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Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom

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SUMMARY

The paper examines predictions of the impact of various one-, two- and three-stage vaccination policies on the incidence of congenital rubella syndrome (CRS) in the United Kingdom with the aid of a mathematical model of the transmission dynamics of rubella virus. Parameter estimates for the model are derived from either serological data or case notifications, and special attention is given to the significance of age-related changes in the rate of exposure to rubella infection and heterogeneous mixing between age groups. Where possible, model predictions are compared with observed epidemiological trends.

The principal conclusion of the analyses is that benefit is to be gained in the UK, both in the short and long term, by the introduction of a multiple-stage vaccination policy involving high levels of vaccination coverage of young male and female children (at around two years of age) and teenage girls (between the ages of 10–15 years), plus continued surveillance and vaccination of adult women in the child-bearing age classes. Model predictions suggest that to reduce the incidence of CRS in future years, below the level generated by a continuation of the current UK policy (the vaccination of teenage girls), would require high rates of vaccination (> 60 %) of both boys and girls at around two years of age. Numerical studies also suggest that uniform vaccination coverage levels of greater than 80–85 % of young male and female children could, in the long term (40 years or more), eradicate rubella virus from the population. The robustness of these conclusions with respect to the accuracy of parameter estimates and various assumptions concerning the pattern of age-related change in exposure to infections and 'who acquires infection from whom' is discussed.

INTRODUCTION

Rubella vaccine was first licensed in 1969 and, since that date, it has been used extensively in Europe and North America. The purpose of immunization is to control CRS in infants by preventing rubella infection in pregnant women. The disease syndrome (CRS) occurs in approximately 80 % of infants born to women

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who had acquired inapparent or apparent rubella infection during the first trimester of pregnancy (Gregg, 1941; Benenson, 1975; Hanshaw & Dudgeon, 1978; Knox, 1980; Miller, Craddock-Watson & Pollack, 1982; Anderson & May, 1983*a*; South & Sever, 1985).

There still exists today some uncertainty over the best vaccination policy to adopt for the control of congenital rubella syndrome (CRS). Currently, different countries adopt different vaccination policies. In the USA, control centres on the immunization of a very high proportion of each yearly cohort (> 90%) of both boys and girls prior to their entry into primary school. The strategy is based on continued routine vaccination of all children aged 15 months or over, vaccination of all school children not vaccinated in infancy, and vaccination of susceptible adults (particularly females and hospital personnel). Rubella vaccine has been administered as MMR (measles, mumps, rubella vaccine) or as MR (measles, rubella vaccine). The control programme has had a marked impact on both the incidences of rubella and CRS (Fig. 1), primarily as a consequence of the high levels of immunization coverage achieved by the Childhood Immunization Initiative (which began in 1977) whose goal is to achieve and maintain immunization levels in excess of 90% for all childhood vaccine-preventable diseases (MMWR, 1984). The attainment of very high levels of vaccination coverage in pre-school children (> 90%) is, in part, a consequence of the USA school immunization laws, which require documentary evidence of immunization against certain common vaccine-preventable infections prior to school entry.

The current policy in the UK is to vaccinate girls, and girls only, between 10 and 15 years of age. This strategy is supplemented by selective postpartum vaccination of women found to be susceptible to rubella. Recent publicity campaigns, mounted by the Department of Health and Social Security, have aimed to encourage women in the child-bearing age classes to be screened for the presence or absence of rubella antibodies and to be vaccinated if found to be seronegative. The average age at vaccination of teenage girls is approximately 12 years, and by the age of 15 years, roughly 85% of each yearly cohort are immunized at present. This policy has had a substantial impact on the incidence of CRS (Fig. 2) but, as intended, a limited effect on the incidence of rubella. Virus transmission is maintained in the male and young female segments of the population. The primary objective of this strategy is to protect those at risk (women in the child-bearing age classes) while allowing rubella virus to circulate freely amongst children such that most girls have naturally acquired immunity prior to entry into the child-bearing age group (16–40 years of age).

Recent research has shown that which of the two strategies (the USA or the UK policies) is the most effective in controlling the incidence of CRS, depends critically on the levels of vaccination coverage achieved under each of the policies (Knox, 1980; Anderson & May, 1983*a*; Hethcote, 1983). The level of herd immunity required to eradicate rubella in both the UK and the USA is thought to be of the order of 85–88% (based on the observation that the average age at which rubella infection was acquired prior to widescale immunization was approximately 9–10 years of age (Anderson & May, 1982, 1983*a*)). As such, the USA policy will eventually eliminate rubella, and hence CRS, after 20–30 years of cohort vaccination, provided roughly 90% of each yearly cohort of boys and girls are immunized

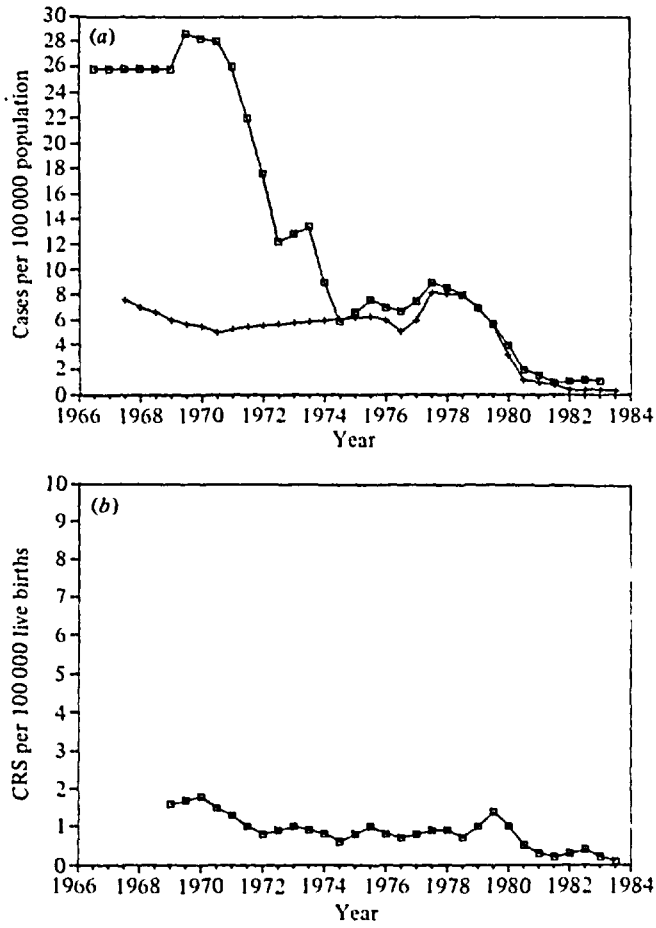

Fig. 1. Incidence of reported rubella and congenital rubella syndrome (CRS) in the United States, 1966–83 (source MMWR, 1984). Graph (*a*): □, number of rubella cases (/100000 population); +, number of cases > 15-year-olds (/100000 population). Graph (*b*): □, reported CRS cases (/100000 live births).

at around 15 months to 2 years of age. Current trends tend to support this prediction (Fig. 1). Under low levels of cohort vaccination (in the range 0–50 %), however, research suggests that the USA policy can result in an increased incidence of CRS over that pertaining prior to the introduction of mass immunization. This arises as a direct consequence of the tendency of mass vaccination to raise the average age at which those still susceptible acquire infection over that prior to control (Anderson & May, 1982, 1983*a*, 1985). This trend was apparent during the early stages of the introduction of the USA policy (see Fig. 1).

By contrast, all levels of vaccination coverage under the UK policy will result (in the long term) in a decrease in the incidence of CRS when compared with the pre-control situation. Oscillations in disease incidence, arising from the 4- to 5-year epidemic cycle of rubella (see Anderson & May, 1983*a*; Anderson, Grenfell & May, 1984), complicate the interpretation of short-term trends (see Fig. 2) but, in the long term (10–20 years), mathematical studies suggest that the incidence of CRS

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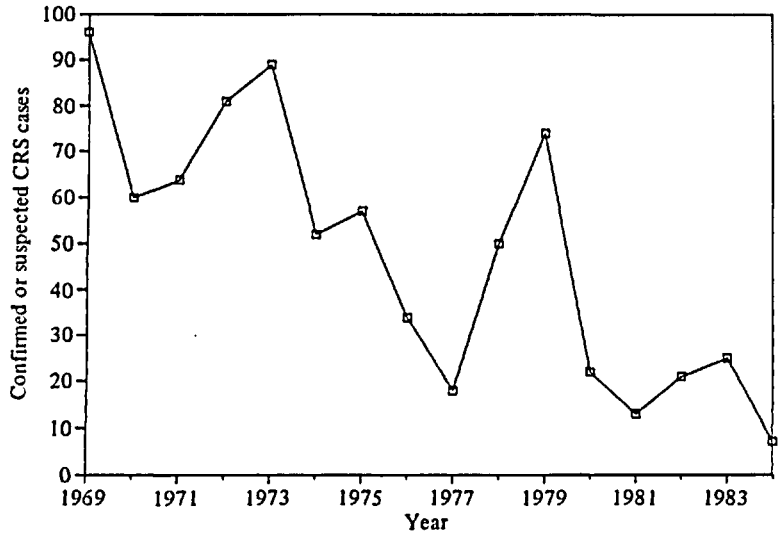

Fig. 2. Confirmed or suspected cases of CRS, by year of birth, from the Northern and Southern Registries of the National Congenital Rubella Syndrome programme in England. The figures for 1982, 1983 and 1984 are provisional.

will show a gradual decline (see fig. 17 in Anderson & May, 1983*a*). These predictions are supported by the observed impact of the UK policy. However, one major disadvantage of the UK policy is that the incidence of CRS will never decline to zero unless 100% of women are immunized prior to joining the child-bearing age classes (virus transmission is maintained in the male and young female segments of the population). In other words, after 20 years of the UK policy, where an average of 80–90% of girls are immunized at around 12 years of age, a small fraction of women will still be susceptible to rubella on entering the child-bearing age classes and at risk from infection during pregnancy. The recently observed decline in the rate of reduction in the incidence of CRS in the UK has therefore prompted discussion of alternate rubella vaccination programmes. One suggestion is to adopt a mixed USA and UK policy, while another is to attempt to increase the rate of vaccination of susceptible women in the 20- to 30-year-old age group, while encouraging an increased level of vaccine uptake in 10- to 15-year-old girls. Although the incidence of CRS in the UK is low at present, it is possible that improvements over the current situation may require a change in policy. In practical terms, it appears unlikely that a 100% coverage of teenage girls will be achieved in the UK.

A mixed UK and USA policy appears attractive at first sight, but past research has suggested that little benefit is to be gained from changing to a two-stage policy unless high levels of coverage ($> 60\%$) are achieved in male and female children aged 1–2 years (Anderson & May, 1983*b*). Current levels of child immunization against measles are around 60% in the UK, and it is to be expected that rubella vaccine uptake would be similar if a combined measles-rubella vaccine was introduced for the immunization of young children. However, very recent improvements in the sophistication of mathematical models for the assessment of the impact of vaccination on the incidence of viral and bacterial infections, have

provided new techniques to aid in the quantitative reappraisal of this problem (Anderson & May, 1985; Schenzle, 1984). Specifically, past predictions have been based on the assumption that the force of rubella infection (the *per capita* rate at which susceptibles acquire infection) is independent of age. New developments take account of heterogeneity in transmission between age groups and facilitate the inclusion of information on 'who acquires infection from whom' (Anderson & May, 1985; Grenfell & Anderson, 1985).

This paper examines the relative merits of a variety of single-stage (basic UK strategy), two-stage (mixed UK and USA strategy) and three-stage (mixed UK and USA strategy, plus the immunization of susceptible women in the child-bearing age groups) vaccination policies for the control of CRS in the UK, with the aid of mathematical models which take explicit account of age-dependent heterogeneity in virus transmission. Model predictions are based on analyses of age-stratified serological data and case reports, and are compared with current patterns of CRS incidence. Discussions of the merits of various policies centre on both the long-and the short-term impact of immunization on disease incidence.

METHODS

Model structure

Predictions of the impact of different vaccination policies on the incidence of CRS are derived from a mathematical model of rubella virus transmission in a large age and sex structured community. The model is compartmental in structure and considers changes in the densities of infants with maternally derived immunity, susceptibles, incubators who are infected but not yet infectious, infectious individuals and immunes (either naturally acquired or protected by vaccination). It consists of a series of coupled partial differential equations which denote changes with respect to time and age, and distinguishes between changes in the male and female segments of the community. The details of model structure have been described in a recent publication (Anderson & May, 1985) but a brief summary is given in the Appendix of this paper.

The central assumption of the model relates to the manner in which virus infection is transmitted between infectious and susceptible individuals. The per capita force of infection (the rate at which susceptibles acquire rubella infection) of susceptibles of age a at time t, $\lambda(a, t)$ is assumed to adopt the form;

$$\lambda(a,t) = \int_0^L \beta(a',a)\, Y(a',t)\, da'. \tag{1}$$

Here L denotes life expectancy (set at 75 years for all of the analyses presented in this paper), $Y(a' t)$ describes the density (or number) of infectious people (of both sexes) of age a at time t, and $\beta(a',a)$ is the transmission coefficient arising from the contact of susceptibles of age a, with infectious individuals of age a' (Anderson & May, 1984, 1985; Schenzle, 1984). The force of infection is a composite parameter denoting the summed rates of contact of susceptibles within a given age class with infectious people of all ages within the population. A given value of the transmission coefficient, $\beta(a',a)$, represents two components; namely, the degree of contact

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between individuals in two different age classes, and the likelihood that a contact between susceptibles and infectious persons will give rise to a new case of rubella infection.

Age-dependent transmission

The term $\beta(a', a)$ essentially denotes 'who acquires infection from whom'. If the age span from birth to life expectancy is divided up into discrete age classes $i = 1, 2, \ldots, n$) then the term β_{ij} represent the coefficient for disease transmission between susceptibles of age class i and infectious people of age class j. The age-specific forces of infection (λ_i, where $i = 1, 2, \ldots, n$) are related to the β_{ij}'s where

$$\lambda_i = \sum_{j=1}^{n} \beta_{ij} \bar{Y}_j. \tag{2}$$

Here $\bar{Y}_j$ denotes the total number of infectious people in age class j.

The set of β_{ij}'s forms the 'who acquires infection from whom' matrix, or WAIFW matrix for short. As detailed in a recent publication (Anderson & May, 1985), estimates of the values of the transmission coefficients (β_{ij}), can be obtained from a knowledge of the age-specific forces of infection (the λ_i's can be derived from case notifications or serological data (Grenfell & Anderson, 1985)). The estimates are dependent on the configuration of the WAIFW matrix. We consider three different configurations for a six age class population. The age classes are chosen to facilitate the estimation of the forces of infection (the λ_i's) from the epidemiological data available for rubella in the UK (serology and case notifications). The classes (numbers 1–6) are as follows: 0–4 years, 5–9 years, 10–14 years, 15–19 years, 20–29 years, 30–75 years. The three WAIFW configurations are defined (labelled WAIFW1, 2 and 3) as:

WAIFW1

Age class	1	2	3	4	5	6
1	β_1	β_1	β_3	β_4	β_5	β_6
2	β_1	β_2	β_3	β_4	β_5	β_6
3	β_3	β_3	β_3	β_4	β_5	β_6
4	β_4	β_4	β_4	β_4	β_5	β_6
5	β_5	β_5	β_5	β_5	β_5	β_6
6	β_6	β_6	β_6	β_6	β_6	β_6

The 6×6 matrix contains 6 distinct β_i values where $i = 1, 2, \ldots, 6$. The principal feature of configuration 1 is the unique transmission coefficient (β_2) for susceptibles in the 5- to 9-year-old age group which represents a high degree of intermixing (and hence virus transmission) in young children. The coefficients defined for the 0- to 4-year-olds and 10- to 14-year-olds (β_1 and β_3 respectively) denote high degrees of mixing within and between the child and young teenage classes. In the remaining age groups, susceptibles have fairly uniform contact rates with infectives from all age classes (in age group 6, the coefficient is identical over all age classes).

WAIFW2

Age class	1	2	3	4	5	6
1	β_1	β_6	β_6	β_6	β_6	β_6
2	β_6	β_2	β_6	β_6	β_6	β_6
3	β_6	β_6	β_3	β_6	β_6	β_6
4	β_6	β_6	β_6	β_4	β_6	β_6
5	β_6	β_6	β_6	β_6	β_5	β_6
6	β_6	β_6	β_6	β_6	β_6	β_6

The main feature of this configuration is the notion that susceptibles in the age classes 1–5 mix most with infectives in their own age class. In other words, within age class mixing is of greater importance in virus transmission than between age class mixing. To keep the number of distinct values equal to the order of the WAIFW matrix (i.e. $n = 6$), the within age class coefficient in class 6 is set equal to the background coefficient for between age class mixing (β_6).

WAIFW3

Age class	1	2	3	4	5	6
1	β_1	β_6	β_6	β_6	β_5	β_6
2	β_6	β_2	β_6	β_6	β_5	β_6
3	β_6	β_6	β_3	β_6	β_6	β_6
4	β_6	β_6	β_6	β_4	β_6	β_6
5	β_5	β_5	β_6	β_6	β_5	β_6
6	β_6	β_6	β_6	β_6	β_6	β_6

This configuration is close to WAIFW2 but defines a similar within-age class-mixing coefficient in class 5 (the 20- to 29-year-olds) to the between-class-mixing coefficients of classes 1 and 2 (the 0- to 9-year-old children). This pattern represents a high degree of mixing between young children and the adult age group in which their parents will (on average) be placed. In other words, this pattern attempts to capture the notion that within family transmission is an important determinant of the epidemiology of rubella (i.e. susceptible mothers with large families are (on average) more likely to come into contact with infectious children, than single females or married females with no children).

The effects of these various configurations, on the predicted impacts of different vaccination policies, are considered in the results section. Table 1 summarizes the main transmission features captured by configurations 1–3.

Epidemiological data

(a) *Forces of infection*

The calculation of age-specific forces of infection (the λ_i's for age classes 1–6 as defined above) was based on two sources of data; namely, (i) a serological survey of samples (over 3000 in total) from a broad span of age classes collected in the South East of England in the early 1980s and (ii) a set of age-stratified case

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Table 1. *The principal feature of virus transmission captured by the different 'who acquires infection from whom' (WAIFW) matrices*

Configuration	Transmission characteristic
WAIFW1	High levels of within age class mixing are a unique feature of the child age groups
WAIFW2	Within-age-class mixing is greater than between-age-class mixing in child, teenage and adult classes
WAIFW3	Adults in the principal parent age class (20–29 years) have a high degree of contact with the infant and child age groups

notification records from the Leeds area of England compiled for the year 1978. Methods of data collection and analysis are described in separate publications (Nokes, Anderson & Anderson, 1985; Grenfell & Anderson, 1985; Anderson & May, 1983*a*). The paper by Nokes, Anderson & Anderson (1985) provides a detailed interpretation of observed age-related changes in the force of infection. In general, observed patterns show low rates of infection in the young child age classes, high rates in the 5- to 15-year-old group and low rates of infection in the adult age classes. These convex patterns of change with age for rubella, however, are not as marked as those recently described for measles infection (Anderson & May, 1985). Estimates of the age-specific forces of infection for rubella, derived from the data sets outlined above, are displayed in Table 2. These were obtained from the serological data for males since the interpretation of the values is simplified in the absence of vaccine induced immunity.

(*b*) *Duration of maternally-derived antibody protection: incubation and infectious periods*

The values of the three epidemiological parameters, average duration of maternally derived antibody protection to rubella infection in infants, the incubation period (time from the acquisition of infection to the beginning of the infectious state) and the infectious period used in the analytical and numerical studies described in this paper, are respectively 4·0 yr^{-1}, 34·76 yr^{-1} and 31·74 yr^{-1} (sources: Nokes, Anderson & Anderson, 1985; Hanshaw & Dudgeon, 1978; Anderson & May, 1983*a*).

(*c*) *Age-specific vaccination records*

In the numerical studies reported in the results section, predictions of the impact of different vaccination policies post 1985 are based on calculations prior to that period which incorporate the recorded age-specific rates of vaccination for teenage girls in England and Wales. These records were supplied by the DHSS and a summary of trends in the cumulative proportions of girls of each age immunized against rubella by year (1970–84) is presented in Table 3. Records for 1985 are, as yet, unavailable and it was therefore assumed that the rates were identical to those reported for 1984. In the numerical studies of model behaviour it is assumed that vaccination induces lifelong protection to rubella infection (O'Shea *et al.* 1982, 1984, 1985).

Table 2. *Age-specific forces of infection* (λ_i'*s*) *for rubella in England* (*See Nokes, Anderson & Anderson, 1985; Grenfell & Anderson, 1985*)

	Forces of infection (λ_i yr^{-1}) Age class (years)					
Data source	0–4	5–9	10–14	15–19	20–29	30+
Serology – South East England, 1980–1, Nokes *et al.* (1985). (Serum samples from males.)	0·081	0·115	0·115	0·083	0·067	0·067
Case notifications (Leeds, 1978)	0·089	0·134	0·151	0·148	0·126	0·126

Table 3. *Percentages of susceptible teenage girls of different ages vaccinated against rubella in England and Wales from 1970 to 1973* (*Source: DHSS vaccination records*)

	Age (years)					
Year	10	11	12	13	14	15
1970	—	9·77	13·32	9·15	—	—
1971	—	30·40	47·67	33·64	—	—
1972	—	22·31	44·72	46·37	—	—
1973	—	19·23	34·60	48·41	—	—
1974	—	18·07	30·65	33·85	—	—
1975	—	18·35	30·97	30·92	—	—
1976	—	20·94	34·09	33·87	—	—
1977	—	23·36	36·60	30·46	—	—
1978	—	22·53	38·90	32·50	12·64	—
1979	0·82	23·53	44·72	41·12	18·68	5·09
1980	0·75	25·45	42·65	40·28	17·66	6·59
1981	1·30	25·37	45·93	38·90	15·53	5·25
1982	3·50	29·60	45·20	40·24	14·54	4·93
1983	5·64	29·96	46·67	41·10	15·31	3·94

Model predictions and display

Analytical and numerical studies of the mathematical model of rubella virus transmission (see Appendix) yield two broad categories of results. First, there are the *steady-state* predictions for the *long-term* effects of the different vaccination policies. That is, the equilibrium that the system approaches after the perturbation to virus transmission induced by the start of mass vaccination. As discussed in a previous paper (Anderson & May, 1983*b*). the steady state is only likely to be arrived at after many decades of cohort vaccination. Furthermore, the approach to the equilibrium will normally be characterized by oscillatory behaviour as a result of the non-linear dynamical processes that are known to influence virus transmission and persistence in human communities (Anderson & May, 1982; Dietz, 1975). Oscillations, or recurrent epidemics, arise as a consequence of the host's ability to acquire lasting immunity on recovering from infection, such that, following an epidemic, a time period elapses while the pool of susceptible people is replenished by new births before a further major outbreak of infection can occur.

Prior to immunization rubella exhibited an inter-epidemic period of roughly 4–5 years (see Anderson, Grenfell & May, 1985). The second category of results is the *short-term* predictions of the *temporal changes* in disease incidence as the system approaches the steady state.

In the results section model predictions are displayed in a variety of ways. We measure the impact of a given vaccination programme by reference to a summary ratio, $w(a_1, a_2, t)$, which records the ratio of the number of cases of CRS in the age range a_1 to a_2 at time t after the start of a mass vaccination divided by the number of CRS cases in the same age range before the instigation of immunization (see Anderson & May, 1983*b*). More formally the ratio is defined a

$$w(a_1, a_2, t) = \frac{\int_{a_1}^{a_2} m(a)\, X(a,t)\, \lambda(a,t)}{\int_{a_1}^{a_2} m(a)\, X(a,0)\, \lambda(a,0)}, \tag{3}$$

where $X(a,t)$ denotes the number (or density) of susceptibles at time t of age a and $\lambda(a,t)$ records the age- and time-specific force of infection as defined in eqn (1) (see Anderson & May, 1983*a*). The function $m(a)$ defines the risk of a susceptible woman being pregnant at age a. This risk function for the UK is described in more detail in a previous publication (Anderson & May, 1983*a*). For simplicity it is assumed to be the age-specific fertility rate (data from the Registrar General's Statistical Review for 1980). The 'at risk' ages a_1 to a_2 are assumed to be the pregnancy classes of 16–40 years of age in which 99% of all pregnancies occur in the UK at present.

Changes in the ratio w with respect to different vaccination policies are examined both in the short term (temporal predictions) and in the long-term (steady state results). Since our main interest lies in the impact of various changes in the current UK vaccination policy (girls and girls only vaccinated between the ages of 10–15 years), we focus on changes in w over a 35-year interval from 1985 to 2020. We assume that the change in policy takes place in 1985 and examine its impact on w over the following 35-year span.

In addition to changes in the ratio of CRS cases after a defined period of control divided by the number before vaccination, we also examine age- and time-dependent changes in the serological profile of the population. These profiles record the proportion immune, $z(a,t)$, at time t of age a, where immunity may result from maternally-derived antibodies, natural immunity following infection, or vaccination. The model allows us to examine these 'serological surfaces' in the male or female segments of the population, or the total community (the sex ratio in each age class is assumed to be 1:1).

RESULTS

Age-dependent rates of infection (heterogeneous mixing)

In this subsection we examine the predictions of the model under the assumption that the force of infection changes with age in the manner suggested by the analyses of the serological data collected in South East England (data for males only) and the case notification reports from Leeds (Nokes, Anderson & Anderson,

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1985; Grenfell & Anderson, 1985) (see Table 2). The results are also based on the assumption that the 'who acquires infection from whom' matrix is of the form defined by WAIFW1 (see Methods section). This structure mirrors the assumption that the child segment of the population has a uniquely high rate of intermixing within their own age classes and lower rates of contact with other age groups (Anderson & May, 1985). Other forms of the WAIFW matrix are examined in the following subsection.

The pattern of change in the force of infection (λ, the *per capita* rate at which susceptibles acquire infection) with age, depends on whether parameter estimates were derived from the serological data or the case notification records (Table 2). Those derived from the serology are, in general, of lesser magnitude and show a more marked decline in the adult age classes. *The manner in which λ changes with age, has a major influence on the predicted impact of the different vaccination policies* (see Anderson & May, 1985). This is especially important when considering a vaccination policy (such as the USA policy) which has a substantive influence on the net rate of virus transmission within a community, and hence the average age at infection. Vaccination of young children tends to increase the average age at infection over that pertaining prior to control (see Anderson & May, 1982, 1983*a*, *b*, 1985). This can result in the *per capita* rate at which susceptibles typically acquire infection differing in the pre- and post-vaccination eras. For example, if the *per capita* rate of infection is high in the 10- to 14-year-old age class and low in the 10- to 15-year-old age class (due to differing rates of mixing and contact) then an increase in the average age at infection as a result of mass vaccination, from the younger age class to the older one, may substantially reduce the probability that those still susceptible acquire the infection. Under the assumption of homogeneous mixing and age-independent rates of infection, the fact that mass vaccination tends to increase the average age at infection does not generate between age class differences in the risk of susceptibles acquiring infection. Age-dependent heterogeneity in mixing will therefore tend to increase the impact of a given level of vaccination coverage when compared with that predicted on the assumption of homogeneous mixing within and between age classes. The discrepancy between the predictions will be most marked for the two-stage policy involving mass vaccination of young boys and girls since this strategy will tend to have a major impact on the average age at infection. We examine this question using estimates of the age-dependent rates of infection derived from both the case notification reports and the serological data.

(*a*) *Parameter estimates derived from case notifications* (Table 2)

Predicted changes in the ratio, w, of cases after control divided by cases before vaccination are recorded in Fig. 3 for each of the four vaccination policies (see Table 4). There is little difference between the predictions of this model and one in which λ is held constant and independent of age, since the forces of infection derived from the case notifications differ little between the various age classes. Fig. 4 displays the long-term steady-state results for the ratio w under various assumptions concerning the levels of vaccination applied in the two-stage UK–USA policy.

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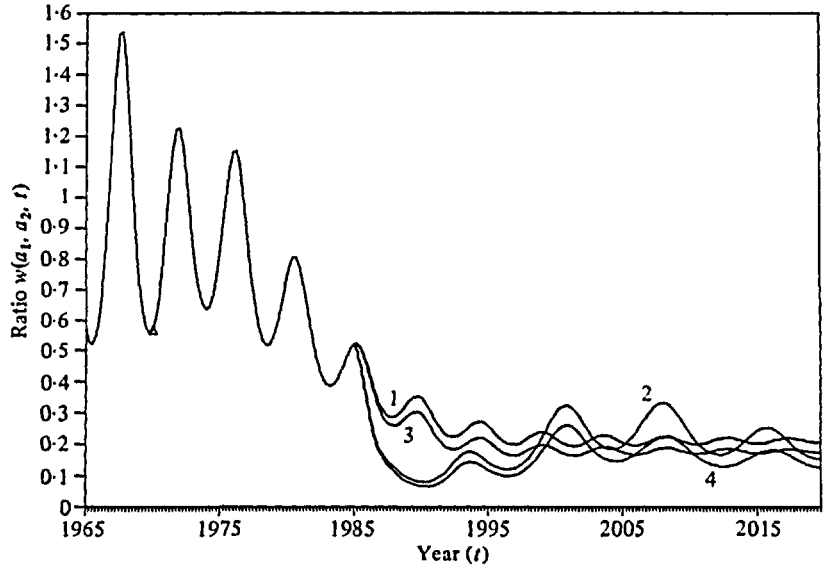

Fig. 3. Age-dependent forces of infection (heterogeneous mixing). Numerical solutions of the partial differential equation model (see Appendix in the main text) recording changes in the ratio w of the number of cases of CRS at various time-points after the start of vaccination in the age range 16–40 years divided by the number of cases of CRS in the same age band before the start of immunization. The triangle in 1970 denotes the start of the single-stage UK policy (girls, and girls only, between the ages of 10–15 years) and, prior to 1970, the ratio w oscillates (with a 4- to 5-year period) around the equilibrium pre-control value of unity. Over the period 1970–84, recorded vaccination rates in the UK were employed in the numerical calculations. After 1985 the graph records the projected changes in the ratio w for the four different vaccination policies documented in Table 4 (these are labelled 1–4 to denote policies 1–4). The 'who acquires infection from whom' matrix configuration was set at WAIFW1 (Table 1).

Table 4. *The vaccination policies*

Type of policy	Description
Single-stage (*policy 1*)	A UK policy in which girls, and girls only, are vaccinated between the ages of 10–15 years
Two-stage – type A (*policy 2*)	A combined UK and USA policy in which girls and boys are vaccinated at 2 years of age, and girls at between 10–15 years of age
Two-stage – type B (*policy 3*)	A UK policy plus the vaccination of susceptible women at around the age of 25 years
Three-stage (*policy 4*)	A combined UK and USA policy plus vaccination of susceptible women of age 25 years

(*b*) *Parameter estimates derived from serology* (Table 2)

The estimates of the rates of infection derived from the serological data (for the male segment of the population) show a marked convex pattern with changes in age. The force of infection is low in the young children (0–4 years of age) and in the late teenage and adult age classes (15+ years of age) (Table 2). It is therefore to be expected that predictions based on these parameters will differ somewhat from those displayed in Fig. 3.

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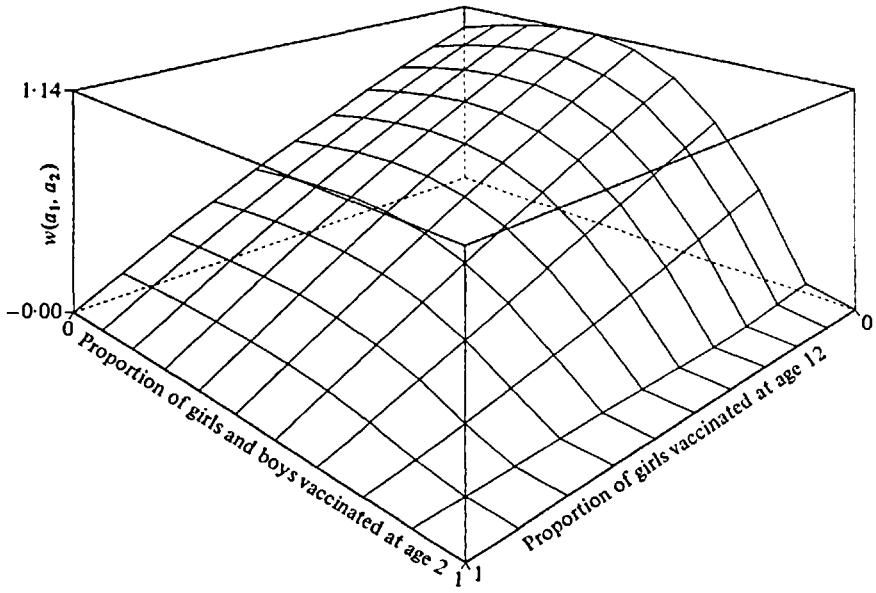

Fig. 4. Age-dependent forces of infection (heterogeneous mixing). The three-dimensional graph records model predictions of the equilibrium ratio w (of cases after/cases before vaccination) under the two-stage UK–USA policy (policy 2) for various levels of immunization of 2-year-old boys and girls, and 12-year-old girls. Parameter estimates based on case notifications.

This is indeed the case, as recorded in Fig. 5, where predicted changes in the ratio w with time are plotted for the various vaccination programmes (Table 4). The multiple stage policies based on the vaccination of boys and girls at around 2 years of age are predicted to have a very substantive impact on the incidence of CRS. This is a direct consequence of the low forces of infection in the late teenage and adult age classes, concomitant with the tendency of mass vaccination to raise the average age of infection over that pertaining prior to control. The majority of those females still susceptible (who have escaped infection or avoided vaccination) are 'shifted' into age classes in which the transmission coefficient of the viral infection is much lower than that in the age classes in which such susceptibles would have typically acquired infection prior to the introduction of the two-stage policy. The effect of childhood immunization is to substantially reduce the overall rate of virus transmission within the community and hence the incidence of CRS. Do note, however, that the marked reduction in net virus transmission substantially lengthens the inter-epidemic period (4–5 years prior to control) to around 20–22 years. As such the model predicts an epidemic rise in the incidence of CRS (as a result of an epidemic of rubella in the population) 20–22 years after the initiation of the two-stage policy involving the USA strategy (policy 2). The predictions suggest that the magnitude of this epidemic can be reduced by the three-stage policy (policy 4) which involves the vaccination of adult females at around 25 years of age (Fig. 5). The lengthened epidemic period is a direct consequence of the impact of childhood immunization on the rate of build up of susceptibles in the population (by new births) combined with the low forces of infection in the

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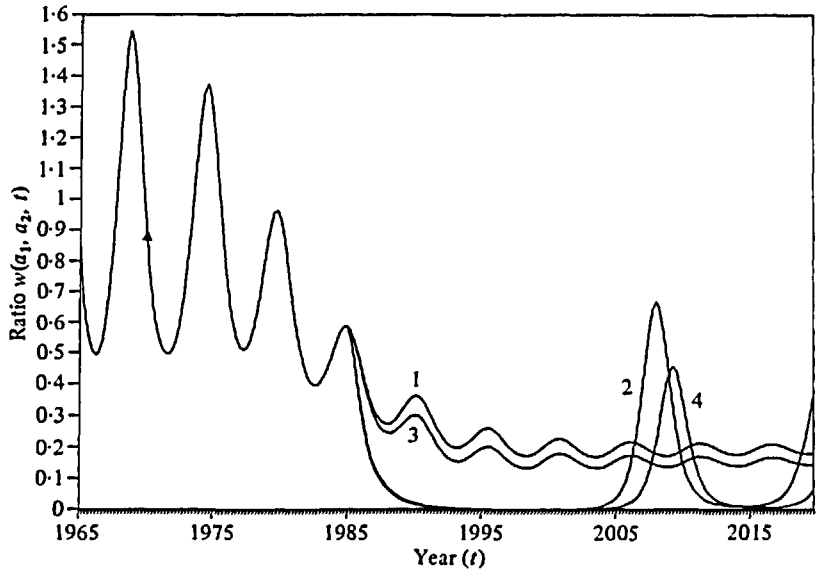

Fig. 5. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serology. The graph is similar to that described in the legend to Fig. 3, but records model predictions based on the age-dependent forces of infection derived from serology. The 'who acquires infection from whom' matrix configuration was set at WAIFW1 (see Table 1).

late teenage and adult age classes. The highly convex pattern of change in the force of infection with age (see Table 2) suggested by the serological data, implies that most virus transmission occurs in the 5- to 14-year-old age groups. The maintenance of virus transmission with the population as a whole is therefore dependent on the rate of recruitment of susceptibles into this age band. Moderate to high levels of vaccination of 2-year-old boys and girls severely restricts such recruitment, and hence substantially lengthens the inter-epidemic period over the small increase induced by the UK policy on its own or the two-stage UK–USA policy under the assumption that the force of infection is independent of age.

In the long term, the two-stage UK–USA policy (policy 2) is predicted to have a greater impact than the continuation of the one-stage UK policy (policy 1). Despite the tendency of policies 2 and 4 to induce long-term epidemic peaks in CRS incidence (the epidemics are of greater magnitude than those induced by policies 1 or 2; Fig. 5), the accumulated number of cases of CRS over many decades is predicted to be less when compared with policies 1 and 3. This point is illustrated in Fig. 6, which records the steady-state values of the ratio w for various levels of vaccination under the UK–USA policy (policy 2). This figure is to be compared with Fig. 4.

Although a mixed strategy policy involving the vaccination of boys and girls at a young age is predicted to be of greatest benefit in the reduction of CRS incidence, this approach can reduce the prevailing level of herd immunity in the total population (in the short and long term) when compared with a strategy based on the continuation of the UK policy alone (policy 1). This point, which appears counter-intuitive at first sight, is illustrated in Figs. 7–9 by reference to the

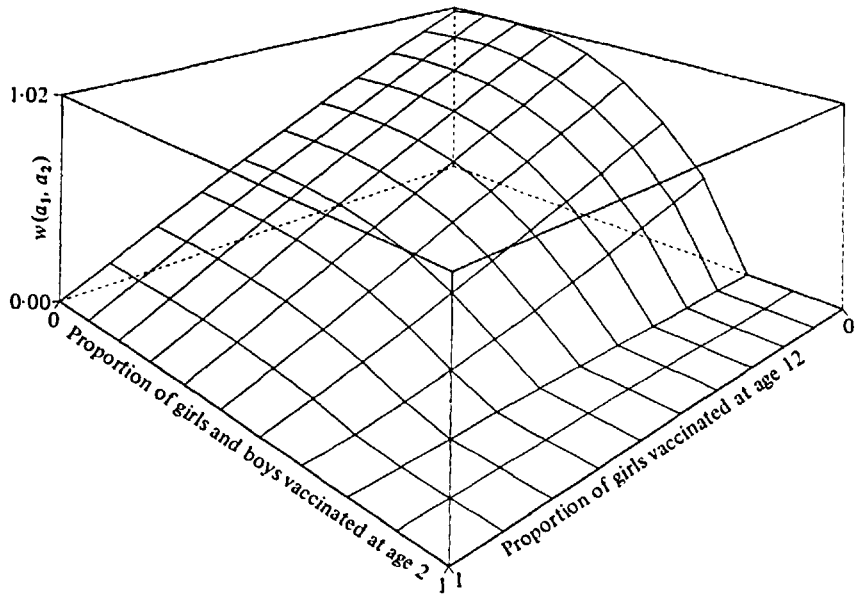

Fig. 6. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. The graph is similar to that defined in the legend to Fig. 4 but records the equilibrium ratio w based on WAIFW1 configuration and the age-dependent forces of infection derived from serological data.

predicted serological surfaces in both the male and female segments of the population (over age and time) under the one-stage UK policy (1970–84, Fig. 7), the two-stage UK–USA policy (1984–2003, Fig. 8) and the one-stage policy (1984–2003, Fig. 9). In the females, policy 2 increases the proportion sero-negative in the late teenage and adult classes (Fig. 8(*a*)), when compared with policy 1 (Fig. 7(*a*)), despite the raised levels of immunity in the young boys and girls. The differing impacts of policies 1 and 2 are even more marked in the male segment of the population (Figs. 8(*b*) and 9(*b*)). *On the one hand, policy 2 reduces the incidence of CRS, yet on the other hand, it reduces the total level of herd immunity prevailing in the population.* This paradox arises as a consequence of the impact of policy 2 (UK plus USA strategies) on the overall transmission of rubella in the community. The incidence of rubella is greatly reduced by the vaccination of boys and girls at a young age, which has a direct impact on the incidence of CRS. However, this reduction also acts to decrease the numbers of teenage boys and girls who acquire immunity by natural infection. This reduction in cases of rubella infection is not completely compensated for by the raised levels of immunity resulting from the vaccination of 60% of boys and girls at around two years of age. The results portrayed in Figs. 8 and 9 illustrate a potential danger associated with the introduction of a two-stage policy. To prevent serious outbreaks of rubella infection (and hence CRS) in future years, as a consequence of the build up in the pool of susceptibles, strenuous efforts must be made to maintain the levels of vaccination of 2-year-old boys and girls at a high level ($> 60\%$).

A simple numerical example serves to illustrate this point. Suppose rubella is eradicated from the population and vaccination is continued under the two-stage

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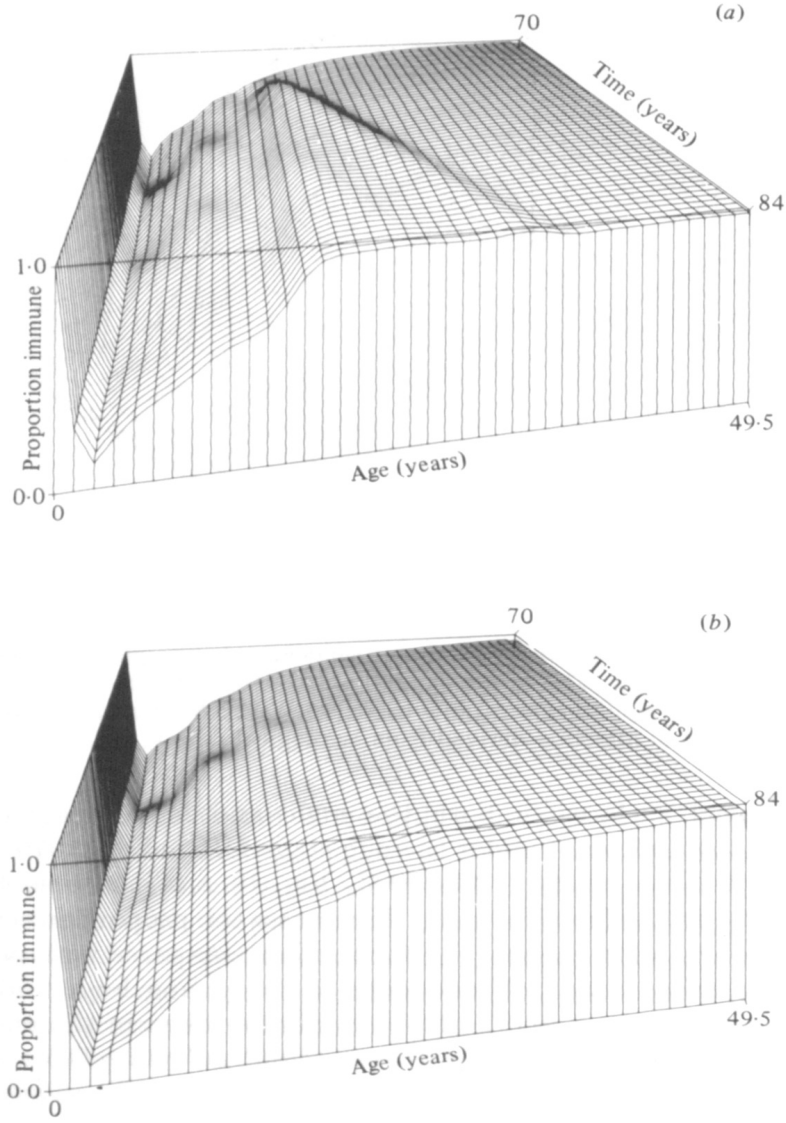

Fig. 7. Age-dependent forces of infection (heterogeneous mixing). Graphs (*a*) and (*b*) record age- and time-related predictions of the change in the proportion of individuals in the community immune to rubella infection (either via maternal antibody protection, naturally acquired immunity following recovery from infection, or vaccination) for females and males respectively. The graphs depict the 'serological surface' of the population, or the prevailing degree of herd immunity, at any one point in time. The numerical simulations plotted cover the age class 0–49·5 years and the time period 1970–84. The calculations were based on the single-stage UK policy, WAIFW1 matrix and recorded vaccination rates were employed to generate the predictions. On the age axis the intervals run from 0, 0·5, 1·5, 2·5, ..., 49·5 years.

policy, with 60% coverage of boys and girls at 2 years of age and 85% of girls at around 12 years of age. This will result in 6% of females remaining susceptible in the child-bearing age classes.This is slightly less than the level of susceptibility observed in 20-year-old women prior to the introduction of rubella vaccination (around 10–12%) (Anderson & May, 1983*b*). If vaccination of children declined this would eventually lead to an increase over the 6% susceptibility in adult females

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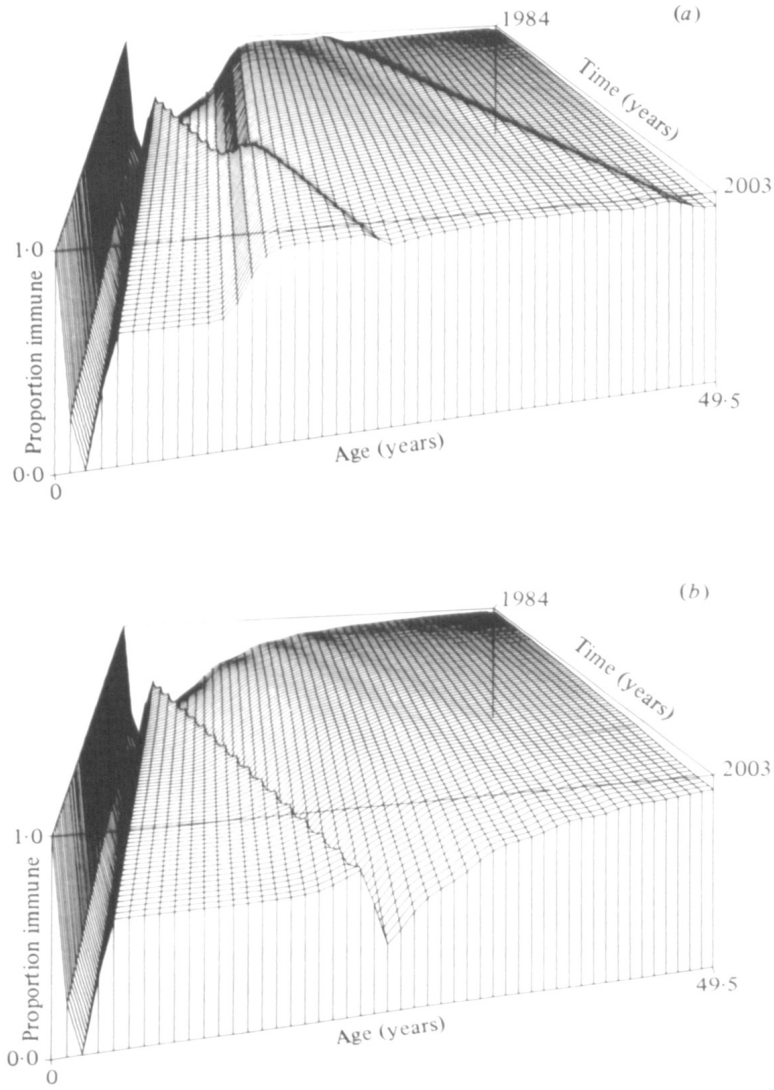

Fig. 8. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. Graphs (*a*) and (*b*) denote the serological surfaces, in the female and male segments of the populations respectively, over the years 1984–2003. The calculations denote changes under the impact of the two-stage UK–USA policy (policy 2) instigated in 1985, with 60% coverage of boys and girls at 2 years of age and the 1984 levels of vaccination of girls between 10 and 15 years of age. The calculations were based on parameter estimates of the forces of infection derived from serological data and the WAIFW1 matrix configuration.

and could create a situation in which rubella virus re-established within the population and induced large numbers of CRS cases.

The dangers inherent in the two-stage UK–USA policy can be reduced by the adoption of a three-stage policy (policy 4). This point is illustrated in Fig. 10 by reference to the impact of policy 4 on the serological surface in the female population. Note that the vaccination of women still susceptible to rubella in their mid-twenties substantially reduces the band of susceptibility in women of child-bearing age (compare Figs. 8 and 10).

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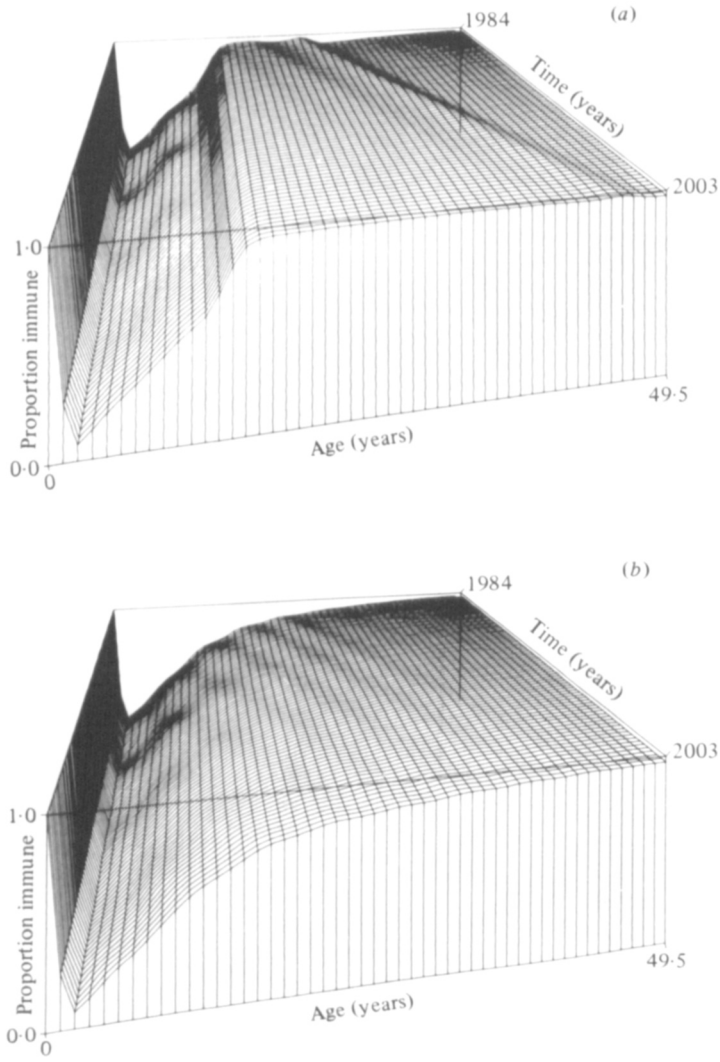

Fig. 9. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. Graphs (*a*) and (*b*) are similar to those defined in the legend to Fig. 8 (graph (*a*), females; graph (*b*), males) but denote predicted changes under a continuation of the one-stage UK policy (policy 1) over the interval 1984–2003. Vaccination levels in each year over this interval were set equal to the observed rates in the UK in 1984.

(*c*) *Comparisons of predictions based on serology and case notification parameter estimates*

The results reported in this section have highlighted the importance of the magnitudes of the forces of infection in each age class on the predicted impacts of different vaccination policies. Where estimates were based on the case notification data, the model predicted little difference in the impact of the four different vaccination policies on the incidence of CRS. By contrast, when estimates were based on the serological data, the model predicted that the optimal strategy for the UK was to shift to a two-stage policy involving the vaccination of medium

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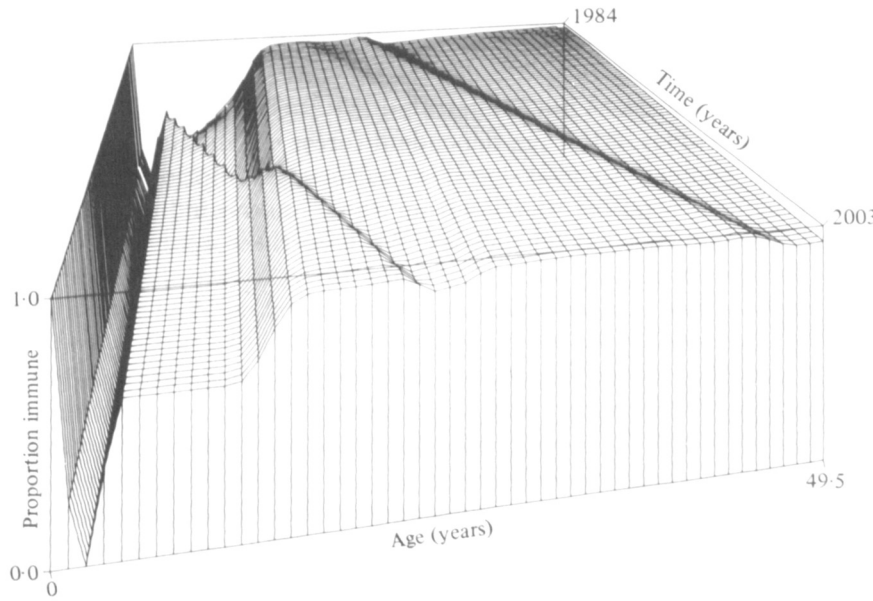

Fig. 10. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. Similar to the graph defined in the legend to Fig. 8(*a*) but denoting predicted changes in serology in the female segment of the population over the interval 1984–2003 where in 1985 a three-stage policy (policy 4 in Table 4) is introduced, involving a mixed UK–USA policy (60% vaccination of 2-year-old boys and girls) plus 50% vaccination of 25-year-old women (parameter estimates based on serological data, WAIFW1 matrix).

to high proportions of boys and girls at 2 years of age, and of high proportions of girls at between 10 and 15 years of age. Which of the two predictions is the more reliable? We favour those based on the serological data for the following reasons. First, and most importantly, case notifications of viral and bacterial infections are known to be subject to age-dependent biases in reporting efficiency. Depending on the specific infection these may be weighted to under-reporting in either the child *or* adult segments of the population (Fales, 1928; Collins, 1929; Sydnestricker & Hedrich, 1929; Griffiths, 1974; Anderson & May, 1982, 1983*a*; Fine & Clarkson, 1982*a*, *b*, 1984). We suspect that for rubella, reporting efficiency is greatest in young children and adult females. This type of bias would account for the relative constancy of the forces of infection, derived from the Leeds case notifications, across all age classes. Serological information is also subject to bias, particularly if antibody titres decay as the period of time between infection and collection of the serum sample increases. This problem would tend to result in the under-estimation of the force of infection in the adult age classes due to the number of false negative sera arising in individuals who were infected early in life. These problems are discussed more fully in Nokes, Anderson & Anderson (1985). On balance, however, we believe the errors arising in the serological information to be less serious than those inherent in case reports. As such, we attach greater significance to the predictions of the model, which incorporates parameter estimates based on serology.

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Different configurations of the 'who acquires infection from whom' (WAIFW) matrix

The preceding subsections have illustrated the sensitivity of model predictions to changes in the values of the age-dependent forces of infection. We now extend this sensitivity analysis to consider how various assumptions concerning the structure of the 'who acquires infection from whom' matrix influence the predicted impacts of different vaccination policies. We base these analyses on parameter estimates derived from the serological data (for the reasons outlined in the preceding section) and compare the predictions based on WAIFW configuration 1 (WAIFW1) discussed in the previous subsection with two further configurations (WAIFW2 and WAIFW3). These two new configurations are outlined in the methods section of this paper, and their principal features are summarized in Table 1. In brief, WAIFW2 incorporates the notion that within age class mixing is more important to virus transmission in all age classes than between age class mixing, while WAIFW3 captures the assumption that child–parent contact is an important component of rubella transmission. In what follows, we simply refer to predictions of the change in the ratio w through time under the two-stage UK–USA policy (policy 2) since the analyses based on the WAIFW1 configuration suggested this to be the optimum for the control of rubella in the UK. Since the values of the age-dependent forces of infection (derived from the serological data, see Table 2) are fixed for all WAIFW configurations, different assumptions concerning 'who acquires infection from whom' have no impact on the serological surfaces (these remain as depicted in Figs. 8–10). The predicted influence of different WAIFW configurations on the ratio w for the two-stage UK–USA policy is displayed in Fig. 11. Note that predictions for WAIFW3 and WAIFW2 are identical. This arises as a consequence of the forces of infection adopting identical values in the 20–29 years class and the 30+ years class (this result can be established by analytical methods, employing the definition of λ_i given in eqn (2) (see Table 2)). This point is illustrated in Fig. 12 by means of a simple example where the identical calculations were performed to those depicted in Fig. 11 excepting that the force of infection in the 20- to 29-year-olds was arbitrarily raised from a value of 0·067 yr^{-1} to a value of 0·091 yr^{-1}. Note that WAIFW2 and WAIFW3 produce different patterns. The important point to note, however, is that the three different WAIFW configurations *do not* result in a major change in the predicted impact of the two-stage UK–USA policy. Quantitative differences arise in both the magnitude of the long-term epidemic outbreaks in CRS incidence and in the interval between such outbreaks, but these discrepancies are of insufficient magnitude to invalidate the prediction that a change to a two-stage policy (policy 2) has a greater *long-term* impact on the incidence of CRS than the continuation of the one-stage UK policy.

More generally, we are drawn to the conclusion that this result is fairly insensitive to substantive changes in the structure of the 'who acquires infection from whom' matrix. A series of summary results upon which this conclusion is based are presented in Fig. 13. The histogram records the average value of the ratio w of cases before control divided by cases after vaccination over the years 1985–2020 (UK policy operating from 1970 to 1985) for (*a*) various CRS con-

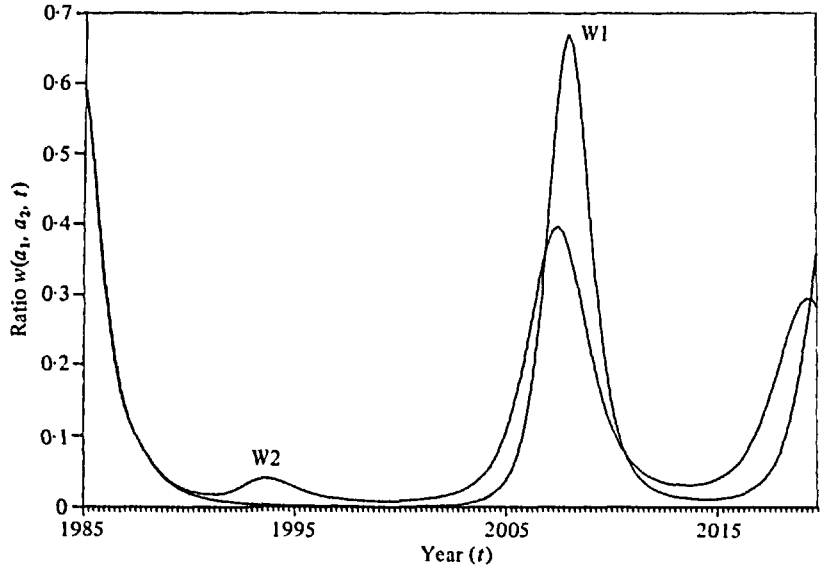

Fig. 11. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. The graph records predicted changes in the ratio w (of cases after divided by cases before vaccination) over the interval 1985 – 2020, after the introduction of a two-stage UK–USA policy (policy 2) in the UK (60% vaccination of boys and girls at 2 years of age, 10- to 15-year-old girls vaccinated at 1983 levels), for three assumptions concerning the structure of the 'who acquires infection from whom' matrix (WAIFW1, 2 and 3, see Table 1). The results for WAIFW2 and 3 identical (see text). The label W1 denotes WAIFW1, and W2 denotes WAIFW2 and WAIFW3.

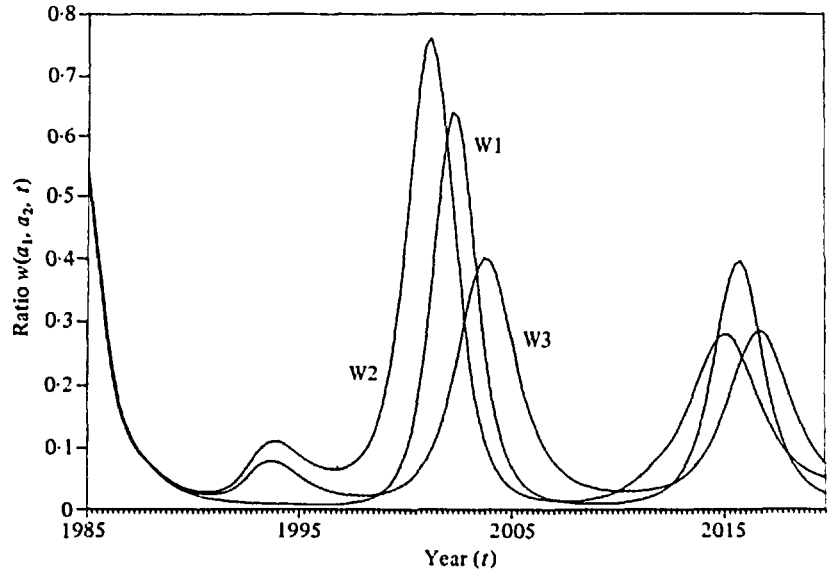

Fig. 12. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. Identical to the graph defined in the legend to Fig. 11 but with the force of infection λ_i in the 20- to 29-year-olds raised to a value of 0·091 yr^{-1} (see text). The labels W1 to W3 denote predictions based on WAIFW configurations 1–3 (see Table 1).

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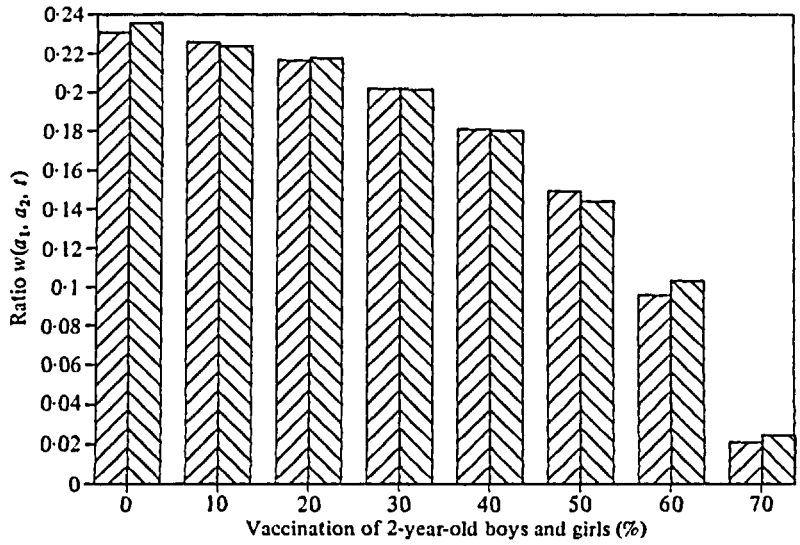

Fig. 13. Age-dependent forces of infection (heterogeneous mixing), parameter estimates based on serological data. The histogram records the predicted average value of the ratio w (cases after divided by cases before vaccination) over the time interval 1985–2020 under the impact of a two-stage vaccination policy (UK–USA, policy 2) with differing levels of vaccination of the 2-year-old boys and girls (levels of vaccination of 10- to 15-year-old girls held at the recorded 1983 levels in the UK). The predictions, based on different WAIFW matrix configurations, are recorded (WAIFW1, 2 and 3); the results for WAIFW2 and WAIFW3 are identical. The histogram illustrates the predicted benefits arising from a change in the UK rubella vaccination policy to a two-stage UK–USA policy (see text). ▨, WAIF1; ▧, WAIFW2.

figurations (all with estimates of the forces of infection based on serology) and (*b*) different levels of vaccination of boys and girls at 2 years of age under policy 2 (two-stage UK–USA). Note how all levels of child immunization reduce the predicted value of the ratio (and hence the incidence of CRS) over that pertaining under a continuation of the UK policy. Also note, however, that substantive improvements only begin to become apparent when the level of vaccination of young boys and girls rises above 50–60 %. At very high levels of child immunization (around 80–84 %) the model predicts the eradication of rubella and hence CRS from the population (Fig. 14). Finally, it is encouraging to see that the predicted benefits of the two-stage policy are relatively insensitive to different assumptions concerning who acquires infection from whom (the different WAIFW configurations in Fig. 13).

DISCUSSION

(*a*) *Model accuracy and limitations*

A quantitative assessment of the accuracy of model predictions can be based on two sources of information; namely, the observed decline in the incidence of CRS under the UK vaccination policy over the interval 1971–84, and the observed age-stratified serological profiles obtained via serum samples collected in the interval 1971–84. Model predictions of the impact of the UK policy over the past

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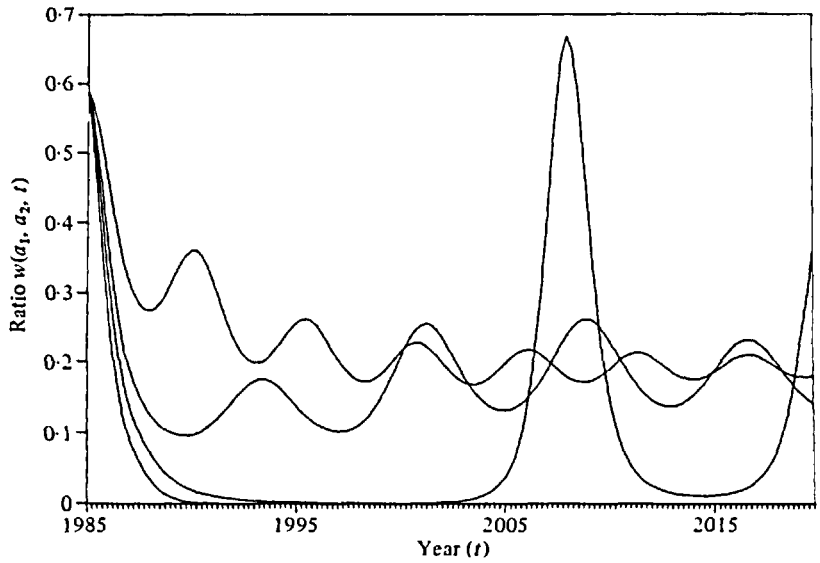

Fig. 14. A comparison of the impact of various levels of vaccination of 2-year-old boys and girls (0, 40, 60 and 80%) on the ratio w of cases after divided by cases before immunization under the two-stage UK–USA policy (WAIFW1, parameter estimates based on serological data). In 1987, the highest value of w denotes 0%, the next highest 40%, the second lowest 60% and the lowest 80%. Note the substantive impact predicted under an 80% coverage of young children (virtual elimination).

15 years on the incidence of CRS are in good qualitative agreement with observed trends (compare Fig. 1 with Figs. 5, 8 and 10). There are, however, discrepancies in quantitative detail where , in general, the model tends to slightly underestimate the observed impact of vaccination. We believe this arises due to a combination of four factors. (1) The rates of vaccination incorporated in the model for the years 1970–1985 took no account of any immunization of adult women found to be susceptible to rubella during routine screening of serum samples. In recent years, particularly as a consequence of the wide publicity of the need for women to be immunized against rubella prior to pregnancy, vaccine uptake in the adult female age classes has become an important component of CRS control in the UK (Miller *et al.* 1985). (2) The model takes no account of the number of pregnancies terminated as a consequence of antenatal screening of pregnant mothers for a change in sero-negativity to rubella virus during the first and second trimesters of pregnancy. The number of abortions carried out in England and Wales over the years 1972–80, in which rubella infection is listed as the primary cause, was of the order of 500 per annum. This practice clearly reduces the incidence of CRS. (3) The recorded incidence figures for CRS tend to underestimate the true picture, particularly in the years 1980–4, since the disease is often only diagnosed in infants and young children some years after birth. (4) The quantitative details of the predicted pattern over the interval 1970–84 depend to some extent on whether vaccination is assumed to start (in 1970) in an epidemic or inter-epidemic year. The greatest impact is achieved by starting vaccination of teenage girls just after a major epidemic.

A better test of the accuracy of model predictions is provided by age-stratified

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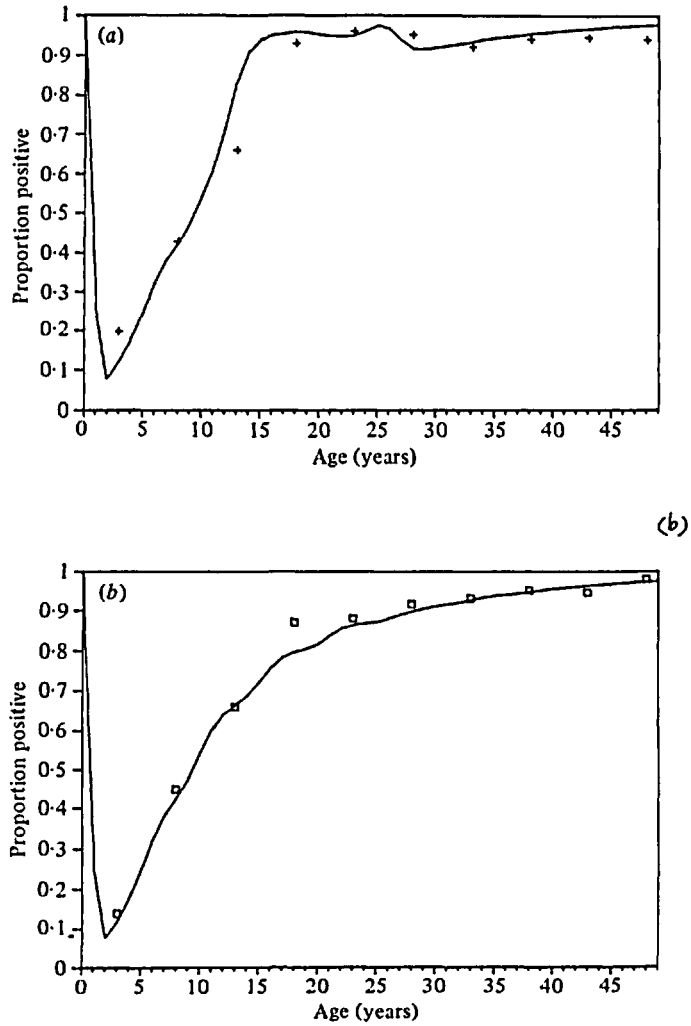

Fig. 15. A comparison of the observed and predicted age-stratified horizontal serological profiles for rubella in the female (graph (*a*)) and male (graph (*b*)) segments of the UK population in 1980–1. The observed data is from Nokes, Anderson & Anderson (1985). The predictions are based on the time-dependent solutions of the model (see Appendix). In these calculations the intrinsic forces of infection (those operating prior to vaccination were derived from the serological data for males) and age-specific vaccination rates were set at recorded levels in England and Wales over the period 1970–84. The WAIFW1 configuration of the 'who acquires infection from whom' matrix is employed. □, +, Observed values; ——, predicted values.

serological data given the various uncertainties over the accuracy of CRS case reports outlined above. A comparison of predictions and observations for the male and female segments of the population for the year 1980–1 is presented in Fig. 15 (model predictions based on forces of infection derived from serology, observed vaccination rates and configuration WAIFW1). The degree of agreement between prediction and observation is extremely good. This result, in particular, gives confidence in the predictions for the impact of different policies beyond 1985. In

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future years such predictions can again be tested against serological data, provided suitable surveys are carried out.

Further refinements in model structure and analysis are required in future studies. At present our analyses are based on a structure which ignores seasonal variation in virus transmission, caused by various factors such as the assembly and disassembly of children for school terms and the influence of climatic conditions on the spread of infection (see Fine & Clarkson, 1982*a*, *b*, 1984). Seasonal oscillations in rubella incidence are known to occur, but these are of lower amplitude than those observed for certain other common viral infections of children, such as measles (see Anderson, Grenfell & May, 1984). Future work should focus on this problem, although we suspect that the inclusion of seasonal transmission in the rubella model structure will not influence the principal conclusions of the analyses reported in this paper. Other refinements that require attention in future research include spatial heterogeneity in virus transmission and the recognition of the fact that children in families of large size tend, on average, to acquire many common viral and bacterial infections at an earlier age than their counterparts in small or single child families (Black, 1959).

(*b*) *Epidemiological data and parameter estimates*

One of the most striking results reported in the results section is the degree of dependency of model predictions on the parameter estimates of age-specific forces of infection. A comparison of Figs. 3 and 5 clearly illustrates this point. The predicted changes in the ratio of cases after control divided by cases before vaccination (w) through time depend critically on whether the estimates of the forces of infection are based on serological data or case notifications. This observation highlights the need for better epidemiological data (particularly prior to the introduction of a vaccination programme, or before any change in vaccination policy). Horizontal cross-sectional serological surveys should be based on large samples of males and females finely stratified according to age. In particular, there is a need to confirm that the forces of rubella infection are indeed low in the adult age groups when compared with children. Some additional support for this conjecture is provided by a serological survey carried out in a Welsh mining village in 1966 (Field, 1967). The convex change in the force of infection with age (low in child and adult age groups) is largely responsible for the predicted benefit of introducing a two-stage policy (UK–USA) over that arising from a continuation of the current UK policy (see Figs. 3 and 5). This caveat should be borne in mind when assessing the accuracy of the conclusions summarized in the following subsection of this discussion. A final advantage of focussing greater attention on the collection of serological data concerns the need to compare model predictions of future trends with observed patterns. This is of particular importance if a change in the UK vaccination policy takes place in the near future.

(*c*) *Future policies for the control of CRS in the UK*

The analyses reported in this paper suggested that the greatest reduction in the incidence of CRS in the UK in future years can be achieved by a *multi-stage policy* involving the following components: (1) a continuation of the current UK policy combined with increased effort to raise current vaccination coverage of 10- to

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15-year-old girls; (2) the introduction of the vaccination of boys and girls at around 2 years of age (by a combined measles-rubella vaccine) given that the level of coverage is greater than 60% within the total population of children; (3) the continued monitoring and surveillance of adult women and the vaccination of those found to be sero-negative for rubella antibodies. This conclusion differs from that described in a previous publication (Anderson & May, 1983*b*) as a direct consequence of the inclusion of heterogeneous mixing between age classes and age-dependent changes in the force of infection in the analyses reported in this present paper.

Model predictions suggest that the policy outlined above will result in an immediate reduction in the incidence of CRS (Fig. 5). It must be noted, however, that the predictions also indicate that this multi-stage policy will result in minor epidemics of rubella (and hence of CRS incidence) at intervals of approximately 20–22 years (Fig. 5). These are to be expected as a direct consequence of the interplay between the transmission dynamics of rubella virus and perturbation introduced by cohort vaccination of young children (boys and girls). Such epidemics do not indicate a failure in the policy since, in the long term, the predictions indicate that the multi-stage approach is more beneficial than the continuation of the UK policy alone (see Fig. 13). Ultimately, the goal should be the eradication of rubella (and hence CRS) and model predictions suggest that this could be achieved by a 80–84% vaccination coverage of 2-year-old boys and girls.

Although the recommendations outlined above are clear-cut when viewed in the light of the analyses reported in this paper, some important caveats must be noted. First, and most importantly, the conclusions are based on the predictions of a mathematical model which, by its very nature, is a simplification of the events occurring in the real world. There are therefore dangers attached to the uncritical acceptance of such predictions. It is important to note, however, that there are perhaps greater dangers inherent in a reliance on predictions based on an intuitive assessment of the problem. The transmission dynamics of viral infections within human communities are non-linear in form and it is difficult to predict the outcome of a particular vaccination policy (in particular, the multi-stage policies) without recourse to detailed quantitative analyses. The *second* point concerns the level of vaccination coverage of the 2-year-old boys and girls. The predictions in Fig. 13 indicate that there is little advantage to be gained from adopting the two- or three-stage policies *unless* the vaccination coverage of young children exceeds 50–60%. If current trends for the uptake of the measles vaccine (around 60–65%) apply if a combined measles-rubella vaccine is introduced then this target should be achieved. Ideally, of course, vaccination coverage for measles and rubella should be raised as high as possible ($> 90\%$) if the goal of eradication is sought. Clearly, if this level of immunization against rubella was achieved in the young boys and girls, then after 30–40 years of cohort vaccination, the routine immunization of teenage girls could cease.

The attainment of high levels of child immunization against a variety of viral and bacterial infections has proved difficult in the UK over the past decade. Given the success of immunization programmes in the United States in recent years, there is a case for enforcing immunization by law (except where medically contra-indicated) as a requirement for school entry in Britain. This is understandably a

controversial question, but it deserves further discussion given the fact that any successful vaccination programme will inevitably create a situation, as the infection becomes rare, where the individual parents choice is at odds with society's needs (on the assumption that vaccination carries some *very small* risk to the individual). If this option were to be adopted, it would clearly be society's responsibility to compensate adequately those few individuals who contracted serious disease as a result of the creation of herd immunity for the well-being of the community as a whole.

The *third* point relates to the predicted influence of a multi-stage policy on the overall level of herd immunity in the population (see Figs. 8, 9 and 10). The analyses suggest that the additional component of child immunization at levels of around 60% of 2-year-olds will decrease herd immunity as a whole despite a predicted decrease in the incidence of CRS. A danger therefore arises if, some years after the introduction of the multi-stage policy, the rate of vaccine uptake amongst children declines to a low level. Under these circumstances a major outbreak of rubella could occur in the increased pool of susceptibles within the population. This danger is minimized by continual surveillance and immunization of adult women in the child-bearing age classes. The *fourth* and final point relates to the dependency of model predictions on the estimated values of the force of infection in the late teenage and adult age classes.The dependency of any prediction on the fine details of parameter estimation is worrying given the many problems that surround the collection and interpretation of large-scale serological survey data (Nokes, Anderson & Anderson, 1985). However, to counteract this worry, it should be noted that the age-stratified serological survey from which parameter estimates were obtained is the largest of its kind in the UK, and hence the best data available at present. In the future, much greater attention should be directed towards the collection of such epidemiological information.

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REFERENCES

Anderson, R. M., Grenfell, B. T. & May, R. M. (1984). Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination. *Journal of Hygiene* **93**, 587–608.

Anderson, T. M. & May, R. M. (1982). Directly transmitted infectious diseases: control by vaccination. *Science* **215**, 1053–1060.

Anderson, R. M. & May, R. M. (1983*a*). Vaccination against rubella and measles: quantitative investigations of different policies. *Journal of Hygiene* **90**, 259–325.

Anderson, R. M. & May, R. M. (1983*b*). Two-stage vaccination programme against rubella. *Lancet* ii, 1416–1417.

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 in Medicine and Biology* **1**, 233–266.

Anderson, R. M. & May, R. M. (1985). Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *Journal of Hygiene* **94**, 365–436.

BENENSON, A. S. (1975). *Control of Communicable Diseases in Man*, 12th ed. Washington, D.C.: American Public Health Association.

BLACK, F. L. (1959). Measles antibodies in the population of New Haven, Connecticut. *Journal of Immunology* **83**, 74–83.

COLLINS, S. D. (1929). Age incidence of the common communicable diseases of children. *United States Public Health Reports* **44**, 763–828.

DIETZ, K. (1975). The incidence of infectious diseases under the influence of seasonal fluctuations. *Lecture Notes in Biomathematics* **11**, 1–15.

FALES, W. T. (1928). The age distribution of whooping cough, measles, chicken pox, scarlet fever and diphtheria in various areas of the United States. *American Journal of Hygiene* **8**, 758–799.

FIELD, A. M. (1967). The occurrence of neutralizing and complement fixing antibiotics in rubella. *Journal of Hygiene* **65**, 409–421.

FINE, P. E. M. & CLARKSON, J. A. (1982*a*). Measles in England and Wales. I. An analysis of factors underlying seasonal patterns. *International Journal of Epidemiology* **11**, 5–14.

FINE, P. E. M. & CLARKSON, J. A. (1982*b*). Measles in England and Wales. II. The impact of the measles vaccination programme on the distribution of immunity in the population. *International Journal of Epidemiology* **11**, 15–25.

FINE, P. E. M. & CLARKSON, J. A. (1984). Distribution of immunity to pertussis in the population of England and Wales. *Journal of Hygiene* **92**, 21–36.

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.

GRIFFITHS, D. A. (1974). A catalytic model of infection for measles. *Applied Statistics* **23**, 330–339.

HANSHAW, J. B. & DUDGEON, J. A. (1978). *Viral Diseases of the Foetus and Newborn*. London: W. B. Saunders Company.

HETHCOTE, H. W. (1983). Measles and rubella in the United States. *American Journal of Epidemiology* **117**, 2–13.

KNOX, E. G. (1980). Strategy for rubella vaccination. *International Journal of Epidemiology* **9**, 13–23.

MILLER, C. L., MILLER, E., SEQUEIRA, P. J. L., CRADDOCK-WATSON, J. E., LANGSON, M. & WISEBERG, E. C. (1985). Effect of selective vaccination on rubella susceptibility and infection in pregnancy. *British Medical Journal* (In the Press.)

MILLER, E., CRADDOCK-WATSON, J. E. & POLLOCK, T. M. (1982). Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* ii, 781–784.

MMWR (1984). *Annual Summary 1983*. U.S. Department of Health and Human Services.

NOKES, J., ANDERSON, R. M. & ANDERSON, M. J. (1985). Rubella transmission in South East England: a horizontal seroepidemiological study. *Journal of Hygiene* **96**, 291–304.

O'SHEA, S., BEST, J. M., BANATVALA, J. E., MARSHALL, W. C. & DUDGEON, J. A. (1982). Rubella vaccination: persistence of antibodies for up to 16 years. *British Medical Journal* **285**, 253–255.

O'SHEA, S., BEST, J. M., BANATVALA, J. E., MARSHALL, W. C. & DUDGEON, J. A. (1984). Persistence of rubella antibody 8–28 years after vaccination. *British Medical Journal* **288**, 1043.

O'SHEA, S., BEST, J. M., BANATVALA, J. E. & SHEPHERD, W. M. (1985). Development and persistence of class-specific antibodies in serum and nasopharyngeal washings of rubella vaccines. *Journal of Infectious Diseases* (In the Press.)

SCHENLE, D. (1984). An Age-structured Model of Pre-and Post-vaccination Measles Transmission. *IMA Journal of Mathematics Applied in Medicine and Biology* **1**, 169–192.

SOUTH, M. A. & SEVER, J. L. (1985). Teratogen update: the congenital rubella syndrome. *Teratology* **31**, 297–307.

SYDENSTRICKER, E. & HEDRICH, A. W. (1929). Completeness of reporting of measles, whooping cough and chicken pox in different ages. *United States Public Health Reports* **44**, 1537–1543.

APPENDIX

This appendix gives a brief outline of the structure of the mathematical model employed to generate the results discussed in this paper. Further details of structure and methods of analysis are given in a separate publication (Anderson & May, 1985).

The numbers of individuals of age a and sex i ($i = 1$, 2 where 1 = male, 2 = female) at time t, who are protected by maternal antibodies, susceptible, infected but not infectious, infectious, and immune (acquired naturally or via vaccination) are defined by the variables $M_i(a,t)$, $X_i(a,t)$, $H_i(a,t)$, $Y_i(a,t)$ and $Z_i(a,t)$ respectively. The rates of change of these variables with respect to both age a, and to time t, are defined as follows:

$$\frac{\partial M_i(a,t)}{\partial t}+\frac{\partial M_i(a,t)}{\partial a} = -[\mu(a)+d]\,M_i(a,t). \tag{A 1}$$

$$\frac{\partial X_i(a,t)}{\partial t}+\frac{\partial X_i(a,t)}{\partial a} = dM_i(a,t)-[\mu(a)+\lambda(a,t)+v(a,t,i)]\,X_i(a,t). \tag{A 2}$$

$$\frac{\partial H_i(a,t)}{\partial t}+\frac{\partial H_i(a,t)}{\partial a} = \lambda(a,t)\,X_i(a,t)-[\mu(a)+\sigma]\,H_i(a,t). \tag{A 3}$$

$$\frac{\partial Y_i(a,t)}{\partial t}+\frac{\partial Y_i(a,t)}{\partial a} = \sigma H_i(a,t)-[\mu(a)+\gamma]\;Y_i(a,t). \tag{A 4}$$

$$\frac{\partial Z_i(a,t)}{\partial t}+\frac{\partial Z_i(a,t)}{\partial a} = \gamma H_i(a,t)+v(a,t,i)\,X_i(a,t)-\mu(a)\,Z_i(a,t). \tag{A 5}$$

Here the force of infection $\lambda(a,t)$ is defined as

$$\lambda(a,t) = \int_0^L \beta(a',a)\sum_{i=1}^{2} Y(a',t)\,da'.$$

Parameter definitions are as follows: $\mu(a)$ is the age-specific mortality rate (assumed to be a step function where $\mu(a) = 0$ for $a < L$ and $\mu(a) = \infty$ for $a > L$, L is life expectancy (75 years)), $1/d$ is average duration of protection provided by maternally derived antibodies, $1/\sigma$ is the incubation period, $1/\gamma$ is the infectious period and $v(a,t,i)$ is the age, time and sex specific rate of vaccination.

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