The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies

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SUMMARY

Data on the pre-vaccination patterns of infection for measles, mumps and rubella are collated from a number of European countries in order to compare the epidemiology of the three viruses. Key epidemiological parameters, such as the age-specific force of infection and the basic reproduction number (R_0) are estimated from case notification or serological data using standard techniques. A method is described to compare force of infection estimates derived from serological data. Analysis suggests that the pre-vaccination patterns of measles and mumps infection in the different countries were similar. In contrast, the epidemiology of rubella was highly variable between countries. This suggests that it may be acceptable to use parameter values estimated from other countries to model measles and mumps transmission, but that this approach to modelling rubella transmission requires more caution. Estimates of R_0 depend on underlying mixing assumptions. Constraints were placed on R_0 estimates by utilising knowledge of likely mixing patterns. The estimates for R_0 were highest for measles, intermediate for mumps, and generally lowest for rubella. Analysis of within- and between-age-group transmission rates suggested that mumps transmission tends to be more concentrated within young children than the other two viruses. The implications for the design of immunization programmes are that mumps may be the easiest to control via infant immunization since it is predominantly transmitted between the very young and the variability in rubella epidemiology requires that careful consideration of the possible effects of vaccination options should be made using local data when planning rubella immunization programmes.

INTRODUCTION

The European Region of the World Health Organisation (WHO) has a target for the elimination of indigenous measles by the year 2007 and the reduction in the incidence of mumps and congenital rubella syndrome (CRS) to negligible levels by the year 2010 [1]. Infant immunization with MMR (measles, mumps, rubella) vaccine will be the primary tool for the achievement of these aims across Europe.

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Large serological surveys of measles, mumps and rubella antibodies have recently been performed in eight different European countries as part of the European Sero-epidemiology Network (ESEN) [2, 3]. The results of these surveys have been used to investigate the current susceptibility of the different populations to the different infections. However, to ascertain whether the observed levels of immunity are sufficient to prevent endemic transmission of measles, mumps and rubella requires knowledge of age-specific transmission rates [4]. These key parameters can be

obtained from the pre-vaccination age-specific force of infection, which can be estimated from pre-vaccination seroprevalence or notification data [5]. They can be summarized by the basic reproduction number, R_0, (the average number of secondary infections generated by a primary case in a fully susceptible population). This gives a measure of the transmission potential of the infection in a given population, and thus, the ease with which the infection can be controlled.

Unfortunately, suitable pre-vaccination data for measles, mumps and rubella are scarce. To model infection in countries that do not have pre-vaccination data of their own (e.g. France) parameter estimates can be derived from available data from epidemiologically similar countries. To investigate the validity of adopting this approach within Europe we have collated the available data from the eight countries participating in ESEN. The data enable comparisons to be made between countries for a given infection, and between infections within a country.

The aims of the study are two-fold: first, to compare the pre-vaccination epidemiology of measles, mumps and rubella across Europe; second, to provide reasonable parameter values for use in dynamic mathematical models for countries in which adequate pre-vaccination data is lacking.

METHODS

Data sets

Two types of data from the pre-vaccination era can be used to make age-specific force of infection estimates: finely age-stratified seroprevalence profiles and age-specific case notifications. These data were collected from as many of the participating countries as possible. The sources are described in Tables 1 and 2. Note from Table 1 that a range of serological tests were used with differing cut-off values. In addition, only the East German study is based on a random sample of the population. Thus care needs to be exercised in comparing the results of the different studies.

Estimation of the inter-epidemic period

The inter-epidemic period was estimated through an analysis of the autocorrelation functions (ACFs) and spectral densities of the time series using SPSS for Windows Version 6. Where the data were not adequate to allow for this level of analysis (in general

where only annual data were available) the inter-epidemic period was estimated by simple inspection of the data.

Estimating and comparing the force of infection

The basic assumption on which the techniques below rely is that the data reflect the endemic equilibrium, that is, there are no long-term trends in the incidence of infection and no effects produced by short-term epidemic cycles [6]. Extra specific assumptions are required for each type of data.

Non-parametric technique for case notification data

Aggregating case notification data for several years reduces the impact of any epidemic cycles. Assuming that the proportion of infections which are clinically apparent and under-reporting of cases are both constant with respect to age; the population is constant with age; and that everyone in the population is infected once during their lifetime, the force of infection in each age class, λ_i, can be directly estimated using the following expression:

$$\lambda_i = -\frac{1}{\Delta a_i}\ln\left(\frac{\sum\limits_{i+1}^{N} C_i}{\sum\limits_{i}^{N} C_i}\right),$$

where C_i is the number of cases notified in age class i and Δa_i is the width of age class i. No estimate of the force of infection in the final (Nth) age class can be calculated.

Parametric technique for serological data

Analysis of serological data requires assumptions that the samples are representative of the population, namely that the test is 100% sensitive and specific in indicating a history of infection and that infection does not cause mortality. The non-parametric technique described above is inappropriate for serological data since random variation can result in the observed prevalence decreasing occasionally with increasing age, under which circumstances the estimated force of infection would be negative. To avoid this problem the force of infection can be assumed to have an underlying functional form that is constrained to be positive. Farrington suggested the following functional form for the force of infection at age a, $\lambda(a)$ [7]:

$$\lambda(a) = (\alpha . a - \gamma)\exp(-\beta . a) + \gamma,$$

in which all the parameters (α, β and γ) are non-

Table 1. *Pre-vaccination seroprevalence data from various European countries*

| Country | Year | Sample source | Sample size | Age range | Test and cut-off* | | | Reference |
					Measles	Mumps	Rubella	
Denmark	1983	Residual sera	2523	1–17 yr	ind ELISA	ind ELISA	ELISA 15 m IU/ml	[23]
East Germany	1990	Random	2097	0–60 yr	–	HI (ELISA on negatives)		[24]
Italy	1978/9	Residual sera	8338	0–13 yr	HI ≥ 1/8			[10]
Netherlands	1970s	Blood donors and paediatric samples	∼1800	All	–	PRT ≥ 1 au	–	[25]
Finland	1979	Sera sent for rubella test	10373	All	–	–	RH ≥ 5 mm	[16]
UK	1986/7	Residual sera	8179	All	–	RH ≥1/10th known pos.	RH 15 m IU/ml	[26]

* ELISA, Enzyme linked immunosorbant assay; ind ELISA, indirect ELISA; RH, Radial haemolysis; PRT, Plaque reduction test; Lat. agg., Latex agglutination test; IU, International Units; au, arbitrary units.

Table 2. *Pre-vaccination notification data from various European countries*

Country	Measles	Mumps	Rubella
East Germany	–	1968–72, 1983–89	1978–89
The Netherlands	–	–	1958–74
Italy	1964–78	1964–1981	1970–81*
UK	1956–65	–	–

* Italy introduced selected vaccination of schoolgirls in 1973, but the level of coverage appears to have been low [3].

negative. This function increases from zero, has one peak, and decreases exponentially to a constant value (γ) in older age groups. The corresponding function for the prevalence of past infection at age a can be obtained analytically and this was fitted to the antibody prevalence data using maximum likelihood methods to derive estimates of the parameters.

The average force of infection was then calculated for the following five age groups: 0–1 years, 2–4 years, 5–10 years, 11–17 years and 18–39 years. These age classes were chosen to reflect patterns of school and pre-school attendance. To account for maternally derived antibodies, assumed to protect infants for the first 6 months of life, the estimated average force of infection in the first age class (0–1 years) was multiplied by 4/3 (= the inverse of the ratio of 1·5/2, as the period of exposure is 1·5 years, not 2).

Comparing force of infection estimates

In order to compare different serological profiles we estimate approximate 95% confidence regions around the best-fit parameter estimates based on the likelihood profiles. Since there are three parameters (α, β and γ) the confidence region is three dimensional in parameter space. However, in all but one case the estimate of γ was not significantly different from zero, reducing the problem to two dimensions. In order to plot the 95% confidence region we utilize the asymptotic result that the distribution of the deviance is χ^2 distributed. The 5th percentile of the χ^2 distribution with 2 degrees of freedom is 5·99. Thus combinations of parameter values which gave a log-likelihood within 3 (5·99/2) of the maximum were within the 95% confidence region. If the confidence regions estimated from different data sets did not overlap, the two serological profiles (or less loosely the force of infection which generates them) were considered significantly different. Alternatively, the goodness of fit of models with common or distinct parameter values (describing the underlying force of infection in different areas) can be compared to each other using the likelihood ratio test, or the serological profiles can be compared directly using logistic regression.
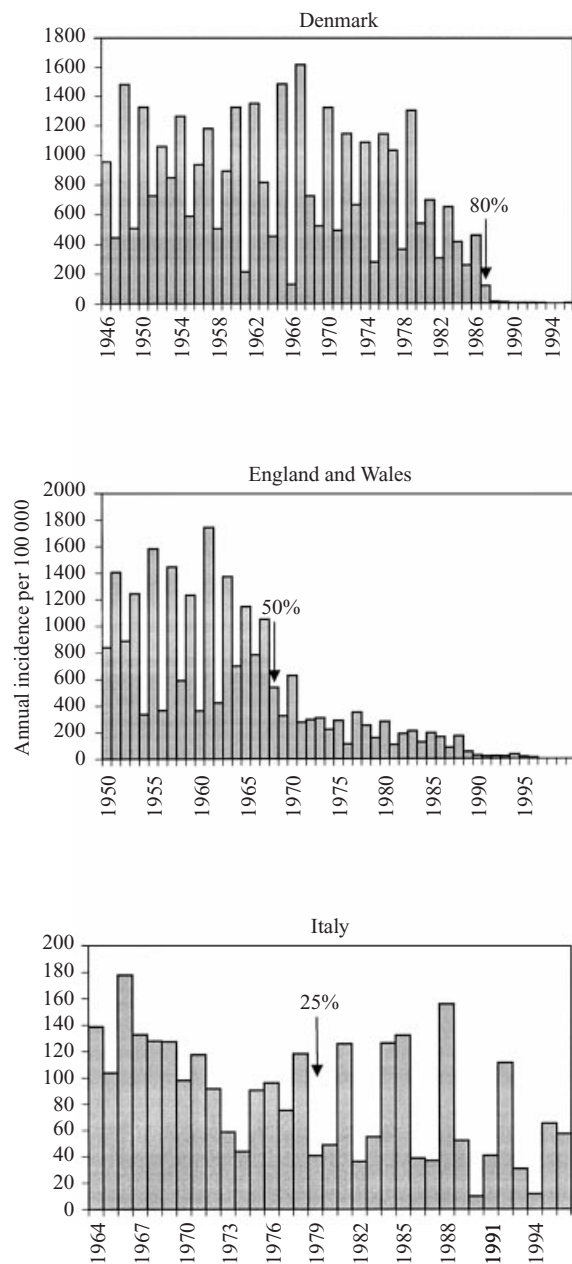
Fig. 1. Annual reported incidence of measles in Denmark, England and Wales and Italy. The year at which infant immunization was introduced and the approximate initial coverage is shown by arrows.

European parameters

To obtain values for the force of infection which broadly reflect patterns of infection in Europe and which could be used in countries without adequate data of their own, we chose values from the estimates made. In doing so we put more weight on force of infection estimates derived from serological profiles, except for those age groups in which the prevalence of antibody was virtually 100%.

Description of contact matrices

Following Anderson and May's methodology [5] we used a contact matrix to describe how individuals mix within and between the five age groups. We chose a common structure for this Who-Acquires-Infection-From-Whom (WAIFW) matrix for each of the infections in each of the countries. The elements of the matrix, β_{ij}, represent the rate at which individuals in age group i make effective contact with individuals in age group j. Three different structures were used, all of which were symmetric such that $\beta_{ij} = \beta_{ji}$ (so that the rate at which individuals in age group i make effective contact with individuals in age group j was the same as the rate at which individuals in age group j make effective contact with individuals in age group i).

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

The structure of the Default matrix was chosen to reflect the presumed importance of school contact for the transmission of these three viruses, thus the value of the coefficient β_3 is presumed to be large. Other features of this matrix are that infants (0–1 years) are assumed to come into contact with all other children at a given rate (β_1) and with adults at a different rate (β_5). Adults are assumed to mix with themselves and all other age groups at the same rate. Pre-school children (2–4 years) are assumed to mix with themselves at a unique rate (β_2). School and pre-school children (2–17 years) are assumed to mix with other children not in their own age class at a constant rate (β_4). By constraining the elements of the matrix to have the same number of unique values ($\beta_1 - \beta_5$) as the number of age groups (5), the β_is can be calculated from the age-dependent force of infection [5].

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

The diagonal matrix has five different diagonal elements and is assumed to reflect mixing patterns which are concentrated within age groups. Mixing between different age groups occurs at the same (background) rate as mixing between adults (β_5).
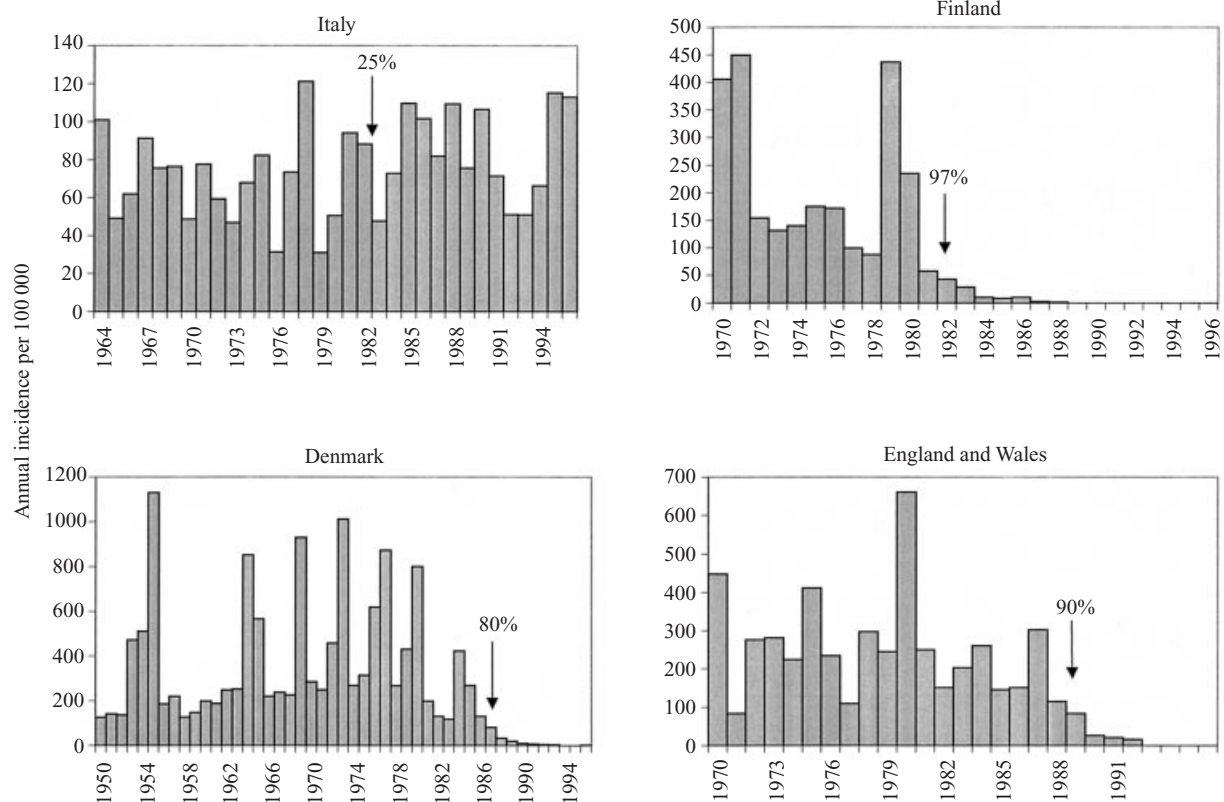
Fig. 2. Annual reported incidence of mumps in four Western European Countries. The year at which infant immunization was introduced and the approximate initial coverage is shown by arrows.

Proportionate mixing

The third configuration places no emphasis on the leading diagonal, but assumes proportionate mixing. Here, individuals are assumed to have an activity rate that is a function of their age. Individuals in age group i mix with individuals in age group j at a rate which is determined by the product of their respective activity rates ($\beta_i \beta_j$). The total number of contacts that individuals in age group i make with age group j will be determined by the size of the groups.

Estimation of R_0

The basic reproduction number, R_0, is the average number of secondary cases generated by a typical case in an entirely susceptible population. It therefore gives a measure of the potential for the infection to spread in the population. In an heterogeneous population, in which there are different mixing patterns between different sub-groups (= age groups) one can define R_{0ij} as the average number of secondary cases arising in age group i from a case in age group j, assuming that everyone in age group i is susceptible (this can be derived from the contact matrix and the proportion of

the population in each age class). This gives the so called 'next generation matrix'. The overall R_0 can be obtained by averaging over the entries of the next generation matrix where the single cases in each age class are weighted according to their contribution to the spread of the infection. The correct weights are given by the eigenvector belonging to the dominant eigenvalue of the next generation matrix [8].

The critical proportion, P_c, is the proportion of infants needed to be immunized at birth to eventually lead to interruption of endemic circulation of virus. Assuming Type I mortality (which approximates the demography of developed countries), this fraction can be derived from R_0 as follows [5]:

$$P_c = 1 - 1/R_0.$$

If vaccination occurs later in life, then the proportion required to be immunized to eliminate the infection will be higher.

RESULTS

Epidemic cycles

Prior to vaccination, statistically significant biennial cycles were observed in measles notifications in the
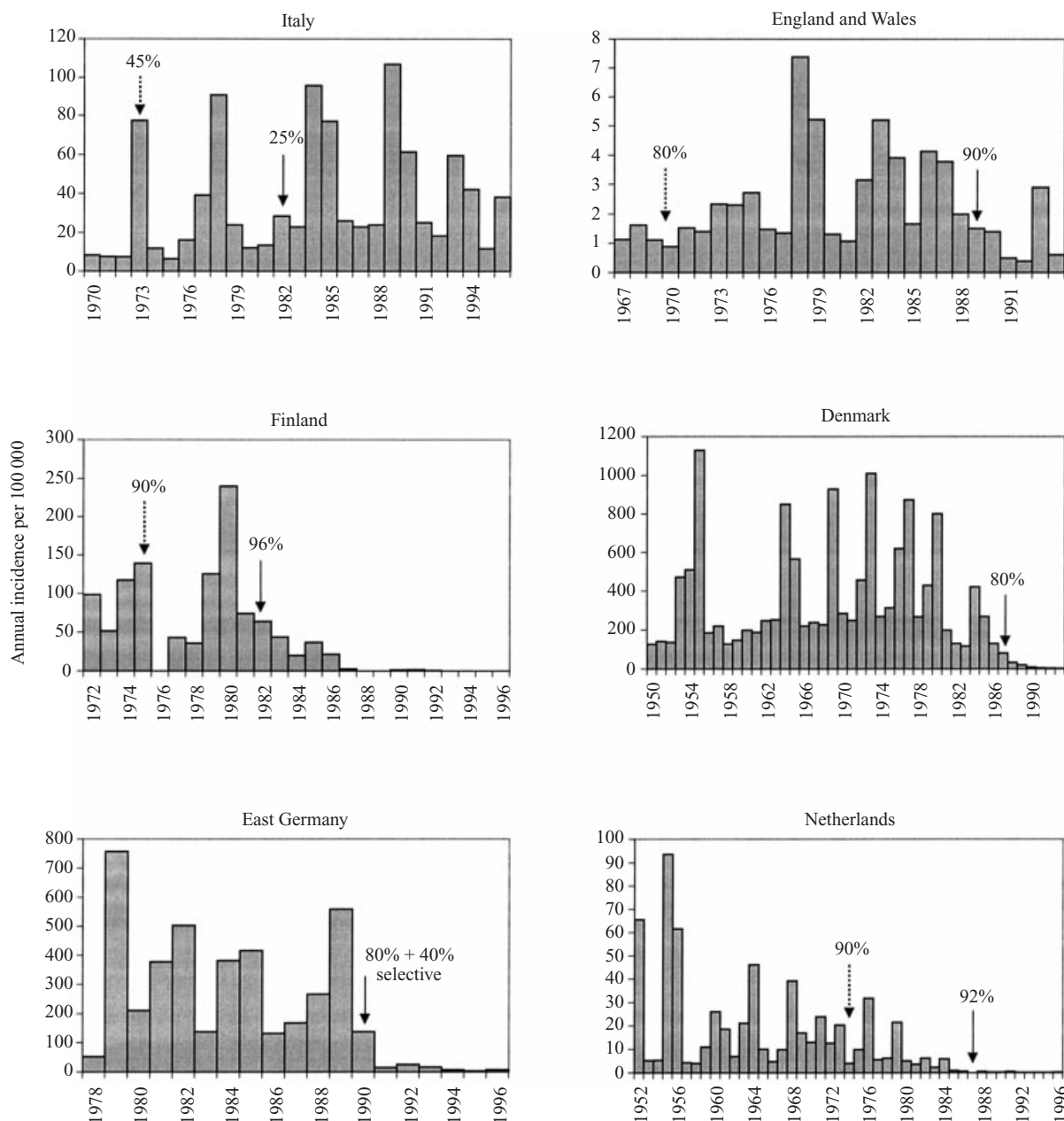
Fig. 3. Annual reported incidence of rubella in six Western European Countries. The year at which infant immunization was introduced and the approximate initial coverage is shown by solid arrows, and the corresponding years and coverage for selective rubella vaccination is shown by dotted arrows.

UK, and 2½ year cycles were apparent in Denmark. However, in Italy no clear epidemic pattern could be discerned (Fig. 1). Mumps, was characterized by 4–5 year epidemic cycles, although only the Danish (monthly) data had a statistically significant (4 year) ACF (Fig. 2). Rubella appeared to have more variable patterns, being typified by a 5-year period in Finland and Italy (the only ACF which was statistically significant), 4-year periods in Denmark and 3- to 4-year periods in East Germany and The Netherlands

Table 3. *Approximate inter-epidemic periods in years*

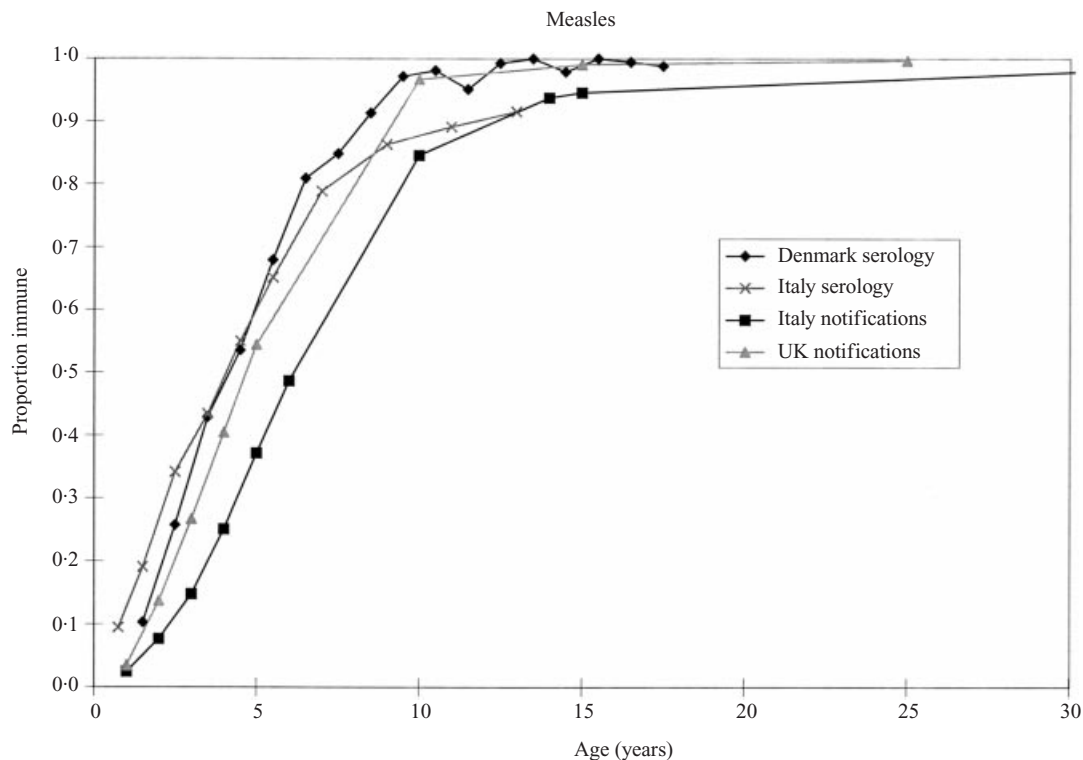|	Measles	Mumps	Rubella
England and Wales	2	5	
The Netherlands			3–4
Finland		4	5
Denmark	2	4	4
East Germany			3–4
Italy		3	5

Measles

Fig. 4. The proportion immune to measles by age, as estimated from case notification data from Italy and the United Kingdom and serological data from Denmark. See Tables 1 and 2 for sources of data.

(Fig. 3). The epidemiology of rubella in the United Kingdom before infant vaccination was introduced was dominated by annual cycles [9]. These patterns in inter-epidemic periods are summarized in Table 3.

Pre-vaccination age distribution of immunity and force of infection estimates

Figures 4–6 show the pre-vaccination cumulative age distribution of infection for measles, mumps and rubella, respectively, in the ESEN countries for which data were available. Since infection is short-lived and results in life-long protection this is also the age distribution of immunity.

The force of infection as measured by the non-parametric technique tends to rise rapidly during young childhood, peak and then decline into adulthood. This is similar to the parametric form that was chosen (Fig. 7), confirming that the functional form was appropriate. Comparing the magnitude of the force of infection estimates (Table 4a–c), it is clear that measles estimates are higher than mumps, which in turn are generally higher than rubella. Note that models predict that the inter-epidemic period is inversely related to the force of infection [5]. Thus one

would expect measles to have a shorter inter-epidemic period than mumps, and rubella to be more variable. These patterns were observed (Figs. 1–3).

Measles

Few data are available for measles, the only pre-vaccination serological profiles being from Denmark and Italy. These profiles are similar to the immunity profile generated from notifications in the United Kingdom (Fig. 4). By 10 years of age virtually everyone appears to have evidence of past measles infection; the slightly lower prevalence in children aged more than 6 years in Italy may be due to lower sensitivity of the assay. Notifications from Italy suggest a somewhat later acquisition of infection; only 37% of reported cases are aged less than 5 years compared with an observed prevalence of 60%. The original report of the Italian seroprevalence study [10] noted this discrepancy with the notification data, which may be due to the underreporting of measles cases being higher in pre-school children.

The force of infection estimates for Denmark and the United Kingdom are reasonably similar, particularly for the younger age groups (Table 4a), and
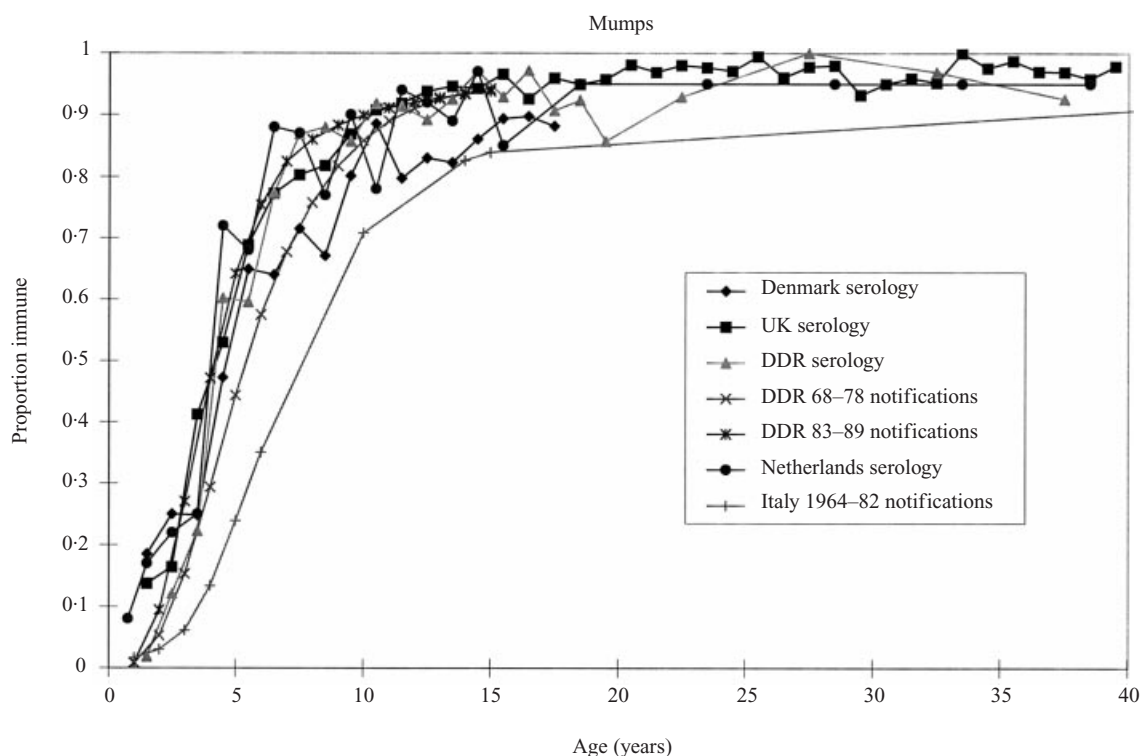
Fig. 5. The proportion immune to mumps by age in selected European countries, as estimated from case notifications (East Germany) and serological surveys (East Germany, Denmark, the Netherlands and the United Kingdom). See Tables 1 and 2 for sources of data. The exact sample sizes were not reported in the Dutch study (approximately 800 children and 1000 adults were reported as being tested). It was assumed that each 1-year-child age class had a sample size of 50 and each 5-year-adult-age-class had a sample size of 100.
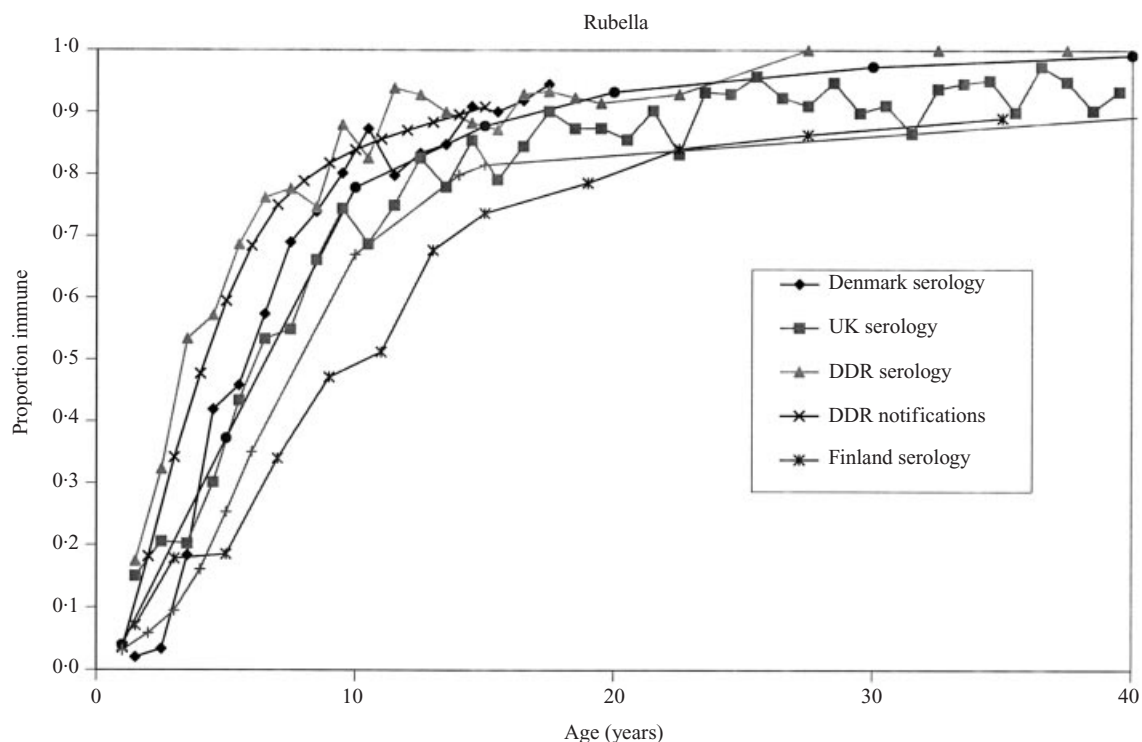

Fig. 6. The proportion immune to rubella by age as estimated from case notification data (The Netherlands and East Germany) and serological data (Finland, United Kingdom and Denmark). See Tables 1 and 2 for sources of data.

are consistent with previously published estimates. The force of infection derived from Italian serological data is similar below 5 years, but lower in 5–10 year olds. The faster decline in the force of infection in Italy caused the two seroprevalence profiles to be considered significantly different, although this may be due to a less sensitive assay in the Italian study.

The 'European' force of infection values for children up to 10 years were based on estimates from the seroprevalence study in Denmark. However, the force of infection estimates for older children from this study are imprecise, because only 15 sera from this age group were negative. It is unlikely that the force of infection in secondary school children is as high as in primary school children, as there are likely to be few infectious individuals in this age group. Hence for the older age groups, the 'European' force of infection estimates were based on United Kingdom values.

Mumps

With the possible exception of Italy, there appears to be a high degree of similarity in the pre-vaccination rates of childhood mumps infections across the European countries (Fig. 5), such that the percentage positive as derived from serological profiles from the United Kingdom and East Germany as well as the later series of case notifications from East Germany almost coincide. Serological results from Denmark suggest that the proportion of older children and adolescents with immunity is lower than in other countries, which may be due to some lack of sensitivity in the assay used. Comparing Figures 4 and 5 suggests that for both measles and mumps approximately 50% of children were infected before age 5 years, but that above this age the prevalence of past measles infection is greater than for mumps.

As expected, the similarity in the pre-vaccination pattern of infection (Fig. 5) is reflected in similar values for the force of infection (Table 4b). The parameters describing the force of infection derived from the Dutch, East German and United Kingdom serological profiles were not significantly different from each other, although the rate of decline in the force of infection (as described by β) is estimated to be higher in Denmark than the other countries (again, this may reflect a lack of test sensitivity). Estimates of the force of infection from Italian case notifications are lower than elsewhere. There is certainly significant under-reporting in the Italian system, but more

importantly it seems plausible that there is increased under-reporting in the younger age groups, as is observed for measles. Recent work has suggested that the current prevalence of past infection (in the presence of vaccination) is about 40% in 5-year-olds [11] whereas the pre-vaccination case notification data suggested that only 35% were infected before their sixth birthday.

The broad similarity in force of infection estimates for mumps suggests that it may be possible to find values for the force of infection which are applicable across a wide range of European countries (including those where no data are available). Values were chosen (Table 4b) based largely on the serologically derived estimates (the United Kingdom, Denmark and East Germany) although they are not inconsistent with estimates derived from East German case notifications, and estimates from other sources [12, 13].

Rubella

In contrast, there were consistent differences in the measured prevalence of rubella antibody in the different countries (Fig. 6). East Germany had the highest prevalence, followed by Denmark, which was somewhat higher than the United Kingdom. The lowest prevalence was observed in Finland. The differences are large. For example, at age 10 years the prevalence of rubella antibody in East Germany was almost 90%, compared with only 50% in Finland.

This leads to wide differences in the age-dependent force of rubella infection estimates (Table 4c). Although estimates display the typical age-dependent pattern (low, high, low) there is clearly far more variability in these estimates than was evident for the other two viruses (Table 4a, b). None of the confidence regions around the maximum likelihood estimates overlap, suggesting that these observed differences are not due to chance. Nevertheless, Table 4c provides 'European' estimates from those derived for the United Kingdom, as well as high and low estimates, from the serologically derived estimates from East Germany and Finland respectively.

Contact matrices and the basic reproduction number

Table 5 provides estimates for the basic reproduction ratio R_0 for each data set, derived using the default matrix and the force of infection values given in Table 4. As expected, R_0 estimates are higher for measles
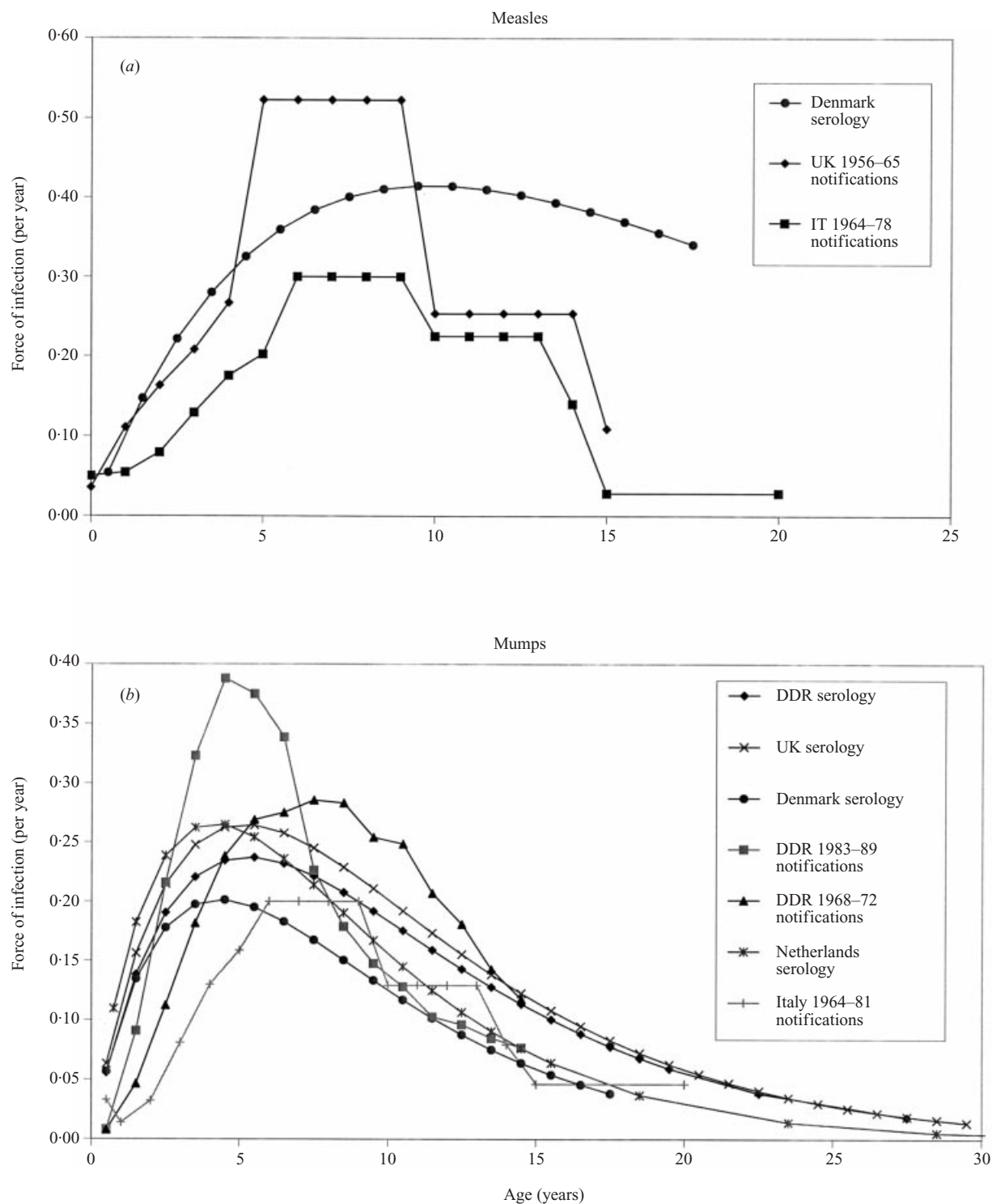
Measles

Mumps

Fig. 7. For legend see opposite.

than for mumps. Estimates for rubella vary considerably between countries.

The sensitivity of R_0 (and therefore P_c) to the mixing assumptions for the 'European' forces of infection is shown in Table 6. It is clear that the choice

of matrix structure can strongly influence the result. To explore this further, the R_{0ij} for each infection and matrix structure are shown in Figure 8; the height of the bars represents the expected number of secondary infections in a totally susceptible population. Note, in
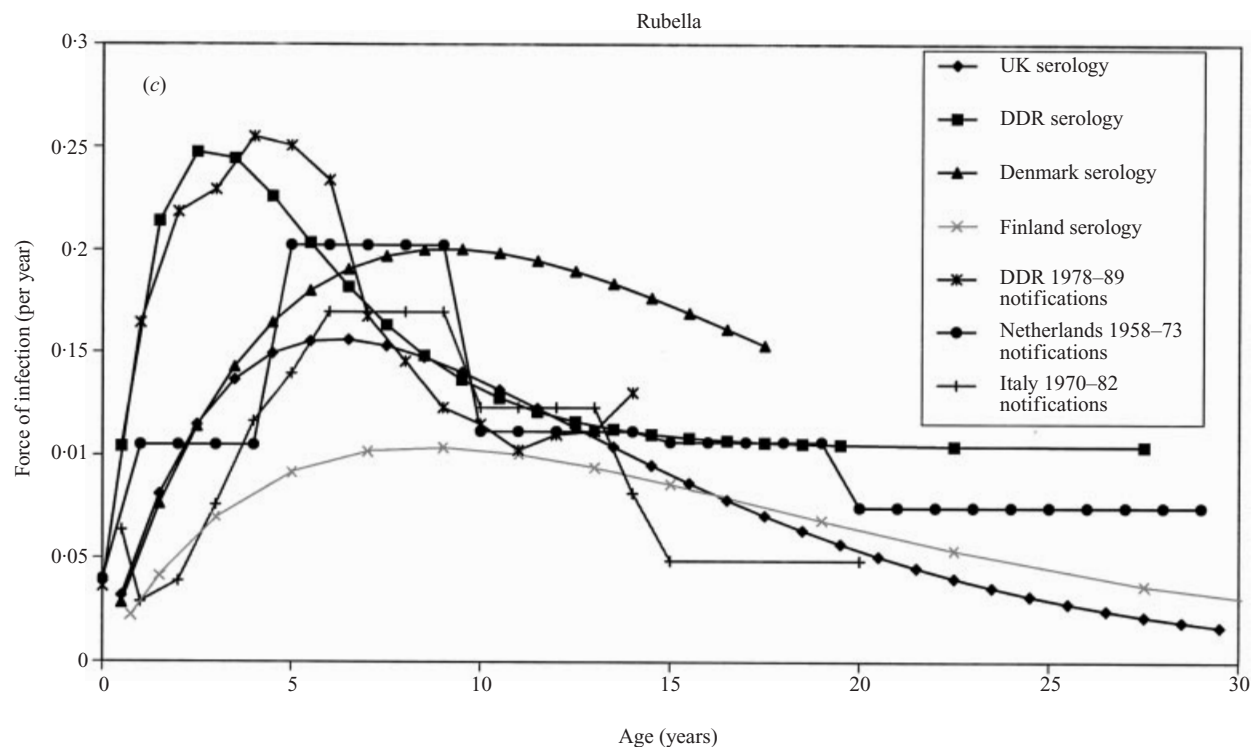
Fig. 7. Estimates of the pre-vaccination force of infection by age for (a) measles, (b) mumps and (c) rubella in different countries.

all cases, the relatively large number of secondary infections in adults. This is caused by the relative size of the adult age class (roughly 3/4 of the population are adults, whereas only about 1 in 40 of the population are in the first age class).

Clearly, the structure of the matrix has a large bearing on the estimated transmission potential of the viruses across age groups, i.e. the estimated values of R_{0ij}. For example, a case of measles aged 11–17 (in a wholly susceptible population) would be expected to cause an average of 1 case aged 11–17 if mixing is proportionate, 6 under the default configuration, and 29 if mixing is largely within group (diagonal matrix). The more contacts are assumed to be concentrated within age groups, the larger the diagonal elements, R_{0ii}, become. The overall R_0, which is a weighted average of all R_{0ij}s, is then further dominated by the terms describing within group transmission and increases likewise. Proportionate mixing does not put any emphasis on the leading diagonal, and hence R_0 estimates derived using this configuration are lower than those for the default and diagonal matrices. Empirical data show that there is a strong tendency to mixing within age groups [14], so the values of R_0 derived using proportionate mixing should be regarded as lower bounds on R_0 estimates. Similarly, R_0

estimates derived using the Diagonal matrix may represent the upper end of estimates for the three infections (see Table 6).

Comparing the estimated values of the R_{0ij} it is evident that measles and rubella have qualitatively similar patterns, whereas the pattern for mumps is somewhat different. In particular, there appears to be very little contact between children and adults that leads to transmission of mumps, regardless of what mixing structure is assumed. The pattern of rubella R_{0ij}s is roughly similar to that of measles, i.e. it appears to be scaled by some factor which is constant across all age groups. Taken together these results tentatively suggest that rubella and measles are spread via similar types of contact (though rubella is less infectious), whereas a different type of contact may be required to transmit mumps. An alternative explanation is that a lack of test sensitivity causes mumps serological profiles to flatten off in the older age groups, resulting in estimates of the adult force of infection which are too low. This would not, however, be expected to affect force of infection estimates derived from case notifications, which are also low in adults (Figs. 5 and 7) suggesting that mumps is poorly transmitted amongst adults or between children and adults.

Table 4. *Force of infection estimates (per year) for (a) measles, (b) mumps, (c) rubella*

		Age group (years)				
Country	Data type	0–1	2–4	5–10	11–17	18+
(a) Measles						
Denmark	Seroprevalence	0·13	0·28	0·40	0·38	
UK	Notifications	0·10	0·21	0·48	0·21	0·11
Italy	Seroprevalence	0·12	0·24	0·20		
Italy	Notifications	0·05	0·13	0·27	0·15	0·07
European		0·12	0·28	0·40	0·20	0·10
(b) Mumps						
Denmark	Seroprevalence	0·13	0·19	0·16	0·08	
UK	Seroprevalence	0·14	0·24	0·23	0·12	0·02
DDR	Seroprevalence	0·13	0·21	0·21	0·12	0·02
DDR 1968–72	Notifications	0·03	0·18	0·27	0·16	
DDR 1983–9	Notifications	0·05	0·31	0·23	0·09	
The Netherlands	Seroprevalence	0·17	0·25	0·20	0·08	0·01
Italy	Notifications	0·02	0·08	0·18	0·10	0·08
European		0·13	0·23	0·22	0·12	0·03
(c) Rubella						
Denmark	Seroprevalence	0·07	0·14	0·19	0·18	
UK	Seroprevalence	0·06	0·14	0·14	0·09	0·04
DDR	Seroprevalence	0·21	0·24	0·16	0·11	0·10
DDR	Notifications	0·13	0·23	0·17	0·11	
The Netherlands	Notifications	0·10	0·11	0·19	0·11	0·08
Italy	Notifications	0·05	0·08	0·16	0·09	0·05
Finland	Seroprevalence	0·04	0·08	0·10	0·09	0·04
High		0·21	0·24	0·16	0·11	0·10
European		0·06	0·14	0·14	0·09	0·04
Low		0·04	0·08	0·10	0·09	0·04

Table 5. R_0 *estimates for measles, mumps and rubella derived from force of infection estimates (Table 3) using the default matrix configuration*

	Measles	Mumps	Rubella
England and Wales	10·2	4·5	3·7
The Netherlands		4·3	6·4
Finland			3·4
Denmark*	9·7	3·6	4·2
East Germany†		4·0	7·8
Italy	6·1	4·2	4·2
European	9·6	4·4	3·7

* No estimate of the force of infection in adults was available so the 'European' value was used.
† Based on serological data not case notifications.

DISCUSSION

This study attempted to compare the epidemiology of measles, mumps and rubella in Europe before the onset of national immunization programmes, and to provide, where practical, parameter estimates for use in mathematical models of measles, mumps and rubella transmission, to assess the future impact of MMR vaccination in Europe.

Comparing the pre-vaccination epidemiology of measles, mumps and rubella

Our comparisons were based on analyses of two types of data: seroprevalence profiles; and reported incidence data. The limitations of these data sets for estimation of key epidemiological parameters, such as the force of infection, needs to be borne in mind. Force of infection estimates based on case reports are subject to a large number of potential sources of bias, the most serious being from mis- or under-reporting, especially selective under-reporting of cases by age group. Comparing force of infection estimates derived from serological data, relies on similar test characteristics and comparable (preferably random) sam-
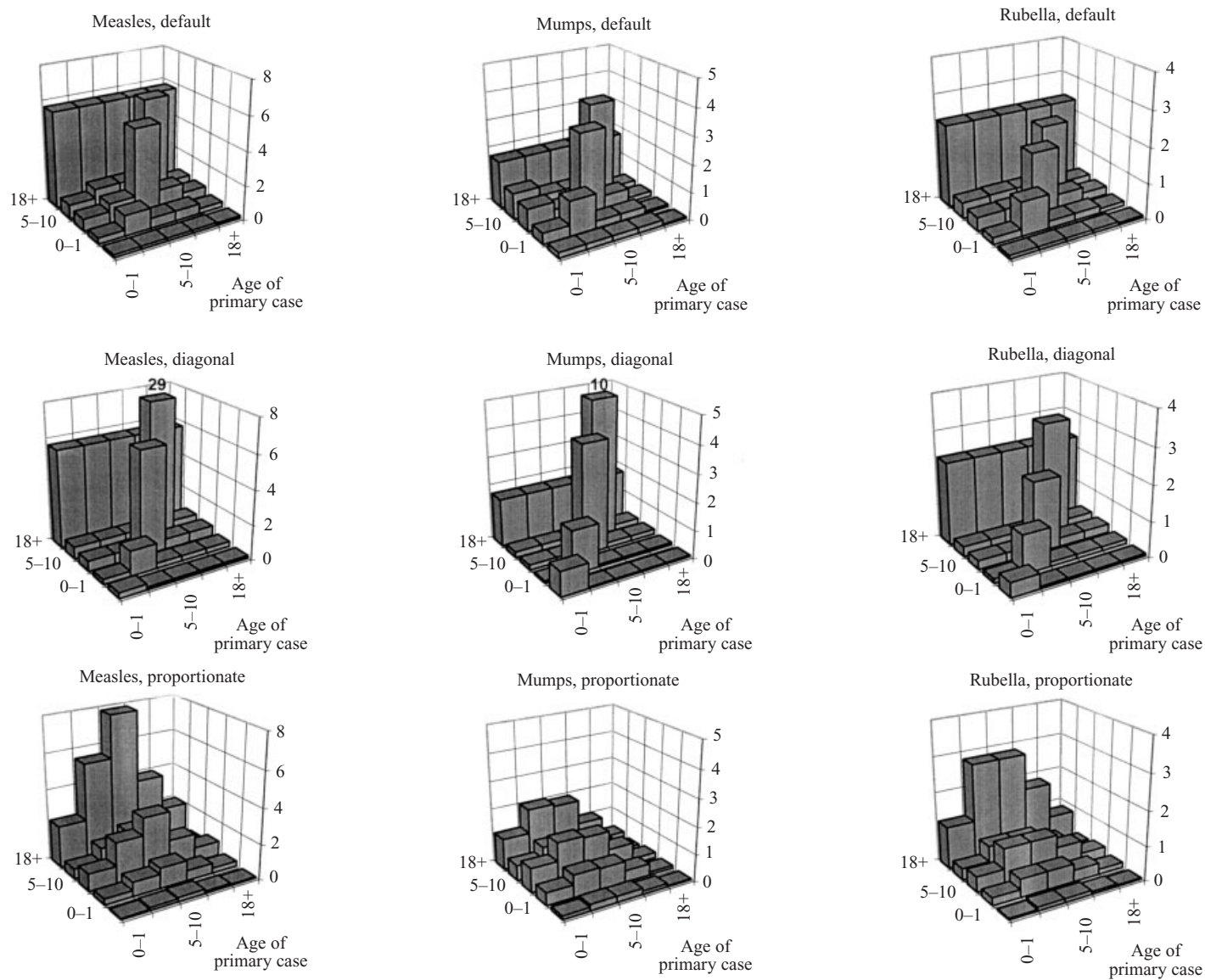
Fig. 8. Estimates of R_{0ij} for measles, mumps and rubella using the default and diagonal matrices and proportionate mixing. The height of the bars represent the R_{0ij} estimates (i.e. the average number of secondary cases generated by a primary case of age group i in age group j in a completely susceptible population). Age groups i (i.e. the age of the initial cases) are shown at the front of each figure, and age groups j (the age of the cases) shown going into the figure. Note the differences in the scales between measles, mumps and rubella. Note also that for measles and mumps with the diagonal matrix, the height of the bars is above the maximum value on the axis and is indicated numerically.

Table 6. R_0 *and* P_c *estimates for measles, mumps and rubella using* *'European' parameter values and three WAIFW matrix structures*

Matrix		Measles	Mumps	Rubella (high)	Rubella	Rubella (low)
Proportionate	R_0	7·1	3·3	5·3	2·9	3·0
	P_c	86%	70%	81%	66%	67%
Default	R_0	9·6	4·4	7·8	3·7	3·4
	P_c	90%	77%	87%	73%	71%
Diagonal	R_0	29·3	10·3	7·8	4·0	3·5
	P_c	97%	90%	87%	75%	71%

pling. It seems unlikely that these prerequisites were met in the original studies making comparison of the epidemiology of the three infections more difficult. For instance, the Finnish serological profiles for rubella are based on samples sent specifically for rubella testing (perhaps because they were thought to be negative). This might well bias the estimated proportion seropositive downwards, hence the conclusion that Finland had a lower force of rubella infection than elsewhere in Europe should be treated with some caution.

Comparison of viruses

Previous estimates of the force of infection and the basic reproduction number for measles have consistently demonstrated that measles is more transmissible than mumps and rubella, an observation we confirm. However, our estimates of the basic reproduction number are lower than many of those previously published. These estimates are sensitive to the underlying mixing assumptions (Table 6) and we attempt to place realistic constraints on estimated values for R_0, based on likely constraints on mixing patterns. Unfortunately, this leaves rather wide ranges of values for measles and mumps estimates (Table 6).

Comparison between countries

One of the most striking findings was that the pre-vaccination patterns of mumps and measles infection appeared to be consistent across countries, whereas large differences were observed in rubella epidemiology. The internal consistency of the rubella force of infection estimates suggest that the observed differences between countries may be real. For instance similar rates of infection in East Germany were

estimated from case-notifications and serological data (Fig. 6 and Table 4c); force of infection estimates from the United Kingdom are similar to previously reported serology-based estimates [15]; and the Finnish serological profiles from the era before infant immunization are similar from year to year [16] (although they may all be similarly biased – see above). Furthermore, other studies have shown wide differences in the epidemiology of rubella both within Europe [17] and elsewhere [18].

It seems therefore that the epidemiology of rubella is more sensitive to differences in mixing patterns than mumps and measles. Exactly what these social/ cultural differences may be is impossible to say given the paucity of our knowledge on mixing patterns for these close-contact infections.

The variability in rubella epidemiology has important implications for the design of immunization programmes. The incidence of CRS depends on the proportion of pregnant women who are susceptible to infection and on the force of infection. Before vaccination, the incidence of CRS is likely to be have been higher in low transmission areas (such as Italy and Finland) because the larger fraction of susceptible women outweighed the lower force of infection. The risk of infant vaccination increasing incidence of CRS is greater in high transmission areas (such as East Germany) if inadequate vaccination coverage is achieved (see [19] for further details).

The epidemiology of mumps, on the other hand, appears to be similar across the countries studied (with the possible exception of Italy). Force of infection estimates were in agreement with other studies [12, 13]; the force of infection increased rapidly over the first few years of life and peaked comparatively early (at about 5–7 years of age). This caused the pattern of R_{0ij} estimates (a measure of the transmission potential in and between age groups) to

be different from that for rubella and measles; the highest values occur within and between young children rather than within older age groups (although a lack of test sensitivity in adults may have contributed to this apparent pattern). These results suggest that the kind of contact required to transmit mumps may be different to the other two viruses, that these effective contact events are more likely to occur between young children (up to 10 years of age) and that the relevant contact patterns in these age groups were similar enough, across Europe, to result in very similar patterns of mumps infection.

Fewer pre-vaccination serological or case notification data are available for measles. Nevertheless estimates of the force of infection from United Kingdom case notifications and Danish and Italian serological data are in close agreement over the first age groups. It is tempting to dismiss force of infection estimates from Italian case notification data as the serological data are likely to be more robust. The European values provided here are similar to those reported previously, for example by Anderson and May [20] who present estimates derived from 13 different data sets (mainly case notifications from North America and the United Kingdom).

Estimating parameter values

Most previous parameter estimates for use in this class of model have been derived from data from a limited number of countries (the United Kingdom in particular). If these mathematical models are to be used to predict the numbers of cases of measles, mumps and rubella, in other countries, then parameters must be estimated from data for these countries, or estimates from similar areas must be adopted.

Is it valid to use parameter values from other European countries? The similarity in measles and mumps epidemiology described here suggests that this would be acceptable for these infections. This study has shown, however, that the pre-vaccination rates of rubella infection differed significantly. Thus it would be dangerous to assume a level of rubella transmission for use in a mathematical model without any other supporting data.

The second issue of validity is the use of historical data to estimate key epidemiological parameters. Epidemiological data from the pre-vaccination era are utilized to estimate the underlying mixing rates (having assumed a contact structure) which are used to model contemporary and future patterns of infection. The implicit assumption is that mixing patterns have, and will continue to, remain unchanged; which is unlikely. Furthermore, accurate force of infection estimates are difficult from adult age classes as in the pre-vaccination era so few adults remained susceptible. However, since mass infant vaccination has lead to an increase in the average age at infection for these viruses [16, 21, 22], then accurate estimates of adult mixing patterns become relatively more important. Additionally, estimates of key epidemiological parameters such as R_0 and P_c depend on mixing patterns. As these had to be assumed (rather than based on firm empirical evidence), there is a degree of arbitrariness in the resulting estimates (see Table 6). We have attempted to provide some sensible constraints on our estimates, based on what little is known of relevant mixing patterns, but if these key epidemiological variables are to have much practical use then the underlying mixing patterns need to be elucidated. Estimates from pre-vaccination data can be refined through an evaluation of the epidemiology in the post vaccination era [9, 19] or through direct approaches. Recent advances in which individuals are asked to self-report the occurrence of presumed risk events, such as conversations, offer a promising alternative for measuring contemporary mixing patterns [14].

This paper has drawn together pre-vaccination data on measles, mumps and rubella infection from a large number of sources and used consistent methodologies to determine key epidemiological variables, such as the basic reproduction number and force of infection. This has allowed a comparison of the epidemiology of three viruses in Europe. In addition, parameter estimates are derived for use in dynamic mathematical models of measles, mumps and rubella transmission, and the feasibility of using estimates from different countries (where suitable data are lacking) is discussed. The use of these transmission dynamic models will allow an assessment of the likely future burden of disease associated with measles, mumps and rubella in Europe.

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