

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

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### 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,  $R_0 = 6.1$  [95% credible region (CR) 4.3–9.2] for rubella and  $R_0 = 19.3$  (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

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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 ( $a_{i-1}$ ,  $a_i$ ),  $i=1, \dots, K$  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  $5 \times 5$  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  $M_i$ ,  $i = 1, \dots, N$ , 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  $p(M_i) = r_i / \sum r_j$ . This is our ‘publication prior’. Here  $\sum r_j$  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

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

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  $\alpha$ . If the routes of transmission were exactly the same, then  $B_M = \alpha \times B_R$ . 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  $\beta = (\beta_1, \beta_2, \dots)$ . We assumed unspecified diffuse priors on  $[0, \infty)$  for the  $\beta_i$  and on  $[0, 1]$  for  $\alpha$ , 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

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

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  $\beta$  and  $\alpha$  under the proportionality assumption, and  $\text{lik}_0$  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  $M_i$ ,  $i=1, \dots, N$ , and prior probabilities  $p(M_i)$ , we obtained the posterior structural probabilities

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

the proportionality constant  $\gamma$  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 *C2* could also be listed in category A, and *C4* 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

Matrix	Priors		Bayes factors ( $\times 100$ )		Matrix	Priors		Bayes factors ( $\times 100$ )	
	Publication	Expert	H: no*	H: yes†		Publication	Expert	H: no*	H: yes†
<i>A1</i>	0.0208	0.0115	4.997	8.759	<i>C1</i>	0.0417	0.0292	0.000	0.000
<i>A2</i>	0.2083	0.0301	3.216	3.044	<i>C2</i>	0.0208	0.0377	1.905	3.041
<i>A3</i>	0.1667	0.0135	51.337	53.376	<i>C3</i>	0.0417	0.0187	0.000	0.000
<i>A4</i>	0.0208	0.0343	0.003	0.003	<i>C4</i>	0.0208	0.1098	0.000	0.000
<i>A5</i>	0.0417	0.0147	2.552	0.874	<i>D1</i>	0.1042	0.0323	2.152	3.744
<i>A6</i>	0.0417	0.0312	100.0	6.596	<i>D2</i>	0.0208	0.0451	0.001	0.001
<i>B1</i>	0.0417	0.0255	0.003	0.369	<i>D3</i>	0.0208	0.0932	0.000	0.000
<i>B2</i>	0.0417	0.0285	0.000	0.000	<i>D4</i>	0.0208	0.0291	64.859	100.00
<i>B3</i>	0.0208	0.0348	0.000	0.0050	<i>D5</i>	0.0208	0.0877	0.010	0.022
<i>B4</i>	0.0208	0.0287	71.763	15.356	<i>E1</i>	0.0208	0.2031	0.220	0.001
<i>B5</i>	0.0208	0.0168	0.000	0.000	<i>E2</i>	0.0208	0.0445	60.814	0.603

\* Relative to *A6*.

† Relative to *D4*.

### Prior structural probabilities

The neutral prior is  $p(M_i) = 1/22$ ,  $i = 1, \dots, 22$ . 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 *A2* (10 mentions) followed by *A3* (8 mentions) and *D1* (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 *E1* first; the fifth ranked it fourth. Thus, averaging the five individual priors is justified. The expert prior is shown in Table 1. Matrix *E1* obtained the highest expert prior probability (0.2031), followed by *C4* (0.1098), *D3* (0.0932) and *D6* (0.0877). None of the others scored more than 0.05.

The Spearman rank correlation between the publication and expert priors is  $-0.47$ ,  $P = 0.029$  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  $4 \times 4$  models, with deviances 41.53 [40 degrees of freedom (D.F.),  $P = 0.40$ ] for rubella, 48.87 (40 D.F.,  $P = 0.16$ ) for mumps, and 141.72 (123 D.F.,  $P = 0.12$ ) for the frailty model. The worst model fit for a regular model was for the  $3 \times 3$  model *A1*, with deviances 48.70 (41 D.F.,  $P = 0.19$ ) for rubella, 56.75 (41 D.F.,  $P = 0.05$ ) for mumps, and 154.20 (125 D.F.,  $P = 0.04$ ) for the frailty model. The regular  $5 \times 5$  and  $6 \times 6$  models achieved a similar goodness of fit to the  $4 \times 4$  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 *A6* gave the maximum probability in eq (1) and so was chosen as reference. The Bayes factors ( $\times 100$ ) relative to matrix *A6* for the models without heterogeneity are shown in Table 1. The smaller the Bayes factor, the less the data supports the matrix relative to *A6*. Five matrices with high Bayes factors relative to *A6* stand out. This group includes *A6*, *B4*, *D4*, *E2* and *A3*, all with Bayes factors in excess of 5 ( $A6 \equiv 100$ ). None of the  $6 \times 6$  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 *D4*. Table 1 shows the Bayes factors

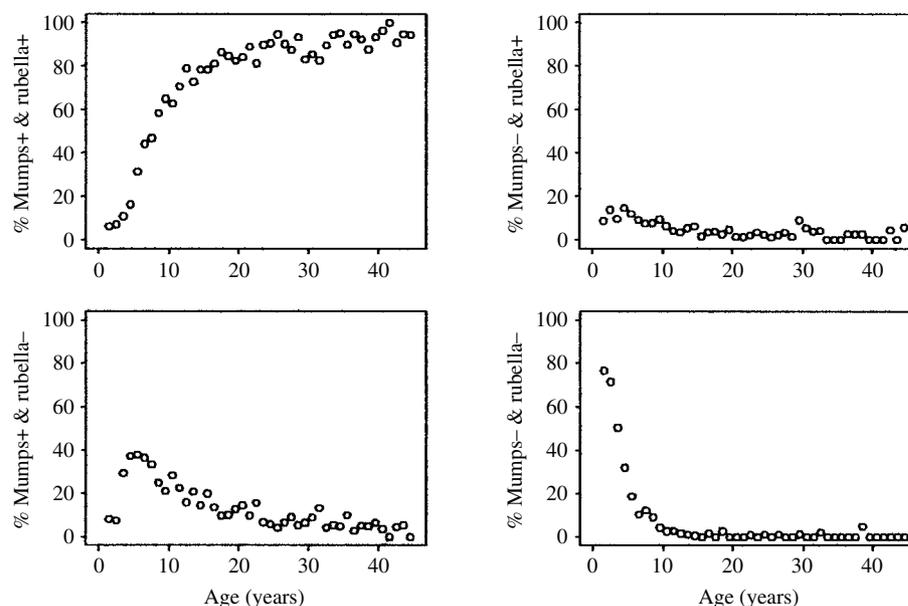


Fig. 1. Joint distribution of mumps and rubella seropositivity by age.

( $\times 100$ ) relative to  $D4$ . The matrices with Bayes factors greater than 5 relative to  $D4$ , are, in descending order,  $A3$ ,  $B4$ ,  $A1$  and  $A6$ . Only  $A1$  is not among the top five without individual heterogeneity, although  $A6$  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  $A6$ ,  $B4$ ,  $D4$ ,  $E2$  and  $A3$  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  $D4$ ,  $A3$ , and  $B4$  are all among the top five whatever the prior. The other two among the top five positions are  $A6$  and  $D1$  for the expert prior,  $A2$  and  $D1$  for the publication prior, and  $A1$  and  $A6$  for the neutral prior.

Matrix  $E1$  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  $E1$  is the presence of parameter  $\beta_5$  in off-diagonal positions, to allow for increased mixing between adults and children. However, the estimate of  $\beta_5$  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  $D4$ ,  $E2$ ,  $A3$ ,  $A6$ ,  $B4$  for the models without heterogeneity, and to  $D4$ ,  $A3$ ,  $A1$ ,  $B4$ ,  $A6$  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

Matrix	No heterogeneity			With heterogeneity		
	Expert	Publi- cation	Neutral	Expert	Publi- cation	Neutral
A1	0-0053	0-0058	0-0137	0-0211	0-0141	0-0447
A2	0-0089	0-0372	0-0088	0-0192	0-0491	0-0155
A3	0-0638	0-4757	0-1411	0-1514	0-6891	0-2726
A4	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
A5	0-0035	0-0059	0-0070	0-0027	0-0028	0-0045
A6	0-2880	0-2317	0-2749	0-0434	0-0213	0-0337
B1	0-0000	0-0000	0-0000	0-0020	0-0012	0-0019
B2	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
B3	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
B4	0-1900	0-0831	0-1972	0-0928	0-0248	0-0784
B5	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
C1	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
C2	0-0066	0-0022	0-0052	0-0241	0-0049	0-0155
C3	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
C4	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
D2	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
D3	0-0000	0-0000	0-0000	0-0000	0-0000	0-0000
D4	0-1739	0-0751	0-1783	0-6117	0-1614	0-5107
D5	0-0000	0-0000	0-0000	0-0004	0-0000	0-0001
E1	0-0041	0-0003	0-0006	0-0000	0-0000	0-0000
E2	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 E1 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.  $\beta_i \geq 0$ . 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

Matrix	No heterogeneity		With heterogeneity		Matrix	No heterogeneity		With heterogeneity	
	Rubella	Mumps	Rubella	Mumps		Rubella	Mumps	Rubella	Mumps
A1	5.19	4.19	8.01	7.48	C1	3.77	3.32	5.36	4.52
A2	3.77	3.21	5.80	4.64	C2	3.68	3.16	6.13	4.56
A3	3.87	3.35	5.86	5.00	C3	3.22	5.26	11.86	9.75
A4	3.56	3.75	5.48	6.61	C4	3.65	4.69	5.73	15.66
A5	3.78	3.28	5.82	4.82	D1	4.15	20.41	6.24	43.93
A6	3.86	5.81	5.93	9.93	D2	4.19	20.40	6.58	43.93
B1	3.79	3.34	6.04	4.79	D3	3.67	8.98	5.35	15.09
B2	3.20	3.58	6.63	5.93	D4	4.12	10.74	6.15	19.40
B3	3.20	3.58	6.54	5.96	D5	10.77	13.20	18.11	23.07
B4	3.87	5.83	5.92	9.83	E1	4.04	13.35	6.01	24.49
B5	3.28	5.68	6.91	12.93	E2	4.08	6.18	6.20	8.00

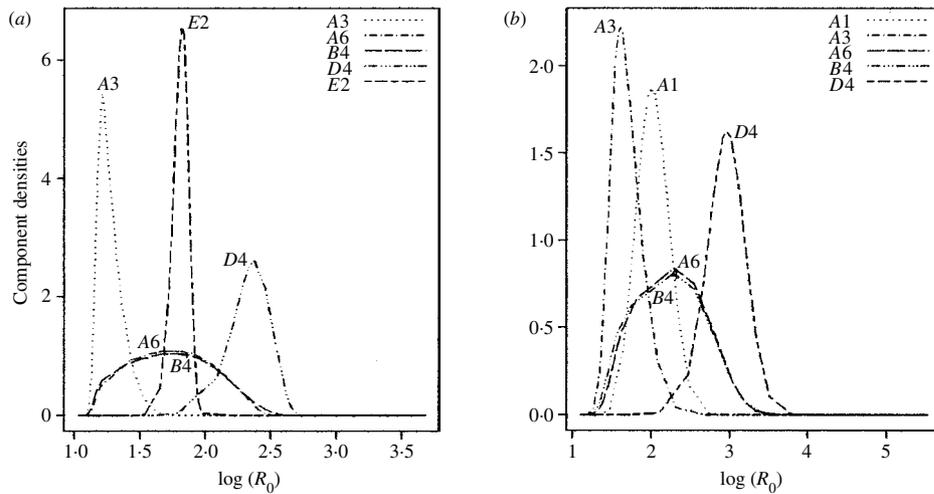


Fig. 2. Mumps: approximate posterior densities of  $\log(R_0)$  for five plausible models. (a) Without heterogeneity; (b) with heterogeneity.

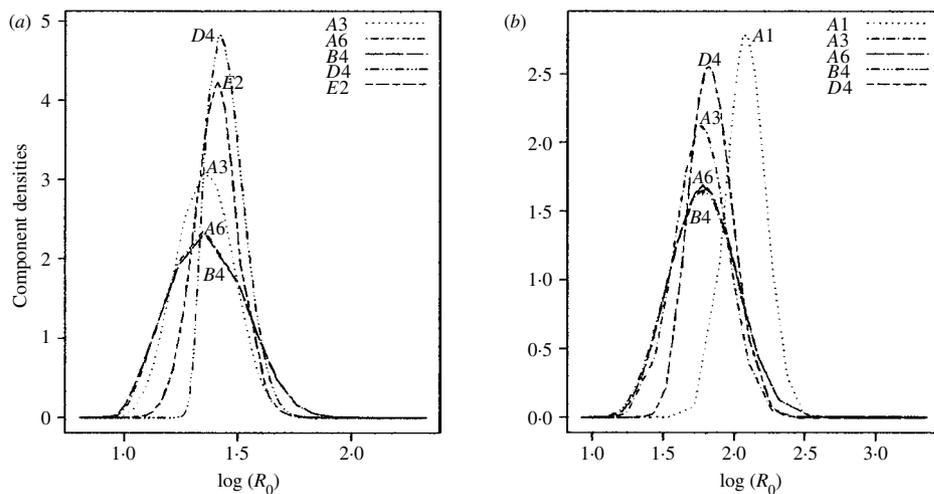
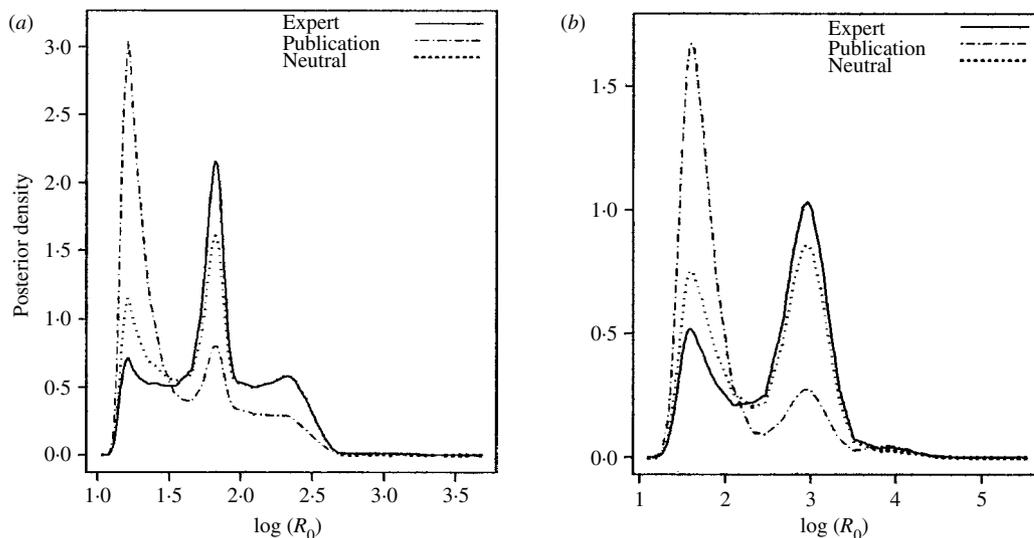
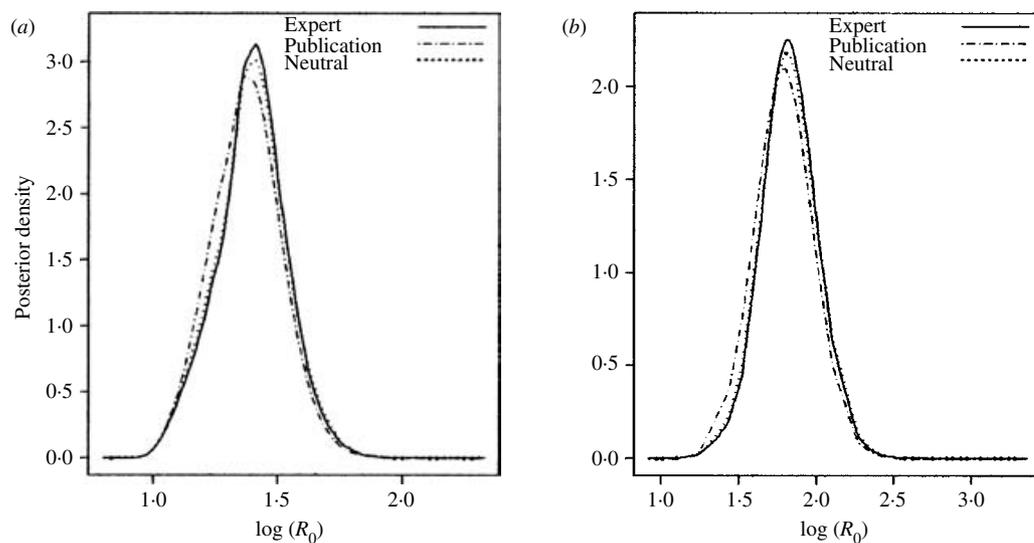


Fig. 3. Rubella: approximate posterior densities of  $\log(R_0)$  for five plausible models. (a) Without heterogeneity; (b) with heterogeneity.



**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  $R_0$

Prior distribution	No heterogeneity				With heterogeneity			
	Rubella		Mumps		Rubella		Mumps	
	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 *D4*.

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.

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**APPENDIX 1. Estimation of contact rates**

Let  $\lambda_i$  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  $\beta_{ij}$  are related to  $\lambda_i$  by:

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

where  $I_j$  describes the distribution of infectious individuals. This is

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

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

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

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  $\lambda_i$ , 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  $j$ th 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**

*A1* [13]

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

*A2* [3, 7, 11, 12, 14, 15, 19, 22, 24, 25]

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

*A3* [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

 $E1$  [20]

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

 $E2$  [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  $\alpha = 1.5$  and  $\beta = 1.75$ .

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