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Frank Ball, Tom Britton and Owen Lyne

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Postal address:

Mathematical Statistics
Dept. of Mathematics
Stockholm University
SE-106 91 Stockholm
Sweden

Internet:

http://www.math.su.se/matstat

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Stochastic multitype epidemics in a community of households: estimation and form of optimal vaccination schemes

Frank Ball[1], Tom Britton[2] and Owen Lyne[3]

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Abstract

This paper treats a stochastic model for an SIR (susceptible → infective → removed) multitype household epidemic. The community is assumed to be closed, individuals are of different types and each individual belongs to a household. Previously obtained probabilistic and inferential results for the model are used to derive the optimal vaccination scheme. By this is meant the scheme that vaccinates the fewest among all vaccination schemes that reduce the threshold parameter below 1. This is done for the situation where all model parameters are known and also for the case where parameters are estimated from an outbreak in the community prior to vaccination. It is shown that the algorithm which chooses vaccinees sequentially, at each step selecting the individual which reduces the threshold parameter the most, is not in general an optimal scheme. As a consequence, explicit characterisation of the optimal scheme is only possible in certain special cases. Two different types of vaccine responses, leaky and all or nothing, are considered and compared for the problems mentioned above. The methods are illustrated with some numerical examples.

Keywords: stochastic epidemic, multitype household epidemic, threshold parameter, estimation, optimal vaccination scheme, critical vaccination coverage, linear programming.

[1]School of Mathematical Sciences, University of Nottingham, University Park, Nottingham, NG7 2RD, England. E-mail: fgb@maths.nott.ac.uk

[2]Postal address: Mathematical Statistics, Stockholm University, SE-106 91, Sweden. E-mail: tomb@math.su.se.

[3]School of Mathematical Sciences, University of Nottingham, University Park, Nottingham, NG7 2RD, England. E-mail: Owen.Lyne@nottingham.ac.uk

1 Introduction

This paper is concerned with SIR (susceptible → infective → removed) epidemic models, describing the spread of an infectious disease in a closed finite community (see, for example, Lefèvre [1] and Andersson and Britton [2]). The effect that vaccination of part of the community has on the fundamental threshold parameter (often referred to as the basic reproduction number R_0, see for example, Heesterbeek and Dietz [3]) is studied. Vaccination schemes which reduce this number to below its threshold value of 1 are said to be *preventive*, since major outbreaks cannot occur in the community once such a vaccination scheme has been launched. A vaccination scheme is said to be *optimal* if it vaccinates the fewest number of individuals among all preventive vaccination schemes. The main focus of the paper lies in deriving the structure of such optimal vaccination schemes. This is done for a fully stochastic model for a multitype community in which individuals reside in households. The different types of individual have different susceptibilities to the disease and/or different infectivities if infected, and could for example reflect different age-groups, sex and/or health status. The household structure reflects the fact that infection rates between individuals of the same household are higher than infection rates between individuals of different households.

Two models for vaccine response are considered. In the first model, a vaccinated individual is either rendered completely immune or the vaccine has no effect. In the second model, vaccinated individuals have a reduced probability of infection given exposure to infection. These models are defined in Smith et al. [4] and, following Halloran et al. [5], are referred to as *all or nothing* and *leaky*, respectively.

Ball and Lyne [6] studied the probabilistic behaviour of the multitype households model treated in this paper. In particular, they derived a threshold parameter R_* (the households model equivalent of the basic reproduction number R_0) that determines whether or not a major outbreak can occur; see also Becker and Hall [7]. Statistical inference for model parameters, based on final outcome data (possibly only for a sample of households in the community) is considered by Ball and Lyne [8]. Ball *et al.* [9] treat inference procedures for the same kind of data, but now for the threshold parameter R_*, both before and after vaccination. It is shown that R_* cannot be estimated consistently. Instead, upper and lower bounds for R_* are derived, both before and after vaccination, which can be estimated consistently from final outcome data. These bounds are sharp, given the available data. This investigation is continued here, by determining how to allocate vaccines in an optimal way, i.e. how to select which individuals to vaccinate. This is done both for the case where all model parameters, and hence also R_*, are known, and for the case where parameters are estimated from final size data. In the latter case, the vaccine allocation which reduces the *upper bound* of R_* down to 1 with minimum vaccine coverage is determined

It is shown that a complex non-linear optimisation problem has to be solved in order to find the optimal vaccination scheme when all parameters are known, except when the between-household transmission parameters satisfy so-called proportionate mixing. For proportionate mixing, sometimes also denoted separable mixing, the optimal vaccination scheme may be found by solving a linear programming problem. When parameters are

estimated, and the upper bound estimate of R_* must be reduced down to 1 for a vaccination scheme to surely be preventive, the derivation of the optimal vaccination scheme is also a linear programming problem. Thus the vaccination problem with parameter estimation proves simpler than the general known parameters case and can be used to provide bounds on the general problem.

A second observation is that the optimal vaccination scheme v_{opt}, giving the smallest overall vaccination coverage c_v, has no explicit form in general. This is in contrast to, for example, the single type household case with all or nothing vaccines. In this scenario it has been proven for some special cases, and conjectured to hold in general, that successive vaccinations within the same household yield diminishing reductions in the threshold parameter R_*, leading to simple characterisations of the optimal vaccination scheme (see Ball and Lyne [10]).

The paper is organised as follows. The stochastic multitype SIR households epidemic model is described in Section 2, where its threshold behaviour is outlined. The threshold parameters following a vaccination scheme, using the two models for vaccine response, are determined and compared in that section, and optimal vaccination schemes are defined. A construction of the optimal vaccination scheme, for the proportionate mixing case with known infection parameters, is given in Section 3. The form of the optimal vaccination scheme is also discussed and examples are presented which demonstrate that (i) successive vaccinations within the same household may not yield diminishing reductions in the threshold parameter R_*, and (ii) the optimal scheme for a given vaccine coverage cannot necessarily be constructed by allocating the vaccines sequentially. Estimation of the epidemiologically important parameters is treated in Section 4. The form of the optimal vaccination scheme for the case when the infection parameters are estimated is considered in Section 5, where examples illustrating that (i) and (ii) above still hold in this setting are given. Some numerical examples are given in Section 6 and the paper concludes with a brief discussion in Section 7. The present paper is a continuation of Ball *et al.* [9], where more details on the model and inferential methods can be found.

2 Model, model properties and vaccination

2.1 Model

The model under consideration in this paper is that of Ball and Lyne [6] for the spread of an SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed) epidemic among a closed, finite population that contains J classes of individuals, labelled $1, 2, \ldots, J$, and is partitioned into households. Let $\mathcal{J} = \{1, 2, \ldots, J\}$ and $\mathcal{N}_0 = \{\boldsymbol{n} = (n_1, n_2, \ldots, n_J) \in \mathbb{Z}^J : n_j \geq 0 \ (j \in \mathcal{J}), \ |\boldsymbol{n}| = \sum_{j=1}^{J} n_j \geq 1\}$. Suppose that, for $\boldsymbol{n} \in \mathcal{N}_0$, the population contains $m_{\boldsymbol{n}}$ households of category $\boldsymbol{n}$, where a household of category $\boldsymbol{n}$ contains n_j individuals of class j $(j \in \mathcal{J})$. Let $m = \sum_{\boldsymbol{n} \in \mathcal{N}_0} m_{\boldsymbol{n}}$ denote the total number of households in the population, $N_j = \sum_{\boldsymbol{n} \in \mathcal{N}_0} n_j m_{\boldsymbol{n}}$ denote the total number of individuals of class j in the population $(j \in \mathcal{J})$ and $N = \sum_{\boldsymbol{n} \in \mathcal{N}_0} |\boldsymbol{n}| m_{\boldsymbol{n}}$ denote the total number of individuals in the population. Assume

that N, and hence N_j ($j \in \mathcal{J}$) and m, is finite. This implies that $m_{\boldsymbol{n}} = 0$ for all but finitely many $\boldsymbol{n}$. Let $\mathcal{N} = \{\boldsymbol{n} \in \mathcal{N}_0 : m_{\boldsymbol{n}} > 0\}$.

The epidemic is initiated by some individuals becoming infected at time $t = 0$, with the remaining individuals in the population all assumed to be susceptible. For $j \in \mathcal{J}$, the infectious periods of class j infectives are each distributed according to a finite random variable $T_I^{(j)}$, having an arbitrary but specified distribution with mean t_j. For $i, j \in \mathcal{J}$, throughout its infectious period a given class i infective makes *global* contacts with any given susceptible of class j in the population at the points of a homogeneous Poisson process having rate λ_{ij}^G/N_j and, additionally, it makes *local* contacts with any given susceptible of class j in its own household at the points of a homogeneous Poisson process having rate λ_{ij}^L. All the Poisson processes describing infectious contacts (whether or not either or both of the individuals involved are the same), as well as the random variables describing infectious periods, are assumed to be mutually independent. A susceptible becomes infective as soon as it is contacted by an infective and is removed (and plays no further part in the epidemic) at the end of its infectious period. The epidemic ceases as soon as there are no infectives present in the population.

2.2 Model properties

Below follows a summary of results which are used in the sequel. Details may be found in Ball and Lyne [6]. Suppose that the number of households m is large. During the early stages of an epidemic initiated by a small number of infectives, the process of infected households in the epidemic can be approximated by a multitype branching process, with type space $\mathcal{J}$, where the type of an infected household is given by the class j of its initial (globally contacted) infective (see [6] for rigorous results). (A more detailed branching process approximation includes also the category of infected households but such detail is not necessary (except possibly for the zeroth generation) since, for $i \in \mathcal{J}$, successive global contacts with class i individuals are with individuals chosen uniformly from all class i individuals in the population, so the categories of type i infected households are independent and identically distributed.) It is said that a *global epidemic* occurs if, in the limit as $m \to \infty$, the epidemic infects infinitely many households, i.e. if the branching process does not go extinct. Let $M = [m_{ij}]$, where for $i, j \in \mathcal{J}$, m_{ij} is the mean number of class j global contacts that emanate from a typical type i infected household. It is assumed that M is positively regular, thus avoiding the possibility of a global epidemic among some, but not all, classes of individual. The threshold theorem for the epidemic process then states that the threshold parameter R_* is defined as the maximal eigenvalue of M, and a global epidemic occurs with non-zero probability if and only if $R_* > 1$.

Expressions for m_{ij} ($i, j \in \mathcal{J}$) are required to compute R_*. For $\boldsymbol{n} \in \mathcal{N}$, let $\alpha_{\boldsymbol{n}} = m_{\boldsymbol{n}}/m$ denote the proportion of households of category $\boldsymbol{n}$ in the population and, for $i \in \mathcal{J}$ and $\boldsymbol{n} \in \mathcal{N}$, let $\alpha_i(\boldsymbol{n}) = n_i m_{\boldsymbol{n}}/N_i$ be the probability that a class i individual chosen at random in the population resides in a household of category $\boldsymbol{n}$. Consider a completely susceptible household of category $\boldsymbol{n}$ in which an i-individual is contacted globally. For $j \in \mathcal{J}$, let $\mu_{\boldsymbol{n},i,j}(\Lambda^L)$, where $\Lambda^L = [\lambda_{ij}^L]$, denote the mean number of class j individuals that are

ultimately infected in the household (neglecting further global infections), including the initial infective if $j = i$. An algorithm for computing $\mu_{\boldsymbol{n},i,j}(\Lambda^L)$ ($\boldsymbol{n} \in \mathcal{N}; i, j \in \mathcal{J}$) is given in the appendix of [9]. In Ball and Lyne [6], Section 4.3, it is shown that

$$m_{ij} = \sum_{\boldsymbol{n}\in\mathcal{N}} \alpha_i(\boldsymbol{n}) \sum_{k\in\mathcal{J}} \mu_{\boldsymbol{n},i,k}(\Lambda^L) t_k \lambda^G_{kj} \quad (i, j \in \mathcal{J}). \tag{2.1}$$

In (2.1) the factor $\alpha_i(\boldsymbol{n})$ conditions on which household category the i-individual belongs to. The factor $\mu_{\boldsymbol{n},i,k}(\Lambda^L)$ is the expected number of k-individuals infected in this category of household when only local infections are considered and the initial infective is of class i, and $t_k\lambda^G_{kj}$ is the expected number of global contacts with j-individuals one such k-individual has during his infectious period.

2.3 Vaccination

Two different types of vaccination response are considered, namely *all or nothing* and *leaky* (cf. Halloran *et al.* [5]).

2.3.1 All or nothing vaccines

All or nothing vaccines are modelled by assuming that the vaccine either renders its recipient complete immunity or else it has no effect, and that vaccinated individuals react independently, with probability ϵ_i for a class i individual ($i \in \mathcal{J}$).

For $\boldsymbol{n} \in \mathcal{N}$ and $\mathbf{0} \le \boldsymbol{r} = (r_1, r_2, \ldots, r_J) \le \boldsymbol{n}$, where inequalities between vectors are to be interpreted elementwise, let $v_{\boldsymbol{n},\boldsymbol{r}}$ denote the proportion of households of category $\boldsymbol{n}$ that have had $\boldsymbol{r}$ members vaccinated, and let $\boldsymbol{v} = \{v_{\boldsymbol{n},\boldsymbol{r}} : \boldsymbol{n} \in \mathcal{N}, \mathbf{0} \le \boldsymbol{r} \le \boldsymbol{n}\}$.

Similar to m_{ij} of the previous section but now also taking vaccination into account, let $m_{ij}(\boldsymbol{v})$ denote the expected number of class j global contacts that emanate from a single household epidemic that is initiated by a randomly chosen class i individual being contacted globally ($i, j \in \mathcal{J}$). Using the notation $\binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{k}} = \prod_{l=1}^J \binom{r_l}{n_l-k_l}$, $\boldsymbol{x}^{\boldsymbol{y}} = \prod_{l=1}^J x_l^{y_l}$, $\sum_{\boldsymbol{r}=\mathbf{0}}^{\boldsymbol{n}} = \sum_{r_1=0}^{n_1}\sum_{r_2=0}^{n_2}\cdots\sum_{r_J=0}^{n_J}$, and letting $\mathbf{1}$ denote the row vector of J ones, it is shown in Ball *et al.* [9] that $m_{ij}(\boldsymbol{v})$ ($i, j \in \mathcal{J}$) is given by

$$m_{ij}(\boldsymbol{v}) = \sum_{\boldsymbol{n}\in\mathcal{N}} \alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=\mathbf{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \sum_{\boldsymbol{k}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{k}} \boldsymbol{\epsilon}^{\boldsymbol{n}-\boldsymbol{k}} (\mathbf{1}-\boldsymbol{\epsilon})^{\boldsymbol{r}-\boldsymbol{n}+\boldsymbol{k}} \frac{k_i}{n_i} \sum_{l\in\mathcal{J}} \mu_{\boldsymbol{k},i,l}(\Lambda^L) t_l \lambda^G_{lj}. \tag{2.2}$$

Here too the result is obtained by first conditioning on the category of household the i-individual belongs to and now also on the vaccination status of the considered household. Then one has to compute the probability that the randomly chosen individual is susceptible – otherwise no further infections occur. Finally, the last sum gives the expected number of global class j contacts emanating from the household of the randomly chosen i-individual.

Let $M(\boldsymbol{v}) = [m_{ij}(\boldsymbol{v})]$ and $R_*^{AoN}(\boldsymbol{v})$ be the maximal eigenvalue of $M(\boldsymbol{v})$. Then $R_*^{AoN}(\boldsymbol{v})$ is a threshold parameter for the epidemic after vaccination with an all or nothing (AoN)

vaccine, in the sense that a global epidemic can occur only if $R_*^{AoN}(\boldsymbol{v}) > 1$. Consequently, a vaccination scheme $\boldsymbol{v}$ having $R_*^{AoN}(\boldsymbol{v}) \leq 1$ is protective for the whole community, the aim of launching a vaccination programme.

There is in general no closed form expression for $R_*^{AoN}(\boldsymbol{v})$. However, if the global infection rates take the proportionate mixing, also denoted separable mixing, form (see, for example, Hethcote and Van Ark [11] or Becker and Marschner [12]) $\lambda_{ij}^G = \eta_i^G \kappa_j^G$ $(i, j \in \mathcal{J})$, then the matrix $M(\boldsymbol{v})$ has rank one, so $R_*^{AoN}(\boldsymbol{v})$ is given by its trace, i.e.

$$R_*^{AoN}(\boldsymbol{v}) = \sum_{i\in\mathcal{J}} \sum_{\boldsymbol{n}\in\mathcal{N}} \alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \sum_{\boldsymbol{k}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{k}} \boldsymbol{\epsilon}^{\boldsymbol{n}-\boldsymbol{k}} (\boldsymbol{1}-\boldsymbol{\epsilon})^{\boldsymbol{r}-\boldsymbol{n}+\boldsymbol{k}} \frac{k_i}{n_i} \sum_{l\in\mathcal{J}} \mu_{\boldsymbol{k},i,l}(\Lambda^L) t_l \eta_l^G \kappa_i^G. \tag{2.3}$$

2.3.2 Leaky vaccines

A leaky vaccine is a vaccine where all vaccinees respond by acquiring partial immunity rather than acquiring either complete immunity or no immunity at all. More specifically it is assumed that all infection rates to vaccinated class j individuals are reduced by a factor ϵ_j $(j \in \mathcal{J})$. Hence, for $i, j \in \mathcal{J}$, the rate at which a class i infective has global contact with a vaccinated class j individual is $\lambda_{ij}^G(1-\epsilon_j)/N_j$ and the corresponding local contact rate is $\lambda_{ij}^L(1-\epsilon_j)$. Note that the *average* vaccine efficacy ϵ_j for each class of individual is the same as in the all or nothing case. As before, a vaccination scheme is specified by $\boldsymbol{v} = \{v_{\boldsymbol{n},\boldsymbol{r}} : \boldsymbol{n} \in \mathcal{N}, \boldsymbol{0} \leq \boldsymbol{r} \leq \boldsymbol{n}\}$, where $v_{\boldsymbol{n},\boldsymbol{r}}$ is the proportion of category $\boldsymbol{n}$ households that have $\boldsymbol{r}$ individuals vaccinated.

It is necessary to derive expressions for $m_{ij}(\boldsymbol{v})$ corresponding to (2.2) in the all or nothing case, and ultimately for $R_*^{Le}(\boldsymbol{v})$, the maximal eigenvalue of the matrix with elements $m_{ij}(\boldsymbol{v})$ assuming a leaky vaccine. It is convenient to introduce some new notation in order to do this. After a vaccination scheme, there are $2J$ classes of individual in the population, i.e. vaccinated and unvaccinated individuals for each of the J original classes. Let $\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{u}:i,l}(\Lambda^L, \boldsymbol{\epsilon})$ $(\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{v}:i,l}(\Lambda^L, \boldsymbol{\epsilon}))$ denote the expected number of infected class l individuals, counting *both* vaccinated and unvaccinated individuals, in a category $\boldsymbol{n}$ household having $\boldsymbol{r}$ vaccinated, and hence $\boldsymbol{n}-\boldsymbol{r}$ unvaccinated, individuals, initiated by an infectious unvaccinated (vaccinated) class i individual, neglecting further outside infections. As in Section 2.3.1, for $i, j \in \mathcal{J}$, let $m_{ij}(\boldsymbol{v})$ be the expected number of global contacts with class j individuals that emanate from a single household epidemic that is initiated by a randomly chosen class i individuals being contacted globally, but now assuming a leaky vaccine. Using similar arguments as in the motivation for 2.1 and 2.2, it is shown in [9] that

$$m_{ij}(\boldsymbol{v}) =$$
$$\sum_{\boldsymbol{n}\in\mathcal{N}} \alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \sum_{k\in\mathcal{J}} \left(\frac{n_i - r_i}{n_i} \mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{u}:i,k}(\Lambda^L, \boldsymbol{\epsilon}) + \frac{r_i(1-\epsilon_i)}{n_i} \mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{v}:i,k}(\Lambda^L, \boldsymbol{\epsilon}) \right) t_k \lambda_{kj}^G.$$

The threshold parameter $R_*^{Le}(\boldsymbol{v})$ is the maximal eigenvalue of the matrix $M(\boldsymbol{v}) = [m_{ij}(\boldsymbol{v})]$. As before, a global epidemic can occur only if $R_*^{Le}(\boldsymbol{v}) > 1$, implying that the main goal of

a vaccination scheme is to make $R_*^{Le}(\boldsymbol{v}) \leq 1$. Here too there is an explicit expression for $R_*^{Le}(\boldsymbol{v})$, analogous to (2.3), if $\Lambda^G = [\lambda_{ij}^G]$ takes the proportionate mixing form, $\lambda_{ij}^G = \eta_i^G \kappa_j^G$ $(i, j \in \mathcal{J})$.

2.3.3 Optimal vaccination schemes

In the previous two subsections we have considered two different types of vaccine responses, and their effect on the threshold parameter R_* when part of the community (specified by $\boldsymbol{v}$) is vaccinated. As noted above, the main aim of any vaccination scheme is to bring the threshold parameter below one, i.e. to ensure that $R_*(\boldsymbol{v}) \leq 1$. (The threshold parameter following the vaccination scheme $\boldsymbol{v}$ is referred to generically as $R_*(\boldsymbol{v})$; $R_*(\boldsymbol{v}) = R_*^{AoN}(\boldsymbol{v})$ if the vaccine is all or nothing and $R_*^{Le}(\boldsymbol{v})$ if it is leaky.) Therefore, for a given community and a given vaccine response, the vaccination scheme $\boldsymbol{v}$ is said to be *preventive* (written $\boldsymbol{v} \in P$) if the induced threshold parameter satisfies $R_*(\boldsymbol{v}) \leq 1$.

It could be the case that no vaccination scheme is preventive if the vaccine response, or efficacy, $\boldsymbol{\epsilon}$ is not large enough. That is, even with $\boldsymbol{v}$ satisfying $v_{\boldsymbol{n},\boldsymbol{n}} = 1$ for all $\boldsymbol{n}$ and $v_{\boldsymbol{n},\boldsymbol{r}} = 0$ $(\boldsymbol{r} \neq \boldsymbol{n})$, meaning that all individuals in all households are vaccinated, it may be that $R_*(\boldsymbol{v}) > 1$. If this is the case a better vaccine or some additional preventive measure, such as improving sanitary conditions, is needed to surely prevent future global outbreaks.

On the other hand, if the vaccine response is large enough there will be many different vaccination schemes $\boldsymbol{v}$ satisfying $R_*(\boldsymbol{v}) \leq 1$. It is then important to determine which such scheme is the best in the sense that it requires the fewest vaccinations. Accordingly, if

$$S(\boldsymbol{v}) = \frac{\sum_{\boldsymbol{n} \in \mathcal{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} |\boldsymbol{r}| v_{\boldsymbol{n},\boldsymbol{r}} \alpha_{\boldsymbol{n}}}{\sum_{\boldsymbol{n} \in \mathcal{N}} |\boldsymbol{n}| \alpha_{\boldsymbol{n}}} \tag{2.4}$$

denotes the proportion of the population that are vaccinated (i.e. the overall vaccination coverage) under the scheme $\boldsymbol{v}$, then any scheme

$$\boldsymbol{v}_{\text{opt}} \in \underset{\boldsymbol{v} \in P}{\text{argmin}}\{S(\boldsymbol{v})\} = \{\boldsymbol{v}' \in P : S(\boldsymbol{v}') \leq S(\boldsymbol{v}) \text{ for all } \boldsymbol{v} \in P\}.$$

is optimal. The corresponding coverage $c_v = S(\boldsymbol{v}_{\text{opt}})$ is called the *critical vaccination coverage*. The definition of $\boldsymbol{v}_{\text{opt}}$ could be generalised to incorporate costs associated with the practical implementation of a vaccination scheme, for example by including an additional cost per household having individuals vaccinated (cf. Ball and Lyne [10]). However, only the simple version, where cost is proportional to the number of vaccinations, is considered here.

In the rest of the paper we focus on how to derive $\boldsymbol{v}_{\text{opt}}$, and to study its structure. It is a non-linear optimisation problem to derive $\boldsymbol{v}_{\text{opt}}$ in general, hence a non-trivial task. The reason for this is that $R_*(\boldsymbol{v})$ does not admit a closed-form expression. However, if the global infection rates take the proportionate mixing form then $R_*(\boldsymbol{v})$ and $S(\boldsymbol{v})$ are both linear functions of $\boldsymbol{v}$, so determining the allocation of vaccines which (a) minimises $R_*(\boldsymbol{v})$ subject to an upper bound on $S(\boldsymbol{v})$ or (b) minimises $S(\boldsymbol{v})$ subject to $R_*(\boldsymbol{v}) \leq 1$ are both

linear programming problems, cf. Becker and Starczak [13]. Note that there are further (linear) constraints on $\boldsymbol{v}$ implicit in the above formulations, specifically that, for $\boldsymbol{n} \in \mathcal{N}$, $v_{\boldsymbol{n},\boldsymbol{r}} \geq 0$ ($\mathbf{0} \leq \boldsymbol{r} \leq \boldsymbol{n}$) and $\sum_{\boldsymbol{r}=\mathbf{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} = 1$.

In the single class case ($J = 1$) with all or nothing vaccines, Ball and Lyne [10] show that, provided a certain convexity conjecture holds (see Section 3.2), successive vaccinations within the same household yield diminishing reductions in the threshold parameter R_*, leading to simple characterisations of the solutions of the above linear programming problems. In particular, if the vaccine is perfect ($\epsilon = 1$), the optimal vaccination scheme is the so-called equalising strategy of Ball et al. [14], in which vaccines are allocated sequentially, always to a household that contains the greatest number of unvaccinated individuals. The form of $\boldsymbol{v}_{\text{opt}}$ for the multitype case, when global mixing is proportionate, is considered in Section 3, where it is shown by example (see Section 3.3) that, in contrast to the single type case, successive vaccinations within the same household do not necessarily yield diminishing reductions in R_*.

2.3.4 Comparison of all or nothing and leaky vaccines

In this section, we show in a precise way that if the vaccine efficacy $\boldsymbol{\epsilon}$ is held fixed, the all or nothing model for vaccine action results in a greater reduction in the spread of disease than the leaky model. To that end, note that since all the contact processes in the model of Section 2.1 are Poisson, that model can be constructed using a Sellke([15])-type construction, in which different initial susceptibles have independent critical exposures to infection, which are each distributed according to a negative exponential random variable with mean 1. For $t \geq 0$, a given susceptible of class i accumulates exposure to infection at rate $\sum_{j \in \mathcal{J}} \left(y_j^G(t) \lambda_{ji}^G N_i^{-1} + y_j^L(t) \lambda_{ji}^L \right)$, where, for $j \in \mathcal{J}$, $y_j^G(t)$ is the total number of class j infectives in the population and $y_j^L(t)$ is the number of class j infectives in the given susceptible's household. A susceptible succumbs to infection as soon as its total exposure to infection reaches its critical level.

Let Q, Q^{AoN} and Q^{Le} denote the critical exposures to infection of typical unvaccinated, vaccinated (all or nothing) and vaccinated (leaky) individuals, respectively. If the vaccine has efficacy $\epsilon \in (0, 1)$, then $Q^{AoN} = \infty$ if the vaccine is successful (i.e. with probability ϵ) and $Q^{AoN} = Q$ otherwise, whilst $Q^{Le} = (1 - \epsilon)^{-1} Q$. Thus, by the convexity of the exponential function,

$$P(Q^{Le} > t) = \exp\Big(-(1-\epsilon)t\Big) \leq \epsilon + (1-\epsilon)\exp(-t) = P(Q^{AoN} > t) \qquad (t \geq 0)\,,$$

with strict inequality for $t > 0$. Hence, Q^{AoN} is stochastically larger than Q^{Le}. It follows that, for the model of Section 2.1, if the same vaccination scheme is used, the ensuing epidemics under the all or nothing and leaky vaccine actions can be coupled so that, with probability one, the set of individuals ultimately infected by the all or nothing epidemic is a subset of those ultimately infected by the leaky epidemic.

Note that, for $i, j \in \mathcal{J}$, the expected number of class j global contacts made by a randomly chosen class i individual is the same under the two models for vaccine action, hence if all

the households are of size 1 (so heterogeneity in the population is due entirely to there being different classes of individuals) then $R_*^{AoN}(\boldsymbol{v}) = R_*^{Le}(\boldsymbol{v})$, and the optimal vaccination scheme will be the same under the two models (see Britton [16]). However, this is not necessarily the case when there are households of size > 1, since then local spread affects $M(\boldsymbol{v})$ and the above coupling argument shows that $R_*^{AoN}(\boldsymbol{v}) \leq R_*^{Le}(\boldsymbol{v})$ (so the critical vaccine coverages satisfy $c_v^{AoN} \leq c_v^{Le}$), with strict inequality except for a few special cases. Indeed, with a households model, it is possible for complete vaccination to be preventive if the action is all or nothing but not preventive for the corresponding leaky model, as illustrated in Section 6.

3 Optimal vaccination schemes, known infection rates

In this section we study how to construct optimal vaccination schemes and their forms, under the assumption that the infection rate matrices Λ^L and Λ^G are known. Since closed form expressions for the threshold parameters are only available when global mixing is proportionate we also assume global proportionate mixing, i.e. that Λ^G takes the form $\lambda_{ij}^G = \eta_i^G \kappa_j^G$ $(i, j \in \mathcal{J})$. As in Section 2.3, suppose that a vaccination scheme is specified by $\boldsymbol{v} = \{v_{\boldsymbol{n},\boldsymbol{r}} : \boldsymbol{n} \in \mathcal{N}, \boldsymbol{0} \leq \boldsymbol{r} \leq \boldsymbol{n}\}$, where $v_{\boldsymbol{n},\boldsymbol{r}}$ is the proportion of households of category $\boldsymbol{n}$ that have $\boldsymbol{r}$ individuals vaccinated. For $\boldsymbol{n} \in \mathcal{N}$ and $\boldsymbol{0} \leq \boldsymbol{r} \leq \boldsymbol{n}$, let $h_{\boldsymbol{n},\boldsymbol{r}} = v_{\boldsymbol{n},\boldsymbol{r}} m_{\boldsymbol{n}}$ be the number of category $\boldsymbol{n}$ households that have $\boldsymbol{r}$ individuals vaccinated. Recalling that $\alpha_i(\boldsymbol{n}) = n_i m_{\boldsymbol{n}}/N_i$, it follows from (2.3) and the equivalent equation for leaky vaccines that

$$R_*(\boldsymbol{v}) = \sum_{\boldsymbol{n}\in\mathcal{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} h_{\boldsymbol{n},\boldsymbol{r}} M_{\boldsymbol{n},\boldsymbol{r}},$$

where

$$M_{\boldsymbol{n},\boldsymbol{r}} = \sum_{i\in\mathcal{J}} \frac{1}{N_i} \sum_{\boldsymbol{k}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{k}} \boldsymbol{\epsilon}^{\boldsymbol{n}-\boldsymbol{k}} (\boldsymbol{1}-\boldsymbol{\epsilon})^{\boldsymbol{r}-\boldsymbol{n}+\boldsymbol{k}} k_i \sum_{l\in\mathcal{J}} \mu_{\boldsymbol{k},i,l}(\Lambda^L) t_l \eta_l^G \kappa_i^G \tag{3.1}$$

for all or nothing vaccines and

$$M_{\boldsymbol{n},\boldsymbol{r}} = \sum_{i\in\mathcal{J}} \frac{1}{N_i} \sum_{k\in\mathcal{J}} \{(n_i - r_i)\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{u}:i,k}(\Lambda^L, \boldsymbol{\epsilon}) + r_i(1-\epsilon_i)\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{v}:i,k}(\Lambda^L, \boldsymbol{\epsilon})\} t_k \eta_k^G \kappa_i^G$$

for leaky vaccines.

3.1 Construction of optimal vaccination scheme

As indicated in Section 2.3.3, the determination of the allocations of vaccines which (a) minimises $R_*(\boldsymbol{v})$ subject to an upper bound on the vaccine coverage

$$S(\boldsymbol{v}) = \frac{\sum_{\boldsymbol{n}\in\mathcal{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} |\boldsymbol{r}| v_{\boldsymbol{n},\boldsymbol{r}} \alpha_{\boldsymbol{n}}}{\sum_{\boldsymbol{n}\in\mathcal{N}} |\boldsymbol{n}| \alpha_{\boldsymbol{n}}} = \frac{\sum_{\boldsymbol{n}\in\mathcal{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} |\boldsymbol{r}| h_{\boldsymbol{n},\boldsymbol{r}}}{\sum_{\boldsymbol{n}\in\mathcal{N}} |\boldsymbol{n}| m_{\boldsymbol{n}}},$$

or (b) minimises the vaccine coverage $S(\boldsymbol{v})$ subject to $R_*(\boldsymbol{v}) \leq 1$, when expressed in terms of the proportions $\boldsymbol{v}$, are both linear programming problems, which, for given household structure $m_{\boldsymbol{n}}$ ($\boldsymbol{n} \in \mathcal{N}$) and vaccine efficacy $\boldsymbol{\epsilon}$, can be solved numerically using standard computer software. It is now shown that the solutions of these linear programming problems can be constructed directly.

Suppose first that all of the m households in the population have the same category, $\boldsymbol{n}$ say. Let $\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_p$ denote the different ways of vaccinating a single household, so $p = \prod_{i \in \mathcal{J}}(n_i + 1)$. Note that the case of no vaccination, $\boldsymbol{r} = \boldsymbol{0}$, is included in this list and suppose that it is given by $\boldsymbol{r}_1$. Consider the convex hull of the points $(\frac{|\boldsymbol{r}_k|}{|\boldsymbol{n}|}, mM_{\boldsymbol{n},\boldsymbol{r}_k})$ $(k = 1, 2, \ldots, p)$ in $\mathbb{R}^2$. The lower edge of this convex hull is a decreasing, piecewise linear convex function, $f : [0,1] \to [R_*(\boldsymbol{v}_{\text{full}}), R_*]$ say, satisfying $f(0) = R_*$ and $f(1) = R_*(\boldsymbol{v}_{\text{full}})$, where $\boldsymbol{v}_{\text{full}}$ corresponds to everyone in the population being vaccinated. For $c \in [0,1]$, $f(c)$ is the minimum achievable value of $R_*(\boldsymbol{v})$ subject to $S(\boldsymbol{v}) = c$. Note that, unless $(c, f(c)) = (\frac{|\boldsymbol{r}_k|}{|\boldsymbol{n}|}, mM_{\boldsymbol{n},\boldsymbol{r}_k})$ for some k, then the corresponding vaccination scheme is mixed, in a sense that is now made clear.

For $i, j = 1, 2, \ldots, p$ with $i \neq j$, let $a(i,j) = M_{\boldsymbol{n},\boldsymbol{r}_i} - M_{\boldsymbol{n},\boldsymbol{r}_j}$ and $b(i,j) = a(i,j)/(|\boldsymbol{r}_j| - |\boldsymbol{r}_i|)$ be, respectively, the absolute and per vaccine reduction in $R_*(\boldsymbol{v})$ achieved by vaccinating a single household according to $\boldsymbol{r}_j$ instead of according to $\boldsymbol{r}_i$. (Note that $a(i,j)$ may be negative and $b(i,j)$ is not defined if $|\boldsymbol{r}_j| = |\boldsymbol{r}_i|$.) Let $i_0 = 1$. For $k = 1, 2, \ldots$, let $\mathcal{I}'_k = \{i : \boldsymbol{r}_i \not\leq \boldsymbol{r}_{i_j} \text{ and } a(i_j, i) > 0, j = 0, 1, \ldots, k-1\}$, $\mathcal{I}_k = \underset{i \in \mathcal{I}'_k}{\operatorname{argmax}}\{b(i_{k-1}, i)\}$ and choose $i_k \in \underset{i \in \mathcal{I}_k}{\operatorname{argmax}}\{a(i_{k-1}, i)\}$. Note that this process must terminate after a finite number of steps, i.e. that $q = \min\{k : M_{\boldsymbol{n},\boldsymbol{r}_{i_k}} = M_{\boldsymbol{n},\boldsymbol{n}}\}$ is well defined (though $\boldsymbol{r}_{i_q}$ may not equal $\boldsymbol{n}$, for example if some classes of individuals are insensitive to the vaccine). For $k = 0, 1, \ldots, q$, let $c_k = |\boldsymbol{r}_{i_k}|/|\boldsymbol{n}|$ be the vaccine coverage if every household in the population is vaccinated according to $\boldsymbol{r}_{i_k}$. Then, by construction, $0 = c_0 < c_1 < \cdots < c_q \leq 1$. Further, for fixed vaccine coverage $c \in [0, c_q]$, if $c = c_k$ for some k then $R_*(\boldsymbol{v})$ is minimised by vaccinating every household according to $\boldsymbol{r}_{i_k}$, whilst if $c \neq c_k$ $(k = 0, 1, \ldots, q)$ then $R_*(\boldsymbol{v})$ is minimised by vaccinating a proportion $\frac{|\boldsymbol{r}_{i_k}| - c|\boldsymbol{n}|}{|\boldsymbol{r}_{i_k}| - |\boldsymbol{r}_{i_{k-1}}|}$ of households according to $\boldsymbol{r}_{i_k}$ and the other households according to $\boldsymbol{r}_{i_{k-1}}$, where $k = \min\{l : c_l > c\}$. It is also straightforward to write down a solution to the optimisation problem (b) above.

It is convenient to make a few observations before proceeding to the general case when more than one household category is present in the population. First, the solutions to the optimisation problems, (a) and (b) above, may not be unique. Secondly, although the above provides explicit solutions to the linear programming problems it may not give an exact solution to the corresponding integer linear programming problems, in terms of $h_{\boldsymbol{n},\boldsymbol{k}}$ $(\boldsymbol{n} \in \mathcal{N}, \boldsymbol{0} \leq \boldsymbol{k} \leq \boldsymbol{n})$, since, for example, $m_{\boldsymbol{n}} \frac{|\boldsymbol{r}_{i_k}| - c|\boldsymbol{n}|}{|\boldsymbol{r}_{i_k}| - |\boldsymbol{r}_{i_{k-1}}|}$ may not be an integer. However, it is clear how one could obtain an exact solution to the integer problem, though the details are messy, and in any case for large populations the solutions of the non-integer problems are quite adequate for practical purposes. Thirdly, although the above construction gives a way of determining a solution to (a) or (b) by continuously increasing the vaccine coverage c from 0, unless it is possible to choose i_k $(k = 0, 1, \ldots, q)$ so that $\boldsymbol{r}_{i_0} \leq \boldsymbol{r}_{i_1} \leq \ldots \leq \boldsymbol{r}_{i_q}$,

one cannot solve (a) for all c by sequentially picking individuals to be vaccinated. An example of such a non-sequential optimal scheme is given in Section 3.4. Fourthly, the above construction is easily generalised to any cost function associated with a vaccination scheme, provided that it is additive over households. More specifically, if $C(\boldsymbol{r}_k)$ denotes the cost of vaccinating one household according to $\boldsymbol{r}_k$ $(k = 1, 2, \ldots, p)$, then the convex hull of $(C(\boldsymbol{r}_k), mM_{\boldsymbol{n},\boldsymbol{r}_k})$ $(k = 1, 2, \ldots, p)$ is considered and the explicit construction of the points on its lower edge is modified accordingly.

Consider now the general case when not all the households in the population have the same category. For $\boldsymbol{n} \in \mathcal{N}$, let $\boldsymbol{r}_{i_1(\boldsymbol{n})}, \boldsymbol{r}_{i_2(\boldsymbol{n})}, \ldots, \boldsymbol{r}_{i_{q(\boldsymbol{n})}(\boldsymbol{n})}$ denote the single household vaccinations used when all the households have category $\boldsymbol{n}$ and denote the corresponding per vaccine reductions in $R_*(\boldsymbol{v})$ by $b_{\boldsymbol{n}}(i_0(\boldsymbol{n}), i_1(\boldsymbol{n})), b_{\boldsymbol{n}}(i_1(\boldsymbol{n}), i_2(\boldsymbol{n})), \ldots, b_{\boldsymbol{n}}(i_{q(\boldsymbol{n})-1}(\boldsymbol{n}), i_{q(\boldsymbol{n})}(\boldsymbol{n}))$. Let

$$\mathcal{A} = \{(\boldsymbol{n}, \boldsymbol{r}) : \boldsymbol{n} \in \mathcal{N} \text{ and } (\boldsymbol{n}, \boldsymbol{r}) = (\boldsymbol{n}, \boldsymbol{r}_{i_k(\boldsymbol{n})}) \text{ for some } k\}.$$

Let $(\boldsymbol{n}^{(1)}, \boldsymbol{r}^{(1)}), (\boldsymbol{n}^{(2)}, \boldsymbol{r}^{(2)}), \ldots, (\boldsymbol{n}^{(q_*)}, \boldsymbol{r}^{(q_*)})$ be an enumeration of $\mathcal{A}$ arranged according to decreasing values of $b_{\boldsymbol{n}}(i_{k-1}(\boldsymbol{n}), i_k(\boldsymbol{n}))$. It is easily seen that, for fixed vaccine coverage c, a solution to the linear programming problem (a) can be obtained by sequentially picking household/vaccination categories $(\boldsymbol{n}^{(k)}, \boldsymbol{r}^{(k)})$ $(k = 1, 2, \ldots, q_*)$, vaccinating all households of category $\boldsymbol{n}^{(k)}$ according to $\boldsymbol{r}^{(k)}$ and stopping the process as soon as the vaccine coverage reaches c. A solution to the linear programming problem (b) can be obtained in a similar fashion, except the process is stopped as soon as $R_*(\boldsymbol{v})$ reaches one. The above observations for the case when all the households have the same category also apply in the general case.

3.2 Form of optimal vaccination scheme

Although the above provides a method for determining optimal vaccination allocations, it would be useful to have a more explicit characterisation of the resulting solution and thereby gain insight into the form of optimal vaccination schemes. For single type epidemics, i.e. when $J = 1$, such a characterisation is possible. Note that for such epidemics $(\boldsymbol{n}, \boldsymbol{r})$ is replaced by (n, r), where n denotes the size of a household and r is the number of individuals in it that are vaccinated. For $n = 1, 2, \ldots$, let $\mu_n(\lambda^L)$ denote the mean size of a single household epidemic, with initially $n - 1$ susceptibles and 1 infective, where λ^L denotes the local infection rate. (As before, $\mu_n(\lambda^L)$ includes the initial infective.) Ball and Lyne [10] considered all or nothing vaccines and showed that, provided the sequence $(n\mu_n(\lambda^L))$ is convex in n, $G(n, r) = M_{n,r} - M_{n,r+1}$ is increasing in n and decreasing in r, so the optimal vaccination scheme is to pick individuals for vaccination sequentially, with the recipient of each vaccine being chosen by maximising $G(n, r)$ over (n, r) with $h_{n,r} > 0$. Note that, if $G(n, r)$ is decreasing in r, then successive vaccinations in the same household yield diminishing reductions in R_* so, under an optimal vaccination scheme, the numbers of vaccinated individuals in two households of the same size can differ by at most one. The convexity of $(n\mu_n(\lambda^L))$ was conjectured by Ball et al. [14], who considered perfect vaccines and showed that, provided the conjecture is true, the optimal vaccination scheme is the equalising strategy, in which vaccines are allocated sequentially, always to a

household that contains the greatest number of unvaccinated individuals. The following examples show for multitype epidemics that, even when the vaccine is perfect, (i) successive vaccinations in the same household need not yield diminishing reductions in R_*; (ii) the optimal vaccination scheme need not be of the equalising type; and (iii) the optimal vaccination scheme cannot necessarily be constructed sequentially.

3.3 Example illustrating increasing reductions in R_*

Suppose that the vaccine is perfect, i.e. that $\boldsymbol{\epsilon} = \mathbf{1}$. Then the all or nothing and leaky formulations coincide and it follows from (3.1) that

$$M_{\boldsymbol{n},\boldsymbol{r}} = M(\boldsymbol{n} - \boldsymbol{r}) \quad (\boldsymbol{n} \in \mathcal{N}, \mathbf{0} \leq \boldsymbol{r} \leq \boldsymbol{n}),$$

where

$$M(\boldsymbol{k}) = \sum_{i \in \mathcal{J}} \frac{1}{N_i} k_i \sum_{l \in \mathcal{J}} \mu_{\boldsymbol{k},i,l}(\Lambda^L) t_l \eta_l^G \kappa_i^G \quad (\boldsymbol{k} \geq \mathbf{0}). \tag{3.2}$$

Suppose that $J = 2$, that local mixing is uniform, so $\lambda_{ij}^L = \lambda^L (i, j \in \mathcal{J})$, and that the distribution of an infective's infectious period is independent of its class, so $T_I^{(1)}$ and $T_I^{(2)}$ are identically distributed.

Lemma 3.1 *Under the above conditions, for $n_1 = 1, 2, \ldots$ and $n_2 = 0, 1, \ldots$,*

$$\mu_{(n_1,n_2),1,1}(\Lambda^L) = \frac{n_2 + (n_1 - 1)\mu_{n_1+n_2}(\lambda^L)}{n_1 + n_2 - 1} \tag{3.3}$$

and

$$\mu_{(n_1,n_2),1,2}(\Lambda^L) = \frac{n_2(\mu_{n_1+n_2}(\lambda^L) - 1)}{n_1 + n_2 - 1}; \tag{3.4}$$

and, for $n_1 = 0, 1, \ldots$ and $n_2 = 1, 2, \ldots$,

$$\mu_{(n_1,n_2),2,1}(\Lambda^L) = \frac{n_1(\mu_{n_1+n_2}(\lambda^L) - 1)}{n_1 + n_2 - 1} \tag{3.5}$$

and

$$\mu_{(n_1,n_2),2,2}(\Lambda^L) = \frac{n_1 + (n_2 - 1)\mu_{n_1+n_2}(\lambda^L)}{n_1 + n_2 - 1}. \tag{3.6}$$

Proof. For $n = 1, 2, \ldots$, let $p_n(\lambda^L)$ denote the probability that a given initial susceptible is ultimately infected by a single type single household epidemic, given that initially there are $n - 1$ susceptibles and 1 infective. Then $p_n(\lambda^L) = (\mu_n(\lambda^L) - 1)/(n - 1)$ $(n = 1, 2, \ldots)$. Equations (3.3) and (3.4) follow on noting that $\mu_{(n_1,n_2),1,1}(\Lambda^L) = 1 + (n_1 - 1)p_{n_1+n_2}(\lambda^L)$ and $\mu_{(n_1,n_2),1,2}(\Lambda^L) = n_2 p_{n_1+n_2}(\lambda^L)$. Equations (3.5) and (3.6) follow by symmetry. □

Suppose that the population consists entirely of households with category $(3, 1)$, so $N_1 = 3N_2$, that only class 2 individuals contribute to global infection, so $\eta_1^G = 0$, and, for the

moment, that it is only possible to vaccinate class 1 individuals. Assume, without loss of generality, that $\eta_2^G = 1$. Suppose further that $\kappa_1^G > 0$ and that the infectious period is constant and equal to the unit of time, and let $q = \exp(-\lambda^L)$. Then, since $N_1 = 3N_2$, it follows from Lemma 3.1 that for $k = 1, 2, 3$,

$$M(k,1) = \Big\{\Big(\mu_{k+1}(\lambda^L) - 1\Big)\kappa_1^G + 3\kappa_2^G\Big\}\Big/ N_1, \tag{3.7}$$

where $M(k,1) = M\left((k,1)\right)$. The final size of a single household epidemic has the same distribution as that of a Reed-Frost chain-binomial epidemic with probability of adequate contact $p = 1 - q$; see, for example, Bailey [17]. It follows, either by listing all possible chains and calculating their probabilities or by using arguments of the Appendix in Ball *et al.* [9], that, writing μ_n for $\mu_n(\lambda^L)$,

$$\begin{aligned} \mu_1 &= 1, \\ \mu_2 &= 2 - q, \\ \mu_3 &= 3 - 4q^2 + 2q^3, \\ \mu_4 &= 4 - 6q^3 - 6q^4 + 15q^5 - 6q^6, \end{aligned} \tag{3.8}$$

so

$$(\mu_4 - \mu_3) - (\mu_3 - \mu_2) = -q(1 - 8q + 10q^2 + 6q^3 - 15q^4 + 6q^5).$$

Thus, there exists $q_0 > 0$ so that $(\mu_4 - \mu_3) - (\mu_3 - \mu_2) < 0$ for $q < q_0$. (Numerical calculation yields $q_0 \approx 0.158$.) Hence, from (3.7), if $\lambda^L > \lambda_0^L = \log(1/q_0)$ then $M(3,1) - M(2,1) < M(2,1) - M(1,1)$. Further, $\frac{1}{3}\Big(M(3,1) - M(0,1)\Big) < \frac{1}{2}\Big(M(3,1) - M(1,1)\Big)$ if and only if $\mu_4 > 3\mu_2 - 2$. From (3.8),

$$\begin{aligned} \mu_4 - 3\mu_2 + 2 &= 3q(1 - 2q^2 - 2q^3 + 5q^4 - 2q^5) \\ &= 3q(1-q)^2\Big(1 + q^2 + 2q(1 - q^2)\Big) > 0, \end{aligned}$$

for $q \in (0,1)$. Suppose that a fraction c of class 1 individuals are to be vaccinated. Then, if $\lambda^L > \lambda_0^L$ and $c \leq \frac{2}{3}$, it is optimal to vaccinate 2 individuals in a proportion c of households and no individuals in the remaining households (so the equalising strategy is not optimal), whilst if $\lambda^L > \lambda_0^L$ and $c > \frac{2}{3}$, it is best to vaccinate 2 individuals in a proportion $3(1-c)$ of households and 3 individuals in the remaining households. Finally, if $\lambda^L \leq \lambda_0$, then the equalising strategy is always optimal.

An intuitive explanation for the form of the optimal vaccination scheme runs as follows. Since class 2 individuals are responsible for all global infections, it is sufficient to consider disease spread between such individuals. Moreover, such spread either occurs directly, by global contact between two class 2 individuals, or indirectly, by global contact between a class 2 and a class 1 individual, who then transmits the infection locally to a class 2 individual. As class 2 individuals cannot be vaccinated, only indirect spread is reduced by vaccination. The contribution to R_* made by indirect spread within a household is linear in the mean size of the local epidemic within that household. When the local infection rate is very high, μ_n $(n = 2, 3, \dots)$ is a concave function of n, so it is better to vaccinate two individuals in the same household than in distinct households.

Note that, since $R_*(\boldsymbol{v})$ is a continuous function of $(\Lambda^L, \Lambda^G, \boldsymbol{\epsilon})$, the example can be extended to allow for non-uniform local mixing, imperfect vaccines, vaccination of class 2 individuals and $\eta_1^G > 0$, with the same conclusions holding provided that elements of Λ^L are sufficiently large and $(\eta_1^G, \epsilon_1, \epsilon_2)$ is sufficiently close to $(0, 1, 0)$.

3.4 Example illustrating non-sequential optimal scheme

For this example, again assume that the vaccine is perfect, i.e. that $\boldsymbol{\epsilon} = \mathbf{1}$, that $J = 2$, that local mixing is uniform, so $\lambda_{ij}^L = \lambda^L(i, j \in \mathcal{J})$, and that the distribution of an infective's infectious period is constant and equal to the unit of time.

Suppose that the population consists entirely of households with category $(2, 1)$, so $N_1 = 2N_2$, and that only class 1 individuals contribute to global infection, so $\eta_2^G = 0$. Assume, without loss of generality, that $\eta_1^G = 1$. Then it follows from (3.2), Lemma 3.1 and (3.8) that $N_1 M(i, j)$ $(i = 0, 1, 2;\ j = 0, 1)$ are as given in the following table, where $q = \exp(-\lambda^L)$.

$N_1 M(i,j)$	$j = 0$	$j = 1$
$i = 0$	0	0
$i = 1$	κ_1^G	$\kappa_1^G + 2(1-q)\kappa_2^G$
$i = 2$	$2(2-q)\kappa_1^G$	$(4 - 4q^2 + 2q^3)\kappa_1^G + (4 - 8q^2 + 4q^3)\kappa_2^G$

Thus it is clear that the optimal use of two doses of vaccine in a household is to vaccinate both individuals of class 1, then that household makes no contribution to the threshold parameter (since $M(0, 1) = 0$). However, the optimal use of one dose depends on the relative sizes of $M(2, 0)$ and $M(1, 1)$. Note that $M(2, 0) < M(1, 1)$ if and only if

$$2(2-q)\kappa_1^G < \kappa_1^G + 2(1-q)\kappa_2^G\,,$$

a necessary and sufficient condition for which is

$$\frac{\kappa_2^G}{\kappa_1^G} > \frac{3-2q}{2-2q}\,.$$

Therefore, for fixed κ_1^G and q, there exists $B_1 > 0$ such that $M(2, 0) < M(1, 1)$, for $\kappa_2^G > B_1$. Thus, for $\kappa_2^G > B_1$, the best use of one dose of vaccine in a household is to vaccinate the individual of class 2, so that the household contributes $M(2, 0)$ rather than $M(1, 1)$ (which would result if a class 1 individual was vaccinated).

To show that the scheme is non-sequential, note that

$$2M(2, 0) < M(0, 1) + M(2, 1)$$

if and only if

$$4(2-q)\kappa_1^G < (4 - 4q^2 + 2q^3)\kappa_1^G + (4 - 8q^2 + 4q^3)\kappa_2^G.$$

For any $0 \leq q < 1$, the coefficient of κ_2^G on the right-hand side is strictly positive, therefore the inequality certainly holds for κ_2^G sufficiently large, say $\kappa_2^G > B_2$. Hence,

for $\kappa_2^G > \max(B_1, B_2)$, the points corresponding to both $M(0,1)$ and $M(2,0)$ are on the lower edge of convex hull of the points $\Big((3-i-j), M(i,j)\Big)$ $(i = 0, 1, 2;\ j = 0, 1)$. Thus the optimal scheme for a small amount of vaccine vaccinates only class 2 individuals, but for a larger amount of vaccine vaccinates only class 1 individuals. This implies that the optimal scheme cannot be constructed sequentially (cf. Cairns [18], who found a similar result for a non-households two-type epidemic).

4 Estimation

4.1 Estimation of local and global infection parameters

When estimating the threshold parameter $R_*(\boldsymbol{v})$ associated with any given vaccination scheme, and to design vaccination schemes that prevent global epidemics with minimal vaccination coverage, it is necessary to have estimates of the local and global infection parameters. In the present section these parameters are assumed to be unknown and are to be estimated from data on one previous outbreak in the population. Suppose that the data consists of the final outcome, for a sample of households, of the previous outbreak. The distributions of the infectious periods $T_I^{(i)}$ $(i \in \mathcal{J})$ are assumed known from previous epidemiological studies. If the distributions of the infectious periods are unknown, then parameters of these distributions can be estimated if some parametric family is assumed, although note that with estimation from final outcome data the scale of these distributions is confounded with the infection rates.

The following method for estimating (Λ^L, Λ^G) is studied in Ball and Lyne [8]. It assumes that the previous outbreak resulted in a global epidemic. Thus we first outline some finer properties of a global epidemic, which are used in the estimation procedure. As before, further details may be found in Ball and Lyne [6].

Assume that the number of initial infectives is small and suppose that a global epidemic occurs. For $j \in \mathcal{J}$, let z_j denote the expected proportion of class j susceptibles that are ultimately infected. Let A_j denote the aggregated sum of the infectious periods of all class j infectives present during the epidemic, so A_j is the sum of $T_I^{(j)}$-variables, one for each j-individual who gets infected. Fix attention on a household that did not contain any initial infectives. The probability that a given class i individual avoids *global* infection throughout the entire epidemic is given by

$$\pi_i = E\left[\exp(-\sum_{j\in\mathcal{J}} A_j \lambda_{ji}^G / N_i)\right] \approx \exp\left(-\sum_{j\in\mathcal{J}} \gamma_j z_j t_j \lambda_{ji}^G/\gamma_i\right) \quad (i \in \mathcal{J}), \tag{4.1}$$

where $\gamma_i = N_i/N$ is the proportion of i-individuals. The approximation on the right follows since m is assumed large so $A_j \approx N_j z_j E[T_I^{(j)}] = N\gamma_j z_j t_j$. Further, when m is large, distinct individuals avoid global infection approximately independently of each other. The ultimate spread of infection within the household under consideration is thus approximately distributed as that of a multitype single household epidemic model, studied by Addy et al. [19], in which, in addition to local infection, during the course of the

epidemic initially susceptible individuals avoid infection from outside the household independently and with probability π_i for a class i susceptible. For $j \in \mathcal{J}$, let $\mu_{\boldsymbol{n},j}(\Lambda^L, \boldsymbol{\pi})$ be the expected number of class j individuals that are ultimately infected by this epidemic, where $\boldsymbol{\pi} = (\pi_1, \pi_2, \ldots, \pi_J)$ and $\boldsymbol{n}$ denotes the category of the household under consideration. An algorithm for computing $\mu_{\boldsymbol{n},j}(\Lambda^L, \boldsymbol{\pi})$ ($\boldsymbol{n} \in \mathcal{N}, j \in \mathcal{J}$) is given in Ball *et al.* [9].

For $i \in \mathcal{J}$, z_i can be interpreted as the probability that a class i initial susceptible chosen at random from the population is ultimately infected by the epidemic. By conditioning on the category of household to which this initial susceptible belongs and noting that if it resides in a household of category $\boldsymbol{n}$ then its chance of ultimate infection is $\mu_{\boldsymbol{n},i}(\Lambda^L, \boldsymbol{\pi})/n_i$, it follows that

$$z_i = \sum_{\boldsymbol{n} \in \mathcal{N}} \alpha_i(\boldsymbol{n}) \mu_{\boldsymbol{n},i}(\Lambda^L, \boldsymbol{\pi})/n_i \quad (i \in \mathcal{J}). \tag{4.2}$$

Together with (4.1) (with "$\approx$" replaced by "$=$"), this is a set of J implicit equations for $\boldsymbol{z} = (z_1, z_2, \ldots, z_J)$. Note that $\boldsymbol{z} = \boldsymbol{0}$ is always a root of (4.2). It is shown in Ball and Lyne [6], Section 5.2, that, provided the $J \times J$ matrix having (i,j)-element $\sum_{k \in \mathcal{J}} t_i \lambda_{ik}^G \sum_{\boldsymbol{n} \in \mathcal{N}} \alpha_k(\boldsymbol{n}) \mu_{\boldsymbol{n},k,j}(\Lambda^L)$ $(i,j \in \mathcal{J})$ is positively regular, if $R_* \leq 1$ then $\boldsymbol{z} = \boldsymbol{0}$ is the only solution of (4.2) in $[0,1]^J$, while if $R_* > 1$ then there is a unique second root, with $z_i > 0$ $(i \in \mathcal{J})$, giving the expected proportions of individuals of different classes that are infected by a global epidemic.

Returning to the estimation procedure, label the m households in the population $1, 2, \ldots, m$. For $i = 1, 2, \ldots, m$, let $\boldsymbol{n}(i)$ be the category of household i and $\delta_i = 1(0)$ if household i is observed (unobserved) in the previous outbreak. The number of susceptibles (of the various classes) in household i that were ultimately infected by the epidemic, is specified by $\boldsymbol{k}_i$ and $\boldsymbol{k}_D = \{\boldsymbol{k}_i : \delta_i = 1\}$ denotes the observed data.

Let $p_{\boldsymbol{n}}(\boldsymbol{k}|\Lambda^L, \boldsymbol{\pi})$ be the probability that the above Addy et al. [19] multitype single household epidemic has final outcome $\boldsymbol{k}$, assuming that the household is of category $\boldsymbol{n}$ ($\boldsymbol{n} \in \mathcal{N}$ and $\boldsymbol{0} \leq \boldsymbol{k} \leq \boldsymbol{n}$). For $\boldsymbol{n} \in \mathcal{N}$, a triangular system of linear equations governing $p_{\boldsymbol{n}}(\boldsymbol{k}|\Lambda^L, \boldsymbol{\pi})$ ($\boldsymbol{0} \leq \boldsymbol{k} \leq \boldsymbol{n}$) is given in Ball *et al.* [9]; see also Addy et al. [19].

Equations (4.1) and (4.2) implicitly determine $\boldsymbol{\pi}$ as a function of (Λ^L, Λ^G), so write $\boldsymbol{\pi} = \boldsymbol{\pi}(\Lambda^L, \Lambda^G)$. There does not exist a feasible method for computing the likelihood of (Λ^L, Λ^G) given $\boldsymbol{k}_D$, so consider estimating (Λ^L, Λ^G) by maximising the pseudolikelihood

$$L(\Lambda^L, \Lambda^G | \boldsymbol{k}_D) = \prod_{i=1}^{m} \{p_{\boldsymbol{n}(i)}\Big(\boldsymbol{k}_i | \Lambda^L, \boldsymbol{\pi}(\Lambda^L, \Lambda^G)\Big)\}^{\delta_i}. \tag{4.3}$$

Note that (4.3) is a pseudolikelihood, and not a likelihood, since the outcomes in different households are not independent. Observe also that (4.3) assumes implicitly that a global epidemic occurred.

The pseudolikelihood (4.3) can be maximised by first maximising it as a function of $(\Lambda^L, \boldsymbol{\pi})$, to yield the estimate $(\hat{\Lambda}^L, \hat{\boldsymbol{\pi}})$, then obtaining an estimate, $\hat{\boldsymbol{z}}$ say, of $\boldsymbol{z}$ by substituting $(\hat{\Lambda}^L, \hat{\boldsymbol{\pi}})$ in the right hand side of (4.2), and finally solving (4.1), with $(\boldsymbol{\pi}, \boldsymbol{z})$ replaced by $(\hat{\boldsymbol{\pi}}, \hat{\boldsymbol{z}})$ for Λ^G. However, the final step in this procedure involves solving J

linear equations in the J^2 unknown quantities λ_{ij}^G $(i,j \in \mathcal{J})$, so Λ^G is not identifiable from the observed data using this approach and the threshold parameters before and after vaccination, R_* and $R_*(\boldsymbol{v})$, cannot be estimated consistently. It is possible that the local infection rates Λ^L may also be unidentifiable, for example if for some $i,j \in \mathcal{J}$ there is no household in the sample that contains individuals of classes i and j, but either this can be avoided by choosing the sample of households suitably, or the relevant λ_{ij}^Ls are redundant for the population at hand.

4.2 Estimation of R_*, $R_*^{AoN}(v)$ and $R_*^{Le}(v)$

Final size data from a sample of households of one epidemic outbreak were used in the previous subsection to derive estimates of the matrix Λ^L and the vectors $\boldsymbol{\pi}$ and $\boldsymbol{z}$. Consider now estimation procedures for the epidemiologically more important parameters R_* and $R_*(\boldsymbol{v})$. It is assumed that the population structure is sufficiently rich for Λ^L to be identifiable. The vaccination effect $\boldsymbol{\epsilon}$ and the type (all or nothing or leaky) of the vaccine are assumed known, as are the distributions of infection periods $T_I^{(i)}$, $i = 1,\ldots,J$. For ease of exposition, it is also assumed that the population structure has not changed since the previous outbreak. However, the methodology is easily extended to the case when the population structure is different for the future epidemic, and this is done in Ball *et al.* [9].

In the previous subsection it was observed that Λ^G was not completely identifiable in that only J estimating equations were available for J^2 unknown quantities. As a consequence, R_* and $R_*(\boldsymbol{v})$, cannot be estimated consistently. In Ball *et al.* [9] a Perron-Frobenius argument is used to show that instead, sharp upper and lower bounds of these quantities can be estimated consistently. (Just like in the multitype case without household structure treated in Britton [16], these bounds are sharp, in that there exists $\Lambda^G = [\lambda_{ij}^G]$ satisfying (4.1), such that upper and lower bounds can be attained.) These bounds for R_* are given by

$$\min_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})\mu_{\boldsymbol{n},i,k}(\Lambda^L) \le R_* \le \max_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})\mu_{\boldsymbol{n},i,k}(\Lambda^L).$$

For the all or nothing vaccine the bounds on $R_*^{AoN}(\boldsymbol{v})$ are given by

$$\min_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})b_{ik}^{\boldsymbol{n},\boldsymbol{v}} \le R_*^{AoN}(\boldsymbol{v}) \le \max_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})b_{ik}^{\boldsymbol{n},\boldsymbol{v}}, \tag{4.4}$$

where

$$b_{il}^{\boldsymbol{n},\boldsymbol{v}} = b_{il}^{\boldsymbol{n},\boldsymbol{v}}(\Lambda^L,\boldsymbol{\epsilon}) = \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \sum_{\boldsymbol{k}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{k}} \boldsymbol{\epsilon}^{\boldsymbol{n}-\boldsymbol{k}}(\boldsymbol{1}-\boldsymbol{\epsilon})^{\boldsymbol{r}-\boldsymbol{n}+\boldsymbol{k}} \frac{k_i}{n_i}\mu_{\boldsymbol{k},i,l}(\Lambda^L). \tag{4.5}$$

Finally, for the leaky vaccine, the bounds on $R_*^{Le}(\boldsymbol{v})$ are given by

$$\min_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})c_{ik}^{\boldsymbol{n},\boldsymbol{v}} \le R_*^{Le}(\boldsymbol{v}) \le \max_k \frac{1}{\gamma_k z_k} \sum_{i,\boldsymbol{n}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n})c_{ik}^{\boldsymbol{n},\boldsymbol{v}}, \tag{4.6}$$

where

$$c_{il}^{\boldsymbol{n},\boldsymbol{v}} = c_{il}^{\boldsymbol{n},\boldsymbol{v}}(\Lambda^L, \boldsymbol{\epsilon}) = \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \left(\frac{n_i - r_i}{n_i} \mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{u}:i,l}(\Lambda^L, \boldsymbol{\epsilon}) + \frac{r_i(1-\epsilon_i)}{n_i} \mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},\mathrm{v}:i,l}(\Lambda^L, \boldsymbol{\epsilon}) \right).$$

A vaccination scheme $\boldsymbol{v}$ is surely preventive only if the upper bound in (4.4) (or (4.6) in case of a leaky vaccine) does not exceed 1.

Note that the upper and lower bounds above contain only known quantities or estimable parameters. Of course, estimates of the bounds are obtained by replacing the unknown parameters π_i, z_k and $\mu_{\mathbf{n},i,k}(\Lambda^L)$ by their estimates.

5 Optimal vaccination schemes, unknown infection rates

5.1 Estimation and form of the optimal vaccination scheme

In Section 2.3.3, an optimal vaccination scheme $\boldsymbol{v}_{\mathrm{opt}}$ was defined as a scheme $\boldsymbol{v}$ which minimises the overall vaccination coverage $S(\boldsymbol{v}) = \sum_{\boldsymbol{n},\boldsymbol{r}} |\boldsymbol{r}| v_{\boldsymbol{n},\boldsymbol{r}} \alpha_{\boldsymbol{n}} / \sum_{\boldsymbol{n}} |\boldsymbol{n}| \alpha_{\boldsymbol{n}}$, among those schemes that are preventive (recall that a vaccination scheme $\boldsymbol{v}'$ is preventive if $R_*(\boldsymbol{v}') \leq 1$). Since $R_*(\boldsymbol{v})$ cannot be estimated consistently, be it a leaky or an all or nothing vaccine, it follows that $\boldsymbol{v}_{\mathrm{opt}}$ cannot be estimated consistently either. Instead, vaccination schemes with associated upper bound for $R_*(\boldsymbol{v})$ not exceeding 1 are considered.

Suppose that the vaccine is all or nothing. (The leaky case is similar and hence omitted.) Let

$$R_*^{(k)}(\boldsymbol{v}) = \frac{1}{\gamma_k z_k} \sum_{i \in \mathcal{J}} \sum_{\boldsymbol{n} \in \mathcal{N}} \gamma_i (-\log \pi_i) \alpha_i(\boldsymbol{n}) b_{ik}^{\boldsymbol{n},\boldsymbol{v}} \quad (k \in \mathcal{J}) \tag{5.1}$$

and

$$R_*^{max}(\boldsymbol{v}) = \max_k R_*^{(k)}(\boldsymbol{v}).$$

Using (4.4) it is seen that $R_*^{max}(\boldsymbol{v})$ equals the upper bound for $R_*^{AoN}(\boldsymbol{v})$, so any vaccination scheme $\boldsymbol{v}$ with $R_*^{max}(\boldsymbol{v}) \leq 1$ is preventive, irrespective of the underlying parameter Λ^G consistent with the data, whilst for any vaccination scheme $\boldsymbol{v}$ with $R_*^{max}(\boldsymbol{v}) > 1$ there exists Λ^G, consistent with the data, so that $R_*(\boldsymbol{v}) > 1$. Thus it is appropriate to consider minimisation of the vaccine coverage $S(\boldsymbol{v})$ subject to the constraints $R_*^{(k)}(\boldsymbol{v}) \leq 1$ ($k = 1, 2, \ldots, J$). Note that this is a linear programming problem since, by (2.4), (4.5) and (5.1), the objective function $S(\boldsymbol{v})$ and the constraints $R_*^{(k)}(\boldsymbol{v}) \leq 1$ ($k = 1, 2, \ldots, J$) are all linear functions of the optimising variables $\boldsymbol{v}$. Let $\boldsymbol{v}_{\mathrm{opt}}$ denote a solution to this minimisation problem and recall that $c_v = S(\boldsymbol{v}_{\mathrm{opt}})$, the critical (or minimal) vaccination coverage required to be sure of preventing a future global outbreak. The form of $\boldsymbol{v}_{\mathrm{opt}}$ is discussed below. Of course, $R_*^{(k)}(\boldsymbol{v})$ is estimated by replacing the unknown parameters in the right hand side of (5.1) by their estimates, yielding $\hat{R}_*^{(k)}(\boldsymbol{v})$ say. Thus, $R_*^{max}(\boldsymbol{v})$ is estimated by $\hat{R}_*^{max}(\boldsymbol{v}) = \max_k \hat{R}_*^{(k)}(\boldsymbol{v})$ and c_v is estimated by solving the above linear programming problem, with $R_*^{(k)}(\boldsymbol{v})$ replaced by $\hat{R}_*^{(k)}(\boldsymbol{v})$ ($k \in \mathcal{J}$), yielding $\hat{\boldsymbol{v}}_{\mathrm{opt}}$ and $\hat{c}_v = S(\hat{\boldsymbol{v}}_{\mathrm{opt}})$.

In Ball *et al.* [9], standard errors for the estimates $\hat{R}_*^{max}(\boldsymbol{v})$ and $\hat{c}_v$, and associated confidence intervals for $R_*^{max}(\boldsymbol{v})$ and c_v, are derived in the situation when the number of households in the observed sample is large. Note that this is not straightforward, since (4.3) is a pseudolikelihood and not a likelihood. Consequently, standard likelihood-based procedures deliver confidence intervals that do not have the correct asymptotic coverage probabilities, unless the proportion of sampled households is very small.

We now return to the study of the form of the optimal vaccination scheme, previously investigated in Section 3, but now for the case when the global infection rates are unknown and allowed to take on any form, and the optimal vaccination scheme is estimated as described above. Attention is restricted to all or nothing vaccines. The leaky case is similar and involves no new ideas. Recalling that $\alpha_i(\boldsymbol{n}) = n_i m_{\boldsymbol{n}}/N_i$, $h_{\boldsymbol{n},\boldsymbol{r}} = v_{\boldsymbol{n},\boldsymbol{r}} m_{\boldsymbol{n}}$ and equation (4.5) for $b_{il}^{\boldsymbol{n},\boldsymbol{v}}$, it follows from (5.1) that

$$R_*^{(k)}(\boldsymbol{v}) = \frac{1}{N_k z_k} \sum_{\boldsymbol{n}\in\mathcal{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} h_{\boldsymbol{n},\boldsymbol{r}} M_{\boldsymbol{n},\boldsymbol{r}}^{(k)}, \tag{5.2}$$

where

$$M_{\boldsymbol{n},\boldsymbol{r}}^{(k)} = \sum_{\boldsymbol{l}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \binom{\boldsymbol{r}}{\boldsymbol{n}-\boldsymbol{l}} \boldsymbol{\epsilon}^{\boldsymbol{n}-\boldsymbol{l}} (\boldsymbol{1}-\boldsymbol{\epsilon})^{\boldsymbol{r}-\boldsymbol{n}+\boldsymbol{l}} \sum_{i\in\mathcal{J}} (-\log \pi_i) l_i \mu_{\boldsymbol{l},i,k}(\Lambda^L) \quad (k \in \mathcal{J}). \tag{5.3}$$

The aim is to determine an allocation of vaccines $\boldsymbol{v}_{\text{opt}}$ which minimises the overall vaccine coverage $S(\boldsymbol{v})$ subject to $R_*^{(k)}(\boldsymbol{v}) \leq 1$ $(k \in \mathcal{J})$. Observe that, for fixed $k \in \mathcal{J}$, $M_{\boldsymbol{n},\boldsymbol{r}}^{(k)}$ takes a similar form to $M_{\boldsymbol{n},\boldsymbol{r}}$ in (3.1). Consequently, the problem of reducing a single $R_*^{(k)}(\boldsymbol{v})$ to 1 with minimum vaccine coverage can be solved using the method described in Section 3.1. However, it is necessary to simultaneously make $R_*^{(k)}(\boldsymbol{v}) \leq 1$ $(k \in \mathcal{J})$, and there does not appear to be a simple way of constructing, or characterising, the solution to the simultaneous problem.

Nevertheless, certain properties of optimal allocations can be investigated. In Section 5.2 it is shown that successive vaccinations in the same household can lead to *increasing* reductions in $R_*^{max}(\boldsymbol{v})$, so again the optimal vaccination scheme need not take the equalising form. In Section 5.3 it is shown that optimal allocations need not be sequential.

5.2 Example illustrating increasing reductions in R_*

The example is similar to the one used in Section 3.3. Thus the vaccine is assumed to be perfect, i.e. $\boldsymbol{\epsilon} = \boldsymbol{1}$, and it follows from (5.3) that

$$M_{\boldsymbol{n},\boldsymbol{r}}^{(k)} = M^{(k)}(\boldsymbol{n}-\boldsymbol{r}) \quad (\boldsymbol{n} \in \mathcal{N}, \boldsymbol{0} \leq \boldsymbol{r} \leq \boldsymbol{n}), \tag{5.4}$$

where

$$M^{(k)}(\boldsymbol{l}) = \sum_{i\in\mathcal{J}} (-\log \pi_i) l_i \mu_{\boldsymbol{l},i,k}(\Lambda^L) \quad (\boldsymbol{l} \geq \boldsymbol{0}). \tag{5.5}$$

Further, suppose that $J = 2$, the population is comprised entirely of households with category $(3,1)$ (so $N_1 = 3N_2$), local mixing is uniform (so $\lambda^L_{ij} = \lambda^L (i, j \in \mathcal{J})$) and $T_I^{(j)} \equiv 1$ $(j = 1, 2)$. Then it follows from (5.5) and Lemma 3.1, that for $n = 0, 1, 2, 3$,

$$\begin{aligned} M^{(1)}(n,1) &= (-\log \pi_1) n \mu_{(n,1),1,1}(\Lambda^L) + (-\log \pi_2) \mu_{(n,1),2,1}(\Lambda^L) \\ &= (-\log \pi_1)\Big(1 + (n-1)\mu_{n+1}(\lambda^L)\Big) + (-\log \pi_2)\Big(\mu_{n+1}(\Lambda^L) - 1\Big) \end{aligned} \quad (5.6)$$

and

$$\begin{aligned} M^{(2)}(n,1) &= (-\log \pi_1) n \mu_{(n,1),1,2}(\Lambda^L) + (-\log \pi_2) \mu_{(n,1),2,2}(\Lambda^L) \\ &= (-\log \pi_1)\Big(\mu_{n+1}(\lambda^L) - 1\Big) + (-\log \pi_2)\mu_1(\lambda^L), \end{aligned} \quad (5.7)$$

where $M^{(k)}(n,1) = M^{(k)}((n,1))$ $(k = 1, 2)$. Hence, it follows from the example in Section 3.3 that if $\lambda^L > \lambda_0^L$ then $M^{(2)}(3,1) - M^{(2)}(2,1) < M^{(2)}(2,1) - M^{(2)}(1,1)$ and $\frac{1}{3}(M^{(2)}(3,1) - M^{(2)}(0,1)) < \frac{1}{2}(M^{(2)}(3,1) - M^{(2)}(1,1))$.

Suppose that $\lambda^L > \lambda_0^L$ and that, as before, it is only possible to vaccinate class 1 individuals. Then, provided that, prior to any vaccination, $R_*^{(2)} > R_*^{(1)}$, it is initially clearly optimal, in terms of reduction in $R_*^{max}(\boldsymbol{v})$, to vaccinate 2 individuals in the same household rather than 2 individuals in distinct households. (Note that $R_*^{(k)} > 1$ $(k = 1, 2)$, since the estimation method described in Section 4 is predicated on the occurrence of a global epidemic.) It is now shown that $R_*^{(2)} > R_*^{(1)}$ and $\lambda > \lambda_0^L$ can hold simultaneously.

To do this it is convenient to use the concept of a (local) *susceptibility set* (Ball and Lyne [6]). Return to the general setting, consider a single household having category $\boldsymbol{n}$ and label the individuals in that household $1, 2, \ldots, |\boldsymbol{n}|$. Let $\mathcal{H} = \{1, 2, \ldots, |\boldsymbol{n}|\}$ and consider the random directed graph, G say, on $\mathcal{H}$, in which for any ordered pair (i, j) of distinct individuals in $\mathcal{H}$ there is a directed arc from i to j if and only if i, if infected, contacts j locally during its infectious period. For $i, j \in \mathcal{H}$, write $i \rightsquigarrow j$ if and only if there is a chain of directed arcs from i to j in G, with the convention that $i \rightsquigarrow i$. For $i \in \mathcal{H}$, the susceptibility set of individual i is defined as $\mathcal{S}_i^{\boldsymbol{n}} = \{j \in \mathcal{H} : j \rightsquigarrow i\}$. Note that for the epidemic among a community of households, if the household under consideration is initially completely susceptible, then individual i avoids infection by the epidemic if and only if none of the individuals in its susceptibility set $\mathcal{S}_i^{\boldsymbol{n}}$ is infected globally. For $\boldsymbol{n} \in \mathcal{N}$ and $i, j \in \mathcal{J}$, let $S_{ij}^{\boldsymbol{n}}$ be the number of class j individuals in the susceptibility set of a typical class i individual who resides in a household of category $\boldsymbol{n}$. Then the probability that a typical class i individual, residing in an initially completely susceptible household of category $\boldsymbol{n}$, avoids infection throughout the course of a global epidemic is given by

$$E\left[\prod_{j \in \mathcal{J}} \pi_j^{S_{ij}^{\boldsymbol{n}}}\right],$$

and arguing as in the derivation of (4.2) yields

$$z_i = 1 - \sum_{\boldsymbol{n} \in \mathcal{N}} \alpha_i(\boldsymbol{n}) E\left[\prod_{j \in \mathcal{J}} \pi_j^{S_{ij}^{\boldsymbol{n}}}\right] \quad (i \in \mathcal{J}); \quad (5.8)$$

see Ball and Lyne [6], Section 5.2, where it is explained that (4.2) and (5.8) yield the same equation for $\boldsymbol{z}$.

Lemma 5.1 *For a two-type epidemic in which all households have category (n_1, n_2) (with $n_1, n_2 > 0$), local mixing is uniform and the infectious period of all infectives have the same distribution*

$$z_2 < z_1 \text{ if and only if } \pi_1 < \pi_2.$$

Proof. Suppressing the explicit dependence on $\boldsymbol{n}$, for $i = 1, 2$, let $S_i = S_{i1} + S_{i2}$ be the total size of the susceptibility set of a typical class i individual. Note that, since local mixing is uniform and $T_I^{(1)}$ and $T_I^{(2)}$ are identically distributed, S_1 and S_2 are also identically distributed, according to S say.

By conditioning on the total size of its susceptibility set, for $i = 1, 2$, the probability that a typical class i individual avoids infection can be written as (using (5.8))

$$\begin{aligned} 1 - z_i &= E_S\Big\{E\Big[\pi_1^{S_{i1}}\pi_2^{S_{i2}} \,|\, S\Big]\Big\} \\ &= E_S\Big\{E\Big[\pi_1^{S_{i1}}\pi_2^{S-S_{i1}} \,|\, S\Big]\Big\}. \end{aligned}$$

For fixed S, let $f_S(x) = \pi_1^x \pi_2^{S-x}$. Then, for $x > y$, $f_S(x) < f_S(y)$ if and only if $\pi_1 < \pi_2$. Now, claiming that $S_{11} \,|\, S$ is stochastically greater than $S_{21} \,|\, S$, observe that if $\pi_1 < \pi_2$ then

$$\begin{aligned} 1 - z_1 &= E_S\Big\{E[f_S(S_{11}) \,|\, S]\Big\} \\ &< E_S\Big\{E[f_S(S_{21}) \,|\, S]\Big\} = 1 - z_2\,, \end{aligned}$$

which implies that $z_2 < z_1$.

To prove the claim that $S_{11} \,|\, S$ is stochastically greater than $S_{21} \,|\, S$, make the following definition. For $n, m \geq 0$ and $0 \leq s \leq n + m$, let $X_{n,m}^s$ be a random variable giving the number of class 1 individuals contained in a random sample without replacement of size s from a population comprising n class 1 individuals and m class 2 individuals. Note that if an individual's susceptibility set is of size S then the probability that a given other individual belongs to that susceptibility set is $\frac{S-1}{n_1+n_2-1}$. Thus, by considering whether or not a particular individual of the opposite class is a member of the susceptibility set, the distribution of $S_{11} \,|\, S$ can be expressed as

$$S_{11} \,|\, S \stackrel{D}{=} \frac{S-1}{n_1+n_2-1}(X^{S-2}_{n_1-1,n_2-1} + 1) + \frac{n_1+n_2-S}{n_1+n_2-1}(X^{S-1}_{n_1-1,n_2-1} + 1)$$

whereas

$$S_{21} \,|\, S \stackrel{D}{=} \frac{S-1}{n_1+n_2-1}(X^{S-2}_{n_1-1,n_2-1} + 1) + \frac{n_1+n_2-S}{n_1+n_2-1}(X^{S-1}_{n_1-1,n_2-1}).$$

Thus the claim is true and the lemma follows. □

Returning to the example, $S_{22} \equiv 1$ and, by symmetry, $P(S_{12} = 1 \,|\, S_1 = s_1) = \frac{s_1 - 1}{3}$ $(s_1 = 1, 2, 3, 4)$. It then follows from (5.8) that

$$z_1 = 1 - P(S = 1)\pi_1 - P(S = 2)(\tfrac{1}{3}\pi_1\pi_2 + \tfrac{2}{3}\pi_1^2) - P(S = 3)(\tfrac{2}{3}\pi_1^2\pi_2 + \tfrac{1}{3}\pi_1^3) - P(S = 4)\pi_1^3\pi_2 \tag{5.9}$$

and

$$z_2 = 1 - P(S = 1)\pi_2 - P(S = 2)\pi_1\pi_2 - P(S = 3)\pi_1^2\pi_2 - P(S = 4)\pi_1^3\pi_2. \tag{5.10}$$

Now setting $\boldsymbol{v} = \mathbf{0}$ in (5.2), using (5.4), (5.6) and (5.7), and noting that $N_1 = 3m$ and $N_2 = m$, yields

$$R_*^{(1)} = \frac{1}{N_1 z_1} m M^{(1)}(3, 1) = \frac{1}{3z_1}\{(-\log \pi_1)(1 + 2\mu_4) + (-\log \pi_2)(\mu_4 - 1)\} \tag{5.11}$$

and

$$R_*^{(2)} = \frac{1}{N_2 z_2} m M^{(2)}(3, 1) = \frac{1}{z_2}\{(-\log \pi_1)(\mu_4 - 1) + (-\log \pi_2)(\mu_1)\}, \tag{5.12}$$

where the explicit dependence of μ_n on λ^L has been suppressed. Suppose that $\pi_1 < \pi_2$. Then, by Lemma 5.1, $z_2 < z_1$ and, since $\mu_1 = 1$ and $\mu_4 \leq 4$, $\frac{\mu_1}{z_2} > \frac{\mu_4 - 1}{3z_1}$. To show that $\frac{\mu_4 - 1}{z_2} > \frac{1 + 2\mu_4}{3z_1}$, note that, in the current Reed-Frost setting, the directed arcs in G are present independently and with probability $p = 1 - q$. It follows that the size S of a typical susceptibility set has the same distribution as the size, C say, of a typical local infectious clump $\mathcal{C}_i = \{j \in \mathcal{H} : i \rightsquigarrow j\}$, where i denotes the initial infective. Thus, S has the same distribution as the total size of a Reed-Frost epidemic, with 1 initial infective and 3 initial susceptibles, so

$$\begin{aligned} P(S = 1) &= q^3, \\ P(S = 2) &= 3pq^4, \\ P(S = 3) &= 3p^2q^3(1 + 2q), \\ P(S = 4) &= p^3(1 + 3q + 6q^2 + 6q^3), \end{aligned}$$

see, for example, Bailey [17], page 245. It then follows, using (3.8), (5.9) and (5.10), that

$$3z_1(\mu_4 - 1) - z_2(1 + 2\mu_4) = q^3\{9(\pi_2 - \pi_1)(1 + \pi_1^2) - 6(1 - \pi_1^3\pi_2)\} + o(q^3) \text{ as } q \downarrow 0,$$

so, provided $\pi_2 - \pi_1 > \frac{2}{3}$, there exists $q_1 = q_1(\pi_1, \pi_2)$ so that $\frac{\mu_4 - 1}{z_2} > \frac{1 + 2\mu_4}{3z_1}$ for all $q \in [0, q_1)$. Hence, if $\pi_2 - \pi_1 > \frac{2}{3}$ and $\lambda^L > \lambda_1^L = \log(1/q_1)$, it follows from (5.11) and (5.12) that $R_*^{(2)} > R_*^{(1)}$.

Finally, note from (5.1) that the reduction in $R_*^{(1)}$ from vaccinating 2 class 1 individuals in the same household is

$$\begin{aligned} G^{(1)} &= \frac{1}{N_1 z_1}\{M^{(1)}(3, 1) - M^{(1)}(1, 1)\} \\ &= \frac{1}{3N_2 z_1}\{(-\log \pi_1)2\mu_4 + (-\log \pi_2)(\mu_4 - \mu_2)\}, \end{aligned}$$

using (5.6), and that the corresponding reduction in $R_*^{(2)}$ is

$$\begin{aligned} G^{(2)} &= \frac{1}{N_2 z_2}\{M^{(2)}(3,1) - M^{(1)}(1,1)\} \\ &= \frac{1}{N_2 z_2}(-\log \pi_1)(\mu_4 - \mu_2), \end{aligned}$$

using (5.7). Thus, $G^{(1)} > G^{(2)}$ if $\mu_2 > \mu_4\Big(1 - (2z_2)/(3z_1)\Big)$, which is clearly satisfied if λ^L is sufficiently large and π_1 sufficiently small (since z_1 and z_2 will then both be close to 1), say $\pi_1 < \pi_1'$ and $\lambda^L > \lambda_2^L$. Hence, provided $\pi_1 < \pi_1'$, $\pi_2 - \pi_1 > \frac{2}{3}$ and $\lambda^L > \lambda_3^L = \max\{\lambda_0^L, \lambda_1^L, \lambda_2^L\}$, $R_*^{(2)} > R_*^{(1)}$, $M^{(2)}(3,1) - M^{(2)}(2,1) < M^{(2)}(2,1) - M^{(2)}(1,1)$ and $\frac{1}{3}(M^{(2)}(3,1) - M^{(2)}(0,1)) < \frac{1}{2}(M^{(2)}(3,1) - M^{(2)}(1,1))$, so it is optimal to start vaccination by vaccinating 2 class 1 individuals in successive households. Further, if such a vaccination scheme is performed then $R_*^{(1)}(\boldsymbol{v}) < R_*^{(2)}(\boldsymbol{v})$, so the optimal scheme is the same as that described for the case $\lambda^L > \lambda_0^L$ at the end of Section 3.3, which need not be equalising. Note that this example can be constructed by first choosing $\pi_1, \pi_2 > 0$ so that $\pi_1 < \pi_1'$ and $\pi_2 - \pi_1 > \frac{2}{3}$, then choosing $\lambda^L > \lambda_3^L$, then using (4.2) to determine $\boldsymbol{z}$ and finally choosing Λ^G so that (4.1) is satisfied.

5.3 Example illustrating non-sequential optimal scheme

The example is identical to the example used in Section 3.4 except that nothing is assumed about the global infection parameters here. Thus the vaccine is perfect, i.e. $\boldsymbol{\epsilon} = \mathbf{1}$, $J = 2$, local mixing is uniform, so $\lambda_{ij}^L = \lambda^L (i, j \in \mathcal{J})$, the distribution of an infective's infectious period is constant and equal to the unit of time and the population consists entirely of households with category $(2,1)$, so $N_1 = 2N_2$. Again let $q = \exp(-\lambda^L)$.

It follows from Lemma 3.1 and (5.5), that $M^{(1)}(l_1, l_2)$ and $M^{(2)}(l_1, l_2)$ (for $l_1 = 0, 1, 2$ and $l_2 = 0, 1$) are as given in the following table.

$M^{(1)}(l_1, l_2)$		l_2	
		0	1
	0	0	0
l_1	1	$-\log \pi_1$	$-\log \pi_1 - (1-q)\log \pi_2$
	2	$-2(\log \pi_1)(2-q)$	$-\log \pi_1\Big(\mu_3(\lambda^L) + 1\Big) - \log \pi_2\Big(\mu_3(\lambda^L) - 1\Big)$
$M^{(2)}(l_1, l_2)$			
	0	0	$-\log \pi_2$
l_1	1	0	$-(1-q)\log \pi_1 - \log \pi_2$
	2	0	$-\log \pi_1\Big(\mu_3(\lambda^L) - 1\Big) - \log \pi_2$

To reduce $R_*^{(2)}$ the best 1-dose scheme in a household is clearly to vaccinate the class 2 individual, since $M^{(2)}(2,0) = 0$. For $R_*^{(1)}$ the best 2-dose scheme in a household is clearly to vaccinate the class 1 individuals, since $M^{(1)}(0,1) = 0$. To show that the optimal scheme is non-sequential, note that the best use of a single dose is to vaccinate the class

2 individual if $M^{(1)}(1,1) > M^{(1)}(2,0)$, and this scheme is on the lower edge of the convex hull of the points $\Big((3-i-j), M^{(1)}(i,j)\Big)$ $(i=0,1,2,\, j=0,1)$ if $M^{(1)}(2,1) > 2M^{(1)}(2,0)$. To examine when these inequalities can be satisfied note that

$$M^{(1)}(1,1) > M^{(1)}(2,0) \iff 3\log\pi_1 - \log\pi_2 > q(2\log\pi_1 - \log\pi_2).$$

Choosing π_1 and π_2 so that $2\log\pi_1 - \log\pi_2 > 0$, the above inequality becomes

$$q < \frac{3\log\pi_1 - \log\pi_2}{2\log\pi_1 - \log\pi_2},$$

which is true for an interval of the form $[0, q_0]$ provided that $3\log\pi_1 - \log\pi_2 > 0$, where $q_0 \in (0,1)$. Thus, if $\pi_1^3 > \pi_2$ then $M^{(1)}(1,1) > M^{(1)}(2,0)$ for all sufficiently large λ^L.

Next, note that

$$\begin{aligned} & M^{(1)}(2,1) > 2M^{(1)}(2,0) \\ \iff\quad & -(\log\pi_1)\Big(\mu_3(\lambda^L)+1\Big) - (\log\pi_2)\Big(\mu_3(\lambda^L)-1\Big) > -4(\log\pi_1)(2-q) \\ \iff\quad & (-1+2q^2-q^3)\log\pi_2 > (-2+2q-2q^2+q^3)\log\pi_1\,, \end{aligned}$$

using (3.8). Suppose that $\pi_1^3 > \pi_2$. If $q=0$, then the left-hand side of the inequality equals $-\log\pi_2$ while the right-hand side equals $-2\log\pi_1$, so the inequality therefore holds. Alternatively, for $q=1$, the left-hand side equals zero while the right-hand side equals $-\log\pi_1$, so the inequality does not hold. Hence, there exists an interval $[0, q_1)$ (with $q_1 \in (0,1)$) such that, for $q \in [0, q_1)$, $M^{(1)}(2,1) > 2M^{(1)}(2,0)$. Let $q_2 = \max(q_0, q_1)$. Then, provided $\pi_1^3 > \pi_2$, $M^{(1)}(1,1) > M^{(1)}(2,0)$ and $M^{(1)}(2,1) > 2M^{(1)}(2,0)$ for $q \in (0, q_2)$, i.e. for $\lambda^L > -\log q_2$.

The implication of the above is that, if $\pi_1^3 > \pi_2$ and $\lambda^L > -\log q_2$, the optimal scheme for a small number of doses is to only vaccinate class 2 individuals, as it corresponds to the best use of a single dose in a household for both bounds and it is on the convex hull for both. Further, this scheme will remain optimal until all class 2 individuals have been vaccinated, at which point $R_*^{(2)} = 0$ and

$$R_*^{(1)} = \frac{mM^{(1)}(2,0)}{N_1 z_1} = \frac{-(2-q)\log\pi_1}{z_1},$$

so $R_*^{(1)} > 1$ if $\pi_1 < e^{-1}$. To reduce $R_*^{(1)}$ further it is necessary to proceed to the next point on the corresponding convex hull, i.e. to vaccinate both class 1 individuals and not the class 2 individual in some households. Thus the optimal vaccination scheme cannot be achieved sequentially.

6 Numerical examples

The first example is derived from the example used in Section 3.4, so that the optimal scheme is non-sequential. The parameters are assumed to be known and the global infection rates take the proportionate mixing form, i.e. $\lambda_{ij}^G = \eta_i^G \kappa_j^G$. The vaccine is perfect,

i.e. $\boldsymbol{\epsilon} = \mathbf{1}$, so that the leaky and all or nothing formulations coincide. There are two classes of individual, i.e. $J = 2$, local mixing is uniform, so $\lambda_{ij}^L = \lambda\,(i, j \in \mathcal{J})$, and the distribution of an infective's infectious period is constant and equal to the unit of time. The population consists entirely of households with category $(2, 1)$, so $N_1 = 2N_2$, and only class 1 individuals contribute to global infection, so $\eta_2^G = 0$. The other global infection rate parameters are given by $\eta_1^G = \lambda$, $\kappa_1^G = 0.6$ and $\kappa_2^G = 2.4$.

Thus both the local and global infection rates are scaled with a common parameter λ. The optimal vaccination scheme (as a function of λ) to reduce R_* to 1 is illustrated in Figure 1, which demonstrates the non-sequential nature of optimal schemes in a different way to Section 3.4 (i.e. as a function of a parameter, rather than in constructing one optimal scheme). For $\lambda = 0.38$, $R_* \simeq 1$, so that for $\lambda < 0.38$ no vaccination is required.

Figure 1: Optimal vaccination scheme as a function of λ, showing the proportion of households using each of the three strategies: no vaccination; vaccinate the one class two individual and vaccinate the two class one individuals. To obtain the optimal scheme for a given λ, read off the proportions of households using each of the three strategies vertically from the graph (note that at most two strategies are used in the optimal scheme for any given λ).

For $0.38 < \lambda < 1.02$, the optimal scheme vaccinates the one class two individual in some households and no-one in the other households. For $\lambda > 1.02$, the optimal scheme vaccinates the one class two individual in some households and both class one individuals in the other households. As $\lambda \to \infty$, the proportion of households with both class one individuals vaccinated increases to 1. (For this example, vaccinating all the class one individuals totally prevents global infection, so the optimal coverage converges to $2/3$ as

$\lambda \to \infty$.) Thus, for $\lambda \simeq 1.02$ (corresponding to $R_* \simeq 4.95$), the optimal scheme is to vaccinate all the class two individuals (optimal coverage $= 1/3$) whereas for λ large, the optimal scheme is to vaccinate all the class one individuals and none of the class two individuals (optimal coverage $= 2/3$).

The intuition for the form of the optimal schemes is as follows. Class two individuals are 4 times more susceptible than class one individuals, while local mixing is homogeneous (with a high rate of infection, λ). So, despite class two individuals not contributing to global infection, the best way to start reducing global infection emanating from a household is to vaccinate the class two individual, conferring more protection on the class one individuals than vaccinating one of them. However, once λ is sufficiently large, this is no longer sufficient to keep the epidemic under control. The best use of two vaccines in any household is clearly to vaccinate both class one individuals, because that entirely eliminates global infection emanating from the household. So the optimal scheme now vaccinates fewer class two individuals, and more class one individuals.

The second example illustrates the superiority of an all or nothing vaccine over a leaky vaccine with the same efficacy (shown in Section 2.3.4). Consider a single class population, with parameters $\lambda^G = 0.25$ and $\lambda^L = 1$ and, as in Addy et al. [19], the infectious period of all individuals is assumed to follow a gamma distribution with mean 4.1 days and shape parameter 2. The value of λ^G is a plausible choice for the global infection rate, whereas the value of λ^L is deliberately chosen to be very high, to emphasise the difference between the two vaccine actions. The household structure used in this example is that of the sample from the influenza epidemics in Tecumseh, Michigan, analysed by Addy et al. [19]. That is, 133 households of size 1, 189 households of size 2, 108 of size 3, 106 of size 4 and 31 of size 5. The sample was an approximate 10% sample from the underlying population (but scaling the household numbers has no effect on the threshold behaviour or the optimal vaccination coverage). Figure 2 shows the resulting threshold parameter as a function of the vaccination coverage for both types of vaccine which have been calibrated by having the same efficacy $\epsilon = 0.55$. As seen from the figure, the all or nothing vaccine considerably outperforms the leaky vaccine and, in particular, the leaky vaccine cannot prevent an epidemic even with complete coverage (resulting threshold greater than 1), while the all or nothing vaccine can (resulting threshold less than 1, the critical coverage is where the dotted line and solid line on the figure intersect). This phenomenon cannot occur in a non-households model. If the vaccines have higher efficacy both types may be able to prevent future epidemics, but the critical vaccination coverage is always smaller for the all or nothing vaccine. For example if $\epsilon = 0.7$, which is typical for the current killed influenza vaccine (Ira M. Longini, personal communication), $v_c^{AoN} = 0.60$ and $v_c^{Le} = 0.80$.

7 Discussion

The present paper is based on an epidemic model allowing for observable (and hence classifiable) individual heterogeneities as well as mixing heterogeneities caused by the presence

Figure 2: Optimal reduction of R_* as a function of coverage, comparing all or nothing (solid line) and leaky (dashed line) vaccines. The dotted line marks $R_* = 1$. In both cases the vaccine efficacy $\epsilon = 0.55$ (see text for further details).

of households. In reality there are also unobservable individual heterogeneities and mixing heterogeneities due to other social structures, for example schools and workplaces, which affect the spread of an infectious disease. Still, it is believed that households, in combination with having different classes of individual, captures the integral part of departures from homogeneity, so models allowing for these two types of heterogeneity should not be too far from real epidemic outbreaks.

Optimal vaccination schemes for the epidemic model are derived under two different scenarios. First it is done when it is assumed that all population and model parameters are known, and then it is done in the case that model parameters have been estimated from final size data from a sample of households of an earlier outbreak. In the latter case the household demography of the population is assumed known, as is the distribution of the infectious periods, and the efficacy of the vaccine.

The notion of an optimal vaccination scheme might at first sight seem purely academic in that in reality, a vaccination program is unlikely to follow such a scheme. Still, the derivation of optimal vaccination schemes can give useful qualitative indications on which household categories are effective in reducing the threshold parameter. The present analysis also derives an expression for $R_*(\boldsymbol{v})$ for any suggested vaccination program $\boldsymbol{v}$, or an estimate in the case when parameters are estimated from a previous outbreak. Thus, a vaccination scheme suggested by health practitioners can be checked to ensure that it reduces the threshold parameter below 1, and for a vaccination scheme that only speci-

fies the relative proportions of various household categories to be vaccinated, the present analysis enables calculation of the minimal absolute proportions for the scheme to be preventive.

Admittedly, the results are somewhat technical. However, there are three main qualitative results of the paper. The first is that there is, in general, no simple sequential algorithm to describe the optimal vaccination scheme as there is, or at least has been conjectured to be, in the single type setting. Instead the optimal vaccination scheme has to be derived by solving a non-linear optimisation problem. The second conclusion from the paper is that the seemingly more complicated case, where parameters have to be estimated from a previous outbreak, admits a simpler solution for the optimal vaccination scheme. Here the optimal vaccination scheme is given by the solution to a linear programming problem. The reason for this simplification comes from the observation that the threshold parameter cannot be estimated consistently, instead upper and lower bounds can be estimated, and it is only vaccination schemes with corresponding upper bounds being smaller than 1 that are surely preventive. To find such a vaccination scheme with upper bound estimate below 1, having minimal vaccination coverage, turns out to be a linear programming problem. Thirdly, we show in a precise way that if the vaccine efficacy ϵ is held fixed, the all or nothing model for vaccine action results in a greater reduction in the spread of disease than the leaky model. This has important implications for the threshold parameter following vaccination in a households model, which usually is different under the two models of vaccine action. By contrast, in a non-households model, the threshold parameter is the same for both all or nothing and leaky vaccines.

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References

[1] C. Lefèvre, Stochastic epidemic models for S-I-R infectious diseases: a brief survey of the recent theory, in Stochastic Processes in Epidemic Theory, J.-P. Gabriel, C. Lefèvre, P. Picard, (Eds.). Springer Lecture Notes in Biomath. 86 (1990) 1–12.

[2] H. Andersson, T. Britton, Stochastic models and their statistical analysis. Springer Lecture Notes in Statistics 151 (2000). New York, Springer.

[3] J. A. P. Heesterbeek, K. Dietz, The concept of R_0 in epidemic theory, Statistica Neerlandica 50 (1996) 89–110.

[4] P. G. Smith, L. C. Rodrigues and P. E. M. Fine, Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies, Int. J. Epidemiol. 13 (1984) 87–93.

[5] M. E. Halloran, M. Haber and I. M. Longini, Interpretation and estimation of vaccine efficacy under heterogeneity, Am. J. Epidemiol. 136 (1992) 328–343.

[6] F. G. Ball, O. D. Lyne, Stochastic multitype SIR epidemics among a population partitioned into households, Adv. Appl. Prob. 33 (2001) 99–123.

[7] N. G. Becker, R. Hall, Immunization levels for preventing epidemics in a community of households made up of individuals of various types, Math. Biosci. 132 (1996) 205–216.

[8] F. G. Ball, O. D. Lyne, Statistical inference for epidemics among a population of households, in preparation.

[9] F. G. Ball, T. Britton, O. D. Lyne, Stochastic multitype epidemics in a community of households: estimation of threshold parameter R_* and secure vaccination coverage. Submitted.

[10] F. G. Ball, O. D. Lyne, Optimal vaccination policies for stochastic epidemics among a population of households, Math. Biosci. 177–178 (2002) 333–354.

[11] H. W. Hethcote and J. W. Van Ark, Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation and immunization programs, Math. Biosci. 84 (1987) 85–118.

[12] N. G. Becker and I. C. Marschner, The effect of heterogeneity on the spread of disease, in J.-P. Gabriel, C. Lefèvre and P. Picard (Eds.) Stochastic Processes in Epidemic Theory, Lecture Notes in Biomathematics 86, Springer-Verlag, Berlin, 1990, 90–103.

[13] N. G. Becker, D. N. Starczak, Optimal vaccination strategies for a community of households, Math. Biosci. 139 (1997) 117–132.

[14] F. G. Ball, D. Mollison, G. Scalia-Tomba, Epidemics with two levels of mixing, Ann. Appl. Prob. 7 (1997) 46–89.

[15] T. Sellke, On the asymptotic distribution of the size of a stochastic epidemic, J. Appl. Prob. 20 (1983) 390–394.

[16] T. Britton, Epidemics in heterogeneous communities: estimation of R_0 and secure vaccination coverage. J. R. Statist. Soc. B. 63 (2001) 705–715.

[17] N. T. J. Bailey, The Mathematical Theory of Infectious Diseases and its Applications. London: Griffin (1975).

[18] A. J. G. Cairns, Epidemics in Heterogeneous Populations: Aspects of Optimal Vaccination Policies, IMA J. Math. Med. Biol. 6 (1989) 137–159.

[19] C. L. Addy, I. M. Longini and M. Haber, A generalized stochastic model for the analysis of infectious disease final size data, Biometrics 47 (1991) 961–974.