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Predicting meningococcal disease outbreaks in structured populations

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SUMMARY

Rational decision making on whether some form of intervention would be necessary to control the spread of a meningococcal epidemic is based on predictions concerning its potential natural progression. Unfortunately, reliable predictions are difficult to make during the early stages of an outbreak. A stochastic discrete time epidemic model was applied to adaptively predict the development of outbreaks of meningococcal disease in 'closed' populations such as military garrisons or boarding schools, which are further divided into subgroups called 'units'. The performance of the adaptive method was assessed by using 3 simulated epidemics representing substantially different realizations in a 'garrison' of 20 units, with 68 men in each. Predictions of the weekly number of disease cases, of the number of carriers, and of the number of new infections were computed. Simulations suggest that predictions based only on the observed numbers of disease cases are generally inaccurate. These predictions can be improved if temporal observations on asymptomatic carriers in different units are utilized *together* with observed time series of the disease. A sample of 15 per cent from all units can be sufficient for a major improvement if the alternative is to obtain a full sample of only some units. Exploiting fully such information requires computer intensive Markov chain Monte Carlo methods. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS: meningitis; epidemic; asymptomatic carrier; prediction; bayesian inference; Markov chain Monte Carlo

1. INTRODUCTION

Decisions on interventions should be made in the early stages of a meningococcal outbreak. They are often based on arbitrary incidence thresholds of disease cases [1, 2]. Prior to any rules of thumb, we need better dynamical modelling of epidemics in order to fully exploit observations that become available sequentically during the ongoing outbreak. Simulating epidemics is fairly straightforward once a model is specified. Early examples of plain simulation

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models can be found, e.g. in FORTRAN code in Reference [3], and even for pocket calculators in Reference [4]. However, such simulators are inflexible because the parameters have to be assigned and fixed beforehand. In order to achieve better predictions for a specific ongoing epidemic it is necessary to be able to employ adaptive methods that account for each temporal sequence of data that becomes observed during the course of events. Stochastic epidemic models exploiting temporal data on invasive meningococcal disease cases have been employed [5], but the weekly numbers of disease cases provide only a limited source of information about the underlying epidemic process. If no observations on the asymptomatic carriers are available, such predictions can be modest in their accuracy. Related recent work on epidemic models can be found, e.g. in References [6, 7].

The predictions in a structured population, e.g. a military garrison or a boarding school consisting of subpopulations called 'units', could be improved by utilizing sample information on the prevalence of carriage obtained at different time points. This same idea was apparently the motivation behind the old practice of culturing pharyngeal swab samples for the presence of meningococci from all members of the units in which meningitis had occurred. In many instances, the percentage of meningococcal carriers has been found to be high in the units in contact with cases, as compared to percentages in other units [8–10], but this has not always been so [11–14]. No apparent useful pattern has emerged from the crude carriage percentages [15, 16]. Instead, meningitis cases tend to occur within a few days after exposure, suggesting that the decisive factor is the acquisition of carriage [11, 12, 14, 17]. Therefore, temporal observations on the number of carriers would contain useful information on the acquisition. Starting initially with only a few carriers, the prevalence of carriage can become very high in only a few weeks. Very different percentages can then be found within the same unit if samples are collected at different times. Figures from less than 20 per cent to over 70 per cent have been reported [14, 18, 19]. Improving the specificity of the culture method to identify carriers of only the particular strain (defined by sulfonamide resistance or serotype, or more recently by serosubtype, or other clonal characteristic) that had caused the disease cases has given more relevant information [10, 12, 13, 20], but still these data could not be directly applied for predicting the course of an outbreak. Unit specific observations on carriers provide direct information on the development of the latent epidemic processes in the units. In practical monitoring of an epidemic, it is then only required that the numbers of invasive disease cases and of carriers found in the units are reported, by linking them to the respective units rather than reporting the total numbers from the entire garrison.

2. BACKGROUND OF MODEL ASSUMPTIONS

The epidemic model below describes the time course of a meningococcal disease outbreak in a closed population, e.g. military garrison, which is further divided into subpopulations, or units. By a 'carrier' we mean an asymptomatic person who carries on the upper respiratory tract mucosa *Neisseria meningitidis* of the same clone as the case(s) occurring in the same population (as far as it has been possible to determine the clone by the typing techniques available). A carrier is then able to spread the infection further.

Meningococcal epidemics can be described temporally by the numbers of susceptibles, carriers, and immunes. We consider a discrete time model, with S_{ji}, I_{ji} and R_{ji} referring to the current sizes of the respective group at the beginning of week i, in unit j. The class of

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immunes comprises all those who are 'removed' from the epidemic, i.e. can no longer acquire or spread the infection. Although it is known that each individual may become a carrier of the bacteria several times, it is assumed here that the study interval is too short to allow more than a single acquisition per individual. There may actually be partial short-term immunity against carriage [21, 22]. Each individual remains a carrier for some time, and the probability of terminating carriage, during a week, is assumed independent from all the other individuals. Thus the number $I_{ji}^{\ominus}$ of asymptomatic infections terminating during week i in unit j follows a binomial distribution, where $0 \leqslant I_{ji}^{\ominus} \leqslant I_{ji}$.

The dynamics of an epidemic are driven by the numbers of infected and susceptible individuals at each time, the size of the population N_j being assumed to be constant in each unit. Each susceptible-infective contact may lead to a transmission within each week with equal probability. Contacts between members of different units are assumed less frequent than within the same unit. The number of new infections $I_{ji}^{\oplus}$ during week i in unit j follows a binomial distribution, where $0 \leqslant I_{ji}^{\oplus} \leqslant N_j - I_{ji} - R_{ji}$. Furthermore, each new infection can lead to an invasive meningococcal disease with a fixed probability. Therefore, the number of new disease cases D_{ji} during week i in unit j is assumed to follow a binomial distribution, where $0 \leqslant D_{ji} \leqslant I_{ji}^{\oplus}$.

Predictions [23, 24] based solely on the numbers of observed disease cases $\{D_i\}$ were shown to be quite crude [5], since there is not much information on the latent epidemic process. These predictions can be markedly improved when, additionally, observations on the number of carriers become available. When applying Bayesian inferential methods, also relevant medical and biological prior knowledge can be utilized, thus providing further support to the predictions that are made.

3. MODELLING THE GARRISON STRUCTURE

A garrison is divided into a number of units. A discrete time model of an outbreak in such a structured population is now formulated as follows:

$$I_{ji} = I_{j,i-1} + I_{j,i-1}^{\oplus} - I_{j,i-1}^{\ominus} - D_{j,i-1}, \quad R_{ji} = R_{j,i-1} + I_{j,i-1}^{\ominus} + D_{j,i-1} \tag{1}$$

$$I_{ji}^{\oplus} \sim \text{Bin}(1 - q_w^{I_{ji}} q_b^{I_{+i} - I_{ji}}, N_j - I_{ji} - R_{ji}) \tag{2}$$

$$D_{ji} \sim \text{Bin}(p, I_{ji}^{\oplus}) \tag{3}$$

$$I_{ji}^{\ominus} \sim \text{Bin}(r, I_{ji}) \tag{4}$$

where $I_{+i} = \sum_j I_{ji}$. Parameter q_w is the avoidance probability within a unit, i.e. when the considered infective and susceptible belong to the same unit, and q_b is the corresponding avoidance probability across two different units. Here, we require that $q_w < q_b$. Equality $q_w = q_b$ would correspond to an unstructured population [5], and $q_w \leqslant q_b = 1$ to complete lack of contacts between different units.

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Let us assume that the carrier prevalence of a unit is completely determined by collecting swab samples soon after an invasive disease case has been found. Most likely, the carrier prevalence is higher in these than in the other units, although, at least in principle, the other units could as well have been completely infected initially, or full of immunes, so that new infections would no longer be possible. In any case, to exploit the observed carrier prevalence we need to quantify the prevalence at the time of recruitment to the army (or school). An estimate of carriage prevalence could be obtained from a random sample at the time of recruitment, or knowledge about the general population prevalence could be utilized. Ideally, an estimate of the most recent carrier prevalence before the epidemic should be used.

If the bacteria are rare, the units will initially have either a small number of carriers, or no carriers at all. Whether such small initial differences are important for the later behaviour of the process depends on the acquisition rates, or the 'avoidance probabilities' q_w and q_b in our model. When q_w and q_b are equal, the epidemic process is homogeneous between and within all units, and carrier prevalences between units are likely to mix fast. Then, each unit is a representative sample of the whole.

In contrast, if $q_b = 1$, there are no contacts between units and new carriers can emerge only in those units in which there were already initially some infected individuals. Under such circumstances, the epidemic is likely to behave differently in different units. If q_b is less than one and if q_w is much smaller, the units with initial carriers will show epidemic behaviour soon (the sooner the lower q_w is), while units without initial carriers will start a similar epidemic at some later time, after transmission from an infected unit has occurred. If q_b is small enough, infections spread rapidly between units and simultaneous occurrence of similar numbers of disease cases in different units is likely because these units were likely in the same phase of an epidemic. If $q_b \approx 1$, and there is no heterogeneity between units with respect to other parameters (q_w, p, r), then phase differences solely due to initial differences of carrier prevalence can occur.

Carrier observations combined with some knowledge of the initial prevalences in the units with disease cases can provide information on the overall acquisition rate in those units, but if the epidemics are in a different phase of development, then this information cannot readily be applied for the rest of the garrison. Often there is no information on which infections were due to sources external to the unit. If some units with no initial carriers have carriers at a later time point, then these must be due to external transmissions. In this special situation we could estimate the between-unit transmission avoidance probability. Otherwise, we have to consider a combination of external and internal transmissions in a joint probability model.

It would be useful to have prevalence data also from some randomly chosen units where disease cases did not occur. When the initial states and model parameters are given prior distributions, one can compute the joint posterior distribution of all unknown variables and parameters. For simplicity, the Bayesian hierarchical model is depicted with only 2 units in Figure 1. Each arrow denotes a conditional distribution between the variables in the nodes. For example, the two arrows from arbitrary nodes ⓐ and ⓑ to ⓒ should be read: 'the conditional distribution of c given a and b'. Unit specific observations are accommodated by treating the unit specific variable I_{ji} as fixed whenever its value becomes known. Extension to account for a sampling experiment is straightforward. The MCMC algorithm for the joint posterior distribution is explained in the appendix.

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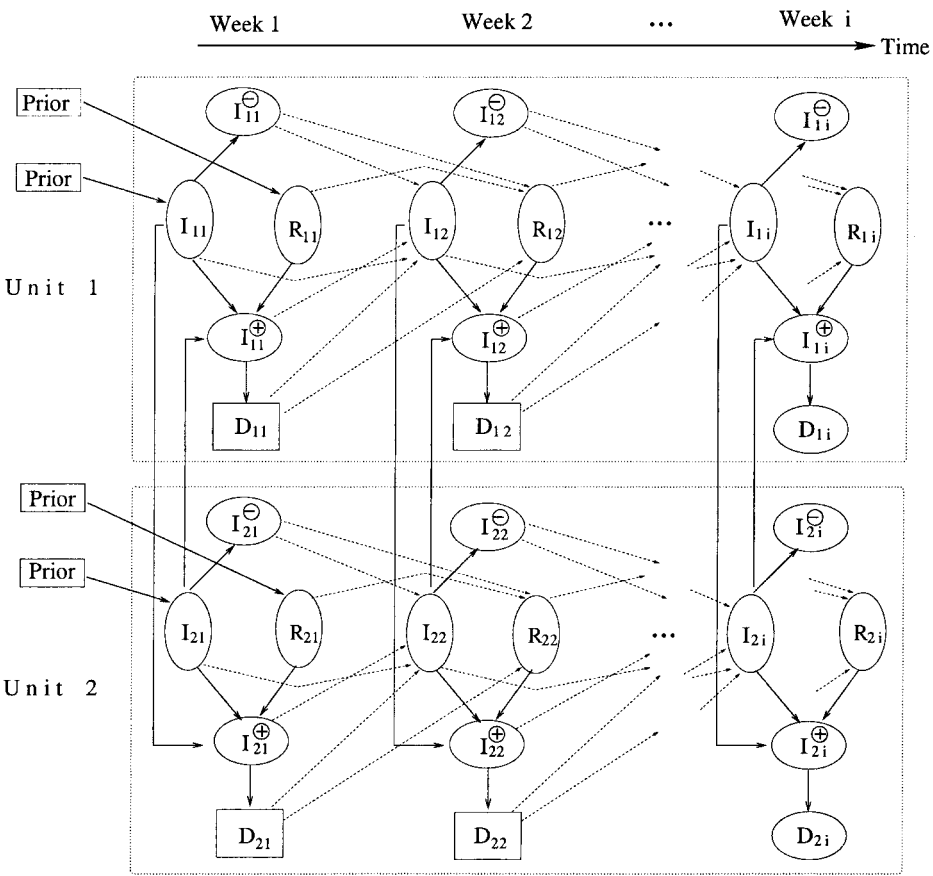

Figure 1. Directed acyclic graph of the hierarchical model with a simple population structure. The population depicted in the graph constitutes of two 'units' (upper and lower box). Solid arrows denote stochastic dependence. For clarity, the (fixed) sizes N_1, N_2 of the units and parameters p, r, q_w, q_b are excluded from the graph. Dotted arrows denote deterministic dependence. Unknown state variables are written in ellipsoids. Observed data and given priors are written in square boxes. The value of I_{ji} becomes known data once the unit is inspected for carriers. Variables to be predicted are the rightmost $I_{ji}^{\ominus}$, I_{ji}, R_{ji}, $I_{ji}^{\oplus}$ and D_{ji}, with, e.g. $i = 3, 4, 5, \ldots$.

3.1. Simulated examples

Unfortunately, we were unable to find records on unit specific developments of an outbreak of *Neisseria meningitidis* [5, 25]. For illustration purposes, a simulated data set was generated from model (1)–(4) with parameters $p = 0.05$, $q_w = 0.97$, $q_b = 0.9999$ and $r = 0.1$ in a population of 20 units, each comprising 68 individuals (the estimated size of a unit in the data used in Reference [3]). The simulated outbreak data are shown in Table I. ($R_{j1} = 0$ for all j). This artificial data set (default) is then used to test the model performance by treating a subset of the data as observations and using the rest of the data for model assessment. Additionally, using the same parameter values we generated 10,000 outbreak realizations from which we

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chose two rather extreme examples. In the first, no disease cases occurred during weeks 1–2. In the second, 15 disease cases occurred during weeks 1–2. Judging from these simulations, the Monte Carlo estimate of the probability of 15 or more disease cases during the first 2 weeks is approximately 6/10,000, whereas the probability of zero disease cases during weeks 1–2 was approximately 62/10,000. Predictions were also computed for these two extreme realizations. All three chosen examples represent outbreaks with almost identical cumulative number of cases over weeks 1–10, but the temporal patterns are different. Therefore, the two extreme realizations could be viewed nearly as worst case situations in which the initial course of the epidemic is strongly misleading.

Table I. Simulated data set for model testing.

$$[D_{ji}] = \begin{bmatrix} 0 & 0 & 2 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 2 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 2 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 2 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2 & 3 & 2 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 & 4 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 3 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 3 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 2 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 3 & 0 & 0 & 0 \end{bmatrix}, \quad [I_{ji}^{\oplus}] = \begin{bmatrix} 5 & 9 & 23 & 18 & 7 & 4 & 0 & 0 & 0 & 0 \\ 7 & 15 & 19 & 18 & 6 & 1 & 0 & 0 & 0 & 0 \\ 4 & 5 & 11 & 15 & 23 & 6 & 1 & 1 & 0 & 0 \\ 4 & 11 & 23 & 17 & 8 & 2 & 1 & 0 & 0 & 0 \\ 2 & 3 & 16 & 17 & 21 & 4 & 1 & 2 & 0 & 0 \\ 5 & 15 & 22 & 14 & 9 & 1 & 0 & 0 & 0 & 0 \\ 3 & 9 & 21 & 21 & 11 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 2 & 7 & 16 & 26 & 14 & 2 & 0 \\ 0 & 0 & 0 & 1 & 8 & 15 & 20 & 12 & 6 & 4 \\ 0 & 0 & 0 & 1 & 5 & 13 & 20 & 20 & 6 & 3 \\ 0 & 0 & 0 & 1 & 3 & 15 & 20 & 19 & 9 & 1 \\ 1 & 3 & 6 & 15 & 23 & 17 & 2 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 7 & 18 & 16 & 23 & 2 & 0 \\ 0 & 0 & 1 & 4 & 11 & 22 & 23 & 6 & 0 & 0 \\ 0 & 1 & 0 & 4 & 8 & 23 & 19 & 12 & 1 & 0 \\ 0 & 0 & 1 & 3 & 7 & 16 & 23 & 12 & 6 & 0 \\ 0 & 0 & 1 & 3 & 9 & 20 & 20 & 12 & 3 & 0 \\ 0 & 0 & 1 & 4 & 12 & 17 & 20 & 9 & 4 & 1 \\ 1 & 1 & 3 & 7 & 18 & 26 & 10 & 1 & 1 & 0 \\ 0 & 0 & 0 & 4 & 13 & 15 & 24 & 9 & 3 & 0 \end{bmatrix}$$

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Table I. *Continued.*

$$[I_{ji}^{\ominus}] = \begin{bmatrix}
0 & 1 & 2 & 5 & 8 & 6 & 6 & 5 & 5 & 2 \\
0 & 1 & 3 & 2 & 7 & 5 & 3 & 6 & 4 & 8 \\
2 & 0 & 0 & 1 & 4 & 6 & 6 & 4 & 4 & 5 \\
0 & 0 & 3 & 7 & 4 & 2 & 8 & 2 & 3 & 5 \\
1 & 0 & 1 & 1 & 5 & 3 & 7 & 5 & 3 & 4 \\
0 & 0 & 1 & 3 & 7 & 8 & 8 & 2 & 6 & 4 \\
0 & 0 & 1 & 1 & 8 & 5 & 1 & 5 & 8 & 6 \\
0 & 0 & 0 & 0 & 0 & 1 & 1 & 2 & 6 & 8 \\
0 & 0 & 0 & 0 & 0 & 1 & 4 & 1 & 4 & 5 \\
0 & 0 & 0 & 0 & 0 & 2 & 2 & 3 & 3 & 9 \\
0 & 0 & 0 & 0 & 0 & 0 & 2 & 5 & 6 & 3 \\
0 & 0 & 0 & 1 & 2 & 2 & 3 & 4 & 4 & 10 \\
0 & 0 & 0 & 0 & 0 & 1 & 2 & 2 & 10 & 7 \\
0 & 0 & 0 & 0 & 0 & 0 & 5 & 7 & 5 & 7 \\
0 & 0 & 0 & 0 & 0 & 2 & 4 & 5 & 8 & 3 \\
0 & 0 & 0 & 0 & 0 & 2 & 3 & 3 & 4 & 4 \\
0 & 0 & 0 & 0 & 0 & 1 & 3 & 5 & 6 & 3 \\
0 & 0 & 0 & 0 & 1 & 6 & 2 & 4 & 4 & 6 \\
0 & 0 & 0 & 0 & 1 & 2 & 5 & 8 & 3 & 4 \\
0 & 0 & 0 & 0 & 0 & 3 & 3 & 3 & 5 & 4
\end{bmatrix}, \quad [I_{ji}] = \begin{bmatrix}
2 & 7 & 15 & 34 & 46 & 45 & 43 & 37 & 32 & 27 \\
2 & 9 & 21 & 36 & 52 & 50 & 46 & 43 & 37 & 33 \\
2 & 3 & 7 & 18 & 32 & 51 & 51 & 46 & 43 & 39 \\
2 & 6 & 16 & 34 & 44 & 48 & 48 & 41 & 39 & 36 \\
2 & 3 & 6 & 17 & 32 & 48 & 49 & 43 & 40 & 37 \\
2 & 7 & 21 & 42 & 53 & 54 & 47 & 39 & 37 & 31 \\
2 & 5 & 13 & 31 & 50 & 53 & 49 & 48 & 43 & 35 \\
0 & 0 & 0 & 0 & 2 & 9 & 24 & 49 & 61 & 57 \\
0 & 0 & 0 & 0 & 1 & 8 & 21 & 35 & 46 & 47 \\
0 & 0 & 0 & 0 & 1 & 6 & 15 & 30 & 45 & 46 \\
0 & 0 & 0 & 0 & 1 & 4 & 17 & 35 & 49 & 52 \\
0 & 1 & 4 & 10 & 24 & 44 & 59 & 58 & 55 & 51 \\
0 & 0 & 0 & 1 & 2 & 8 & 24 & 38 & 55 & 47 \\
0 & 0 & 0 & 1 & 4 & 14 & 36 & 53 & 52 & 47 \\
0 & 0 & 1 & 1 & 5 & 13 & 33 & 48 & 55 & 48 \\
0 & 0 & 0 & 1 & 3 & 10 & 21 & 41 & 49 & 50 \\
0 & 0 & 0 & 1 & 4 & 12 & 31 & 45 & 51 & 48 \\
0 & 0 & 0 & 1 & 5 & 16 & 26 & 42 & 46 & 46 \\
0 & 1 & 2 & 4 & 11 & 27 & 50 & 55 & 48 & 46 \\
0 & 0 & 0 & 0 & 4 & 17 & 29 & 47 & 53 & 51
\end{bmatrix}$$

Note: Each row in a matrix is a time series for a unit. Each column denotes the values of a variable during, or in the beginning of, a week as explained in the text.

4. SPECIFICATION OF PRIOR DISTRIBUTIONS

The prior distributions of the disease probability p upon infection, and of the clearance probability r of carriage in a week, were chosen as follows:

$$P(p) = \text{Beta}(p \mid 1.1, 9.4)$$

$$P(r) = \text{Uniform}(r \mid 0.0043, 0.1591)$$

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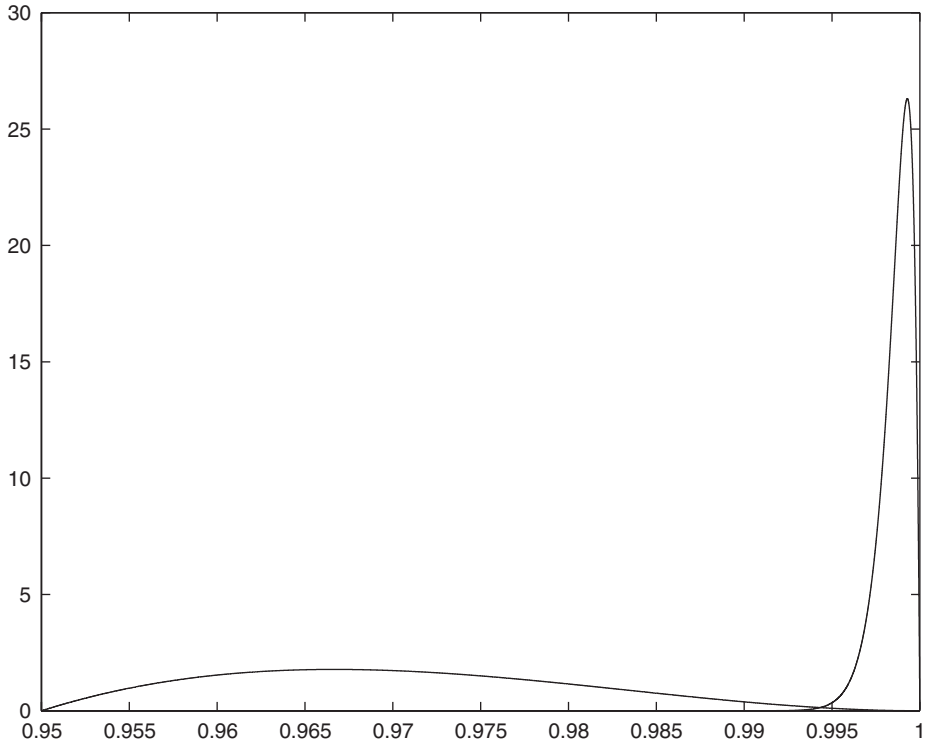

Figure 2. The two priors for q_w. Pessimistic (flat) and optimistic (peaked).

An empirical motivation for these choices was given in Reference [5]. The prior expectation of p is 0.1048 and the prior standard deviation is 0.0903. For the avoidance probability q_w we specify two alternative priors, shown in Figure 2:

Pessimistic:

$$P((q_w - 0.95)/0.05) = \text{Beta}(q_w \mid 2, 3)$$

Optimistic:

$$P((q_w - 0.95)/0.05) = \text{Beta}(q_w \mid 70, 2)$$

Moreover, for a joint prior we should specify a range of plausible values that a pair (q_w, q_b) can take. It is reasonable to require the obvious constraint $q_w < q_b$. In addition to this we need to account for the actual number of units in order to specify the relative chances of infectious contacts between and within the units. Suppose that there are x infectives in each unit. Then, the chance of avoiding an infection (during a week) is $q_w^x q_b^{19x}$. It is clear that even when q_w is only somewhat smaller than q_b, the transmissions between units will dominate. The prior of q_b should therefore simultaneously account for both q_w and the total number J of units. For q_b, we propose a conditional Beta distribution over the range $[q_w, 1]$, with conditional

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mean and conditional variance

$$E(q_b \mid q_w, J) = q_w^{1/(J-1)} \quad \text{and} \quad \text{Var}(q_b \mid q_w, J) = v(1 - q_w)^2$$

where

$$v = \left(0.5\left(1 - \frac{q_w^{1/(J-1)} - q_w}{1 - q_w}\right)\right)^2$$

The pessimistic prior of q_w leads to prior predictions with fairly rapidly growing outbreaks whereas the optimistic prior generates slowly growing outbreaks. On the other hand, the pessimistic prior leads to quickly ending epidemics and the optimistic prior to prolonged epidemics.

It should also be noted that the 'pessimistic' prior is very vague compared to the 'optimistic' prior. At first sight, it can be expected that a pessimist is more easily converted to an optimist than an optimist to a pessimist, after having observed the data. For a more 'balanced' specification, we could define the pessimistic prior to be as peaked as the optimistic one, but in general, strong priors should be avoided unless one has substantial *a priori* knowledge. The two priors seem quite extreme when compared in Figure 2. Yet, the transition from slow and minor outbreaks to fast and large outbreaks is not linear when moving from $(q_b, q_w) = (1, 1)$ towards $(0, 0)$. Due to the 'mass action' effect, rapid outbreaks occur for all but the values very close to $(1, 1)$. It is therefore not only in terms of parameters but also in terms of the outbreaks that we should evaluate our priors. Both optimistic and pessimistic prior predictions can be seen in Figure 3 compared to the default data set.

For the initial number of carriers I_{j1} in each unit j, we considered the binomial prior distribution $\text{Bin}(I_{j1} \mid 0.01, N_j)$ corresponding to the assumed 1 per cent endemic population prevalence of carriers. The same prior distribution was also used for the numbers R_{j1} of initially removed,

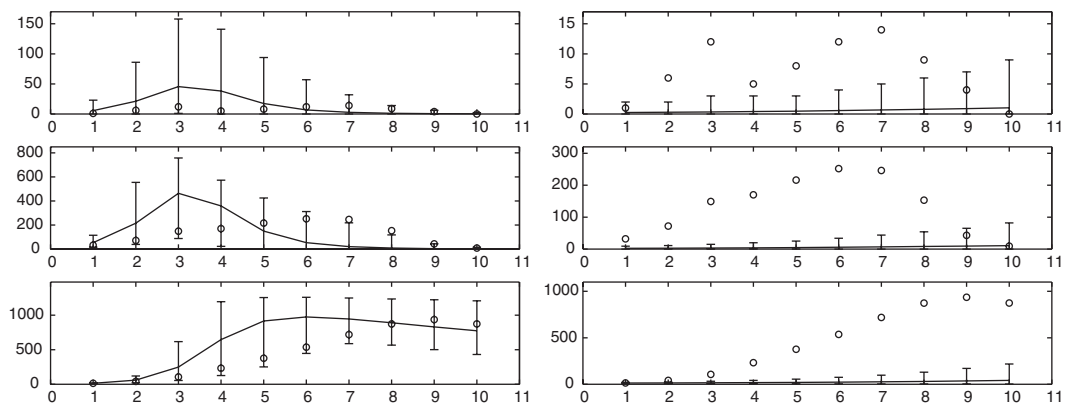

Figure 3. Prior predictive distributions of the weekly numbers of new disease cases (upper frame), new infections (middle frame), and carriers (lower frame). These are based on a pessimistic prior (left), and an optimistic prior (right). The default realization is denoted by circles, and marginal predictive means are connected with a solid line. Vertical bars show the 95 per cent probability intervals. Notice different scaling in the figures!

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although some other prior could have been more relevant. For example, in Reference [15] it was reported that carrier percentages among new naval recruits varied from 25 to 34 per cent. However, only the virulent clones of the bacteria can cause a disease outbreak, and one should try to estimate the corresponding prevalence instead of that of all types of meningococcal bacteria. If this is not investigated in each unit, one must define a prior distribution for the initial state according to the best available information on the plausible number of carriers I_{j1} of a virulent clone and the number of susceptibles $N_j - I_{j1} - R_{j1}$.

5. OUTBREAK FORECASTING

Using subsets of the artificial data as our unit specific 'observations', predictions were computed according to two different sampling designs. In both of these, a complete sample from an inspected unit is assumed and no samples from other units. In the first design, the numbers of disease cases from the first 2 weeks in all units, *and* the numbers of carriers in those units with disease cases, were treated as observations, see Figure 4. The obtained number of carriers was taken to represent the carrier status of the unit at the beginning of the next week rather than at the beginning of the same week. There were 5 units with disease cases during weeks 1 and 2 in the default data. In one of those units there was a new disease case during both weeks. Consequently, 6 observations on the number of carriers became available according to our simulated surveillance. In the second sampling design, these observations were supplemented with carrier observations from six randomly selected units without disease cases, see Figure 5.

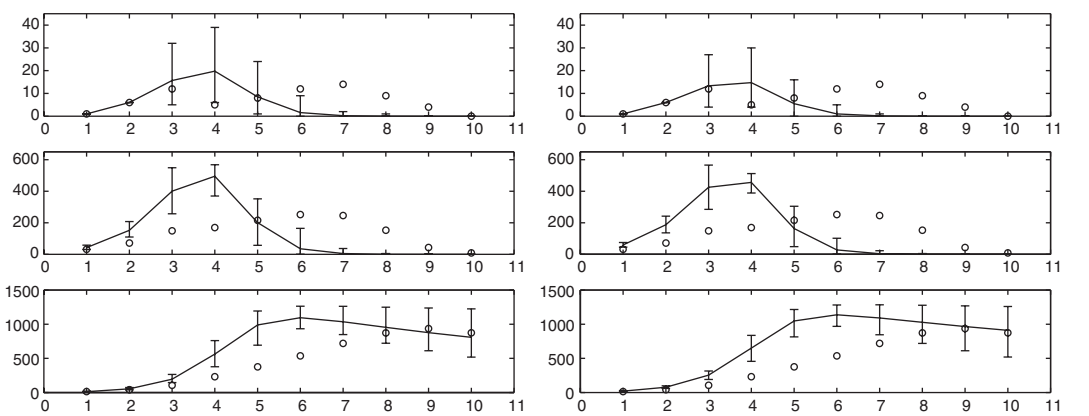

Figure 4. Posterior predictive distributions of the weekly numbers of new disease cases (upper frame), new infections (middle frame), and carriers (lower frame). These are based on a pessimistic prior (left), and an optimistic prior (right). The true realization is denoted by circles, and marginal predictive means are connected with a solid line. Vertical bars show the 95 per cent probability intervals. The posterior was computed conditional on unit specific observations on disease cases in the first 2 weeks, and on the number of carriers in each unit with positive number of disease cases, in the end of weeks 1 and 2, following the disease occurrence.

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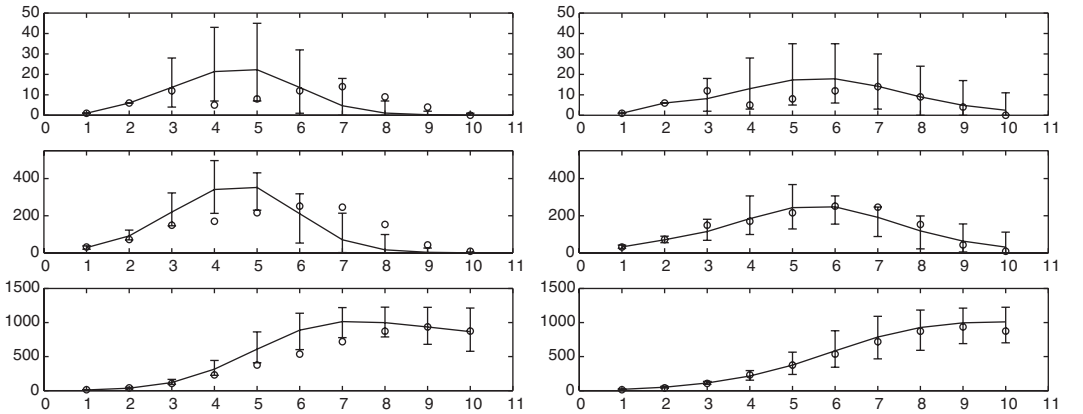

Figure 5. Posterior predictive distributions of the weekly numbers of new disease cases (upper frame), new infections (middle frame), and carriers (lower frame). These are based on a pessimistic prior (left), and an optimistic prior (right). The true realization is denoted by circles, and marginal predictive means are connected with a solid line. Vertical bars show the 95 per cent probability intervals. The posterior was computed conditionally on unit specific observations on disease cases in the first 2 weeks, and on the number of carriers in equally many units with and without disease cases, in the end of weeks 1 and 2, following the disease occurrence.

Carrier observations from disease units only do not provide a representative sample of the whole garrison. The resulting predictions of the epidemic as a whole can then be biased (Figure 4). This is only partially counterweighted by the observation that in other units there were no disease cases at all. 'No disease cases' can also be explained by a low invasive disease probability upon acquisition which is why the number of disease cases provides only indirect (weak) information about the latent epidemic. The marginal posterior distributions of q_w and q_b are quite different under the two priors, although those of the epidemic realization may not be, because a higher q_w value can be compensated by a smaller q_b value, and conversely.

All the predictions are strongly dependent on the data that become observed—which is indeed natural and even desirable but can also be a disadvantage if the initial phase of the epidemic happens to be atypical from the point of view of the assumed epidemic model. Therefore, all predictions can be misguided by sparse data that happen to be misleading. This effect is clear in the two additional 'extreme' data sets that were generated using the same parameter values as with the more 'typical' default data. These additional epidemics were chosen so that the temporal pattern differs but the cumulative number of disease cases over 10 weeks is similar. In the first additional data set, the number of disease cases was zero for the first 2 weeks. Six units were then randomly selected for inspecting the number of carriers. The predictions were then computed conditionally on the observed disease cases (zero) for the first 2 weeks, and on the observed number of carriers in the six inspected units (Figure 8, upper 3 frames). In the second additional data set, 15 disease cases occurred during the first two weeks. Only the corresponding units were then chosen to be inspected for carriers (Figure 10, upper 3 frames).

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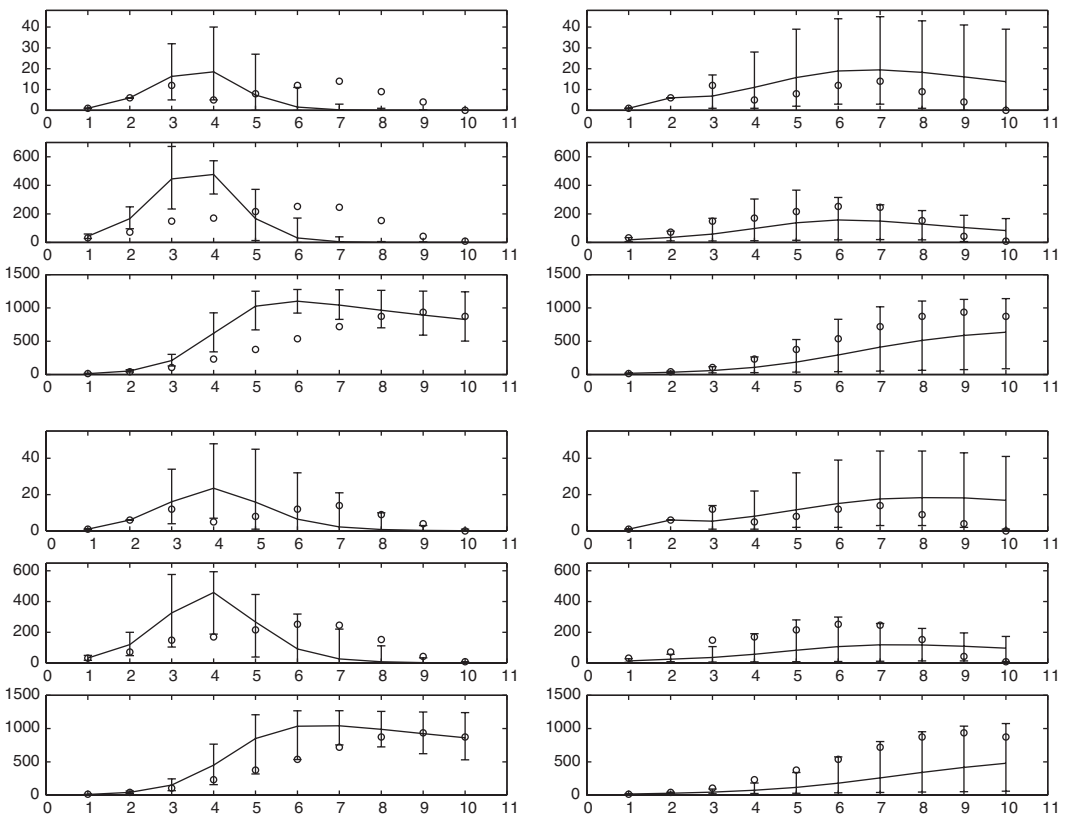

Figure 6. Posterior predictive distributions when a sample of 10 per cent (upper 3 frames) and 15 per cent (lower 3 frames) is collected from all units in the beginning of week 2. Disease case data were observed for weeks 1 and 2 (default data set). Pessimistic prior left, optimistic prior right.

The predictions for individual units can be particularly unreliable if there are no carriage data concerning that specific unit. However, the model has the ability to learn from any additional datapoints. This is crucial in any attempt to model as difficult phenomena as an infectious disease outbreak with latent infections: the model should be able to adapt to every new fragment of data. An open question is how such adaptation could be tuned so that the method could perform optimally both for the benefit of individual units and the total population. This problem is closely connected to the specification of prior densities for parameters linking 'global' and 'local' characteristics.

As a rule of thumb, a more informative alternative to testing all individuals in an inspected unit is to take a sample of individuals from several, or all, units. This was studied, using the default data, by simulating a sample of 10 and 15 per cent from all units in the beginning of the second week (Figure 6). Similarly, a sample of 15 per cent was simulated for the extreme data sets (Figures 8 and 10, lower 3 frames). With this sample size, the number of tested individuals is equivalent to the whole population in only 3 units out of 20. The resulting predictive distributions of the cumulative number of disease cases are shown in Figures 7

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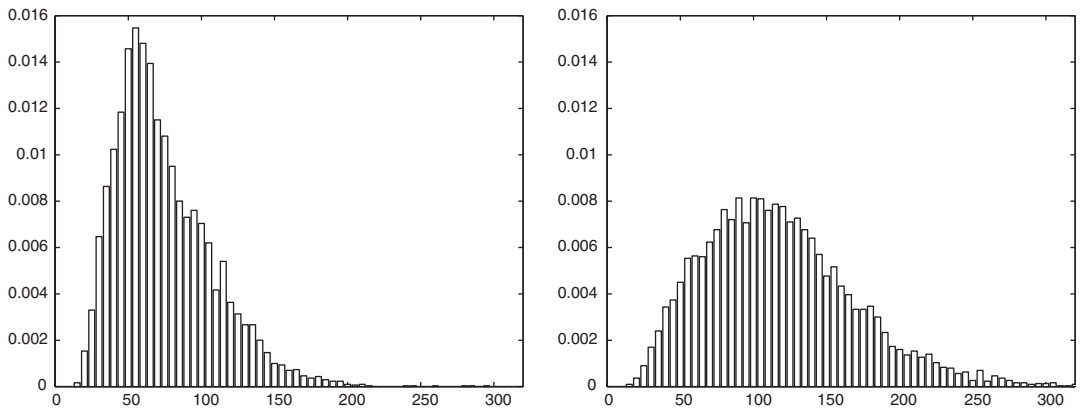

Figure 7. Posterior predictive distribution of the cumulative number of cases during weeks 1–10. Based on a sample of 15 per cent from each unit in the beginning of week 2, and disease data from weeks 1–2 (default data set). Pessimistic prior (left), and optimistic (right). Ninety-five per cent probability intervals: [27, 152], and [37, 237], respectively. Correct number was 71.

(default data) 9 and 11. It is clear that the distribution of the cumulative number of cases will be different with different temporal data and different priors.

Let us assume that the carrier status of all individuals would be tested for all units for both weeks 1–2. In the three generated examples this would count 56, 52 and 58 positive results. In units with no disease cases, the numbers were 24, 52 and 13. In units with disease cases these were 32, NA (not defined if zero cases) and 45. Units with disease cases tend to have more carriers than non-affected units. The number of carriers can also vary considerably. If one would use only these numbers to calculate a simple rule-of-thumb predictor for the epidemics, the following problems would be evident: (i) it is not at all clear how the number of positive test results (in non-affected or affected units) could be best mapped to the total epidemic size as a simple function, (ii) the errors due to chance can be manifold and without a model there is no systematic way to quantify the prediction uncertainty, and (iii) expert knowledge would not be easily merged in the prediction. The model based approach provides an answer to questions (i), (ii) and (iii), but the method, like any approach, is still vulnerable to extreme situations. However, the probability of such an extreme situation could be very small and the method may perform reasonably in more typical situations.

Convergence of the MCMC algorithm was verified by visual monitoring of the sample paths of individual parameters, some state variables, as well as the log of posterior joint density. Computation was done in batches of 100,000 iterations. The first batch was discarded as a burn-in period, after which 3,000,000 more iterations were computed, but saving only every 500th sample point for the results. A random scan algorithm was used. By ‘one iteration’ we mean selecting randomly only one of the parameters or one of the unknown state variable pairs to be updated. This is described in more detail in the appendix. Autocorrelations of the log joint density were computed from this thinned sample path. With lag 10 these were typically around or below 0.5. Dispersed initial values for the state variables and parameters led to the same results. Marginal posterior distributions of state variables of those units with identical observations, and with identical priors, were nearly equal.

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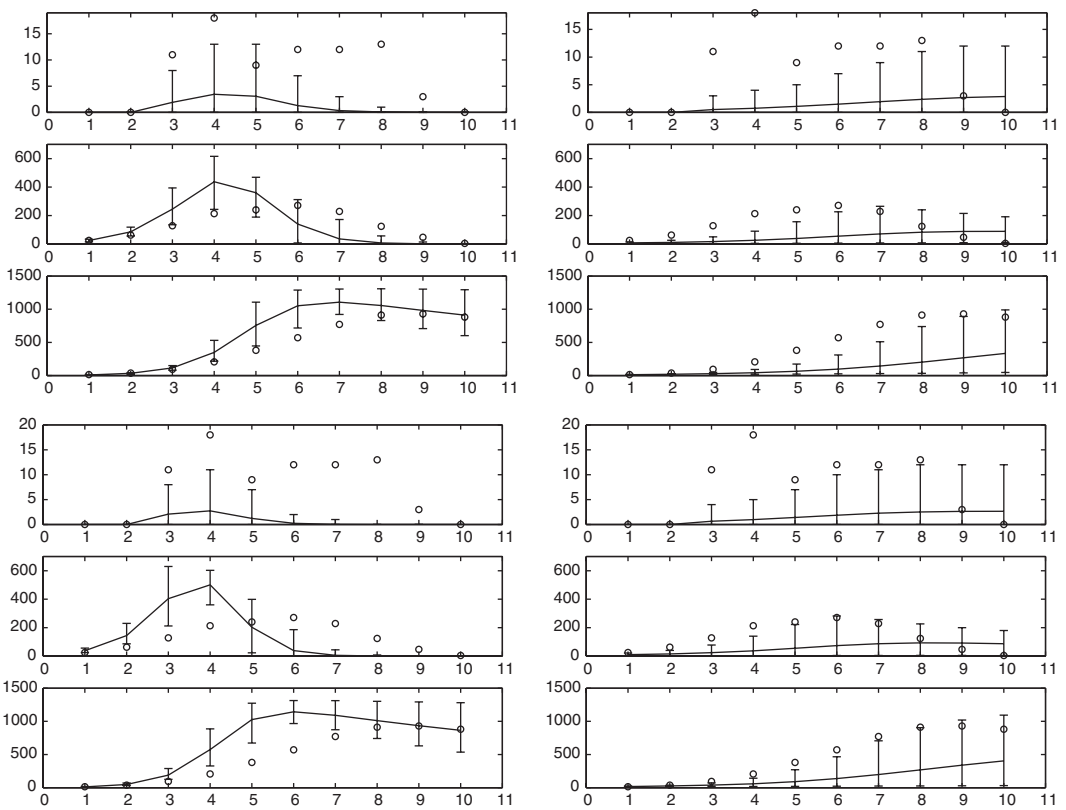

Figure 8. Posterior predictive distributions of weekly numbers of new disease cases, new infections, and carriers. The 'true' realization is denoted by circles, and marginal predictive means are connected with a solid line. Vertical bars show the 95 per cent probability intervals. Based on unit specific observations on disease cases in the first two weeks (zero) and on the number of carriers in 6 randomly chosen units without disease cases, in the end of weeks 1 and 2. Predictions based on the same disease data, and on a sample of individuals (15 per cent from each unit) in the beginning of week 2 are shown in lower 3-frame figures (pessimistic prior: frames left; optimistic prior: frames right).

6. DISCUSSION

We have shown here how unit specific observations of both the invasive disease cases and observations on the numbers of carriers can be combined for the purpose of predicting the natural course of a meningococcal disease outbreak in a military establishment. The same approach could be applied to other semiclosed communities such as boarding schools. Although it may be of interest to provide realistic predictions only of the total number of resulting disease cases, instead of a time series of cases, it is important that such predictions are based on the actual temporal development of the epidemic, and for this a dynamic statistical model is needed. If required, predictions of the cumulative numbers can be obtained as a straightforward by-product of the computed MCMC sample of the week and unit specific variables by plotting the sample histogram of their cumulative sum. The advantage of using carrier

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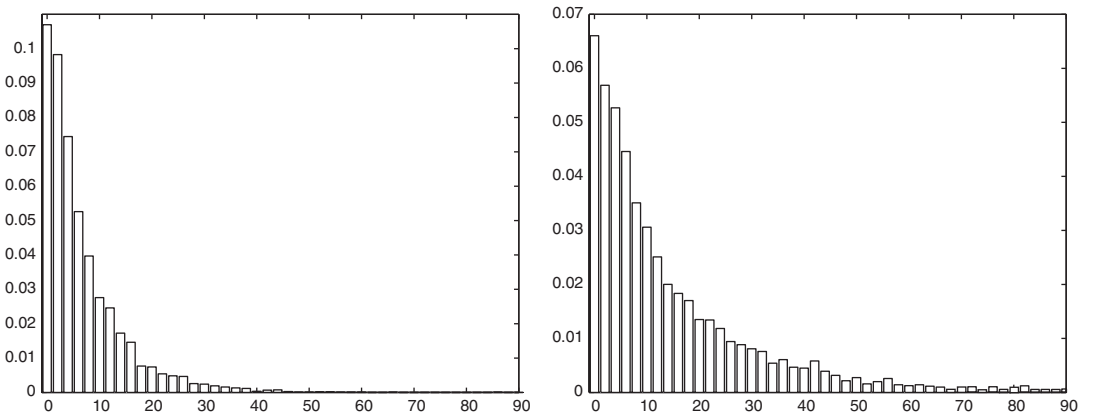

Figure 9. Posterior predictive distribution of the cumulative number of cases during weeks 1–10. Based on disease case data (zero) from weeks 1–2, and a sample of 15 per cent from each unit in the beginning of week 2. Pessimistic prior (left), and optimistic (right). Ninety-five per cent probability intervals: $[0, 29]$, and $[0, 63]$, respectively. Correct number was 78.

data is more direct in predictions concerning the inspected units themselves. However, the overall predictions improved when carriage prevalences in a few other units, where no disease cases had occurred, were exploited as well. Further improvement was achieved by sampling a proportion of individuals from all units. The number of swabs may then be considerably smaller than if, e.g. affected units were inspected thoroughly, and the prediction quality is increased.

A commonly referred measure of potential severity of an epidemic is the basic reproduction number $\mathscr{R}_0$, which is defined as the expected number of secondary infections that one infective person will cause during his/her infectious period in a completely susceptible population [26]. This is an idealized quantity in the sense that an unlimited number of susceptibles is assumed to be within the reach of each infected individual [27, 28]. In models for the control of epidemic, $\mathscr{R}_0$ has been used to describe the initial 'potential' of an epidemic. However, once the epidemic has started, this is of little practical predictive value. Instead, one needs a more flexible characterization that can be updated when new observations become available. The decision on whether or not an intervention is made depends crucially on the likely course of the epidemic in the future under no intervention. For that purpose, the posterior predictive distributions of both latent and observable disease cases and carriers are of concrete value and, in principle, can be updated as soon as new observations become available.

In real epidemics, various intervening events may occur, some due to precautions taken by the individuals occupying the units and alerted by disease cases among their fellows. External factors may come into play, distorting the contact patterns and altering the chances of further infections in unpredictable ways. It is thus unlikely that an outbreak could be throughout governed by the same biological conditions, i.e. 'parameters'. A further generalization of the model would result from treating parameters p, q_w, and q_b as time dependent, thus accounting for temporal changes in the biological and environmental conditions. The results derived from our simulated data provide an illustration of the kind of analysis that could be done. Until

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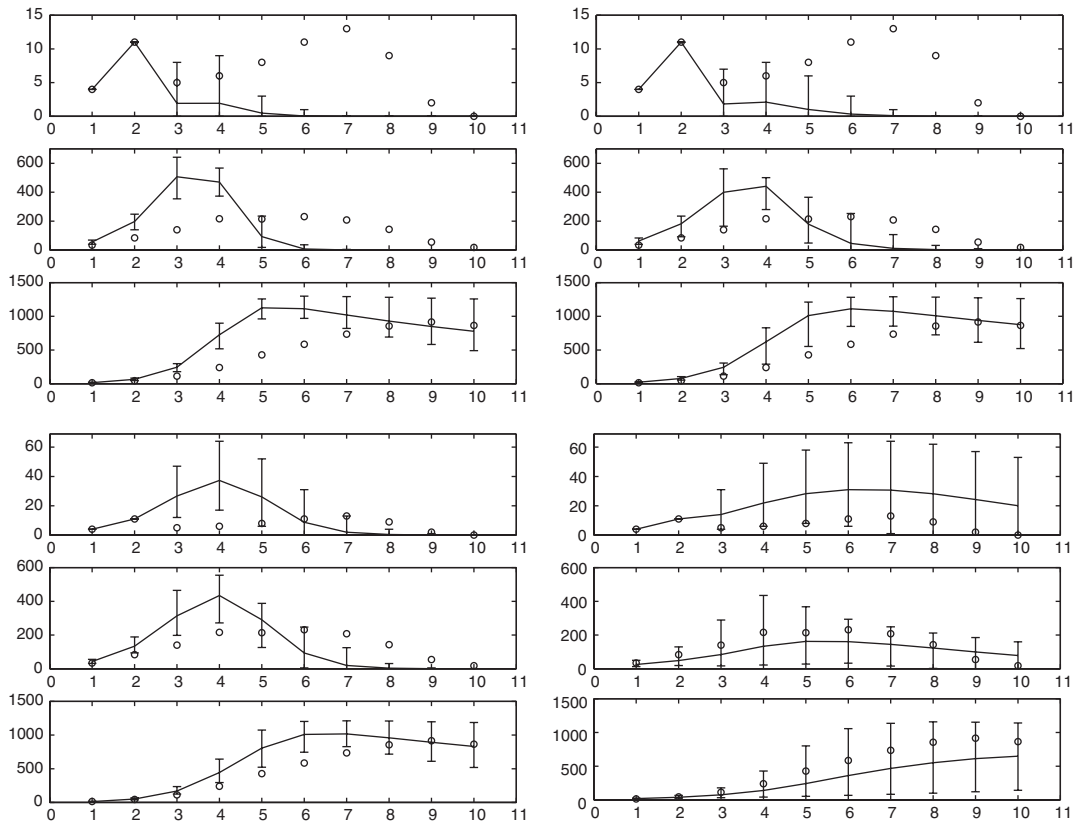

Figure 10. Posterior predictive distributions of weekly numbers of new disease cases, new infections, and carriers. The 'true' realization is denoted by circles, and marginal predictive means are connected with a solid line. Vertical bars show the 95 per cent probability intervals. Based on unit specific observations on disease cases in the first two weeks (15), and on the number of carriers in those units with disease cases, in the end of weeks 1 and 2. Predictions based on the same disease data, and on a sample of individuals (15 per cent from each unit) in the beginning of week 2 are shown in lower 3-frame figures (pessimistic prior: frames left; optimistic prior: frames right).

more detailed real data become available, a larger simulation study based on several different sets of test data could be useful. However, it is not obvious what scenarios and models should be used to generate the data for such general testing. Yet, only simulated data will allow one to compare the predictions of all model quantities with their 'actual' values, a task that is never fully possible with real data.

In conclusion, significantly better predictions can be expected by collecting additional data on the number of carriers from all units. However, sample sizes should be fairly large, at least 15 per cent. This may still be more economical than sampling all individuals only in units where invasive disease cases occurred (if there are several such units). The prior distributions of infection parameters (here q_w, q_b) should not be too restrictive unless there is substantial prior information. With limited data, it is recommendable to use fairly strong prior knowledge

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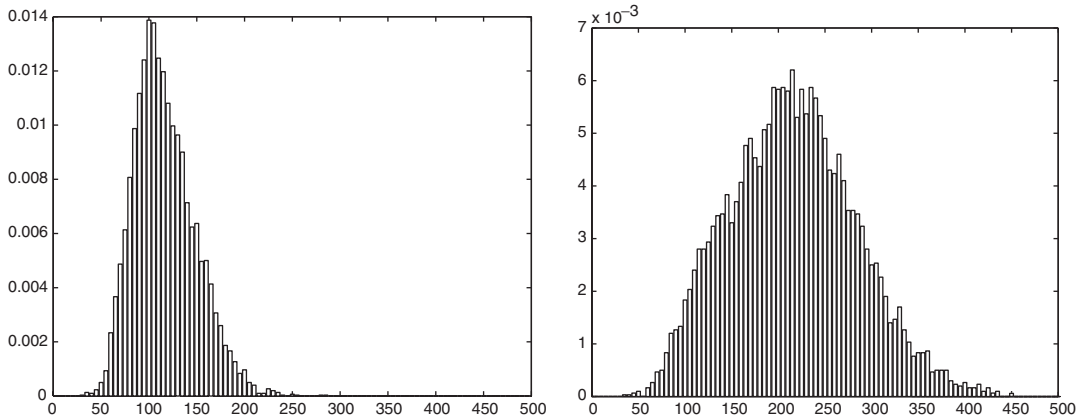

Figure 11. Posterior predictive distribution of the cumulative number of cases during weeks 1–10. Based on disease case data (15) from weeks 1–2, and a sample of 15 per cent from each unit in the beginning of week 2. Pessimistic prior (left), and optimistic (right). Ninety-five per cent probability intervals: $[64, 187]$, and $[93, 356]$, respectively. Correct number was 69.

about the disease probability (p), or even treat it as a fixed parameter. This could be based on reliable external knowledge about the invasiveness of the bacteria, if this was considered as a universal biological property. Otherwise, one may end up with difficulties of parametric identifiability especially in extreme situations of very low or very high disease incidence. In all situations, the predictions can be improved by additional data.

The essential feature of the model is its ability to learn from new observations as they appear along the epidemic process. When such data are combined with knowledge about the initial carriage prevalence, we have gained useful information on acquisition and on the expected course of an outbreak.

APPENDIX

The results were computed by Markov chain Monte Carlo simulation by applying Metropolis–Hastings random scan algorithm. This means that at each iteration one of the model unknowns is chosen randomly and the Metropolis–Hastings updating scheme is applied for that quantity. Then the next unknown quantity is chosen randomly to be updated, etc. The updating step of parameters p, q_w, q_b and r is relatively straightforward to compute and details are not given here. However, since the number of carriers I_{ji} is now observed for some (j, i)'s, these become data in the nodes of the model graph and therefore fixed quantities in the algorithm. Updating a pair of $I_{jk}^{\oplus}$, $I_{jk}^{\ominus}$ for some week k propagates a change in I_{ji} and R_{ji} for all $i > k$. For this reason, quadruples $(I_{ji}^{\oplus}, I_{ji}^{\ominus}, I_{j,i+1}^{\oplus}, I_{j,i+1}^{\ominus})$ are sampled blockwise by proposing new values from uniform distribution, centered at the current values of the first pair $(I_{ji}^{\oplus}, I_{ji}^{\ominus})$, then determining the proposed values of the second pair so that the epidemic chain is unaffected by the proposal from week $i+2$ onwards. In addition to the quadruple, this scheme will only affect the values of $I_{j,i+1}$ and $R_{j,i+1}$.

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There is an exception to the rule. When updating a quadruple would change the value of $I_{j,i+i}$ which should be kept constant (data), we only update the first pair $(I_{ji}^{\oplus}, I_{ji}^{\ominus})$ so that $I_{j,i+1}$ remains unaffected, but $R_{j,i+1}$ does not. (Consequently, $R_{j,i+2}, R_{j,i+3}, \ldots$ will change too). This can be done by proposing $I_{ji}^{\ominus}$ (or $I_{ji}^{\oplus}$) and then determining the proposed value for $I_{ji}^{\oplus}$ (or $I_{ji}^{\ominus}$). To avoid systematic moves, we can 'flip a coin' at each iteration to decide which one is proposed freely, but the order should not be crucial. All state variables of all units can be updated by the described block sampling algorithm, keeping some I_{ji}-variables fixed as needed. If no I_{ji} values need to be kept as fixed constants, then the latter updating step can be omitted.

An exceptional situation occurs when some I_{ji} is observed to be zero. Such data will immediately determine two other state variables, namely $I_{j,i-1}^{\oplus} = 0$ and $I_{ji}^{\ominus} = 0$. Moreover, $I_{j,i-1}^{\ominus}$ and $I_{j,i-1}$ must be equal. Adding a new move type would provide better mixing. With some probability, e.g. $\frac{2}{3}$, we propose adding either $+1$ (probability 0.5) or -1 jointly to the variables $(I_{j,i-2}^{\oplus}, I_{j,i-1}, I_{j,i-1}^{\ominus})$.

Initial states I_{j1}, R_{j1} may also be treated as unknown quantities if prior distributions $P(I_{j1})$ and $P(R_{j1})$ are specified. The associated sampling step can be constructed from several possible move types. There are five different ways in which we can propose independently new values for two out of the four variables $(I_{j1}, R_{j1}, I_{j1}^{\oplus}, I_{j1}^{\ominus})$, then determining the other two proposals so that the rest of the epidemic chain is not affected. Additionally, we can propose to keep $I_{j1}^{\oplus}$ at its current value, but propose new values for (R_{j1}, I_{j1}) (or $(R_{j1}, I_{j1}^{\ominus})$) independently, and determine $I_{j1}^{\ominus}$ (or I_{j1}) so that $I_{j2}, I_{j3}, \ldots$ are not affected, but $R_{j2}, R_{j3}, \ldots$ are allowed to change. It is good to propose different move types for better mixing.

If only a sample of individuals is drawn from a unit, and their carrier status are examined, we need to add the corresponding hypergeometrical sampling distribution to the likelihood. Hence, sampling would proceed without having to keep any I_{ji} fixed. This formulation would provide an alternative algorithm. As a special case, when the sample size in unit j is equal to N_j, the hypergeometric distribution becomes singular, corresponding with the previous algorithm.

REFERENCES

1. Kaninda A-V, Belanger F, Lewis R *et al*. Effectiveness of incidence thresholds for detection and control of meningococcal meningitis epidemics in northern Togo. *International Journal of Epidemiology* 2000; **29**: 933–940.
2. Hashimoto S, Murakami Y, Taniguchi K *et al*. Detection of epidemics in their early stage through infectious disease surveillance. *International Journal of Epidemiology* 2000; **29**:905–910.
3. Elveback LR, Fox JP, Ackerman E *et al*. An Influenza Simulation model for immunization studies. *American Journal of Epidemiology* 1976; **103**(2):152–165.
4. Franco ELF, Simons AR. Epidemiologic programs for computers and calculators: simple algorithms for the representation of deterministic and stochastic versions of the Reed-Frost epidemic model using a programmable calculator. *American Journal of Epidemiology* 1986; **123**(5):905–915.
5. Ranta J, Mäkelä PH, Takala A, Arjas E. Predicting the course of meningococcal disease outbreaks in closed subpopulations. *Epidemiology and Infection* 1999; **123**:359–371.
6. Cardinal M, Roy R, Lambert J. On the application of integer-valued time series models for the analysis of disease incidence. *Statistics in Medicine* 1999; **18**:2025–2039.
7. O'Neill PD, Roberts GO. Bayesian inference for partially observed stochastic epidemics. *Journal of the Royal Statistical Society Series A* 1999; **162**:121–129.
8. Aycock WL, Mueller JH. Meningococcus carrier rates and meningitis incidence. *Bacteriological Reviews* 1950; **14**:115–160.
9. Peltola H, Mäkelä OH, Käyhty H *et al*. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. *New England Journal of Medicine* 1977; **297**:686–691.

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10. Sivonen A, Renkonen O-V, Weckström P, Koskenvuo K, Raunio V, Mäkelä PH. The effect of Chemoprophylactic use of rifampin and minocycline on rates of carriage of *Neisseria meningitidis* in army recruits in Finland. *Journal of Infectious Diseases* 1978; **137**:238–244.
11. Bristow WM, Van Peenen PFD, Volk R. Epidemic meningitis in naval recruits. *American Journal of Public Health* 1965; **77**:1039–1045.
12. Smith I, Lehmann AK, Lie L *et al*. Outbreak of meningococcal disease in western Norway due to a new serogroup C variant of the ET-5 clone: effect of vaccination and selective carriage eradication. *Epidemiology and Infection* 1999; **123**:373–382.
13. Fernández S, Arreaza L, Santiago I *et al*. Carriage of a new epidemic strain of *Neisseria meningitidis* and its relationship with the incidence of meningococcal disease in Galicia, Spain. *Epidemiology and Infection* 1999; **123**:349–357.
14. Varela GE, Gilmore GD. Meningococcal disease outbreak at Fort Leonard Wood, Missouri. *Military Medicine* 1971; September:723–727.
15. Fraser PK, Bailey GK, Abbott JD, Gill JB, Walker DJC. The meningococcal carrier-rate. *The Lancet* 1973; June **2**:1235–1237.
16. Wenzel RP, Davies JA, Mitzel JR, Beam Jr WE. Non-usefulness of meningococcal carriage-rates. *The Lancet* 1973; July **28**:205.
17. Cook SS. The incidence of cerebrospinal fever in the United States Navy as related to length of service and season of enlistment. *American Journal of Hygiene* 1936; **23**:472–485.
18. Block C, Gdalevich M, Ruber R, Ashkenazi I, Ashkenazi S, Keller N. Factors associated with pharyngeal carriage of *Neisseria meningitidis* among Israel Defense Force Personnel at the end of their compulsory service. *Epidemiology and Infection* 1999; **122**:51–57.
19. Pether JVS, Lightfoot NF, Scott RJD, Morgan J, Steele-Perkins AP, Sheard SC. Carriage of *Neisseria meningitidis*: investigations in a military establishment. *Epidemiology and Infection* 1988; **101**:21–42.
20. Andersen J, Berthelsen L, Jensen BB, Lind I. Dynamics of the meningococcal carrier state and characteristics of the carrier strains: a longitudinal study within three cohorts of military recruits. *Epidemiology and Infection* 1998; **121**:85–94.
21. Gotschlich EC, Goldschneider I, Artenstein MS. Human immunity to the meningococcus, V. The effect of immunization with the meningococcal group C polysaccharide on the carrier state. *Journal of Experimental Medicine* 1969; **129**:1385–1395.
22. Sivonen A. Effect of *Neisseria meningitidis* group A polysaccharide vaccine on nasopharyngeal carrier rates. *Journal of Infection* 1981; **3**:266–272.
23. Gelman A, Carlin J, Stern H, Rubin D. *Bayesian Data Analysis* (Chapters 1, 5, 11, 17). Chapman & Hall: London, 1995.
24. Gilks WR, Richardson S, Spiegelhalter DJ (eds), *Markov Chain Monte Carlo in Practice* (Chapters 1, 8, 11). Chapman & Hall: London, 1995.
25. Edwards EA, Devine LF, Sengbuscp CP, Ward PW. Immunological investigations of meningococcal disease. *Scandinavian Journal of Infectious Diseases* 1977; **9**:105–110.
26. Sanchez MA, Blower SM. Uncertainty and sensitivity analysis of the basic reproductive rate. *American Journal of Epidemiology* 1997; **145**:1127–1137.
27. Nokes DJ, Anderson RM. The use of mathematical models in epidemiological study of infectious diseases and in the design of mass immunization programmes. *Epidemiology and Infection* 1988; **101**:1–20.
28. Anderson RM, May RM. *Infectious Diseases of Humans*. Oxford University Press: Oxford, 1992.

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