

SPECIAL ARTICLE

The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes

Community-based immunization is the primary method available today by which to reduce the scale of morbidity, and, in certain countries, mortality, associated with the most common childhood viral and bacterial infections. The decline in the incidences of a number of important vaccine preventable infections, such as polio, diphtheria and measles, in many countries, and the worldwide eradication of the smallpox virus, is testimony to the effectiveness of this method of control.

Surprisingly, however, appreciation of how vaccination influences the incidence and distribution (say, between age classes) of infections within a community is often poor amongst medical and public health personnel. The expectation that vaccination of 50% of a community will result in a 50% reduction in the incidence of infection is but one example of a misunderstanding of the underlying epidemiological principles. In reality, the behaviour of a human host/infectious disease agent interaction is invariably non-linear (i.e. complex) at the population level. As such the impact of large-scale immunization programmes may not be intuitively obvious and, thus, not easy to predict. The effects are as much dependent upon the typical course of infection within the individual patient, the biology of the infectious agent and the social and demographic makeup of the community, as on the type of mass vaccination policy implemented to control the spread of infection.

Given the complexity of the association between host (human) and parasite (infectious agent), at both the individual and the population levels of observation, is it possible to make rational, informed decisions about the optimal strategy of immunization for a specific infectious agent in a particular country, population or community? Mathematical descriptions of the typical course of infection in the individual and of the details of transmission between people have begun to provide a scientific framework to aid decision makers in predicting the outcome of different vaccination programmes and of highlighting problems that may arise in the future (Anderson & May, 1985*a*; Dietz, 1982).

A major goal of theoretical or mathematical study in epidemiology is to develop understanding of the interplay between the variables that determine the course of infection within an individual, and the variables that control the pattern of infections within communities of people. In view of the successes achieved by combining empirical and theoretical work in the physical sciences, it is surprising that many people still question the potential usefulness of mathematical models in epidemiology. Much of the doubt centres on the simplicity of many mathematical models, in the face of known biological complexity. However, it is often the case in scientific study that although many factors influence a particular

process, a few dominate the observed outcome. The role of simple models is to provide a precise framework on which to build complexity as quantitative understanding improves, in a manner akin to the design of controlled experiments in the laboratory where a number of factors are held constant and one or more are varied.

Over the past few years this journal has published a number of articles which describe mathematical models of infectious disease transmission and control. These articles have aimed to help in the interpretation of observed epidemiological trends, to guide the collection of data towards further understanding, and to design programmes for the control of infection and disease (Anderson & May, 1983; Anderson, Grenfell & May, 1984; Anderson & May, 1985*b*; Grenfell & Anderson, 1985; Nokes, Anderson & Anderson, 1986; Anderson, Crombie & Grenfell, 1987; McLean & Anderson, 1988). This present article is intended to provide a summary of the aims and uses of mathematical models for the study of directly transmitted viral and bacterial infections. We highlight the major concepts underlying the transmission of vaccine-preventable infections that are fundamental to a sound understanding of the impact of mass immunization in the community. The article is written with the medical epidemiologist and public health worker in mind and emphasis is therefore given to basic principles, epidemiological data and the practical implications of model predictions. Mathematical details are kept to a minimum and the interested reader is referred to technical references for descriptions of model structure and assumptions.

MODEL CONSTRUCTION

Which infectious organisms?

Much of the theory developed to date describes the transmission of directly transmitted viral and bacterial infections that induce lasting immunity to reinfection (often assumed to be lifelong) in those who recover, and have a relatively short duration (a matter of days or weeks from infection to recovery/elimination) in relation to human life expectancy (many decades) (Kermack & McKendrick, 1927; Bailey, 1975; Anderson & May, 1985*a*). A sound understanding of the typical course of infection within an individual is a prerequisite for model construction and investigation. It is important to have quantitative information on the latent and infectious periods of the infection and, in some cases, the incubation period of the disease. As depicted in Fig. 1, the latent period is defined as the average period from the time of infection to the point where an individual becomes infectious to others, the infectious period as the average period for which an individual is capable of transmitting the infection, and the incubation period as the average time from infection to the appearance of symptoms of disease. All these periods are variable but the measurement of an average often suffices provided the duration is short in relation to the life expectancy of the human host and the average age at which individuals acquire infection (Anderson, 1982).

Given these data requirements it is no surprise that much of the mathematical literature has centred on the common childhood infections such as measles, rubella, mumps, pertussis and diphtheria. Unfortunately, for many infections the

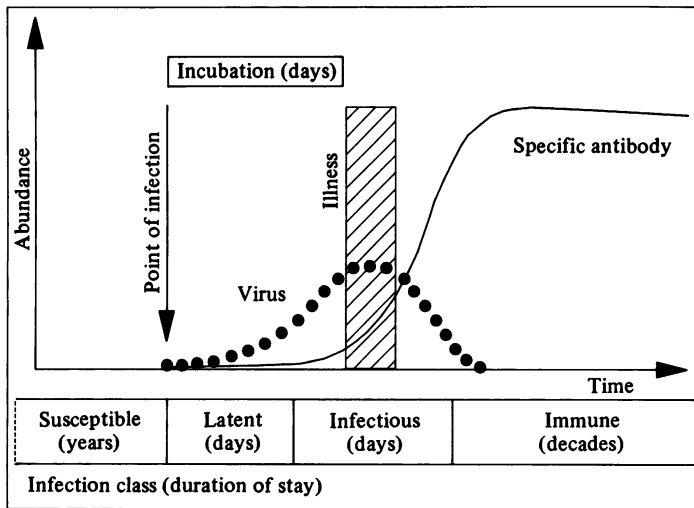


Fig. 1. Diagrammatic representation of the typical time course of an acute viral or bacterial infection in an individual and concomitant progression through infection classes. The average stay within the latent and infectious classes is seen to be only transient when compared with that within the susceptible or immune classes.

details regarding the life history of the infectious organism within the host and the rate of transmission between hosts are inadequate to permit accurate mathematical descriptions (e.g. *Haemophilus influenzae* and cytomegalovirus). Genetic variability that generates distinct strains of the virus or bacterium can seriously complicate the process of model construction and hence most attention has focussed on infectious agents such as measles and rubella viruses which appear to be antigenically stable by comparison with, say, the influenza and echo viruses.

What do models describe?

The unit of epidemiological study in the investigation of viral and bacterial infections (microparasites) is invariably the infected host, given the practical difficulties associated with the accurate measurement of viral abundance (concentration) within the infected individual (Anderson & May, 1979). A further important unit, in the case of infections that induce lasting immunity in those who recover, is the individual with antibodies specific to antigens of the infectious agent under study. These seropositive individuals denote those who have current infections or who have experienced infection at some time in the past. For most common directly transmitted viral infections, the production of specific antibodies appears to continue (even in the absence of re-exposure) for the life of the individual.

With these two measures in mind, the individuals in a population can be segregated according to their current or past infection status. In practice, finer divisions (perhaps further stratified by age, sex or spatial location) are desirable to specify individuals who are (i) protected from infection by maternally derived antibodies (the duration of protection in infants is usually short, being of the order of 6 months); (ii) susceptible to infection; (iii) infected but not yet infectious

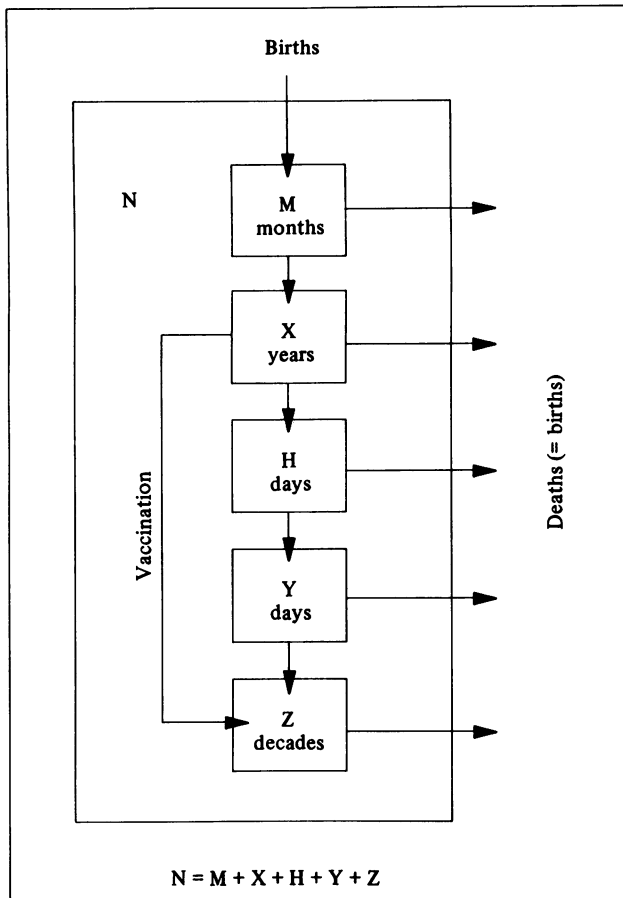


Fig. 2. The flow of individuals within a stable population between infection compartments for a directly transmitted microparasitic infection. The categories M , X , H , Y and Z denote the number (or density) of neonates with maternal antibody protection, susceptibles who are not yet infectious, infectious individuals and immunes (natural or vaccine-induced), respectively, and are shown together with the relative duration of stay in each class. Arrows indicate the rate of movement of individuals from one infection class to the next.

(latent); (iv) infectious to others (capable of transmitting the infection); and (v) recovered, thus immune to reinfection (with antibodies specific to antigens of the infectious agent). With the passage of time, and, inevitably, with increasing age, individuals pass from one class or infection category to another. Mathematical models attempt to capture this flow of individuals between the different infection-status compartments within a population, and, as such, are often referred to as compartmental models. A diagrammatic illustration of this flow is presented in Fig. 2.

The number of individuals within any one compartment at one point in time is dependent upon the average duration of stay within that compartment. The shorter the period of stay, the smaller the proportion of the total population in that infection class. So, for example, in the case of measles whose average infectious period is roughly 7 days, the mean age at first exposure (in a developed

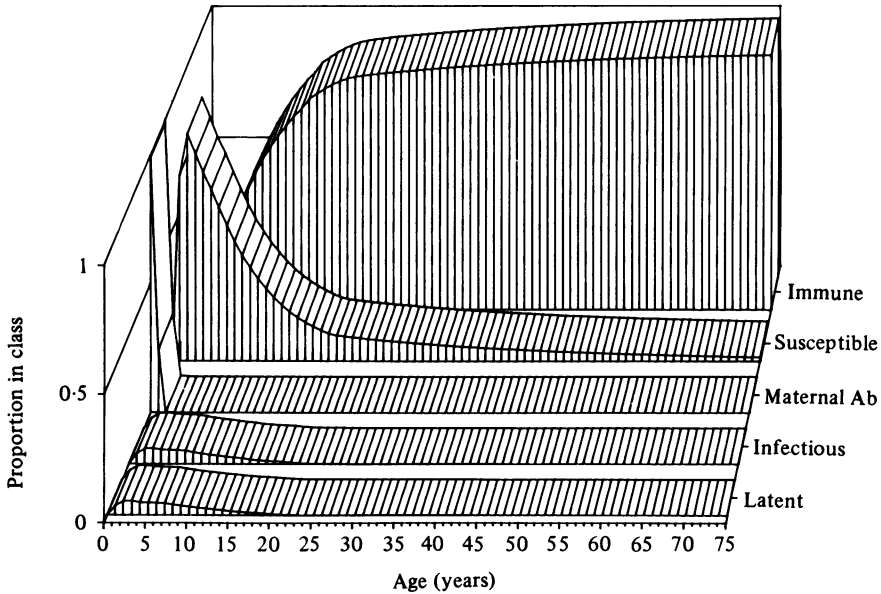


Fig. 3. Equilibrium proportions of a population, stratified by age, in each infection class for an acute infectious disease (based on data for rubella in the United Kingdom) at one point in time. The proportion of individuals in the latent and infectious classes have been scaled by a factor of 25 to make them visible.

country prior to mass vaccination) is approximately 4–5 years, and immunity is lifelong (say with a human life expectancy of 75 years), we would expect (and we observe) a very small proportion of a population with a current infection, a larger proportion susceptible to infection and a very large proportion (the vast majority) recovered and immune to reinfection (serologically positive). These notions are depicted diagrammatically in Fig. 3.

Compartmental models, of the sort most widely used in the study of childhood viral and bacterial infections, are simply sets of differential or partial differential (where populations are stratified by age or spatial location) equations that describe the rates of flow between compartments by reference to the numbers or proportions in each infection category (e.g. susceptibles, infecteds or immunes) and the epidemiological rate parameters that determine transmission, the course of infection in the individual and the demography in the human community (i.e. birth and death). These equations clearly specify the population structure and the rates involved and any biological and epidemiological assumptions which have been made. They therefore define what epidemiological variables and parameters need to be measured or monitored, and permit analytical or numerical investigations of how the epidemiology of a given infection is influenced by different biological and demographic assumptions and different control programmes. With respect to mass immunization they facilitate the quantitative study of time- and age-dependent changes in the pattern of infection under different immunization policies.

EPIDEMIOLOGICAL CONCEPTS

Transmission

A central concept in simple theory of infectious disease transmission is the mass-action principle which states that the net rate at which new cases of infection arise is proportional to the density (or number) of susceptible individuals, X , times the density of infectious persons, Y , times the probability of transmission from infectious to susceptible individual, β (i.e. βXY). The probability of transmission β is formed from two components, namely, the likelihood of close contact between two individuals such that transmission can occur (dependent upon the pattern of mixing in the population), plus the probability that transmission will occur as a result of close contact (dependent upon the innate contagiousness of the infectious organism and, perhaps, on the genetic or behavioural 'susceptibility' of the individual host).

This mass-action principle is based on the assumption that susceptible and infectious individuals mix in a homogeneous (= random) manner. In practice this rarely occurs but the principle can be modified to take account of age- and space-dependent mixing or other forms of heterogeneity that exist in host or parasite populations (Anderson & May, 1984).

The net rate at which new infections arise (e.g. βXY in the homogeneous case) defines the incidence of infections, I , which can be recorded by direct observation. Unfortunately, the measurement of I tells us nothing about the respective densities of susceptibles or infecteds (X or Y), nor of the magnitude of the transmission coefficient β . On an individual basis, the per capita rate of infection of susceptible people, λ , is simply the transmission coefficient β times the density of infectious persons, Y (i.e. $\lambda = \beta Y$). This rate is often referred to as the 'force of infection' (FOI), and can be measured by reference to the serological status of an individual through time (or as he or she ages) with respect to antibodies specific to the infectious agent in question.

The basic reproductive rate of infection, R_0

The average number of secondary cases of infection generated by one primary case in a susceptible population is simply the number of susceptibles present with which the primary case can make contact (X) times the length of time the primary case is infectious to others, D , times the transmission coefficient, β (rate of mixing and innate contagiousness of the infectious agent). This quantity defines the transmission potential of an infection and is called the basic (= potential) reproductive rate of infection, R_0 , where

$$R_0 = \beta X D. \quad (1)$$

Note that R_0 is a dimensionless quantity that defines the potential to produce secondary cases (in a totally susceptible population) per generation time (i.e. the duration of infectiousness) of the infection.

The basic reproductive rate is of major epidemiological significance since the condition $R_0 = 1$ defines a threshold below which the generation of secondary cases is insufficient to maintain the infection within the human community. For values equal to or greater than one the infection will persist. The threshold defines

the problem of control by mass vaccination. To block transmission, sufficient numbers of susceptible people must be immunized such that on average each primary case of infection generates less than one secondary case.

The magnitude of R_0 not only defines the difficulty of the control problem but also determines the rapidity with which the proportion of individuals in an age class who have experienced infection rises as age increases. The magnitude of the transmission potential is therefore related to the average age, A , at which an individual typically experiences infection; the larger the magnitude of R_0 the smaller the value of A . The relationship is given by

$$R_0 \cong B/(A-F), \quad (2)$$

where B is the reciprocal of the finite birth rate of the population (which is usually expressed as births per year per head of population) and F is the average duration of protection in infants provided by maternally derived antibodies (Anderson & May, 1985*a*). In developed countries, with stable populations, the quantity B can be replaced by life expectancy from birth, L (life expectancy = $1/\text{birth rate}$). The magnitude of the average age at infection, A , can be determined from horizontal (or longitudinal) age-stratified serological surveys that record age related changes in the force of infection (FOI) (see Grenfell & Anderson, 1985) prior to the introduction of mass vaccination (Nokes, Anderson & Anderson, 1986; Nokes, Anderson & Jennings, 1987). It is important to remember here that changes in the proportion of the population seropositive for a particular infection roughly mirrors the changes one would observe in the proportion of a cohort of individuals infected as time passes, when monitored from birth. The rate at which the proportion who have experienced the infection rises with time (= age) (i.e. the steepness of an age-serological profile) is an indication of the magnitude of transmission of the infection in the population, which as we have seen is inversely related to the average age at infection, A . Estimates of F can also be determined from serological surveys of infants and young children, while the magnitude of B or L can be obtained from demographic data.

Herd immunity

In a population in which an infection is persisting stably, such that the net rate at which new cases of infection arise is exactly balanced by the net rate of recovery from infection, the effective reproductive rate of the infection, R , is unity in value. In practice, for many common viral and bacterial infections the incidence of infection fluctuates both on a seasonal and longer-term cycle (see next section). The effective reproductive rate therefore fluctuates below and above unity in value as the incidence of infection, and hence the density of susceptibles, change. However, the average value over a series of incidence cycles (both seasonal and longer term) will be approximately equal to unity in the absence of control intervention or changing social and demographic patterns. The effective reproductive rate, R , is related to the basic reproductive rate, R_0 (the potential to generate secondary cases in a totally susceptible population) by the simple equation

$$R = R_0 \bar{x}. \quad (3)$$

Here, \bar{x} is the equilibrium fraction of susceptibles in the population. The

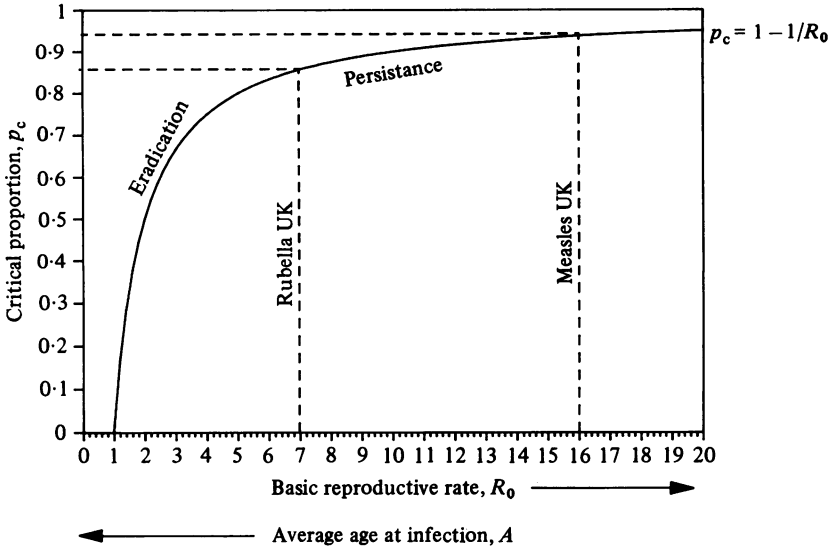


Fig. 4. Relationship between the critical proportion of a population required to be vaccinated (as near to birth as possible) for eradication of an infection and the basic reproductive rate of the infectious agent. Two example infections for the United Kingdom are illustrated; measles is shown to be more difficult to control than rubella.

magnitude of \bar{x} can be determined from cross-sectional serological surveys given data on the age structure of a population (if x_i is the proportion susceptible in age class i and p_i is the proportion of the population in the same age class then $\bar{x} = \sum_{i=1}^n x_i p_i$ in a population with n age classes). Thus at equilibrium where $R = 1$, the basic reproductive rate is equal to the reciprocal of the proportion susceptible;

$$R_0 \cong 1/\bar{x}. \quad (4)$$

To eradicate an infection (or block transmission) by mass vaccination it is necessary to reduce the magnitude of R_0 to less than unity in value. If we immunize a proportion p of the population then the new reproductive rate is equal to $R_0(1-p)$. Since this quantity must be less than unity in value in order to prevent the spread of the infection in the community, this gives a condition for the critical proportion of the population that must be immunized to eradicate the infection, p_c , where

$$p_c > [1 - 1/R_0]. \quad (5)$$

The relationship is depicted diagrammatically in Fig. 4; the larger the magnitude of R_0 the greater the proportion that must be immunized to block transmission. Note that this relationship shows it is not necessary to vaccinate everyone in the community to prevent the spread of infection (as for the examples of rubella and measles in Fig. 4). This result is the manifestation of what is known as the principle of herd immunity, in which the protection of the individual is achieved by the protection (= vaccination) of the population. The mechanism underlying this concept is that of a critical density of susceptibles required to maintain the value of R_0 at or above unity (i.e. one or more secondary cases per primary case of infection). Although derived by theoretical study its validity is

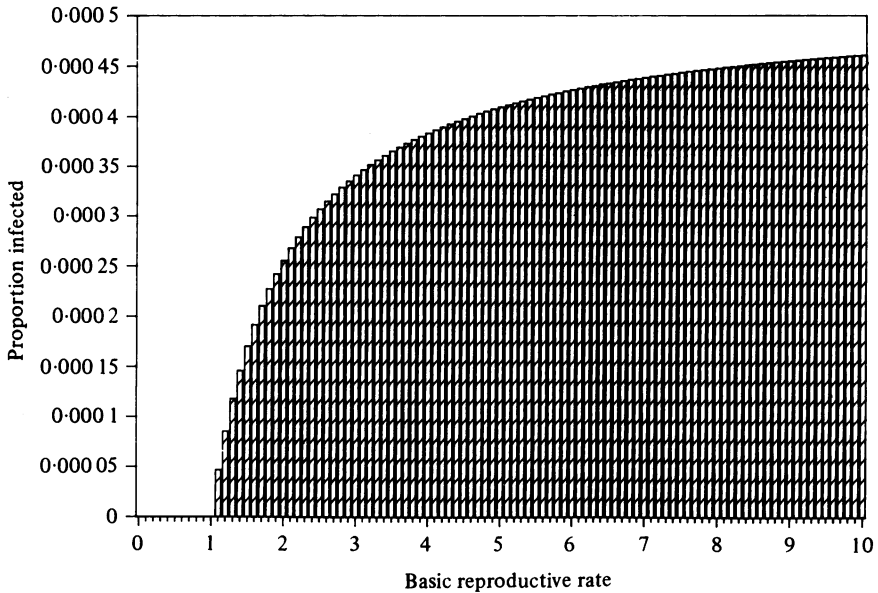


Fig. 5. Predicted equilibrium proportion of infected individuals in a population as a function of the basic reproductive rate, R_0 (the transmission potential), of the infectious agent. Note (i) that as a fraction of the total population, the proportion infected is very small, for all values of R_0 , and (ii) how the greatest changes in this proportion occur over the first few increments of R_0 above unity.

confirmed by empirical studies (e.g. Bartlett, 1960 ; Black 1966 ; Anderson & May, 1986).

Another epidemiological feature generated by the requirement of a critical density of susceptibles to maintain infections concerns the relationship between the magnitude of the basic reproductive rate and the equilibrium prevalence of infection (latent plus infectious individuals), or the equilibrium incidence of infection. Theory predicts that this relationship is non-linear as depicted in Fig. 5. Thus, marked reductions in the endemic prevalence or incidence of infection will only occur as the transmission potential is reduced to an extent where it approaches the threshold level of $R_0 = 1$. The practical implication of this observation is that we should not expect the decline in the incidence of infection induced by mass vaccination to be directly proportional to the level of vaccination coverage. The greatest changes will occur when coverage attains high levels.

In practice, immunization programmes are introduced by focussing on cohorts of children such that the level of immunization coverage is built up over many years of cohort vaccination. In these circumstances the p_c of eq (5) must be interpreted as the proportion of each cohort vaccinated as soon after birth as is practically feasible (taking account of the need to immunize after the decay in maternally derived specific antibody). It will clearly take many years of cohort immunization to achieve the desired level of artificially induced herd immunity. A further complication is introduced by the problem of vaccinating a series of age classes. In this case, if V is the average age at which vaccine is administered, then the critical level of cohort immunization required to prevent transmission is given approximately by :

$$p_c > [1 + V/L]/[1 + A/L], \tag{6}$$

Table 1. *Summary epidemiological parameters for a number of viral and bacterial infections in the UK (based on various sources – see text for details)*

Infection	Average age of infection prior to immunization (years)	Inter-epidemic period (years)	Vaccination coverage for elimination (%)	Basic reproductive rate
Measles	4–5	2	90–95	16–21
Pertussis	4–5	3–4	90–95	16–21
Mumps	6–7	3	85–90	11–14
Rubella	9–10	4–5	80–85	7–9

where A is the average age at infection prior to the introduction of mass vaccination and L is life expectancy (Anderson & May, 1982, 1983). It is clear from this expression that transmission cannot be interrupted unless the average age at vaccination, V , is less than the average age at infection, A , prior to control. In other words, no matter what the coverage, if immunization occurs at any age above the pre-vaccination average for infection sufficient transmission for the perpetuation of the infection in the population can occur in those too young to have received the vaccine.

As noted earlier, estimates of R_0 and p_c can be obtained from age-stratified serological data recording changes in the proportion seropositive with age. Table 1 records a series of estimates of A , R_0 and the level of cohort vaccination required to eradicate infection, for various common childhood infections. Note the high levels of immunization required to block transmission. Unfortunately, in the United Kingdom today we are some way from achieving the optimal levels of immunization for the majority of these infections. Legislation in the United States, that requires immunization for school entry, has resulted in the virtual elimination of common childhood infections such as measles, mumps, rubella and pertussis. This example, and the calculations displayed in Table 1, set a target for public health authorities in the United Kingdom.

A final point to stress in this issue of mass vaccination is the importance of heterogeneity within populations of the host (spatial, age-related, and genetic) and the parasite (different strains of the same infectious organism with differing infectivities) (Anderson & May, 1986). One example relates to spatial distribution of vaccination uptake. Levels of measles and rubella vaccine coverage in the United Kingdom, for example, vary widely between different regions (see Fig. 6). To effectively block transmission countrywide it is necessary to ensure that the targets laid out in Table 1 are attained in each area. Otherwise, pockets of infection in regions with poor vaccination coverage will continually trigger small epidemics in other areas.

A second example is that of age-related variation in the rate of transmission. The preceding arguments based upon the principle of mass-action assume a homogeneously mixing host population and, therefore, one in which mixing does not vary with age. One consequence of this premise is that the rate of transmission of infection is assumed constant across all ages. In reality, however, we see various degrees of mixing between individuals according to the age class to which they

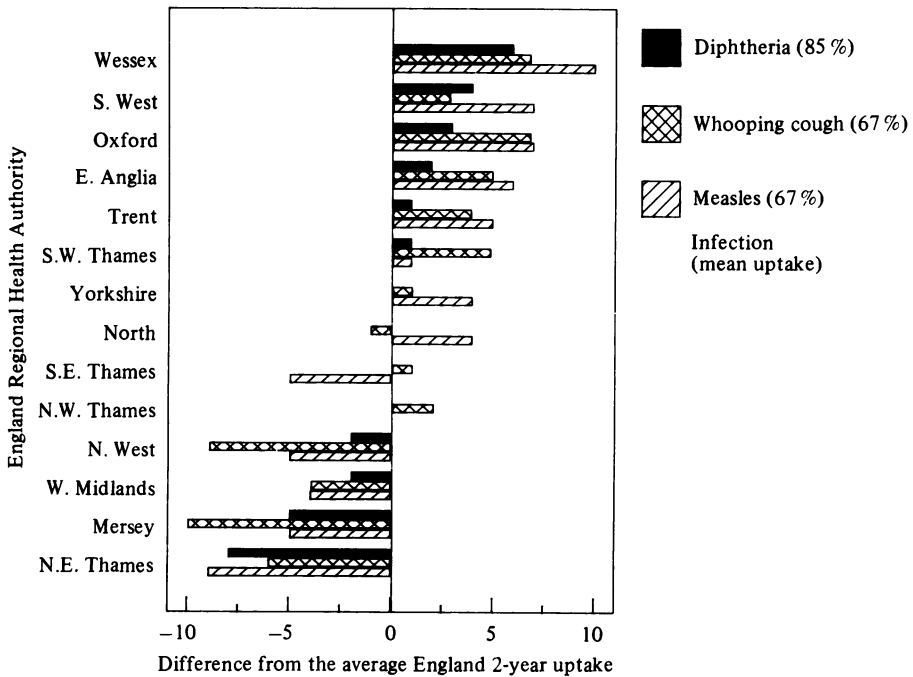


Fig. 6. Vaccination against diphtheria, pertussis and measles. Regional variations in uptake from the average coverages in England in 1986 (source DHSS, Research and Statistics Division).

belong. Analyses of horizontal cross-sectional serology and case notification data have confirmed this observation, revealing a consistent pattern of change in the force of infection, with increasing age, for a number of common childhood infections (e.g. measles, rubella, mumps, chickenpox, scarlet fever and pertussis) in developed countries. The rate of infection is seen to be low for the younger age classes, high in those of school age and low again in adulthood (Anderson & May, 1985a; Nokes, Anderson & Anderson, 1986; Anderson, Crombie & Grenfell, 1987). The implications of this age-related variation in the force of infection to vaccination policy are realised as a result of the rise in the age-distribution of susceptibility in a population under mass vaccination (see later section). The main issue here is that as a consequence of the changes in the FOI, susceptibles who avoid vaccination may move from an age class with a high rate of transmission into an older age class with a lower FOI, and a concomitant lower chance of becoming infected. As a consequence, theoretical studies which have taken into account the age-dependent nature of the FOI predict somewhat lower rates of vaccination needed for the eradication of infection than those shown in Table 1. However, it should be emphasised that the values indicated in Table 1 provide a good first approximation on which to base vaccination policy.

Inter-epidemic period, T

Many viral and bacterial infections that induce lasting immunity to re-infection on recovery and which have high transmission potentials (R_0 large) tend to exhibit oscillatory fluctuations in incidence. A typical example is that of measles, which in

the United Kingdom prior to the introduction of mass vaccination oscillated on a seasonal basis (due to the aggregation and disaggregation of children for school term and holiday periods) and a longer term 2 year cycle with years of high incidence separated by years of low incidence (Anderson, Grenfell & May, 1984). Time series analyses reveal that these longer term cycles for infections such as measles, mumps, rubella and pertussis, are not due to chance fluctuations but arise from the dynamic interaction between populations of susceptible and infected persons.

Simple theory, based on the cornerstone of the mass-action principle of transmission, suggests that the inter-epidemic period, T , of the longer-term (non-seasonal) cycles is determined by the generation time of the infection, K , defined as the sum of the latent and infectious phases, and the transmission potential of the infection inversely measured by the average age at infection, A , where

$$T \cong 2\pi(AK)^{\frac{1}{2}}. \quad (7)$$

This simple prediction well matches observation for a variety of common childhood infections prior to mass vaccination (i.e. the 2-year cycles of measles, the 3-year cycles of mumps, the 4- to 5-year cycles of rubella and the 3-4 year cycles of pertussis). Non-seasonal oscillations arise as a consequence of the exhaustion of the supply of susceptibles as an epidemic passes through a population plus the time lag that arises before new births replenish the pool of susceptibles to once again trigger a new epidemic. As such, the inter-epidemic period is influenced by the birth rate of a community and also by mass vaccination which acts to reduce the transmission potential of the infection (see next section). Note that the parameter A can be replaced in equation (7) by $(B/R_0) + F$ where B and F are the average birth rate and duration of maternally derived antibodies, respectively (see equation 2). For example, in developing countries such as Kenya, with high birth rates, measles tends to cycle on a 1-year time scale as opposed to 2 years in the United Kingdom (McLean & Anderson 1988).

THE IMPACT OF MASS VACCINATION

Incidence of infection

When viewed in practical terms the level of vaccination coverage in a given community or country is determined by a variety of economic and logistic problems (developing countries) or motivational or legislative issues (industrialized countries). What changes in the epidemiology of an infection are we likely to observe as cohort vaccination is introduced and how are these changes dependent on the level of coverage attained in a particular country? Models provide an ideal framework for examining these questions, and their predictions are now supported by a growing body of empirical evidence.

Childhood immunization has the direct effect of reducing the number of cases of infection as a result of protection conferred by vaccination. Since this reduces the number of infectious individuals in the vaccinated population (see Fig. 2 where vaccination transfers susceptibles, X , to the immune class, Z , thus avoiding H and Y , the infected classes), an indirect effect is a reduction in the net rate of transmission of the virus or bacterium. This is the principle of herd immunity in

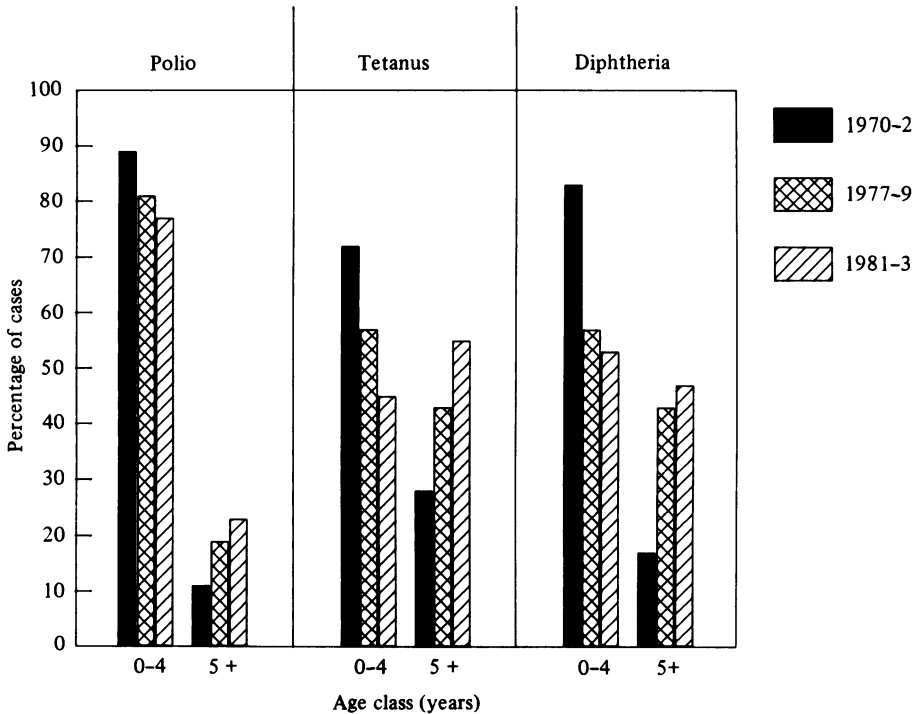


Fig. 7. Changes observed in the age-distribution of cases of three vaccine-preventable infections in Bangkok, following the WHO Expanded Programme on Immunization initiative. These are proportions; the total number of reported cases of each infection have significantly declined in the population over the period indicated (Report, 1987).

action, where susceptible individuals gain protection from the vaccinated proportion of the population. Two consequences arise from a lowering of the rate of transmission and the concomitant reduction in the reproductive rate of the infection.

First, the age at which susceptibles typically acquire infection will rise such that there is an upward shift in the age distribution of susceptibility in the population. Figure 7 records a number of examples in which the average age at infection has risen following introduction of mass vaccination. Most interestingly, however, following the initial perturbation created by the introduction of cohort vaccination, the reduction in transmission will result in the total proportion of the population susceptible to infection remaining approximately equal to that pertaining prior to immunization. It is simply the age distribution of susceptibility which is altered by vaccination. This concept is represented diagrammatically in Fig. 8.

Provided the infection is able to persist endemically (i.e. the level of coverage is less than that required for eradication), the equilibrium proportion of susceptibles in the population will remain constant irrespective of the level of coverage below the critical point for eradication. An illustration of this point is provided in Fig. 9 where longitudinal changes in the age profile of seropositivity for antibodies to rubella virus are recorded, both prior to, and during the

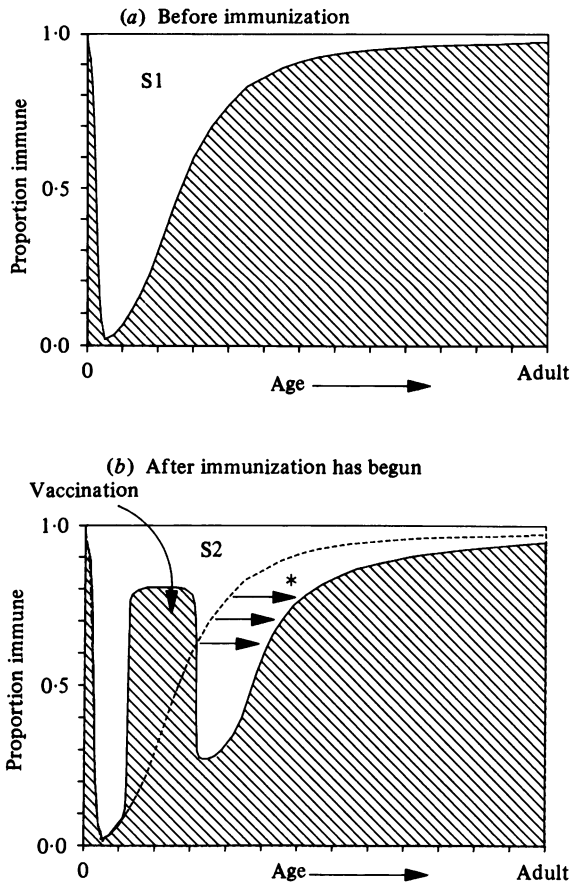


Fig. 8. Schematic illustration of the predicted impact of mass immunization (against a typical childhood viral or bacterial infection) on the distribution of the ages of susceptible individuals. Before immunization (graph *a*) there is a 'valley' of susceptibles (*S1*) in the young age classes. Attempts to fill in this 'valley' by vaccination (graph *b*) reduces the rate of transmission of the infection in the population, thus lowering the probability of unvaccinated susceptible individuals being infected. As a consequence there is an upward shift in the age-distribution of susceptibles (indicated by the arrows marked *), from that pertaining prior to vaccination (shown by the dotted line). This gives the surprising result that the number or proportion of susceptibles after immunization has begun (area *S2*) is roughly unchanged from that which existed before immunization (area *S1*). However, the average age of the susceptibles has increased.

vaccination programme in England. Vaccination has little effect on the overall proportion susceptible to infection (Nokes, Anderson & Jennings, 1987). The level of coverage simply alters the proportions of seropositive individuals who acquired immunity either artificially or by natural infection. As the level of coverage approaches the critical point, the proportion possessing vaccine-induced immunity approaches unity.

The second consequence of a reduced rate of transmission in the vaccinated community is that the inter-epidemic period tends to lengthen when compared with the pre-control state. This trend is widely observed (Anderson & May, 1983).

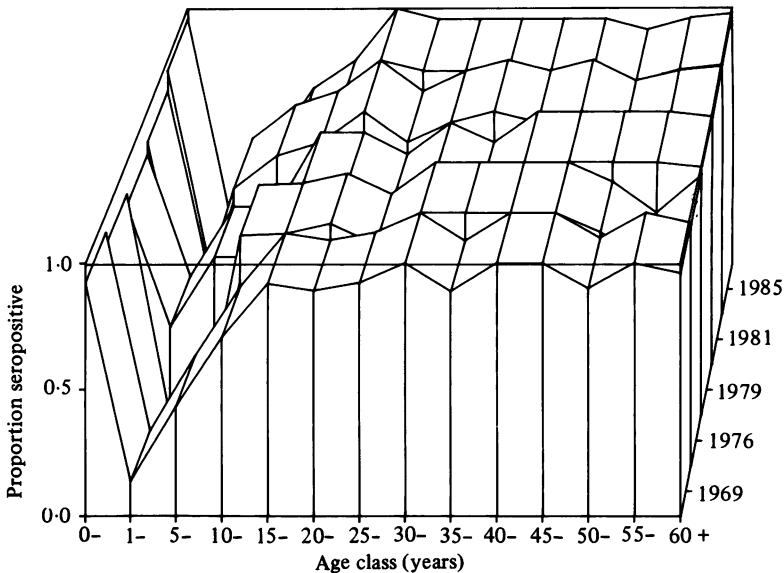


Fig. 9. Cross-sectional serological profiles of rubella antibodies in South Yorkshire, 1969–85. Little change can be seen in the age-serological profiles when observed longitudinally, from pre-vaccination 1969 through a number of post-vaccination years. (Note that sample sets for each of the years are independent.)

Practical problems may arise from both of these consequences. Changes in the age distribution of susceptibility and incidence of infection can influence the incidence of disease arising from infection if older people differ in their vulnerability to complications from infection when compared with younger people. Long inter-epidemic periods can create problems in motivating parents to vaccinate their children when the incidence of infection is very low during the period between epidemics, particularly if there is some small but measurable risk associated with vaccination.

Incidence of disease

The morbidity induced by many common viral and bacterial infections is often associated with the age of the infected person. A good example is rubella where disease in infants results from trans-placental transmission of the rubella virus from infected mother to foetus (particularly during the first trimester of pregnancy) (Gregg, 1941; Knox, 1980; Anderson & May, 1983; Anderson & Grenfell, 1986). The likelihood of an infected female being pregnant is clearly age dependent. Other examples include encephalitis resulting from infection with the measles virus and orchitis resulting from mumps (CDC, 1982; Anderson, Crombie & Grenfell; 1987). If the risk of disease resulting from infection rises with age, then mass vaccination, which raises the mean age at infection, may increase the incidence of disease over that which pertained prior to control.

The critical issue in this problem is whether the rise in the *proportion* of cases that occur in older people as a result of vaccination (see Figs 7 and 8) results in an increase in the *absolute* numbers of cases of serious disease or case complications. The answer to this question is crucially dependent on the change with age in the

force of infection (i.e. how the rate of transmission varies from one age class to another) and in the case complication rate, plus the rate or extent of vaccination in each age class (Anderson & May, 1983; 1985*b*; Anderson & Grenfell, 1986; Anderson, Crombie & Grenfell, 1987). The quantitative detail of these parameters is central to the outcome. Data records for complications arising from common viral and bacterial infections are often misleading in that the majority of case-complications occur in the young, in spite of an associated low risk of disease, because the vast majority of cases of infection occur in the young. To obtain a reliable estimate of the relative risk of complications it is necessary to divide the number of reports of case-related illness within a particular age class by the number of infections (complicated and benign) that occur in that age class (Anderson, Crombie & Grenfell, 1987). The latter is best estimated from serological data as opposed to reports of infection.

A related problem in this issue concerns the aim of mass vaccination. Should a policy aim to reduce the incidence of infection, or the incidence of serious disease resulting from infection or both? If the risk of serious disease rises steeply with age, these aims may be in conflict. Under such circumstances it may be better to target immunization to those most at risk of disease. This approach has been adopted in the United Kingdom for the control of congenital rubella by vaccinating girls, and girls only, just before they enter the reproductive age classes (i.e. 12–15 years of age).

Recent mathematical studies of these problems have revealed that in the case of measles, mumps and rubella, the likelihood of increasing the incidence of disease by mass vaccination can be minimized by immunizing a high proportion of children as early as is practically feasible (Anderson & May, 1983, 1985*b*; Anderson & Grenfell, 1986; Nokes & Anderson, 1987; Anderson, Crombie & Grenfell, 1987). These studies, which are based on the available epidemiological data, suggest that for rubella and mumps the target should be to immunize in excess of 60–70% by the age of 2 years. If vaccine uptake is less than this level, mass immunization is predicted to increase the incidence of case complications over that pertaining prior to control. In this summary we have omitted much detail to prevent confusion and the interested reader is urged to consult the source references.

Patterns of change in the incidence of infection and disease become much more complex under the impact of multi-stage vaccination programmes. An example is rubella, where in the United Kingdom a change is about to occur from a policy which targets immunization at teenage girls and susceptible women of childbearing age, to one in which the measles–mumps–rubella (MMR) vaccine will be administered en masse to young male and female children. With this change in policy an important question arises. Can we cease immunizing teenage girls once the cohort vaccination of children is introduced? Mathematical models provide a framework for examining this problem. In brief the answer again depends critically on the quantitative details, such as what proportions of children are immunized at what age. The general conclusion to emerge from extensive analyses is that a mixed policy must be continued for many years, perhaps decades, if one is to realise the full benefits of the mass immunization of young children (Nokes & Anderson, 1987).

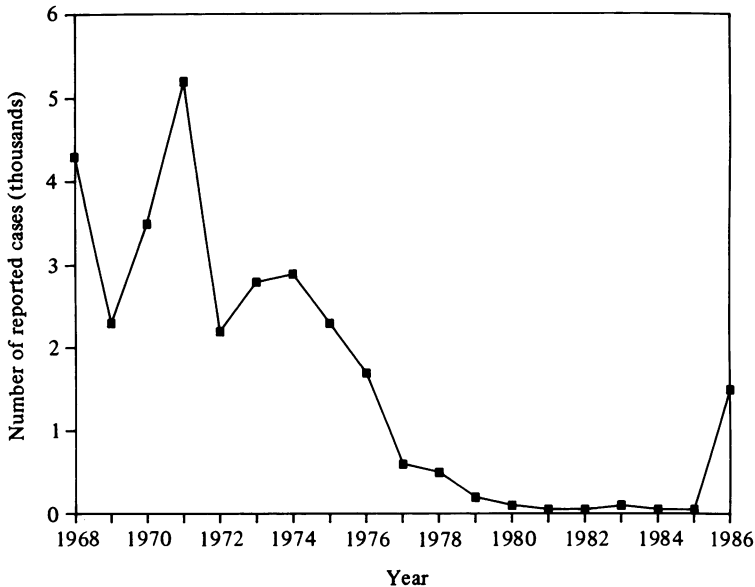


Fig. 10. The incidence of reported mumps cases in the State of Tennessee, USA, between 1968 (the year of mumps vaccine introduction) and 1986. The recent rise in cases is probably all the more alarming because it follows a decade of relatively low incidence (an explanation is given in text). (Source of data: Tennessee Department of Health and Environment.)

Mathematical models also provide a means of assessing how the incidence and age distribution of infection and disease will change through time after the introduction of mass vaccination or after a change in vaccination policy. One important prediction to emerge from such studies is the lengthening of the inter-epidemic period under high levels of mass vaccination. It will often be the case that as vaccination coverage rises to high levels, the interval between epidemics may extend to many years or even decades. Such trends have been observed in the United States in the incidences of rubella (Bart *et al.* 1985) and mumps (illustrated in Fig. 10). An epidemic after a long period of low incidence induced by vaccination should not be interpreted as a failure in vaccination coverage or of a particular policy. These dynamic changes are a simple and direct consequence of the impact of vaccination on the dynamic (and oscillatory) interaction between host and infectious agent populations. What matters in assessing the impact of vaccination is the long-term average in the incidence of infection, not short-term peaks.

CONCLUSIONS

We have glossed over much detail in this short review and ignored many complications that arise from heterogeneities in transmission generated by genetic, social, behavioural, spatial and demographic factors (Anderson & May, 1986). Our aim has been to define, as simply as possible, the central concepts underpinning the transmission dynamics of directly transmitted viral and bacterial disease agents, and to illustrate the application of mathematical models that embody these concepts in the design of vaccination programmes.

The recent convergence of mathematical theory and observation in epidemiology has created a powerful set of tools for the creation and evaluation of community-based programmes of infection and disease control, provided they are used sensibly. At present the potential value of these techniques is not widely appreciated amongst public and community health personnel, and epidemiologists. We believe there is a good case for the introduction of taught courses on the transmission dynamics of infectious diseases (employing some mathematical content) in the training of doctors and others associated with public health in the United Kingdom. One of the best illustrations, in our view, of the advantages of model construction lies in the design of vaccination programmes and the interpretation of their impact. Simple models can define target levels of cohort vaccination (Table 1) while more complex formulations can discriminate between the potential implications of various multi-stage programmes on the incidence of infection and disease in a population. These studies show clearly that the outcome of a given policy depends implicitly on the quantitative detail of the problem, with respect to levels of vaccination coverage by age class, the typical course of infection in an individual, and age-related changes in the rates of infection and case complications. In our view it would be difficult, if not impossible, to decide on the relative merits of different multi-stage vaccination programmes in the absence of some formal framework to guide scientific assessment.

An additional, but important, role of mathematical models is to guide the collection of epidemiological data to aid understanding and interpretation. Aside from the obvious need for epidemiological surveillance which focuses on longitudinal trends in the incidence of infection and disease (stratified by age, sex, geographical location), and accurate records of vaccine uptake, models highlight the need for detailed serological data. Such information should be collected by horizontal age-stratified (fine divisions by age in regions where the proportion seropositive changes rapidly with age) surveys and longitudinal cohort surveys both before and during the implementation of a vaccination programme. The need for data prior to the introduction of control centres on the estimation of age-specific rates of infection and risks of case complications by age. These parameters are central to the quantitative assessment of the likely impacts of different vaccination programmes. Insufficient detailed survey work of this nature has been undertaken in the United Kingdom (Nokes, Anderson & Anderson, 1986; Nokes, Anderson & Jennings, 1987). With changes in the vaccination policies imminent (e.g. the introduction of the MMR vaccine) it is important to plan for immediate and continued serological surveillance. The development of tests for antibodies to viral and bacterial antigens in human saliva would greatly facilitate sampling in the general population (Parry, Perry & Mortimer, 1987).

To conclude we return to the predictions that high levels of cohort vaccination are required to interrupt the transmission of many common childhood viral and bacterial infections. With the introduction of the triple MMR vaccine, target levels should be in the region of 95% or more around the ages of 2-3 years, with uniform coverage in different regions of the country a major priority. Past trends in vaccine uptake in the United Kingdom do not encourage the belief that publicity aimed at the general public and the medical professions will achieve the desired goals. We hope it will, but believe there is a strong argument for a more

central approach to the problem, perhaps by legal enforcement of immunization as a requirement for school entry in Britain.

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REFERENCES

- ANDERSON, R. M. (1982). Directly transmitted viral and bacterial infections of man. In *The Population Dynamics of Infectious Diseases* (ed. R. M. Anderson), pp. 1–37. London: Chapman & Hall.
- ANDERSON, R. M., CROMBIE, J. A. & GRENFELL, B. T. (1987). The epidemiology of mumps in the UK: a preliminary study of virus transmission, herd immunity and the potential impact of immunization. *Journal of Hygiene* **99**, 65–84.
- ANDERSON, R. M. & GRENFELL, B. T. (1986). Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. *Journal of Hygiene* **96**, 305–333.
- ANDERSON, R. M., GRENFELL, B. T. & MAY, R. M. (1984). Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination: time series analysis. *Journal of Hygiene* **93**, 587–608.
- ANDERSON, R. M. & MAY, R. M. (1979). Population biology of infectious diseases: part 1. *Nature* **280**, 361–367.
- ANDERSON, R. M. & MAY, R. M. (1982). Directly transmitted infectious diseases: control by vaccination. *Science* **215**, 1053–1060.
- ANDERSON, R. M. & MAY, R. M. (1983). Vaccination against rubella and measles: quantitative investigations of different policies. *Journal of Hygiene* **90**, 259–325.
- ANDERSON, R. M. & MAY, R. M. (1984). Spatial, temporal and genetic heterogeneity in host populations and the design of immunization programmes. *IMA Journal of Mathematics Applied to Medicine and Biology* **1**, 233–266.
- ANDERSON, R. M. & MAY, R. M. (1985*a*). Vaccination and herd immunity to infectious disease. *Nature* **318**, 323–329.
- ANDERSON, R. M. & MAY, R. M. (1985*b*). Age-related changes in the rate of disease transmission: implications to the design of vaccination programmes. *Journal of Hygiene* **94**, 365–436.
- ANDERSON, R. M. & MAY, R. M. (1986). The invasion, persistence and spread of infectious diseases within animal and plant communities. *Philosophical Transactions of the Royal Society B* **314**, 533–570.
- BAILEY, N. T. J. (1975). *The Mathematical Theory of Infectious Disease and its Applications*. London: Griffin.
- BART, K. J., ORENSTEIN, W. A., PREBLUD, S., HINMAN, A. R., LEWIS, F. L. & WILLIAMS, N. M. (1985). Elimination of rubella and congenital rubella from the United States. *Pediatric Infectious Disease* **4**, 14–21.
- BARTLETT, M. S. (1960). The critical community size for measles in the United States. *Journal of the Royal Statistical Society B* **123**, 37–44.
- BLACK, F. L. (1966). Measles endemicity in insular populations: critical community size and its evolutionary implications. *Journal of Theoretical Biology* **11**, 207–211.
- CENTERS FOR DISEASE CONTROL (1981). Measles encephalitis – United States 1962–1979. *Morbidity and Mortality Weekly Report* **31**, 217–224.
- DIETZ, K. (1982). Overall population patterns in the transmission cycle of infectious disease agents. In *Population Biology of Infectious Disease* (ed. R. M. Anderson and R. M. May), pp. 87–102.

- GREGG, N. M. (1941). Congenital cataract following German measles in the mother. *Transactions of the Ophthalmic Society of Australia* **3**, 35.
- GRENFELL, B. T. & ANDERSON, R. M. (1985). The estimation of age-related rates of infection from case notifications and serological data. *Journal of Hygiene* **95**, 419–436.
- KERMACK, W. O. & MCKENDRICK, A. G. (1927). A contribution to the Mathematical theory of epidemics. *Proceedings of the Royal Society A* **115**, 13–23.
- KNOX, E. G. (1987). Evolution of rubella vaccine policy for the UK. *International Journal for Epidemiology* **16**, 569–578.
- MCLEAN, A. R. & ANDERSON, R. M. (1988). The transmission dynamics of the measles virus in developing countries. I. Epidemiological parameters and patterns. *Epidemiology and Infection* **100**, 111–133.
- NOKES, D. J., ANDERSON, R. M. & ANDERSON, M. J. (1986). Rubella epidemiology in South East England. *Journal of Hygiene* **96**, 291–304.
- NOKES, D. J. & ANDERSON, R. M. (1987). Rubella vaccination policy: a note of caution *Lancet* *i*, 1441–1442.
- NOKES, D. J., ANDERSON, R. M. & JENNINGS, R. (1987). Longitudinal serological study of rubella in South Yorkshire. *Lancet* *ii*, 1156–1157.
- PARRY, J. V., PERRY, K. R. & MORTIMER, P. P. (1987). Sensitive assays for viral antibodies in saliva: an alternative to tests on serum. *Lancet* *ii*, 72–75.
- REPORT (1985). Expanded Programme on Immunization – programme impact: decreasing morbidity in Bangkok. *WHO Weekly Epidemiological Record* **60**, 141–144.