Epidemiol. Infect. (2005), **133**, 1009–1021. © 2005 Cambridge University Press
doi:10.1017/S0950268805004528 Printed in the United Kingdom

Matrix models for childhood infections: a Bayesian approach with applications to rubella and mumps

M. N. KANAAN[1] AND C. P. FARRINGTON[2*]

[1] *Department of Epidemiology and Population Health, American University of Beirut, Lebanon*
[2] *Department of Statistics, The Open University, Milton Keynes, UK*

(*Accepted 19 August 2004, first published online 2 June 2005*)

SUMMARY

Mathematical modelling is an established tool for planning and monitoring vaccination programmes. However, the matrices describing contact rates are based on subjective choices, which have a large impact on results. This paper reviews published models and obtains prior model probabilities based on publication frequency and expert opinion. Using serological survey data on rubella and mumps, Bayesian methods of model choice are applied to select the most plausible models. Estimates of the basic reproduction number R_0 are derived, taking into account model uncertainty and individual heterogeneity in contact rates. Twenty-two models are documented, for which publication frequency and expert opinion are negatively correlated. Using the expert prior with individual heterogeneity, $R_0 = 6{\cdot}1$ [95% credible region (CR) 4·3–9·2] for rubella and $R_0 = 19{\cdot}3$ (95% CR 4·0–31·5) for mumps. The posterior modes are insensitive to the prior for rubella but not for mumps. Overall, assortative models with individual heterogeneity are recommended.

INTRODUCTION

Infectious disease modelling is an important element in the planning of mass vaccination programmes. While many models are available [1–5], most commonly used are the deterministic age-stratified SIR (susceptible–infected–removed) models and their variants. For a modern treatment, see ref. [3]. These models have been used to study measles [6–18], mumps [18,19], rubella [12, 14, 15, 18–21], whooping cough [22], *Haemophilus influenzae* type b (Hib) [23], varicella [24–26], parvovirus B19 [19], hepatitis A [27] and hepatitis B [28]. They have helped guide the introduction of mass vaccination programmes [20, 24] and monitor their implementation [29]. They have also been used to estimate epidemiological parameters, including forces of infection, reproduction numbers and immunization thresholds [3, 19, 30].

In this paper we document some of these models, distinguished primarily by assumptions about contact patterns. These are represented by matrices of contact rates, describing the contacts between individuals in a small number of distinct age groups. Our review is, therefore, one of contact rate matrices, known variously as contact, mixing, or WAIFW (Who Acquires Infection From Whom) matrices [3].

The contact matrix cannot generally be estimated directly from epidemiological data without strong assumptions. Four approaches have been taken. The first and least satisfactory is to allow mathematical tractability to determine model choice. In the simplest model, contact rates do not vary with age [31]. More elaborate tractable models include those based on proportional mixing [32, 33] in which the age

* Author for correspondence: Professor C. P. Farrington, Department of Statistics, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK.
(Email: c.p.farrington@open.ac.uk)

distribution of contacts is the same at all ages. Such models ignore important epidemiological features of many infections. The second approach, most commonly used, is to reduce the number of parameters so that they become identifiable, without sacrificing key epidemiological features [3]. However, there is no obvious way of choosing between models: different models fit the data equally well, but can produce quite different values of quantities such as the basic reproduction number R_0 [19, 27]. R_0 is the average number of secondary infections produced by a single typical infective in a completely susceptible population. It is a measure of the epidemic potential of an infection: the larger the value of R_0 the more difficult the infection will be to eradicate. A third approach [34, 35] is to survey a measurable proxy variable, for example frequency of conversations. This method is attractive, but relies on the questionable assumption that conversations are representative of contacts. The fourth approach, which we adopt in this paper, is to exploit the fact that different infections may share the same route of transmission. This has been described in Farrington et al. [19]. Briefly, if two infections share the same route of transmission, then their contact matrices should be roughly proportional. This can be formulated in a Bayesian statistical framework to derive a criterion with which to assess the relative plausibility of different models.

We determine a collection of matrix models used for modelling common childhood infections, and specify informative prior probabilities for these models. We then derive posterior probabilities for each model and obtain point and interval estimates of R_0 for mumps and rubella, taking into account both sampling variability and model uncertainty. Throughout, we also investigate the impact of individual variability in contact rates.

METHODS

Modelling contact rates

The underlying assumption of all matrix models is that contacts between individuals occur at rates that differ between a small number K of age groups $(a_{i-1}, a_i]$, $i=1, \ldots, K$ where $a_0=0$ and a_K is the maximum age, taken to be 100 years. Contacts are described by a $K \times K$ matrix B whose entries denote the rate at which individuals in one age group make contacts with individuals in another age group. 'Contacts' refers to those that are epidemiologically relevant, depending on the transmission route of the infection. For infections transmitted by airborne droplets, for example, contact implies close spatio-temporal proximity.

The contact matrix is not usually directly observed. We obtain it from the force of infection, namely the rate at which susceptible individuals become infected, estimated from serological survey data [36–38]. The method is outlined in Appendix 1. In principle, B could have up to K^2 distinct entries. For infections mainly transmitted by droplets, it is sensible to assume B symmetric, thus reducing the number of distinct entries to $K(K+1)/2$. However, only K separate parameters are estimable. Thus, the entries of B must be restricted to at most K different values.

A typical 5×5 matrix is represented below. The numbers 1–5 represent five distinct parameters distributed among the 25 possible positions.

$$\begin{pmatrix} 1 & 1 & 4 & 4 & 5 \\ 1 & 2 & 4 & 4 & 5 \\ 4 & 4 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}.$$

For example, the three 1's in the top left-hand corner of the matrix imply that the contact rate within the first age group is the same as the contact rates between the first and second age groups. No further constraints are placed upon the parameters other than that they should be non-negative.

Mumps and rubella data

A serological survey was undertaken in the United Kingdom in 1986 to establish baseline immunity prior to the introduction of measles, mumps and rubella vaccine. The survey has been described in ref. [39]. We used paired mumps and rubella data for males aged 1–44 years published in ref. [19]. The UK population age structure in 1986 was obtained from ref. [40]. We used only data on males as some teenage girls and pregnant women were vaccinated against rubella infection. This selective vaccination programme reduces slightly the force of infection in males by reducing contacts with infectious teenage girls and older women. However, the effect is small as relatively few infections occur in older age groups, and we therefore decided to ignore it.

Matrix models

We searched the epidemiological literature up to 2001 for age-stratified compartmental models. We

restricted our search to symmetric models used for modelling infections of childhood in developed countries including measles, mumps, rubella, pertussis, varicella, Hib, parvovirus, hepatitis A and hepatitis B. With the exception of hepatitis A and B, all these infections are transmitted by a combination of airborne droplets and direct contact [41]. We included models for hepatitis A and B provided they did not incorporate any features specific to faecal–oral or sexual transmission. We excluded two asymmetric models for Hib designed to capture specific features of close contact in Hib transmission [23].

We restricted our search to models of the type popularized by Anderson and May [3]. Thus, we excluded continuous mixing models [42, 43]. We excluded models used primarily for their mathematical tractability, such as homogeneous and proportional mixing models [33, 44]. We excluded models that we deemed to be unreasonable on epidemiological grounds, such as purely assortative models with zero off-diagonal entries [30, 45], or with contact rates depending only on the age of the infective or of the susceptible [3, 7, 12]. More generally, we only included models if they had been used for estimation rather than mathematical modelling *per se* [46]. Finally, we excluded finely age-stratified models [16, 47] which we could not accommodate owing to the limitations of our data.

Prior structural probabilities

Given a contact matrix M, the prior structural probability $p(M)$ quantifies the *a priori* plausibility of structure M. We used three sets of prior structural probabilities.

The first was obtained by assigning an equal probability to each model. Thus, if there are N models M_i, $i=1, \ldots, N$, we set $p(M_i)=1/N$. This prior is uninformative: it does not exploit any additional expert knowledge. We call this our 'neutral prior'.

Our second prior was obtained by counting the number of times r_i each matrix M_i was used in the published literature, and set $p(M_i)=r_i/\Sigma r_j$. This is our 'publication prior'. Here Σr_j refers to the total number of matrices referred to, not the total number of papers. This prior sought to capture the implicit beliefs of the epidemiological research community through their actual model choices.

Finally, we elicited a prior from a panel of five epidemiologists currently actively engaged in mathematical modelling of infectious diseases (other than this qualification, our choice of experts was entirely *ad hoc*). To these experts we sent a document including (*a*) the rationale of the study, (*b*) our list of models with references to their use in the epidemiological literature, and (*c*) a questionnaire. Panelists were invited to state whether we had overlooked a model that they considered important, to assign scores to the models in the list proposed to them, and to comment on the models and the elicitation procedure. If panelist j assigned score s_{ij} to matrix model M_i, we calculated

$$p(M_i)=\frac{1}{5}\sum_{j=1}^{5}\left(\frac{s_{ij}}{\Sigma_i s_{ij}}\right).$$

The rationale behind this 'expert prior' was to quantify the explicit preferences of experts currently working in the field.

Bayesian model choice

We used a Bayesian approach to discriminate between models [19, 48]. Mumps and rubella are transmitted by similar routes, and hence should have similar contact matrices B_{M} and B_{R}, up to some constant of proportionality α. If the routes of transmission were exactly the same, then $B_{\mathrm{M}}=\alpha\times B_{\mathrm{R}}$. In practice we would expect the matrices not to be exactly proportional, owing to differences between mumps and rubella virus. Our criterion for model choice was that the plausibility of a model structure M increases as the proportionality assumption is more closely met, as measured by the log likelihood when fitting proportional matrices. We distinguished between the mixing structure M and the model B, which comprises M together with a set of parameters $\beta=(\beta_1, \beta_2, \ldots)$. We assumed unspecified diffuse priors on $[0, \infty)$ for the β_i and on [0,1] for α, and relied on asymptotic theory. For large sample size n, the posterior probability of the serological data y given structure M, $p_0(y|M)$, is approximated by

$$\log\ p_0(y|M) \simeq \log\left\{\mathrm{lik}_0(\hat{\beta}, \hat{\alpha};\ y, M\right\} - \tfrac{1}{2}\,(k+r)\,\log(n) + \tfrac{1}{2}\,(k-r)\,\log(2\pi), \quad (1)$$

where k is the number of parameters, r is the number of parameters estimated on a boundary, $\hat{\beta}$ and $\hat{\alpha}$ are the maximum-likelihood estimates of β and α under the proportionality assumption, and lik_0 is the maximized likelihood. We followed Draper [48] in including the term $\frac{1}{2}(k-r)\log(2\pi)$, which gives greater weight to more complex models. Equation (1) also

differs from the Bayesian information (or Schwartz) criterion [49] by allowing for parameters estimated on the boundary, as described by ref. [50, pp. 170–171]. This is necessary since the priors on the parameters are informative in this region. The effect of this adjustment is to downweight models for which some of the contact rates are estimated to be zero.

Given two model structures M_1 and M_2, the Bayes factor $p_0(y|M_2)/p_0(y|M_1)$ measures the relative extent to which the data support M_1 and M_2: a large value of the Bayes factor favours M_2, a small value favours M_1. Given a comprehensive universe of models M_i, $i=1, \ldots, N$, and prior probabilities $p(M_i)$, we obtained the posterior structural probabilities

$$p(M_i|y)=\gamma p_0(y|M_1)p(M_1),$$

the proportionality constant γ being chosen so that the probabilities sum to 1. These posterior probabilities combine evidence from the data and prior knowledge, and can be used as the basis for choosing one or several models.

Estimates of the basic reproduction number that take into account the variation attributable to model choice were also obtained. For a given model structure M we approximated the posterior distributions of log R_0 for mumps and rubella, $p_m(\log R_0; y,M)$ and $p_r(\log R_0; y,M)$, by the normalized profile likelihoods of log R_0 with the matrix parameters for mumps and rubella no longer subject to a proportionality assumption [19]. The joint posterior distributions over all models are then

$$\sum_i p_m(\log R_0; y, M_i)p(M_i|y) \quad \text{and}$$
$$\sum_i p_r(\log R_0; y, M_i)p(M_i|y)$$

from which posterior modes and 95% credible regions (CR) based on regions of high posterior density are derived. We used the log R_0 scale to improve the normal approximations involved.

Individual heterogeneity

So far we have only considered age variation in contact rates. Variation in individual behaviour induces further heterogeneity: individuals vary in their sociability, and hence in their propensity to come into contact with others. It is well known that heterogeneity increases the value of R_0 [5, 51]. Nevertheless, individual heterogeneity is seldom allowed for in practice. However, with paired serological survey data, this effect can be estimated by incorporating it into the model as a gamma-distributed frailty U [19]. We undertook all calculations both without and with allowance for (individual) heterogeneity.

RESULTS

Matrix models

Our final list included 22 matrix models, listed in Appendix 2. To avoid a proliferation of combinations, we chose a single age grouping for each model dimension. The following age groups (in years) were chosen empirically so as to produce good model fits:

3 age groups: 1 matrix:	0–3, 3–10, 10+
4 age groups: 4 matrices:	0–3, 3–8, 8–15, 15+
5 age groups: 14 matrices:	0–3, 3–8, 8–13, 13–20, 20+
6 age groups: 3 matrices:	0–3, 3–8, 8–13, 13–20, 20–30, 30+

The matrices were classified according to type in five categories labelled A to E.

Category A (6 matrices) comprised models with one special mixing group for children of pre-school and early primary-school age. These models have a single dedicated parameter (a dedicated parameter is a parameter occurring in just one cell) to model within-group transmission in young children.

Category B (5 matrices) comprised models allowing for teenage or secondary-school mixing. These models have one or two dedicated parameters, one of which models within-group mixing between teenagers or older children.

Category C (4 matrices) comprised models allowing for mixing with or within pre-school children. These models either have a single dedicated parameter corresponding to mixing within pre-school children, or have special off-diagonal parameters corresponding to mixing between adults and children of pre-school age.

Category D (5 matrices) comprises assortative mixing models, with dedicated parameters on all but one or two of the diagonal positions. These models broadly differentiate between general background mixing, and preferential contacts within age groups.

Category E (2 matrices) comprises models that are essentially assortative, with some allowance for mixing between adults and children.

This typology of contact structures is by no means unique or exclusive. For example, matrix *C*2 could also be listed in category A, and *C*4 in category E. None of the expert panelists felt that there were any major omissions in the list of matrix models proposed to them, within the limits of the exercise.

Table 1. *Publication and expert priors and Bayes' factors without (H: no) and with (H: yes) individual heterogeneity*

	Priors		Bayes factors (×100)			Priors		Bayes factors (×100)	
Matrix	Publication	Expert	H: no*	H: yes†	Matrix	Publication	Expert	H: no*	H: yes†
*A*1	0·0208	0·0115	4·997	8·759	*C*1	0·0417	0·0292	0·000	0·000
*A*2	0·2083	0·0301	3·216	3·044	*C*2	0·0208	0·0377	1·905	3·041
*A*3	0·1667	0·0135	51·337	53·376	*C*3	0·0417	0·0187	0·000	0·000
*A*4	0·0208	0·0343	0·003	0·003	*C*4	0·0208	0·1098	0·000	0·000
*A*5	0·0417	0·0147	2·552	0·874	*D*1	0·1042	0·0323	2·152	3·744
*A*6	0·0417	0·0312	100·0	6·596	*D*2	0·0208	0·0451	0·001	0·001
*B*1	0·0417	0·0255	0·003	0·369	*D*3	0·0208	0·0932	0·000	0·000
B2	0·0417	0·0285	0·000	0·000	*D*4	0·0208	0·0291	64·859	100·00
B3	0·0208	0·0348	0·000	0·0050	*D*5	0·0208	0·0877	0·010	0·022
*B*4	0·0208	0·0287	71·763	15·356	*E*1	0·0208	0·2031	0·220	0·001
*B*5	0·0208	0·0168	0·000	0·000	*E*2	0·0208	0·0445	60·814	0·603

* Relative to *A*6.
† Relative to *D*4.

Prior structural probabilities

The neutral prior is $p(M_i) = 1/22$, $i = 1, \ldots, 22$. The publication prior is shown in Table 1; the references used to construct it are listed in Appendix 2. The most frequently used matrix was *A*2 (10 mentions) followed by *A*3 (8 mentions) and *D*1 (5 mentions). None of the others was used more than twice.

The five panelists scored the 22 matrices in broadly concordant fashion: four panelists ranked *E*1 first; the fifth ranked it fourth. Thus, averaging the five individual priors is justified. The expert prior is shown in Table 1. Matrix *E*1 obtained the highest expert prior probability (0·2031), followed by *C*4(0·1098), *D*3(0·0932) and *D*6(0·0877). None of the others scored more than 0·05.

The Spearman rank correlation between the publication and expert priors is $-0{\cdot}47$, $P = 0{\cdot}029$ calculated using a two-tailed Monte Carlo permutation test: the two priors are significantly negatively correlated.

Mumps and rubella data, models and posterior distributions

Paired serological survey data were available on $n = 4193$ boys. Figure 1 shows the bivariate distribution of serological test results for mumps and rubella by age.

Goodness of fit

All regular models gave acceptable deviances when fitted separately to the mumps and rubella data, and when fitted to the paired data using frailty models; the regular models are those for which the unrestricted maximum-likelihood estimates satisfy the non-negativity constraints. The best fit was achieved with the regular 4×4 models, with deviances 41·53 [40 degrees of freedom (D.F.), $P = 0{\cdot}40$] for rubella, 48·87 (40 D.F., $P = 0{\cdot}16$) for mumps, and 141·72 (123 D.F., $P = 0{\cdot}12$) for the frailty model. The worst model fit for a regular model was for the 3×3 model *A*1, with deviances 48·70 (41 D.F., $P = 0{\cdot}19$) for rubella, 56·75 (41 D.F., $P = 0{\cdot}05$) for mumps, and 154·20 (125 D.F., $P = 0{\cdot}04$) for the frailty model. The regular 5×5 and 6×6 models achieved a similar goodness of fit to the 4×4 models. Non-regular models, namely those with a contact rate parameter constrained to zero, generally produced considerably worse fits than regular models of the same dimension.

Bayes factors: no individual heterogeneity

Matrix *A*6 gave the maximum probability in eq (1) and so was chosen as reference. The Bayes factors (×100) relative to matrix *A*6 for the models without heterogeneity are shown in Table 1. The smaller the Bayes factor, the less the data supports the matrix relative to *A*6. Five matrices with high Bayes factors relative to *A*6 stand out. This group includes *A*6, *B*4, *D*4, *E*2 and *A*3, all with Bayes factors in excess of 5 ($A6 \equiv 100$). None of the 6×6 matrices scored highly, all producing non-regular fits under proportionality.

Bayes factors: with individual heterogeneity

Allowing for heterogeneity, the matrix with the highest probability is *D*4. Table 1 shows the Bayes factors

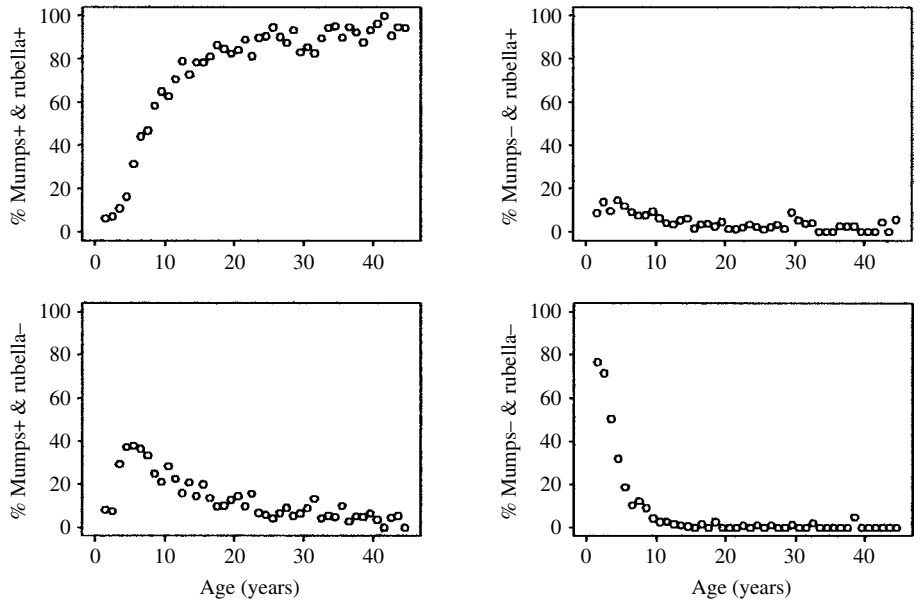

Fig. 1. Joint distribution of mumps and rubella seropositivity by age.

(×100) relative to *D*4. The matrices with Bayes factors greater than 5 relative to *D*4, are, in descending order, *A*3, *B*4, *A*1 and *A*6. Only *A*1 is not among the top five without individual heterogeneity, although *A*6 is now considerably less plausible.

Posterior structural probabilities

Table 2 gives the posterior structural probabilities $p(M_i|y)$ for the three prior distributions. Whatever the choice of structural prior, the matrices with highest posterior probability are *A*6, *B*4, *D*4, *E*2 and *A*3 for the models without heterogeneity. For the models with heterogeneity, the models with highest posterior probability are a little more dependent on the priors. Models *D*4, *A*3, and *B*4 are all among the top five whatever the prior. The other two among the top five positions are *A*6 and *D*1 for the expert prior, *A*2 and *D*1 for the publication prior, and *A*1 and *A*6 for the neutral prior.

Matrix *E*1 is not among the high scoring matrices, in spite of a high prior probability from the elicitation procedure and good fits to the data under proportionality. The defining feature of matrix *E*1 is the presence of parameter β_5 in off-diagonal positions, to allow for increased mixing between adults and children. However, the estimate of β_5 is zero when the contact matrices for mumps and rubella are assumed proportional. The term $-\frac{1}{2}(k+r)\log(n)$ in equation (1) strongly penalizes models with parameters estimated on the boundary.

Basic reproduction number

As expected [19, 27], the estimates of the reproduction number R_0 vary widely according to the model used; allowing for heterogeneity increases their value (see Table 3). The approximate posterior distributions of $\log(R_0)$ with and without heterogeneity for mumps and rubella for the five most plausible models are shown in Figures 2 and 3. Figures 4 and 5 show the overall posterior densities for $\log(R_0)$ for mumps and rubella, taking into account both the sampling variation and the uncertainty in model selection between all 22 models. Table 4 gives the principal modes and 95% CR for R_0 based on high density regions of the posterior of $\log(R_0)$. For mumps, the position of the principal posterior mode is sensitive to the structural prior distribution used: the publication prior tends to favour lower values of R_0; the expert and neutral priors produce broadly similar results. In contrast, the 95% CR are largely insensitive to the choice of prior.

Sensitivity to approximations

We repeated all calculations after omitting the term $\frac{1}{2}(k-r)\log(2\pi)$ from equation (1), as advocated by Raftery [52]. The only effect was to permute the ranking of the five most plausible matrices: to *D*4, *E*2, *A*3, *A*6, *B*4 for the models without heterogeneity, and to *D*4, *A*3, *A*1, *B*4, *A*6 for the models with heterogeneity. As expected, inclusion of this term tends to favour the models with more parameters. The posterior distributions of $\log(R_0)$ were largely unaffected.

Table 2. *Posterior structural probabilities calculated using three prior distributions*

	No heterogeneity			With heterogeneity		
Matrix	Expert	Publi-cation	Neutral	Expert	Publi-cation	Neutral
*A*1	0·0053	0·0058	0·0137	0·0211	0·0141	0·0447
*A*2	0·0089	0·0372	0·0088	0·0192	0·0491	0·0155
*A*3	0·0638	0·4757	0·1411	0·1514	0·6891	0·2726
*A*4	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*A*5	0·0035	0·0059	0·0070	0·0027	0·0028	0·0045
*A*6	0·2880	0·2317	0·2749	0·0434	0·0213	0·0337
*B*1	0·0000	0·0000	0·0000	0·0020	0·0012	0·0019
*B*2	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*B*3	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*B*4	0·1900	0·0831	0·1972	0·0928	0·0248	0·0784
*B*5	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*C*1	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*C*2	0·0066	0·0022	0·0052	0·0241	0·0049	0·0155
*C*3	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*C*4	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
D1	0·0064	0·0125	0·0059	0·0255	0·0302	0·0191
*D*2	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*D*3	0·0000	0·0000	0·0000	0·0000	0·0000	0·0000
*D*4	0·1739	0·0751	0·1783	0·6117	0·1614	0·5107
*D*5	0·0000	0·0000	0·0000	0·0004	0·0000	0·0001
*E*1	0·0041	0·0003	0·0006	0·0000	0·0000	0·0000
*E*2	0·2495	0·0704	0·1671	0·0056	0·0010	0·0031

DISCUSSION

The availability of good serological survey data has enhanced the practical application of age-stratified matrix models for infectious diseases. However, such data are insufficient to identify the contact matrix without strong assumptions. Our search of the literature revealed a great diversity of modelling assumptions, leading to widely different estimates of R_0. In this paper we sought to select the 'best' models and allow for model uncertainty using the methods of ref. [19].

The underlying rationale for our approach merits discussion. The choice of matrix model in a particular study may be guided by the specific epidemiological question the investigator is seeking to elucidate. It may, therefore, be objected that, in working from our list of 22 models, we have ignored the context in which they were developed. However, while it is true that different models may have been developed for different purposes, it is also true that the investigator's aim in each case is to capture some important feature of infection transmission. Our approach provides a way of ranking and combining these features. Furthermore, the expert prior allows for contextual judgements, at least as perceived by the experts. Nevertheless, we recognize that the Bayesian model averaging approach remains controversial (see the discussion in ref. [48]).

The preferences expressed in our 'publication prior' are likely to be strongly influenced by precedent and seminal publications such as ref. [3], a form of publication bias. For this reason we do not regard the publication prior as a reliable indicator of current best expert opinion. On the other hand, the neutral and expert prior produced broadly similar results. Interestingly, the models preferred by the experts tended not to be supported by the data. This could suggest that expert opinion is unreliable and may be ignored. Perhaps more likely, it could also suggest that our elicitation procedure, based on the simple approach of allocating overall scores, did not successfully exploit the panel's expertise. More work on elicitation methods in this area is required.

The elicitation exercise raised interesting issues. Experts tended to prefer higher dimensional over lower dimensional models *per se* rather than for substantive epidemiological reasons, a preference not supported by the data. We suspect also that their choice of matrix structure was influenced by beliefs about matrix parameters. For example, four of the five experts ranked matrix *E*1 first, probably with the idea that $\beta_5 > \beta_6$. Specifying such orderings may provide further discrimination.

We limited our elicitation exercise to matrix structure. In particular, we chose not to make any explicit assumptions about priors on the parameters, other than their range, e.g. $\beta_i \geqslant 0$. Instead we relied on approximations for Bayes factors. This was sufficient to identify the groups of most plausible models; the orderings within these subgroups are perhaps of lesser importance. In averaging over values for the basic reproduction number R_0 we used profile likelihoods approximations to the posterior distributions. This is not unreasonable since we are interested primarily in 'ball park' values of R_0.

We kept the analyses with and without individual heterogeneity separate as the literature generally ignores it. However, the evidence for it is strong and its magnitude is readily quantifiable. Ignoring individual heterogeneity produces estimates of R_0 that are far too low.

The results for rubella are insensitive to the structural prior. For mumps, the posterior distribution of log R_0 is not unimodal and the relative height of the

Table 3. *Estimates of R_0 for rubella and mumps for each matrix*

	No heterogeneity		With heterogeneity			No heterogeneity		With heterogeneity	
Matrix	Rubella	Mumps	Rubella	Mumps	Matrix	Rubella	Mumps	Rubella	Mumps
*A*1	5·19	4·19	8·01	7·48	*C*1	3·77	3·32	5·36	4·52
*A*2	3·77	3·21	5·80	4·64	*C*2	3·68	3·16	6·13	4·56
*A*3	3·87	3·35	5·86	5·00	*C*3	3·22	5·26	11·86	9·75
*A*4	3·56	3·75	5·48	6·61	*C*4	3·65	4·69	5·73	15·66
*A*5	3·78	3·28	5·82	4·82	*D*1	4·15	20·41	6·24	43·93
*A*6	3·86	5·81	5·93	9·93	*D*2	4·19	20·40	6·58	43·93
*B*1	3·79	3·34	6·04	4·79	*D*3	3·67	8·98	5·35	15·09
*B*2	3·20	3·58	6·63	5·93	*D*4	4·12	10·74	6·15	19·40
*B*3	3·20	3·58	6·54	5·96	*D*5	10·77	13·20	18·11	23·07
*B*4	3·87	5·83	5·92	9·83	*E*1	4·04	13·35	6·01	24·49
*B*5	3·28	5·68	6·91	12·93	*E*2	4·08	6·18	6·20	8·00

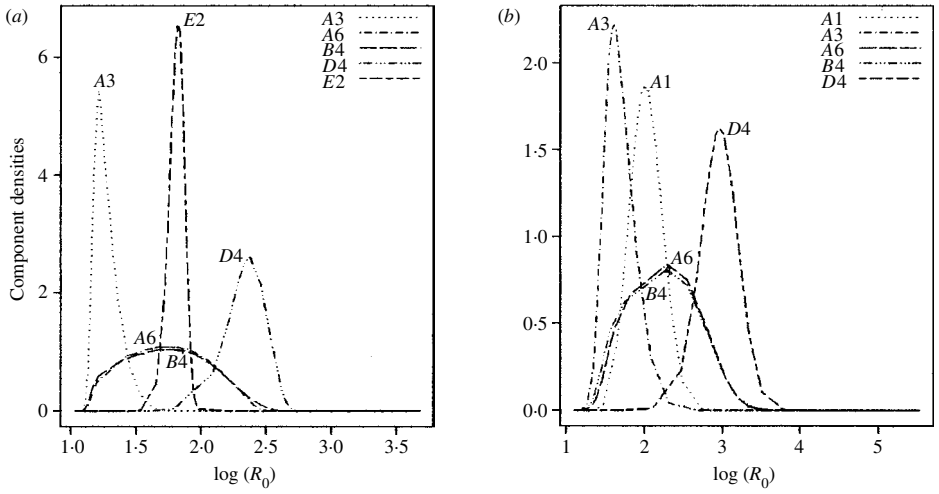

Fig. 2. Mumps: approximate posterior densities of log(R_0) for five plausible models. (*a*) Without heterogeneity; (*b*) with heterogeneity.

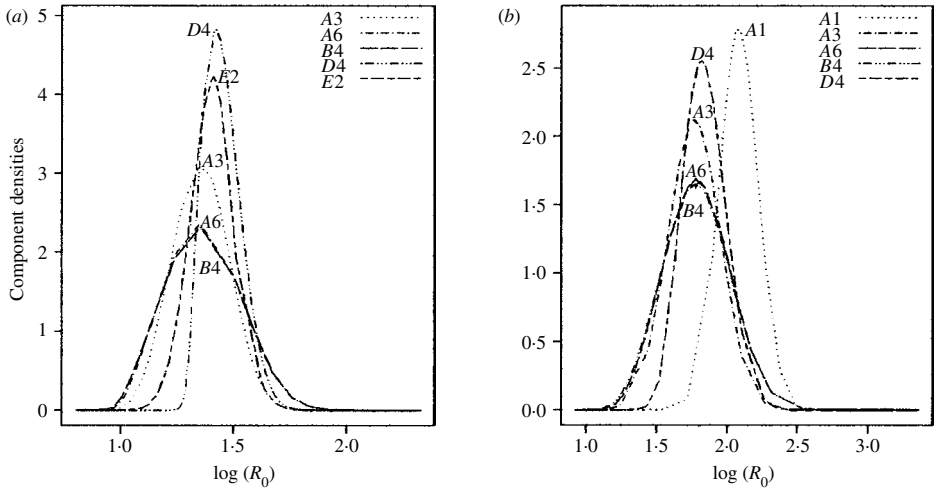

Fig. 3. Rubella: approximate posterior densities of log(R_0) for five plausible models. (*a*) Without heterogeneity; (*b*) with heterogeneity.

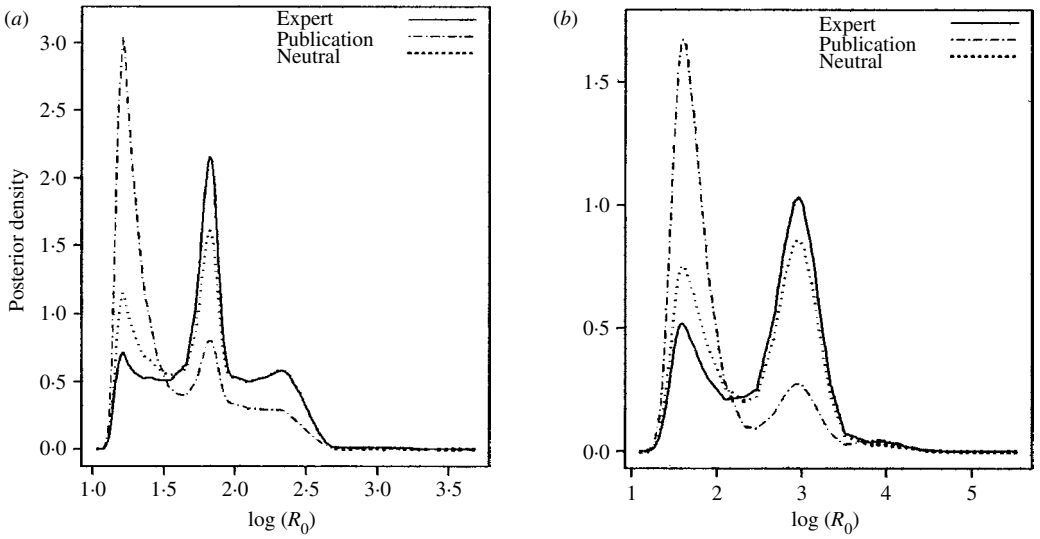

Fig. 4. Mumps: approximate overall posterior densities of log(R_0) based on three structural prior distributions. (*a*) Without heterogeneity; (*b*) with heterogeneity.

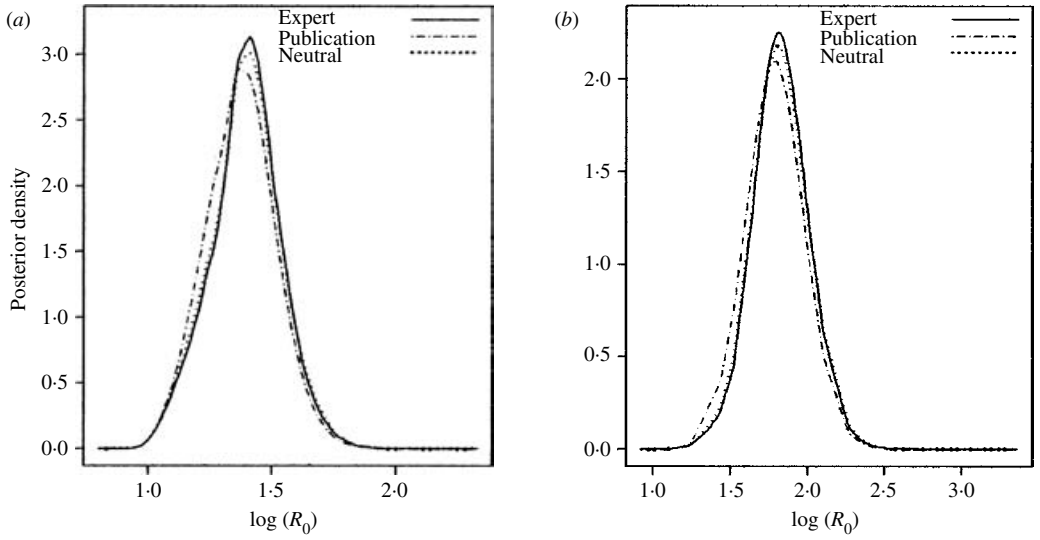

Fig. 5. Rubella: approximate overall posterior densities of log(R_0) based on three structural prior distributions. (*a*) Without heterogeneity; (*b*) with heterogeneity.

Table 4. *Principal modes and 95% credible regions (CR) for* R_0

	No heterogeneity				With heterogeneity				
	Rubella		Mumps		Rubella		Mumps		
Prior distribution	Mode	CR	Mode	CR	Mode	CR	Mode	CR	
Expert	4·10	3·00–5·31	6·17	3·16–11·82	6·11	4·31–9·21	19·30	4·01–31·50	
Publication	3·90	2·97–5·21	3·35	3·06–10·70	5·99	4·06–8·94	4·44	3·71–11·59	∪12·06–27·39
Neutral	4·10	2·97–5·31	6·17	3·16–11·82	6·05	4·31–9·30	19·30	3·97–29·67	

modes is sensitive to the prior. This is because the seroprevalence profile for mumps is virtually flat in older age groups, and hence there is very little information in the data on contact rates between adults. However, the credible regions were not unduly sensitive to the prior. Overall, our preferences are for the expert prior, and for the analyses with heterogeneity. We conclude that R_0 for rubella lies between 4·3 and 9·2 with mode 6·1, while R_0 for mumps lies between 4·0 and 31·5, with (principal) mode 19·3. If pressed to select a 'best' model type among those surveyed, we would recommend assortative mixing models such as *D*4.

At the heart of our approach lies the proportionality criterion for infections transmitted via the same route: better fit under proportionality implies greater plausibility. However, alternative methods based on contact surveys [34, 35] imply direct proportionality of contact matrices, and in this sense make still stronger assumptions. The factors influencing transmission of infections via the same route call for further investigation [53]. The problem of identifying the contact matrix is likely to continue to be a fertile area of further research.

ACKNOWLEDGEMENTS

We thank our panellists John Edmunds, Mirjam Kretzchmar, Graham Medley, James Nokes and Jacco Wallinga. We also thank two anonymous referees for their constructive comments. This work was supported by the Wellcome Trust, Project grant 061830.

APPENDIX 1. Estimation of contact rates

Let λ_i denote the force of infection in age group i, D the duration of the infectious period, N the population size and L the life expectancy. The contact rates β_{ij} are related to λ_i by:

$$\lambda_i = \frac{ND}{L} \sum_{j=1}^{K} \beta_{ij} \mathrm{I}_j, \tag{A 1}$$

where I_j describes the distribution of infectious individuals. This is

$$\mathrm{I}_j = \sum_{a=a_{j-1}}^{a_j-1} m(a)\{S(a) - S(a+1)\},$$

where $m(a)$ is the proportion of the population alive at ages $a = 0, 1, \ldots, 99$. We set $m(100) = 0$. $S(a)$ is the proportion of individuals of age a remaining uninfected:

$$S(a) = \exp\{-\lambda_1(a_1 - a_0) \ldots - \lambda_{j-1}(a_{j-2} - a_{j-1}) - \lambda_j(a - a_{j-1})\}, \quad \text{for } a_{j-1} < a \leqslant a_j. \tag{A 2}$$

Let B denote the $K \times K$ matrix with entries $(ND/L)\beta_{ij}$. Given a model for B, solve eqn (A 1) to obtain the corresponding forces of infection λ_i, obtain the proportions susceptible in each age group from eqn (A 2), and fit them to serological survey data using a binomial model. The procedure is iterated to obtain the maximum-likelihood estimate of matrix B. The basic reproduction number is the leading eigenvalue of the matrix $E \times B$, where E is the $K \times K$ diagonal matrix with jth diagonal element $\sum_{a=a_{j-1}}^{a_j-1} m(a)$.

APPENDIX 2. The matrix models

The references for each model are given in square brackets.

Category A models

*A*1 [13]

$$\begin{pmatrix} 1 & 1 & 3 \\ 1 & 2 & 3 \\ 3 & 3 & 3 \end{pmatrix}$$

*A*2 [3, 7, 11, 12, 14, 15, 19, 22, 24, 25]

$$\begin{pmatrix} 1 & 1 & 3 & 4 & 5 \\ 1 & 2 & 3 & 4 & 5 \\ 3 & 3 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

*A*3 [6, 8–10, 16, 26, 27, 45]

$$\begin{pmatrix} 1 & 1 & 3 & 4 \\ 1 & 2 & 3 & 4 \\ 3 & 3 & 3 & 4 \\ 4 & 4 & 4 & 4 \end{pmatrix}$$

$A4$ [20]
$$\begin{pmatrix} 1 & 1 & 3 & 4 & 5 & 6 \\ 1 & 2 & 3 & 4 & 5 & 6 \\ 3 & 3 & 3 & 4 & 5 & 6 \\ 4 & 4 & 4 & 4 & 5 & 6 \\ 5 & 5 & 5 & 5 & 5 & 6 \\ 6 & 6 & 6 & 6 & 6 & 6 \end{pmatrix}$$

$A5$ [3, 7]
$$\begin{pmatrix} 1 & 1 & 1 & 4 & 5 \\ 1 & 2 & 3 & 4 & 5 \\ 1 & 3 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$A6$ [18, 21]
$$\begin{pmatrix} 1 & 1 & 1 & 1 & 5 \\ 1 & 2 & 4 & 4 & 5 \\ 1 & 4 & 3 & 4 & 5 \\ 1 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

Category B models

$B1$ [7, 29]
$$\begin{pmatrix} 1 & 1 & 1 & 4 & 5 \\ 1 & 2 & 2 & 4 & 5 \\ 1 & 2 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$B2$ [17, 29]
$$\begin{pmatrix} 1 & 1 & 1 & 1 & 5 \\ 1 & 2 & 2 & 2 & 5 \\ 1 & 2 & 3 & 4 & 5 \\ 1 & 2 & 4 & 3 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$B3$ [29]
$$\begin{pmatrix} 1 & 1 & 1 & 1 & 5 \\ 1 & 2 & 2 & 2 & 5 \\ 1 & 2 & 3 & 4 & 5 \\ 1 & 2 & 4 & \alpha.3 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$
with $\alpha = 2$

$B4$ [19]
$$\begin{pmatrix} 1 & 1 & 4 & 4 & 5 \\ 1 & 2 & 4 & 4 & 5 \\ 4 & 4 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$B5$ [27]
$$\begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 2 & 2 & 2 \\ 1 & 2 & 3 & 4 \\ 1 & 2 & 4 & 4 \end{pmatrix}$$

Category C models

$C1$ [7, 28]
$$\begin{pmatrix} 1 & 2 & 3 & 4 & 5 \\ 2 & 2 & 3 & 4 & 5 \\ 3 & 3 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$C2$ [7]
$$\begin{pmatrix} 1 & 1 & 3 & 4 & 1 \\ 1 & 2 & 3 & 4 & 5 \\ 3 & 3 & 3 & 4 & 5 \\ 4 & 4 & 4 & 4 & 5 \\ 1 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$C3$ [27, 45]
$$\begin{pmatrix} 1 & 2 & 3 & 2 \\ 2 & 2 & 2 & 2 \\ 3 & 2 & 4 & 4 \\ 2 & 2 & 4 & 4 \end{pmatrix}$$

$C4$ [23]
$$\begin{pmatrix} 1 & 5 & 5 & 1 & 5 \\ 5 & 2 & 5 & 5 & 5 \\ 5 & 5 & 2 & 5 & 5 \\ 1 & 5 & 5 & 3 & 5 \\ 5 & 5 & 5 & 5 & 4 \end{pmatrix}$$

Category D models

$D1$ [3, 12, 18, 19, 21]
$$\begin{pmatrix} 1 & 5 & 5 & 5 & 5 \\ 5 & 2 & 5 & 5 & 5 \\ 5 & 5 & 3 & 5 & 5 \\ 5 & 5 & 5 & 4 & 5 \\ 5 & 5 & 5 & 5 & 5 \end{pmatrix}$$

$D2$ [20]
$$\begin{pmatrix} 1 & 6 & 6 & 6 & 6 & 6 \\ 6 & 2 & 6 & 6 & 6 & 6 \\ 6 & 6 & 3 & 6 & 6 & 6 \\ 6 & 6 & 6 & 4 & 6 & 6 \\ 6 & 6 & 6 & 6 & 5 & 6 \\ 6 & 6 & 6 & 6 & 6 & 6 \end{pmatrix}$$

$D3$ [23]
$$\begin{pmatrix} 1 & 5 & 5 & 5 & 5 \\ 5 & 2 & 5 & 5 & 5 \\ 5 & 5 & 2 & 5 & 5 \\ 5 & 5 & 5 & 3 & 5 \\ 5 & 5 & 5 & 5 & 4 \end{pmatrix}$$

$D4$ [45]
$$\begin{pmatrix} 1 & 4 & 4 & 4 \\ 4 & 2 & 4 & 4 \\ 4 & 4 & 3 & 4 \\ 4 & 4 & 4 & 4 \end{pmatrix}$$

$D5$ [30]
$$\begin{pmatrix} 1 & 5 & 5 & 5 & 5 \\ 5 & 2 & 5 & 5 & 5 \\ 5 & 5 & 3 & 5 & 5 \\ 5 & 5 & 5 & 3 & 5 \\ 5 & 5 & 5 & 5 & 4 \end{pmatrix}$$

Category E models

*E*1 [20]

$$\begin{pmatrix} 1 & 6 & 6 & 6 & 5 & 6 \\ 6 & 2 & 6 & 6 & 5 & 6 \\ 6 & 6 & 3 & 6 & 6 & 6 \\ 6 & 6 & 6 & 4 & 6 & 6 \\ 5 & 5 & 6 & 6 & 5 & 6 \\ 6 & 6 & 6 & 6 & 6 & 6 \end{pmatrix}$$

*E*2 [53]

$$\begin{pmatrix} 1 & 4 & 4 & 4 & 4 \\ 4 & 2 & 3 & 4 & 4 \\ 4 & 3 & \alpha.2 & 4 & 4 \\ 4 & 4 & 4 & \beta.2 & 4 \\ 4 & 4 & 4 & 4 & 4 \end{pmatrix}$$

with $\alpha = 1{\cdot}5$ and $\beta = 1{\cdot}75$.

REFERENCES

1. **Bailey NTJ.** Mathematical theory of infectious diseases, 2nd edn. London: Griffin, 1975.
2. **Becker NG.** Analysis of infectious disease data. London: Chapman and Hall, 1989.
3. **Anderson RM, May RM.** Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press, 1991.
4. **Daley DJ, Gani J.** Epidemic modelling. Cambridge: Cambridge University Press, 1999.
5. **Diekmann O, Heesterbeek JAP.** Mathematical theory of infectious diseases. Chichester: Wiley, 2000.
6. **Schenzle D.** An age-structured model of pre- and post-vaccination measles transmission. IMA J Math Appl Med Biol 1984; **1**: 169–191.
7. **Anderson RM, May RM.** Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. J Hyg 1985; **94**: 365–436.
8. **Garnett GP, Grenfell BT.** The epidemiology of varicella-zoster virus infections: a mathematical model. Epidemiol Infect 1992; **108**: 495–511.
9. **Bolker B.** Chaos and complexity in measles models: a comparative numerical study. IMA J Math Appl Med Biol 1993; **10**: 83–95.
10. **Bolker BM, Grenfell BT.** Chaos and biological complexity in measles dynamics. Proc R Soc Lond B Biol Sci 1993; **251**: 75–81.
11. **Agur Z, Cojocaru L, Mazor G, Anderson RM, Danon YL.** Pulse mass measles vaccination across age cohorts. Proc Natl Acad Sci USA 1993; **90**: 11698–11702.
12. **Rouderfer V, Becker NG, Hethcote HW.** Waning immunity and its effects on vaccination schedules. Math Biosci 1994; **124**: 59–82.
13. **Nokes DJ, Swinton J.** The control of childhood viral infections by pulse vaccination. IMA J Math Appl Med Biol 1995; **12**: 29–53.
14. **Rouderfer V, Becker NG.** Assessment of two-dose vaccination schedules: availability for vaccination and catch-up strategies. Math Biosci 1995; **129**: 41–66.
15. **Becker NG, Rouderfer V.** Simultaneous control of measles and rubella by multidose vaccination schedules. Math Biosci 1996; **131**: 81–102.
16. **Ferguson NM, Nokes DJ, Anderson RM.** Dynamical complexity in age-structured models of the transmission of the measles virus: epidemiological implications at high levels of vaccine uptake. Math Biosci 1996; **138**: 101–130.
17. **Begg NT, Gay NJ.** Theory of infectious disease transmission and herd immunity. In: Topley and Wilson's microbiology and microbial infections: bacterial infections. London: Arnold, 1998; **3**: 147–165.
18. **Edmunds WJ, Gay NJ, Kretzchmar M, et al.** The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. Epidemiol Infect 2000; **125**: 635–650.
19. **Farrington CP, Kanaan MN, Gay NJ.** Estimation of the basic reproduction number for infectious diseases from age-stratified serological survey data. Appl Statist 2001; **50**: 1–33.
20. **Anderson RM, Grenfell BT.** Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. J Hyg 1986; **96**: 305–333.
21. **Edmunds WJ, Van De Heijden OG, Eerola M, et al.** Modelling rubella in Europe. Epidemiol Infect 2000; **125**: 617–634.
22. **Grenfell BT, Anderson RM.** Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination. Proc R Soc Lond B Biol Sci 1989; **236**: 213–252.
23. **Coen PG, Heath PT, Garnett GP.** The Hib immunization programme in the Oxford region: an analysis of the impact of vaccine administration on the incidence of disease. Epidemiol Infect 1999; **123**: 389–402.
24. **Halloran ME, Cochi SL, Lieu TA, Wharton M, Fehrs L.** Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States. Am J Epidemiol 1994; **140**: 81–104.
25. **Halloran ME, Watelet L, Struchiner CJ.** Epidemiologic effects of vaccines with complex direct effects in age-structured populations. Math Biosci 1994; **121**: 193–225.
26. **Ferguson NM, Anderson RM, Garnett GP.** Mass vaccination to control chickenpox: the influence of zoster. Proc Natl Acad Sci USA 1996; **93**: 7231–7235.
27. **Greenhalgh D, Dietz K.** Some bounds on estimates for reproductive ratios derived from the age-specific force of infection. Math Biosci 1994; **124**: 9–57.
28. **Edmunds WJ, Medley GF, Nokes DJ.** The transmission dynamics and control of Hepatitis B virus in the Gambia. Stat Med 1996; **15**: 2215–2233.

29. **Gay NJ, Hesketh LM, Morgan-Capner P, et al.** Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. Epidemiol Infect 1995; **115**: 139–156.
30. **Wallinga J, Levy-Bruhl D, Gay NJ, Wachmann CH.** Estimation of measles reproduction ratios and prospects for elimination of measles by vaccination in some Western European countries. Epidemiol Infect 2001; **127**: 281–295.
31. **Dietz K.** Transmission and control of arbovirus diseases. In: Ludwig D, Cooke KL, eds. Epidemiology. Philadelphia: Society for Industrial and Applied Mathematics, 1975: 104–121.
32. **Dietz K, Schenzle D.** Proportionate mixing models for age-dependent infection transmission. J Math Biol 1985; **22**: 117–120.
33. **Hethcote HW, Van Ark JW.** Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation, and immunization programs. Math Biosci 1987; **84**: 85–118.
34. **Edmunds WJ, O'Callaghan CJ, Nokes DJ.** Who mixes with whom? A method to determine the contact patterns of adults that may lead to the spread of airborne infections. Proc R Soc Lond B Biol Sci 1997; **264**: 949–957.
35. **Wallinga J, Edmunds WJ, Kretzschmar M.** Perspective: human contact patterns and the spread of airborne infectious diseases. Trends in Microbiology 1999; **7**: 372–377.
36. **Griffiths DA.** A catalytic model of infection for measles. Appl Statist 1974; **23**: 330–339.
37. **Grenfell BT, Anderson RM.** The estimation of age-related rates of infection from case notifications and serological data. J Hyg 1985; **95**: 419–436.
38. **Farrington CP.** Modelling forces of infection for measles, mumps and rubella. Stat Med 1990; **9**: 953–967.
39. **Morgan-Capner P, Wright J, Miller CL, Miller E.** Surveillance of antibody to measles, mumps, and rubella by age. Br Med J 1988; **297**: 770–772.
40. **OPCS.** Mortality Statistics 1986. London, DH1 (HMSO) 1989: 18.
41. **Chin J.** Control of communicable diseases manual. Washington: American Public Health Association, 2000.
42. **Eichner M, Zehnder S, Dietz K.** An age-structured model for measles vaccination. In: Isham VS, Medley GF, eds. Models for infectious diseases of humans. Cambridge: Cambridge University Press, 1993.
43. **Azevedo Neto RS, Silveira ASB, Nokes DJ, et al.** Rubella seroepidemiology in a nonimmunized population of Sao Paulo state, Brazil. Epidemiol Infect 1994; **113**: 161–173.
44. **Keiding N.** Age-specific incidence and prevalence: a statistical perspective. J Roy Statist Soc Series A 1991; **154**: 371–412.
45. **Greenhalgh D.** Contribution to the discussion of the paper by Farrington CP, Kanaan MN, Gay NJ (2001). Estimation of the basic reproduction number for infectious diseases from age-stratified serological survey data. Appl Statist 2001; **50**: 1–33.
46. **Roberts G, Tobias MI.** Predicting and preventing measles epidemics in New Zealand: application of a mathematical model. Epidemiol Infect 2000; **124**: 279–287.
47. **Babad HR, Nokes DJ, Gay NJ, et al.** Predicting the impact of measles vaccination in England and Wales: model validation and analysis of policy options. Epidemiol Infect 1995; **114**: 319–344.
48. **Draper D.** Assessment and propagation of model uncertainty. J Roy Statist Soc, Series B 1995; **57**: 45–97.
49. **Kass RE, Raftery AE.** Bayes factors. J Am Statist Assoc 1995; **90**:773–795.
50. **Barndorff-Neilsen OE, Cox DR.** Asymptotic techniques for use in statistics. London: Chapman and Hall, 1989.
51. **Adler FR.** The effects of averaging on the basic reproduction ratio. Math Biosci 1992; **111**: 89–98.
52. **Raftery AE.** Contribution to the discussion of the paper by Draper D (1995). Assessment and propagation of model uncertainty. J Roy Statist Soc, Series B 1995; **57**: 45–97.
53. **Keeling MJ, Grenfell BT.** Individual-based perspectives on R_0. J Theor Biol 2000; **203**: 51–61.