REVIEWS IN MEDICAL MICROBIOLOGY

Mathematical models of infectious agent transmission and the impact of mass vaccination

D. J. Nokes and R. M. Anderson

Parasite Epidemiology Research Group, Department of Biology, Imperial College of Science Technology and Medicine, London SW7 2BB, UK

Summary. This short review provides an introduction to the development of mathematical models of infectious disease transmission and their use in gaining a better understanding of the impact of mass immunisation on the epidemiology of childhood viral and bacterial infections. We focus on the major epidemiological concepts that underpin model formulation, in particular the basic reproductive rate of an infection and herd immunity. These concepts are central to a sound understanding of how mass immunisation acts to control infectious disease and its predicted (and observed) population consequences. We give an account of the construction of a compartmental mathematical model with which to describe the transmission dynamics of a typical childhood infection, emphasising the underlying assumptions, their possible limitations, and the data necessary in order to couple theory with observation. The review is published in two parts. In the second part[*] we illustrate the use of mathematical models in the design of immunisation programmes.

Introduction

We begin with a description of the epidemiological concepts that underpin our understanding of the behaviour of directly-transmitted viral and bacterial infections in developed countries. Attention is focused on the childhood infections such as measles, mumps and rubella in industrialised countries in which transmission is effected by respiratory secretions and close contact between people. The rate of transmission or circulation of infection in the community is assumed to be directly related to the number of infectious and susceptible individuals present and to the rate of mixing that brings individuals into contact with one another.[1,2] These infectious agents are classified as microparasites, which, typically, multiply directly and rapidly within the host and elicit strong immunological responses. The latter result in short infectious periods (hence low prevalence in the community) and lifelong specific immunity to reinfection.[3]

We concentrate on two particular concepts, namely, the basic reproductive rate of a parasite and the principle of herd immunity.[4,5] We discuss the relevance of these concepts to the design of community-wide immunisation and the determination of both the vaccination coverage required to block transmission in a particular community and the optimal age at which to vaccinate. The impact of mass immunisation on the transmission of childhood infections may be viewed as an example of the influence of herd immunity.[6] We show how vaccination acts to increase both the average age at infection and the inter-epidemic period. Theoretical predictions compare well with observed trends following the introduction of mass vaccination. We also explain why mass immunisation does not result in a long-term reduction in susceptible numbers within a population until the critical coverage required for eradication is exceeded.

Request reprints to: D J N

[*] Part 2 of this review will appear in Reviews in Medical Microbiology 1992, 4

Many problems surrounding our understanding of the likely impact of mass immunisation on the incidence of infection are either quantitative in character and/or involve non-linear interactions between several variables. For example, how will the incidence of infection, and its distribution by age, change over time as a result of a particular immunisation programme, and how will this be reflected in the incidence of morbidity when the risk of severe complications resulting from infection is known to be age-dependent? What are the implications of achieving different levels of coverage on incidence and morbidity? Such questions often arise when considering the relative merits of different programmes of vaccine administration within a community. A striking example is that of the past debate concerning the desirability of selective or mass rubella immunisation for the prevention of congenital rubella infection. In these circumstances it is often helpful to examine, in quantitative terms, the relative effect of numerous factors at the same time, i.e. epidemiological (age-dependent rates of infection, and risk of complication), programmatical (age at vaccination, uptake, efficacy) and motivational (risk of vaccine-induced complications). Complex issues of this nature involving many interacting variables can be sensibly addressed using a formal mathematical framework to compare the effectiveness of different combinations of variable or parameter values (i.e. various vaccination programmes). Mathematical models which capture the complexities of transmission and morbidity in an age-structured population have proved to be of some value in improving understanding and clarifying the realities of designing effective programmes for the control of infection and disease.[7-15]

We outline the components of a mathematical model which describes the transmission dynamics of a typical microparasite infection within a human community, emphasising the assumptions upon which such models are based their limitations and the data needed to simulate events in the real world. In the second part of this review we proceed to illustrate the use of mathematical models to predict the potential impact of different vaccination strategies for a variety of viral infections. The emphasis is placed on the design of optimal policies for the control of infection and disease.

Community vaccination

The rate of spread of an infectious disease

When first introduced into a totally susceptible population a microparasitic infection will exhibit an intrinsic capacity to spread from person to person. The magnitude of this capacity is dependent upon a number of factors, namely:

1. The time period over which infected individuals are infectious to others, D.
2. The rate of mixing of ind within the population determining the f d of contact between infectious and susceptible individuals per unit time.
3. The ability of the infectious agent to establish within the exposed individual ((2) and (3) together are referred to as the transmission coefficient, β).
4. The density or number of susceptible individuals, X, with whom the infectious individuals may make contact during the infectious period.

The intrinsic potential for spread is usually referred to as the basic reproductive rate of the infectious agent, R_0, which is defined as the number of secondary cases that are generated from the introduction of one infectious individual into a totally susceptible population[1,16]

$$R_0 = \beta X D \qquad (1)$$

This expression contains many simplifying assumptions but serves as a useful starting point to further understanding.

The greater the potential for the parasite to spread within the host population (i.e. higher the value of R_0) the lower will be the average age at first infection, A. A good example is provided by a comparison between measles (high R_0, low A) and rubella (lower R_0, higher A).[16] If $R_0 < 1$ then, no matter how many infectious individuals are introduced, the infection will be unable to perpetuate itself. If $R_0 > 1$ then the infection can establish and an epidemic will ensue. The latter case is equivalent to either the introduction of a new influenza strain following a major antigenic shift into a population which has no experience of the variant, or the introduction of measles into a primary school setting where the vast majority may be too young to have previously been exposed. The rate of rise in new cases in the early stages of the epidemic (measured as the doubling time) is directly related to the magnitude of R_0.[1]

If we follow the course of an epidemic, as the infection spreads through the study population the pool of susceptibles is reduced as those who recover from infection pass into the immune class. As the size of the population available for infection is depleted the potential of the infection to spread (the effective reproductive rate of the parasite in a community in which only a fraction are susceptible) is lowered. Immunity is thus acting to regulate the spread of infection, and the rate of rise in new cases of infection will slow and eventually decline as the effective reproductive rate falls below unity in value. A stage will be reached when there are too few susceptibles remaining in the population to enable each primary infectious person to transmit to at least one other individual during the infectious period and, under these circumstances, without the replenishment of the susceptible pool by births, migration or waning immunity, the infection will be unable to persist and the epidemic will fade out as a consequence of herd immunity.

There is a threshold point where there are just enough susceptibles in the population to maintain the spread of infection, where on average each infectious person generates just one new infectious person, and the infection is neither growing nor declining. In fact, endemic infections such as measles, mumps and rubella in the UK were essentially in an equilibrium state in the period from 1920 until the introduction of mass immunisation. Although incidences oscillated both seasonally and over longer time periods (e.g. 2 years for measles, 3–4 for mumps, and roughly 3 for rubella[1–3]) they showed no secular trends for increase or decrease in incidence. This dynamic equilibrium was maintained by the sequential depletion of susceptibles by infection and replenishment of the pool by births.

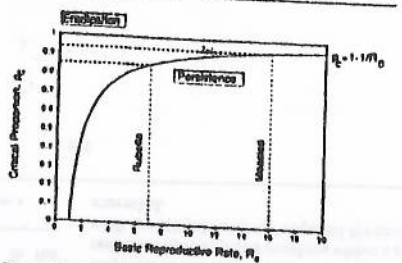

Fig. 1 What coverage for eradication? The threshold proportion of the population, p_c, which must be vaccinated at or near to birth in order to interrupt transmission, for increasing values of the basic reproductive rate, R_0.[1] Two examples are given of infections in the UK, that illustrate the relationship between transmissibility within a population (measles greater than rubella) and the ability to control by mass vaccination (rubella more easy than measles). Estimates of R_0 and p_c for a variety of common childhood infections are found in refs 1 and 6.

Herd immunity and mass vaccination

If only a fraction of the host population, x, is susceptible to infection (the majority being in the immune category) then assuming homogeneous mixing (i.e. random mixing where the rate is independent of age, sex, geographic location, etc.) the effective reproductive rate, R, will be reduced in proportion to the probability that any one contact is with a susceptible individual, hence $R = R_0x$.[7] Thus for a stable endemic infection, where $R = 1$ (i.e. each primary case generating on average one secondary case) and x_c is the critical fraction of the population remaining susceptible[1,6]

$$R_0 = 1/x_c \qquad (2)$$

The magnitude of x_c (and thence R_0) can be determined from cross-sectional serological survey data[6] as can the average age at infection, A, which is related to the value of R_0 by the simple expression

$$A = L/R_0 \qquad (3)$$

where L denotes life expectancy.[1]

In order to interrupt the spread of infection it is only necessary to reduce the susceptible proportion of the population to less than x_c, thereby reducing $R < 1$. Thus by vaccinating a proportion $p_c > 1 - x_c$, too few susceptibles will remain in the population to perpetuate the transmission process. Since from Eq (2) we know that $x_c = 1/R_0$, then

$$p_c > 1 - 1/R_0 \qquad (4)$$

Figure 1 illustrates the dependence of this critical level of vaccination, p_c, on the magnitude of R_0. As R_0 increases (lower A) the vaccination coverage required for eradication increases. Note that it is not necessary to vaccinate everyone in a community in order to block transmission. It is necessary only to reduce the number of susceptibles to below that which will enable each primary case to give rise to at least one secondary case, which in turn depends upon the magnitude of R_0. The preceding discussion outlines the concept of herd immunity in which protection from infection is afforded to susceptible individuals by the level of immunity in the community.[3,5] Refinements of this concept are detailed in a subsequent section.

Age at vaccination and vaccination coverage required for eradication

Mass vaccination of a population across all ages is rarely implemented and most programmes involve a type of cohort immunisation aimed at the child age classes. From introduction the benefits of mass vaccination will take some time to fully manifest themselves as the degree of herd immunity builds up by progressive cohort immunisation. In addition, the value of p_c implicitly assumes that infants are vaccinated at as young an age as is practicable.[1] For live virus vaccines this is as soon after the waning of maternal antibody protection as practicably possible. In reality there is often much variation in age of vaccination in a community. The implication is that some infection is allowed to circulate in the very young, and accordingly, a higher level of vaccination must be achieved in the remainder of the population in order to attain adequate herd immunity to interrupt transmission. More precisely, if the average age at vaccination is V and the average age at infection prior to immunisation is A, then the expression for p_c can be redefined as

$$p_c = \frac{1 + V/L}{1 + A/L} \qquad (5)$$

where L is again life expectancy.[7] In extreme circumstances where the average age at vaccination, V, approaches the average age at infection, A, pertaining prior to the introduction of immunisation, p_c will approach unity and eradication will be impossible.[1,7]

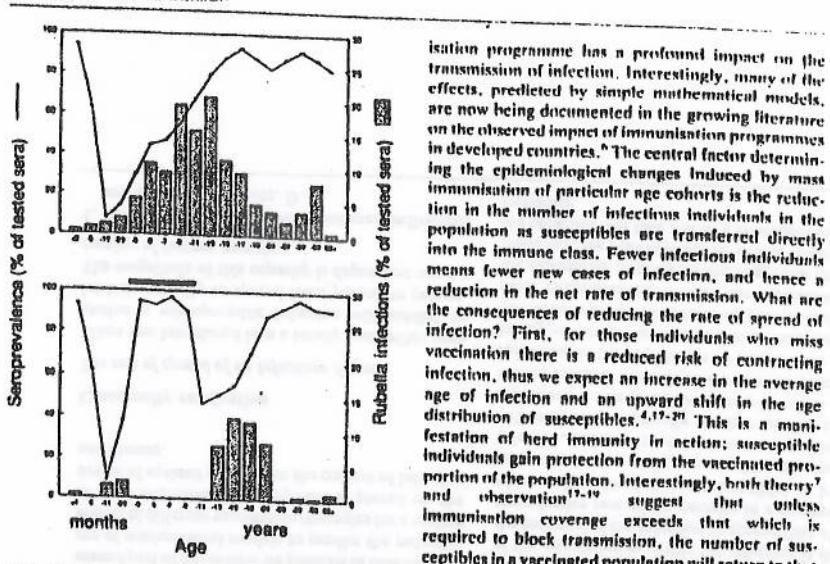

Fig. 2 Surveillance of the impact of mass immunisation on rubella immunity and incidence of infection in Finland (source of data: ref. 17). Age-prevalence of specific rubella IgG antibodies (solid line) and age-distribution of virologically-proven rubella infections (histogram bars) in males and females (pooled data) in 1990 (upper graph) and males only in 1999 (lower graph). Mass immunisation began in November 1982, the solid bar indicating the ages covered by 1986. Herd immunity effects of high uptake cohort immunisation are clearly observable: (i) there has been upward shift in age-distribution of susceptibles in 1999 compared with 1990 (whilst the total proportion of the population susceptible to rubella has changed little), and (ii) although incidence of infection is reduced through mass immunisation, of the remaining cases a higher proportion occur in the older age classes than was the case in 1990, hence there has been an increase in the average age at infection. It is clear that had Finland not maintained its policy of selective schoolgirl immunisation, begun in 1974, after the introduction of mass childhood vaccination in 1982, many cases of maternal infection would not have been prevented.

If vaccine efficacy is less than 100% this problem is further exacerbated. With respect to the USA vaccination programme, in which children require a certificate of vaccination prior to school entry (age 4–5 years), it is clear that since the prevaccination average age at infection with measles was also around 4–5 years, this age of certification is too late to prevent substantial amounts of viral circulation in the very young before they attend school.

The impact of community-based immunisation

Reducing the spread of infection

The introduction of a community-based immunisation programme has a profound impact on the transmission of infection. Interestingly, many of the effects, predicted by simple mathematical models, are now being documented in the growing literature on the observed impact of immunisation programmes in developed countries.[8] The central factor determining the epidemiological changes induced by mass immunisation of particular age cohorts is the reduction in the number of infectious individuals in the population as susceptibles are transferred directly into the immune class. Fewer infectious individuals means fewer new cases of infection, and hence a reduction in the net rate of transmission. What are the consequences of reducing the rate of spread of infection? First, for those individuals who miss vaccination there is a reduced risk of contracting infection, thus we expect an increase in the average age of infection and an upward shift in the age distribution of susceptibles.[4,17–20] This is a manifestation of herd immunity in action; susceptible individuals gain protection from the vaccinated proportion of the population. Interestingly, both theory[7] and observation[17–19] suggest that unless immunisation coverage exceeds that which is required to block transmission, the number of susceptibles in a vaccinated population will return to that which pertained prior to the introduction of vaccination. It is the age distribution of susceptibles that is altered by vaccination not their absolute numbers. This outcome is clearly illustrated in longitudinal surveillance data following the introduction of mass rubella immunisation in Finland as recorded in Figure 2.[17]

A second consequence of lowering the reproductive rate of an infection by vaccination, is to increase the period between epidemics.[6,21] Of particular interest is the time of low incidence which follows the introduction of cohort immunisation. Such an interval may be of longer duration than successive interepidemic periods, and reflects the transition from preimmunisation to postimmunisation equilibrium age-distributions of those susceptible to infection.

These phenomena help to explain the observed resurgence of vaccine-preventable infections in older children seen recently in many developed countries with effective mass immunisation programmes (e.g. the USA).

Age-dependent processes

Epidemiological studies show that for many common childhood viral and bacterial infections the rate at which susceptibles are infected (known as the force of infection — see section below) is markedly age-dependent, varying from low in the preschool age classes, to high in the school ages, to low again in adulthood (Fig. 3).[22–26] This is thought to be associated with age-specific mixing patterns in the community, in particular due to congregation at schools and disaggregation during school vacation

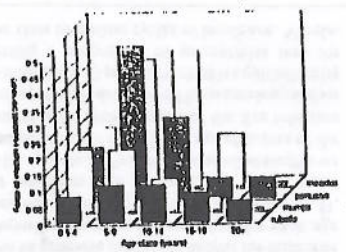

Fig. 3 Age-related force of infection for a variety of directly-transmitted childhood infections. Case notification data from England and Wales 1948–1968[24] and 1958[25] were used to generate values for measles and pertussis, respectively. Values for rubella and mumps were estimated from serological surveys in South East England 1980–1984[27] and England 1986,[26] respectively. The relatively high force of mumps infection in the youngest age class (0.5–4 years) may reflect social changes in recent times, e.g. more frequent use of pre-school play groups resulting in a decrease in the average age at infection.[25]

periods.[25–27] The tendency for mass immunisation to increase the average age of susceptibles in a community may result in these individuals moving from an age class with an intrinsically high force of infection (in the absence of immunisation) to an age class with an intrinsically lower level of transmission, perhaps due to lower mixing rates. Under these circumstances it will be easier to interrupt the spread of infection than predicted on the basis of homogeneous mixing (i.e. Equation 4). The predicted level of coverage required for eradication is therefore less than if the force of infection did not vary with age[28] (i.e. less than that predicted in Fig. 1).

Numerous childhood infections have been shown to induce more severe disease manifestations as the age at primary exposure increases.[29] Two examples are illustrated in Figure 4. Clearly, if mass immunisation increases the average age of infection, the likelihood of complications arising per case of infection will increase if the risk of morbidity rises with age. A perverse scenario of mass immunisation may then occur. As a direct result of increasing the proportion of cases of infection in the older age classes, mass immunisation whilst decreasing the incidence of infection in a community may actually increase the incidence of the associated disease. The impact of a particular vaccination programme on the incidence of a disease such as congenital rubella syndrome in a population will therefore depend on the relationship between the reduction in the total number of infections and the increased risk of disease in those who do become infected.[8,30]

A mathematical model of transmission

Introduction to model construction

In choosing a framework with which to describe the transmission dynamics of an infection in a population, we place particular emphasis on the observation that microparasitic viral and bacterial infections have the capacity for rapid and direct multiplication within the host. For these infectious agents it is generally impractical to attempt to describe changes through time in numbers of viral particles or bacteria and hence we define the host as the basic unit of study and compartmentalise the human population according to their experience of the specific infectious agent. In constructing a compartmental model, an example of which is given in Figure 5, we need detailed information of three kinds, namely,

1. The typical natural history of the infection within the individual the pattern of which dictates the various stages of infection (i.e. latent, infectious, incubation, immune) and the duration of time spent within each stage.
2. The mode by which the infectious agent is transmitted from infectious to susceptible individual (for example, is transmission direct by close contact through respiratory secretions or through

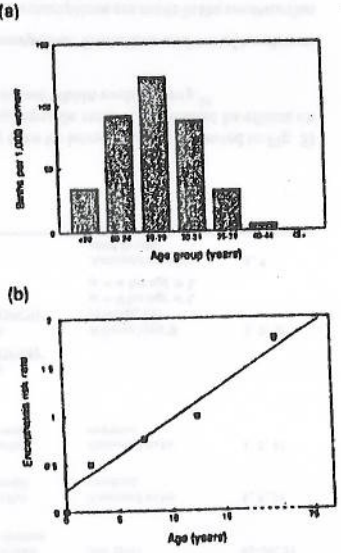

Fig. 4 Age-specific risk of complications associated with childhood infections. (a) The probability of vertical transmission of rubella and, therefore, risk of congenital rubella syndrome, following infection, will be directly related to age-specific fertility of women, data which is shown here for England and Wales 1990 (births per 1000 women in age group) (source: OPCS Monitor FM1 19 1992). (b) Data from the USA showing an increased risk of measles encephalitis (expressed per 100000 cases of measles) with increasing age (adapted from ref. 31.

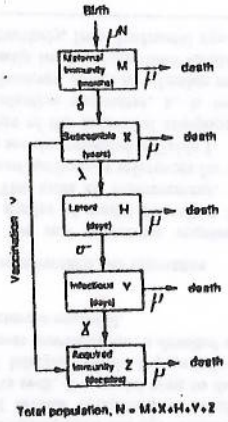

Fig. 5 Basic compartmental model structure for a typical directly-transmitted virus infection such as measles.[7,27] The diagram illustrates the flow of individuals within a population into and out of various infection categories, the basis of which is the typical life history of the infection within the host. Directions and rates of progression into and from each category are expressed by the arrows and greek symbols, estimates for which are provided in Table 1 for the UK. It is assumed that only upon waning of maternally-derived passive immunity is an individual responsive to vaccination (i.e. appropriate for live virus vaccines). Other assumptions are outlined in the text.

sexual contact, or perhaps, through faecal-oral contamination).

3. The behavioural and demographic characteristics of the host population (i.e. population size and growth rate, and the patterns of mixing within and between age classes determining who acquires infection from whom[26,27]).

Before constructing a model a detailed knowledge of the biology of infection is required. For example, we need to know the following details; the duration of infectiousness, the existence of long-term carriers of infection, and the duration of immunity. In relation to the transmission process, we might ask, how long can the agent survive in the external environment, can the infection be transmitted vertically via the placenta or perinatally, and, regarding the host population, what is its size, to what degree is it affected by migration and to what extent can it be considered as a single homogeneously mixing population? These factors are all important in determining the observed pattern of spread of infection within the host population, in dictating whether or not an infection has the capacity to persist endemically in a population of a particular size, and in determining whether or not cyclical changes in the incidence of infection and associated disease occur and at what frequency.[3,29,30]

Model structure

For a directly transmitted viral or bacterial infection requiring close contact to effect transmission we divide the population into five distinct classes as illustrated in Figure 5. These are: those who are passively protected from infection by maternally-derived specific antibody (M), those in whom maternal antibody protection has waned and are susceptible to infection (X), individuals infected but not yet infectious — termed latent (H), infected who are infectious to others (Y) and those who have recovered from infection and are now immune to reinfection (Z). The total population is thus $N = M+X+H+Y+Z$. Individuals pass from one class to the next at rates (indicated by greek symbols in Fig. 5) determined from epidemiological studies; as a rule of thumb it is useful to think of the rates of movement out of each class as the reciprocal of the duration of stay within that class. Relative durations of stay within each class for an infection like measles are indicated in Figure 5 and more precise details of parameter estimates, units of measurement, source of estimates and estimation procedures are given in Tables 1 and 2. It should be recognised that the proportion of the total population represented within a class from which individuals leave rapidly (short-stay) will be small compared with a class in which individuals spend a relatively long period of time (long-stay). Hence, for many viral and bacterial infections of childhood the majority of individuals will be found in the immune classes and very few in the latent and infectious classes (hence a low prevalence of infection).

A major component of the model is the force of infection, λ, which determines the per capita rate at which susceptibles (X) are infected and move into the latent class (H). The magnitude of this rate parameter of infection (i.e. the likelihood of a susceptible person being infected per unit of time) is often assumed to be determined by the product of the number of infectious individuals in the population (Y), the rate of contact between individuals and the probability of transmission of infection following exposure (together called β, hence $\lambda = \beta Y$). Models of these processes are called 'dynamic' because they describe changes in the numbers of individuals in each class through time, and also, because they monitor changes in the number of infectious individuals within the community, changes which act to alter the magnitude to the force of infection for the remaining susceptibles (i.e. $\ln \lambda = \beta Y$). The interplay between the number of infectious persons, the magnitude of the force of infection and the rate at which susceptibles acquire infection is the central non-linear process that acts to trigger cycles in the incidence of infection.

To mirror age-dependent changes in the force of infection we first assume that the population is divided into a number of age classes, within each of

Table 1 Demographic and epidemiological rate parameters used in mathematical models of directly transmitted microparasitic infections (data for UK only)

Definition (reciprocal)	Notational form	Numerical value or range	Source data and method of estimation	Age-dependence	References
Epidemiological					
Rate of loss of maternal antibody protection (Duration of passive immunity = average)	δ (D)	2–4 year [-1] 0.25–0.5 year	Serological or seroconversion studies	Probably, but usually assumed to be constant	1, 6, 7 22, 23, 31
Force of infection (Average age of infection)	λ (A)	See Figure 3	Serology or case notifications Catalytic infection models	Very important (see text)	1, 6, 7 22–26, 31
(Latent period)	σ (1/σ)	See Table 2	Clinical studies Chain binomial models	Assumed to be constant	1, 7, 31
(Infectious period)	γ (1/γ)	See Table 2	Clinical studies Chain binomial models	Assumed to be constant	1, 7, 31
Demographic					
Total population size	N	49.7 million	Population statistics (OPCS)*		
Mortality (Life expectancy)	μ (L)	0.011333 (75 years)	Population statistics (OPCS)*	Assume type B survival, i.e. $\mu = 0$ for age < L, $\mu = \alpha$ for age > L	1, 7, 31
Net birth rate	μN	660000		Assumed equal to total deaths	1, 7

* OPCS - Office of Population Censuses & Surveys, London, UK.

which there are a number of infectious individuals, and that individuals of one age class mix with individuals of the same age and with individuals of all other age classes according to some defined pattern of mixing (β matrix of β values to denote who mixes with whom). The rate at which susceptibles of one age are infected can then be defined in terms of the rate of mixing between these individuals and individuals from each of the other age classes, multiplied by the number of infectious individuals within each of the age classes. Thus the rate of infection in susceptibles of one age class is dependent both upon the number and distribution of infectious individuals in all age classes and upon the pattern of mixing within and between age classes. The problem with models of this kind, however, is the need to estimate this pattern of mixing.[26,27]

Conversion of the framework shown in Figure 5 into a set of coupled non-linear differential equations allows us to generate numerical output for incidence and proportion immune through time for each age class (see below) for populations of different size, N, and for infections with different sets of rate parameters (λ, σ, μ etc.). To initiate numerical studies we set up an equilibrium or endemic age-structure of the numbers of individuals in each of the five infection categories (which is determined from serological data or case notifications) and 'perturb' this equilibrium by transferring a proportion of susceptibles into the immune class to initiate cycles of incidence. Vaccination may then be introduced (as indicated in Fig. 5) at some age-specific rate, ν, to monitor its effects on the proportions within each category.[26]

Model assumptions, limitations and initial conditions

A variety of assumptions are made in the construction of models of this kind of which the most important are as follows:[10]

1. All individuals are assumed to be born with maternal antibody protection.
2. Immunity to reinfection is assumed to be lifelong.
3. The disease induced death rate is taken to be negligible.
4. The population is regarded as closed (no migration) and stationary (i.e. is not growing, where total births match total deaths).
5. The rates of loss of maternal antibody, progression into the infectious class and recovery from infection are all assumed constant and independent of age.
6. The rate of infection is assumed not to change from season to season.
7. It is assumed that spatial heterogeneity is unimportant in defining the force or rate of infection.

Most of these assumptions, whilst greatly simplying analysis, do not significantly alter the ability of the model to crudely mimic the typical behaviour of many directly transmitted viral and bacterial infections in

Table 2 Estimates of epidemiological parameters used in models of a variety of childhood infections

Infection	Latent period 1/σ (days)	Infectious period 1/γ (days)	References
Measles	7	7	26
Pertussis	7	32	32
Chickenpox	14	5	11
Mumps	13	6	10
Rubella	18.5	11.5	8

human communities in developed countries. However, to make precise predictions to capture the detail of seasonal and spatial changes in incidence, added complexity must be included in the model framework. Future work on model development should incorporate seasonality in transmission, and increase complexity in areas that will improve their usefulness to address specific issues.[3] Such complexity includes age-dependent loss of maternal antibody protection in connection with the use of high-dose live vaccines, the incorporation of spatial heterogeneity, and the specification of waning immunity or differential immunity between those individuals who are vaccinated and those who recover from natural infection.

The importance of age-structure

Many factors with a bearing on the rate of spread of an infection in a population are heterogeneous with respect to age.[3] These include mixing of individuals within and between age classes and the rate of acquisition of infection. Other rate parameters may also vary by age. Mass vaccination, for example, is often administered to a number of age classes at differing rates. Furthermore, some studies suggest that the rate of loss of maternal protection in infants may be age-dependent. The net effect of herd immunity generated by mass immunisation is also dependent upon age-related factors such as age-specific rates of transmission and age-related changes in the risk of serious complications resulting from infection. As such, if a model aims to describe the patterns of infection within a population and the effects of mass immunisation, a detailed description of age-structure is essential.

Parameter requirements and estimation

A list of the rate parameter requirements for numerical studies of model behaviour is given in Table 1. The units of measurement, sources of estimates and methods or references for methods of estimation are also provided in Table 1.

Estimation of the individual components of the force of infection parameter, λ, is not straightforward. However, forces of infection may be estimated directly from age-stratified notification data or, more precisely, from horizontal age-serological profiles (as in Fig. 3). Ideally, serological data should be finely divided into age groups (e.g. yearly), with large sample size (e.g. 50 per yearly group), cover a wide range of ages (0+ to 60+ years), and span at least one epidemic period to average out the effects of seasonal and longer term fluctuations in incidence. For an endemically-stable infection, a horizontal serological profile which records the change with age in the proportion of the population who have experienced infection, is a reflection of the age-specific rate of acquisition of infection.[25]

In attempting to predict the impact of a mass immunisation programme it is important to measure the risk of serious disease resulting from each infection. Absolute measures of risk, or relative measures between age classes, may be determined for various childhood infections.[6] These invariably reveal an increase in the likelihood of complications with increasing age, as recorded in Figure 4.

Conclusion

Changes in the pattern of infection within a community following the introduction of mass immunisation, such as an increase in the average age at infection and a lengthening of the inter-epidemic period, may be explained on the basis of an understanding of the population dynamics of infectious agent transmission within a human community. This understanding can be strengthened by the use of mathematical models that capture the often complex interplay between the factors that determine the course of infection in individuals and those that determine spread in populations. In designing immunisation strategy and comparing the merits of different policies, it is necessary to consider this interplay in quantitative detail.

Acknowledgements

D.J.N. is supported by a Royal Society University Research Fellowship

References

1. Anderson RM, May RM. Infectious disease of humans: dynamics and control. Oxford: Oxford Scientific, 1991.
2. Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. Proceedings of the Royal Society of London Series A 1927; 115: 700–721.
3. Anderson RM, May RM. Vaccination and herd immunity to infectious disease. Nature 1985; 318: 323–329.
4. Nokes DJ, Anderson RM. The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes. Epidemiol Infect 1988; 101: 1–20.
5. Fox JP, Elveback L, Scott W, Gatewood L, Ackerman E. Herd immunity: basic concept and relevance to public health immunization practices. Am J Epidemiol 1971; 94: 179–189.
6. Anderson RM, Nokes DJ. Mathematical models of transmission and control. In: Holland WW, Detels R, Knox G, eds. Oxford textbook of public health, vol 2, 2nd ed. Oxford: Oxford Medical, 1991: 225–252.

7. Anderson RM, May RM. Vaccination against rubella and measles: quantitative investigations of different policies. J Hyg (Lond) 1983; 90: 259–325.
8. Anderson RM, Grenfell BT. Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. J Hyg (Lond) 1986; 96: 305–333.
9. Nokes DJ, Anderson RM. Vaccine safety versus vaccine efficacy in mass immunisation programmes. Lancet 1991; 338: 1309–1312.
10. Anderson RM, Crombie JA, Grenfell BT. The epidemiology of mumps in the UK: a preliminary study of virus transmission, herd immunity and the potential impact of immunization. Epidemiol Infect 1987; 99: 65–84.
11. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus: a mathematical model. Epidemiol Infect 1992; 108: 495–511.
12. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus: the influence of varicella on the prevalence of herpes-zoster. Epidemiol Infect 1992; 108: 513–528.
13. McLean AR, Anderson RM. Measles in developing countries, part II. The predicted impact of mass vaccination. Epidemiol Infect 1988; 100: 419–442.
14. Nokes DJ, McLean AR, Anderson RM, Grabowsky M. Measles immunization strategies for countries with high transmission rates: interim guidelines predicted using a mathematical model. Int J Epidemiol 1990; 19: 703–710.
15. McLean AR, Nokes DJ, Anderson RM. Model-based comparisons of measles immunization strategies using high dose Edmonston-Zagreb type vaccines. Int J Epidemiol 1991; 20: 1107–1117.
16. Anderson RM, May RM. Directly transmitted infectious diseases: control by vaccination. Science 1982; 215: 1053–1060.
17. Ukkonen P, von Bonsdorff C-H. Rubella immunity and morbidity: effects of vaccination in Finland. Scand J Infect Dis 1988; 20: 255–259.
18. Fine PEM, Clarkson JA. Distribution of immunity to pertussis in the population of England and Wales. J Hyg (Lond) 1984; 92: 21–36.
19. Fine PEM, Clarkson JA. Measles in England and Wales — II. The impact of the measles vaccination programme on the distribution of immunity in the population. Int J Epidemiol 1982; 11: 15–25.
20. Fine PEM, Clarkson JA. Measles in England and Wales – III: Assessing published predictions of the impact of vaccination on incidence. Int J Epidemiol 1983; 12: 332–339.
21. Anderson RM, Grenfell BT, May RM. Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination: time series analysis. J Hyg (Lond) 1984; 93: 587–608.
22. Nokes DJ, Anderson RM, Anderson MJ. Rubella epidemiology in South East England: 1981–1984. J Hyg (Lond) 1986; 96: 291–301.
23. Nokes DJ, Wright J, Morgan-Capner P, Anderson RM. Serological study of the epidemiology of mumps virus infection in north-west England. Epidemiol Infect 1990; 105: 175–195.
24. Farrington CP. Modelling forces of infection for measles, mumps and rubella. Stat Med 1990; 9: 953–967.
25. Grenfell BT, Anderson RM. The estimation of age-related rates of infection from case notifications and serological data. J Hyg (Lond) 1985; 95: 419–436.
26. Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications to the design of vaccination programmes. J Hyg (Lond) 1985; 94: 365–436.
27. Schenzle D. An age-structured model of pre- and post-vaccination measles transmission. IMA J Math Appl Med Biol 1984; 1: 169–192.
28. Mims CA. The pathogenesis of infectious disease. 3rd ed. London: Academic Press, 1987.
29. Anderson RM, May RM. Spatial, temporal and genetic heterogeneity in host populations and the design of immunization programmes. IMA J Math Appl Med Biol 1984; 1: 233–266.
30. Anderson RM, May RM. The invasion, persistence and spread of infectious diseases within animal and plant communities. Philos Trans R Soc Lond [Biol] 1986; 314: 533–570.
31. May RM. Population biology of microparasitic infections. In: Hallam TG, Levin SA, eds. Mathematical ecology. Biomathematics 1986; 17: 405–442.
32. Grenfell BT, Anderson RM. Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination. Proc R Soc Lond [Biol] 1989; 236: 213–252.