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

Frank Ball [a,*], Tom Britton [b], Owen Lyne [a]

[a] School of Mathematical Sciences, University of Nottingham, University Park, Nottingham, NG7 2RD, England, UK
[b] Department of Mathematics, Stockholm University, SE-106 91 Stockholm, Sweden

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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 vaccines 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

* Corresponding author. Tel.: +44-115 951 4969; fax: +44-115 951 4951.
*E-mail addresses:* frank.ball@maths.nottingham.ac.uk, fgb@maths.nott.ac.uk (F. Ball), tom.britton@math.su.se (T. Britton), owen.lyne@nottingham.ac.uk (O. Lyne).

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## 1. Introduction

This paper is concerned with SIR (susceptible $\rightarrow$ infective $\rightarrow$ 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 $R_0$) 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, sharp upper and lower bounds for $R_*$ are derived, both before and after vaccination, which can be estimated consistently from final outcome 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, in which case 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 $v_{\mathrm{opt}}$, 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. Optimal vaccination schemes and their form are considered in Sections 3, for the case when global mixing is proportionate and all infection rates are known, and in Section 4, for the case when the infection rates need to be estimated from final outcome data. Some numerical examples are given in Section 5 and the paper concludes with a brief discussion in Section 6.

## 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 epidemic among a closed, finite population that contains $J$ classes of individuals, labelled $1,2,\ldots,J$, and is partitioned into households. Let $\mathscr{J}=\{1,2,\ldots,J\}$ and $\mathscr{N}_0=\{\boldsymbol{n}=(n_1,n_2,\ldots,n_J)\in\mathbb{Z}^J\colon\ n_j\geqslant 0\ \ (j\geqslant\mathscr{J}),\ |\boldsymbol{n}|=\sum_{j=1}^{J}n_j\geqslant 1\}$. Suppose that, for $\boldsymbol{n}\in\mathscr{N}_0$, the population contains $m_{\boldsymbol{n}}$ households of category $\boldsymbol{n}$, where a household of category $\boldsymbol{n}$ contains $n_j$ individuals of class $j$ $(j\in\mathscr{J})$. Let $m=\sum_{\boldsymbol{n}\in\mathscr{N}_0}m_{\boldsymbol{n}}$ denote the total number of households in the population, $N_j=\sum_{\boldsymbol{n}\in\mathscr{N}_0}n_jm_{\boldsymbol{n}}$ denote the total number of individuals of class $j$ in the population $(j\in\mathscr{J})$ and $N=\sum_{\boldsymbol{n}\in\mathscr{N}_0}|\boldsymbol{n}|m_{\boldsymbol{n}}$ denote the total number of individuals in the population. Assume that $N$, and hence $N_j(j\in\mathscr{J})$ and $m$, is finite. This implies that $m_{\boldsymbol{n}}=0$ for all but finitely many $\boldsymbol{n}$. Let $\mathscr{N}=\{\boldsymbol{n}\in\mathscr{N}_0:m_{\boldsymbol{n}}>0\}$.

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 $j\in\mathscr{J}$, 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 $i,j\in\mathscr{J}$, 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 $\lambda_{ij}^{\mathrm{G}}/N_j$ 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 $\lambda_{ij}^{\mathrm{L}}$. 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. Threshold behaviour

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 (which assumes that all global contacts are with individuals residing in an otherwise completely susceptible household), with type space $\mathscr{J}$, where the type of an infected household is given by the class $j$ of its initial (globally contacted) infective (see Ball and Lyne [6] for rigorous results). 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 $i, j, \in \mathscr{J}$, $m_{ij}$ 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 $m_{ij}$ $(i, j \in \mathscr{J})$ are required to compute $R_*$. For $\boldsymbol{n} \in \mathscr{N}$, let $\alpha_{\boldsymbol{n}} = m_{\boldsymbol{n}}/m$ denote the proportion of households of category $\boldsymbol{n}$ in the population and, for $i \in \mathscr{J}$ and $\boldsymbol{n} \in \mathscr{N}$, 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 a class-$i$ individual is contacted globally. For $j \in \mathscr{J}$, let $\mu_{\boldsymbol{n},i,j}(\Lambda^{\mathrm{L}})$, where $\Lambda^{\mathrm{L}} = [\lambda^{\mathrm{L}}_{ij}]$, 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 $\mu_{\boldsymbol{n},i,j}(\Lambda^{\mathrm{L}})$ $(\boldsymbol{n} \in \mathscr{N}; i, j, \in \mathscr{J})$ is given in the appendix of [9]. In Ball and Lyne [6], Section 4.3, it is shown that

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

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

### 2.3. Vaccination

#### 2.3.1. Post-vaccination threshold parameter

Suppose that vaccination may reduce an individual's susceptibility to a disease but not his or her ability to transmit it if infected. For $\boldsymbol{n} \in \mathscr{N}$ and $\boldsymbol{0} \leqslant \boldsymbol{r} = (r_1, r_2, \ldots, r_J) \leqslant \boldsymbol{n}$, 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 $\boldsymbol{v} = \{v_{\boldsymbol{n},\boldsymbol{r}} : \boldsymbol{n} \in \mathscr{N}, \boldsymbol{0} \leqslant \boldsymbol{r} \leqslant \boldsymbol{n}\}$. 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 $(i, j, \in \mathscr{J})$. Arguing as

in the derivation of (2.1), but conditioning also on the number of vaccinated people in the class-$i$ individual's household, yields

$$m_{ij}(\boldsymbol{v}) = \sum_{\boldsymbol{n}\in\mathscr{N}} \alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \sum_{l\in\mathscr{J}} \mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}}) t_l \lambda^{\mathrm{G}}_{lj} \quad (i,j\in\mathscr{J}), \tag{2.2}$$

where $\mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}})$ denotes the mean number of class-$l$ cases in a category $\boldsymbol{n}$ household having $\boldsymbol{r}$ vaccinated, when a randomly chosen class-$i$ individual in that household is contacted globally.

The quantity $\mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}})$ depends on the model for vaccine action. Two different types of vaccination response are considered, namely *all-or-nothing* and *leaky*. The all-or-nothing model assumes that the vaccine either renders its recipient complete immunity or else it has no effect, and that vaccinated individuals react independently, with probability $\epsilon_i$ for a class-$i$ individual ($i\in\mathscr{J}$). Conditioning on the number of susceptible individuals $\boldsymbol{k}$ in a category $\boldsymbol{n}$ household having $\boldsymbol{r}$ vaccinated, and noting that the probability that a randomly contacted class-$i$ individual from that household is susceptible (and thus triggers a local epidemic) is $k_i/n_i$, shows that

$$\mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}}) = \sum_{\boldsymbol{k}=\boldsymbol{n}-\boldsymbol{r}}^{\boldsymbol{n}} \left\{ \prod_{p=1}^{J} \binom{r_p}{n_p-k_p} \epsilon_i^{n_p-k_p} (1-\epsilon_i)^{r_p-n_p+k_p} \right\} \frac{k_i}{n_i} \mu_{\boldsymbol{k},i,l}(\Lambda^{\mathrm{L}}). \tag{2.3}$$

The leaky model assumes that vaccinated individuals respond by acquiring partial immunity rather than acquiring either complete immunity or no immunity at all. Specifically, it is assumed that all infection rates to vaccinated class-$j$ individuals are reduced by a factor $\epsilon_j$ ($j\in\mathscr{J}$). Hence, for $i,j\in\mathscr{J}$, the rate at which a class-$i$ infective has global contact with a vaccinated class-$j$ individual is $\lambda^{\mathrm{G}}_{ij}(1-\epsilon_j)/N_j$ and the corresponding local contact rate is $\lambda^{\mathrm{L}}_{ij}(1-\epsilon_j)$. Note that the *average* vaccine $\epsilon_j$ for each class of individual is the same as in the all-or-nothing case. Let $\boldsymbol{\epsilon}=(\epsilon_1,\epsilon_2,\ldots,\epsilon_J)$ and let $\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},u:i,l}(\Lambda^{\mathrm{L}},\boldsymbol{\epsilon})$ ($\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},v:i,l}(\Lambda^{\mathrm{L}},\boldsymbol{\epsilon})$) 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. Suppose that a randomly chosen class-$i$ individual in such a household is contacted globally. The probability that this individual becomes infected, and hence triggers a local epidemic, is $1-\epsilon_i$ if it is vaccinated and 1 if it is unvaccinated. Further, the probability that this individual is vaccinated is $r_i/n_i$. Thus,

$$\mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}}) = \frac{n_i-r_i}{n_i}\mu_{\boldsymbol{n}-\boldsymbol{r},\boldsymbol{r},u:i.l}(\Lambda^{\mathrm{L}},\boldsymbol{\epsilon}) + \frac{r_i(1-\epsilon_i)}{n_i}\mu_{\boldsymbol{n}-\boldsymbol{r},v:i,l}(\Lambda^{\mathrm{L}},\boldsymbol{\epsilon}). \tag{2.4}$$

Let $M(\boldsymbol{v})=[m_{ij}(\boldsymbol{v})]$. Then $R_*(\boldsymbol{v})$, the maximal eigenvalue of $M(\boldsymbol{v})$, is a threshold parameter for the epidemic after vaccination, in the sense that a global epidemic can occur only if $R_*(\boldsymbol{v})>1$. Consequently, a vaccination scheme $\boldsymbol{v}$ having $R_*(\boldsymbol{v})\leqslant 1$ is protective for the whole community, the aim of launching a vaccination programme.

There is in general no closed form expression for $R_*(\boldsymbol{v})$. 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]) $\lambda^{\mathrm{G}}_{ij}=\eta^{\mathrm{G}}_i\kappa^{\mathrm{G}}_j$ ($i,j,\in\mathscr{J}$), then the matrix $M(\boldsymbol{v})$ has rank one, so $R_*(\boldsymbol{v})$ is given by its trace, i.e.

$$R_*(\boldsymbol{\nu}) = \sum_{i\in\mathscr{I}} \sum_{\boldsymbol{n}\in\mathscr{N}} \alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} \nu_{\boldsymbol{n},\boldsymbol{r}} \sum_{l\in\mathscr{I}} \mu^V_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}}) t_l \eta^{\mathrm{G}}_l \kappa^{\mathrm{G}}_i. \tag{2.5}$$

*2.3.2. 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-type [13] 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 $t \geqslant 0$ a given susceptible of class $i$ accumulates exposure to infection at rate $\sum_{j\in\mathscr{I}}(y^{\mathrm{G}}_j(t)\lambda^{\mathrm{G}}_{ji}N_i^{-1} + y^{\mathrm{L}}_j(t)\lambda^{\mathrm{L}}_{ji})$, where, for $j \in \mathscr{I}$, $y^{\mathrm{G}}_j(t)$ is the total number of class-$j$ infectives in the population and $y^{\mathrm{L}}_j(t)$ 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 $Q$, $Q^{\mathrm{AoN}}$ and $Q^{\mathrm{Le}}$ 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 $Q^{\mathrm{AoN}} = \infty$ if the vaccine is successful (i.e. with probability $\epsilon$) and $Q^{\mathrm{AoN}} = Q$ otherwise, whilst $Q^{\mathrm{Le}} = (1-\epsilon)^{-1}Q$. Thus, by the convexity of the exponential function,

$$P(Q^{\mathrm{Le}} > t) = \exp(-(1-\epsilon)t) \leqslant \epsilon + (1-\epsilon)\exp(-t) = P(Q^{\mathrm{AoN}} > t) \quad (t \geqslant 0),$$

with strict inequality for $t > 0$. Hence, $Q^{\mathrm{AoN}}$ is stochastically larger than $Q^{\mathrm{Le}}$. 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.

Let $R^{\mathrm{AoN}}_*(\boldsymbol{\nu})$ and $R^{\mathrm{Le}}_*(\boldsymbol{\nu})$ denote the post-vaccination threshold parameter assuming an all-or-nothing and leaky vaccine, respectively. For $i, j \in \mathscr{I}$, 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 (assuming common efficacy $\boldsymbol{\epsilon}$), 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 $R^{\mathrm{AoN}}_*(\boldsymbol{\nu}) = R^{\mathrm{Le}}_*(\boldsymbol{\nu})$ (see Britton [14]). However, when there are households of size >1, local spread affects $M(\boldsymbol{\nu})$ and the above coupling argument shows that $R^{\mathrm{AoN}}(\boldsymbol{\nu}) \leqslant R^{\mathrm{Le}}_*(\boldsymbol{\nu})$, with strict inequality except for a few special cases.

## 3. Optimal vaccination schemes, known infection rates

As noted in Section 2.3.1, the main aim of any vaccination scheme is to bring the threshold parameter below one, i.e. to ensure that $R_*(\boldsymbol{\nu}) \leqslant 1$. Therefore, for a given community and a given vaccine response, the vaccination scheme $\boldsymbol{\nu}$ is said to be *preventive* (written $\boldsymbol{\nu} \in P$) if the induced threshold parameter satisfies $R_*(\boldsymbol{\nu}) \leqslant 1$. If the vaccine response, or efficacy, $\boldsymbol{\epsilon}$ is not large enough, it could be that no vaccination scheme is preventive, i.e. that $R_*(\boldsymbol{\nu}_{\mathrm{full}}) > 1$, where $\boldsymbol{\nu}_{\mathrm{full}}$ corresponds to everyone in the population being vaccinated. In that 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 may be many different vaccination schemes $\boldsymbol{v}$ satisfying $R_*(\boldsymbol{v}) \leqslant 1$. It is then important to determine which such scheme is the best in the sense that it requires the fewest vaccinations. Accordingly, if

$$S(\boldsymbol{v}) = \frac{\sum_{\boldsymbol{n}\in\mathscr{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} |\boldsymbol{r}| v_{\boldsymbol{n},\boldsymbol{r}} \alpha_{\boldsymbol{n}}}{\sum_{\boldsymbol{n}\in\mathscr{N}} |\boldsymbol{n}| \alpha_{\boldsymbol{n}}} \tag{3.1}$$

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

$$\boldsymbol{v}_{\mathrm{opt}} \in \operatorname*{argmin}_{\boldsymbol{v}\in P}\{S(\boldsymbol{v})\} = \{\boldsymbol{v}' \in P : S(\boldsymbol{v}') \leqslant S(\boldsymbol{v}) \text{ for all } \boldsymbol{v} \in P\} \tag{3.2}$$

is optimal. The corresponding coverage $c_v = S(\boldsymbol{v}_{\mathrm{opt}})$ is called the *critical vaccination coverage*. The definition of $\boldsymbol{v}_{\mathrm{opt}}$ 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.

It is generally a non-trivial task to determine $\boldsymbol{v}_{\mathrm{opt}}$, since $R_*(\boldsymbol{v})$ may be non-linear and 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 $R_*(\boldsymbol{v}) \leqslant 1$ (i.e. find $\boldsymbol{v}_{\mathrm{opt}}$) are both linear programming problems, cf. Becker and Starczak [15]. Note that there are further (linear) constraints on $\boldsymbol{v}$ implicit in the above formulations, specifically that, for $\boldsymbol{n} \in \mathscr{N}$, $v_{\boldsymbol{n},\boldsymbol{r}} \geqslant 0$ $(\boldsymbol{0} \leqslant \boldsymbol{r} \leqslant \boldsymbol{n})$ and $\sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} = 1$.

### 3.1. Construction of optimal vaccination scheme

It is possible to construct the solutions of the above linear programming problems directly. For $\boldsymbol{n} \in \mathscr{N}$ and $\boldsymbol{0} \leqslant \boldsymbol{r} \leqslant \boldsymbol{n}$, 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. Recall that $\alpha_i(\boldsymbol{n}) = n_i m_{\boldsymbol{n}}/N_i$. From (2.5),

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

where

$$M_{\boldsymbol{n},\boldsymbol{r}} = \sum_{i\in\mathscr{I}} \frac{n_i \kappa_i^{\mathrm{G}}}{N_i} \sum_{l\in\mathscr{I}} \mu^{V}_{\boldsymbol{n},\boldsymbol{r},i,l}(\Lambda^{\mathrm{L}}) t_l \eta_l^{\mathrm{G}}. \tag{3.3}$$

From (3.1), the vaccine coverage is given by

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

Suppose 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 $p = \Pi_{i\in\mathscr{I}}(n_i + 1)$. Note

that the case of no vaccination, $\boldsymbol{r} = \mathbf{0}$, is included in this list. 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 $f(1) = R_*(\boldsymbol{v}_{\text{full}})$. For $c \in [0, 1]$, $f(c)$ is the minimum achievable value of $R_*(\boldsymbol{v})$ subject to $S(\boldsymbol{v}) = c$. An explicit solution to this problem is given in Appendix A, where extension to unequal household sizes and the determination of $\boldsymbol{v}_{\text{opt}}$ (see (3.2)) are also considered. 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 made clear in the following example.

For this example, assume that $J = 2$, that the vaccine is all-or-nothing and has equal efficacy of 98% for both classes, so that $\boldsymbol{\epsilon} = (0.98, 0.98)$, that local mixing is uniform, with $\lambda^{\text{L}}_{ij} = 1.7$ $(i, j, \in \mathscr{J})$, 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 $N_1 = 2N_2$, that $\eta^{\text{G}} = (1, 0)$ and $\kappa^{\text{G}} = (1, 4)$, so that only class 1 individuals contribute to global infection. Then the points $(\frac{|\boldsymbol{r}_k|}{|\boldsymbol{n}|}, mM_{\boldsymbol{n},\boldsymbol{r}_k})$ $(k = 1, 2, \ldots, p)$ in $\mathbb{R}^2$ and their convex hull are as shown in Fig. 1.

To read off the optimal vaccination policy find the intersection of the lower edge of the convex hull with the $R_*(\boldsymbol{v}) = 1$ dashed line, which for this example yields a coverage of 0.5111. The policy that achieves this optimal reduction in $R_*(\boldsymbol{v})$ with minimal coverage is a mixture of the two policies represented by the stars on the figure which are the end-points of this segment of the convex hull. The relative proportions in the mixture are equal to the proportions of the line segment to the left and right of the intersection with $R_*(\boldsymbol{v}) = 1$. These proportions may not yield an integer number of households, in which case the right-hand number of households must be rounded up and the left-hand rounded down to provide an optimal integer solution. Since the section of convex hull

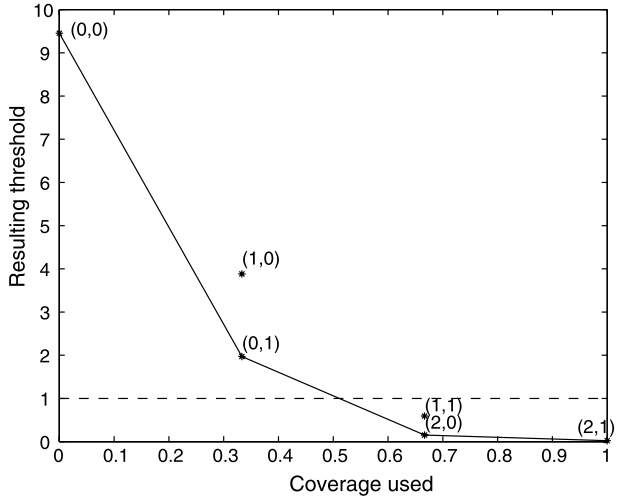


Fig. 1. Reduction of $R_*$ as a function of coverage, marking the points $\left(\frac{|\boldsymbol{r}_k|}{|\boldsymbol{n}|}, mM_{\boldsymbol{n},\boldsymbol{r}_k}\right)$ $(k = 1, 2, \ldots, p)$ in $\mathbb{R}^2$ by stars (the numbers in brackets by each star indicate the number of individuals of class-1 and class-2 vaccinated respectively) and the lower edge of the convex hull of the stars by the solid lines. The dashed line marks $R_* = 1$ (see text for further details).

connects the stars marked (0,1) and (2,0) the best use of one dose of vaccine in a household is to give it to the class-2 individual, but the best use of two doses is to give both doses to class-1 individuals. Thus a sequential construction by continuously increasing the vaccine coverage (see Section 3.2) cannot yield this section of the convex hull.

The construction using the convex hull 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.

### 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 $\mu_n(\lambda^{\mathrm{L}})$ denote the mean size of a single household epidemic, with initially $n - 1$ susceptibles and 1 infective, where $\lambda^{\mathrm{L}}$ denotes the local infection rate. (As before, $\mu_n(\lambda^{\mathrm{L}})$ includes the initial infective.) Ball and Lyne [10] considered all-or-nothing vaccines and showed that, provided the sequence $(n\mu_n(\lambda^{\mathrm{L}}))$ 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 $(n\mu_n(\lambda^{\mathrm{L}}))$ was conjectured by Ball et al. [16], 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.

Multitype epidemics without household structure can be studied within the framework of the model of Section 2.1 by assuming that all the households are of size 1, i.e. that $m_{\boldsymbol{n}} = 0$ if $|\boldsymbol{n}| > 1$. For such epidemics, let $\boldsymbol{v} = (v_1, v_2, \ldots, v_J)$, where $v_i$ is the proportion of class-$i$ individuals that are vaccinated. Using (2.2)–(2.4), under both the all-or-nothing and the leaky models, the post-vaccination threshold parameter, $R_*(\boldsymbol{v})$ say, is given by the maximal eigenvalue of the matrix $M(\boldsymbol{v}) = [m_{ij}(\boldsymbol{v})]$, where $m_{ij}(\boldsymbol{v}) = (1 - v_i\epsilon_i)t_i\lambda_{ij}^{\mathrm{G}}$ $(i, j \in \mathscr{J})$. Optimal vaccination schemes for this class of epidemics are considered by Cairns [17], but when $J \geqslant 3$ there is no general solution. However, if mixing is proportionate then $R_*(\boldsymbol{v}) = \sum_{i\in\mathscr{J}}(1 - v_i\epsilon_i)t_i\lambda_{ii}^{\mathrm{G}}$, so if the classes are labelled so that $x_1 \geqslant x_2 \geqslant \ldots \geqslant x_J$, where $x_i = \epsilon_i t_i \lambda_{ii}^{\mathrm{G}}$, it is easily seen that a scheme in which vaccines are allocated sequentially, always to an individual with greatest $x_i$ among unvaccinated individuals, is optimal.

The above numerical example suggests that, even when global mixing is proportionate, the optimal vaccination scheme for the multitype households model does not generally admit a simple characterisation.

## 4. Optimal vaccination schemes, unknown infection rates

### 4.1. Estimation

#### 4.1.1. 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 $T_I^{(i)}(i \in \mathscr{J})$ are assumed known from previous epidemiological studies.

The following method for estimating $(\Lambda^{\mathrm{L}}, \Lambda^{\mathrm{G}})$ 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 $j \in \mathscr{J}$, 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 class-$j$ individual who gets infected. The probability that a given class-$i$ individual avoids *global* infection throughout the entire epidemic is given by

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

where $\gamma_i = N_i/N$ is the proportion of class-$i$-individuals. The approximation on the right follows since $m$ is assumed large so $A_j \approx N_j z_j E\left[T_I^{(j)}\right] = N\gamma_j z_j t_j$. Further, when $m$ is large, distinct individuals avoid global infection approximately independently of each other. The ultimate spread of infection within an initially completely susceptible category-$\boldsymbol{n}$ household is thus approximately distributed as that of a multitype single household epidemic model, studied by Addy et al. [18], 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 $\pi_i$ for a class-$i$ susceptible. Denote this single household epidemic by $E_{\boldsymbol{n}}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ where $\boldsymbol{\pi} = (\pi_1, \pi_2, \ldots, \pi_J)$. For $j \in \mathscr{J}$, let $\mu_{\boldsymbol{n},j}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ be the expected number of class-$j$ individuals that are ultimately infected by $E_{\boldsymbol{n}}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$. An algorithm for computing $\mu_{\boldsymbol{n},j}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ $(\boldsymbol{n} \in \mathscr{N}, j \in \mathscr{J})$ is given in Ball et al. [9].

For $i \in \mathscr{J}, z_i$ 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, $\boldsymbol{n}$ say, of household to which this initial susceptible belongs and noting that its chance of ultimate infection is then $\mu_{\boldsymbol{n},i}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})/n_i$, it follows that

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

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 under a mild regularity condition, if $R_* \leqslant 1$ 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 $z_i > 0$ $(i \in \mathscr{J})$, 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 $p_{\boldsymbol{n}}(\boldsymbol{k}|\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ be the probability that the epidemic $E_{\boldsymbol{n}}(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ has final outcome $\boldsymbol{k}$ $(\boldsymbol{n} \in \mathscr{N}$, $\boldsymbol{0} \leqslant \boldsymbol{k} \leqslant \boldsymbol{n})$. For $\boldsymbol{n} \in \mathscr{N}$, a triangular system of linear equations governing $p_{\boldsymbol{n}}(\boldsymbol{k}|\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$ $(\boldsymbol{0} \leqslant \boldsymbol{k} \leqslant \boldsymbol{n})$ is given in Ball et al. [9]; see also Addy et al. [18].

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

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

Note that (4.3) is a pseudolikelihood, and not a likelihood, since the outcomes in different households are not independent.

The pseudolikelihood (4.3) can be maximised by first maximising it as a function of $(\Lambda^{\mathrm{L}}, \boldsymbol{\pi})$, to yield the estimate $(\hat{\Lambda}^{\mathrm{L}}, \hat{\boldsymbol{\pi}})$, then obtaining an estimate, $\hat{\boldsymbol{z}}$ say, of $\boldsymbol{z}$ by substituting $(\hat{\Lambda}^{\mathrm{L}}, \hat{\boldsymbol{\pi}})$ 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 $\Lambda^{\mathrm{G}}$. However, the final step in this procedure involves solving $J$ linear equations in the $J^2$ unknown quantities $\lambda^{\mathrm{G}}_{ij}$ $(i, j \in \mathscr{J})$, so $\Lambda^{\mathrm{G}}$ is not identifiable from the observed data using this approach. It is possible that the local infection rates $\Lambda^{\mathrm{L}}$ may also be unidentifiable, for example if for some $i, j \in \mathscr{J}$ 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 $\lambda^{\mathrm{L}}_{ij}$s are redundant for the population at hand.

#### *4.1.2. Estimation of $R_*$, $R_*(\boldsymbol{v})$ and optimal vaccination scheme*

Consider now estimation of the pre- and post-vaccination threshold parameters, $R_*$ and $R_*(\boldsymbol{v})$, for a future epidemic having the same $(\Lambda^{\mathrm{L}}, \Lambda^{\mathrm{G}})$ as the observed epidemic. The vaccination efficacy $\epsilon$ and the type (all-or-nothing or leaky) of the vaccine are assumed known, as are the distributions of the infection periods $T_I^{(i)}$ $(i \in \mathscr{J})$. 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].

Observe that $R_*$ and $R_*(\boldsymbol{v})$ cannot be estimated consistently using the above pseudolikelihood methodology, since $\Lambda^{\mathrm{G}}$ is not identifiable. In Ball et al. [9] a Perron–Frobenius argument is used to show that, subject to the constraint (4.1) on $\Lambda^{\mathrm{G}}$,

$$\min_k R_*^{(k)}(\boldsymbol{v}) \leqslant R_*(\boldsymbol{v}) \leqslant \max_k R_*^{(k)}(\boldsymbol{v}), \tag{4.4}$$

where

$$R_*^{(k)}(\boldsymbol{v}) = \frac{1}{\gamma_k z_k} \sum_{i\in\mathscr{I}} \sum_{\boldsymbol{n}\in\mathscr{N}} \gamma_i(-\log\pi_i)\alpha_i(\boldsymbol{n}) \sum_{\boldsymbol{r}=0}^{\boldsymbol{n}} v_{\boldsymbol{n},\boldsymbol{r}} \mu^V_{\boldsymbol{n},\boldsymbol{r},i,k}(\Lambda^{\mathrm{L}}) \quad (k\in\mathscr{J}). \tag{4.5}$$

Fix $k\in\mathscr{J}$ and let $\Lambda^{\mathrm{G}}$ be given by $\lambda^{\mathrm{G}}_{kj} = (-\log\pi_j)\gamma_j/(\gamma_k z_k t_k)$ $(j\in\mathscr{J})$ and $\lambda^{\mathrm{G}}_{ij} = 0$ if $i\neq k$. It is easily verified that, with this choice of $\Lambda^{\mathrm{G}}$, (4.1) is satisfied and $R_*(\boldsymbol{v}) = R_*^{(k)}(\boldsymbol{v})$. Thus the bounds in (4.4) can be attained. Bounds for $R_*$ are obtained by letting $\boldsymbol{v}$ be the null vaccination scheme in (4.4). The bounds in (4.4) can be estimated consistently by replacing $(\boldsymbol{\pi}, \boldsymbol{z}, \Lambda^{\mathrm{L}})$ by the estimate $(\hat{\boldsymbol{\pi}}, \hat{\boldsymbol{z}}, \hat{\Lambda}^{\mathrm{L}})$.

As $R_*(\boldsymbol{v})$ cannot be estimated consistently, neither can the optimal vaccination scheme $\boldsymbol{v}_{\mathrm{opt}}$. Let $R_*^{\max}(\boldsymbol{v}) = \max_k R_*^{(k)}(\boldsymbol{v})$. Then it follows from (4.4) that any vaccination scheme $\boldsymbol{v}$ with $R_*^{\max}(\boldsymbol{v})\leqslant 1$ is preventive, irrespective of the underlying parameter $\Lambda^{\mathrm{G}}$ consistent with the data, whilst for any vaccination scheme $\boldsymbol{v}$ with $R_*^{\max}(\boldsymbol{v}) > 1$ there exists $\Lambda^{\mathrm{G}}$, 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 $R_*^{(k)}(\boldsymbol{v})\leqslant 1$ $(k\in\mathscr{J})$. Note that this is a linear programming problem since, by (3.1) and (4.5), the objective function $S(\boldsymbol{v})$ and the constraints $R_*^{(k)}(\boldsymbol{v})\leqslant 1$ $(k\in\mathscr{J})$ are all linear functions of the optimising variables $\boldsymbol{v}$.

### 4.2. Form of optimal vaccination scheme

Recall that $\alpha_i(\boldsymbol{n}) = n_i m_{\boldsymbol{n}}/N_i$, $\gamma_i = N_i/N$ and $h_{\boldsymbol{n},\boldsymbol{r}} = v_{\boldsymbol{n},\boldsymbol{r}} m_{\boldsymbol{n}}$. It follows from (4.5) that

$$R_*^{(k)}(\boldsymbol{v}) = \frac{1}{N_k z_k} \sum_{\boldsymbol{n}\in\mathscr{N}} \sum_{\boldsymbol{r}=\boldsymbol{0}}^{\boldsymbol{n}} h_{\boldsymbol{n},\boldsymbol{r}} M^{(k)}_{\boldsymbol{n},\boldsymbol{r}}, \tag{4.6}$$

where

$$M^{(k)}_{\boldsymbol{n},\boldsymbol{r}} = \sum_{i\in\mathscr{I}} (-\log\pi_i) n_i \mu^V_{\boldsymbol{n},\boldsymbol{r},i,k}(\Lambda^{\mathrm{L}}) \quad (k\in\mathscr{J}). \tag{4.7}$$

The aim is to determine an allocation of vaccines $\boldsymbol{v}_{\mathrm{opt}}$ which minimises the vaccine coverage $S(\boldsymbol{v})$ subject to $R_*^{(k)}(\boldsymbol{v})\leqslant 1$ $(k\in\mathscr{J})$. For *fixed* $k\in\mathscr{J}$, $M^{(k)}_{\boldsymbol{n},\boldsymbol{r}}$ takes a similar form to $M_{\boldsymbol{n},\boldsymbol{r}}$ in (3.3), so the problem of reducing $R_*^{(k)}(\boldsymbol{v})$ to 1 with minimum vaccine coverage can be solved using the method described in Section 3.1. However, it is necessary to *simultaneously* make $R_*^{(k)}(\boldsymbol{v})\leqslant 1$ $(k\in\mathscr{J})$. 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 4.2.1 it is shown that successive vaccinations in the same household can lead to *increasing* reductions in $R_*^{\max}(\boldsymbol{v})$, so the optimal vaccination scheme need not take the equalising form. In Section 4.2.2 it is shown that optimal allocations need not be sequential.

#### 4.2.1. Example illustrating increasing reductions in $R_*$

Suppose that the vaccine is perfect, i.e. $\boldsymbol{\epsilon} = \mathbf{1}$, where $\mathbf{1}$ denotes the row vector of $J$ ones. Then the all-or-nothing and leaky formulations coincide and $\mu^V_{\boldsymbol{n},\boldsymbol{r},i,k}(\Lambda^{\mathrm{L}}) = \frac{n_i - r_i}{n_i}\mu_{\boldsymbol{n}-\boldsymbol{r},i,k}(\Lambda^{\mathrm{L}})$. It follows from (4.7) that

$$M^{(k)}_{\boldsymbol{n},\boldsymbol{r}} = M^{(k)}(\boldsymbol{n}-\boldsymbol{r}) \quad (\boldsymbol{n}\in\mathscr{N}, \mathbf{0}\leqslant\boldsymbol{r}\leqslant\boldsymbol{n}), \tag{4.8}$$

where

$$M^{(k)}(\boldsymbol{l}) = \sum_{i\in\mathscr{J}}(-\log\pi_i) l_i \mu_{\boldsymbol{l},i,k}(\Lambda^{\mathrm{L}}) \quad (\boldsymbol{l} \geqslant \mathbf{0}). \tag{4.9}$$

Suppose that $J = 2$, that local mixing is uniform, so $\lambda^{\mathrm{L}}_{ij} = \lambda^{\mathrm{L}}$ $(i, j \in \mathscr{J})$, 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. Recall the definition of $\mu_n(\lambda^{\mathrm{L}})$ given in Section 3.2.

**Lemma 4.1.** *Under the above conditions, for* $n_1 = 1, 2, \ldots$ *and* $n_2 = 0, 1, \ldots$,

$$\mu_{(n_1,n_2),1,1}(\Lambda^{\mathrm{L}}) = \mu_{(n_2,n_1),2,2}(\Lambda^{\mathrm{L}}) = \frac{n_2 + (n_1-1)\mu_{n_1+n_2}(\lambda^{\mathrm{L}})}{n_1+n_2-1} \tag{4.10}$$

*and*

$$\mu_{(n_1,n_2),1,2}(\Lambda^{\mathrm{L}}) = \mu_{(n_2,n_1),2,1}(\Lambda^{\mathrm{L}}) = \frac{n_2(\mu_{n_1+n_2}(\lambda^{\mathrm{L}})-1)}{n_1+n_2-1}. \tag{4.11}$$

**Proof.** For $n = 1, 2, \ldots$, let $p_n(\lambda^{\mathrm{L}})$ 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 $p_n(\lambda^{\mathrm{L}}) = (\mu_n(\lambda^{\mathrm{L}})-1)/(n-1)$ $(n = 1, 2, \ldots)$. Eqs. (4.10) and (4.11) follow on noting that $\mu_{(n_1,n_2),1,1}(\Lambda^{\mathrm{L}}) = 1 + (n_1-1)p_{n_1+n_2}(\lambda^{\mathrm{L}})$ and $\mu_{(n_1,n_2),1,2}(\Lambda^{\mathrm{L}}) = n_2 p_{n_1+n_2}(\Lambda^{\mathrm{L}})$. Finally, $\mu_{(n_1,n_2),1,1}(\Lambda^{\mathrm{L}}) = \mu_{(n_2,n_1),2,2}(\Lambda^{\mathrm{L}})$ and $\mu_{(n_1,n_2),1,2}(\Lambda^{\mathrm{L}}) = \mu_{(n_2,n_1),2,1}(\Lambda^{\mathrm{L}})$ by symmetry. □

Suppose that the population is comprised entirely of households with category (3,1), so $N_1 = 3N_2$. Then it follows from (4.9) and Lemma 4.1 that, for $n = 0, 1, 2, 3$,

$$\begin{aligned} M^{(1)}(n,1) &= (-\log\pi_1) n \mu_{(n,1),1,1}(\Lambda^{\mathrm{L}}) + (-\log\pi_2)\mu_{(n,1),2,1}(\Lambda^{\mathrm{L}}) \\ &= (-\log\pi_1)(1 + (n-1)\mu_{n+1}(\lambda^{\mathrm{L}})) + (-\log\pi_2)(\mu_{n+1}(\Lambda^{\mathrm{L}}) - 1) \end{aligned} \tag{4.12}$$

and

$$\begin{aligned} M^{(2)}(n,1) &= (-\log\pi_1) n \mu_{(n,1),1,2}(\Lambda^{\mathrm{L}}) + (-\log\pi_2)\mu_{(n,1),2,2}(\Lambda^{\mathrm{L}}) \\ &= (-\log\pi_1)(\mu_{n+1}(\lambda^{\mathrm{L}}) - 1) + (-\log\pi_2)\mu_1(\lambda^{\mathrm{L}}), \end{aligned} \tag{4.13}$$

where $M^{(k)}(n,1) = M^{(k)}((n,1))$ $(k = 1, 2)$.

Suppose further that the infectious period is constant and equal to the unit of time, and let $q = \exp(-\lambda^{\mathrm{L}})$. Then 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 $p = 1 - q$. It follows, for example from Bailey [19, p. 245], that

$$\mu_1 = 1, \quad \mu_2 = 2 - q, \quad \mu_3 = 3 - 4q^2 + 2q^3, \quad \mu_4 = 4 - 6q^3 - 6q^4 + 15q^5 - 6q^6, \tag{4.14}$$

so

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

where $\mu_n = \mu_n(\lambda^{\mathrm{L}})$. 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 (4.13), if $\lambda^{\mathrm{L}} > \lambda^{\mathrm{L}}_0 = -\log q_0$ then

$M^{(2)}(3,1) - M^{(2)}(2,1) < M^{(2)}(2,1) - M^{(2)}(1,1)$. Further, $\frac{1}{3}(M^{(2)}(3,1) - M^{(2)}(0,1)) < \frac{1}{2}(M^{(2)}(3,1) - M^{(2)}(1,1))$ if and only if $\mu_4 > 3\mu_2 - 2$. Using (4.14), for $q \in (0,1)$,

$$\mu_4 - 3\mu_2 + 2 = 3q(1 - 2q^2 - 2q^3 + 5q^4 - 2q^5) = 3q(1-q)^2(1 + q^2 + 2q(1-q^2)) > 0.$$

Suppose that $\lambda^{\mathrm{L}} > \lambda_0^{\mathrm{L}}$ and that 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 $R_*^{\max}(\boldsymbol{\nu})$, to vaccinate two individuals in the same household rather than two individuals in distinct households. (Note that $R_*^{(k)} > 1$ $(k = 1,2)$, since the estimation method described in Section 4.1 is predicated on the occurrence of a global epidemic.) It is now shown that $R_*^{(2)} > R_*^{(1)}$ and $\lambda^{\mathrm{L}} > \lambda_0^{\mathrm{L}}$ can hold simultaneously.

To do this it is convenient to use the concept of a (local) *susceptibility set* [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 $\mathscr{H} = \{1, 2, \ldots, |\boldsymbol{n}|\}$ and consider the random directed graph, $G$ say, on $\mathscr{H}$, in which for any ordered pair $(i,j)$ of distinct individuals in $\mathscr{H}$ there is a directed arc from $i$ to $j$ if and only if $i$, if infected, contacts $j$ locally during its infectious period. For $i, j \in \mathscr{H}$, 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 $i \in \mathscr{H}$, the susceptibility set of individual $i$ is defined as $\mathscr{S}_i^{\boldsymbol{n}} = \{j \in \mathscr{H} : j \rightsquigarrow i\}$. 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 $\mathscr{S}_i^{\boldsymbol{n}}$ is infected globally. For $\boldsymbol{n} \in \mathscr{N}$ and $i, j \in \mathscr{J}$, 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

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

and arguing as in the derivation of (4.2) yields

$$z_i = 1 - \sum_{\boldsymbol{n} \in \mathscr{N}} \alpha_i(\boldsymbol{n}) E\left[\prod_{j \in \mathscr{J}} \pi_j^{S_{ij}^{\boldsymbol{n}}}\right] \quad (i \in \mathscr{J}); \tag{4.15}$$

see Ball and Lyne [6], Section 5.2, where it is explained that (4.2) and (4.15) yield the same equation for $\boldsymbol{z}$.

**Lemma 4.2.** *For a two-class 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 $S_1$ and $S_2$ have the same distribution (written $S_1 \stackrel{D}{=} S_2$), since local mixing is uniform and $T_I^{(1)} \stackrel{D}{=} T_I^{(2)}$. By (4.15), the probability that a typical class-$i$ individual avoids infection is given by

$$1 - z_i = E\{E[\pi_1^{S_{i1}}\pi_2^{S_{i2}}|S_i]\} = E\{E[\pi_1^{S_{i1}}\pi_2^{S_i - S_{i1}}|S_i]\} \quad (i = 1, 2), \tag{4.16}$$

so $z_1 = z_2$ if $\pi_1 = \pi_2$. Suppose that $\pi_1 < \pi_2$. Then, for $s = 1, 2, \ldots, n_1 + n_2$ and $0 \leqslant s_{21} \leqslant s_{11} \leqslant s$, $\pi_1^{s_{11}}\pi_2^{s-s_{11}} \leqslant \pi_1^{s_{21}}\pi_2^{s-s_{21}}$, with strict inequality if $s_{21} > s_{11}$. Thus, if $(S_{11}|S_1 = s) \overset{\text{st}}{>} (S_{21}|S_2 = s)$ $(s = 1, 2, \ldots, n_1 + n_2)$, where $\overset{\text{st}}{>}$ denotes stochastically greater than, it follows using (4.16) that $z_2 < z_1$. A similar argument would also show that $z_2 > z_1$ if $\pi_1 > \pi_2$.

To complete the proof we show that $(S_{11}|S_1 = s) \overset{\text{st}}{>} (S_{21}|S_2 = s)$ $(s = 1, 2, \ldots, n_1 + n_2)$. For $n, m \geqslant 0$ and $0 \leqslant s \leqslant n + m$, let $X^s_{n,m}$ 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,

$$(S_{11}|S_1 = s) \overset{D}{=} \frac{s-1}{n_1+n_2-1}(X^{s-2}_{n_1-1,n_2-1} + 1) + \frac{n_1+n_2-s}{n_1+n_2-1}(X^{s-1}_{n_1-1,n_2-1} + 1)$$

and

$$(S_{21}|S_2 = s) \overset{D}{=} \frac{s-1}{n_1+n_2-1}(X^{s-2}_{n_1-1,n_2-1} + 1) + \frac{n_1+n_2-s}{n_1+n_2-1}(X^{s-1}_{n_1-1,n_2-1}).$$

Hence, $(S_{11}|S_1 = s) \overset{\text{st}}{>} (S_{21}|S_2 = s)$, as required. □

In 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 (4.15) that

$$z_1 = 1 - P(S=1)\pi_1 - P(S=2)\left(\frac{1}{3}\pi_1\pi_2 + \frac{2}{3}\pi_1^2\right) - P(S=3)\left(\frac{2}{3}\pi_1^2\pi_2 + \frac{1}{3}\pi_1^3\right) - P(S=4)\pi_1^3\pi_2 \tag{4.17}$$

and

$$z_2 = 1 - P(S=1)\pi_2 - P(S=2)\pi_1\pi_2 - P(S=3)\pi_1^2\pi_2 - P(S=4)\pi_1^3\pi_2. \tag{4.18}$$

Now setting $\boldsymbol{\nu} = \mathbf{0}$ in (4.6), using (4.8), (4.12) and (4.13), and noting that $N_1 = 3m$ and $N_2 = m$, yields

$$R_*^{(1)} = \frac{1}{N_1 z_1} m M^{(1)}(3,1) = \frac{1}{3z_1}\{(-\log\pi_1)(1 + 2\mu_4) + (-\log\pi_2)(\mu_4 - 1)\} \tag{4.19}$$

and

$$R_*^{(2)} = \frac{1}{N_2 z_2} m M^{(2)}(3,1) = \frac{1}{z_2}\{(-\log\pi_1)(\mu_4 - 1) + (-\log\pi_2)(\mu_1)\}, \tag{4.20}$$

where the explicit dependence of $\mu_n$ on $\lambda^{\mathrm{L}}$ has been suppressed. Suppose that $\pi_1 < \pi_2$. Then, by Lemma 4.2, $z_2 < z_1$ and, since $\mu_1 = 1$ and $\mu_4 \leqslant 4$, $\frac{\mu_1}{z_2} > \frac{\mu_4 - 1}{3z_1}$. 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 $\mathscr{C}_i = \{j \in \mathscr{H} : i \rightsquigarrow j\}$, 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 $P(S=1) = q^3$, $P(S=2) = 3pq^4$, $P(S=3) = 3p^2q^3(1+2q)$ and $P(S=4) = p^3(1+3q+6q^2+6q^3)$, see, for example, Bailey [19, p. 245]. It then follows, using (4.14), (4.17) and (4.18), that

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

Thus, 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 $\lambda^{\mathrm{L}} > \lambda_1^{\mathrm{L}} = -\log q_1$, it follows from (4.19) and (4.20) that $R_*^{(2)} > R_*^{(1)}$.

Finally, note from (4.6), (4.12) and (4.13) that the reductions in $R_*^{(1)}$ and $R_*^{(2)}$ from vaccinating two class-1 individuals in the same household are

$$G^{(1)} = \frac{1}{N_1 z_1}\{M^{(1)}(3,1) - M^{(1)}(1,1)\} = \frac{1}{3N_2 z_1}\{(-\log\pi_1)2\mu_4 + (-\log\pi_2)(\mu_4-\mu_2)\} \tag{4.21}$$

and

$$G^{(2)} = \frac{1}{N_2 z_2}\{M^{(2)}(3,1) - M^{(2)}(1,1)\} = \frac{1}{N_2 z_2}(-\log\pi_1)(\mu_4-\mu_2), \tag{4.22}$$

respectively. Thus, $G^{(1)} > G^{(2)}$, if $\mu_2 > \mu_4(1-(2z_2)/(3z_1))$, which is clearly satisfied if $\lambda^{\mathrm{L}}$ is sufficiently large and $\pi_1$ sufficiently small (since $z_1$ and $z_2$ are then both close to 1), say $\pi_1 < \pi_1'$ and $\lambda^{\mathrm{L}} > \lambda_2^{\mathrm{L}}$. Hence, provided $\pi_1 < \pi_1'$, $\pi_2 - \pi_1 > \frac{2}{3}$ and $\lambda^{\mathrm{L}} > \lambda_3^{\mathrm{L}} = \max\{\lambda_0^{\mathrm{L}}, \lambda_1^{\mathrm{L}}, \lambda_2^{\mathrm{L}}\}$, $R_*^{(2)} > R_*^{(1)}$, $M^{(2)}(3,1) < M^{(2)}(2,1) < M^{(2)}(2,1) - M^{(2)}(1,1)$ 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 $R_*^{(1)}(\boldsymbol{\nu}) < R_*^{(2)}(\boldsymbol{\nu})$. Hence, if a fraction $c$ of class-1 individuals are to be vaccinated, if $c \leqslant \frac{2}{3}$ 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 $c > \frac{2}{3}$ it is best to vaccinate 2 individuals in a proportion $3(1-c)$ of households and 3 individuals in the remaining households. 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 $\lambda^{\mathrm{L}} > \lambda_3^{\mathrm{L}}$, then using (4.2) to determine $\boldsymbol{z}$ and finally choosing $\Lambda^{\mathrm{G}}$ so that (4.1) is satisfied.

An intuitive explanation for the form of the optimal vaccination scheme runs as follows. Since the bound $R_*^{(2)}$ is achieved when 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 $R_*^{(2)}$ 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, $\mu_n$ $(n = 2, 3, \ldots)$ 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 $R_*^{\max}(\boldsymbol{\nu})$ is a continuous function of $(\Lambda^{\mathrm{L}}, \boldsymbol{\pi}, \boldsymbol{\epsilon})$, the example can be extended to allow for non-uniform local mixing, imperfect vaccines and vaccination of class-2 individuals, with the same conclusions holding provided that elements of $\Lambda^{\mathrm{L}}$ are sufficiently large and $(\epsilon_1, \epsilon_2)$ is sufficiently close to (1,0).

*4.2.2. 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 $\lambda^{\mathrm{L}}_{ij} = \lambda^{\mathrm{L}}(i, j \in \mathscr{J})$, 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 $N_1 = 2N_2$. It follows from Lemma 4.1 and (4.9), 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 |
| $l_1$ | | |
| 0 | 0 | 0 |
| 1 | $-\log\pi_1$ | $-\log\pi_1 - (1-q)\log\pi_2$ |
| 2 | $-2(\log\pi_1)(2-q)$ | $-\log\pi_1(\mu_3(\lambda^{\mathrm{L}})+1) - \log\pi_2(\mu_3(\lambda^{\mathrm{L}})-1)$ |
| $M^{(2)}(l_1, l_2)$ | | |
| $l_1$ | | |
| 0 | 0 | $-\log\pi_2$ |
| 1 | 0 | $-(1-q)\log\pi_1 - \log\pi_2$ |
| 2 | 0 | $-\log\pi_1(\mu_3(\lambda^{\mathrm{L}})-1) - \log\pi_2$ |

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 $((3-i-j),\ M^{(1)}(i,j))$ $(i = 0,1,2, j = 0,1)$ 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 $\pi_1$ and $\pi_2$ 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 $\lambda^{\mathrm{L}}$.

Next, note that

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

using (4.14). Suppose that $\pi_1^3 > \pi_2$. If $q = 0$, then the left-hand side of the above inequality equals $-\log \pi_2$ while the right-hand side equals $-2\log \pi_1$, so the inequality 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 $\lambda^{\mathrm{L}} > -\log q_2$.

The implication of the above is that, if $\pi_1^3 > \pi_2$ and $\lambda^{\mathrm{L}} > -\log q_2$, 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.

## 5. Numerical examples

The first example is similar to that used in Section 4.2.2. Here the parameters are assumed to be known and the global infection rates take the proportionate mixing form, i.e. $\lambda_{ij}^{\mathrm{G}} = \eta_i^{\mathrm{G}} \kappa_j^{\mathrm{G}}$. 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 $\lambda_{ij}^{L} = \lambda$ $(i, j \in \mathscr{J})$, 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 $\eta_2^{\mathrm{G}} = 0$. The other global infection rate parameters are given by $\eta_1^{\mathrm{G}} = \lambda$, $\kappa_1^{\mathrm{G}} = 0.6$ and $\kappa_2^{\mathrm{G}} = 2.4$.

Thus both the local and global infection rates are scaled with a common parameter $\lambda$. The optimal vaccination scheme (as a function of $\lambda$) to reduce $R_*$ to 1 is illustrated in Fig. 2. For $\lambda = 0.38$, $R_* \simeq 1$, so that for $\lambda < 0.38$ no vaccination is required. For $0.38 < \lambda < 1.02$, the optimal scheme vaccinates the one class-2 individual in some households and no-one in the other households. For $\lambda > 1.02$, the optimal scheme vaccinates the one class-2 individual in some households and both class-1 individuals in the other households. As $\lambda \to \infty$, the proportion of households with both class-1 individuals vaccinated increases to 1. (For this example, vaccinating all the class-1 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-2 individuals (optimal coverage = 1/3) whereas for $\lambda$ large, the optimal scheme is to vaccinate all the class-1 individuals and none of the class-2 individuals (optimal coverage = 2/3).

The intuition for the form of the optimal schemes is as follows. Class-2 individuals are 4 times more susceptible than class-1 individuals, while local mixing is homogeneous (with a high rate of infection, $\lambda$). So, despite class-2 individuals not contributing to global infection, the best way to

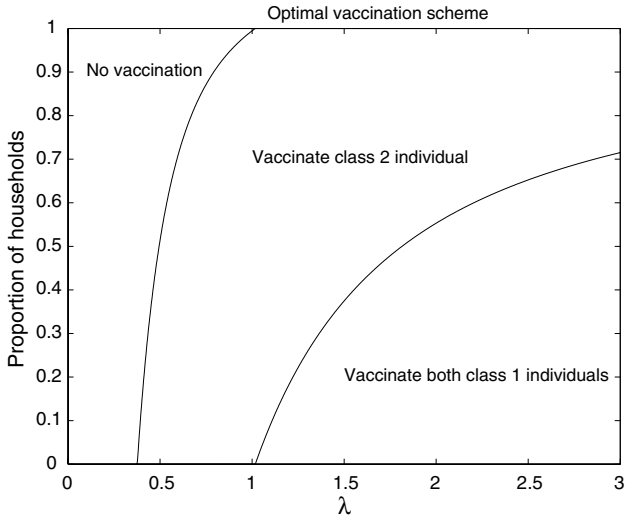


Fig. 2. Optimal vaccination scheme as a function of $\lambda$, showing the proportion of households using each of the three strategies: no vaccination; vaccinate the one class two individual and vaccinate the two class one individuals. To obtain the optimal scheme for a given $\lambda$, read off the 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 $\lambda$).

start reducing global infection emanating from a household is to vaccinate the class-2 individual, conferring more protection on the class-1 individuals than vaccinating one of them. However, once $\lambda$ 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-1 individuals, because that entirely eliminates global infection emanating from the household. So the optimal scheme now vaccinates fewer class-2 individuals, and more class-1 individuals.

The second example illustrates the superiority of an all-or-nothing vaccine over a leaky vaccine with the same efficacy (shown in Section 2.3.2). Consider a single type population, with parameters $\lambda^{\mathrm{G}} = 0.25$ and $\lambda^{\mathrm{L}} = 1$ and, as in Addy et al. [18], 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 $\lambda^{\mathrm{G}}$ is a plausible choice for the global infection rate, whereas the value of $\lambda^{\mathrm{L}}$ 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. [18]. 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). Fig. 3 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

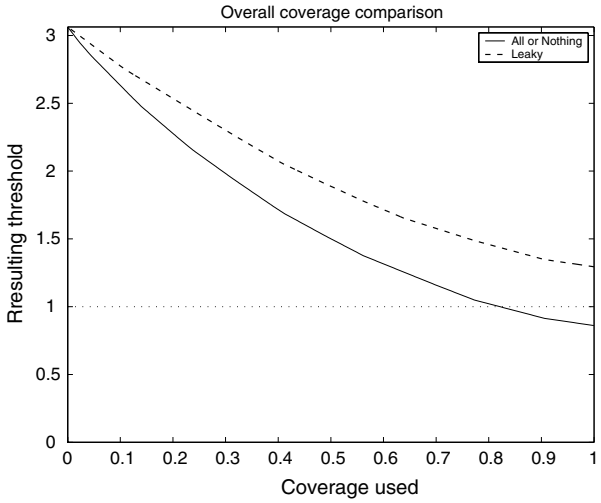


Fig. 3. Optimal reduction of $R_*$ as a function of coverage, comparing all-or-nothing (solid line) and leaky (dashed line) vaccines. The dotted line marks $R_* = 1$. In both cases the vaccine efficacy $\epsilon = 0.55$ (see text for further details).

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), $c_v^{\mathrm{AoN}} = 0.60$ and $c_v^{\mathrm{Le}} = 0.80$.

## 6. Discussion

This paper considers optimal vaccination schemes for an epidemic model allowing for observable (and hence classifiable) individual heterogeneities as well as mixing heterogeneities caused by the presence 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, capture 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.

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 $R_*(\boldsymbol{\nu})$ for any suggested vaccination program $\boldsymbol{\nu}$, 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 specifies 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.

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-class 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 $\epsilon$ 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. 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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## Appendix A

As in Section 3, suppose first that all households have category $\boldsymbol{n}$. Let $\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_p$ denote the different ways of vaccinating a single household and suppose that the null vaccination scheme $\boldsymbol{r} = \boldsymbol{0}$ is given by $\boldsymbol{r}_1$. 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 $\mathscr{I}'_k = \{i : \boldsymbol{r}_i \not\leqslant \boldsymbol{r}_{i_j}$ and $a(i_j, i) > 0, j = 0, 1, \ldots, k-1\}$, $\mathscr{I}_k = \operatorname{argmax}_{i \in \mathscr{I}'_k}\{b(i_{k-1}, i)\}$ and choose $i_k \in \operatorname{argmax}_{i \in \mathscr{I}'_k}\{a(i_{k-1}, i)\}$. 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, $0 = c_0 < c_1 < \cdots < c_q \leqslant 1$. 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 $\frac{|\boldsymbol{r}_{i_k}| - c|\boldsymbol{n}|}{|\boldsymbol{r}_{i_k}| - |\boldsymbol{r}_{i_{k-1}}|}$ households according to $\boldsymbol{r}_{i_k}$ and the other households according to $\boldsymbol{r}_{i_{k-1}}$, where $k = \min\{l : c_l > c\}$.

Consider now the general case when not all the households in the population have the same category. For $\boldsymbol{n} \in \mathscr{N}$, 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

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

Let $(\boldsymbol{n}^{(1)}, \boldsymbol{r}^{(1)}), (\boldsymbol{n}^{(2)}, \boldsymbol{r}^{(2)}), \ldots, (\boldsymbol{n}^{(q*)}, \boldsymbol{r}^{(q*)})$ be an enumeration of $\mathscr{A}$ 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 $c$, $R_*(\boldsymbol{v})$ is minimised 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 (typically with a mixed scheme) as soon as the vaccine coverage reaches $c$. The problem of determining $\boldsymbol{v}_{\text{opt}}$, defined by (3.2), can be solved in a similar fashion, except the process is stopped as soon as $R_*(\boldsymbol{v})$ reaches one.

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