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Estimation of measles reproduction ratios and prospects for elimination of measles by vaccination in some Western European countries

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SUMMARY

The objective of this study is to estimate the measles reproduction ratio for eight Western European vaccination programmes. Because many plausible age-structured transmission patterns result in a similar description of the observations, it is not possible to estimate a unique value of the reproduction ratio. A method is developed to estimate bounds and confidence intervals for plausible values of the reproduction ratios using maximum likelihood methods. Lower and upper bounds for plausible values of the basic reproduction ratio are estimated to be 7·17 (95% CI 7·14–7·20) and 45·41 (95% CI 9·77–49·57), corresponding to lower and upper bounds on critical vaccine coverage of 86·6% and 98·1%. Of the eight evaluated vaccination programmes, four have vaccine coverage below the lower bound and allow measles to persist, and four have vaccine coverage at the upper bound and may eventually eliminate measles.

INTRODUCTION

Measles is a highly infectious viral disease that eventually infects almost every individual in an unvaccinated population [1]. In industrialized countries up to 10% of measles cases are associated with complications, the most common being otitis media, pneumonia, encephalitis, and mortality [2]. Since the measles virus relies entirely on man as a host, it is possible, at least in principle, to eradicate globally the measles virus by vaccination of man. Three regions of the World Health Organization (WHO) have already targeted elimination, and one of them is the European region. A variety of vaccination strategies are being used throughout Europe in an attempt to interrupt transmission of the measles virus. In order to co-ordinate and standardize the serological surveillance of immunity to several vaccine preventable diseases, including measles, the European Sero-Epidemiology Network (ESEN) was established. The participating countries are, in order of increasing level of reported incidence of measles, Finland, Sweden, the Netherlands, England and Wales, Denmark, France, Germany, and Italy [3, 4].

The level of immunity required to eliminate a disease can be elucidated using the net reproduction

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ratio, which is defined as the expected number of secondary cases produced by one primary case in a population with known levels of immunity [5, 6]. In this paper we focus on a net reproduction ratio that is obtained if the levels of immunity are projected from continued application of the ongoing vaccination programme, in absence of natural infection, henceforth indicated as 'projected reproduction ratio'. The projected reproduction ratio quantifies the level of herd immunity attained by a vaccination programme, and is a measure of the capability of the vaccination programme to eliminate the measles virus.

Estimation of reproduction ratios from available pre-vaccination case-notifications has usually relied on the assumption that transmission of measles is not structured by age [7]. However, several studies have shown that the age structure of the population must be taken into account if the age-specific level of susceptibility is to be described accurately [8, 9]. A major problem is that a given data set may be fitted equally well by different sets of age-specific transmission rates such that a reproduction ratio cannot be predicted uniquely [10, 11]. The problem can be circumvented by calculating the lower and upper bounds for reproduction ratios without making strong assumptions about the age-specific transmission structure [12, 13]. It is of practical interest to have such bounds on the projected reproduction ratio for a given vaccination programme, as an upper bound that is less than one implies that the disease will be eliminated by that vaccination programme, and a lower bound which exceeds unity implies that the given vaccination programme allows for the persistence of measles.

In this paper we are interested in the capability of measles vaccination programmes in various Western European countries to eliminate the measles virus. How confident can we be in stating that the vaccination programmes will eliminate the measles virus or that they allow persistence of measles? The objective is to assess the bounds on projected reproduction ratios for various vaccination programmes in Western Europe, accounting for the age-structured transmission. With the estimated bounds on projected reproduction ratios it is possible to distinguish between vaccination programmes that possibly eliminate measles and those that allow measles to persist. We developed a new method for estimating the reproduction ratios directly from case-notification data and serological data, using maximum likelihood techniques. The strength of this method, as compared to previous approaches, is that it becomes possible to quantify the accuracy of the resulting estimates.

METHODS

The estimation procedure for the measles reproduction ratios is explicated in six sections. Central to our exposition in all sections is the concept of the next generation matrix, which is used to describe the contact patterns in a population. First, we introduce the next generation matrix and some assumptions that will be used throughout this paper. Then we describe how for a given vaccination strategy the reproduction ratios are calculated from the next generation matrix, and how different structures of the next generation matrix can be used to estimate bounds on the reproduction ratios. We show how an age-specific susceptibility profile is derived from a next generation matrix, and how this age-specific susceptibility profile is fitted to pre-vaccination data by using maximum likelihood techniques. Finally we describe how the confidence intervals around the estimated measles reproduction ratios are constructed.

The basic assumptions and the next generation matrix

Basic assumptions

The basic assumptions that we use throughout the paper are as follows. Individuals in the population are distinguished according to their age. It is assumed that all infants are protected from measles infection by maternally derived antibodies for the first half year after birth, after which they become susceptible. A susceptible individual can become infected with the measles virus. After passing through a latent, non-infectious phase of 7 days, the infected individual becomes infectious. The duration of the infectious period is on average 7 days. Upon recovery from infection, an individual becomes immune for the rest of its life. It is assumed that everybody survives up to the life expectancy at birth, and measles-related mortality is ignored. With regard to social behaviour, five different age classes are distinguished: infants of 0–1 years; young children of 2–4 years; primary schoolers of 5–10 years; secondary schoolers of 11–17 years; and adults of 18–75 years. We will assume that persons within the same age-class mix according to the 'true' mass action principle [14], which means that the number of potential infectious contacts per

infectious individual does not depend on the population size.

The next generation matrix

The transmission of measles within a population is determined by the patterns of mixing between and within different age classes. The pattern of mixing is represented by the so-called next generation matrix **K** [15]. This matrix has elements k_{ij} in the ith row and the jth column. These elements represent the expected number of persons in the ith age class that are infected by an infectious person in the jth age class upon introduction into an entirely susceptible population. The next generation matrix **K** is of utmost interest because it contains the information on the mixing pattern that is required for calculation of reproduction ratios.

Reproduction ratios and vaccination strategies

Vaccine programmes: structure, coverage and observed age-specific susceptibility profiles

All eight countries participating in the European Sero-Epidemiology Network (ESEN) supplied data on measles vaccine programme organisation, historical vaccine coverage and age-specific incidence of measles [3]. The average age at vaccination was used whenever the age at vaccination was given as a range. Official statistics on vaccine coverage for Germany were not available at the country level, instead the level of MMR vaccine coverage at age of 3 years in Germany was estimated from serological data collected in 1996 (N.J. Gay, unpublished observations).

Sera were collected during the period 1995–8 in seven Western European countries that participated in the European Sero-Epidemiology Network (ESEN). To achieve quantitative comparability of assay results between countries, the results of measles antibody testing were standardized [4, 16].

Calculation of the basic reproduction ratio

The basic reproduction ratio, often denoted as R_0, is defined as the expected number of secondary cases after introduction of a typical infectious individual in an entirely susceptible population. Thus, the basic reproduction ratio measures the intrinsic capacity of measles to cause outbreaks in the population. If the basic reproduction ratio is smaller than one, the infection cannot persist in the population, and if it is larger than one, the infection can invade the population and is capable of producing a large outbreak. Mathematically, the basic reproduction ratio is defined as the largest eigenvalue of the next generation matrix **K** [15]. Denoting the largest eigenvalue of a matrix **A** by $r(\mathbf{A})$, the basic reproduction ratio can thus be written as

$$R_0 = r(\mathbf{K}) \tag{1}$$

Calculation of the projected reproduction ratio

The projected reproduction ratio is defined as the expected number of secondary cases after introduction of a typical infectious individual in a population with an age-specific susceptibility that results from the continuation of the ongoing vaccination programme in absence of natural infection. The projected reproduction ratio measures the intrinsic capacity of the vaccination programme to eliminate measles. If the projected reproduction ratio is smaller than one, the vaccination programme is able to eliminate measles, and if it is larger than one, measles may persist in spite of the vaccination programme [6].

We estimate the projected proportion of susceptibles in each age class if the ongoing vaccination programme will be continued forever. We assume that only those children that accepted vaccination at the first age would also accept the vaccinations offered at the second vaccination age, so for a two-dose vaccination schedule children are either vaccinated twice or not at all. Furthermore, it is assumed that vaccination offers life long immunity. The duration of protection by maternal antibodies is estimated to be 0·5 years, the life expectancy at birth is estimated to be 75 years. We can then infer the probability $\tilde{\sigma}(\alpha)$ for an individual of age α to be susceptible:

$$\tilde{\sigma}(\alpha) = \begin{cases} 0 & 0 \leqslant \alpha < 0{\cdot}5 \\ 1 & 0{\cdot}5 \leqslant \alpha < v_1 \\ 1-wu & v_1 \leqslant \alpha < v_2 \\ 1-wu(2-w) & v_2 \leqslant \alpha \leqslant 75 \end{cases}$$

where u is the proportion of each age cohort that accepts vaccine, w is the proportion of susceptible children that seroconverts when offered vaccine, and v_1 and v_2 are the ages at which vaccine is offered. These parameters are derived from reports on vaccination programmes [3]. Throughout this paper, the vaccine efficacy is estimated to be 95%, that is, $w = 0{\cdot}95$. Now we can determine the proportion of

projected susceptibles per age class, $\tilde{s}_i$, by averaging the probability $\tilde{\sigma}(\alpha)$ within each age class. We denote the vector containing the projected proportion of susceptibles per age class by $\tilde{\mathbf{s}}$. The value of the projected reproduction ratio is

$$R_p = r(diag(\tilde{\mathbf{s}}) \cdot \mathbf{K}) \quad (2)$$

where $r(.)$ denotes again the largest eigenvalue, $diag(\tilde{\mathbf{s}})$ denotes the matrix with values of $\tilde{\mathbf{s}}$ on the diagonal, and $\mathbf{K}$ denotes again the next generation matrix. Essentially the same procedure can be used to estimate the lowest vaccination coverage for the vaccination schedule that will eliminate measles, we then calculate the vaccine uptake, u, that makes the projected reproduction ratio R_p equal to one for the given next generation matrix. This lowest vaccine coverage that results in elimination will be referred to as the critical vaccination coverage.

Calculation of the effective reproduction ratio

We also calculate a third reproduction ratio, termed the effective reproduction ratio. The effective reproduction ratio measures the actual rate of increase of measles infections per generation of infection. We denote the vector containing the actual, observed proportion of susceptibles per age class by $\hat{\mathbf{s}}$. These proportions of susceptibles are estimated from serological cross-sectional surveys [4, 16]. The value of the projected reproduction ratio is then calculated as

$$R_e = r(diag(\hat{\mathbf{s}}) \cdot \mathbf{K}) \quad (3)$$

where $r(.)$ denotes again the largest eigenvalue, $diag(\hat{\mathbf{s}})$ denotes the matrix with values of $\hat{\mathbf{s}}$ on the diagonal, and $\mathbf{K}$ denotes again the next generation matrix. If measles is endemic in the population, each measles case produces on average one other case, and therefore the effective reproduction ratio should be close to one [5]. Thus the effective reproduction ratio allows exploration of the match between the next generation matrix, the observed age-specific susceptibility, and the observed presence of measles.

Next generation matrices that represent bounds on reproduction ratios

Relation between next generation matrices and transmission matrices

Each element of the next generation matrix $\mathbf{K}$ can be decomposed as

$$k_{ij} = q n_i m_{ij} \quad (4)$$

where q is the average duration of infectious period of measles, n_i is the fraction population in the ith age class, and m_{ij} is the transmission rate between age classes i and j. There is no straightforward epidemiological interpretation of the transmission rate m_{ij}, but the interpretation of $n_i m_{ij}$ is relatively simple: this is the number of potentially infectious contacts per unit of time that an infectious individual in age class i has with individuals in age class j. The transmission matrix $\mathbf{M}$ contains the values of the transmission rates m_{ij} between age classes i and j. The variables q and n_i are known but the transmission rates m_{ij} are not known. Therefore, the transmission matrix $\mathbf{M}$ constitutes the most uncertain component of the next generation matrix $\mathbf{K}$. We use a number of different transmission matrices $\mathbf{M}$ and their corresponding next generation matrices $\mathbf{K}$ to calculate the bounds on the reproduction ratios.

Feasible values for the basic reproduction ratio

We are interested in all feasible values of the basic reproduction ratio. The only two conditions we impose on the next generation matrix are that it must describe the observations well, and that its elements are not negative. Greenhalgh and Dietz [12] showed that the lower bound for feasible values of the basic reproduction ratio is obtained by a transmission matrix that assumes the infants are the source for all infections. This matrix will be termed 'infant mixing matrix' $\mathbf{M}_{\mathrm{I}}$. Greenhalgh and Dietz [12] also showed that the upper bound for feasible values of the basic reproduction ratio is obtained by a transmission matrix that assumes that all infectious contacts occur within age classes. This matrix will be indicated as 'assortative mixing matrix' $\mathbf{M}_{\mathrm{A}}$. Both matrices are determined completely by five positive values for transmission rates $c_1, c_2, \ldots, c_5$. The matrices are:

$$\mathbf{M}_{\mathrm{I}} = \begin{pmatrix} c_1 & 0 & 0 & 0 & 0 \\ c_2 & 0 & 0 & 0 & 0 \\ c_3 & 0 & 0 & 0 & 0 \\ c_4 & 0 & 0 & 0 & 0 \\ c_5 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{M}_{\mathrm{A}} = \begin{pmatrix} c_1 & 0 & 0 & 0 & 0 \\ 0 & c_2 & 0 & 0 & 0 \\ 0 & 0 & c_3 & 0 & 0 \\ 0 & 0 & 0 & c_4 & 0 \\ 0 & 0 & 0 & 0 & c_5 \end{pmatrix}.$$

Plausible values for the reproduction ratios

We are also interested in the plausible values of the reproduction ratio. For this purpose we follow a more heuristic line of thought, very similar to the one used by Edmunds et al. [13]. We impose more constraints on the structure of the transmission matrix. Apart

from the condition that the matrix must describe observations well, it is supposed that the transmission rates within and between age classes should be larger than zero, and transmission rates never reflect an aversion to contact others in the same age class. The lower bound for plausible values of reproduction ratios is then obtained by a transmission matrix that allows for a difference in activity between age classes, but not for a difference in preference for contacting individuals from any particular age class. This matrix will be termed 'proportional mixing matrix' $\mathbf{M}_P$ [17]. The upper bound for plausible values of reproduction ratios is obtained by a transmission matrix that allows for contact between all age classes, but that enforces preference for contacting individuals of the own age class. This mixing matrix will be termed 'semi-assortative mixing matrix' $\mathbf{M}_S$. Again, both matrices are determined completely by 5 positive values for transmission rates $c_1, c_2, \ldots, c_5$. These matrices are:

$$\mathbf{M}_P = \begin{pmatrix} c_1 & \sqrt{c_1c_2} & \sqrt{c_1c_3} & \sqrt{c_1c_4} & \sqrt{c_1c_5} \\ \sqrt{c_2c_1} & c_2 & \sqrt{c_2c_3} & \sqrt{c_2c_4} & \sqrt{c_2c_5} \\ \sqrt{c_3c_1} & \sqrt{c_3c_2} & c_3 & \sqrt{c_3c_4} & \sqrt{c_3c_5} \\ \sqrt{c_4c_1} & \sqrt{c_4c_2} & \sqrt{c_4c_3} & c_4 & \sqrt{c_4c_5} \\ \sqrt{c_5c_1} & \sqrt{c_5c_2} & \sqrt{c_5c_3} & \sqrt{c_5c_4} & c_5 \end{pmatrix},$$

$$\mathbf{M}_S = \begin{pmatrix} c_1+c_5 & c_5 & c_5 & c_5 & c_5 \\ c_5 & c_2+c_5 & c_5 & c_5 & c_5 \\ c_5 & c_5 & c_3+c_4+c_5 & c_5 & c_5 \\ c_5 & c_5 & c_5 & c_3+c_4+c_5 & c_5 \\ c_5 & c_5 & c_5 & c_5 & c_4+c_5 \end{pmatrix}.$$

For the proportional mixing matrix $\mathbf{M}_P$ all transmission rates are equal when $c_1 = c_2 = c_3 = c_4 = c_5$, and for $\mathbf{M}_S$ all transmission rates are equal when c_1, c_2, c_3, c_4 approach zero. The matrix where all transmission rates are equal will be referred to as the 'homogeneous mixing matrix'

$$\mathbf{M}_H = \begin{pmatrix} c & c & c & c & c \\ c & c & c & c & c \\ c & c & c & c & c \\ c & c & c & c & c \\ c & c & c & c & c \end{pmatrix}.$$

Henceforth we will denote the results obtained with a next generation matrix based on the homogeneous mixing matrix $\mathbf{M}_H$ as 'results for model H', and results obtained with the next generation matrix based on the proportionate mixing matrix $\mathbf{M}_P$ as 'results for model P', and so on.

Deriving a susceptibility profile from a next generation matrix

In this section we show how the next generation matrix $\mathbf{K}$ determines the age-specific susceptibility profile in an endemic steady state without vaccination. The calculation of this endemic steady state follows the same arguments as presented in, for instance, the work of Anderson and May [18] and Diekmann and Heesterbeek [19]. Here, we briefly summarize the results while using our terminology.

This susceptibility profile is calculated for a specified next generation matrix $\mathbf{K}_x$, which is determined by the transmission matrix $\mathbf{M}_x$ and transmission rates $c_1, c_2, \ldots, c_5$. The probability of an individual being susceptible in an endemic steady state, without vaccination, at age α will be denoted by $\sigma(\alpha, \mathbf{K}_x)$. This probability of being susceptible will be zero for infants during the first half year of their lives when they are protected by maternal antibodies. After release of this protection they become susceptible. The probability of being susceptible will decline exponentially with age within each age class. The rate of decline for age class i will be denoted by λ_i, and this is the so-called force of infection or hazard rate of infection. The actual value of the force of infection λ_i depends on the next generation matrix $\mathbf{K}_x$ and the average fraction of susceptibles in each age class. Thus the susceptibility profile depends on the force of infection, and the force of infection depends on the susceptibility profile and the next generation matrix. The susceptibility profile and force of infection are given by the following equations:

$$\sigma(\alpha, \mathbf{K}_x) = \begin{cases} 0 & a_0 < \alpha \leqslant \mu \\ \exp[-\lambda_1(\alpha-\mu)] & \mu < \alpha \leqslant a_1 \\ \sigma(a_i, \mathbf{K}_x)\exp[-\lambda_i(\alpha-a_i)] & a_i < \alpha \leqslant a_{i+1} \end{cases} \quad (5)$$

with

$$\lambda_i = \frac{1}{a_i - a_{i-1}} \left\{ k_{x,i1}(\sigma(\mu, \mathbf{K}_x) - \sigma(a_1, \mathbf{K}_x)) + \sum_{j=2}^{j=5} k_{x,ij}(\sigma(a_{j-1}, \mathbf{K}_x) - \sigma(a_j, \mathbf{K}_x)) \right\}$$

where α is age, λ_i is the force of infection in age class i, μ is the duration of protection by maternal antibodies (here, this duration is 0·5 year), $a_0, a_1, \ldots, a_5$ are bounds on age classes that display different social behaviour (here, these bounds are set at 0, 2, 5,

11, 18 and 75 years), and $k_{x,ij}$ are the elements of next generation matrix $\mathbf{K}_x$. For any specified next generation matrix equation 5 can be solved numerically by iteration until convergence.

Fitting the susceptibility profile to pre-vaccination data

Pre-vaccination data

Prior to the introduction of measles vaccination in England and Wales, age-stratified case notifications were collected [20]. Notifications were pooled for the years 1956–65; in this period a total number of 4895296 cases were notified. In 1983, before introduction of a routine MMR vaccination in Denmark, a total of 2523 serum samples were collected from Danish children from 1–17 years of age. The measles IgG antibody levels of these samples were assessed by indirect enzyme-linked immunosorbent assay [21].

Likelihood function

The case notifications for England and Wales (1956–65) were classified into nine age groups (the age groups being 0–1 years, 1–2 years, 2–3 years, 3–4 years, 4–5 years, 5–10 years, 10–15 years, 15–25 years, and 25 and older). This data set is indicated as Y_E. The number of notified cases in age group k is denoted by z_k, and the total number of notified cases over all ages is denoted by Z. The observed number of notified cases per age group, $z_1, z_2, \ldots, z_9$ follows a multinomial distribution $M(Z, f_1, f_2, \ldots, f_9)$, where the probability for each case to be notified in age group k is given by f_k. From this probability $\sigma(\alpha, \mathbf{K}_x)$ we can derive the fraction of all cases that occur in age group k with $a_{n,k-1}$ and $a_{n,k}$ as the lower bound and upper bound for that age group

$$f_k(\mathbf{K}_x) = \sigma(a_{n,k-1}, \mathbf{K}_x) - \sigma(a_{n,k}, \mathbf{K}_x)$$

The log-likelihood of observing the notified cases for England and Wales is then

$$\ell_n(Y_E \mid \mathbf{K}_x) = \log[Z!] + \sum_{k=1}^{k=9} \{z_k \log f_k(\mathbf{K}_x) - \log[z_k!]\} \quad (6a)$$

The serum samples for Denmark (1983) were classified into 17 age groups (the age groups being 1–2 years, 2–3 years, … 17–18 years). This data set is indicated by Y_D. The probability of observing S_k susceptibles among a sample of N_k individuals in a particular age group k follows a binomial distribution $B(N_k, p_k)$ where the probability of finding a susceptible in particular age group k is given by p_k. The average proportion of susceptibles among those in age group k, with $a_{s,k-1}$ and $a_{s,k}$ as the lower bound and upper bound for that age group:

$$p_k(\mathbf{K}_x) = \frac{1}{a_k - a_{k-1}} \int_{a_{k-1}}^{a_k} \sigma(\alpha, \mathbf{K}_x) \mathrm{d}\alpha$$

The log-likelihood of observing the age-specific number of susceptibles in the Danish serological study, Y_D, is then

$$\ell_s(Y_D \mid \mathbf{K}_x) = \sum_{k=1}^{k=17} \left\{ \log \begin{pmatrix} N_k \\ S_k \end{pmatrix} + S_k \log p_k(\mathbf{K}_x) + (N_k - S_k) \log[1 - p_k(\mathbf{K}_x)] \right\} \quad (6b)$$

Note that we cannot estimate a complete next generation matrix $\mathbf{K}$ from the Danish data set because we lack information about fraction of susceptibles among infants and adults.

Similarly, we cannot estimate a complete next generation matrix $\mathbf{K}$ from the notification data either because we don't know the probability of escaping infection (and thus notification), which we need to convert notifications to meaningful estimates of age-specific prevalence of susceptibles. Combining the two data sets solves both problems: the serological data shows how the notification data should be converted to fraction susceptibles, and the notification data provides information on the fraction susceptibles among infants and adults. The combined log-likelihood function for both data sets is

$$\ell_{n+s}(Y_E, Y_D \mid \mathbf{K}_x) = \ell_n(Y_E \mid \mathbf{K}_x) + \ell_s(Y_D \mid \mathbf{K}_x) \quad (7)$$

Maximum likelihood estimation

The equations 6a, b and 7 specify the log likelihood of the pre-vaccination data, and allow for maximum likelihood estimation of the transmission rates. The procedure for obtaining the maximum likelihood estimates is as follows. For any given set of transmission rates $c_1, c_2, \ldots, c_5$ and transmission matrix $\mathbf{M}_x$ we can calculate the next generation matrix $\mathbf{K}_x$ using equation 4. With the next generation matrix $\mathbf{K}_x$ we compute the age-specific susceptibility profile

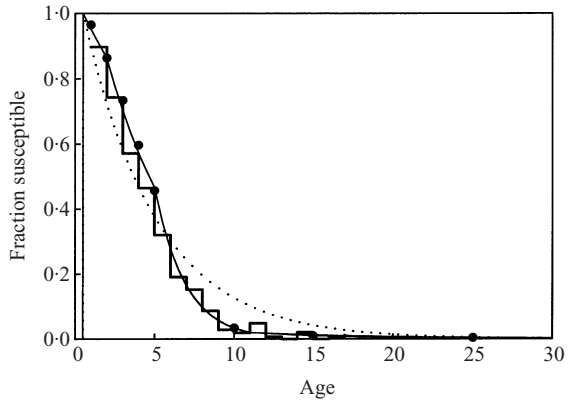

Fig. 1. Age-specific susceptibility profile for measles, as observed before introduction of measles vaccination. The drawn step-wise line indicates observations from a serological study in Denmark in 1983, and points indicate fraction susceptibles inferred from case notifications in England and Wales over the period from 1956–65. Lines indicate the maximum likelihood fit of the models. The dotted line indicates results for model H (homogeneous mixing). Results for models P, S, I, and A (proportionate mixing, semi-assortative mixing, infant mixing, assortative mixing) are very similar, and are indicated by the drawn line.

$\sigma(\alpha, \mathbf{K}_x)$ using equation 5. For this age-specific susceptibility profile $\sigma(\alpha, \mathbf{K}_x)$ we calculate the log likelihood, given the pre-vaccination data sets for Denmark and England and Wales, using equations 6a, b. The maximum likelihood estimates for transmission rates $\hat{c}_1, \hat{c}_2, \ldots, \hat{c}_5$ are then found as those transmission rates that maximize the combined log likelihood given by equation 7. With the next generation matrix $\mathbf{K}_x$ that corresponds to those maximum likelihood estimates we calculate the basic reproduction ratio using equations 1, the projected reproduction ratio and the critical vaccination coverage using equation 2 and the effective reproduction ratio using equation 3.

Ascertaining the accuracy of the estimates

There are several methods to check the reasonability and usefulness of the resulting estimates of transmission rates and reproduction ratios. One method is to ask whether the confidence intervals of estimated reproduction ratios are small enough to distinguish between the various vaccination strategies. An alternative method is to compare the next generation matrices for their ability to describe the pre-vaccination data. Another method is to see if the next generation matrices are capable to predict observations in the vaccination era reasonably well. Below we describe each of these methods.

Confidence intervals of reproduction ratios

The 95% confidence intervals of the reproduction ratios under the different mixing assumption were obtained by the parametric bootstrap method [22]. These 95% confidence intervals, henceforth indicated as CI, only account for variation that is introduced by the sampling of populations inherent to the notification data and the serological data. Hence, the confidence intervals do not account for the uncertainty pertaining to, for instance, actual vaccine coverage, infectious period, and the duration of protection by maternal antibodies.

Comparison between next generation matrices for their description of pre-vaccination observations

The models are compared for their goodness-of-fit to the pre-vaccination data. Because model H can be considered as a simplification of model P, we can invoke a likelihood ratio test between a model with age structure (model P) and the corresponding model without age structure (model H). In such a test we make use of the fact that the quantity $2[\ell_{n+s}(Y_E, Y_D \mid \mathbf{K}_P) - \ell_{n+s}(Y_E, Y_D \mid \mathbf{K}_H)]$ has a χ^2 distribution with the degrees of freedom equal to the difference in number of parameters between the models, cf. [23]. A similar test was performed for model H against model S. For comparison of goodness-of-fit between models P, S, I, and A we use the log likelihood, with a higher value of log likelihood indicating a better fit.

Comparison between next generation matrices for their capability to explain observations in the vaccination era

The models H, P and S are compared in their capability to explain the data obtained in the vaccination era. For this purpose we used numerical simulation techniques to study spread of measles in a population that mixes according to the next generation matrix. Specifically, we used a standard, age-structured epidemic model, where individuals are either protected by maternal antibodies, susceptible, latent infected, infectious or immune. This model is given by a system of partial differential equations (as described in for instance [18], and the endemic equilibrium without vaccination according to this system of equations corresponds with the endemic

Table 1. *Estimated transmission rates of measles. Maximum likelihood estimate and 95% confidence interval are given. Units: year*$^{-1}$

Mixing hypothesis	Model		Transmission rates
No age structure			
Homogeneous	H	c	851·1 (850·59–851·64)
Age structure			
Proportionate	P	c_1	112·0 (111·4–112·6)
		c_2	498·2 (496·7–499·7)
		c_3	3212·3 (3206·1–3220·0)
		c_4	356·8 (349·7–364·6)
		c_5	79·8 (77·6–82·0)
Semi-assortative	S	$c_1 + c_5$	388·1 (385·6–394·6)
		$c_2 + c_5$	1436·9 (1433·8–11440·8)
		$c_3 + c_4 + c_5$	4129·2 (4116·9–4138·9)
		$c_4 + c_5$	3098·0 (386·3–3385·2)
		c_5	385·0 (383·5–387·3)
Infant, assortative	I, A	c_1	2792·1 (2791·4–2792·6)
		c_2	2024·8 (2023·8–2025·8)
		c_3	4552·1 (4544·9–4562·5)
		c_4	47333 (47041–47716)
		c_5	52855 (52066–53713)

equilibrium we have studied here, as given by equation 5). The system of equations has been implemented as a computer programme, which takes the estimated transmission rates and the specified vaccination programme as input variables and then calculates the susceptibility profile that results from the vaccination programme and the estimated transmission pattern [5]. The calculated susceptibility profiles for the year 1996 were compared with the results from the serological surveys. In addition we checked whether the effective reproduction ratio is close to unity for those countries where measles is reported to be endemic.

RESULTS

Parameter estimation

The fit of the models to the pre-vaccination data of Denmark and England and Wales is shown in Figure 1. Both models P and S (proportionate and semi-assortative mixing) describe the data significantly better than model H (homogeneous mixing) (model P versus model H, χ^2: $1{\cdot}49\ 10^6$, D.F. $= 4$, P ≈ 0; model S versus model H, χ^2: $1{\cdot}48\ 10^6$, D.F. $= 4$, P ≈ 0). Models P, I and A (proportionate, infant and assortative mixing) describe the data slightly better than model S (semi-assortative mixing), that is, the log likelihood of model P, I and A is slightly higher than that of model S (model P, I, A: $\ell_{n+s} = -5{\cdot}39\ 10^4$; model S: $\ell_{n+s} = -5{\cdot}69\ 10^4$). The maximum likelihood estimates of the transmission rates of measles are presented in Table 1. According to models S, I and A (semi-assortative, infant, and assortative mixing) the confidence intervals for transmission rates for secondary schoolers and adults are wider than those for younger age classes. For model P (proportionate mixing) there is no distinct trend for confidence intervals to become larger with increasing age.

Models H, P and S, as parameterized with maximum likelihood estimates in Table 1, were used to calculate the susceptibility profiles for Denmark and England and Wales after introduction of vaccination against measles, as observed in 1996 (Fig. 2*a*,*b*). Models P and S (proportionate and semi-assortative mixing) provide an almost equally good description of the observations, both better than model H (homogeneous mixing). The models were also used to calculate age-specific susceptibility profiles for other Western European countries after introduction of vaccination against measles. For Finland, the country with the highest vaccine coverage, all models produce very similar outcomes (Fig. 2*c*). For Italy, the country with the lowest vaccine coverage, model H (homogeneous mixing) gives the best description of observations (Fig. 2*d*).

Estimates of reproduction ratios

The basic reproduction ratios for measles are presented in Table 2. There are large differences between

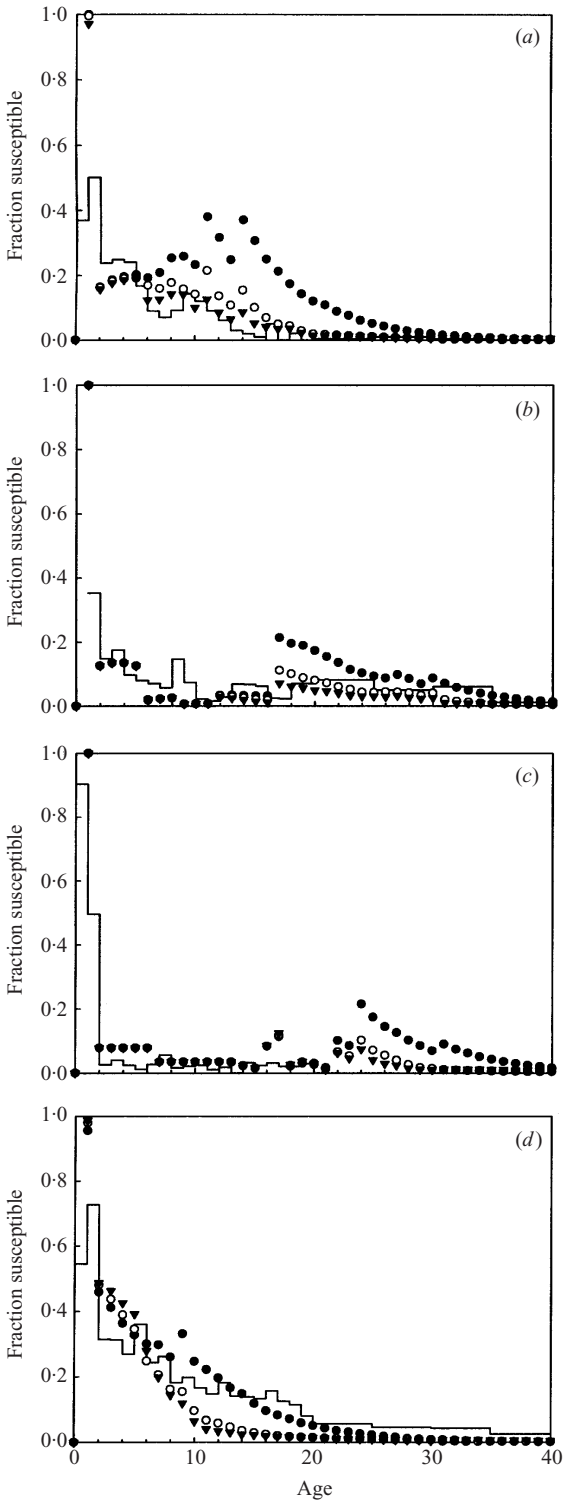

Fig. 2. Age-specific susceptibility profiles for measles, after introduction of measles vaccination for (a) Denmark, (b) England and Wales, (c) Finland, (d) Italy. The drawn stepwise line indicates observations from serological studies. Symbols indicate calculated point estimates for the age-specific fraction of susceptibles. Filled circles indicate results for model H (homogenous mixing), open circles indicate results for model P (proportionate mixing), filled triangles indicate results for model S (semi-assortative mixing).

the age-structured models in their resulting estimates of basic reproduction ratios. The lower bound for feasible values of the basic reproduction ratio for measles is 1·43 (CI 1·43–1·43), the upper bound for feasible values of the basic reproduction ratio for measles is 770·38 (CI 758·88–782·88). The lower bound for plausible values of the measles basic reproduction ratio is 7·17 (CI 7·14–7·20) and the upper bound for plausible values of the measles basic reproduction ratio is 45·41 (CI 9·77–49·57). The estimate for the simplest case (homogeneous mixing) turns out to be in between the bounds for plausible values, and is 16·32 (CI 16·31–16·33).

The effective reproduction ratios for measles are presented for each country for which a complete age-specific susceptibility profile after vaccination was available (Table 3). The effective reproduction ratio is for most countries smaller than one. Exceptions are the estimate of the effective reproduction ratio for Germany according to model S (semi-assortative mixing), and the estimates for Italy according to all three models. The estimates for countries with endemic measles are closest to unity for model S (semi-assortative mixing).

The projected reproduction ratios for the various measles vaccination programmes are presented in Table 4. The projected reproduction ratio for the Finnish and Swedish vaccination programme are lower than unity for the models H and P (homogeneous and proportionate mixing) and near unity for model S (semi-assortative mixing). The vaccination programmes of the Netherlands and of England and Wales have a projected reproduction ratio lower than unity for model P (proportionate mixing), but not for model H and S (homogeneous and semi-assortative mixing). The projected reproduction ratios for the Danish, French, German and Italian vaccination programme are larger than unity for all three models.

Critical levels for vaccine coverage

The vaccination coverage at which the projected reproduction ratio equals one is presented in Table 5. If estimates according to model P (proportionate mixing) are regarded as plausible lower bounds to the actual reproduction ratios, measles can persist if the vaccination coverage is below the range of 86·6%–90·9% (depending on the exact ages at which vaccine is offered). If estimates according to model S (semi-assortative mixing) are regarded as plausible upper bounds to the actual reproduction ratios, it is possible,

Table 2. *Basic reproduction ratio* R_0 *for measles. Estimated value and 95% confidence interval are given*

Mixing hypothesis	Bound	Model	Basic reproduction ratio, R_0
No age structure			
Homogeneous	—	H	16·32 (16·31–16·33)
Age structure			
Proportionate	Lower (plausible)	P	7·17 (7·14–7·20)
Semi-assortative	Upper (plausible)	S	45·41 (9·77–49·57)
Infant	Lower (feasible)	I	1·43 (1·43–1·43)
Assortative	Upper (feasible)	A	770·38 (758·88–782·88)

Table 3. *Effective reproduction ratios* R_e *of measles in six Western European countries, as inferred from serological studies in 1994–8. Estimated value and 95% confidence interval are given*

	Serological survey		Effective reproduction ratio of measles, R_e		
Country	Cut-off value*	Sample size	Model H (Homogeneous mixing)	Model P (Proportionate mixing)	Model S (Semi-assortative mixing)
Finland	62	3099	0·52 (0·45–0·60)	0·20 (0·14–0·28)	0·53 (0·25–0·74)
Sweden	—	—	—	—	—
Netherlands	149	8303	0·50 (0·45–0·55)	0·29 (0·22–0·37)	0·47 (0·34–0·57)
England and Wales	—	—	—	—	—
Denmark	150	3106	0·60 (0·53–0·68)	0·70 (0·56–0·85)	0·75 (0·57–0·93)
France	193	2879	0·64 (0·55–0·73)	0·57 (0·42–0·73)	0·64 (0·51–0·83)
Germany	152	5152	0·90 (0·81–0·99)	0·62 (0·53–0·70)	0·93 (0·68–1·16)
Italy	155	3567	1·49 (1·35–1·62)	1·45 (1·29–1·61)	1·94 (1·48–2·30)

* Cut-off values are given in international units per litre.

Table 4. *Projected reproduction ratios* R_p *of measles for vaccination strategies of eight Western European countries. Estimated value and 95% confidence interval are given*

	Vaccination strategy			Projected reproduction ratio of measles, R_p		
	Target age (year)					
Country	MMR1	MMR2	Coverage (%)	Model H (Homogeneous mixing)	Model P (Proportionate mixing)	Model S (Semi-assortative mixing)
Finland	18/12	6	98	0·62 (0·62–0·62)	0·24 (0·24–0·25)	1·03 (0·32–1·13)
Sweden	18/12	12	97	0·84 (0·84–0·84)	0·51 (0·51–0·51)	1·50 (0·57–1·63)
Netherlands	14/12	9	94	1·22 (1·22–1·22)	0·63 (0·63–0·63)	2·85 (0·75–3·10)
England and Wales	15/12	4	92	1·51 (1·51–1·51)	0·62 (0·62–0·62)	3·75 (0·85–4·09)
Denmark	15/12	12	88	2·22 (2·22–2·22)	1·12 (1·12–1·12)	5·56 (1·37–6·07)
France	12/12	4·5	83	2·91 (2·91–2·91)	1·26 (1·25–1·26)	7·82 (1·71–8·54)
Germany	15/12	6	70	5·04 (5·04–5·04)	2·21 (2·21–2·22)	13·71 (2·99–14·96)
Italy	18/12	—	56	7·70 (7·70–7·71)	3·36 (3·35–3·38)	21·26 (4·59–23·20)

at least in theory, to achieve elimination of measles for two-dose strategies by increasing vaccine coverage up to 98·1%.

DISCUSSION

In this paper we have assessed the efficacy of vaccination programmes of various Western European countries to eliminate the measles virus. As a measure of capability of the vaccination programmes to eliminate measles we used the projected reproduction ratio. The epidemiological interpretation of the projected reproduction ratio is straightforward: it measures the transmission potential of measles in the vaccinated population, and if the projected reproduction ratio is smaller than one, measles will be

Table 5. *The required coverage for elimination measles, given the ages at which the measles-mumps-rubella vaccine is offered. '×' indicates the programme is incapable of eliminating measles at 100% coverage. Estimated value and 95% confidence interval are given*

	Actual vaccination strategy			Coverage at first dose (%) required for elimination of measles		
	Target age (year)			Model H* (Homogeneous mixing)	Model P (Proportionate mixing)	Model S (Semi-assortative mixing)
Country	MMR1	MMR2	Coverage (%)			
Finland	18/12	6	98	95·6	87·3 (87·2–87·4)	98·1 (90·8–98·3)
Sweden	18/12	12	97	96·0	89·8 (89·8–89·9)	98·1 (92·2–98·3)
Netherlands	14/12	9	94	95·4	88·7 (88·6–88·7)	98·1 (91·3–98·3)
England and Wales	15/12	4	92	95·2	86·7 (86·6–86·7)	98·1 (90·5–98·3)
Denmark	15/12	12	88	95·7	89·7 (89·7–89·8)	98·1 (92·0–98·3)
France	12/12	4·5	83	94·9	86·6 (86·6–86·7)	98·1 (90·3–98·3)
Germany	15/12	6	70	95·3	87·2 (87·2–87·3)	98·1 (90·7–98·3)
Italy	18/12	—	56	×	90·9 (90·9–91·0)	×

*The difference between the maximum likelihood estimate and 95% confidence bounds is smaller than 0·1% for all countries.

eliminated. We have used an estimation procedure that allows us to quantify the accuracy attained in estimating the reproduction ratio. This accuracy depends on several factors, such as the estimation procedure itself, the quality of the pre-vaccination data, the appropriateness of the next generation matrices that were used, and the resulting uncertainty about the transmission rates. We will discuss these factors in order to determine the possibilities for elimination of measles in Western Europe with the present vaccination programmes.

Estimation procedure

In this paper we have explicated an estimation procedure to obtain transmission rates (and reproduction ratios) directly from pre-vaccination data. There already exist many methods to estimate the age-specific force of infection from pre-vaccination data [24, 25], and there already exist methods to infer transmission rates from the age-specific force of infection for a given transmission matrix [18]. However, combined use of both existing methods may lead to a number of problems. Such a combined method is vulnerable to inconsistency because the assumptions used to estimate the force of infection do not necessarily agree with the assumptions used to infer the transmission rates. For instance, the age-specific force of infection may be represented by a fifth-order polynomial when it is estimated from notification data, whereas the same age-specific force of infection is represented by a piece-wise constant function as transmission rates are inferred from it. Such an inconsistency may produce erroneous outcomes. Moreover, the combined method does not provide any information on the agreement between the transmission structure and the pre-vaccination data. Only when the transmission structure is incommensurable with observations to the extent that resulting estimated transmission rates are negative, there is an indication that the chosen transmission structure is inappropriate to the observed age-specific force of infection [26]. In contrast, the estimation procedure that has been used in this paper has no such inconsistency problems, the resulting estimated transmission rates are always positive, and an eventual lack of fit is indicated by broad confidence intervals for transmission rates or by low values of the likelihood.

Pre-vaccination data

The two pre-vaccination data sets that are used in this paper provide slightly different information. The serological data provide information on how many Danish persons of a certain age have escaped infection in the 1980's; the notification data provide information on age distribution of notified measles cases in England and Wales in the 1950's and 1960's. Each data set has its own sources of potential bias and error. For the serological data, some individuals might have been already vaccinated before introduction of routine vaccination; we have to assume that the vaccination of a few individuals did not

influence the age-specific fractions susceptible. For the notification data, there might be age-specific bias in diagnosis and notification; we have to assume that the effects of such bias were negligible. We can check these assumptions by comparing the two data sets: similar patterns of age-specific prevalence of susceptibility and immunity would indicate that the potential bias is negligibly small. Comparison of both pre-vaccination data sets shows very similar patterns of age-specific prevalence of susceptibility and immunity (Fig. 1). Therefore, there appears to be little difference between the pre-vaccination age-specific susceptibility profiles measured at different countries at different times by different methods.

Models versus observations

It is interesting to see which of the alternative mixing matrices clearly fail to explain the observations. The pre-vaccination age-specific susceptibility profiles for Denmark and England and Wales are better described by models with age structured transmission (models P, S, I and A, that is, proportionate, semi-assortative, infantile and assortative mixing) than the model without age structured transmission (model H, homogeneous mixing). This provides statistically significant evidence that age-structure in transmission pattern does matter, thus confirming earlier findings [8, 9]. The very high χ^2 values and the resulting very low P values, are due to the very high number of observations that are taken into account (almost 5 million case notifications and over 2·5 thousand serum samples).

The age-specific susceptibility profiles for Denmark and England and Wales after introduction of vaccination are predicted rather well by the models P and S (Fig. 2*a*, *b*), and this suggests that transmission models calibrated on pre-vaccination data still apply in the vaccination era. The equally good fit of the models P and S to data obtained after introduction of vaccination in Finland (Fig. 2*c*), suggests that the transmission models calibrated for Danish and British data may also apply to other countries with a high vaccination coverage. The relatively poor description of the data obtained after introduction of vaccination in Italy (Fig. 2*d*) suggests that one should be cautious in applying the transmission models to other countries and to situations with lower levels of vaccine coverage.

In countries where measles is endemic the effective reproduction ratios are expected to be close to unity. For Italy, one of the countries where measles is still endemic, the effective reproduction ratio is larger than unity for all models. This might be due to the poor fit of the model to the Italian data (Fig. 2*d*). In contrast, for Germany, where measles is also endemic, the effective reproduction ratio is estimated to be close to unity by models H and S (homogeneous and semi-assortative mixing), but not by model P (proportionate mixing). This suggests that model P underestimates the actual reproduction ratios substantially. For Finland, a country where measles is not endemic [27], the effective reproduction ratio is expected to be below unity. The estimated effective reproduction ratios are indeed all smaller than unity.

Uncertainty due to estimation of transmission rates

The estimated confidence intervals make it possible, for the first time, to test the suggestion of Dietz and Schenzle [11] that the scarceness of susceptibles among older age classes leads to high uncertainty regarding the transmission rates within and among adolescents and adults. Indeed, the most uncertain values are for the transmission rates within or between adolescents and adults. For model S (semi-assortative mixing) the range of the confidence intervals is extremely wide for transmission rates among adults, resulting in a wide confidence interval for the reproduction ratio (see Tables 1, 2). However, for other models the wider confidence intervals for transmission rates within or between adolescents or adults did not result in such a wide confidence interval for the reproduction ratio. Thus scarceness of susceptibles among the older age classes results in more uncertain estimates of transmission rates with or between adolescents and adults, but this does not necessarily pose a problem on estimation of reproduction ratios.

Bounds due to unknown transmission structure

Many previous studies have reported estimates of the basic reproduction ratio of measles, with most estimates relying on the assumption of homogeneous mixing. For instance, Anderson and May [7] found basic reproduction ratios from 13·7 to 18 in Britain from 1944 to 1979, and Hethcote [28] estimated a basic reproduction ratio of 15 from data obtained in large cities in the United States in 1942. These values are in agreement with the estimate of the basic reproduction ratio as 16·32 (CI 16·32–16·33) derived here for model H (homogeneous mixing). If the

hypothesis of homogeneous mixing were correct, one could accurately estimate the basic reproduction ratio for measles. But the test of models P and S versus model H has provided statistically significant evidence to reject homogenous mixing in favour of the age-structured mixing hypotheses.

The problem of age-structured transmission is that we do not know the exact structure of the transmission matrix, and therefore cannot uniquely predict a value for the reproduction ratio. Our results on the bounds on reproduction ratios provide quantitative information how the accuracy of the estimate increases as more knowledge on transmission is accounted for. If we account only for the fact that transmission rates cannot be negative, we obtain a lower bound on the basic reproduction ratio of 1·43 (CI 1·43–1·43) and an upper bound of 770·38 (CI 758·88–782·88). We can account for more information regarding the transmission process by assuming that all the transmission rates should be larger than zero, and the transmission matrix should be symmetric. Moreover, the transmission rate within age classes should be larger than that between age classes. This is consistent with taking model P (proportionate mixing) as a lower bound and model S (semi-assortative mixing) as an upper bound, and leads to a range of plausible values for the basic reproduction ratio from 7·17 (CI 7·14–7·20) up to 45·41 (CI 9·77–49·57).

If we would have more information on the transmission process such that we know which particular transmission matrix reflects the actual situation, the uncertainty about the value of the reproduction ratio is represented by the 95% confidence interval. Depending on the exact transmission structure, the width of this interval can be much smaller than the range of plausible values. This suggests that there is an enormous potential for improvement in accuracy with improvement of the knowledge of transmission structure. Novel approaches, such as for instance interviewing people on their social behaviour [29, 30], might provide the required empirical knowledge about the transmission structure.

Prospects for elimination of measles in Western Europe

The broad bounds on plausible reproduction ratios translate into broad limits on plausible values for the critical vaccine coverage. The critical vaccine coverage differs between vaccination programmes. For the French vaccination programme, for instance, the lowest value is obtained for model P (proportionate mixing) and is 86·6% (CI 86·6%–86·7%). The highest value is obtained for model S (semi-assortative mixing) and is 98·1% (CI 90·3%–98·3%). A more precise analysis requires the use of projected reproduction ratios that are specific to each vaccination programme.

The projected reproduction ratios according to model S (semi-assortative mixing) are used as an upper bound for plausible values of the projected reproduction ratios. If the upper bound is not significantly larger than one, as is the case for the vaccination programmes of Finland, Sweden, the Netherlands, and England and Wales, measles may be eliminated by the vaccination programme. The projected reproduction ratios according to model P are used as a lower bound for plausible values of the projected reproduction ratios. If the lower bound exceeds one, which is the case for the Danish, French, German and Italian vaccination programmes, measles will persist in spite of the vaccination programme.

One should bear in mind that the estimated figures for actual vaccination coverage, and thus the estimated projected reproduction ratios, are in a state of flux. The estimates used for France and Germany reflect the coverage at age two, but there might be improvement in coverage after this age. In Italy and Denmark, the coverage has been rising over the last years. In contrast, the coverage in England and Wales has fallen over the last couple of years. Using the most recent figure, which is around 88%, the vaccination programme for England and Wales would be listed in the category of vaccination programmes that allow measles to persist. The Netherlands has faced an epidemic of measles in 1999, and the coverage for measles vaccination in the Netherlands has now increased from 94% to 96%.

Concluding remarks

Our ignorance with respect to the actual transmission structure permits us only to set broad bounds on both the reproduction ratio and the critical vaccination coverage. More accurate estimation of reproduction ratios and critical vaccine coverage for measles is only possible if more empirical knowledge about the age-structured mixing patterns becomes available. In spite of the wide bounds on the reproduction ratios and

critical vaccine coverages, it is still possible to determine for which vaccination programme one should be confident that it will eliminate measles or that it allows persistence of measles. Beyond a level of 98% vaccine coverage for a first dose of a two-dose programme one can be confident about eventual elimination. Among the vaccination programmes we have evaluated here, there are two vaccination programmes with a high coverage close to this value, of which one (Finland) is reported to have already eliminated measles [27]. These facts show that eventual elimination of measles virus in Western Europe by vaccination is feasible.

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