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Modelling rubella in Europe

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SUMMARY

The prevention of congenital rubella syndrome (CRS), as a complication of rubella infection during pregnancy, is the main aim of rubella vaccination programmes. However, as vaccination of infants leads to an increase in the average age at which those who were not immunized become infected, certain rubella vaccination programmes can lead to an increase in the incidence of CRS. In this paper we use a mathematical model of the transmission dynamics of rubella virus to investigate the likely impact of different vaccination policies in Europe. The model was able to capture pre-and post-vaccination patterns of infection and prevalence of serological markers under a wide variety of scenarios, suggesting that the model structure and parameter estimates were appropriate. Analytical and numerical results suggest that endemic circulation of rubella is unlikely in Finland, the United Kingdom, The Netherlands, and perhaps Denmark, provided vaccine coverage is uniform across geographical and social groups. In Italy and Germany vaccine coverage in infancy has not been sufficient to interrupt rubella transmission, and continued epidemics of CRS seem probable. It seems unlikely that the immunization programmes in these countries are doing more harm than good, but this may be partly as a result of selective immunization of schoolgirls. Indeed, in both these countries, selective vaccination of schoolgirls with inadequate vaccination histories is likely to be an important mechanism by which CRS incidence is suppressed (unlike the other countries, which have had sufficiently high infant coverage rates to withdraw this option). Reducing inequalities in the uptake of rubella vaccine may bring greater health benefits than increasing the mean level of coverage.

INTRODUCTION

Mass infant immunization with a vaccine that protects against infection (not just disease) results in an increase in the average age at infection in those who are not immunized. Since the serious consequences of rubella infection are largely restricted to infection in adults (in particular pregnant mothers) there is a danger that infant immunization can result in an increase in the incidence of congenital rubella.

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Mathematical models of infectious disease transmission have proved to be useful tools for analysing the possible consequences of changes to immunization programmes [1–6] since they allow a quantitative exploration of the possible effects of vaccination without the expense and possible detrimental public health consequences of a natural experiment. For instance, an intuitive assessment of different rubella immunization policies might suggest that low-coverage infant immunization might lead to an increase of congenital rubella syndrome (CRS), but what level of

coverage would be required to avoid this, and by how much is the incidence of CRS likely to increase are questions which can only practicably be addressed by the use of a carefully constructed model. In this paper we utilize a mathematical model of rubella transmission to simulate current and historic immunization practice in a number of European countries and explore if any of the current immunization programmes are likely to lead to perverse health outcomes. For those countries in which rubella is likely to continue to circulate we go on to investigate the likely effects of changes to their immunization schedules.

As part of the European Sero-Epidemiological Network (ESEN) project 6 of the 8 participating countries (England and Wales, The Netherlands, Finland, Germany, Denmark and Italy) each tested at least 3400 serological samples for rubella antibodies [7] (as well as measles, mumps, diphtheria and pertussis) [8]. Samples were collected between 1994 and 1998 and were intended to be broadly reflective of the general population (The Netherlands used a random sample, other countries used residual sera sent to laboratories for routine diagnostic purposes). Although a variety of tests were used the results were all expressed in International Units and then further standardized to those of the reference laboratory (Preston PHL, UK) [9]. The resulting age-serological profiles thus provide a rich source of data for mathematical models of rubella transmission, and a unique opportunity to compare the epidemiology of rubella across different countries in Europe.

METHODS

The structure of the model

The model is a deterministic age-structured SEIR model (susceptible, exposed, infectious and recovered), similar to that described elsewhere [1, 2]. It assumes that all hosts are in one of the following mutually exclusive epidemiological classes: infants protected by maternal antibody; susceptibles who have neither been infected nor vaccinated; vaccine failures, i.e. vaccinated but remaining susceptible; latently infected individuals, who have been infected but are not yet infectious; infectious individuals; and immune persons. Immunity can be gained via vaccination or via natural infection and is assumed to be permanent. All individuals are assumed to be born into the maternally derived protection class. They remain in the class for 6 months. All individuals are assumed to live until life expectancy (75 years) and then die (so called Type I survivorship). There is assumed to be no additional mortality associated with rubella infection. The model describes the flow of individuals through these epidemiological classes with respect to age and time. It consists of a system of partial differential equations, one for each epidemiological state, which is solved numerically on a personal computer using standard techniques (the Euler method with a time-step of 3·5 days). The initial conditions are given by the pre-vaccination equilibrium fractions of susceptibles, latents, etc. which can be derived by setting the time-dependencies to zero and solving the resulting set of ordinary differential equations. The initial equilibrium is then perturbed by shifting 10% of susceptibles, in all age groups, into the immune class, resulting in the generation of (damped) oscillations. Since males and females, of a given age, are assumed to mix equally with one another, there is no need to subdivide the population by gender. This reduces the number of calculations performed each time-step, so improving the performance of the model. A selective vaccination programme of girls with 90% coverage was therefore implemented as having an overall coverage of 45% as the sex ratio is assumed to be 1:1. It is then possible to calculate the proportion of cases in females as $1-f$, where f is the fraction of women in the age class who have been selectively immunized (that is, in the above example the proportion of the cases which are in females is simply 1–90% which equals 10%).

The model assumes that the force of infection (the per-capita rate at which susceptibles become infected) is a function of the rate at which susceptible individuals make effective contact with infectious individuals. Since the force of infection typically varies with age [1, 2, 10] it is necessary to take account of the rate at which susceptibles of a given age come into contact with infectious individuals of their own, and all other ages. That is, the force of infection acting on susceptibles in age group i at time t, $\lambda_i(t)$, is assumed to take the following form:

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

where $\bar{Y}_j(t)$ is the number of infectious individuals in age group j (i.e. the total summed over the entire age class), and β_{ij} is an $n*n$ mixing matrix whose elements describe the rate of effective contact between individuals in age group i with those in age group j. The elements of the Who-Acquires-Infection-From-

Whom matrix (the β_{ij}s) cannot be estimated directly (although recent work has attempted to do this in adults [11]). Instead we get them as solutions to the above equation when the force of infection in each age group is first estimated from the pre-vaccination data and the stationary proportion of infectives are derived from them. In order to have identifiability, the contact matrix must be restricted to have only n distinct values. Even having made such a restriction there are a large number of possible matrix structures which can be assumed. In this study we explore the effect of two such structures as part of a sensitivity analysis. The matrices that we chose represent our best guess assumption (termed Default matrix here) which attempts to capture the presumed importance of school-based mixing, and a matrix which implies a large amount of within age group mixing (termed here Diagonal matrix to reflect that it has a strong diagonal element). The structures of the matrices are described in more detail in another publication [10] and are shown below, where the 5 rows and columns represent the 5 age groups used in the model (0–1, 2–4, 5–10, 11–17, 18+ years), which were chosen so that school and pre-school contact patterns could be taken into account.

$$\text{Default} = \begin{bmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_5 \\ \beta_1 & \beta_2 & \beta_4 & \beta_4 & \beta_5 \\ \beta_1 & \beta_4 & \beta_3 & \beta_4 & \beta_5 \\ \beta_1 & \beta_4 & \beta_4 & \beta_3 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{bmatrix}$$

$$\text{Diagonal} = \begin{bmatrix} \beta_1 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \\ \beta_5 & \beta_2 & \beta_5 & \beta_5 & \beta_5 \\ \beta_5 & \beta_5 & \beta_3 & \beta_5 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_4 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{bmatrix}$$

Parameter estimates and assumptions

Parameter values were estimated from field data (wherever possible). The biological parameters, such as the average infectious period were estimated from the literature; the epidemiological parameters concerning, for instance, the pre-vaccination force of infection, were estimated from case notification or serological data, where these were available, or from an analysis of the rates of infection in other European countries [10]. Vaccine coverage data were taken from official data [12], or where this was not available or deemed unreliable was estimated from serological data [13].

In all tables the following convention is used: EG stands for Eastern Germany (the former DDR); WG represents Western Germany; UK the United Kingdom (although parameter estimates were, in fact, derived from data from England and Wales); FIN stands for Finland; NL, The Netherlands; DK, Denmark; IT(N), stands for Northern and Central Italy (comprising Lazio and all regions north of here); and IT(S), stands for Southern Italy (Abruzzi and all regions south of here including Sardegna). Eastern and Western Germany were subdivided as historically they have had different vaccination programmes. Italy was subdivided as there is strong evidence to suggest that on average there have been and are currently significantly lower vaccine uptake rates in the South [14, 15].

The natural history of rubella and host demography

All individuals are assumed to be protected for exactly 180 days after birth (a step function is assumed). The average latent period and infectious period are assumed to be 10 and 11 days respectively [16] and both are assumed to be exponentially distributed (recent work has shown that this assumption may have important implications for calculations of the likelihood of fade-out in a stochastic version of this model [17], though as this is not of direct interest to this work – indeed the deterministic framework is not capable of investigating elimination – we made the usual simplistic assumption of exponentially distributed latent and infectious periods).

In all instances, Type I mortality was assumed with a life-expectancy of 75 years. Immigration and emigration was assumed to be negligible (except where indicated). The birth rate was assumed to equal the death rate (the population is constant in size) thus 1/75th of the population die each year (all of them exactly 75 years of age) and are replaced by the same number of births. Table 1 shows the size of the populations in the study countries and regions.

Transmission parameters

The pre-vaccination equilibrium force of infection was estimated from pre-vaccination case notification, or age-serological data from the individual countries and regions where this was available using standard techniques [2, 18]. In West Germany no pre-vaccination data were available to estimate the force of infection, thus values from East Germany were used (see Figure 3e). Details of the estimation of the pre-

Table 1. *Population size for each of the participating countries*

Population parameters	EG	WG	FIN	DK	UK	NL	IT(N)	IT(S)
Size in millions	17	60	5	4·9	56	15	36·5	21

Table 2. *Force of infection (FOI) estimates for each of the participating countries. East German parameter estimates were used for West Germany (see Figure 3). UK estimates of the force of infection were used for adults in Denmark as the Danish study did not include individuals in this age group*

Epidemiological parameters	EG	WG	FIN	DK	UK	NL	IT (N and S)
FOI at age 0–1	0·21	0·21	0·04	0·07	0·06	0·10	0·05
FOI at age 2–4	0·24	0·24	0·08	0·14	0·14	0·11	0·08
FOI at age 5–10	0·16	0·16	0·10	0·19	0·14	0·19	0·16
FOI at age 11–17	0·11	0·11	0·09	0·18	0·09	0·11	0·09
FOI at age 18+	0·10	0·10	0·04	0·04	0·04	0·08	0·05
FOI estimated from	Serology	Serology	Serology	Serology	Serology	Notification	Notification

vaccination force of infection are given in [10], and the parameter estimates used are shown in Table 2. The values of the transmission coefficients (the β_{ij}s) were then derived from the force of infection estimates having assumed one or other of the above matrix structures.

Seroconversion rates and coverage data

In all cases it was assumed that 95% of vaccinees seroconvert, developing life-long immunity. In those countries and regions which had reliable coverage data (the UK, The Netherlands, Finland and Denmark) we based our parameter estimates on these (summarized in [12]). Elsewhere, estimates where derived using Gay's technique [13]. This method uses serological evidence of measles mumps and rubella antibodies in individuals to calculate the proportion of those who have been vaccinated with MMR from the fraction who have antibodies to all three (accounting for seroconversion rates) additional to that expected if the viruses circulated independently.

To estimate the coverage of rubella vaccine in teenage girls we utilized the assumption that any sex difference in the proportion seropositive for rubella antibodies in vaccinated cohorts is likely to be due to vaccination rather than differences in exposure. This allows the coverage to be estimated from age-serological data if we make a further assumption about the timing and age-range vaccinated. That is, a sex-difference in proportion seropositive over a 5-year age range, for instance, can be due to a one-off campaign aimed at that age range, or 5 years of vaccinating the youngest aged girls. We utilized the available data on immunization programmes to guide which of the alternatives was most plausible [12]. Table 3 shows the evolution of rubella immunization programmes in the various countries and describes the default vaccination parameter values used in the model.

RESULTS

Comparison of model results to data

Before using the model for predictive purposes we attempt to validate it by comparing model output to observed patterns of infection. In the following section we compare the predicted serological profiles from Finland with those that were observed [19]. In the following two sections we compare the model results with observed case notification data from those countries in which this is available and reliable and the current age-related pattern of serological markers.

Evolution of observed and predicted serological profiles in Finland

Figure 1 shows the observed serological profiles from Finland for the period 1979–90 (solid bars) and compares this to model results (note that these observed serological profiles are not necessarily representative of the general population as samples were sent specifically for rubella testing [19]). Mass infant vaccination was introduced in 1983 at high levels of coverage along with a catch-up programme for young children, therefore serological results in the younger ages groups after this time point largely reflect the effective coverage of the vaccination

Table 3. *Vaccination parameter values used in simulations for each of the study countries. The coverage (in %) is shown for each year as a series of numbers separated by commas. The last number in the series refers to the assumed coverage for coming years. '10∗90' means 10 years at 90% coverage. Coverage amongst vaccine failures is the proportion of those who have previously been vaccinated (only those who remain susceptible are relevant) who are vaccinated again. In Germany (both East and West) the current infant programme consists of two doses: one at 18 months and one at 6 years of age. However, to reflect the slow uptake of vaccination with age it is assumed that 50% receive their first dose at 18 months and the remaining 20% (40% of those who are left) receive their first dose at 3·5 years (for East Germany the relevant figures are 70% and 25%). Only those who have previously been vaccinated (75% of them) are assumed to receive the booster dose in their sixth year*

Country	Programme	Dates	Target age (yr)	Coverage in unvaccinated individuals	Coverage among vaccine failures
East Germany	Selective	1991–…	10	40%…	0%…
	Mass, 1st dose	1991–…	1·5	70%…	0%…
	Mass, 2nd dose	1993–…	3·5	50%…	0%…
	Mass, 3rd dose	1991–…	6·5	20, 40, 3∗50, 0%…	75%…
West Germany	Selective	1981–…	10	60%…	0%…
	Mass, 1st dose	1981–…	1·5	50%…	0%…
	Mass, 2nd dose	1983–…	3·5	40%…	0%…
	Mass, 3rd dose	1991–…	6·5	0%…	75%…
Finland	Selective	1975–87	13	90%	0%
	Mass	1988–92	13	95%	0%
	Catch up	1983–6	5·5	95%	0%
	Military	1986–…	20	82%…	82%…
	Mass, 1st dose	1982–…	1·5	96%…	0%…
	Mass, 2nd dose	1982–…	6	98%…	98%…
Denmark	Pulse	1987	2–4	50%	0%
	Pulse	1987	5–11	10%	0%
	Mass, 1st dose	1987–…	1·25	77, 78, 79, 83, 85, 84, 85, 86, 88%…	0%…
	Mass, 2nd dose	1987–…	12	45, 45, 43, 52, 72, 85, 91, 82, 80%…	10∗0%, 80%…
England and Wales	Pulse	1994	5–16	91%	91%
	Selective	1970–93	12	45, 79, 87, 73, 66, 65, 68, 71, 77, 3∗84, 86, 2∗87, 9∗86%	0%
	Mass, 1st dose	1989–…	1·25	75, 86, 90, 92, 91, 91, 92, 92%…	0%…
	Mass, 1st dose catch-up	1989–91	4·25	80%	0%
	Mass, 2nd dose	1997–…	4·25	35%…	75%…
Netherlands	Selective	1974–89	11	8∗90, 91, 92, 92, 4∗93%	0%
	Catch up	1989–91	4·17	89, 92, 93	0%
	Mass, 1st dose	1987–…	1·17	94%…	0%…
	Mass, 2nd dose	1987–…	9	91, 92, 93, 94, 94	5∗0%, 97%…
Northern and Central Italy	Selective	1973–…	10	45%…	17∗0%, 45%…
	Mass	1982–…	1·25	6∗25, 30, 35, 40, 65, 70%…	0%…
Southern Italy	Selective	1981–…	10	45%…	0%, 45%…
	Mass	1982–…	1·25	6∗25, 30, 35, 40, 40, 40, 55%…	0%…

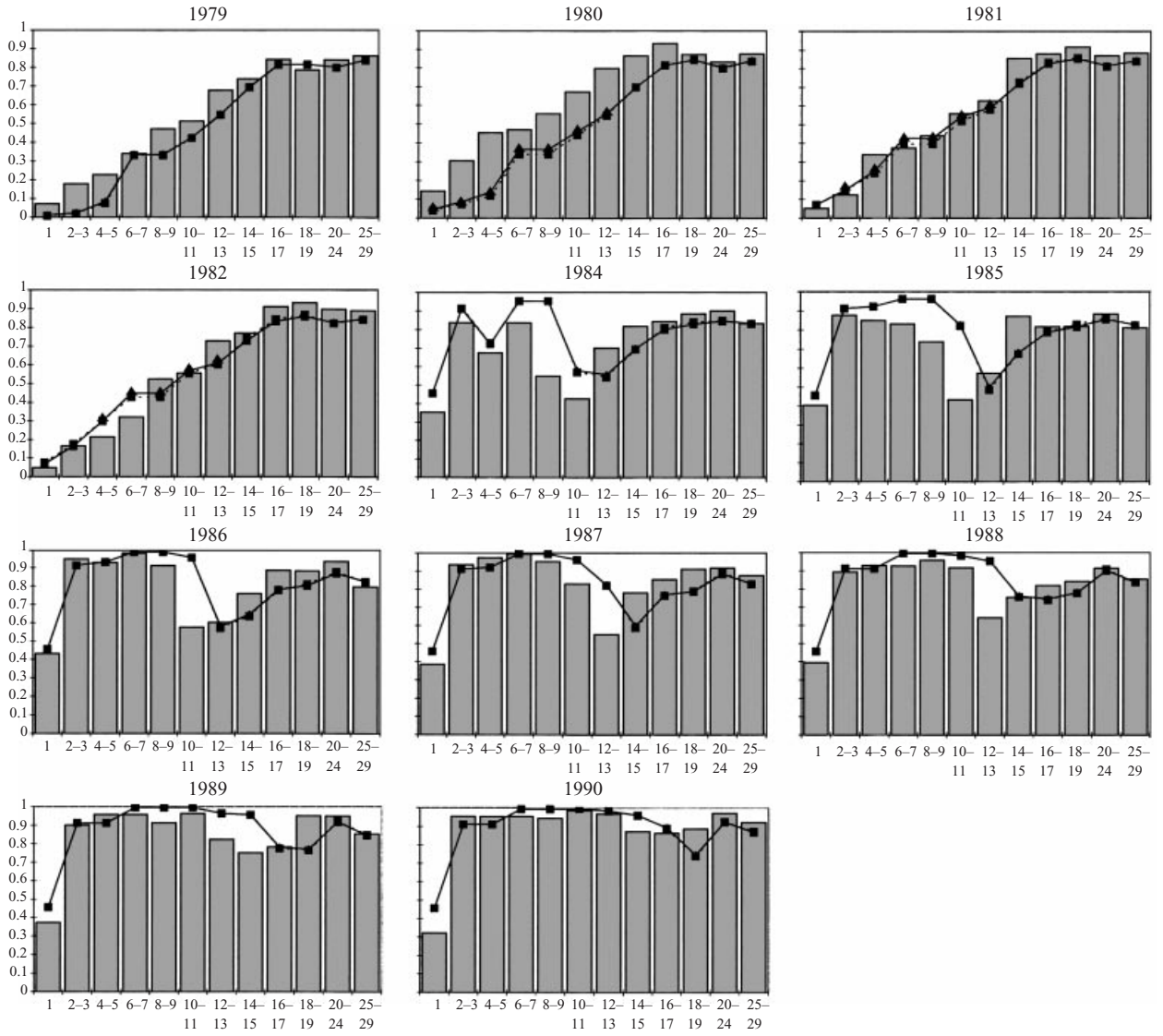

Fig. 1. Observed and predicted age-serological profiles from Finland over the period 1979–90. Solid bars are data [19] and lines are model results. Triangles (unbroken line) are results of the default matrix and squares (dotted line) those of the diagonal matrix. The parameter values used in the model are given in Tables 1–3.

programme. Data from before this era (when only selected vaccination was in place) are more useful for assessing the behaviour of the model. It can be seen that, with the exception of 1980 (which had inexplicably higher observed prevalence of markers in all age groups) both model configurations provide a reasonable description of the data. However, since the model results are so similar to each other it is not possible to choose which matrix configuration is likely to more accurately reflect relevant mixing patterns.

Observed and predicted inter-epidemic period

Figure 2 compares model results of the crude incidence over time with observed data from Finland and Denmark (*a* and *b* respectively). Note the differences in scales. The model outputs cases of infection, whereas the data are reported cases of disease per year (many cases of rubella infection are sub-clinical and there appears to be significant under-reporting of clinical rubella, particularly in Finland which had a laboratory-based reporting system). Although data are incomplete, it seems from Figure 2*a* that prior to the introduction of MMR in Finland in 1983, rubella continued to circulate with an inter-epidemic period of 5 years (or perhaps 4 years depending on the number of cases in 1976, for which data are missing). Both matrix configurations predict a 5 year inter-epidemic period. This again suggests that both models provide a reasonable description of the patterns of

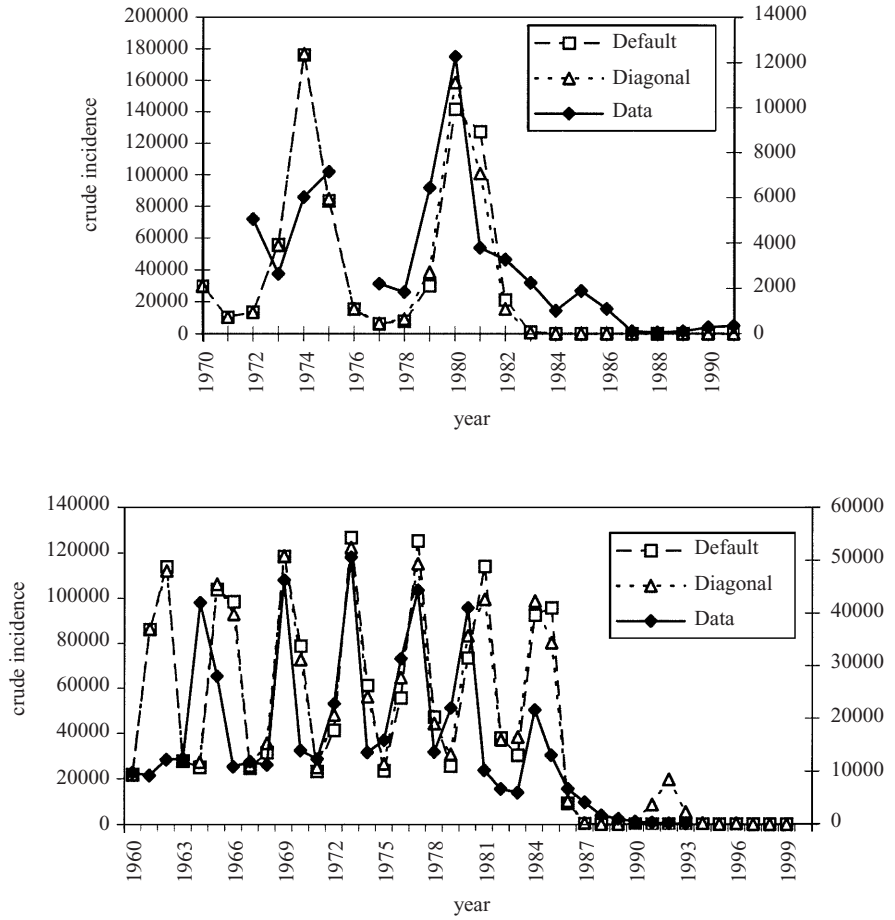

Fig. 2. Observed and predicted annual number of cases in (*a*) Finland, and (*b*) Denmark. In both instances the observed data (reported cases of disease) are plotted against the right hand axis (diamonds), the model results (cases of infection) are plotted against the left hand axis using both the Default (open squares) and Diagonal (open triangle) matrices.

Table 4. *Estimated values for the basic reproduction number*, R_0, *the critical fraction of newborns required to be immunized to eliminate rubella*, P_c, *the pre-vaccination % of women aged 18–40 years infected with rubella, and the threshold level of infant immunization* (*at 2 years, in the absence of a selective policy*) *required to avoid perverse health outcomes*, P_p. *Values are given for the default and diagonal matrices*

	Germany (E & W)	UK	Italy (N & S)	Denmark*	Netherlands	Finland
R_0 (default)	7·8	3·7	4·2	4·2	6·4	3·4
(diagonal)	7·8	4·0	4·3	7·7	6·6	3·5
P_c (default)	87%	73%	76%	76%	84%	71%
(diagonal)	87%	75%	77%	87%	85%	71%
% women infected	5·6%	8·1%	9·9%	3·1%	7·6%	12·7%
P_p (default)	74%	44%	44%	69%	65%	23%
P_p (diagonal)	76%	6%	37%	0%	61%	0%

* Figures for Denmark are unreliable (note the sensitivity of results to the different mixing assumptions) as the force of infection in teenagers (11–17 years) was estimated to be high.

infection, but it is not possible to choose between them on this basis.

A similar comparison of the observed and predicted crude incidence is shown in Figure 2*b* using case notification data from Denmark. MMR vaccination was introduced in Denmark in 1987 in conjunction with a catch-up campaign (Table 3). It is clear that before this period rubella circulated in Denmark with an approximate 4 year periodicity – a cycle which is predicted by the model using either of the matrix

configurations (the exception being the 1980 epidemic which occurred 3 years after the previous one, hence model results are 1 year out of phase after this year). Indeed the model predicts that in East Germany the inter-epidemic period was of the order of 3 years whereas in The Netherlands a 4-year cycle is predicted. These patterns are in agreement with the observed data [10], although after the introduction of selective vaccination in The Netherlands the observed inter-epidemic period appears to have shortened (not shown), possibly as a result of increases in the birth rate.

Observed and predicted patterns of infection in different countries

Age-stratified serological data provide a better test to the model given the uncertainties and biases surrounding reported cases of rubella. The serological results of the ESEN project provide an ideal opportunity to test the behaviour of the model in different epidemiological situations and under a variety of past immunization programmes, as any differences between countries in observed serological patterns are likely to be real (samples were large and laboratory results were standardized). Figure 3 shows the observed age-serological profiles for six countries and compares this with model results. Note that transmission parameters were not estimated from the current serological profiles (Fig. 3), but from pre-vaccination data [10]. If the model and parameter estimates are reasonable, then the results generated should resemble the current, observed, serological patterns. It is clearly illustrated in Figure 3 that there is a high degree of agreement between the model predications and the observed patterns of serological markers. This is particularly noteworthy given the range of pre-vaccination patterns of infection [10] and the variety of vaccination policies which have been pursued in the different countries and regions (Table 3). In general, the model provides a better fit to the data if equivocals are treated as being positive (not shown), suggesting that most of them are low positives. Although the model is able to capture the post immunization age-distribution of serological markers it should be borne in mind that for the countries which have maintained high rates of coverage, there is very little endemic circulation of virus [20–22], hence both the observed and predicted profiles in the vaccinated cohorts are largely reflections of past immunization programmes.

Apart from providing a check for model output, the data presented in Figure 3 also allow a comparison of the epidemiology of rubella in the different European countries and an assessment of the effectiveness of their various immunization policies. The different countries and regions can be classified according to their levels of susceptibility to rubella (Fig. 3). Finland, The Netherlands and the United Kingdom each have very few susceptibles in all age groups over the age of 1 year. In these countries very little endemic circulation of rubella occurs (particularly in the younger, vaccinated, age groups) thus the observed (and predicted) serological profiles in the younger age groups is almost entirely a function of past vaccination programmes.

Italy and Germany appear to have relatively high levels of susceptibility in the younger age groups and the model predicts that viral circulation is likely to continue in these areas (see later). As circulation of the virus is expected to be maintained, data from these areas can in principle be used to check the appropriateness of the model assumptions (specifically with regard the matrix configuration). In practice, however, both configurations provide very similar results (data not shown for West Germany).

Although no pre-vaccination data were available for West Germany the results shown in Figure 3 allow certain parameter values to be ruled out. The results clearly demonstrate that force of infection values from East Germany (that is a high rubella transmission area [10]) provide a better fit to the data than those of the UK (that is an area of intermediate transmissibility [10]).

Denmark appears to be intermediate between these two different epidemiological patterns. Reasonably high levels of coverage (roughly 80%) appears to have been maintained since rubella vaccination was introduced in 1987. However the model predicts, and the data confirm, that the introduction of vaccination has resulted in a peak of susceptibles in pre-teens (roughly 10 years of age). It is possible, therefore, that chains of rubella transmission may continue in this age group (this possibility is explored below).

Taking the results of the above sections together it is clear that the model is able to capture the pre-and post-vaccination patterns of infection observed in a wide variety of epidemiological situations. Thus we can feel reasonably confident that the future predictions of the model are likely to broadly reflect future trends in rubella prevalence and incidence. It is also clear that the model results are relatively

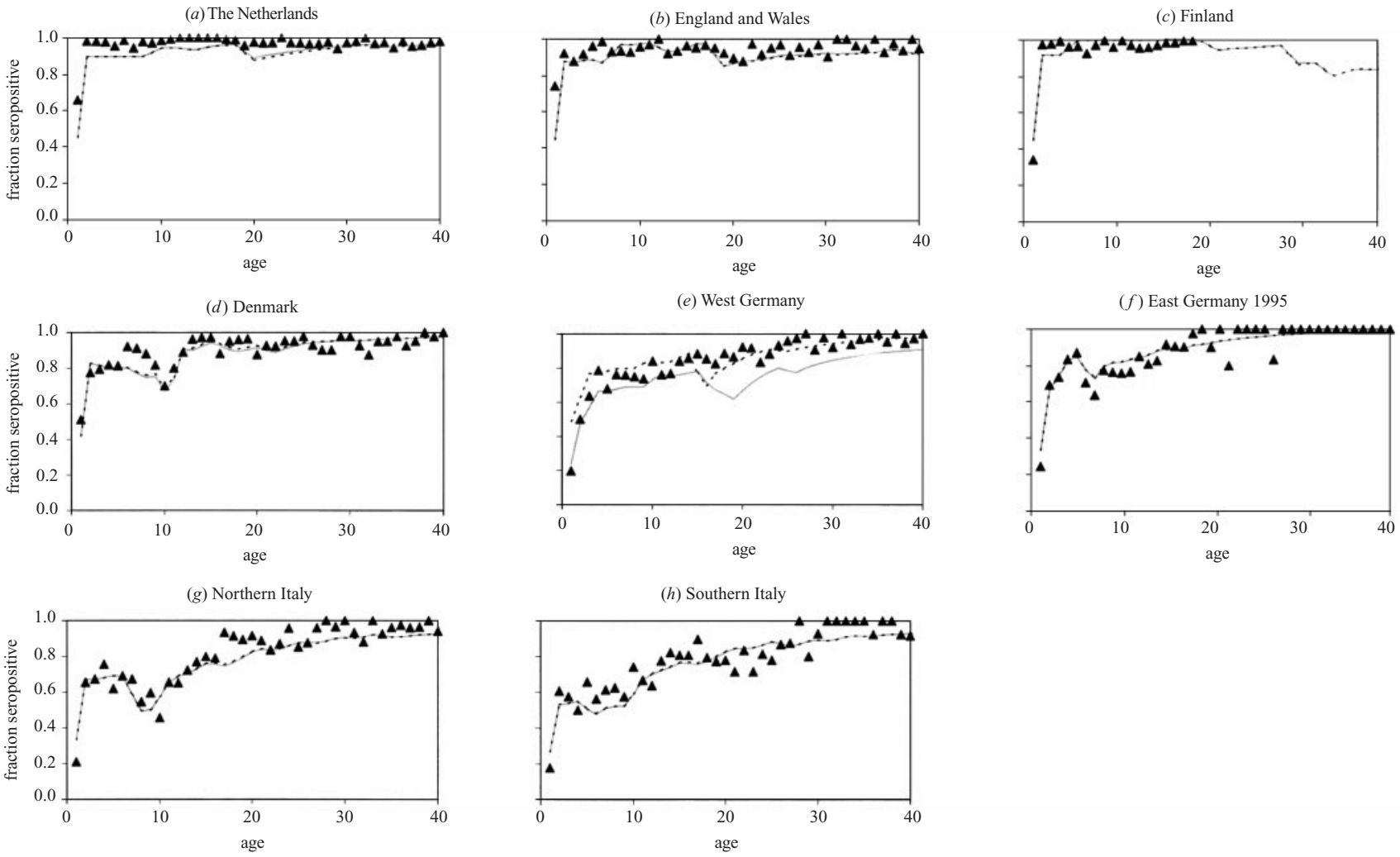

Fig. 3. The observed (triangles [7]) and predicted proportion serologically positive (including those who were termed equivocal) by age in eight European regions. Model results using the Default matrix are given by a solid line and those using the Diagonal contact matrix by a dotted line. For West Germany, model results are provided using the United Kingdom (solid line) and East German (dotted line) force of infection estimates [10] and the Default matrix only (results using the Diagonal matrix are similar).

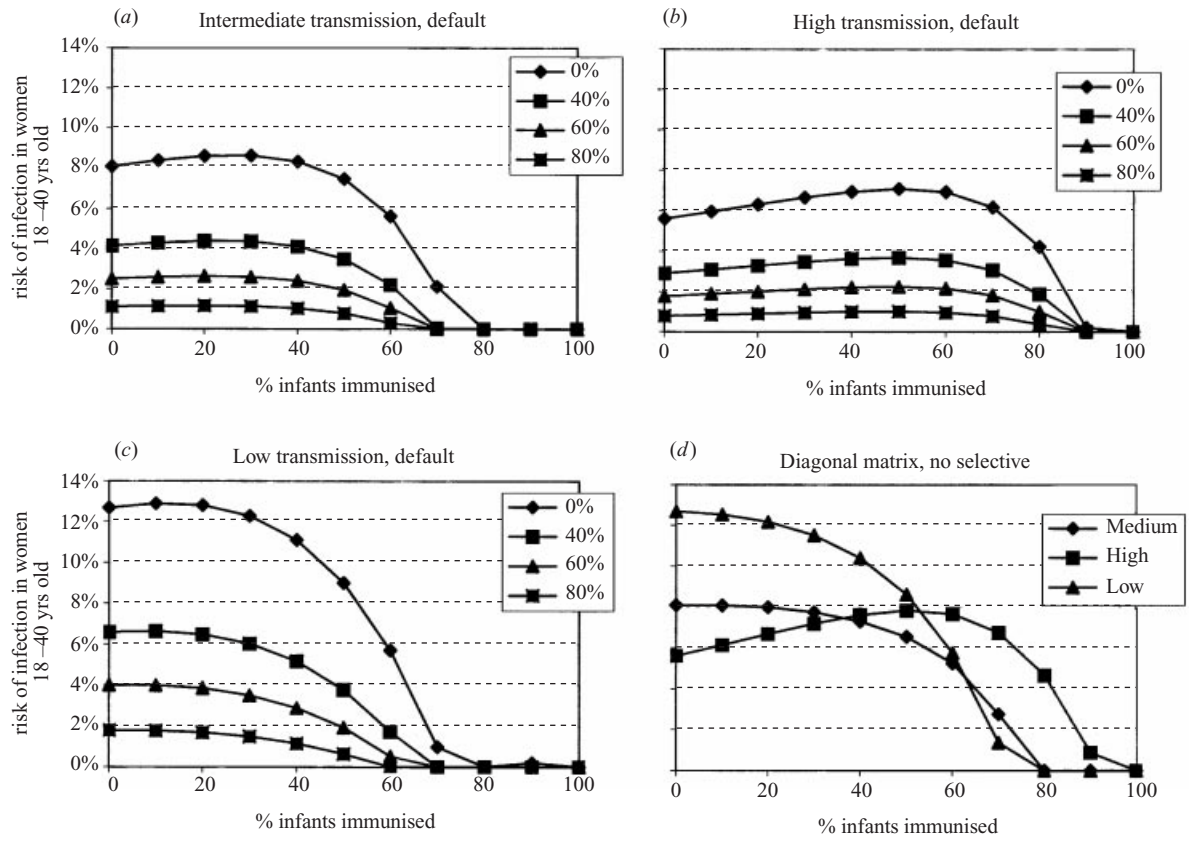

Fig. 4. Steady state predictions of the proportion of women of childbearing age (18–40 years) infected with rubella under various immunization programmes. The level of effective coverage at 2 years is shown on the *x*-axis. The different lines represent different levels of effective coverage of 11-year-old girls. 4(*a–c*) Shows the results of the default matrix with force of infection estimates taken from the United Kingdom (intermediate) East Germany (high transmission) and Finland (low transmission). 4(*d*) Shows results for the diagonal matrix, for high, medium and low transmission areas (as above). Results are shown for infant immunization only.

insensitive to the alternative mixing assumptions (the only component of the model which had to be *assumed* rather than estimated from data).

Equilibrium results

The basic reproduction number, the average number of secondary infections generated by a typical case in an entirely susceptible population, can be derived from the dominant eigenvalue of the next generation matrix [23]. Using the default matrix, the basic reproduction number, R_0, was estimated to be 7·8 in high transmission areas, 3·7 in the medium transmission areas, and 3·4 in low transmission areas (Table 4). The elimination criterion, P_c, (the threshold fraction of infants immunized at birth needed to block endemic transmission of the virus) can be calculated from $P_c = 1 - 1/R_0$ [2] to be 87% in high transmission areas, 73% in intermediate areas, and 71% in low transmission areas (estimates are similar, though somewhat higher, under the diagonal matrix configuration). The estimated basic reproduction numbers using the default and diagonal matrices, and the associated elimination criteria are given in Table 4.

The long-term impact of different combinations of vaccination programmes (infant immunization of girls and boys at 2 years of age and vaccination of 11-year old school girls) can be explored by solving the system of partial differential equations at time-independent equilibrium. Figure 4 shows the predicted post-immunization equilibrium proportion of women ever infected during their childbearing years (18–40 years) under different levels of infant and schoolgirl immunization. The cumulative risk of infection between the ages of 18 and 40 years (H_{18-40}) is calculated thus:

$$H_{18-40} = S_{18}(1 - e^{-22\lambda}),$$

where S_{18} is the proportion of women susceptible at 18 years of age, and λ is the force of infection in adults (expressed as an annual per-capita rate). Results are

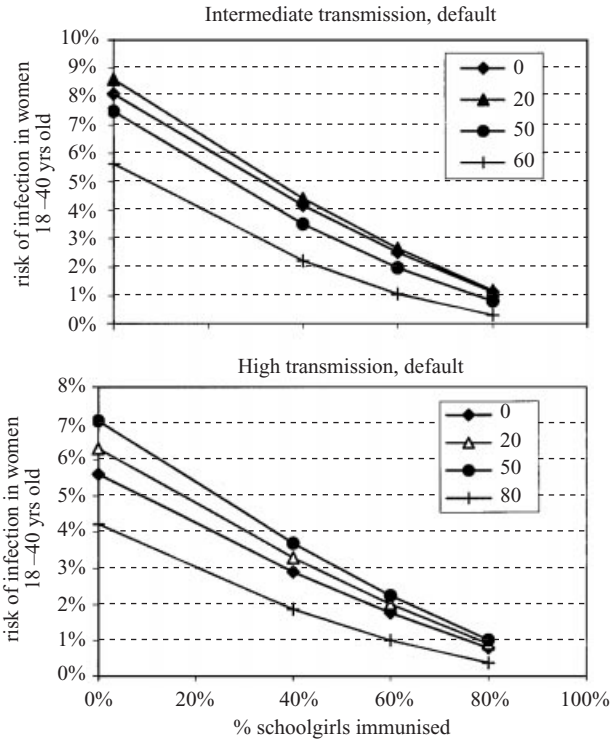

Fig. 5. As for Figure 4 except the level of effective coverage in 11-year-old girls is shown on the *x*-axis and the different lines represent different levels of effective infant immunization.

shown for intermediate, high and low transmission areas in Figure 4*a–c* (representatives of which are the United Kingdom, East Germany and Finland respectively). Figure 4*d* explores the sensitivity of these results to the alternative (diagonal) mixing assumption. Note that in this section the coverage levels, for both the selective and infant programmes, represent effective coverage, that is the proportion of individuals *immunized* not the proportion vaccinated.

As the level of infant vaccination increases (in the absence of selective vaccination) there is an initial rise in the proportion of women expected to be infected during their at-risk years. If infant vaccination coverage is high enough then the decrease in incidence of infection is sufficiently large to result in fewer infections in adult women than occurred before immunization. Vaccination of schoolgirls has very little effect on the transmission dynamics as immunization occurs after a significant proportion of the population are already immune. Thus such programmes result in a roughly proportionate reduction in the risk of infection in adult women. Figure 5 shows this approximately linear relationship.

Figure 4 also shows the pre-vaccination proportion of women (aged 18–40) who are likely to be infected (0% coverage in infants in the absence of a selective programme – see also Table 4). Comparing Figure 4*a* with Figure 4*b* and 4*c* it is clear that the risk of women being infected is predicted to be higher in low transmission areas (such as Finland) than in higher transmission areas (such as the United Kingdom and East Germany). This is because in low transmission areas a significant proportion of women are still susceptible on entering the childbearing age classes (note how sensitive model predictions are to the values of the β_{ij}s: R_0 is similar in Finland and the UK but the risk of infection in adult women is estimated to have been roughly 50% higher in Finland).

Although the absolute risk of infection in pregnancy is estimated to have been lower in high transmission areas, the likelihood of perverse outcomes arising from an infant immunization programme is much greater in these areas than in lower transmission areas (comparing Fig. 4*b* with Fig. 4*a* and *c*). That is, the higher the force of infection the greater the relative increase in CRS cases for low-intermediate levels of infant immunization, and the wider the range of coverage likely to lead to adverse public health effects. In high transmission areas (such as East Germany) vaccination of infants alone is expected to lead to an increase in cases of CRS for all levels of coverage up to 70–80% (Fig. 4*b*). Furthermore, this result is insensitive to the different mixing assumptions (Fig. 4*d*). In fact, in these high transmission areas the level of infant immunization required to avoid causing more harm than good (defined here as β_i) is close to the elimination criterion (Table 4). Perverse outcomes arising from infant immunization can be avoided by implementing a selective programme of schoolgirls. If both programmes are in place any reduction in the burden of disease due to CRS is then largely due to the selective programme rather than the infant programme (unless the coverage of the infant programme is sufficiently high). It is also evident from Figure 4*b* that, particularly in high transmission areas, endemic circulation of rubella virus can be maintained even at levels of infant coverage above the elimination criterion (roughly 87% under East German parameter values). This is because vaccination is assumed to be delivered at 2 years of age, allowing transmission to occur in the youngest age groups at 90% coverage – highlighting the importance of early vaccination if an infant programme is to be relied on to control rubella infection.

The sensitivity of the predictions to different mixing assumptions are explored in Figure 4*d* and Table 4.

The figure shows the predicted proportion of women (aged 18–40 years) infected using the diagonal, as opposed to the default matrix configuration for different levels of infant immunization in the absence of selective vaccination. The underlying contact structure clearly has an important influence on the likelihood of perverse health outcomes arising from infant immunization. Thus under the diagonal matrix, in which contact is largely restricted to within age-groups, mass immunization of infants in areas of low or intermediate transmission is not expected to result in an increase in CRS regardless of the coverage.

Taken together, the above analytical results suggests that, other things being equal, it is likely to be much more effective to vaccinate in low transmission areas as the incidence of CRS is higher, the likelihood of perverse outcomes is much reduced and the virus is easier to control. In high transmission areas the relative importance of selective vaccination of schoolgirls is increased to avoid the perverse effects of infant immunization at all but the higher levels of coverage.

Dynamic results: alternative scenarios for countries with intermediate coverage

In those countries that have combined high levels of rubella vaccine coverage with catch-up campaigns (Finland, The Netherlands and the United Kingdom) the model predicts that very little or no endemic rubella would be expected. If current levels of coverage are maintained in these countries rubella infection is likely to be confined to isolated outbreaks which cannot be adequately modelled using the deterministic framework utilized in this study. We therefore turn our attention, in the following section, to modelling the future number of cases in those countries in which endemic circulation of rubella is still likely (Germany and Italy) or possible (Denmark). The effects of the actual immunization programmes (or close approximations of them; Table 3) are modelled rather than idealized vaccination programmes, as in the previous section. Results are derived from numerical solution of the system of equations and are presented in terms of the annual incidence of cases in adult women (aged 18–75 years). That is, the dynamic effects of the various immunization programmes are explored.

Italy

In Italy selective immunization of schoolgirls was introduced in 1973 (45% coverage), although serological evidence suggests that coverage in the South was negligible until the early 1980s. In 1982 MMR was introduced. Coverage appears to have steadily increased since this time, and currently stands at around 70% in the North and 55% in the South. No second MMR dose is offered (Table 3).

The current programme in the North (70% coverage in infants and 45% coverage in schoolgirls) would be expected to be just sufficient to block endemic viral transmission (Fig. 4*a*) and is unlikely to result in large epidemics in the near future (Fig. 6*a*, *b*). Improving the coverage of the infant programme is therefore not expected to have a significant effect (Fig. 6*a*, *b*). These results are, however, potentially misleading. They assume that Northern Italy can be modelled as a homogenous unit, which is highly unlikely. Coverage of MMR vaccine in Italy varies greatly between regions and even between individual health units within regions [14]. Thus it is likely that some areas within Northern Italy will continue to experience significant numbers of cases in adult women. Although improving the average, or overall, coverage is predicted to have little effect, reducing the variability between localities would almost certainly result in significant public health improvements.

It can be clearly seen from Figure 6(*c*, *d*) that the average level of vaccination currently achieved in Southern Italy is predicted to be insufficient to interrupt rubella transmission (the same caveats apply regarding local variation as in the North). Large epidemics are predicted to occur resulting in significant numbers of cases in adult women, although the inter-epidemic period is expected to lengthen considerably. In the long-term the infant immunization programme (around 55% coverage) is expected to have very little impact on the incidence of infection in women of childbearing age (Fig. 4*a*). Almost all reductions in the incidence of CRS over the pre-vaccination state are likely to be due to the selective programme. Improving the coverage of the infant programme is therefore expected to have a significant long-term as well as immediate effect (in the simulations presented here infant coverage is increased to 80% starting in 1999) as shown in Figures 4*a* and 6*c*, *d*.

Withdrawal of either of the components of the immunization programme (infant or selective) would be expected to cause an increase in cases in adult women, although the timing of such an increase is sensitive to mixing assumptions. Note that although the long-term effect of withdrawing infant immuniz-

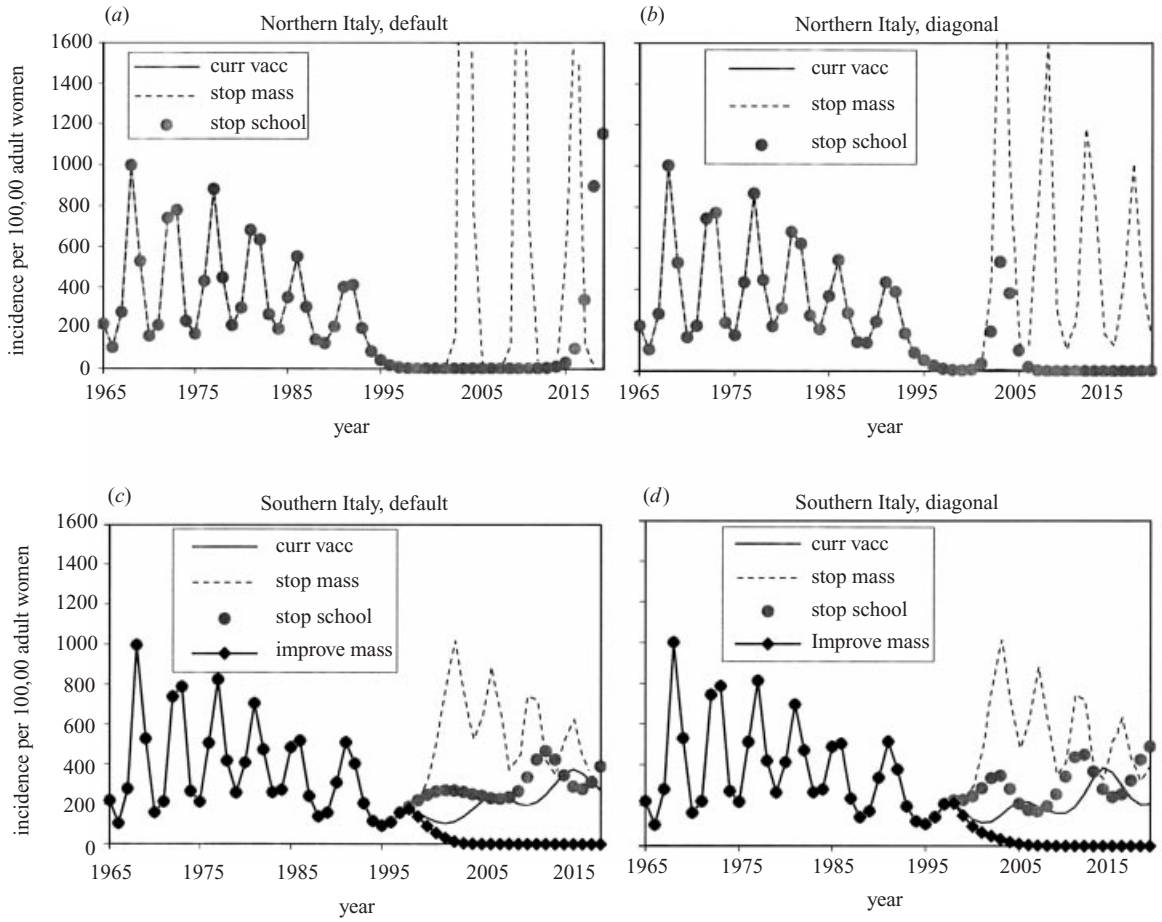

Fig. 6. Model predictions of the annual number of cases occurring in adult women (aged 18–75 years) in Northern (*a*, *b*) and Southern (*c*, *d*) Italy. Predictions are shown for the default (*a*, *c*) and diagonal (*b*, *d*) matrices. Vaccination parameter values for the current strategy are shown in Table 3. The line marked 'curr vac' assumes that the current vaccination programme will remain unchanged. The lines 'stop mass' and 'stop school' are model predictions in which the infant or schoolgirl immunization campaigns are withdrawn in January 1999; and 'improve mass' are model predictions in which 90% of infants in the North and 80% in the South receive MMR at 15 months as of 1 January 1999 (as opposed to the current programme in which 70% and 55% receive MMR at 15 months respectively).

ation is predicted to be little change in the incidence of infection in women of childbearing age (Fig. 4*a*), the short-term effect would be the stimulation of large epidemics (interspersed with very low troughs) as the system moves back to a relatively undisturbed state.

Germany

Selective vaccination was introduced in West Germany in 1981 at an estimated coverage of 60%. MMR was introduced at the same time and a booster dose of MMR was introduced in 1991 at the age of 6 years (Table 3). First dose coverage is spread out so that only about 50% of infants have evidence of being vaccinated by their third year, building to about 70% by the age of 5 years. Rubella vaccine was not offered in the former East Germany. Both selective and infant vaccination were started in 1991. The coverage of the selective programme appears to be lower at around 40% but on average infants appear to be vaccinated at an earlier age in East Germany than in the west (roughly 70% appear to have evidence of vaccination by the age of 2 [13]). As in West Germany, a second MMR dose is given at about 6 years of age (Table 3).

The model predicts that the current programme in West Germany is not sufficient to block endemic transmission (Fig. 7*a*, *b*) and that epidemics of rubella are likely to continue. Almost half of the cases are likely to be in adults and about 40% of these are expected to be in women. The timing and the shape of the expected epidemics is sensitive to the matrix structure (as well as other variables such as the immigration rate), and it is likely that outbreaks

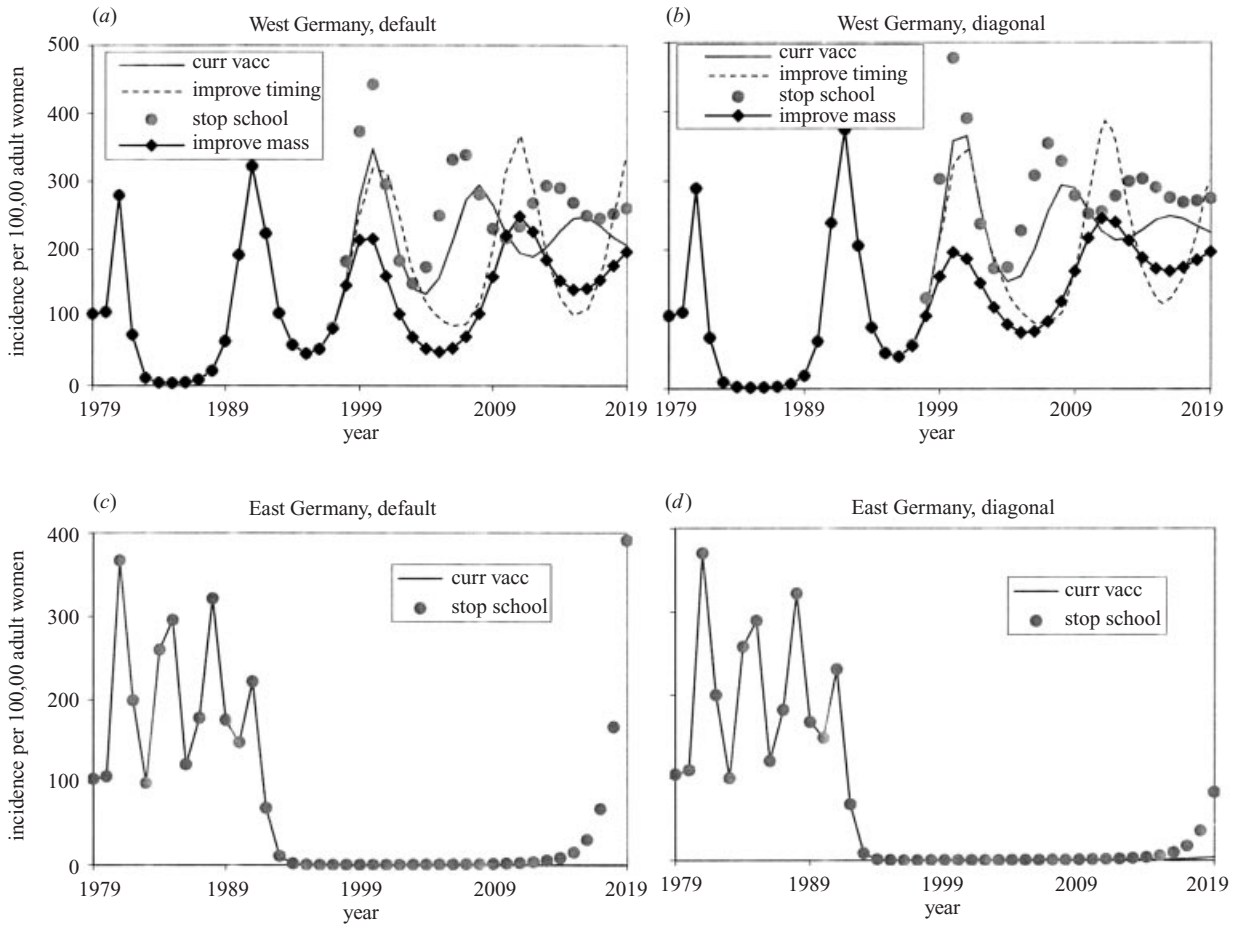

Fig. 7. Model predictions of the annual number of cases occurring in adult women (aged 18–75 years) in Western (*a*, *b*) and Eastern (*c*, *d*) Germany. Predictions are shown for the default (*a*, *c*) and diagonal (*b*, *d*) matrices. As in Figure 6 vaccination parameter values for the current strategy are shown in Table 3 and the line marked 'curr vac' assumes that the current vaccination programme will remain unchanged. 'Improve time' assumes that all 70% of infants who receive a first dose of MMR do so at 18 months of age. Improve mass assumes that the coverage level is raised to 80% at 3·5 years of age (coverage at 18 months is assumed to remain unchanged at 50%). As before 'stop school' represents the withdrawal of the selective programme. The above changes to the are assumed to take place in January 1999.

would occur before a major epidemic (particularly in subgroups with higher mixing rates, such as university students), though this cannot be captured within the current deterministic framework. The model predicts that it is unlikely that there will be an increase in the average incidence of CRS over the pre-vaccination state partly as a result of vaccinating schoolgirls. Indeed, the figure illustrates the continuing importance of vaccinating schoolgirls with inadequate history of vaccination. Neither a moderate increase in the coverage of the infant programme (to 80% by 3·5 years of age), nor improved timing of the first dose (so that all 70% of children receive their first dose of MMR during their second year) are expected to be sufficient to prevent cases of rubella in adult women, though increasing the coverage is likely to be more beneficial. Significant improvements in both coverage and timing are required to prevent endemic transmission.

As both the selective and infant immunization programmes were introduced simultaneously in East Germany and the coverage is higher in young children than in West Germany the model predicts that the current programme will result in an 'honeymoon period' before post-immunization epidemics become likely. The exact length of this honeymoon period is sensitive to immigration assumptions as well as the contact structure. The model does not, however, predict that the current strategy is sufficient to block endemic circulation of rubella (Fig. 4*b* and 7*d*). Since the model predicts that there are likely to be few cases of rubella in the short to medium term in East Germany comparison of the current strategy to alternative programmes is not feasible, although, once

again, withdrawing selective vaccination would not be advisable.

Denmark

The model suggests that the current vaccination programme in Denmark is sufficient to block endemic transmission of rubella, though small epidemics cannot be ruled out in the short term (Fig. 2*b*). Larger post-immunization epidemics may however, still occur if coverage is not maintained at uniformly high levels. Some care should be exercised in interpreting these results, however, as the pre-vaccination force of infection may have been erroneously estimated in teenagers (estimates of the force of infection from age-groups in which very few remain susceptible is particularly subject to chance).

DISCUSSION

Predicting the future impact of mass vaccination programmes requires a model as experimental or observational studies are not possible. We utilize here an age-structured dynamic mathematical model of rubella transmission to simulate the different rubella vaccination policies which have been in place in six European countries and the likely impact of changes to these policies in Italy and Germany. The advantage of using such a dynamic model is that it explicitly accounts for the decrease in the risk of infection after immunization. For rubella this is critical, since this decrease in the risk of infection can actually have a deleterious effect on public health. It leads to an increase in the average age at which those who were unimmunized become infected, which can result in an increase in the risk of infection in pregnant women. A model which fails to take account of the reduction in the force of infection after immunization, or which is not age-structured, is of limited value in evaluating rubella immunization policies.

Although there is little alternative to using mathematical models for predicting the impact of different vaccination policies, it is important to be aware of their limitations when considering any recommendations arising from their results. A number of the caveats arising from the use of a deterministic age-structured model to evaluate different vaccination policies are discussed below. As stochastic (chance) effects are ignored the model is suited for use only in large populations where each of the subgroups (in practice the infectious and latent groups) are large enough. Otherwise the chance effects are likely to dominate the dynamics of infection. In practice this means that the model results become increasingly unreliable after high levels of infant immunization has been maintained for some time. Indeed, we did not attempt to use the model to simulate future numbers of rubella cases in The Netherlands, the United Kingdom and Finland. In countries such as these, the epidemiology of rubella is likely to be dominated by outbreaks linked in most (or all) instances to an imported case. Under these circumstances stochastic models could prove useful in predicting the size and duration of such outbreaks.

The only heterogeneity included in the model is that of age. One might expect that the inclusion of social or geographical heterogeneity (including immigration) might moderate the results of the model: lowering the epidemic peaks and raising the troughs between them, and, importantly, decreasing the likelihood of elimination.

The underlying contact patterns which give rise to the different rates of infection by age cannot be directly inferred from epidemiological data. Instead, it is necessary to define, *a priori*, a mixing matrix on which a number of restrictions are placed. These restrictions mean that the matrix may bear little resemblance to actual mixing patterns. Unfortunately, although the broad patterns of infection do not appear to be sensitive to mixing assumptions the exact predictions regarding CRS incidence appear to be so (Table 4 and Figs 6, 7). Clearly there is a need for further work in this area. A recent development has been to use proxies for at-risk events (such as conversations) which can be recorded by individuals to directly measure relevant mixing patterns [11]. This technique should enable geographical, temporal and cultural differences in contact patterns to be incorporated into epidemiological models which could lead to significant improvements in their predictive powers, although children's mixing patterns and mixing during large social gatherings will still prove difficult to measure.

The accuracy of model predictions depend critically on high quality data from which parameter estimates can be derived. Unfortunately, those countries which are likely to continue to experience significant numbers of cases of rubella (Italy and Germany), and therefore have the greatest need, tend to have the poorest available data. The availability of a large serological survey from these countries (in addition to the other ESEN countries) allowed us to circumvent

this lack of data to a large extent, though the results from these areas (particularly West Germany) must be regarded as more speculative than those from elsewhere.

Because of the caveats outlined above, we were careful to check the behaviour of the model against a wide variety of data before proceeding to project model results forward. In light of the variable epidemiology of rubella across Europe [10, 24], the complex and variable vaccination programmes implemented in these different countries [12], and the variety of tests used [9], the model performed well at predicting post-vaccination patterns of infection. Thus one can be reasonably confident in its projections.

A number of important findings arise from the equilibrium results of the model. First, the basic reproduction number for rubella (the average number of secondary cases generated by a primary case in a wholly susceptible population) is likely to be variable across the different European countries. The rate of infection determines the proportion of women infected during their childbearing years in the absence of vaccination. However, in general, it is not the high transmission (high R_0) areas which were likely to have had high incidences of CRS before vaccination but areas in which R_0 was lower (although this does depend on the relative magnitude of the force of infection in the different age groups). This is because in high transmission areas most females are infected before they pass into the adult age classes. Although the absolute risk of infection during pregnancy is likely to be lower in high transmission areas than lower ones, the likelihood of perverse public health consequences arising from the implementation of an infant programme alone are much higher. This is for precisely the same reason – before vaccination most females were infected before adulthood. As infant immunization leads to a lowering in the force of infection and thus a concomitant increase in the average age at infection in those who were not immunized, then most infant-only immunization programmes at levels of coverage below the critical proportion, will lead to an increase in cases of CRS in high transmission areas. Selective vaccination, on the other hand, has virtually no effect on the force of infection, and thus reduces the incidence of infection in pregnancy in a roughly proportional manner. Selective vaccination of schoolgirls and women is a critical component of CRS prevention strategies in high transmission areas and/or areas in which infant coverage is low.

Turning to results of the models for specific countries, one can divide the countries into two regions: those which have had lower levels of vaccine coverage and in which rubella is likely to continue to circulate at appreciable levels (Italy and Germany), and those in which sustained chains of rubella transmission are unlikely (The Netherlands, Finland, the United Kingdom and Denmark), but which may still experience minor epidemics and isolated outbreaks. The deterministic framework of the model does not allow an assessment of these epidemiological situations, hence the model was used to simulate the current and alternative vaccination programmes in those countries (Italy and Germany) where endemic circulation of rubella is likely.

Although costs were not estimated in this study it is interesting to speculate on the economics of rubella immunization in Europe. If costs are equal, then one would expect that infant immunization is more cost-effective in low transmission areas than in high transmission areas, as the pre-vaccination incidence of CRS is likely to be higher, the virus is easier to control (lower critical proportion), and the likelihood of causing more harm then good is reduced. Within areas the relative cost-effectiveness of the different policy options are linked, so that the cost-effectiveness of selective vaccination programme depends on the level of coverage in the infant programme and vice versa. In general, the lower the level of infant coverage, the more cost-effective selective vaccination becomes. This is particularly important in high transmission areas, where selective immunization is likely to be more cost-effective than infant immunization at all but the highest levels of infant coverage. The effectiveness (and thus cost-effectiveness) of infant immunization critically depends on the level of coverage achieved, such that low levels of coverage might not be expected to be effective in the long run (indeed may cause more harm than good). Thus it might be tempting to withdraw the rubella component of infant immunization on cost-effectiveness grounds. However, as the results of Figure 6 show, great care should be exercised in considering this option as, large epidemics can be stimulated in the short-medium term by the withdrawal of infant vaccination. The only alternative is to improve vaccine coverage levels, even though at low levels of coverage the marginal cost-effectiveness (at equilibrium) of increasing coverage might be negative.

These subtle interactions between the level of infant vaccine coverage and the incidence of infection in

pregnant mothers raise a number of equity (i.e. distributional) issues. Assuming that the population is reasonably well mixed then at high levels of coverage (around or above P_c) unimmunized women benefit from others in the population being vaccinated. That is, although not everyone is vaccinated, most are protected, so differences in vaccine coverage across socio-economic, geographical or ethnic groups, result in minimal differences in outcomes across these groups. On the other hand, at lower levels of vaccine coverage those groups in the population who are less likely to be immunized (for whatever reason) bear the extra risk of CRS. Even at or above P_p where, in the long-term there is no net gain in incidence of CRS, infant vaccination shifts the burden of disease away from the vaccinated groups and towards those groups who are less likely to be immunized. For instance, if P_p is 50% (as appears to be the case for the UK and other intermediate transmission areas) then an infant only programme at this level of effective coverage will result in no net long-term change in the incidence of CRS. But 50% of women are protected, therefore the remaining 50% will experience twice the risk of acquiring rubella during pregnancy.

We have shown here and in the accompanying publications that the epidemiology of rubella is variable in the six different Western European countries studied here. Four of the countries appear to have, via their vaccination programmes, interrupted endemic rubella transmission and are, in the future, likely to experience relatively small epidemics or isolated outbreaks. On the other hand, two of the four countries (Germany and Italy) are likely to continue to experience significant numbers of cases of infection and probably CRS. It is salient to note that those countries with the lower rubella vaccine coverage rates tend to rely proportionately more heavily on private finance and provision of rubella vaccine [12], and have poorer surveillance mechanisms for vaccine coverage and incidence of disease. It seems that strong central co-ordination may be preferable to ensure the efficient and equitable use of resources.

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