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Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy

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SUMMARY

Serological surveillance of measles immunity has been carried out in England since 1986/7. Results from sera collected in 1989–91 revealed that the proportion of school age children who were susceptible to measles was increasing, following the introduction of the measles, mumps and rubella vaccination programme in October 1988. Mathematical models are used to interpret these data and determine whether this increasing susceptibility is sufficient to allow a resurgence of disease from the low levels achieved by 1993. The models summarize serological profiles by a single parameter, the reproduction number R, which quantifies the level of herd immunity in the population. Results showed that there was cause for concern over the levels of susceptibility to measles, with an epidemic of over 100000 cases likely in 1995/6. These predictions are consistent with trends in the incidence and age distribution of measles and have enabled the planning of a major vaccination campaign.

INTRODUCTION

Measles is the most infectious of the vaccine-preventable diseases, causing significant morbidity and mortality if not controlled by vaccination. Before vaccination was introduced in England in 1968, measles epidemics occurred in alternate years causing an average of 100 deaths per year. Almost everyone experienced measles infection as a young child: only 3% of notified cases were in persons aged 10 years or more [1].

Vaccine uptake was initially low with only about 50% of children being vaccinated up to 1980. Coverage then increased steadily reaching 80% by 1988. Over this period measles notifications and deaths showed a downward trend, but coverage was sufficiently low for the virus to remain endemic (Fig. 1). Infections in children who were not vaccinated resulted in continuing morbidity and mortality, with case-fatality rates highest in older age groups (Fig. 2).

The introduction of the combined measles, mumps and rubella vaccine (MMR) in October 1988 was accompanied by an increase in vaccine coverage, which has now reached 92–93% [2]. An MMR 'catch up' programme, targeted at pre-school children, ran for 3 years until the first cohorts of children who had been offered

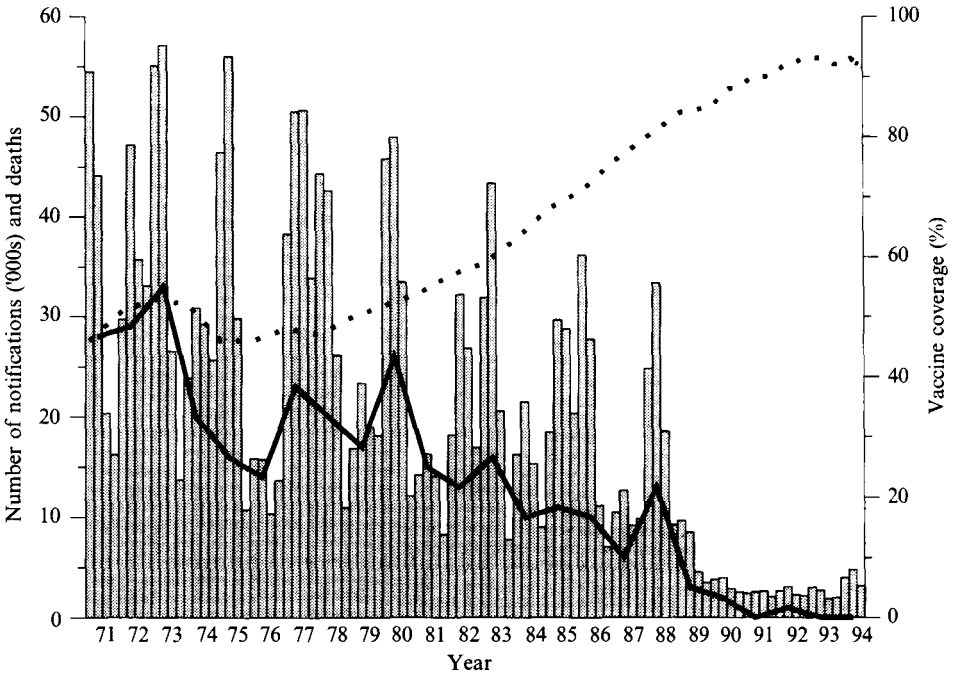

Fig. 1. Measles in England and Wales, 1971–94 (third quarter): notifications of disease ('000s per quarter – bars), acute deaths (per year, ——) and vaccine coverage (·····).

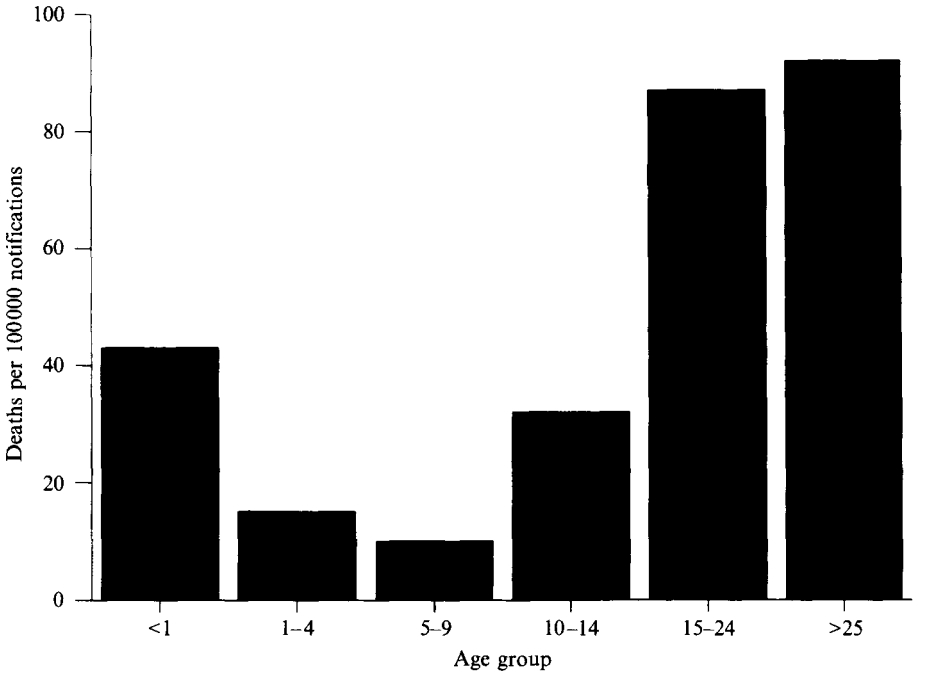

Fig. 2. Measles mortality rate: acute measles deaths per 100000 notifications by age group in England and Wales, 1971–88.

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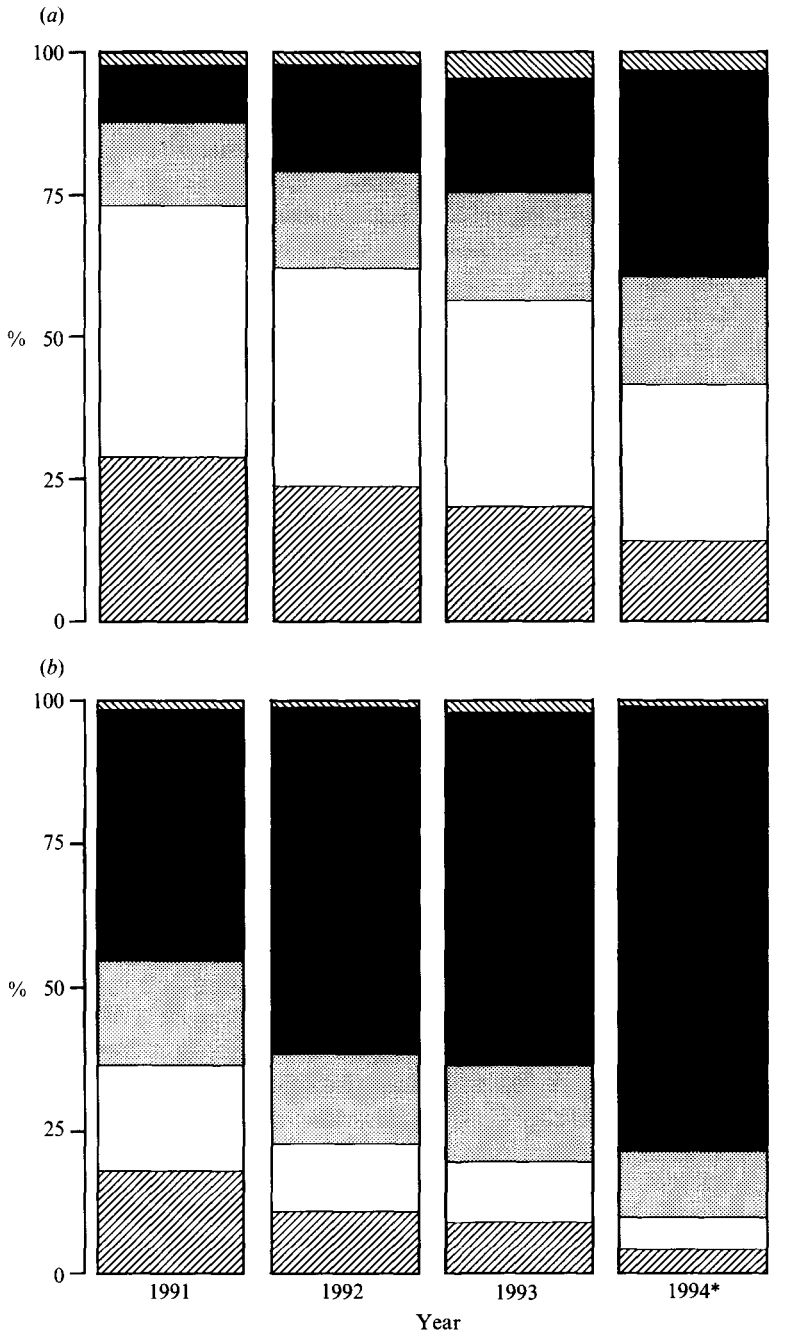

Fig. 3. Age distribution of measles in England and Wales, 1991–4 (* first 6 months of 1994 only): (*a*) actual notifications; (*b*) notifications corrected for misdiagnosis using the results of a laboratory confirmation study [3]. ▧, 25+; ■, 15–24; ▩, 10–14; ▨, 5–9; □, 1–4; ▨, under 1.

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MMR at 15 months reached school age. Notifications of measles declined to their lowest ever levels and there was a marked change in their age distribution, with a higher proportion occurring in older age groups (Fig. 3*a*). A study to confirm the clinical diagnosis of notified measles cases using measles specific IgM antibodies in serum suggested that notifications underestimate this shift into older age groups due to incorrect diagnoses of measles in young children [3]. Laboratory diagnosis suggests that approximately 70% of measles infections in the first half of 1994 occurred in persons aged 10 years or more [4]. The estimated age distribution of measles infection, calculated by applying the confirmation rates observed in the laboratory diagnosis study [3] to all notifications is shown in Fig. 3*b*.

The Public Health Laboratory Service (PHLS) established a programme of serological surveillance in 1986/7 to monitor the effects of the MMR vaccination programme [5]. If a vaccination programme achieves sufficiently high coverage to make a large impact on disease incidence, the reduced opportunity for unvaccinated children to acquire disease may result in increasing susceptibility in older age groups [6]. Regular surveys of age-specific antibody prevalence enable the identification of any susceptible cohorts, so that vaccination strategy can be updated accordingly [5].

Here, mathematical models are used to interpret susceptibility data from the surveillance programme and evaluate the potential for an epidemic. The models are based on the dynamic age dependent models of disease transmission used in many previous studies [7, 8]. However, rather than performing dynamic simulations, the models are used to interpret the serological data by summarizing the level of susceptibility of the population using a single parameter, the reproduction number.

LABORATORY METHODS

Collection and testing of sera

Residues of sera submitted for routine diagnostic examination to nine Public Health Laboratories in England (Ashford, Birmingham, Bristol, Exeter, Leeds, Manchester, Norwich, Preston and Reading) were collected. Sera from immunocompromised patients were excluded, as were those submitted for testing for hepatitis B virus and antibody to human immunodeficiency virus, in order to minimize any risk to laboratory staff. It was not possible to exclude samples submitted for testing for measles, but these comprised a negligible proportion of the total. In 1989–91 approximately 3000 sera were collected each year from children aged 1–14 years.

All sera were tested at Preston Public Health Laboratory by haemagglutination inhibition (HI). HI titres $\geqslant 8$ were considered positive; titres < 4, negative. Samples with titres $= 4$ were retested by ELISA (Behringwerke) and categorized according to the ELISA result. This procedure for determining susceptibility is identical to that used previously [5].

MATHEMATICAL MODELS

The population is divided into several age groups and the transmission rates between these groups are derived from pre-vaccination case notification data. The

transmission rates are combined with data on the levels of susceptibility in the population to formulate a 'next generation matrix'. The reproduction number, R, (sometimes called the *effective* reproduction/reproductive number/ratio/rate) is calculated from this matrix. It can be thought of as the number of secondary cases arising from a 'typical' primary case. If $R > 1$, the number of cases of disease will increase; if $R < 1$ the number of cases decreases. Any vaccination programme aimed at elimination must keep the value of R as small as possible and certainly less than one. Calculating the value of R for a series of susceptibility profiles shows how the level of herd immunity changes over time. The expected distribution of cases between the age groups is described by the typical primary case. Calculation of R involves a generalization of the method used to calculate the basic reproduction number of a disease [9]. Methodological details are given in the appendix.

The basic reproduction number R_0 is the value that the reproduction number would take if the entire population were susceptible. The proportion of a population p that must be immunized in order to eliminate a disease if vaccine is administered routinely at a young age is given by [7]

$$p = 1 - \frac{1}{R_0}. \tag{1}$$

Model structure – transmission rates

Patterns of mixing between and within different age groups are fundamental in determining the transmission of a disease within a population. The WAIFW ('who acquires infection from whom') matrix contains the values of the transmission rates between groups: the element in the ith row and jth column denotes the probability that an infective in the jth group will infect a susceptible in the ith group per unit time [6]. The transmission rates cannot be measured directly, but can be calculated from the age-specific pre-vaccination force of infection (the *per capita* rate at which susceptibles are infected [6]) which may be estimated from age-stratified case notification or serological data [6, 10]. However, if the model has N age groups, only N distinct transmission rates may be calculated from the data [6]. Since there are N^2 elements in the WAIFW matrix, we need to assume that many elements are equal [6]. Differences in transmission rates between age groups are thought to result mainly from differences in age-related contact rates, suggesting that the matrix should be symmetric [6]. Further simplifications, via the allocation of the N distinct transmission rates $\beta_1, \ldots, \beta_N$ to the WAIFW matrix, should be consistent with the underlying epidemiology. For example, the contact rate between adults and 5–9-year-olds is unlikely to be substantially different to the contact rate between adults and 10–14-year-olds. In contrast, contact rates within an age group are likely to be substantially higher than contact rates with other groups, especially for school age children.

Many previous studies have used age groups of 0–4, 5–9, 10–14, 15–19 and 20–74 years. Five age groups are also used here but these are chosen as 0–1, 2–4, 5–9, 10–14 and 15–74 years. The notification data from which the force of infection is calculated are not sufficiently detailed to calculate a separate value for the 15–19

age group [11] and so this group is combined with the 20+ age group. The large differences in susceptibility within 0–4-year-olds (pre- and post-vaccination) and the approximate linear increase in the force of infection in this age group [10] suggest the creation of separate groups for 0–1 and 2–4-year-olds.

Two models are used, with differing structures of the WAIFW matrix.

Model 1

Age group	0–1	2–4	5–9	10–14	15+
0–1	β_1	β_1	β_1	β_4	β_5
2–4	β_1	β_2	β_2	β_4	β_5
5–9	β_1	β_2	β_3	β_4	β_5
10–14	β_4	β_4	β_4	β_4	β_5
15+	β_5	β_5	β_5	β_5	β_5

This WAIFW matrix is a generalized version of one used in many studies [7, 8]. It features a unique transmission rate, β_3, for within group mixing of 5–9-year-olds to reflect the high transmission rates in primary schools. β_1 and β_2 define the other transmission rates between the under 10 year age groups. Above this age, persons have fairly uniform transmission rates with all age groups. One of the advantages of this configuration is that the values obtained for $\beta_1, \ldots, \beta_5$ are relatively insensitive to small changes in the force of infection estimates. This makes it extremely useful for a whole range of childhood infections. Insufficient importance, however, is attached to within group mixing in the 10–14 year age group; there is little reason to suppose that contact rates in secondary schools are substantially lower than those in primary schools. When attempting to match historical data this deficiency is concealed as almost all children were immune to measles by age 10 and so little infection occurred in the 10–14 age group. However, as susceptibility in 10–14-year-olds rises, the within-group transmission rate will be critical in determining whether or not an epidemic will occur.

It is possible to prescribe a WAIFW matrix structure that has a unique coefficient for the transmission rate within the 10–14 year age group. However, the small number of infections that occurred in this age group in the pre-vaccination era causes difficulty in calculating its value. The small number of infectives in the 10–14 year age group not only makes a unique coefficient extremely sensitive to the pre-vaccination force of infection estimate for the 10–14 year age group, but also limits the accuracy with which the force of infection in this age group can be estimated. This highly sensitive dependence on a parameter which is difficult to estimate suggests that an alternative approach should be taken.

Model 2

$$\begin{bmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_5 \\ \beta_1 & \beta_2 & \beta_2 & \beta_2 & \beta_5 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ \beta_1 & \beta_2 & \beta_4 & \alpha\beta_3 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{bmatrix}$$

In an attempt to overcome these problems, and the inadequacies of model 1,

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model 2 assumes that the transmission rate within the 10–14 year age group is a multiple α of the transmission rate within the 5–9 year age group. The values $\beta_1, \ldots, \beta_5$ are calculated from the age specific force of infection using $\alpha = 1$. The sensitivity of the model's predictions to the value of the transmission rate within the 10–14 year age group can be explored by varying the value of α. A wide range of values of α is used, although it is probable that the true value is greater than one. The greater size of secondary schools, coupled with the fact that secondary school children are often taught in different classes for different lessons, suggests that contact rates are higher than in primary schools.

Epidemic size

Knowledge of the likely number of cases in a predicted epidemic is crucial if cost/benefit analyses of possible interventions are to be carried out. However, predicting the size of an epidemic is not straightforward. Although dynamic models which simulate disease transmission provide good correlation with observed epidemics in periods of no or low vaccination coverage, results are less encouraging when vaccination coverage is high [11]. Thus a method based on the reproduction number is used.

The reproduction number, R, is a measure of the potential for an epidemic. A large epidemic will not necessarily occur as soon as R exceeds 1, especially if the disease has been reduced to very low levels. However, unless there are no infectives, their number will start to build gradually. R may increase further whilst this occurs, increasing the rate at which the epidemic grows. Once an epidemic becomes established the value of R will start to fall, as susceptibles who acquire infection become immune. The peak of the epidemic will be reached when R falls to 1, with a continuing reduction in R as the epidemic dies out. Therefore, using the age distribution of infections to determine the reduction of susceptibility in each age group, the epidemic size is estimated as twice the number of infections required to reduce R from its pre-epidemic value to 1. The expected number of deaths for a given epidemic is calculated using the age specific case-fatality rates.

Model parameters

The force of infection estimates, derived from 1956–65 case notifications in England and Wales [11], that were used to calculate transmission rates for the models are shown in Table 1. The transmission rates derived from these values are shown, for each model, in Fig. 4. A comparison of the models reveals that setting $\alpha = 0{\cdot}27$ in model 2 produces transmission rates similar to those in model 1.

Susceptibility

In order to make projections of susceptibility in years after 1991, a baseline susceptibility for each birth cohort is established. Projections are made on the assumption that the low level of infection occurring after this date has an insignificant effect on the baseline, i.e. the susceptibility of each birth cohort remains unchanged. The proportions susceptible in the models' age groups in each year are determined by the aggregation of the appropriate birth cohorts. Calculations of the reproduction number are based on these aggregated figures.

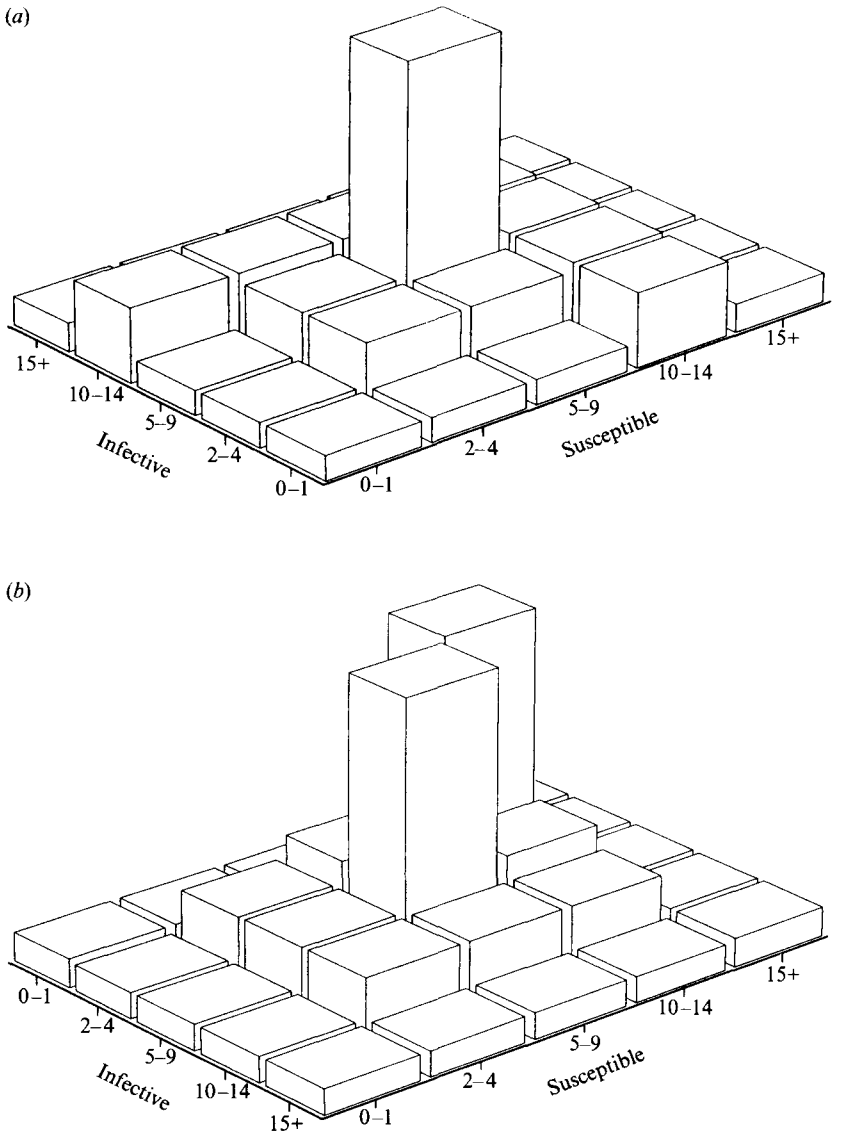

Fig. 4. Relative transmission rates between age groups, calculated for: (*a*) model 1; (*b*) model 2 (with $\alpha = 1$).

Sufficient serological data exist for cohorts born between 1973/4 and 1984/5 for the baseline susceptibility to be calculated. There is a lack of suitable data in older cohorts, and the average susceptibility of persons born before 1973 is assumed to be 0·5%. Susceptibility of cohorts born during or after 1985/6 cannot be derived from sera collected in 1989–91, as they were subject to vaccination during this period. Projections of susceptibility in these cohorts are therefore based on assumptions regarding vaccine coverage and efficacy. Two alternative scenarios are investigated.

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Table 1. *Estimated timing and size of a measles epidemic for different values of* α *(the parameter defining the contact rate amongst 10–14-year-old children) under scenario A (16·3% susceptibility in cohorts born in or after 1985/6) and scenario B (11·7% susceptibility in cohorts born in or after 1985/6)*

	Scenario A					Scenario B	
α	1·25	1·50	1·75	2·00	2·00	1·75	2·00
Year of epidemic	1997	1996	1995	1994	1995	1996	1995
Cases (000's)	120	150	120	110	230	60	100
Deaths	32	40	32	31	63	18	31

Scenario A: susceptibility in all cohorts born in or after 1985/6 is 16·3%. This would result from a coverage of 93% (the current coverage in England and Wales [2]) using a single dose of vaccine with 90% efficacy [3, 12, 13]. Although not all these cohorts have experienced 93% coverage, the cohorts in which coverage was lowest (1985/6 to 1987/8) may have acquired immunity through infection before the decline in the incidence of measles after 1989, or may have been vaccinated in the MMR catch-up programme. The combined effect of all these factors may even have reduced susceptibility below 16·3%.

Scenario B: susceptibility in cohorts born in or after 1985/6 is 11·7%. This would result from an initial coverage of 80% (the average achieved in 1986–8) combined with a coverage of 65% in a catch-up programme, using a vaccine of 90% efficacy. Susceptibility of 11·7% would also result from a 93% coverage with a single dose of vaccine of 95% efficacy. It may therefore be regarded as a minimum estimate of susceptibility in those cohorts born after 1988/9 that have had only one opportunity for vaccination and have experienced little risk of infection.

Susceptibility in the 0–1 year (i.e. 0–23 month) age group is calculated assuming the average duration of protection through maternal antibody is 3 months, and that vaccination occurs at age 15 months.

RESULTS

Susceptibility

The baseline susceptibility by birth cohort that is used to make projections of susceptibility is shown in Fig. 5. Susceptibility rises from 5% or less in cohorts born in or before 1977/8, to 10% or more in those born in or after 1981/2.

Modelling

It is not possible to determine accurately the value of α, the factor by which contact rates amongst 10–14-year-olds are greater than amongst 5–9-year-olds. The transmission rates were calculated from the estimated pre-vaccination forces of infection with $\alpha = 1$. Changing α does affect the pre-vaccination force of infection in 10–14-year-olds, but any α between 0 and 2 produces a value within 10% of the estimate (Fig. 6). (The effect on the force of infection in other age groups is negligible.) Since epidemiological arguments suggest that $\alpha > 1$, results are presented for a range of values between 1 and 2.

The critical immunization coverage required for elimination, calculated using

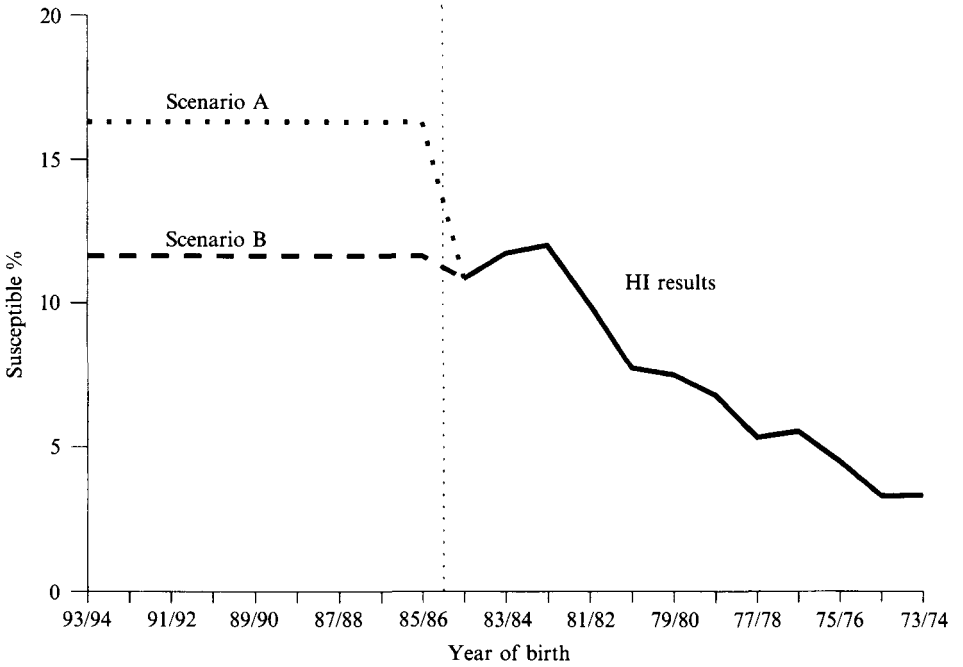

Fig. 5. Profiles of susceptibility in each cohort that are used to calculate the susceptibility in each age group for the years 1989–97.

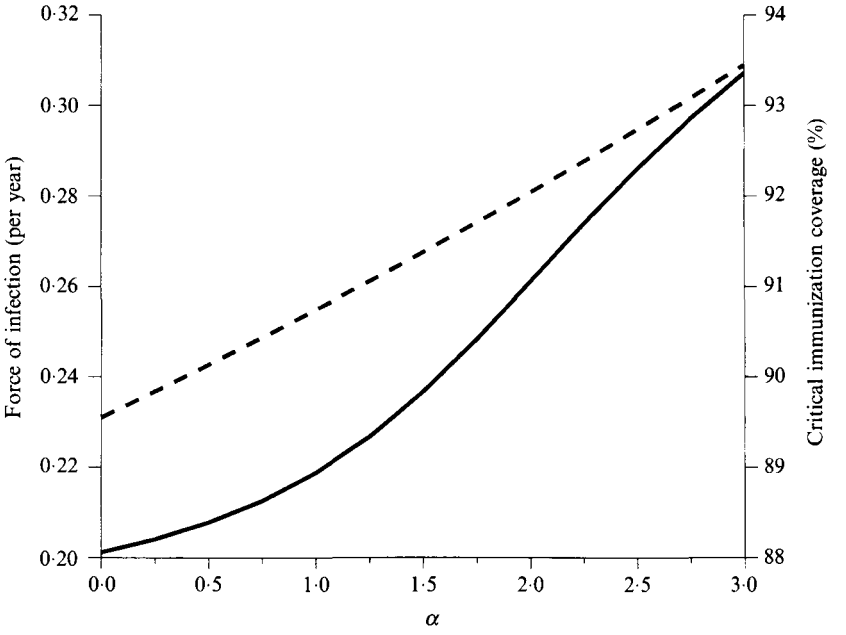

Fig. 6. Effect of the transmission rate within the 10–14 year age group on the pre-vaccination force of infection in this age group (– – –), and on the critical immunization coverage required for elimination (——).

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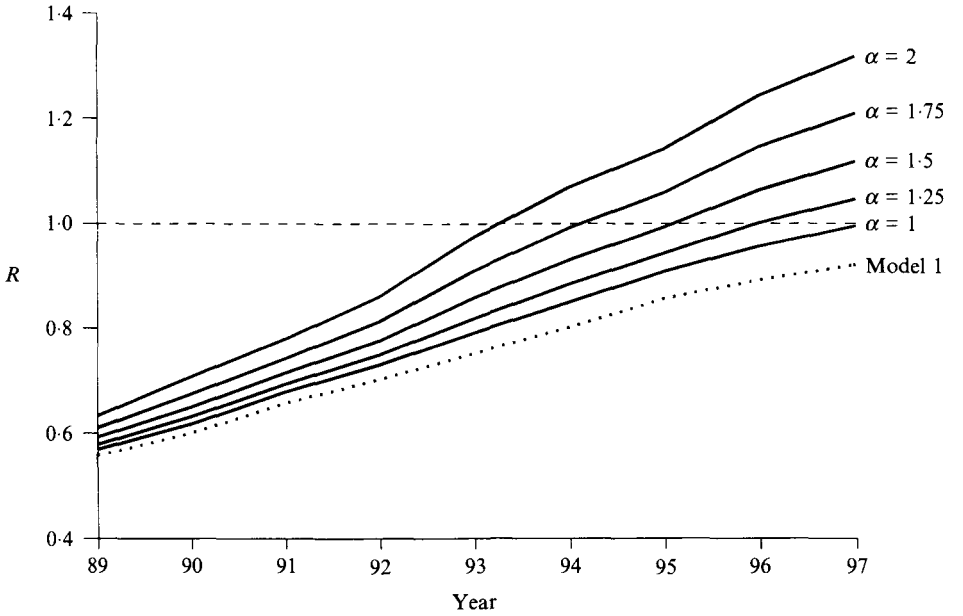

Fig. 7. Reproduction number for measles, 1989–97; scenario A.

equation (1) is shown in Fig. 6. This is the proportion of infants that must be vaccinated successfully (i.e. develop immunity following vaccination) in order to maintain $R < 1$ in the long term. For values of $\alpha > 1$ the critical coverage is greater than 89%. Vaccination coverage of 93% would require a vaccine efficacy in excess of 95% to reach this critical level.

Scenario A

The reproduction number R calculated assuming a susceptibility of 16·3% in cohorts born in or after 1985/6 is shown in Fig. 7. All models suggest that the reproduction number will eventually exceed one; the year in which this occurs depends on the value of α. When $R > 1$ the potential for an epidemic exists, the expected sizes of such epidemics are shown in Table 1.

Different models and values of α also predict different age distributions; the higher the value of α, the more cases are predicted in the 10–14 year age group. Model 1 gives a fairly constant age distribution, with approximately 50% of cases occurring in 5–9-year-olds (Fig. 8). This does not reflect the changing pattern seen in notifications of measles (Fig. 3). The increasing proportion of cases seen in older age groups is more similar to the pattern given by model 2, with $\alpha = 2$ (Fig. 9).

Scenario B

The reproduction number R calculated assuming a susceptibility of 11·7% in cohorts born in or after 1985/6 is shown in Fig. 10. Although any value of α greater than 0·4 suggests that R will exceed 1 in the long term, only models with $\alpha > 1·5$ predict the potential for an epidemic before 1997. The expected sizes of such epidemics are shown in Table 1. The age distribution given by model 2 with $\alpha = 2$ shows a considerable increase in the proportion of cases occurring in older age groups (Fig. 11), similar to the adjusted notifications (Fig. 3*b*).

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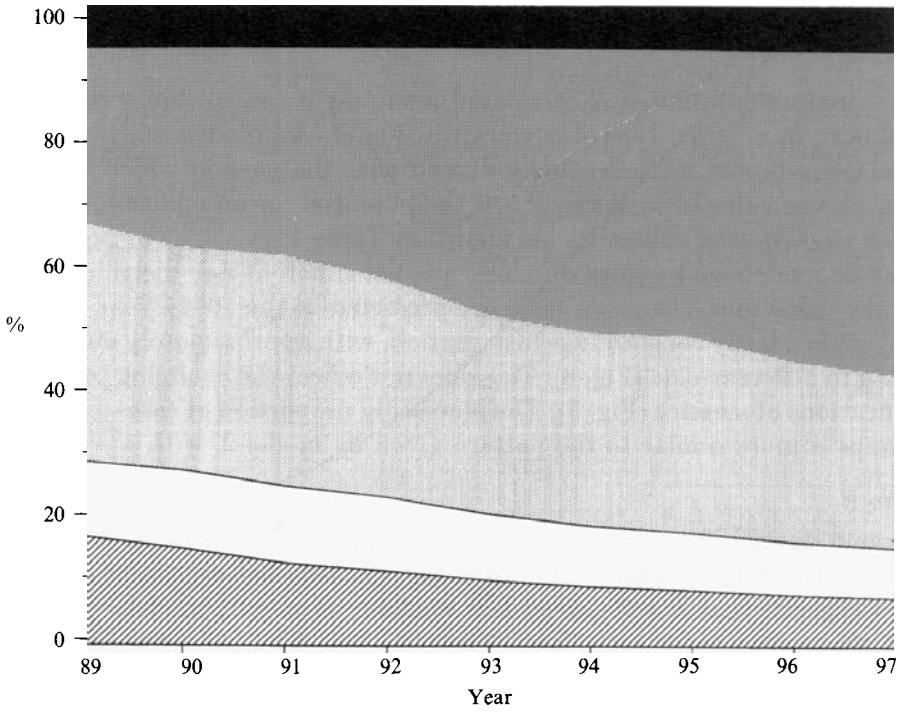

Fig. 8. Predicted age distribution of measles, 1989–97: model 1, scenario A.
■, 15+; ▩, 10–14; ▨, 5–9; □, 2–4; ▨, 0–1.

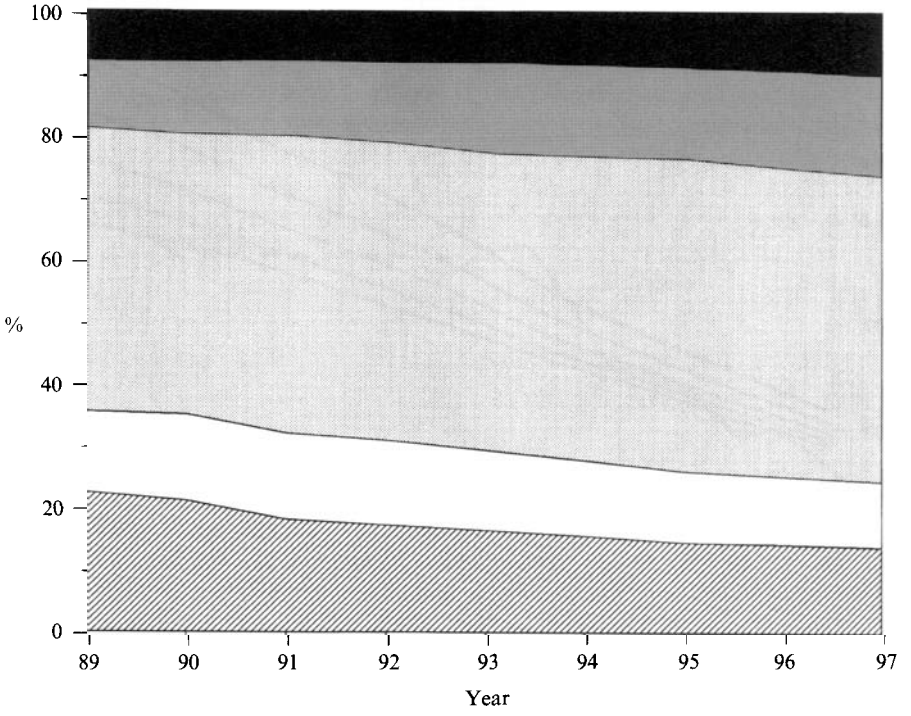

Fig. 9. Predicted age distribution of measles, 1989–91: model 2 ($\alpha = 2$), scenario A.
■, 15+; ▩, 10–14; ▨, 5–9; □, 2–4; ▨, 0–1.

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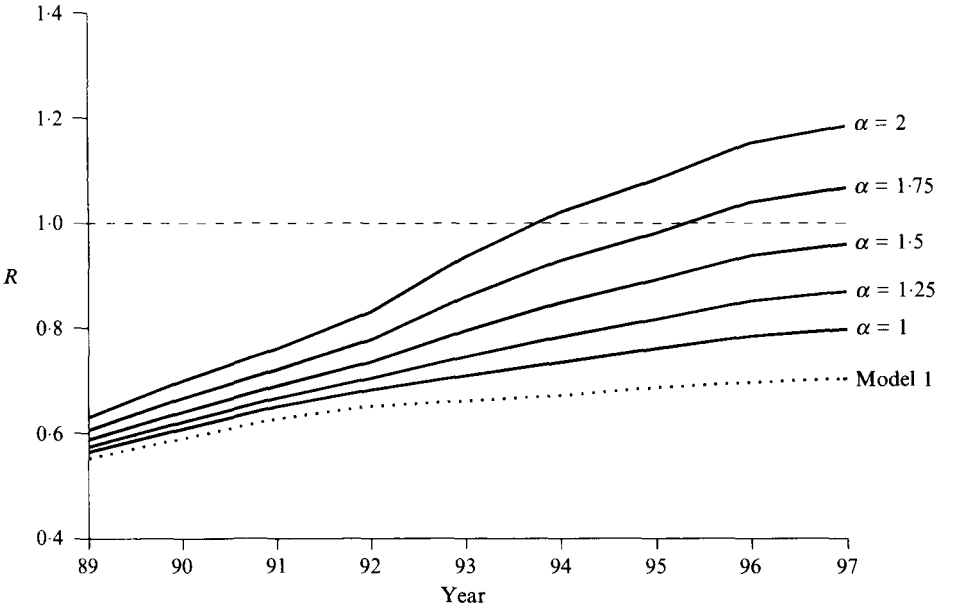

Fig. 10. Reproduction number for measles, 1989–97: scenario B.

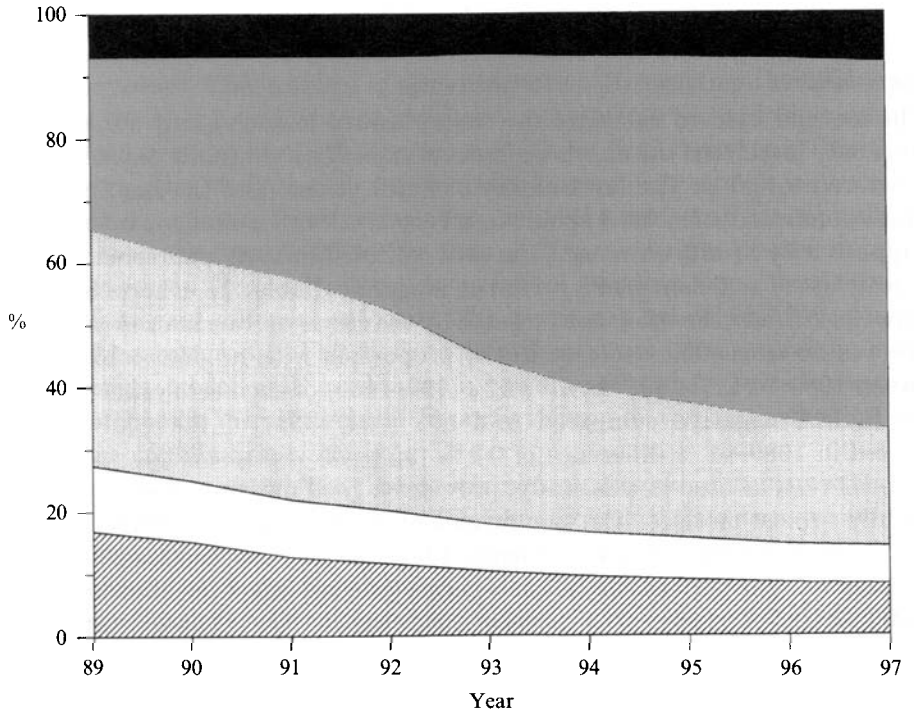

Fig. 11. Predicted age distribution of measles, 1989–97: model 2 ($\alpha = 2$), scenario B. ■, 15+; ▩, 10–14; ⊡, 5–9; □, 2–4; ▨, 0–1.

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DISCUSSION

The models suggest that the increasing proportion of schoolchildren susceptible to measles provided the potential for a major epidemic of measles in the mid 1990s. Such an epidemic would have involved more than 100000 cases, with a large proportion in persons aged more than 10 years. Since measles mortality is greatest in this age group, a disproportionately high number of deaths would have been expected. Identification of the potential for an epidemic, using results from sera collected up to 1991, has enabled the planning and implementation of a major vaccination campaign [14].

Confirmation of predictions using other data

A major resurgence of measles, with incidence similar to that predicted here for England and Wales, occurred in Scotland in 1993/4 [15]. No serological data from Scotland are available, so it is not certain that levels of susceptibility were similar to those in England, but vaccination coverage and disease incidence there had been similar to those in England and Wales.

In 1994, the number of notifications of measles in England and Wales increased (14957 by week 47) from the record low levels seen in the previous 3 years (9680, 10268 and 9612 annual notifications respectively). The increase was especially apparent in older age groups; over 70% of cases occurred in persons over 10 years, often as a result of outbreaks in secondary schools [4].

Susceptibility

The method used to calculate the susceptibility in each group for years after 1991 is only justified if the number of infections and vaccinations occurring in each cohort are negligible. The low number of notifications (and the small proportion of these confirmed as measles) point to a very low level of endemic infection. This is supported by results obtained from sera collected in 1993 and tested by ELISA (HI reagents of sufficient quality were no longer available). In cohorts born in and before 1984/5 (and therefore not targeted by the catch-up vaccination programme) there was no consistent decrease in the proportion with no detectable antibody between 1989–91 and 1993. In all 8·9% (130/1460) of such sera collected in 1993 were ELISA negative compared to 9·1% (394/4331) of the equivalent sera collected in 1989–91, a difference of 0·2% (95% CI −1·5 to 1·9%).

The HI test, as used in this study, provides a good measure of susceptibility to clinically typical measles. The significance of the low levels of antibody that are detected by the most sensitive serological tests is not clear. Such antibody levels (probably vaccine derived) do not necessarily prevent infection, clinical disease or infectiousness. A study of a measles outbreak in the United States, which measured pre- and post-exposure titres using a plaque reduction neutralization test, demonstrated that clinically typical disease could occur in persons with detectable antibody. It identified a titre below which exposure produced clinically typical disease [16], and showed that mild infection (causing symptoms not sufficient to meet the case definition) occurred in some persons with titres above this level. It is not clear whether persons with mild or sub-clinical infection are capable of transmitting disease [16]. The significance of low levels of antibody

detected by ELISA is being investigated, by documenting the IgM and IgG responses to vaccination in such children in relation to their prior vaccination history. Further studies will involve parallel testing of sera using ELISA and a plaque reduction neutralization assay.

Outbreak studies [12, 13] and surveillance data [3] suggest a vaccine efficacy against clinical measles of approximately 90%, and hence that 10% of vaccinees are susceptible to clinical measles. If there are other vaccinees who are at risk of sub-clinical measles infection and are potential infectives, calculations of the reproduction number and expected epidemic size are too low. It has been suggested that studies of outbreaks may underestimate the true vaccine efficacy [17]. But this only applies in highly vaccinated populations [17] and is therefore not relevant to the outbreaks in England and Wales in cohorts with moderate vaccine coverage. However, our results show that even a vaccine with an efficacy of 95% might not have been capable of preventing an epidemic.

Models

The difficulty in determining unique contact rates within older age groups is caused by the very small number of infections that occurred in older children before vaccination was introduced. Calculations of such transmission rates would be very sensitive to the estimates of the force of infection in older age groups; a small error in the force of infection estimate could cause the calculated transmission rate to be the wrong order of magnitude entirely. Calculations of the other transmission rates are much more robust, due to the larger numbers of infectives involved. The problem of the uncertainty surrounding the transmission rate within the 10–14 age group is addressed in this study by exploring a range of values around a robust first estimate, namely the transmission rate within the 5–9 year age group. It is likely that the contact rate in secondary schools is even greater than in primary schools. Firstly, secondary schools have many more pupils than primary schools (perhaps 1000 rather than 200), providing a greater number of potential contacts. Secondly, secondary school children are often taught in different classes for different subjects, whilst primary school children generally remain in the same groups. This leads to greater mixing within secondary schools. Results from a model with transmission rates in secondary schools two times higher than those in primary schools (i.e. $\alpha = 2$) provide the best reflection of the observed age distribution of cases.

An alternative approach may be to make comparisons of transmission rates with other, less infectious diseases if sufficient serological data become available. Similar work may also enable the inclusion of an extra age group in the models, to incorporate the high transmission rates that exist within colleges and universities. Measles outbreaks in universities have not occurred to date in England and Wales because of the very low levels of susceptibility by this age. In the United States, where such outbreaks had become common (especially at large, residential establishments [18]), pre-matriculation immunization requirements have now been introduced at many colleges [18].

The age groups used in the model are not ideal, being dictated by the groups used by the Office of Population Censuses and Surveys when reporting notification data, from which the pre-vaccination forces of infection are derived. It would be

more meaningful for the age groups to reflect school system, e.g. 5–10, 11–15, 16–20, etc, but this would require the availability of disaggregated pre-vaccination data. Further development of the models might address other sources of heterogeneity, such as variations in population density and vaccine coverage, to identify whether such factors might hinder the elimination of a disease.

Future

The measles vaccination campaign carried out in England and Wales in November 1994 is expected to have a dramatic effect on susceptibility to measles. All children aged 5–16 were offered vaccine, irrespective of a previous history of vaccination or disease. If this has been successful in immunizing even only half of the susceptibles in this age range, R would be reduced to 0·5–0·6. This would be of considerable value in guarding against any resurgence of measles in the short and medium term.

For the longer term, the models suggest that the effective immunization coverage required for the elimination of measles is in excess of 90%. The effective coverage achieved with a vaccination coverage of 93% is below this level, even if vaccine efficacy is as high as 95%. Thus a vaccination programme incorporating only a single dose will not be sufficient to eliminate measles. A second dose of vaccine, offered to all children, will be required to achieve the necessary level of immunity.

This study illustrates a new role for mathematical models in a public health setting. Models have been used previously to assist in the design of vaccination programmes, by highlighting potential risks and benefits. Applying these methods to the interpretation of serological surveillance data allows the potential for an epidemic to be identified, and provides time to plan and implement appropriate interventions.

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APPENDIX

Following an approach similar to that adopted by Diekmann and colleagues [9], let $A(a, a', \tau)$ denote the infectivity of a person who was aged a' when infected time τ ago towards a susceptible of age a. Then the force of infection $\lambda(a,t)$ satisfies [9]

$$\lambda(a,t) = \int_0^L \int_0^L A(a,a',\tau)\,\lambda(a',t-\tau)\,x(a',t-\tau)\,da'\,d\tau,$$

where $x(a,t)$ is the proportion of persons of age a who are susceptible at time t. Consider a model in which the population is divided into N age groups $(a_{i-1}, a_i]$, with $a_0 = 0$ and $a_N = L$. The force of infection is assumed to be constant on each age group (i.e. $\lambda(a,t) = \lambda_i(t)$ if $a \in (a_{i-1}, a_i]$). The contact rate between individuals is assumed to depend on their respective age groups, so that

$$A(a,a',\tau) = \beta_{ij}\,e^{-v\tau} \quad \text{if } a \in (a_{i-1}, a_i] \quad \text{and} \quad a' + \tau \in (a_{j-1}, a_j],$$

where $1/v$ is the average duration of infectiousness.

Hence, integrating over each age group,

$$\lambda_i(t) = \sum_j \int_0^L e^{-v\tau}\left(\beta_{ij} + \frac{\tau}{\alpha_j - a_{j-1}}(\beta_{ij+1} - \beta_{ij}) + \ldots\right)\lambda_j(t-\tau)\,X_j(t-\tau)\,d\tau,$$

where

$$X_i(t) = \int_{a_{i-1}}^{a_i} x(a,t)\,da,$$

and the higher-order terms are the contributions from infectives who move into older age groups.

Seeking a solution of the form $\lambda_i(t) = \lambda_{0i}(t)\, e^{(R(t)-1)\,vt}$, yields

$$\lambda_{0i}(t) = \sum_j \int_0^L \left(\beta_{ij} + \frac{\tau}{a_j - a_{j-1}}(\beta_{ij+1} - \beta_{ij}) + \dots\right) e^{-R(t-\tau)\,v\tau} \lambda_{0j}(t-\tau)\, X_j(t-\tau)\, d\tau.$$

We assume that X_j, R and λ_{0i} vary much more slowly than $e^{-Rv\tau}$ and may be considered constant when performing the integration with respect to τ. Hence

$$\lambda_{0i} = \sum_j \frac{\beta_{ij} X_j}{vR} \lambda_{0j} \left(1 + \frac{1}{vR(a_j - a_{j-1})} \frac{\beta_{ij+1} - \beta_{ij}}{\beta_{ij}} + \dots\right).$$

The higher-order terms, corresponding to an infective moving up one or more age group whilst still infectious, can be ignored if

$$\epsilon_{ij} = \frac{|\beta_{ij+1} - \beta_{ij}|}{v\beta_{ij}(a_j - a_{j-1})} \ll 1 \quad \text{for all } i, j.$$

The largest value of ϵ_{ij} for any of the configurations used in this study is approximately $1/v$. The infectious period for measles is 7 days, so $v = 52\ \text{yr}^{-1}$, $\epsilon_{ij} < 0{\cdot}02$ and the higher-order terms make a negligible contribution. Thus

$$\lambda_{0i} = \sum_j \frac{\beta_{ij} X_j(t)}{vR(t)} \lambda_{0j}$$

and so $R(t)$ is the dominant eigenvalue of the matrix with elements $\beta_{ij} X_j(t)/v$, and the corresponding eigenvector has elements λ_{0i}.

It is worth noting, as a corollary to this result, that if $Y_i(t)$ is defined by

$$\lambda_{0i}(t) = \sum_j \beta_{ij}\, Y_j,$$

$R(t)$ is the eigenvalue of the matrix with elements $\beta_{ij} X_i/v$, and the corresponding eigenvector has elements Y_i. Y_i can be interpreted as representing infectives in the ith age group.

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