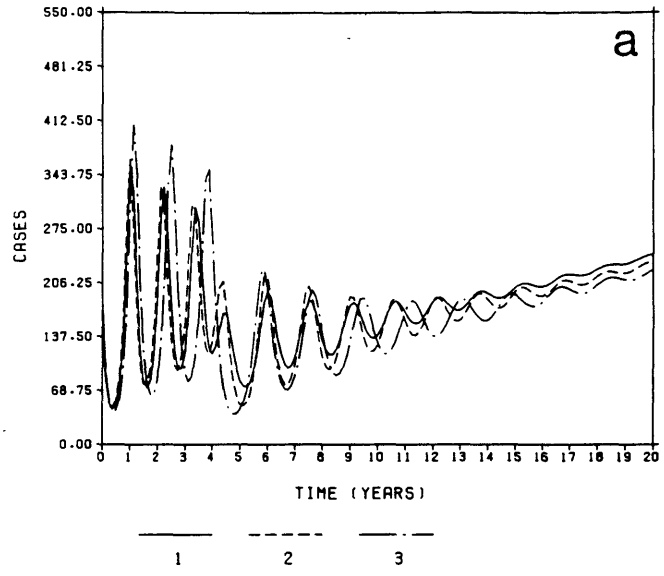
is discussed in more detail in section 8.8. In figure 8.6(b) the increase in the number of cases amongst older people is more noticeable. This is because the Ueda serology predicts a force of infection for the top age class greater than that estimated from the Boue serological profile.

8.7 Sensitivity to variation in the rate of loss of maternal antibody.

One benefit of the introduction of mass vaccination is the easing of the window problem. The severity of the window problem is intricately bound up with the length of duration of protection provided by maternal antibodies. It would therefore seem useful to know the sensitivity of predicted changes in the window problem to different values of δ, the rate of loss of protection by maternal antibody. In chapter 7 two sets of experiments were described in the context of attempting to understand the rôle of the magnitude of δ in the model's dynamical behaviour. In this chapter only the experiments where the serological profile is fixed are performed. Using both the Ueda and the Boué data, the effect of assuming three different values for the parameter δ are studied. The forces of infection λ are varied when δ is varied, so that the serological profiles at the start of the simulation ($t = 0$) are identical. Notice that in the experiments on the Ueda data set δ only varies between 2 and 2.5, whilst the experiments on the Boué data allow variation of δ between 2 and 4. Figures 8.7(a) and 8.8(a) show total cases through time for the Boué and Ueda experiments. These figures show that a higher assumed value of δ (shorter duration of maternal antibody protection) leads to greater impact induced by mass immunisation (fewer cases). This result can also be seen in figures 8.7(b) and 8.8(b) where greater values of δ imply smaller

Figure 8.7
Sensitivity of the model's predictions under variation of the parameter δ, the rate of loss of maternal antibodies. Results generated using the Boué baseline parameter set and deviations from it.
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 δ = 2.0 Peak of the last epidemic is at time t = 20 years.
2 δ = 3.0 Peak of the last epidemic is at time t = 18.375 years.
3 δ = 4.0 Peak of the last epidemic is at time t = 19.25 years.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550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
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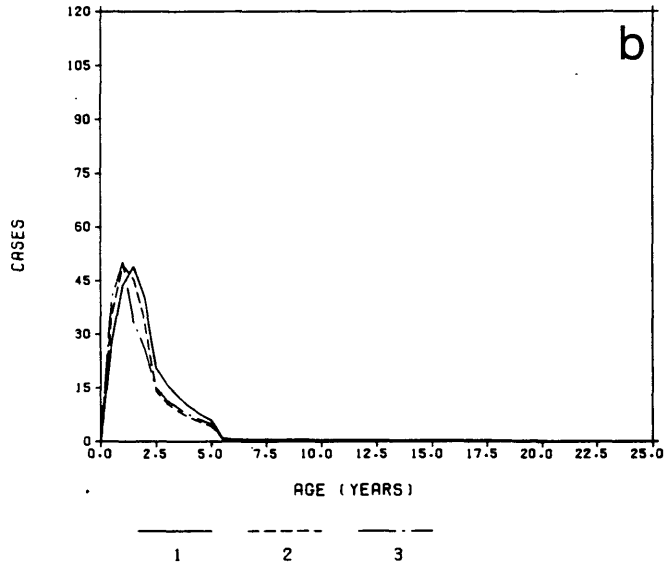
CASES
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1
2
3


b
120
105
90
75
60
45
30
15
0
CASES
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2
3

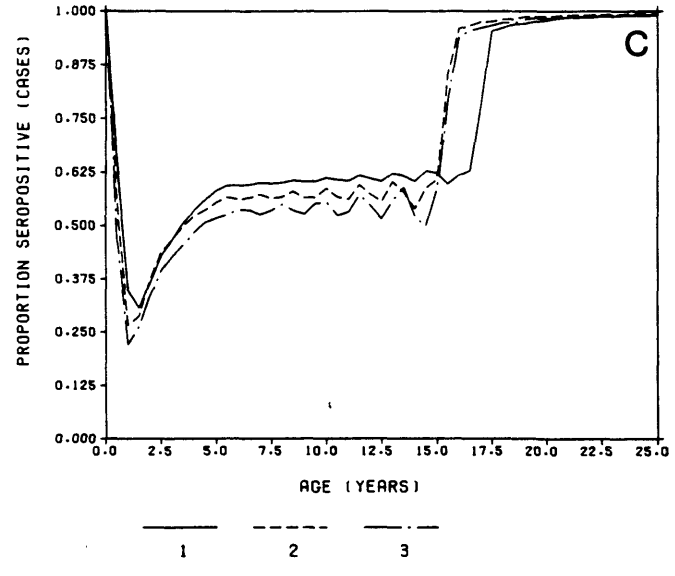
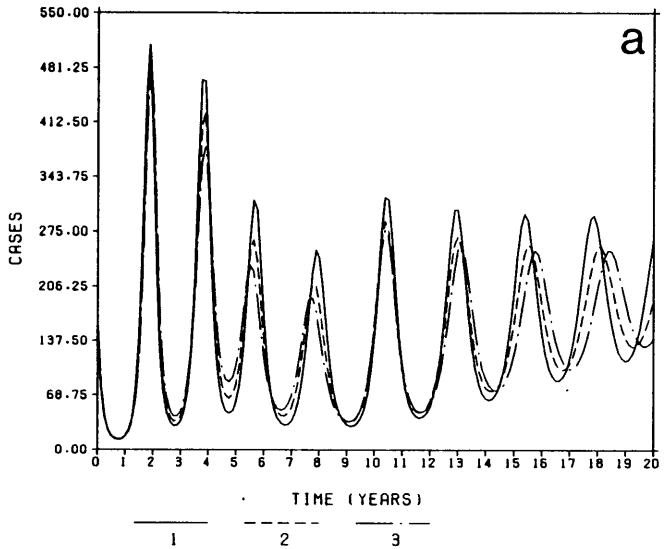
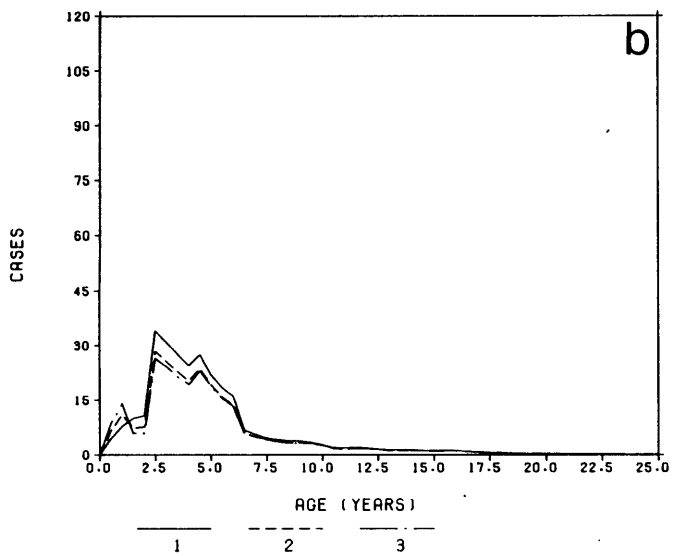

c
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
PROPORTION SEROPOSITIVE (CASES)
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2
3

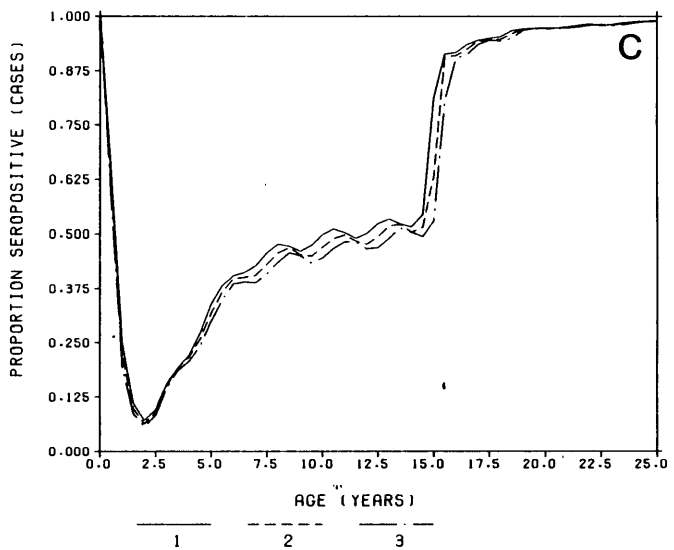
Figure 8.8
Sensitivity of the model's predictions under variation of the parameter δ, the rate of loss of maternal antibodies. Results generated using the Ueda baseline parameter set and deviations from it.

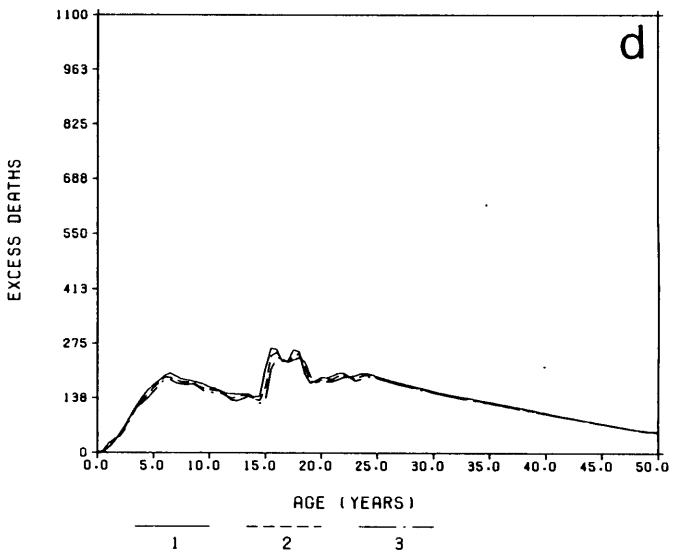
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 $\delta = 2.0$ Peak of the last epidemic is at time t = 18.375 years.
2 $\delta = 2.25$ Peak of the last epidemic is at time t = 18.125 years.
3 $\delta = 2.5$ Peak of the last epidemic is at time t = 18.375 years


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1
2
3


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2
3


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1
2
3


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1
2
3

proportions seropositive as a result of having had the disease, and a greater improvement in the window problem.

8.8 One stage programmes.

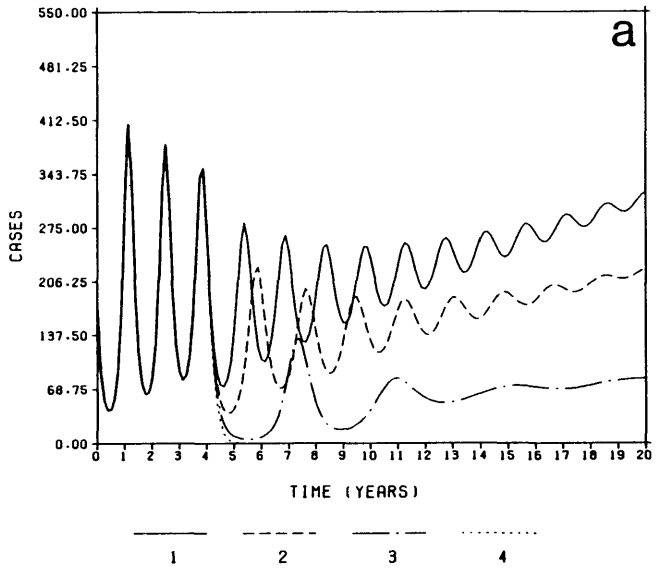
The first set of one stage programmes to be considered compares the effect of different levels of vaccination. Levels of 25% 50% 75% and 100% are tried on both the Boué and the Ueda data; the results are shown in figures 8.9 and 8.10. Investigation of the effects of different levels of vaccination is then pursued further with a study of the effects of vaccination of 80% 85% 90% and 95% using the Ueda data. The results of this investigation are shown in figure 8.11. The last of this series of investigations applies a vaccination coverage of 97% to the Ueda data, and simulates events for 56 years after the introduction of vaccination, as opposed to the period of 16 years employed in the majority of the numerical simulations. Results are shown in figure 8.12. Apart from the trivial observation that greater levels of vaccination have greater impact upon morbidity (figs 8.9(a), 8.10(a) and 8.11(a)) and mortality (figs 8.9(d), 8.10(d) and 8.11(d)); there are a number of points of interest to note. These are dealt with in the order of the figures in which they are illustrated.

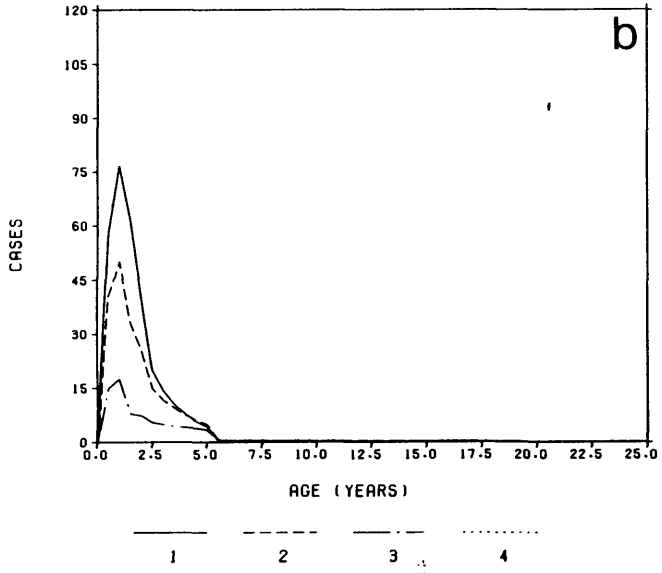
In figure 8.9(a) it can be seen that the time that elapses between the introduction of mass vaccination and the subsequent epidemic depends upon the level of vaccination. Thus at 25% coverage there is barely any perceptible change in the inter-epidemic period, whilst with 75% coverage there is a significant delay before the next outbreak. This 'honeymoon

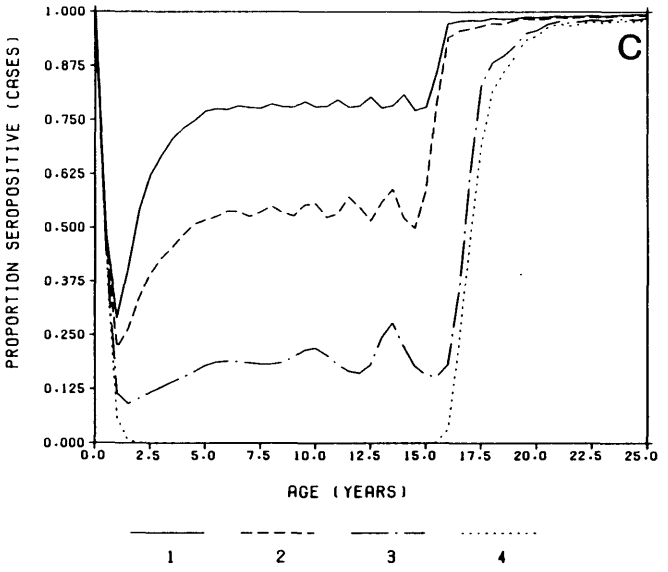
Figure 8.9
The impact of a range of different vaccination regimes which reach different percentages of the susceptible population. All the programmes tested here administer vaccine at age 9 months. Predictions generated using the Boué baseline parameter set.

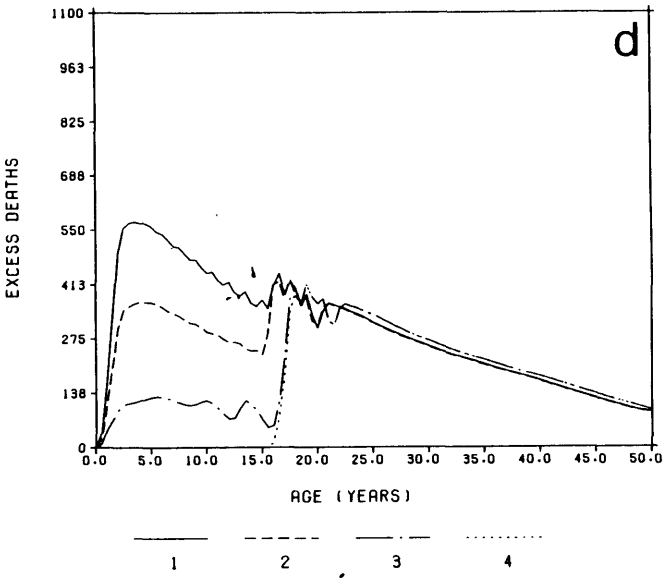
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 25% The peak of the last epidemic is at time t = 18.625 years
2 50% The peak of the last epidemic is at time t = 18.5 years
3 75% The peak of the last epidemic is at time t = 20 years
4 100% The peak of the last epidemic is at time t = 20 years


a
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
CASES
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4


b
120
105
90
75
60
45
30
15
0
CASES
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4


c
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
PROPORTION SEROPOSITIVE (CASES)
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4


d
1100
963
825
688
550
413
275
138
0
EXCESS DEATHS
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4

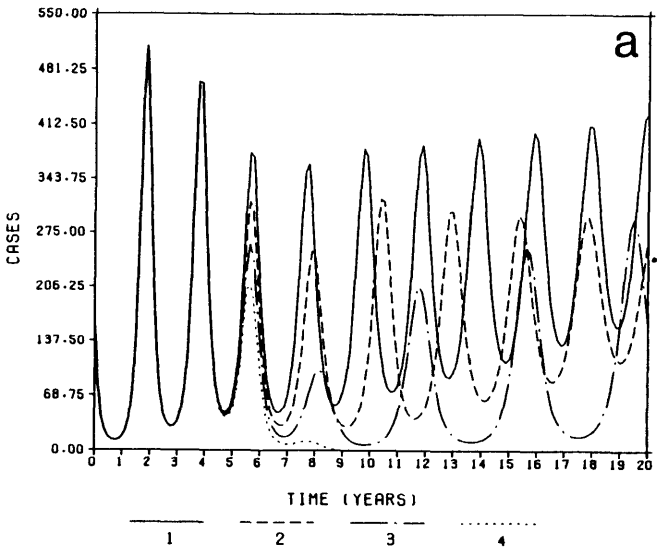
period' has been observed in The Gambia (Jobe, personal communication) where very high levels of immunisation were introduced over a short period of time. The length of the 'honeymoon period' depends not only on the level of vaccination coverage but also on the way in which the force of infection changes with age. The period of low incidence of infection immediately following the introduction of vaccination leads to low levels of immunity amongst those individuals who (if it were not for immunisation) would have acquired infection during the period of low incidence. This is illustrated in figure 8.9(c) where there is low disease induced immunity amongst 14 -16 year olds at time 20 years. These are the individuals who were born in the two years immediately following the start of mass vaccination, so were 0 - 2 years old during the years of low incidence. These are the ages when the force of infection is at its highest. It should be stressed that figure 8.9(c) only registers <u>disease induced</u> immunity and protection by maternal antibody. Individuals seropositive as a result of having been successfully immunised are not registered on this graph.

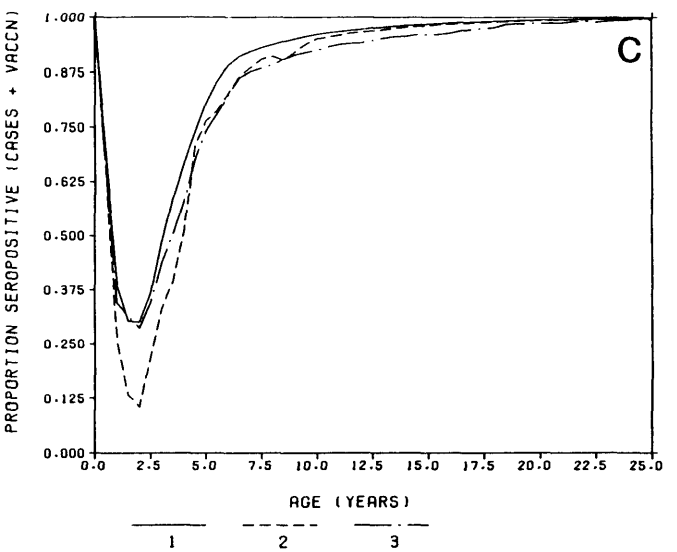
Figure 8.10(a) illustrates total cases through time when widely varying levels of vaccination (25% - 100%) are applied in a community where the average age at infection is comparatively old ($A \simeq 3$ for the Ueda baseline parameter set) and the duration of protection by maternal antibody is long. It is apparent that the impact of the introduction of vaccination is much slower under these circumstances. Even with 100% coverage it is almost 5 years before the number of cases sinks to zero, and the 'honeymoon effect' isn't visible until the <u>second</u> epidemic following the initiation of control measures. Figure 8.10(b) shows that peak incidence occurs at approximately age three, so that it takes two years before vaccination at age 9 months

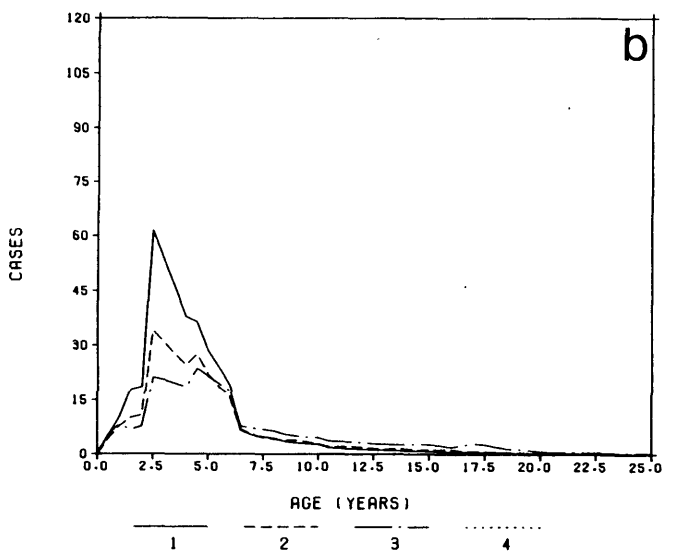
Figure 8.10
The impact of a range of different vaccination regimes which reach different percentages of the susceptible population. All the programmes tested here administer vaccine at age 9 months. Predictions generated using the Ueda baseline parameter set.

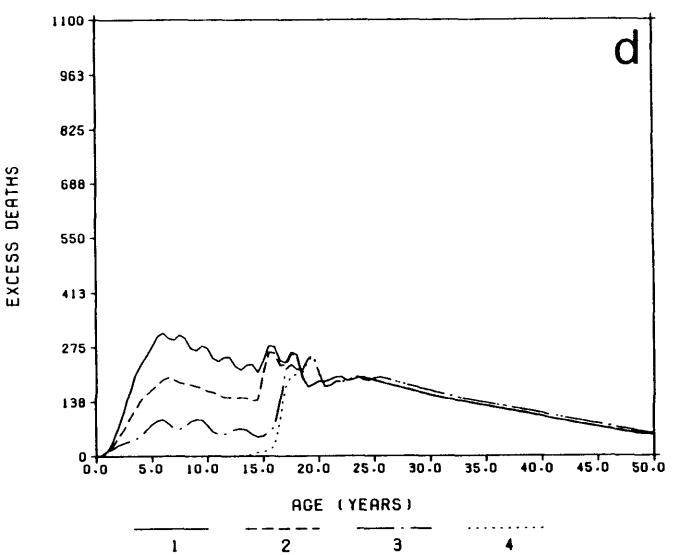
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 25% The peak of the last epidemic is at time t = 17.875 years
2 50% The peak of the last epidemic is at time t = 17.875 years
3 75% The peak of the last epidemic is at time t = 19.5 years
4 100% The peak of the last epidemic is at time t = 19.5 years


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4


c
PROPORTION SEROPOSITIVE (CASES + VACCN)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4

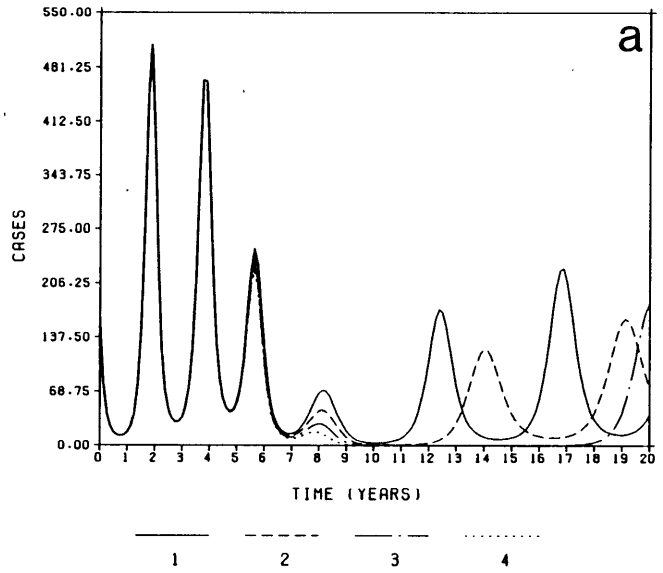

d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4

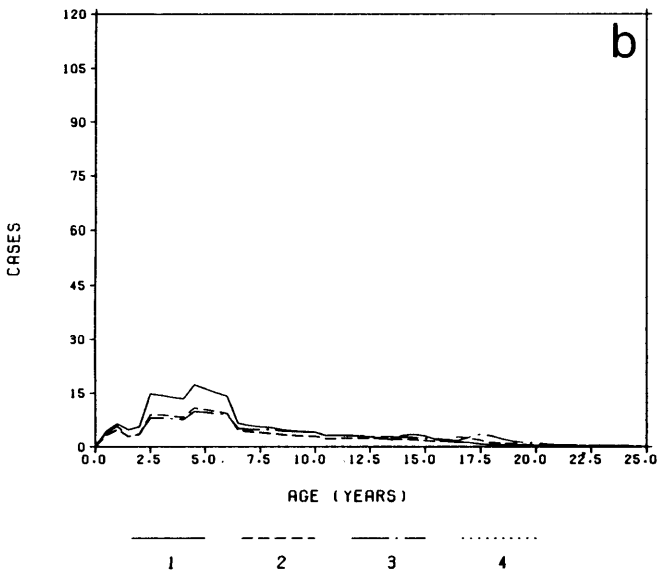
has a dramatic influence on the number of cases. The slow rate of loss of protection by maternal antibody means that lower rates of seroconversion are achieved when vaccinating at 9 months. These two factors combine to cause this different pattern.

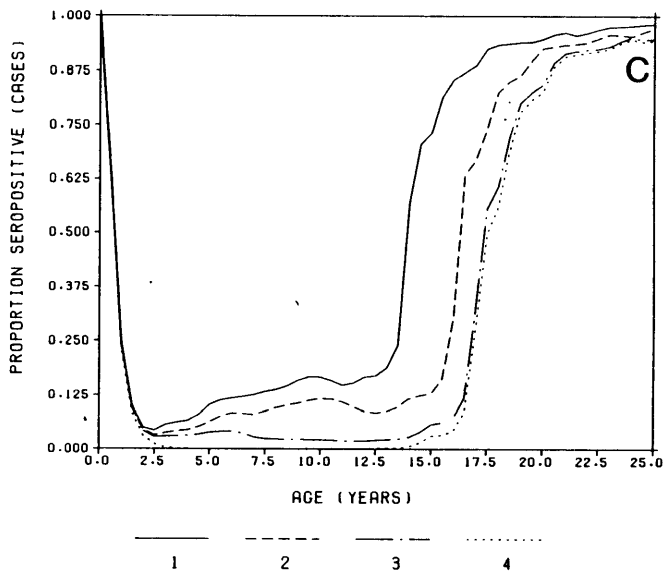
Figures 8.11(a) to (d) illustrate the impact of a different set of levels of vaccination, with a narrower range but at a higher level. Thus the four levels compared are 80%, 85% 90% and 95%. As coverage levels increase the 'honeymoon period' gets longer (fig 8.11(a)) and the age distribution of cases after sixteen years of vaccination skews more towards the older individuals (fig 8.11(b)) From this simulation it would appear that immunisation of 95% of those susceptible at age 9 months would eradicate the disease, but figure 8.12 shows this to be incorrect. The latter figure shows total cases through time for 60 years, using the Ueda baseline parameter set, and vaccinating 97% of 9 month olds. There is a very long period with no cases, and then a large outbreak 42 years after the introduction of mass vaccination. This might seem surprising, until it is pointed out that if the average duration of protection by maternal antibody is 6 months, 22% of a cohort will still be protected by maternal antibody at the age of 9 months. Under the assumption that this 22% will not seroconvert when vaccinated, vaccination of 97% at age 9 months is only equivalent to successful immunisation of 76% of each cohort. The crucial question of the age at which vaccine should be administered is studied in the next section. The example shown in figure 8.12 illustrates two shortcomings of this model. When cases drop to very low levels - as they do between times t = 6 years and t = 44 years - stochastic effects become relatively more important. Thus if a stochastic element had been

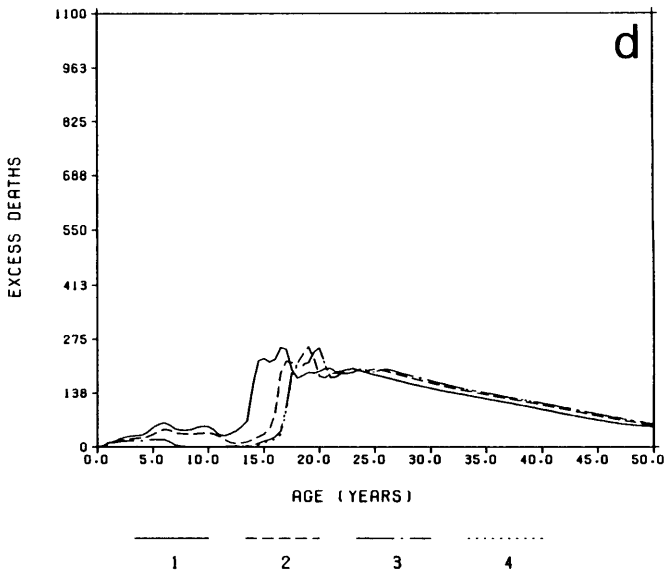
Figure 8.11
The impact of a range of different vaccination regimes which reach different percentages of the susceptible population. All the programmes tested here administer vaccine at age 9 months. Predictions generated using the Ueda baseline parameter set.
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 80% The peak of the last epidemic is at time t = 16.875 years
2 85% The peak of the last epidemic is at time t = 19.125 years
3 90% The peak of the last epidemic is at time t = 20 years
4 95% The peak of the last epidemic is at time t = 20 years


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4

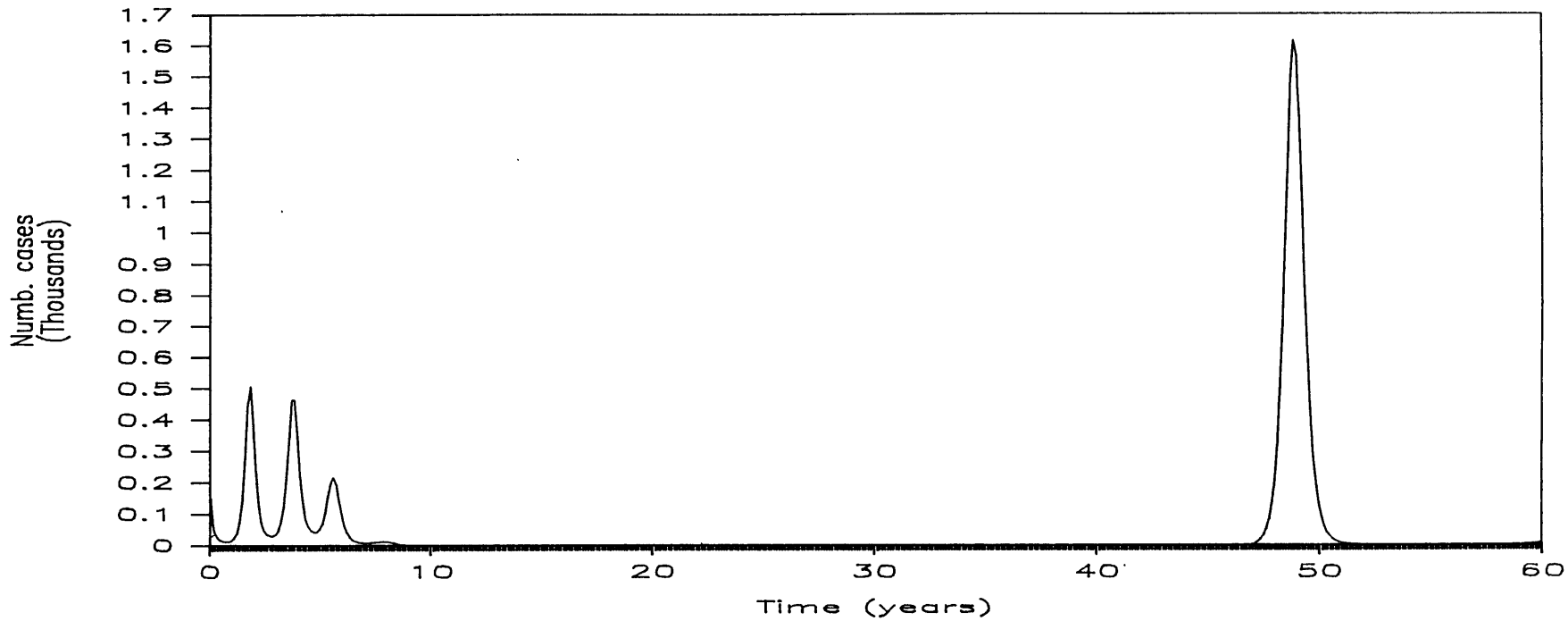


Figure 8.12
Long term predicted impact of vaccinating 97% of 9 month old susceptibles. The results were generated using the Ueda baseline parameter set.

incorporated into the model, the case illustrated in the figure would have led to true eradication because stochastic effects would have lead to fade-out of the disease. The model assumes that the community under consideration is so isolated that no cases would be imported. This is clearly quite unrealistic and an element of spatial heterogeneity allowing disease transmission between different communities needs to be considered. If occasional new infectives were introduced to the community modelled here, the post-vaccination epidemic would occur sooner.

The next two sets of experiments investigate the changes that come about as a result of varying the age at which vaccine is administered. Table 8.1 shows the percentage of a cohort that will still be protected by maternal antibody at a range of ages. The youngest age considered is 3 months, and the oldest age for which results are tabulated is 1 year 6 months. The table shows the percentage protected by maternal antibody at each age for two values of the parameter δ. The second and fourth columns show the maximum effective immunisation rates that could be achieved by vaccinating 50% of a cohort at each age, assuming that no child protected by maternal antibody will seroconvert upon vaccination. The figures in this column are calculated assuming that no vaccine is wasted on individuals who have already experienced the disease; in practice this is a weak assumption. Figure 8.13(a) shows the predicted total number of cases under six different regimes of vaccination. In each case 50% of each cohort are vaccinated, but the age at which vaccine is administered is varied. The youngest age at which vaccine is administered is 3 months and the oldest age is 1 year 6 months The predictions shown in these figures were calculated using the Boué parameter set, so the average duration of

	Average Duration of Maternal Antibodies			
	3 months ($\delta = 4\ yr^{-1}$)		6 months ($\delta = 2\ yr^{-1}$)	
	% protected by maternal antibodies	max. successful immunisation rate at 50% coverage	% protected by maternal antibodies	max. successful immunisation rate at 50% coverage
3mo	36,8%	31,6%	60,7%	19,7%
6mo	13,5%	43,3%	36,8%	31,6%
9mo	5,0%	47,5%	22,3%	38,9%
1yr	1,8%	49,1%	13,5%	43,3%
1yr 3mo	0,7%	49,7%	8,2%	45,9%
1yr 6mo	0,2%	49,9%	5,0%	47,5%

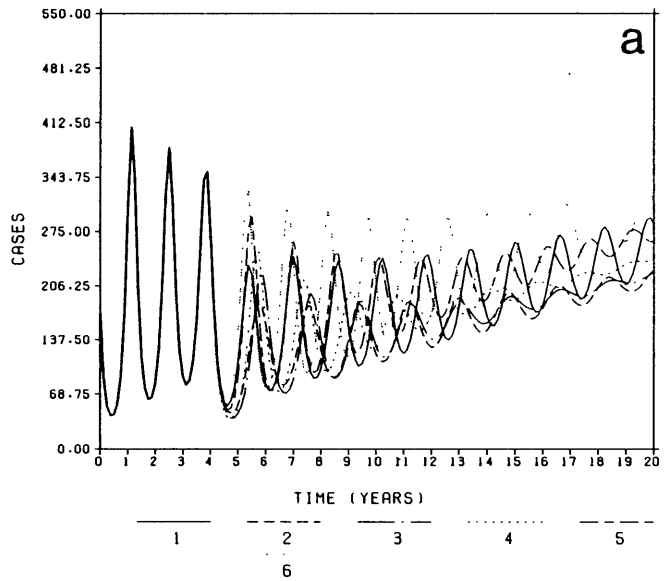
Table 8.1

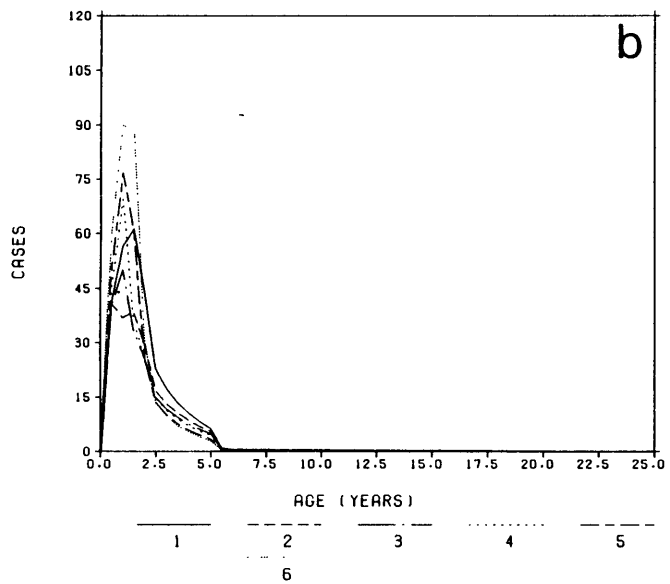
Programme efficacy at different ages for two different rates of loss of protection by maternal antibody.

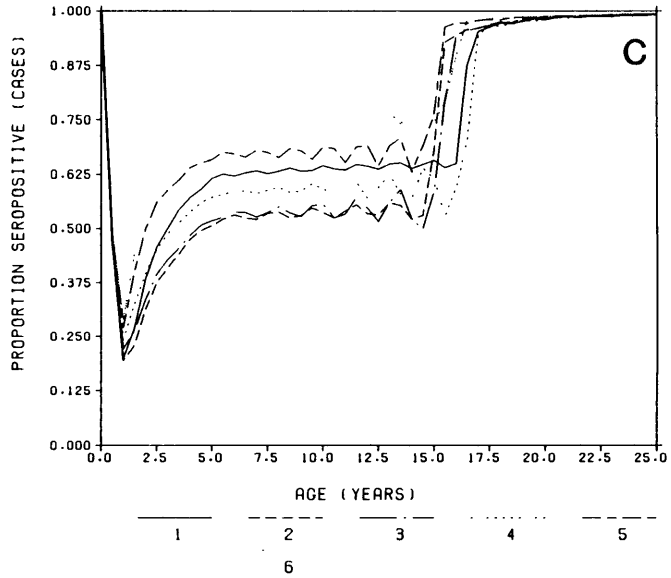
Figure 8.13
Predicted impact of different vaccination regimes which immunise 50% of susceptibles at a range of ages. The results were generated using the Boué baseline parameter set.

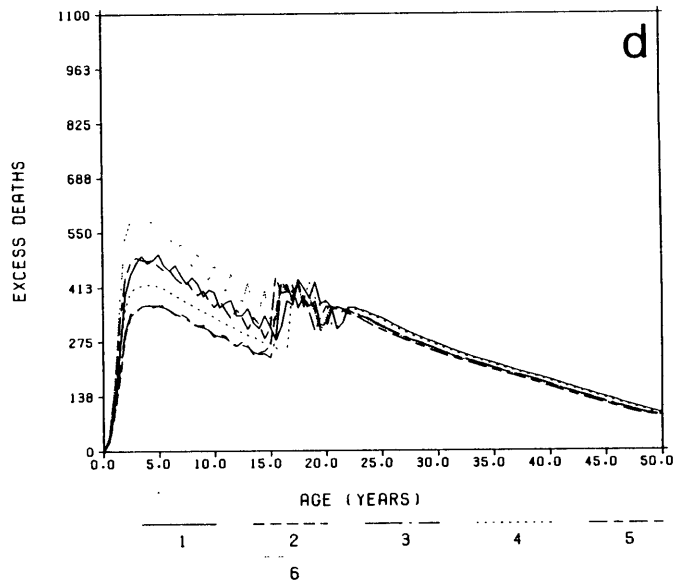
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 Vaccine administered at age 3 months. The peak of the last epidemic is at time t = 20 years
2 Vaccine administered at age 6 months. The peak of the last epidemic is at time t = 18.375 years
3 Vaccine administered at age 9 months. The peak of the last epidemic is at time t = 18.5 years
4 Vaccine administered at age 1 year. The peak of the last epidemic is at time t = 19.5 years
5 Vaccine administered at age 1 year 3 months. The peak of the last epidemic is at time t = 17.75 years
6 Vaccine administered at age 1 year 6 months. The peak of the last epidemic is at time t = 18.25 years


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4 5
6


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5
6


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5
6


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4 5
6

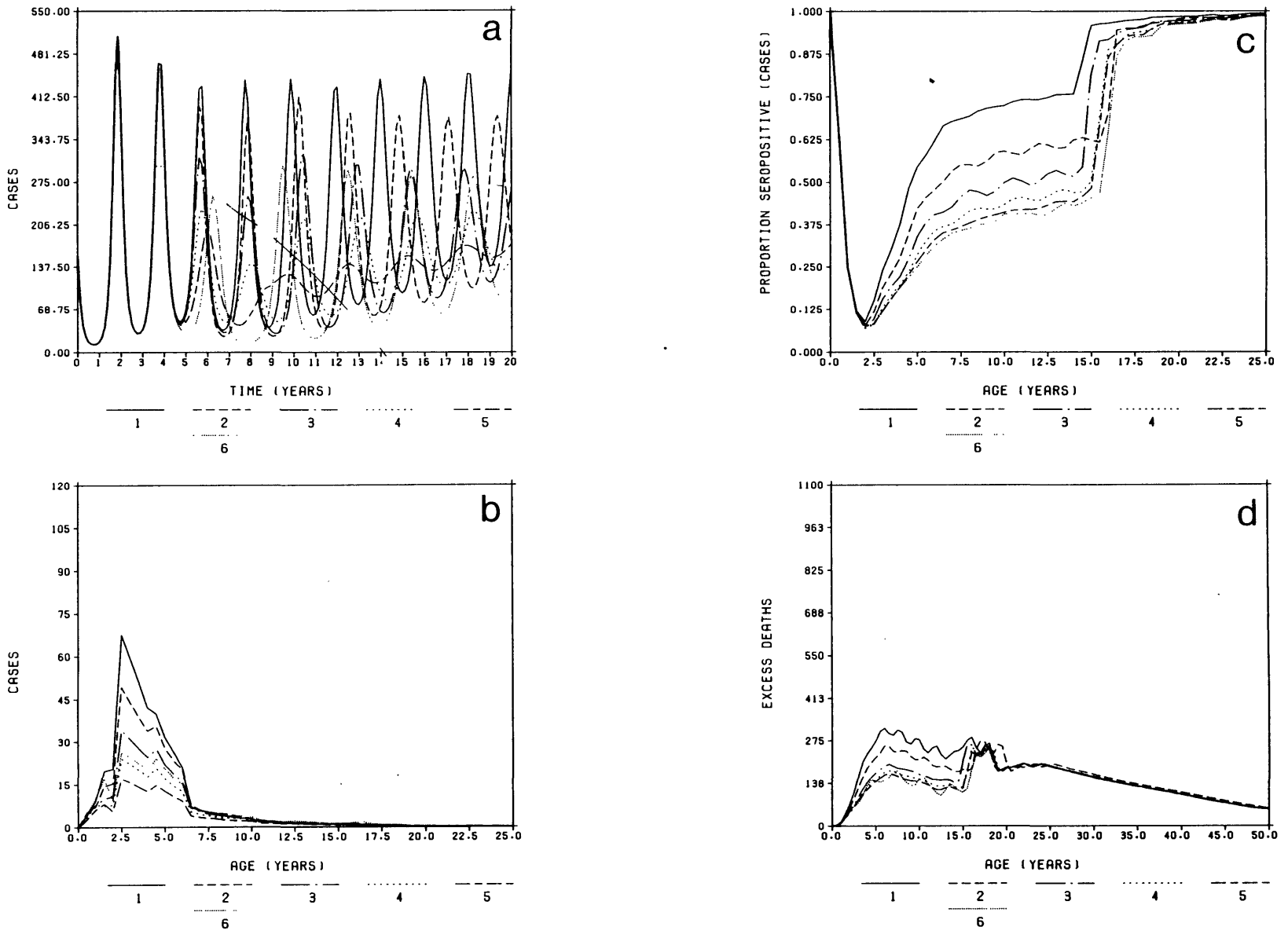
maternal antibody protection was assumed to be 3 months. Thus columns 1 and 2 of table 8.1 apply. In figure 8.13(a) it can be seen that the best ages at which to vaccinate are 6 - 9 months, as at these ages there is the greatest reduction in the number of cases. At younger than 6 months too much vaccine is wasted on individuals still protected by maternal antibody, and at older than 9 months too many people have already had measles. Figure 8.13(c) shows that these regimes of immunisation serve to greatly improve the window problem, whilst the regimes which vaccinate at a later age do much less to increase the average age at infection. Figure 8.13(d) reveals that vaccinating at 6 to 9 months also results in the greatest reduction in the number of excess deaths.

Figures 8.14(a) to (d) show the results of the same experiment performed using the Ueda baseline parameter set. Here the rate of loss of protection by maternal antibody is much slower, and the average age at infection is older. Columns 2 and 4 of table 8.1 give the proportion protected by maternal antibodies and the maximum effective immunisation rates for the six possible ages at vaccination. The combination of long lasting protection from maternal antibodies, and a relatively low risk of infection at a young age combine to make vaccination at age 1 year 3 months the best choice for reducing the number of cases and also for the reduction in disease induced mortality. The best age at which vaccine should be administered depends, therefore, upon the age distribution of cases that prevails in the community before the introduction of mass vaccination. Although the W.H.O.'s recommendation for immunising at age 9 months provides a useful guide-line for health planners, the results

Figure 8.14
Predicted impact of different vaccination regimes which immunise 50% of susceptibles at a range of ages. The results were generated using the Ueda baseline parameter set.

(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

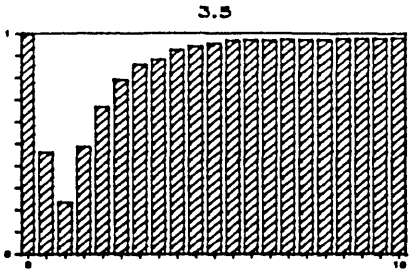
1 Vaccine administered at age 3 months. The peak of the last epidemic is at time t = 18 years
2 Vaccine administered at age 6 months. The peak of the last epidemic is at time t = 19.375 years
3 Vaccine administered at age 9 months. The peak of the last epidemic is at time t = 17.875 years
4 Vaccine administered at age 1 year. The peak of the last epidemic is at time t = 18.25 years
5 Vaccine administered at age 1 year 3 months. The peak of the last epidemic is at time t = 18 years
6 Vaccine administered at age 1 year 6 months. The peak of the last epidemic is at time t = 18.25 years


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3 4 5 6
b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5 6
c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3 4 5 6
d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3 4 5 6

reported in this chapter indicate that it cannot be the best strategy in all situations.

Before moving on to discuss the next series of experiments a brief consideration is given to the observed pattern of disease incidence that immediately follows the introduction of mass vaccination, in particular the observation that there is an extended inter-epidemic period. In the paragraphs above this phenomenon has been dubbed the 'honeymoon period'. In order to explain its cause, it is necessary to refer to the concept of herd immunity. This is an expression of the idea that there is a certain threshold density of susceptibles below which disease transmission will cease. When the force of infection depends upon the age of susceptibles this threshold is a sum of the susceptible population in different age classes, weighted by age. In the absence of vaccination the susceptible population oscillates about this threshold with an age distribution determined by the rate of loss of protection by maternal antibody and the age-dependent forces of infection. After the introduction of mass vaccination the susceptible population oscillates about an equilibrium determined by the rate of loss of protection by maternal antibody , the forces of infection and the age specific vaccination regime. The weighted sum of this post-vaccination susceptible population is the same as the weighted sum of the pre-vaccination susceptible population, but the age distribution that gives the sum is different. The 'honeymoon period' is generated during the shift from the pre-vaccination to the post-vaccination age distribution of susceptibles. Figure 8.15 is a sequence of serological profiles recording proportions seropositive through protection by maternal antibodies, naturally acquired immunity or vaccine induced immunity. The

Figure 8.15
A sequence of serological profiles recording proportions seropositive from cases and from vaccination. The unshaded area represents the susceptible pool. The figure shows serological profiles taken at 6 monthly intervals between time t = 3.5 years and time t = 8.5 years. These results are from a simulation where at time t = 4 years a vaccination programme reaching 75% of 9 month old susceptibles was introduced. The figures are drawn such that this immunisation is visible in the third block of the histograms. The bottom right hand figure shows cases through time for this simulation. The black dots represent moments in time when the slices have been taken.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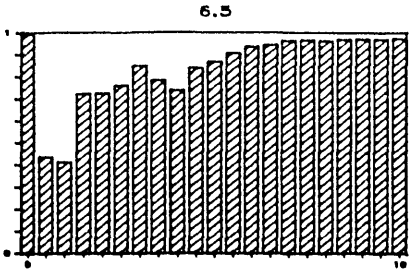
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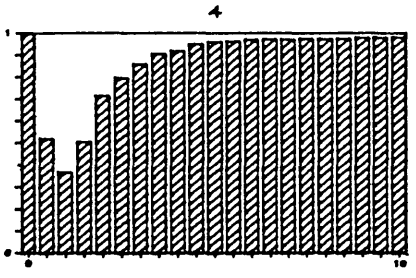
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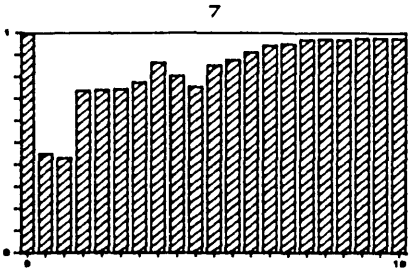
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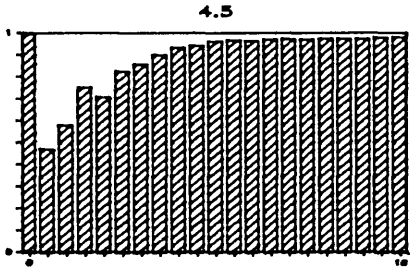
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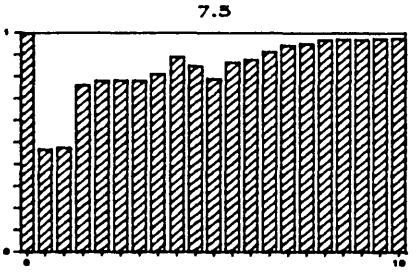
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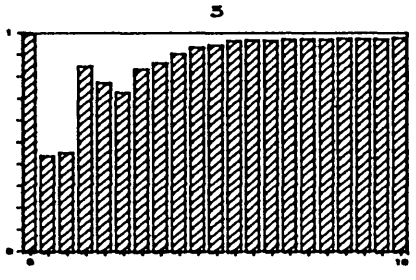
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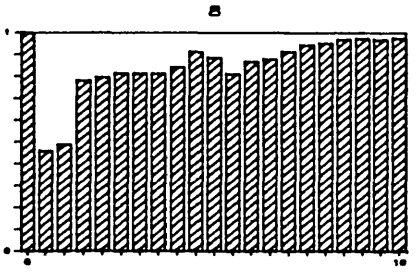
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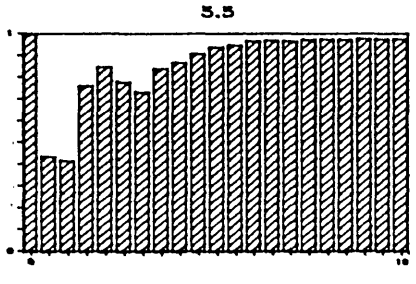
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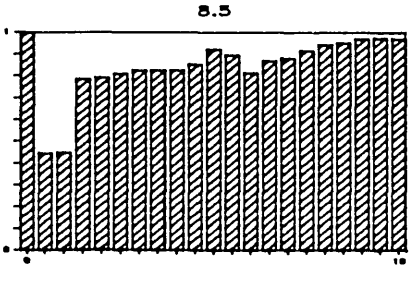
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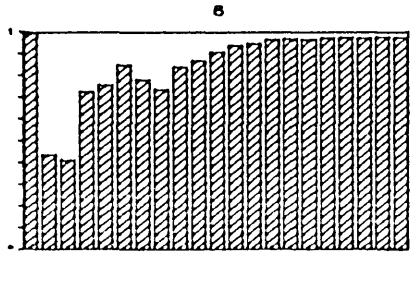
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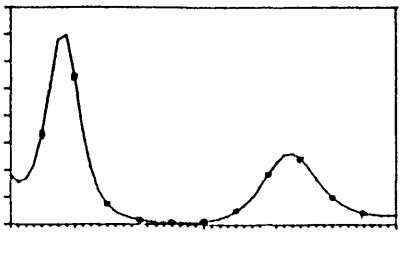


unshaded areas represent the susceptible pool. Vaccination of 75% of 9 month olds is introduced at time t=4 years. The post-vaccination epidemic starts at time t=6 years, reaches its peak at time t=7.5 years, and is over by time t=8.5 years. Comparing the age distribution of cases at times t=3.5 and t=7.5 years one can see the difference between the pre-vaccination and the post-vaccination age distribution of susceptibles. In the pre-vaccination distribution there are a large proportion susceptible at around age 1 year, and very few susceptibles amongst children over 5. In the post-vaccination age distribution there are fewer 1 year old susceptibles (as a result of immunisation) but more susceptibles between the ages of 5 and 10. Between time t=4.5 years and t=6 years, the combination of a low proportion of one year olds susceptible (because of immunisation) and a low proportion of older children susceptible (because they were infected before the introduction of immunisation) leads to a very small susceptible pool. It therefore takes longer than usual for the density of susceptibles to rise above the threshold density, and trigger another epidemic.

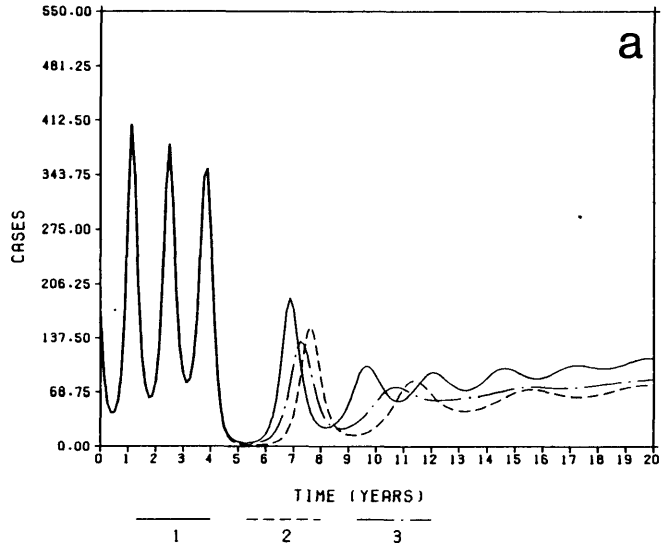
8.9 Two-stage programmes.

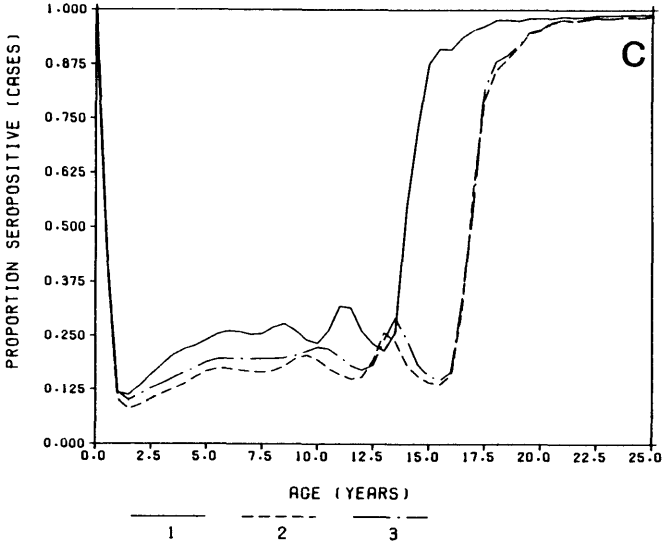
The experiments described in this section consider the impact of immunisation programmes that vaccinate at two different ages. At each age, 50% of susceptibles are assumed to be successfully immunised. As before, results are displayed using four summary graphs. Figure 8.16 shows results derived using the Boué parameter set, vaccinating at 3 months and 1 year, 6 months and 1 year, and 9 months and 1 year. Figure 8.17 shows the results of the same experiment performed on the Ueda parameter set. For the Boué parameter set the regime that vaccinates at 6 months and 1 year is best

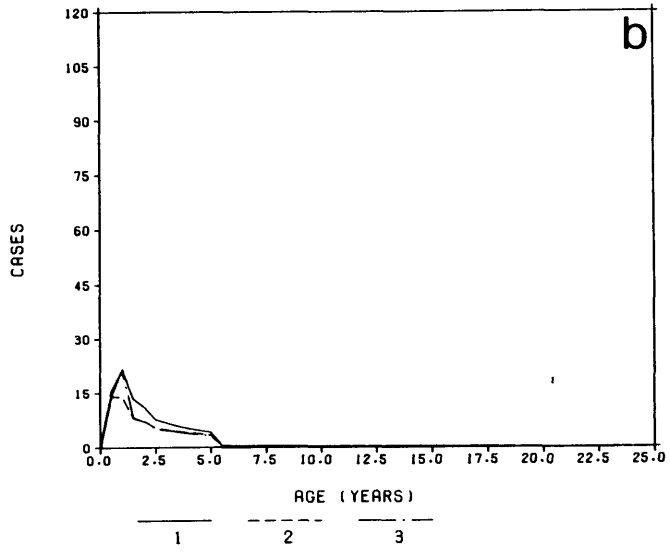
Figure 8.16
Two stage programmes. Predicted impact of a range of vaccination regimes which immunise 50% of susceptibles at two different ages. The results were generated using the Boué baseline parameter set.

(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 Vaccine administered at age 3 months and at age 1 year. The peak of the last epidemic is at time t = 17.25 years.
2 Vaccine administered at age 6 months and at age 1 year. The peak of the last epidemic is at time t = 20 years.
3 Vaccine administered at age 9 months and at age 1 year. The peak of the last epidemic is at time t = 20 years.


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3

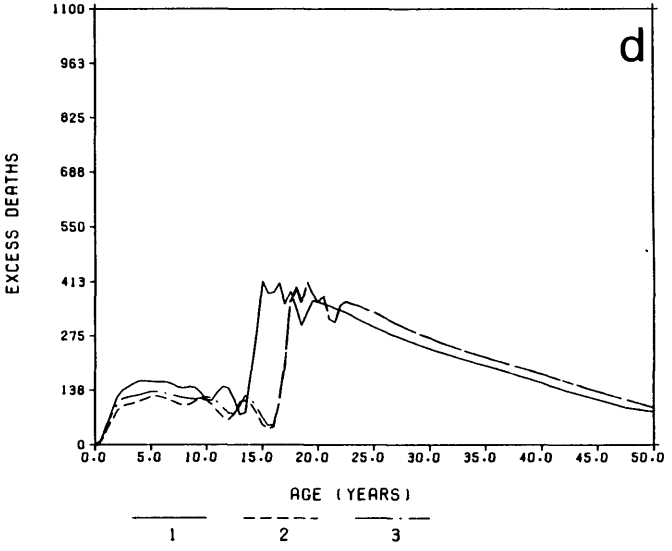
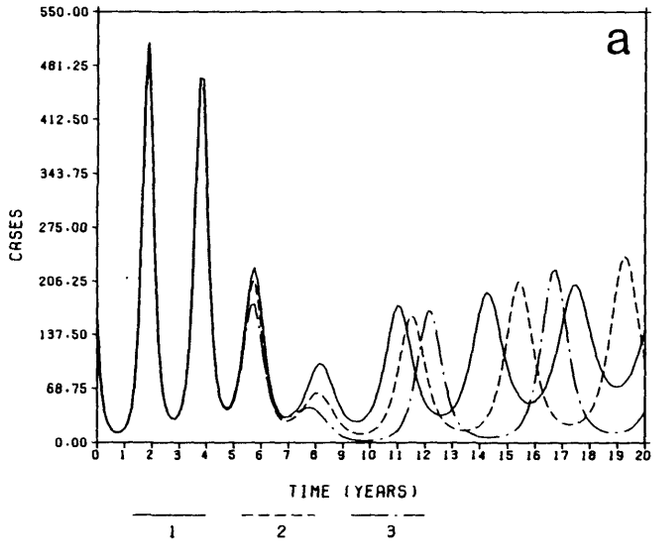
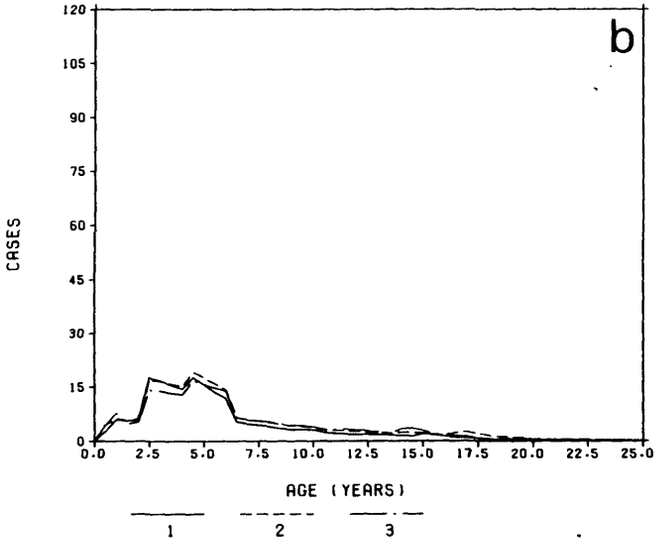

d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3

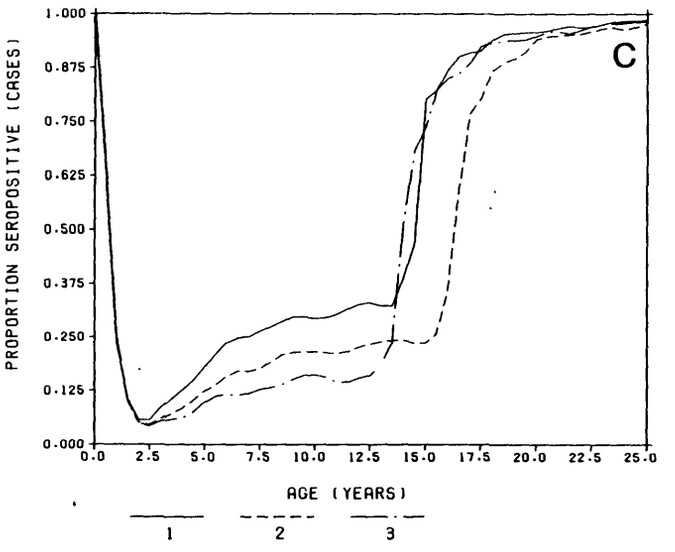
Figure 8.17
Two stage programmes. Predicted impact of a range of vaccination regimes which immunise 50% of susceptibles at two different ages. The results were generated using the Ueda baseline parameter set.

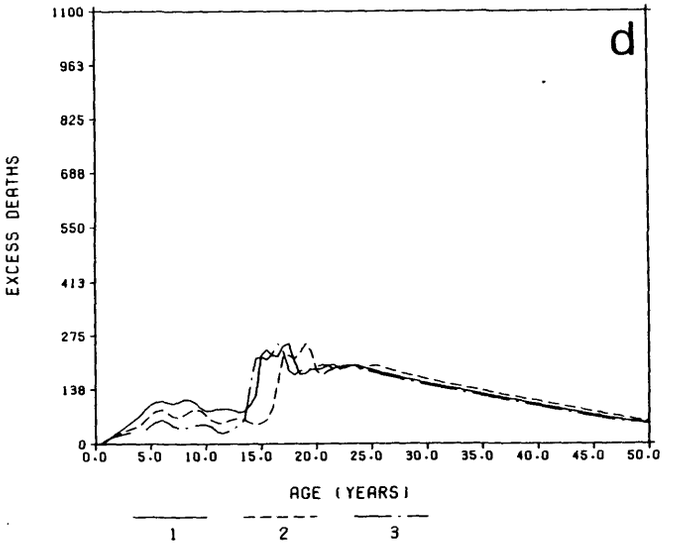
(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

1 Vaccine administered at age 3 months and at age 1 year. The peak of the last epidemic is at time t = 17.25 years.
2 Vaccine administered at age 6 months and at age 1 year. The peak of the last epidemic is at time t = 19.25 years.
3 Vaccine administered at age 9 months and at age 1 year. The peak of the last epidemic is at time t = 16.75 years.


a
CASES
550.00
481.25
412.50
343.75
275.00
206.25
137.50
68.75
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (YEARS)
1 2 3


b
CASES
120
105
90
75
60
45
30
15
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


c
PROPORTION SEROPOSITIVE (CASES)
1.000
0.875
0.750
0.625
0.500
0.375
0.250
0.125
0.000
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
AGE (YEARS)
1 2 3


d
EXCESS DEATHS
1100
963
825
688
550
413
275
138
0
0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0
AGE (YEARS)
1 2 3

(in that it does most to reduce both the number of cases and the number of excess deaths), whilst for the Ueda parameter set vaccinating at 9 months and 1 year is the most beneficial regime. This underlines the point made previously, that the optimal vaccination policy can only be determined with a knowledge of existing patterns of disease incidence.

8.10 Two-phase programmes

In this final comparison of different regimes of vaccination, a study is made of the impact of a vaccination campaign that starts by vaccinating at one age and then switches to a different age. This experiment was suggested by the observation that for a year after the introduction of high levels of immunisation, the transmission of disease falls to a very low level. Given this low level of disease transmission, it was felt that it might be possible, by increasing the age at which vaccine was administered, to enhance the impact of the campaign. By waiting until a later age for the administration of vaccine, more people would have lost their maternal antibodies, and could therefore be successfully immunised. The low levels of disease transmission would mean that these individuals would not be at risk from infection. In other words, the plan was to use the 'honeymoon period' to overcome the window problem.

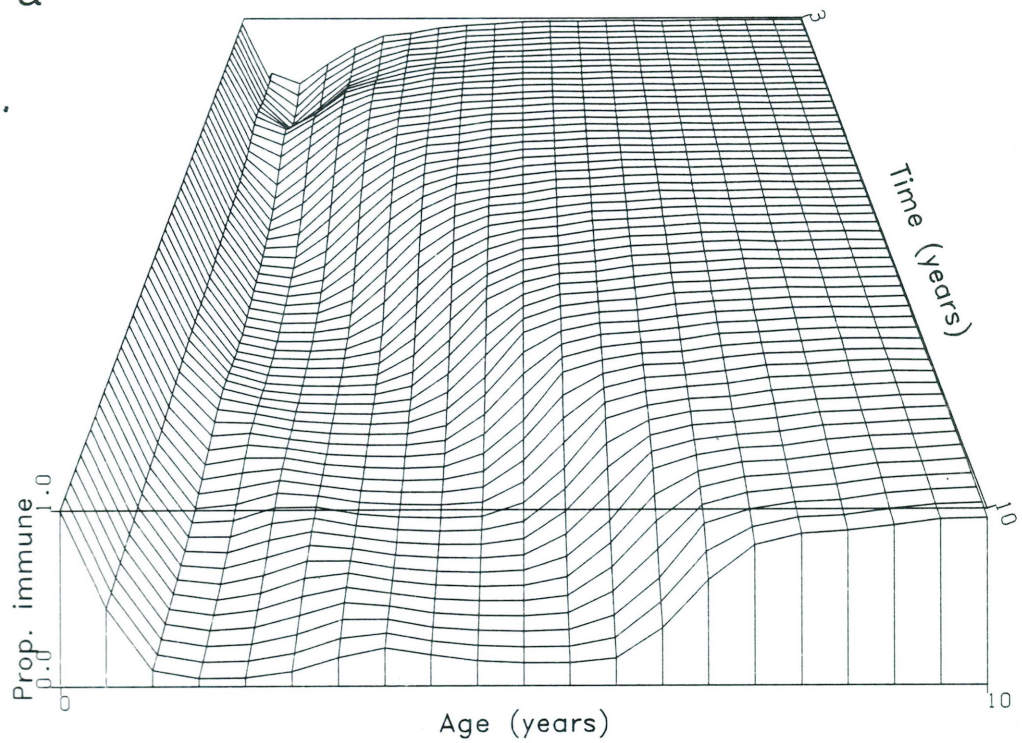
Figures 8.18(a) and (b) show the serological surface, and some slices through it that are produced under the influence of a vaccination regime of 75% at 9 months old starting at time t=4 years. These have been drawn using results generated with the Boué baseline parameter set. This experiment was performed upon this parameter set because it is the one that

Figure 8.18
Illustrations of the easing of the window problem as a result of the introduction of immunisation. The results illustrated show the impact of immunising 75% of susceptibles at age 9 months, starting at time t = 4 years.

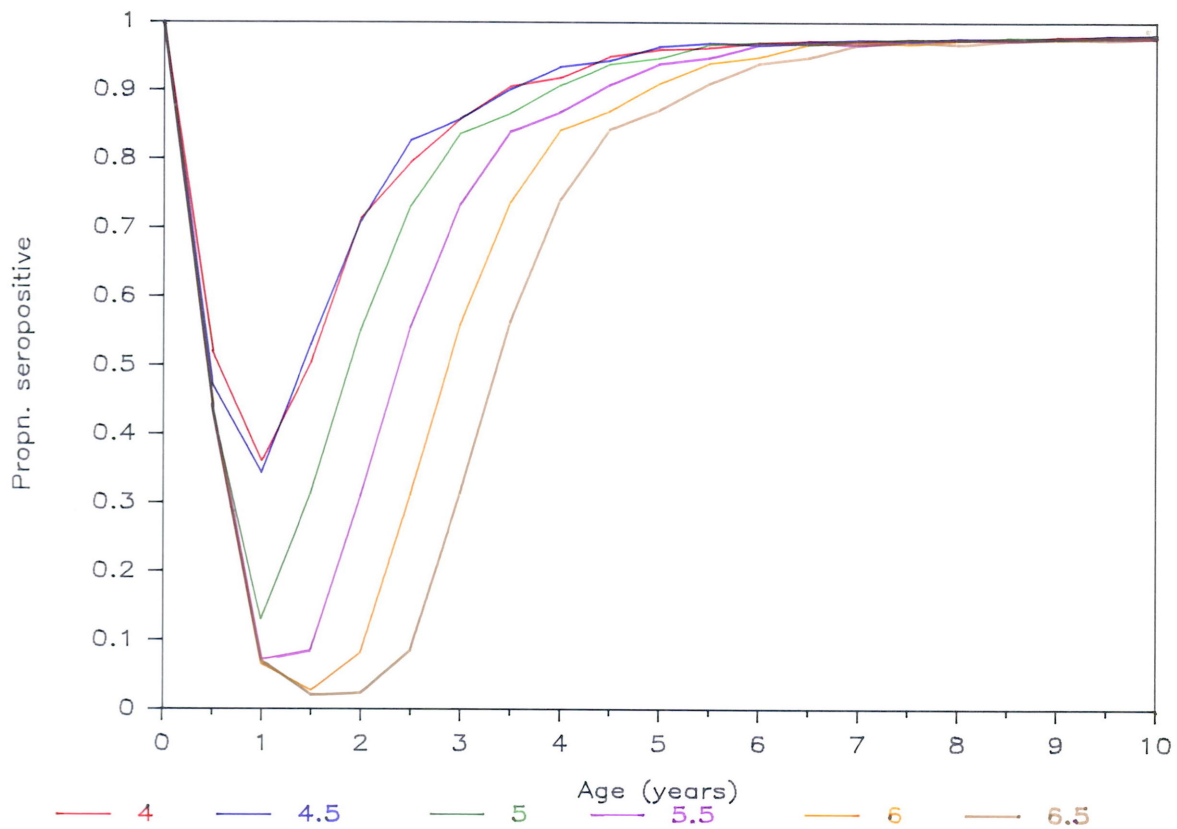
(a) Three dimensional view of the proportion seropositive through the presence of maternal antibody or naturally acquired immunity following infection. Time ranges from t = 3 years to t = 10 years, and age ranges from 0 to 10 years.

(b) Two dimensional view of the proportion seropositive through the presence of maternal antibody or naturally acquired immunity following infection. These are slices taken through the surface above at 6 monthly intervals from t = 4 years until t = 6.5 years.

a


Prop. immune
1.0
0.0
0
Age (years)
10
Time (years)
3
10

b


Propn. seropositive
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10
Age (years)
4
4.5
5
5.5
6
6.5

best illustrates the window problem. The two graphs show the proportion seropositive through infection only. This procedure is adopted to illustrate the way in which the window problem becomes less severe after the introduction of vaccination. The experiment tests the outcome of changing the policy at time 6 years to vaccinate at either 1 year or 1 year 6 months. The proportion of susceptibles immunised is assumed to be the same - i.e. 75% - but because the age at vaccination is older, the overall proportion vaccinated was expected to be greater (fewer people protected by maternal antibodies), and the impact of the campaign was expected to improve. However as can be seen in figure 8.19(a) to (d) the reverse happened, and the impact of the campaign was greatly reduced. In every aspect, the two phase programmes give poorer results than a programme that continues to vaccinate at 9 months. There are more cases (8.19(a) and (b)), resulting in more people being immune through infection at the end of the twenty year simulation (8.19(c)), and more excess deaths (8.19(d)) in the altered programme than in the original one. Figures 8.20(a), (b) and (c) are three dimensional illustrations of cases by age for each of the three different strategies. They show that the two phase programmes fail because they do not immunise enough people to eradicate the disease, and leave at risk large numbers of individuals below the age at which vaccination is administered.

8.11 Summary

The impact of a range of different regimes of vaccination has been studied with the following conclusions. Vaccination acts to decrease the number of cases and increase the inter-epidemic period. The age

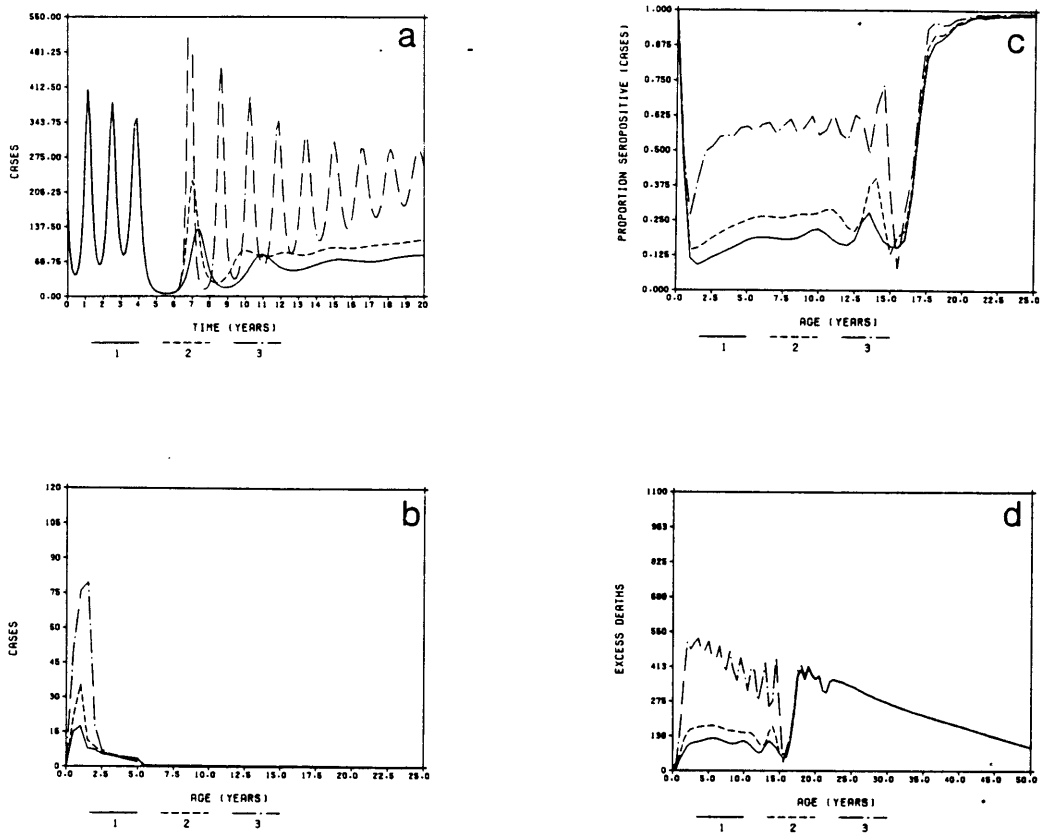


Figure 8.19
Two-phase programmes. Predicted impact of vaccination programmes which start off with one regime and then switch to another. In all three cases the initial regime is to vaccinate 75% of 9 month old susceptibles starting at time t = 4 years. The results were generated using the Boué baseline parameter set.

(a) Total cases through time.
(b) Age incidence of measles at the peak of the last epidemic.
(c) Proportions seropositive through the presence of maternal antibodies or naturally acquired immunity following infection. Taken at the time of the peak of the last epidemic.
(d) Numbers by age in the excess deaths class at the peak of the last epidemic.

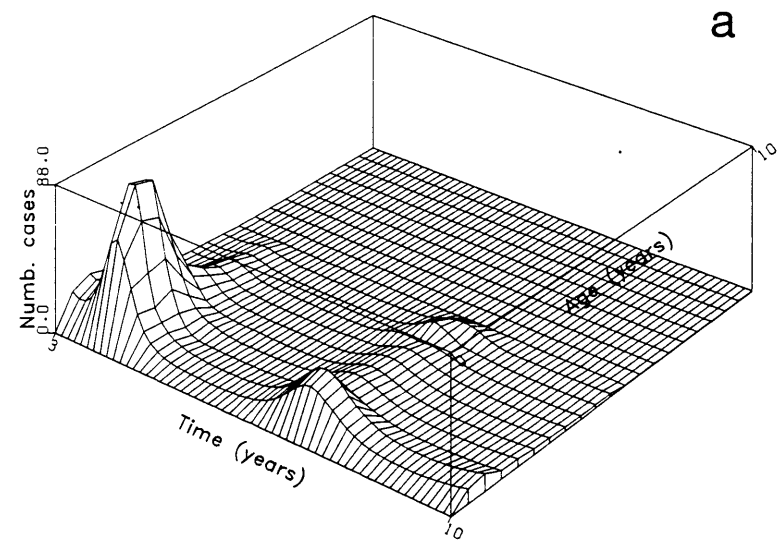
1 Unchanging regime reaching 75% of 9 month old susceptibles. The peak of the last epidemic is at time t = 20 years.
2 At time t = 4 years a regime reaching 75% of 9 month old susceptibles is introduced, and at time t = 6 years this is changed to 75% of 1 year old susceptibles. The peak of the last epidemic is at time t = 20 years.
3 At time t = 4 years a regime reaching 75% of 9 month old susceptibles is introduced, and at time t = 6 years this is changed to 75% of 15year old susceptibles. The peak of the last epidemic is at time t = 19.5 years.

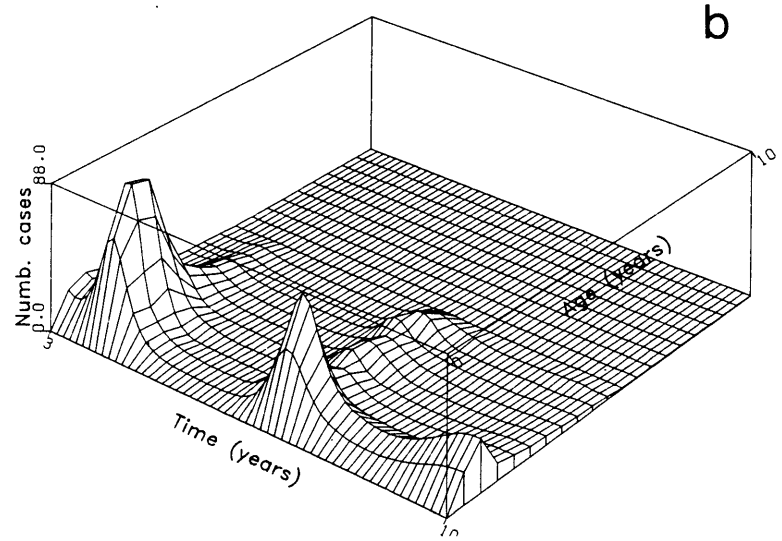
Figure 8.20
Three dimensional views of cases by age and time for the two-phase programes as compared with an unchanging regime. Time ranges from t = 3 years to t = 10 years, and age ranges from 0 to 10 years.

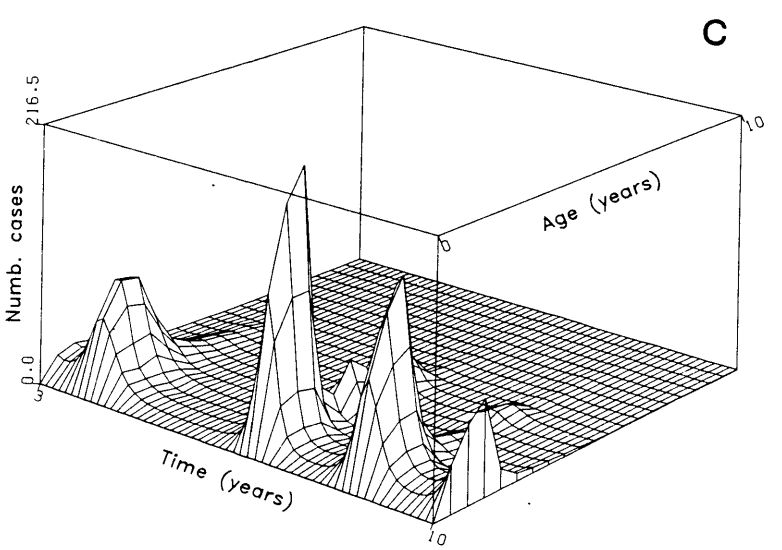
(a) Unchanging regime reaching 75% of 9 month old susceptibles.

(b) At time t = 4 years a regime reaching 75% of 9 month old susceptibles is introduced, and at time t = 6 years this is changed to 75% of 1 year old susceptibles.

(c) At time t = 4 years a regime reaching 75% of 9 month old susceptibles is introduced, and at time t = 6 years this is changed to 75% of 15year old susceptibles.


a
88.0
Numb. cases
0.0
Time (years)
Age (years)
10
10


b
88.0
Numb. cases
0.0
Time (years)
Age (years)
10
10


c
216.5
Numb. cases
0.0
Time (years)
Age (years)
0
10
10

distribution of cases is altered so that there are more cases amongst older children, and the window problem is eased. Immediately after the introduction of immunisation there is a long period of low disease incidence. This phen omenon has been called the 'honeymoon period'. This effect becomes more marked with increasing levels of immunisation. The effect is generated during the shift from the stable age distribution of susceptibles that exists before the introduction of vaccination, to that which exists after its introduction. Studies on the impact of regimes which administer vaccine at different ages find that the optimal age to vaccinate is dependent on the patterns of disease prevalence that exist in the community before the introduction of immunisation. Thus for a community with a very low average age at infection and a severe window problem, the optimum age for vaccination is around $\frac{6\text{-}9}{4}$ months. For a community where the average age at infection is older and the window problem less severe, the best results are obtained by immunising at age 1 year 3 months. Studies of two stage programmes (which vaccinate each cohort twice) underline the point that optimal control policy can only be determined with a knowledge of existing patterns of disease incidence. Studies of two-phase programmes (which start with one vaccination regime, and then switch to another) suggest that switching strategy in the middle of a programme can act to reduce the impact of mass vaccination.

Chapter 9

Alternative Definitions of the Force of Infection.

9.1 Aims of chapter 9.

In this, the last chapter of results, the aim is to consider a variety of ways in which the force of infection could be related to the number of infectious people and the size of the total population. The chapter investigates one family of such relationships and studies how it can influence patterns of measles incidence in growing populations. Particular attention is paid to the manner in which the age prevalence of disease changes as population size grows. Consideration is given to the type of data that would be required to measure the parameters that are introduced in a new definition of the force of infection.

9.2 Chapter layout.

The chapter commences with a discussion of the exact meanings of the model's compartments M, X, H...etc. Two possible ways in which the force of infection might be related to community size are then presented. The new parameters introduced in their definitions are then discussed. Attention then focuses on three pieces of data concerning changes in age prevalence that come about as a result of increases in community size. The next section of the chapter studies one particular range of definitions of the

force of infection. First the sensitivity of the model's predictions to variations in this definition is considered. This is followed by consideration of the predicted impact of mass vaccination, and the way in which assumptions built into the definition of the force of infection changes such a prediction.

9.3 Semantics and definitions.

In the preceding chapters it has been the practice to refer to the quantity M(a,t) as the number of children in the community of age a at time t who are protected by maternal antibodies; to X(a,t) as the number of susceptibles of age a at time t; and so on. Existing studies using these types of models have tended to define the quantities X, Y, and so on as densities of susceptibles, infectives, or whatever. When studying epidemics within populations of constant size, interchangeable use of the words 'number' and 'density' does not cause confusion. However once the assumption of constant population size is dropped it becomes very important to be clear about which definition is being used. In what follows the definition of X(a,t) continues as the number of susceptibles of age a at time t.

In chapter 4 a working definition of the force of infection was adopted (equation 4.8) and all the work in subsequent chapters has been based upon this definition. The definition is as follows;

$$\lambda(a,t) = \frac{\int_0^\infty \beta(a,a')\ Y(a',t)\ da'}{\int_0^\infty N(a',t)\ da'} \qquad (9.1)$$

This definition, by assuming that the force of infection is determined by the proportion of the community that are infectious, renders the force of infection independent of community size. In a study of the epidemiology of endemic infections in growing populations May and Anderson (1985) have used the following definition of the force of infection;

$$\lambda(a,t) = \int_0^\infty \beta(a,a')\ Y(a',t)\ da' \qquad (9.2)$$

Using this definition for a growing population implies the assumption that the force of infection rises linearly with increasing community size. It seems clear that the true relationship between the rate of disease transmission and the size of the community lies somewhere between these two extremes. There is of course an endless variety of functions that, upon parameter variation, will provide a continuum between the two, but in this chapter two possibilities are discussed, and one is studied in detail. The latter (which was first suggested by Anderson (1982b) is as follows;

$$\lambda(a,t) = \frac{\int_0^\infty \beta(a,a')\ Y(a',t)\ da'}{\left[\int_0^\infty N(a',t)\ da'\right]^\rho} \qquad (9.3)$$

where the parameter ρ lies between 0 and 1. Setting $\rho = 1$ recaptures definition (9.1), so that the force of infection is independent of community size, and setting $\rho = 0$ recaptures definition (9.2), where the force of infection rises linearly with community size. So what does the parameter ρ measure? It is a composite measure of two quantities; a physical one and a sociological one. The physical measurement describes the relationship between community size and population density. It is therefore a measure of the way in which the area of a city changes as the number of people increases. The sociological component is more subtle, and is a

measure of changes in people's lifestyles that come about as their population density or community size increases or decreases.

The alternative intermediate definition that is discussed here has been suggested by Dietz (1982) and takes the form of a saturation function along the lines;

$$\lambda(a,t) = \frac{\int_0^{\infty} \beta(a,a')\ Y(a',t)\ da'}{A + B\int_0^{\infty} N(a',t)\ da'} \qquad (9.4)$$

Setting A equal to 0 and B to 1 recaptures definition 9.1, and setting A to 1 and B to 0 recaptures definition 9.2. For intermediate values of A and B, when the total population is small the constant term A dominates and the relationship resembles that in definition 9.2. That is the force of infection increases as the population grows. But when the total population is large the term B × total population dominates and the force of infection becomes less dependent on community size.

9.4 Data and data interpretation.

In the years 1883 to 1902 the town council of Aberdeen made it compulsory to notify all cases of measles, and prosecuted those found to have failed to do so. The data is of particular value because the cases were recorded by age stratified into single years rather than grouping into five year age bands. This gives an unusually fine 'grain' to the data and allows the construction of an interesting view of annual age incidence over the twenty year time span. The data is portrayed graphically in figure 9.1. Over

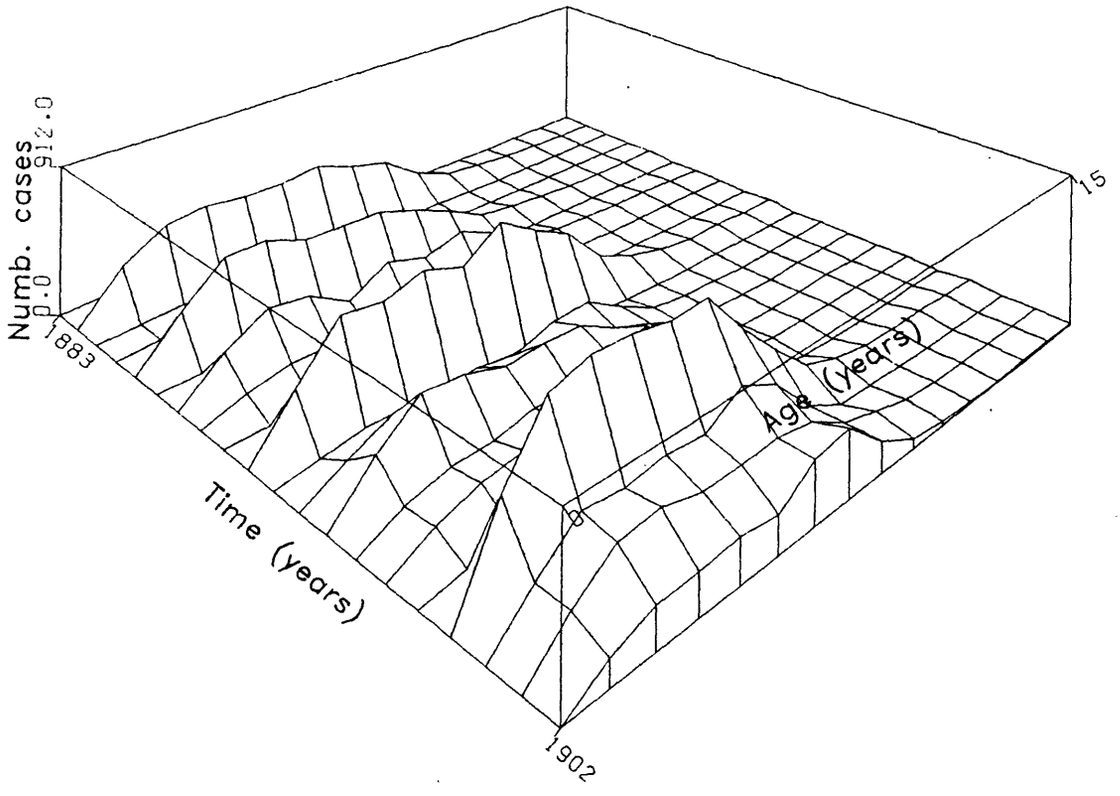


Figure 9.1
Measles age prevalence from Aberdeen in the years 1883 to 1902. Data are from Wilson (1904)

Year	Population
1881	105,538
1891	123,348
1901	154,295

Table 9.1
Population of Aberdeen between 1883 and 1902. Data are from Wilson (1904)

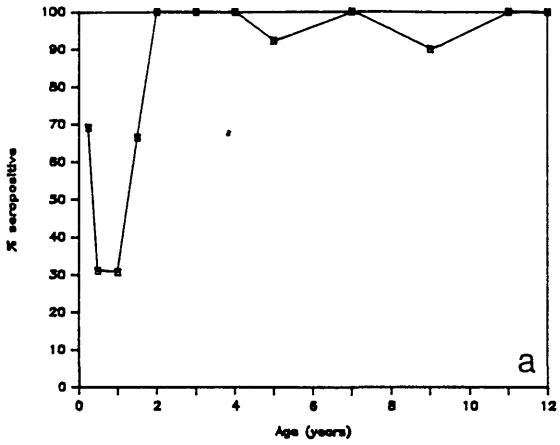
Figure 9.2
Age specific serology and cumulative cases by age from community studies in urban and rural populations in developing countries. These illustrate the younger average age at infection in urban centres.

(a) & (b) Serological profiles from Senegal: Dakar and Popenguine, a small fishing village. Data are from Boué (1964)

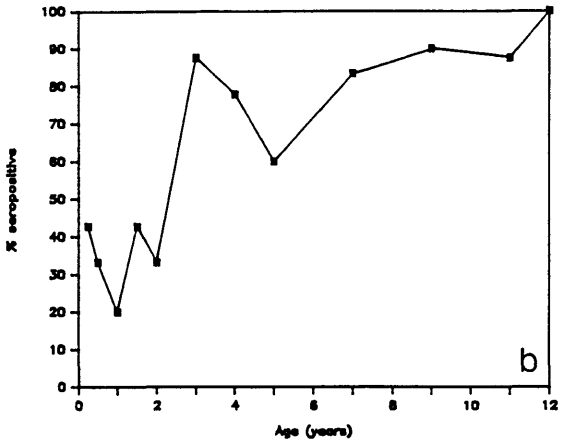
(c) & (d) Serological profiles from Nepal : The flatter more densely populated Terai areas and hill regions. Data are from Brink & Nakano (1978)

(e) & (f) Cumulative cases by age from Urban and Rural South Africa. Data are from Loening & Coovadia (1983)

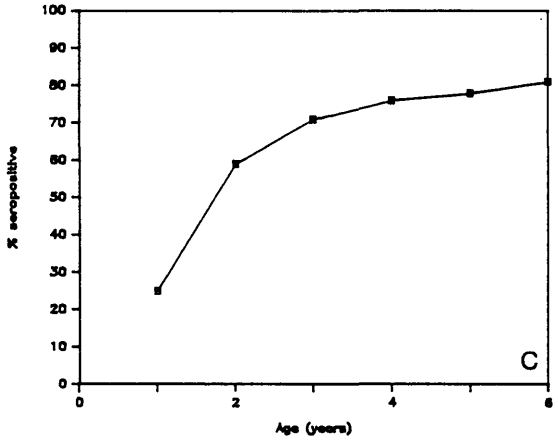
Senegal: Dakar



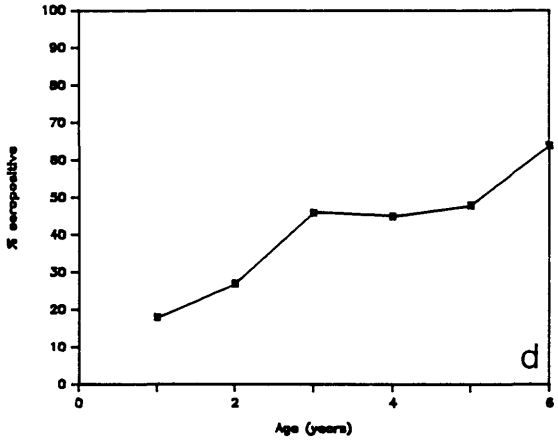
Senegal: Popenguine



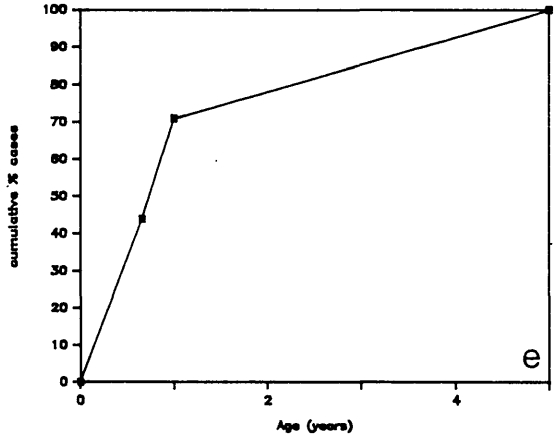
Nepal: Terai



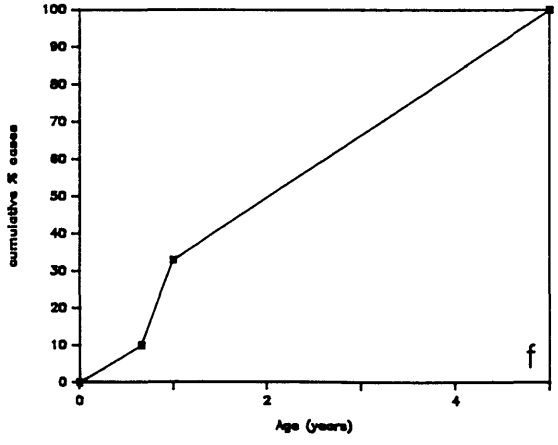
Nepal: Hills



S. Africa: Urban



S. Africa: Rural



the course of twenty years (1883 - 1902) the population of Aberdeen grew by 50% (table 9.1) but there was no detectable shift in the age distribution of cases over this time. This is evidence on the side of setting the parameter ρ of definition 9.3 to zero, and making the force of infection independent of community size. However this is incompatible with the wealth of data that show that in urban areas the average age at infection is lower than in rural areas. Figure 9.2 shows data from a selection of three such studies that are from developing countries. This information reveals that in denser populations the rate of disease transmission is higher than in low density (or small) communities.

The sort of data that is available to allow the estimation of the parameter ρ compares the average age at infection with community size. In order to interpret such data the following argument is used.

To a first approximation,

$$\lambda \simeq 1 / A \qquad (9.5)$$

The definition 9.3 (in its age independent form) can be rewritten;

$$\lambda = \beta y \bar{N}^{(1-\rho)} \qquad (9.6)$$

where y is the <u>proportion</u> infectious, and as before $\bar{N}$ is the total population. Then taking logarithms yields the following linear relationship between $\log \lambda$ and $\log \bar{N}$,

$$\log \lambda \simeq \log (\beta y) + (1 - \rho) \log \bar{N} \qquad (9.7)$$

Figure 9.3 shows some data collected in New York State at the beginning of this century which compares community size and average age at infection. Figure 9.4 shows the same data under a log transformation. The best

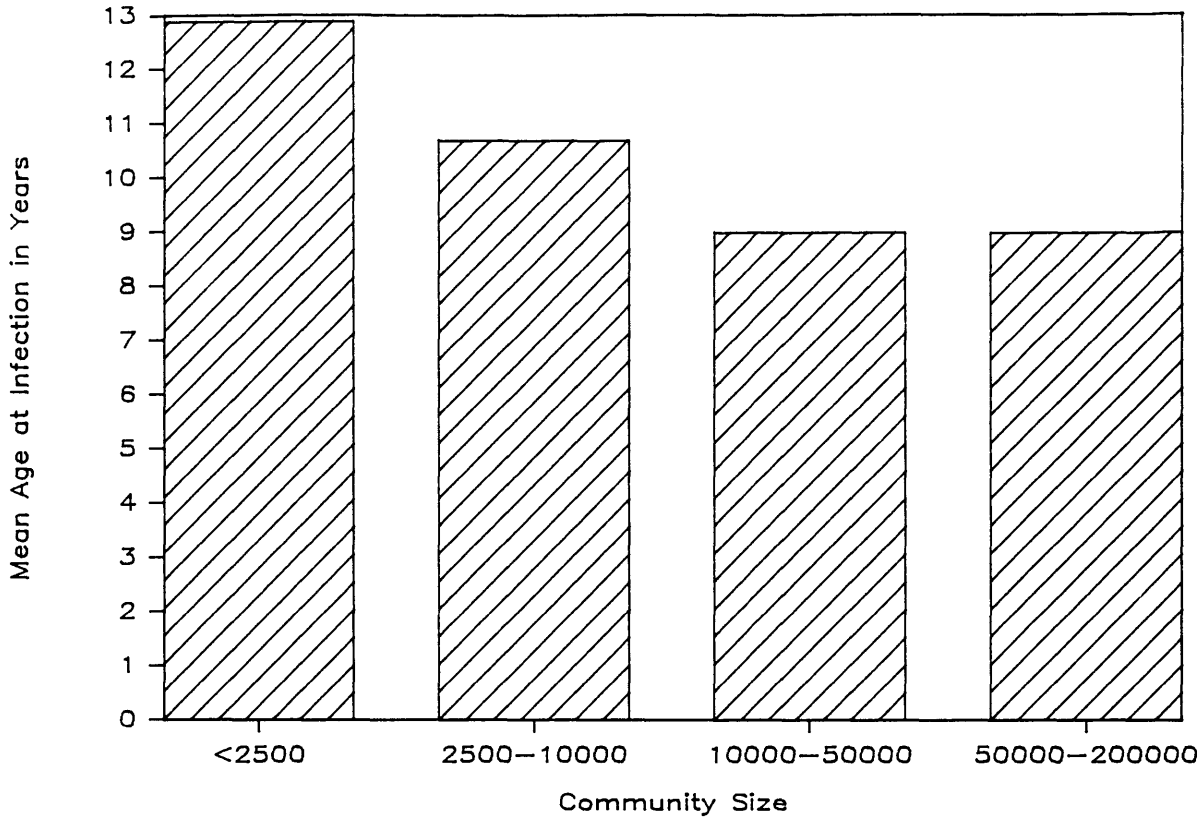


Figure 9.3
Average age at infection for a range of different sized towns in New York State. Data are from Fales (1928)

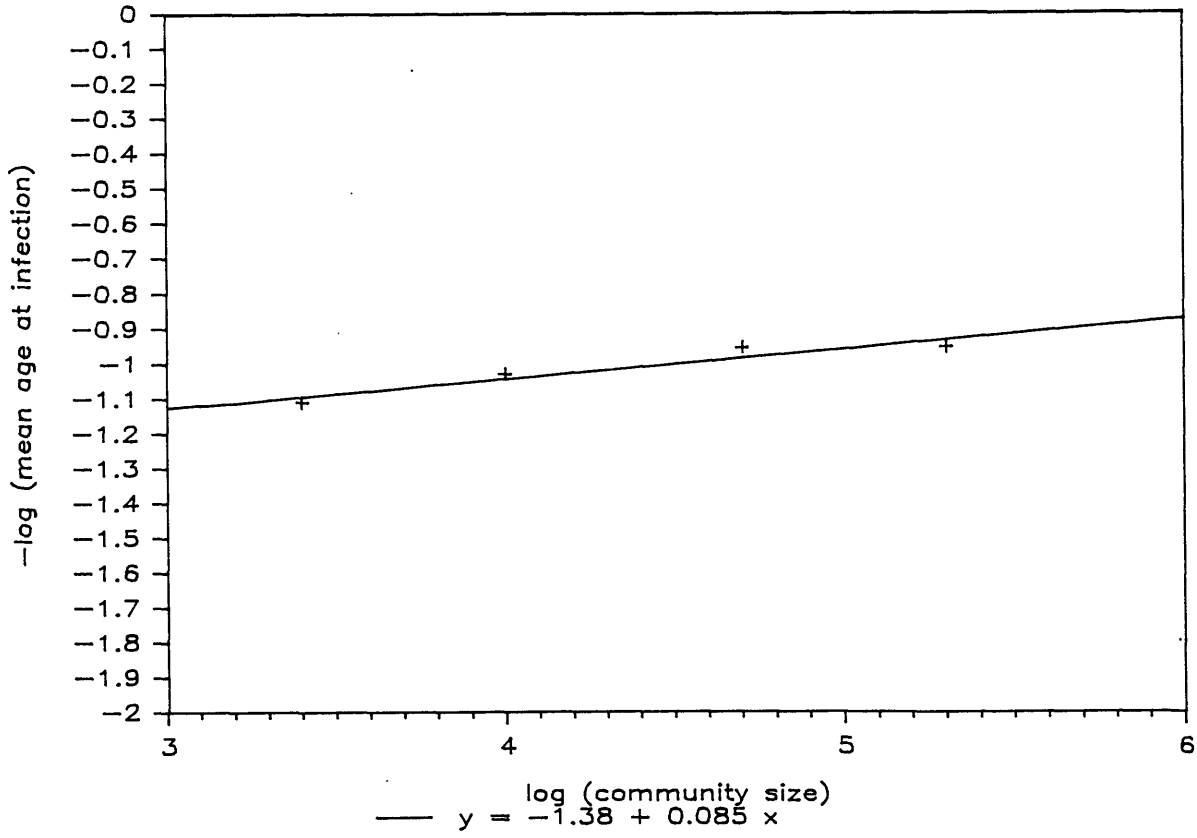


Figure 9.4
Data from figure 9.3 under the logarithmic transformation.
\+ Transformed data.
--- Best estimate for a straight line through the points.
The slope of the line is estimated as .085 ± .09

estimate for the slope of the line is 0.085 giving an estimated value of ρ of 0.915. The 95% confidence interval for the estimated value of ρ is $\pm$ 0.090

It is hard to see a way in which field data could be interpreted so as to indicate which of the definitions 9.3 or 9.4 would be the best to use. However having chosen a relationship between λ and N it should be possible to collect data that would allow the estimation of the value of the parameter ρ. Ideally such data would be in the form of a series of serological profiles taken over the course of time in the same place whilst a population grew in size such that the population density rose. However the serology would only be easy to interpret if drawn from an unvaccinated population, and for measles such populations are disappearing fast. However, in the late 1950's and early 1960's quite a lot of serological profiles were collected in developing countries. It would be of great value to return to those communities now and collect further serological data to see if the age prevalence has changed over the past twenty years. The alternative is to repeat the data collection exercise performed in New York State early this century and collate age prevalence data from a variety of unvaccinated communities of different size. For example this could be done in India where there is as yet no well organised mass vaccination programme against measles. The need for such a study is urgent since the Indian Health Authorities are under increasing pressure from the World Health Organisation to introduce mass measles vaccination.

9.5 Sensitivity of model predictions to variation in the parameter ρ.

Using the numerical analysis programme developed for the work in chapters 7 and 8 it has been possible to carry out simulations aimed at investigating the effect of assigning different values to the parameter ρ. These simulations use the definition of the force of infection given in equation 9.3. Figure 9.5 shows serological profiles at time t = 4 years and t = 18 or 20 years from two experiments using the Ueda baseline parameter set. In figure 9.5(a) the value of ρ in definition 9.3 was set to 1, so the definition of the force of infection is the same as in previous chapters. The serological profile remains constant in shape over the 16 years. Figure 9.5(b) is drawn from a simulation where the parameter ρ was assigned the value 0.5. In this case the serological profile shifts so that there is a steeper rebound following loss of protection by maternal antibody after the 16 years. Figure 9.6 shows the results of an experiment where the value of ρ was varied over 5 values from 1 to 0. The experiment was performed employing the Ueda parameter set, which assumes a high birth rate and a low death rate. The total population at the start of the experiment illustrated in figure 9.6 is 200,000 and at the end of the twenty years for which the simulation runs the total population is 440,000. The smaller the value of ρ the shorter the inter-epidemic period becomes (fig 9.6(a)). However, the total number of cases is not affected. This reflects the fact that virtually everybody eventually experiences measles infection, and changes in the force of infection only affect the age at which the disease is contracted. Figures 9.6(b) and (c) illustrate the fact that when ρ is less than 1 the age distribution of cases shifts towards younger children as the population grows, and that smaller values of ρ lead to greater

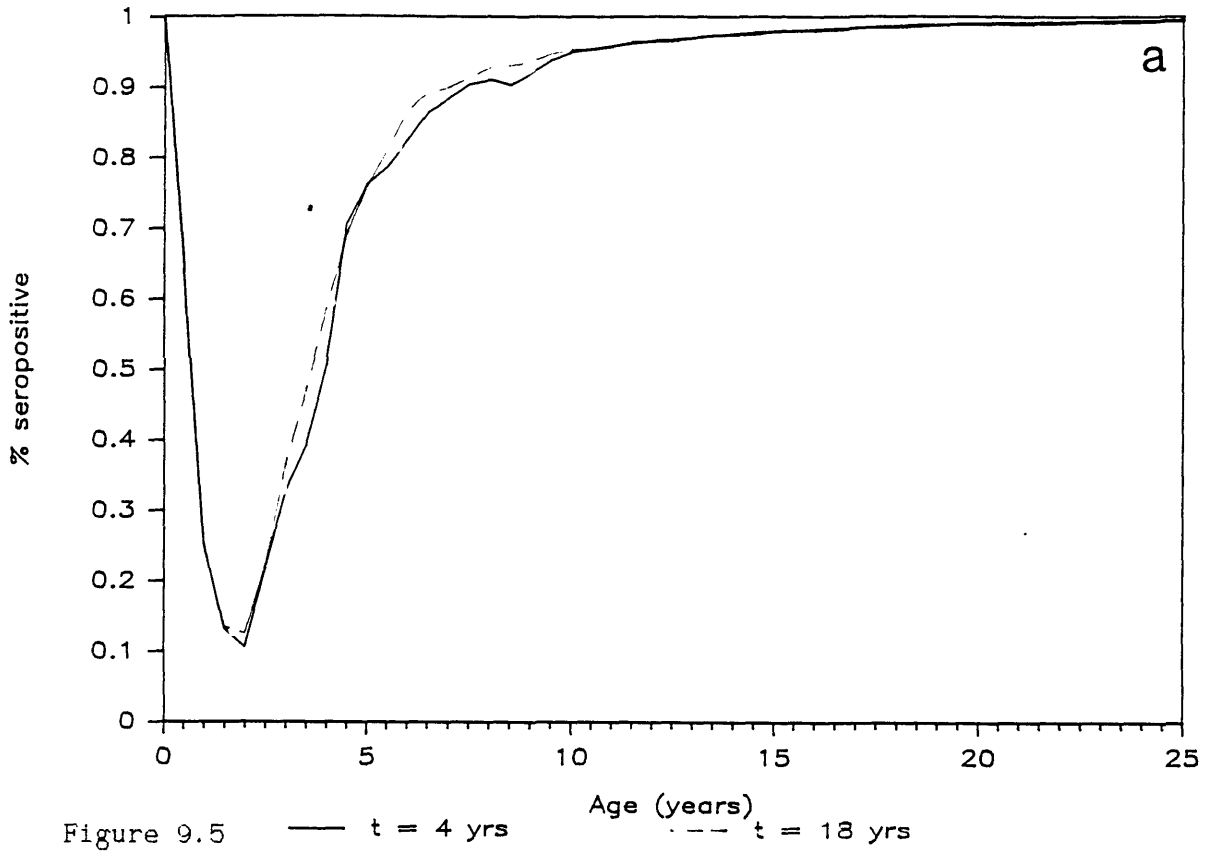
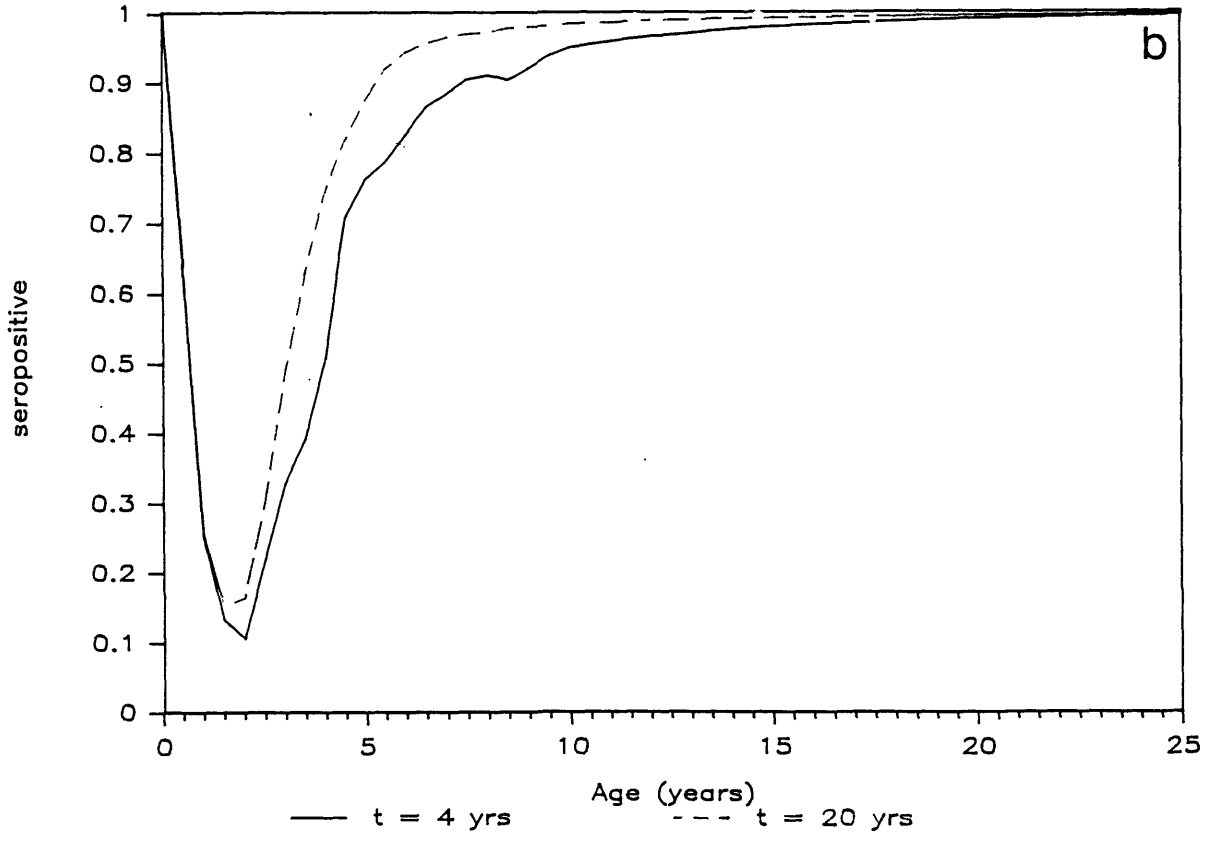


Figure 9.5
Serological profiles at time t = 4 years and at the peaks of the last epidemics. In (a) the parameter ρ was assigned value 1 and the profile does not change. In (b) the parameter ρ was assigned value 0.5 and the profile has become steeper over the course of the sixteen years.



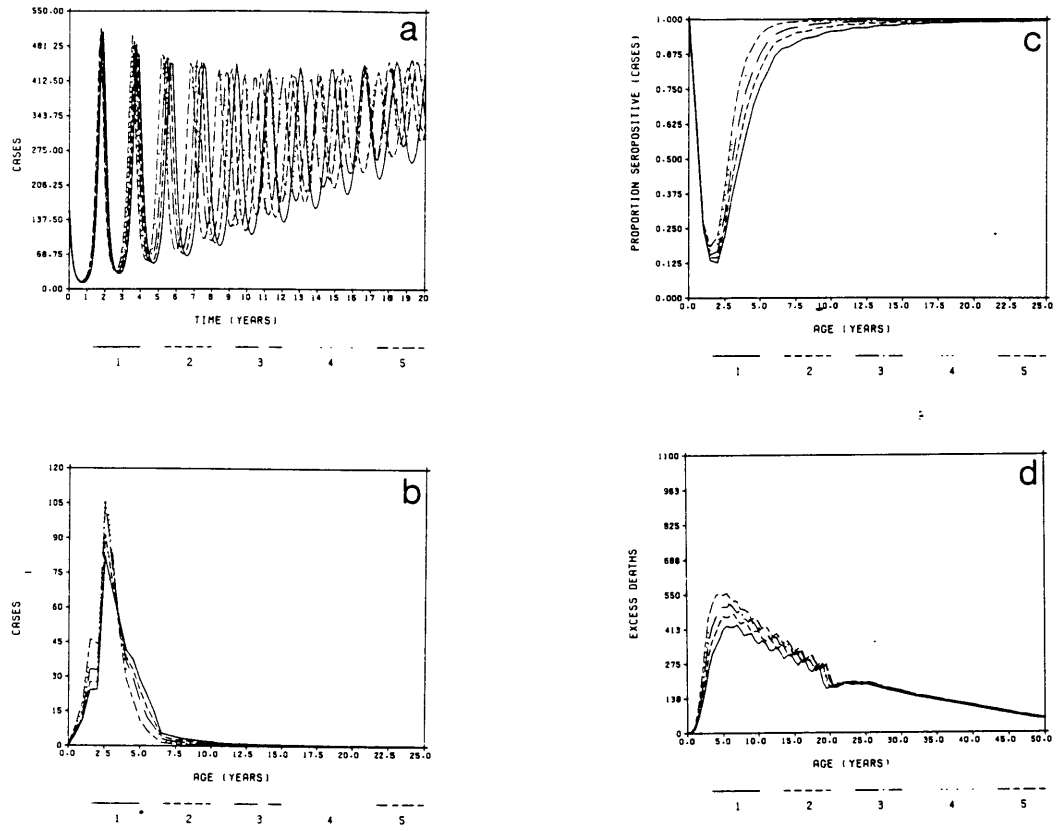


Figure 9.6
Sensitivity of the model's predictions to variation in the parameter ρ. Results generated using the Ueda baseline parameter set.
(a) Total cases through time.
(b) Age incidence of measles after twenty years.
(c) Proportions seropositive through the presence of maternal antibody or naturally acquired immunity following infection.
(d) Numbers by age in the excess deaths class.

1 ρ = 1.0
2 ρ = 0.75
3 ρ = 0.5
4 ρ = 0.25
5 ρ = 0.0

shifts in age distribution. The result of the changes in age distribution is greater numbers of excess deaths because the case fatality rate is greater amongst the younger individuals (fig 9.6(d)). Figure 9.7 shows results of this experiment illustrated by three dimensional views of cases by age and time for three different values of ρ. These show the changes in age distribution of cases that occur when ρ is assigned a value less than 1. Figures 9.8 and 9.9 illustrate a variant of this experiment that considers long term predictions for different values of ρ. The simulations cover 60 years rather than the usual 20, but only the two extreme cases $\rho = 1$ and $\rho = 0$ are studied. As before the number of cases is largely unaffected, but when $\rho = 0$ the inter-epidemic period gets shorter and shorter and the rate of damping of the oscillations is increased (fig 9.8). After 60 years the change in age distribution of cases is even more marked (fig 9.9(a) and (b)), and the differences in the number of excess deaths even greater (fig 9.9(c)). The final figure of this chapter (fig 9.10) illustrates the sensitivity of the predicted impact of immunisation to the definition of the force of infection. The results were generated using the Ueda baseline parameter set, and based on introducing a vaccination regime of 97% of susceptibles at age 1 year 3 months. The figure illustrates the predicted number of cases for the two possibilities $\rho = 1$ and $\rho = 0$. When ρ is set at a value of 1 the vaccination regime is adequate to eradicate the disease. But when ρ is set to 0 there is a huge epidemic 24 years after the introduction of vaccination.

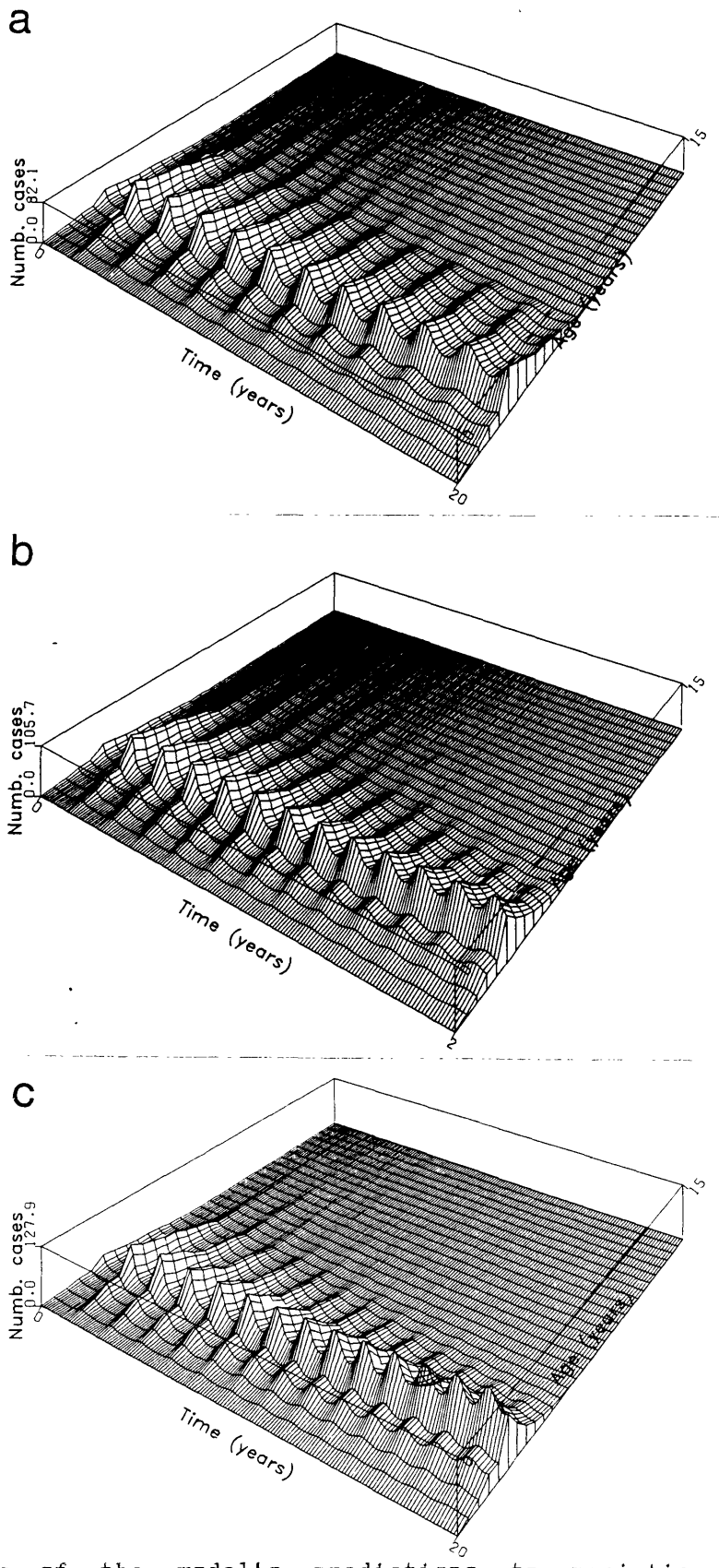


Figure 9.7
Sensitivity of the model's predictions to variation in the parameter ρ. Three dimensional views of cases by age over the course of time.

(a) $\rho = 1$. There is no change in the age distribution of cases over the twenty years.

(b) $\rho = 0.5$. There is a slight shift in age distribution towards younger individuals.

(c) $\rho = 0$. There is a more marked shift in age distribution towards younger individuals.

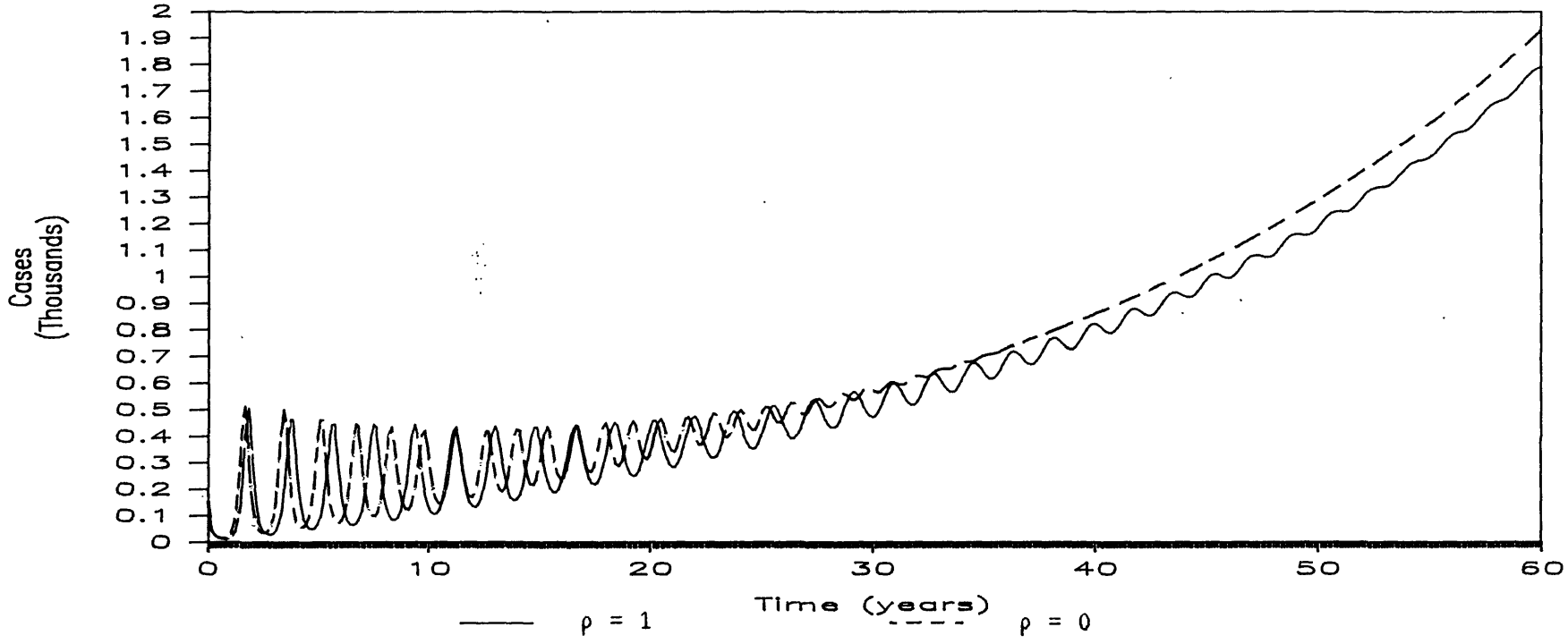
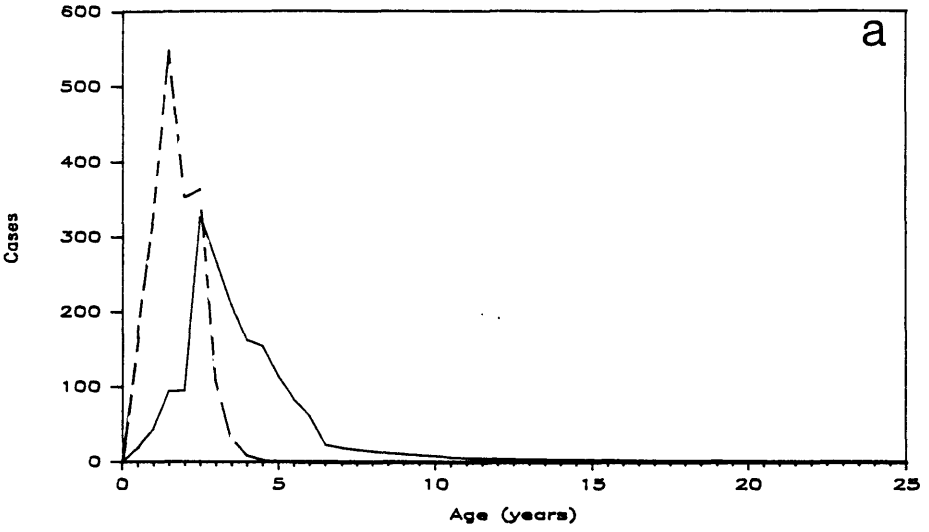
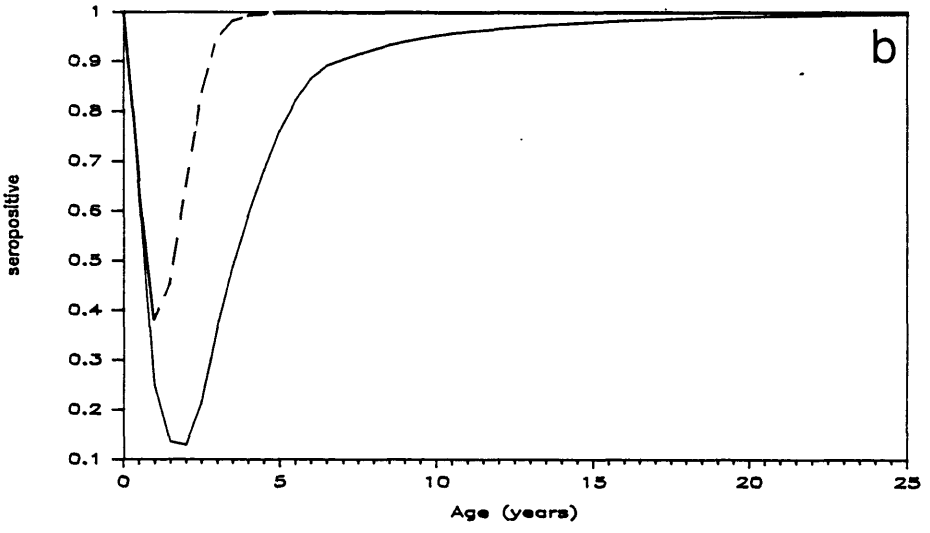


Figure 9.8
Total cases through time over the course of sixty years for the two extreme values of ρ; ρ = 1 and ρ = 0. Results generated using the Ueda baseline parameter set.

Figure 9.9
Sensitivity of long term model predictions to variation in the parameter ρ for the two extreme values $\rho = 1$ and $\rho = 0$. Results generated using the Ueda baseline parameter set.
(a) Cases by age after 60 years
(b) Proportion seropositive by age after 60 years.
(c) Numbers by age in the excess deaths class after 60 years.


a
Cases
600
500
400
300
200
100
0
0
5
10
15
20
25
Age (years)


b
seropositive
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5
10
15
20
25
Age (years)


c
excess deaths (thousands)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
30
35
40
45
50
Age (years)

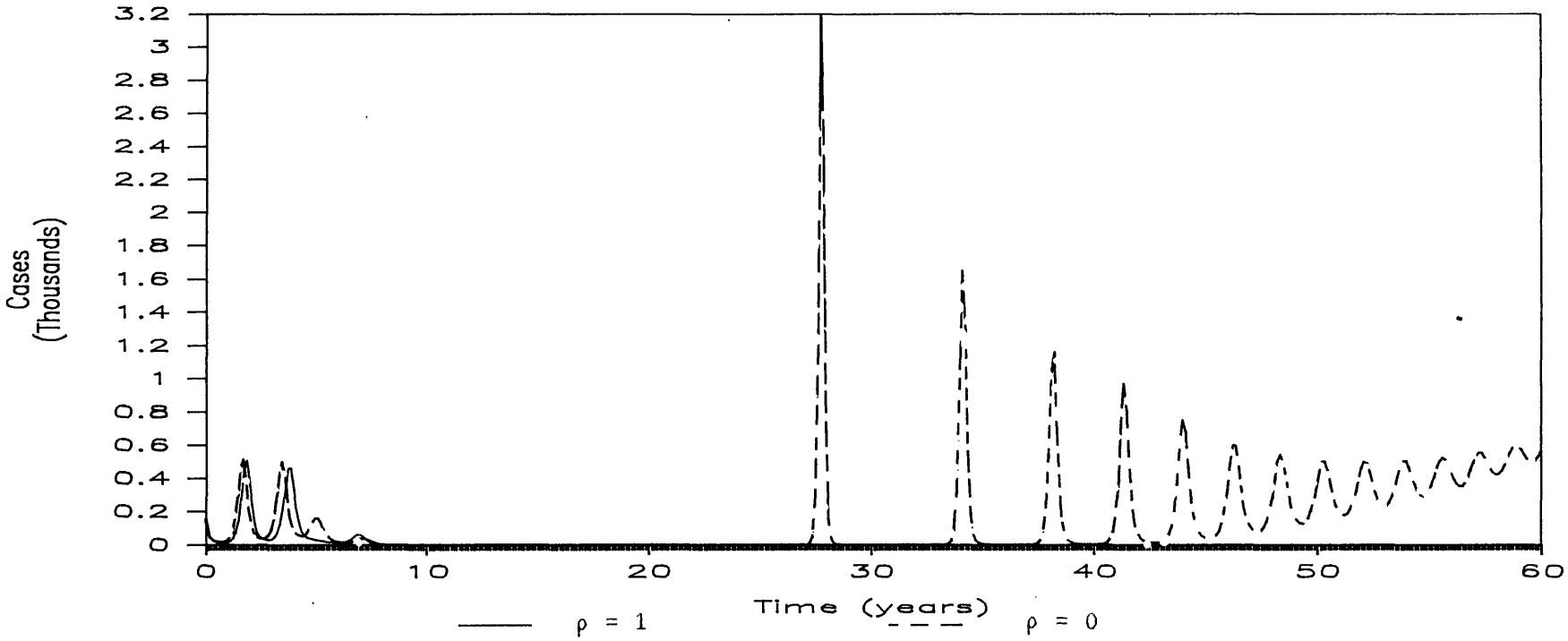


Figure 9.10
Sensitivity of the predicted long term impact of vaccination under variation of the parameter ρ. Results generated using the Ueda baseline parameter set and assuming vaccination of 97% of susceptibles at age 1 year 3 months.

9.6 Summary.

One possible range of definitions of the force of infection has been studied, and a range of responses to population growth generated. If the force of infection is assumed to be strongly dependent upon the size of the population, the age distribution of cases shifts towards younger children over the course of time. This results in more excess deaths, and decreases the impact of control programmes.

Chapter 10

Implications for Public Health Policy

10.1 Aims of chapter 10.

The purpose of this chapter is to present a brief summary of the practical implications of results discussed in previous chapters.

10.2 Chapter layout

There are five results felt to be of direct relevance to the design of vaccination programmes, and these are discussed in the following sequence. First attention is focused upon the relationship between the critical vaccination proportion and the average birth rate. The second conclusion concerns the necessity of acquiring adequate quantitative information on the epidemiology of measles before an optimal programme can be selected. The period of low incidence that follows the introduction of an immunisation programme (the 'honeymoon period') is then discussed. The fourth section considers the outcome of two-phase programmes (i.e. programmes that begin with one strategy and then switch to another). The fifth and final section deals with potential changes in age prevalence of measles as a result of increases in population size, and the way in which such changes would influence the outcome of a vaccination campaign.

10.3 The critical vaccination proportion and the average birth rate.

In chapter 5 the following two results were derived:

$$R_0 \simeq B / A \qquad (5.23)$$

$$p_c \simeq 1 - 1 / R_0. \qquad (5.26)$$

where R_0 is the basic reproductive rate, B is the reciprocal of the average birth rate, A is the average age at infection and p_c is the critical vaccination proportion for eradication.

If equation 5.23 is rewritten as follows,

$$A \simeq B / R_0$$

one can see that the average age at infection in a community is dependent upon two factors, one demographic (B) and one determined by the degree of mixing and magnitude of disease transmission (R_0). A low average age at infection can therefore be caused by two things; a high birth rate (thus low B) or a high basic reproductive rate (thus large R_0). If the average age at infection is low because the average birth rate is high, eradication will be much easier than if the low average age at infection is the result of a large basic reproductive rate.

10.4 Necessity of acquiring good epidemiological and demographic data.

In chapter 8 section 8 comparisons were made to establish the effect of administering vaccine at different ages, and it was found that the best age for vaccination was quite different for the two different parameter sets. (See figures 8.13(a), 8.14(a), 8.16(a) and 8.17(a)) That is, the optimal control programme for a community is strongly dependent upon the pattern

of age incidence of disease prevailing in that community. It is therefore essential to perform some kind of study of age incidence of disease before embarking upon the design of a vaccination programme. The sort of study that is performed must, clearly, depend upon the resources available, but the minimum adequate information would consist of a community survey of the average age at infection. For a disease like measles where the severity of the symptoms is strongly age dependent, a hospital based survey is bound to be biased towards younger individuals. The most reliable way to find the age prevalence of disease is to perform a serological survey based on the collection of a large number of serum samples over a broad spectrum of ages. However in many places such a project would be beyond the scope of existing facilities. In such cases, community based studies which record all cases over the course of a complete epidemic cycle could be used to estimate the average age at infection. Because of the great variation in age prevalence patterns between communities, (as illustrated in chapter 5), and the importance of accurate information about such patterns when designing a control programme, indiscriminate use of data from one place when designing a control programme for another is inadvisable.

Another aspect of data requirements is that of the completeness of data sets. This point was first emphasised in chapter 6 in the context of the estimation of epidemiological parameters such as the basic reproductive rate and the critical vaccination proportion. It is highly desirable to have reliable information on the demographic characteristics of a community for whom a vaccination campaign is being planned in addition to the kind of age prevalence data discussed above. Demographic data - particularly the

annual birth rate - have an important bearing upon the critical vaccintaion proportion for eradication as discussed in section 10.3.

10.5 The 'honeymoon period'.

At the end of chapter 8 section 8 a special emphasis was laid upon the long period of low incidence that follows the introduction of mass immunisation, which has been dubbed the 'honeymoon period'. Because of different patterns of age prevalence, patchy vaccine administration (in a spatial sense) and the gradual introduction of immunisation these patterns have not been clearly identifiable in developed countries following the initiation of mass vaccination. However in developing countries low average ages at infection and a comparatively sharp initiation of large scale immunisation programmes will give rise to more obvious manifestations of this phenomenon. Health planners should therefore be warned that the apparent initial success of a vaccination campaign may be followed by a large epidemic. The timing and size of such an epidemic will depend upon the level of coverage, the details of the age specific rate of disease transmission, and the age structure of the community.

10.6 Two-phase programmes.

In chapter 8 section 10 a study was made of the impact of programmes which start with one vaccination regime and then switch to another (two-phase programmes). The experiments were performed to see if it would be possible to improve the efficacy of a control programme by changing the strategy after a few years of mass vaccination. It has been postulated

(Black, 1982) that following the rise in the average age at infection (which comes about as a direct consequence of mass immunisation) it should be possible to raise the age at vaccination and achieve higher rates of seroconversion. In the small number of cases that have so far been studied raising the age at vaccination two years after programme initiation reduces the impact of the control programme. This reduction in the efficacy of the programme comes about because there are large numbers of cases at ages below the new age at vaccination. It may be that for higher levels of vaccination than those tested there is an advantage to be gained by switching strategies, or that the strategy should not be switched until a longer period than two years has elapsed. If there is an advantage to be gained by switching strategies, there is clearly a fine balance to be achieved and caution would be necessary in assessing when to switch.

10.7 Changes in community size.

Chapter 9 investigated the impact of population growth upon age prevalence of disease. The results showed that in circumstances where age prevalence does shift towards younger individuals as population grows, the changes are slow, but can have a dramatic affect upon the impact of a vaccination programme. Figure 9.10 showed the predicted impact of a vaccination programme applied to a growing community under two different assumptions about the relationship between the rate of disease transmission and the size of the community. Under the 'best' assumption (rate of disease transmission independent of community size) the vaccination regime was enough to eradicate the disease. But when the 'worst' assumption (strong correlation between increases in population size and increase in the rate of

disease transmission) was applied the vaccination regime was not adequate to eradicate the disease because of the increases in the rate of disease transmission which accompanied population growth.

It is hard to determine a very precise way in which to define the force of infection $\lambda(a,t)$, and the work presented in the chapter has been based upon only one of the many possible definitions. Because of these shortcomings, and the general lack of reliable data on the subject it would seem unwise to interpret the results of the chapter as other than a general caution. This could be stated as; 'beware of shifts in age prevalence towards younger children that may accompany population growth as these may render an optimal control programme obsolete'.

10.8 Summary

Five major results that have emerged during the course of the project have been singled out as being of particular relevance to the planning of public health policy in developing countries.

Chapter 11

Final Discussion.

In this the final chapter of the thesis a discussion is presented that concerns itself with the project's successes and failures, alternative approaches, and directions in which further progress could be made.

The bulk of the new results are presented in the preceding chapter. There are, however, some points that do not conform to that chapter's brief which could provide new insights into old problems. The concept of excess deaths has proved a useful idea, both for the interpretation of case fatality rates as disease related death rates, and for the interpretation of serological profiles drawn from communities that have suffered significant case fatalities. Furthermore the concept already has currency amongst physicians working in the field of tropical public health who have long been aware that deaths are postponed, not prevented. In more general terms, the rigour involved in the estimation of model parameters is an aid to the understanding of interactions between different data sets and can therefore act as a guide in the collection of data.

Looking back to the introductory chapter it can be seen that one of the stated aims of the project was to construct a tool that could be used to compare the impact of different regimes of vaccination. To some extent this has been achieved: the use of this tool produced several of the points

discussed in chapter 10. Its potential is not yet exhausted, and discussion turns below to further ways in which it might be used.

In a catalogue of the project's failures,the most unsatisfactory area of inquiry concerns the critical vaccination proportion for eradication, p_c. This result (presented in chapter 5) has been derived from a simplified version of the model which ignores the existence of maternal antibodies. The only defence for this approach is that it has led to the result discussed in chapter 10 section 3 which does offer some general insight into levels of vaccination required for eradication. A more specific, and perhaps more serious criticism of the project is that the two types of objectives (understanding and deciding) that were identified in the introductory chapter have to some extent become inseparable. Thus a model containing all the complications (useful when trying to choose between regimes of vaccination) has been used in the sections that try to understand the interactions between different processes. The failure to understand the cause of the results presented in chapter 7 sections 7 and 9 (namely the effects of changes in the relative values of the forces of infection and the configuration of the WAIFW matrix $\overset{o}{\underset{\Delta}{\wedge}}$ the model's dynamic behaviour) are the most glaring manifestations of the problems arising from working with a very complex (and supposedly more realistic) model.

A better way to approach the problem of complexity versus simplicity is to introduce the complications one at a time. First of all a model for a population of fixed size that suffers significant case fatalities might have been studied. Then a model for a growing population without case fatalities could have been considered. Throughout all this, age dependence in the force

of infection could have been omitted. Only at the time when different programmes of immunisation were to be compared should all the complications have been included at once.

Looking forward rather than back, the following are seen as possible directions for future development. The computer programme that generates the numerical solutions for the model could be used to investigate the impact of other strategies of immunisation. Two phase programmes with high coverage rates are of immediate interest, as are 'pulse' programmes. The latter consist of annual periods of intense activity which aim to immunise all children in the target group over the course of a few days each year. Such strategies have been adopted in some South American countries and have aroused much interest. Another approach might be to try and build some very simple economic parameters into the model. Most of the cost of delivering vaccine to a child lies in administration and transport rather than in the actual cost of the dose (Henderson 1984). Many communities have very infrequent access to immunisation services. These two points raise some interesting questions about the logic of a rigid decree that children should not be immunised until they are nine months old. In general a model of this type would form a good basis from which to make a rigorous analysis of the economics of vaccination in developing countries.

A subject area that might benefit from further analytic investigation is the immunological status of infants as they lose their protection by maternal antibodies. Seroconversion studies show that for some children there is a period of time when they neither have measles antibody titres that would be expected to protect them from measles infection, nor can they

be successfully immunised. In this model it has been assumed that infants pass straight from the maternal antibody protected class to the susceptible (and immunisable) class. It might prove interesting to introduce an intermediate class of susceptible but not immunisable individuals in order to assess how this affected the predicted impact of vaccination programmes.

When many different factors are known to influence the epidemiology of a disease, the rigour introduced by the use of a mathematical model can serve to unravel what may appear to be a complex web of cause and effect. The work that has been presented here is the result of expressing in mathematical terms what are believed to be the essential features of the epidemiology of measles in developing countries. The purpose of this approach has been to clarify and extend the understanding of these essential features their relative importance and their interreaction in determining the epidemiology of measles in developing countries.

P.S.

In planning immunity for the herd
One observation should not be blurred
With effective protection
From viral infection
Deaths aren't prevented, just deferred.

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