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Estimating vaccine efficacy from small outbreaks

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SUMMARY

Let C_V and C_0 denote the number of cases among vaccinated and unvaccinated individuals, respectively, and let v be the proportion of individuals vaccinated. The quantity $\hat{e} = 1 - (1-v)C_V/(vC_0) = 1 - (\text{relative attack rate})$ is the most used estimator of the effectiveness of a vaccine to protect against infection. For a wide class of vaccine responses, a family of transmission models and three types of community settings, this paper investigates what $\hat{e}$ actually estimates. It does so under the assumption that the community is large and the vaccination coverage is adequate to prevent major outbreaks of the infectious disease, so that only data on minor outbreaks are available. For a community of homogeneous individuals who mix uniformly, it is found that $\hat{e}$ estimates a quantity with the interpretation of

$1 - (\text{mean susceptibility, per contact, of vaccinees relative to unvaccinated individuals})$.

We provide a standard error for $\hat{e}$ in this setting. For a community with some heterogeneity $\hat{e}$ can be a very misleading estimator of the effectiveness of the vaccine. When individuals have inherent differences, $\hat{e}$ estimates a quantity that depends also on the inherent susceptibilities of different types of individual and on the vaccination coverage for different types. For a community of households, $\hat{e}$ estimates a quantity that depends on the rate of transmission within households and on the reduction in infectivity induced by the vaccine. In communities that are structured, into households or age-groups, it is possible that $\hat{e}$ estimates a value that is negative even when the vaccine reduces both susceptibility and infectivity.

Some key words: Epidemic; Estimation; Infectivity; Measles outbreak data; Multitype branching process; Susceptibility; Vaccine efficacy.

1. INTRODUCTION

An ideal vaccine induces complete protection against infection in every vaccinee. In practice, some vaccinated individuals become cases, so this ideal is not achieved. It is therefore important to have measures of vaccine efficacy and methods for estimating these from data, in a variety of settings. Here we consider such estimation from data on outbreaks in a community having a vaccination coverage that is adequate to prevent major

epidemics. For example, countries such as Finland and some Pan-American countries have achieved vaccination coverages adequate to eliminate measles. Current measles incidence in such countries is due to minor outbreaks arising from importation of infected individuals and the subsequent chains of transmission. De Serres et al. (2000) propose the use of such data for monitoring the process of elimination for the disease.

It may seem to be of minor importance to estimate the effectiveness of a vaccine when it is effective enough to achieve the state of elimination. However, it is thought that immunity may wane over time unless it is occasionally boosted by exposure to disease, and it is therefore quite important to monitor the effectiveness of a vaccine when the opportunity for exposure to disease has been reduced dramatically.

We introduce our assumptions about the transmission of infection for a community of homogeneous susceptible individuals who mix uniformly in § 2. In § 3 we describe a model for the way individuals respond to vaccination, in terms of how susceptible to infection vaccinated individuals are and how infectious they are, should they become infected. Some measures of vaccine efficacy are given. The rest of the paper investigates what

$$\hat{e} = 1 - \frac{C_V/v}{C_0/(1-v)}, \tag{1·1}$$

which is used very widely in epidemiological studies of 'vaccine efficacy', actually estimates in our model formulations. Here v is the known vaccination coverage, C_V is the observed number of vaccinated cases and C_0 is the observed number of unvaccinated cases. In § 4 we look at the estimator $\hat{e}$ for a community of homogeneous individuals who mix uniformly. In the derivation of its standard error we obtain expressions, interesting in their own right, for the variance-covariance matrix of the total progeny of a multitype Galton–Watson branching process. Section 5 proposes a way of combining data from a number of minor outbreaks, and the method is applied to measles outbreak data from Australia. In § 6 we show that, in a heterogeneous community, $\hat{e}$ estimates a quantity that depends on the relative susceptibility, both inherent and vaccine-induced, of different types of individual and on the vaccination coverages of different types. In § 7 we show that, in a community of households, $\hat{e}$ estimates a quantity that depends on the reduction in susceptibility induced by the vaccine, but also on the rate of transmission within households and the reduction in infectivity induced by the vaccine.

The importance of the results lies in showing that in this setting, with homogeneous individuals, the widely-used $\hat{e}$ gives a useful estimator of vaccine efficacy for a wide class of vaccine responses. This does not happen generally. For example, Smith et al. (1984) point out that $\hat{e}$ depends on the vaccine response when each individual is subjected to a constant force of infection, while Becker & Utev (2002) show that $\hat{e}$ generally underestimates e, given by equation (3·2), from data on major outbreaks. It is also important to point out that there are many real-world settings where $\hat{e}$ can seriously mislead us, and to quantify this bias.

Throughout the paper we consider a closed community of n individuals, where n is assumed to be large.

2. TRANSMISSION OF INFECTION

We begin by outlining the assumptions made about transmission of infection, with reference to a community of homogeneous individuals who mix uniformly. Assume, for the moment, that there is no vaccine-induced immunity in the community. Individuals

may be susceptible to infection, currently infectious or removed. Removed individuals are those who acquired immunity after recovering from infection. We define an infectious contact by an infected individual as one that is sufficiently close for the infection to be transmitted if the contacted person is a susceptible individual. Following infection, an infected individual has infectious contacts with other individuals at a rate depending on the stage of the infection within the infected individual. We describe this rate by an infectiousness function $\beta(x)$, where x is the time since infection; see Becker (1989, § 3·1). The infection has a latency period if $\beta(x) = 0$ for small x. For larger x the infectiousness function typically rises to a peak after which it declines to zero, at which time the individual becomes a removal. In general, $\beta(x)$ is any individual-specific nonnegative stochastic process defined for positive x. Infectiousness functions corresponding to different individuals are assumed to be mutually independent. It is known, see for example Ball & Clancy (1993), that the final outcome of susceptible-infective-removed epidemic models depends on $\beta(x)$ only through the distribution of $B_0 = \int_0^\infty \beta(x)dx$, the total area under the infectiousness function. In particular, a latency period does not affect the distribution of the final size of the epidemic. A common choice for $\beta(x)$ is

$$\beta(x) = \beta \quad (0 \leqslant x \leqslant T),$$

where β is a constant. Setting $T \equiv 1$ gives the Reed–Frost model in continuous time, for which $B_0 \equiv \beta$, while $T \sim \mathrm{Ex}(1)$ gives the general stochastic epidemic, for which $B_0 \sim \mathrm{Ex}(1/\beta)$; see for example Andersson & Britton (2000, p. 16).

When the infected individual mixes uniformly with other community members each individual is equally likely to be contacted, so the contact rate exerted on a specific individual x time units after infection is $\beta(x)/n$. Contacts with individuals who are already infected or removed have no effect.

3. Response to vaccination

The response to vaccination consists of a change in the way an individual's immune system responds to invasion by, and internal development of, the infection agent. Our concern lies with the way this is reflected by a change in the susceptibility to infection and a change in the individual's infectiousness function. We first describe the effect of vaccination on susceptibility. At time t, let the probability that a susceptible individual makes an infectious contact in the small time increment $[t, t + dt)$ be given by $\lambda_t dt$. Here λ_t is the sum of the values of all infectiousness functions at time t, divided by n. The probability that the individual is infected, in this time increment, is $\lambda_t dt$ if he is unvaccinated and $A\lambda_t dt$ if he is vaccinated. The fact that individuals respond differently to vaccination is accommodated by taking A to be a random variable.

It may be that an individual in whom vaccination induces an immunological response acquires a milder form of the illness, if ever infected, making them less infectious. To quantify a possible reduction in the potential to infect others let B_0 denote the total area under the infectiousness function when the infected individual is unvaccinated and let $B_V = BB_0$ when the infected individual is vaccinated. The relative infection potential B lies between zero and unity when vaccination reduces infectivity. In our formulation B is taken to be random, to allow for variation in vaccine response, and for simplicity is assumed to be independent of B_0. A value of $B < 1$ arises when the duration of the infectious period or the level of infectiousness achieved at different times, or both, are reduced by vaccination.

The effect of vaccination on susceptibility and infectivity is described by the joint probability distribution

$$\text{pr}(A = a_i,\ B = b_i) = p_i \quad (i = 1, 2, \ldots, k). \tag{3·1}$$

This discrete formulation can provide a good approximation to any realistic distribution by suitable choices of k, a_i, b_i and p_i. It is likely that A and B are correlated in practice.

There are several different ways of measuring the efficacy of a vaccine; see Halloran et al. (1999) for a survey. For example, $e_S = 1 - E(A)$ measures the reduction in susceptibility, while $e_{SI} = 1 - E(AB)$ measures the combined effect of reduced susceptibility and reduced infectivity. The measure of 'vaccine efficacy' given by

$$e = 1 - \frac{\text{pr}(\text{a vaccinated individual becomes infected})}{\text{pr}(\text{an unvaccinated individual becomes infected})} = 1 - \frac{E(C_V)/v}{E(C_0)/(1-v)} \tag{3·2}$$

is widely used in epidemiological studies; see Orenstein et al. (1985, 1988). A disadvantage of the measure e is that it is not clear how it relates to the parameters $\{a_i, b_i, p_i\}$ which describe the effect of vaccination on disease transmission. The popularity of e stems from its simple interpretation and the fact that it has an obvious estimator, namely

$$\hat{e} = 1 - \frac{\text{proportion of cases among vaccinated individuals}}{\text{proportion of cases among unvaccinated individuals}} = 1 - \frac{C_V/v}{C_0/(1-v)}.$$

Below we express e in terms of model parameters for three community settings with the aim of determining what $\hat{e}$ estimates in those settings.

4. COMMUNITY OF HOMOGENEOUS INDIVIDUALS

Consider a large population of homogeneous individuals who mix uniformly and who are all susceptible to a certain infectious disease, with a transmission process as described in § 2. The expected number of infectious contacts an initial infected individual has during the course of his infection is $R_0 = E(B_0)$, where B_0 is defined in § 2. The reproduction number of infectives is less than R_0, the basic reproduction number, when some community members have acquired immunity from previous exposure to the infection or by vaccination.

Now suppose that a fraction v of individuals are vaccinated and that their responses, in terms of susceptibility and infectivity, vary independently in the manner described in § 3. Individuals are then of type 0, 1, 2, . . . , k, where label 0 refers to unvaccinated individuals and 1, 2, . . . , k refer to vaccinated individuals with different responses to vaccination. A minor outbreak in such a population can be described by a multitype epidemic model, where type is specified by vaccination status and vaccine response. Type-i individuals have susceptibility a_i and infectivity b_i, with $a_0 = b_0 = 1$ by definition. Then π_i, the proportion of community members of type i, is given by

$$\pi_0 = 1 - v, \quad \pi_i = vp_i \quad (i = 1, 2, \ldots, k).$$

For this setting, the reproduction number after vaccination is given by

$$R_V = R_0 \sum_{i=0}^{k} a_i b_i \pi_i = R_0\{1 - v + vE(AB)\}; \tag{4·1}$$

see for example Becker & Marschner (1990), Becker & Starczak (1998) and below. Assume that the vaccination coverage is high enough to prevent epidemics; that is, assume that $R_V \leqslant 1$. Then the size of an outbreak initiated by a small number of introductory cases can be approximated by the total progeny in a branching process, with infections interpreted as births; see Ball & Clancy (1993). A heuristic argument for this approximation is that, when few individuals are infected, it is unlikely that a contact occurs with a previously infected individual. As a consequence, each infectious individual infects new individuals essentially independently, and whenever individuals 'give birth' to new individuals independently we are in the branching process paradigm. Let $C_i^{(n)}$ denote the eventual number of type-i individuals who are infected in a community of size n ($i = 0, \ldots, k$). We approximate the distribution of these random variables by the corresponding random variables of a multitype branching process, using C_i to denote the total progeny of type i. Below we drop the index n and interchangeably mean the epidemic and the approximating branching process, the approximation relying on n being large. We are interested in the distribution of

$$C = \begin{pmatrix} C_0 \\ C_1 \\ \vdots \\ C_k \end{pmatrix} = Z_0 + Z_1 + Z_2 + \ldots,$$

where Z_t denotes the vector of the various types of infected individual in generation t. Generation 0 consists of the primary cases of the outbreak, generation 1 consists of the individuals infected by the primary cases, and so on.

With the aim of obtaining an expression for the e of (3·2), we derive an expression for the mean of C, namely

$$E(C) = E(Z_0) + E(Z_1) + E(Z_2) + \ldots, \tag{4·2}$$

which gives the expected number eventually infected for each of the various types of individual. To this end we introduce the matrix $M = (m_{ij})$, where m_{ij} is the mean number of type-i individuals infected by a single type-j infective. From the formulation for the transmission and the vaccine response it follows that

$$m_{ij} = R_0 a_i b_j \pi_i.$$

To see this note that the infection rate between an infectious type-j individual and a given susceptible type-i individual is $a_i b_j \beta(x)/n$, x time units after infection of the former. The probability of infection for this pair is therefore

$$1 - E\left\{\exp\left(-a_i b_j \int \beta(x)dx/n\right)\right\} = 1 - E\{\exp(-a_i b_j B_0/n)\} \doteqdot E(a_i b_j B_0/n).$$

Since there are $n\pi_i$ type-i individuals the expected number of infectious contacts with type-i individuals is $a_i b_j E(B_0/n) n\pi_i = m_{ij}$. In matrix form, M satisfies

$$M = R_0 \begin{pmatrix} \pi_0 & b_1\pi_0 & \ldots & b_k\pi_0 \\ a_1\pi_1 & a_1 b_1 \pi_1 & \ldots & a_1 b_k \pi_1 \\ \vdots & \vdots & \ddots & \vdots \\ a_k\pi_k & a_k b_1 \pi_k & \ldots & a_k b_k \pi_k \end{pmatrix} = \begin{pmatrix} \pi_0 R_0 \\ a_1 \pi_1 R_0 \\ \vdots \\ a_k \pi_k R_0 \end{pmatrix} (1 \;\; b_1 \;\; \ldots \;\; b_k) = d_{\mathrm{U}} b^{\mathrm{T}},$$

say. The subscript in vector d_U indicates that this formulation is for a community of uniformly-mixing individuals.

We now return to the expected final size of the epidemic given in equation (4·2). Using $E(Z_{i+1}|Z_i) = MZ_i$, we find $E(Z_i) = M^i E(Z_0)$ and

$$E(C) = (I + M + M^2 + \ldots)E(Z_0) = (I - M)^{-1} E(Z_0), \tag{4·3}$$

where I is the identity matrix and the last equality requires the largest eigenvalue of M to be less than 1. The largest eigenvalue of M is $R_V = R_0 \sum_i a_i b_i \pi_i = a_U^T b$ as noted in equation (4·1). The assumption $R_V < 1$ simply ensures that a major outbreak cannot occur. Furthermore, it is easily verified that the form for M implies that

$$(1 - M)^{-1} = I + \frac{1}{1 - d_U^T b} M = I + \frac{1}{1 - R_V} M.$$

A natural assumption is that the types of the initial infectives depend on their relative susceptibility and their abundance; that is, $E(Z_0) = cd_U$ is plausible, where c is some scalar constant. A little algebra then shows that

$$E(C) = (I - M)^{-1} E(Z_0) = c\left(I + \frac{1}{1 - R_V} d_U b^T\right) d_U = \frac{c}{1 - R_V} d_U. \tag{4·4}$$

We now use this to obtain an expression for the vaccine efficacy e in terms of model parameters. Note that

$$\begin{aligned} e &= 1 - \frac{\text{pr(a vaccinated individual becomes infected)}}{\text{pr(an unvaccinated individual becomes infected)}} \\ &= 1 - \frac{\text{expected proportion of vaccinated individuals who become infected}}{\text{expected proportion of unvaccinated individuals who become infected}} \\ &= 1 - \frac{E(C_1 + \ldots + C_k)/nv}{E(C_0)/n(1 - v)} \\ &= 1 - \frac{E(C_V)/v}{E(C_0)/(1 - v)}, \end{aligned}$$

where $C_V = C_1 + \ldots + C_k$ is the number of vaccinated individuals who become cases. Using

$$E(C_0) = (1, 0, \ldots, 0)E(C), \quad E(C_V) = (0, 1, \ldots, 1)E(C),$$

and equation (4·4) in the expression for e, we obtain

$$e = 1 - \sum_{i=1}^{k} a_i p_i = 1 - E(A) = e_S.$$

We have shown that, if enough individuals are vaccinated in a community of homogeneous individuals, thus ruling out the possibility of a major outbreak, then e is equivalent to e_S, which is a measure of the reduction in susceptibility due to vaccination.

The result is important in two ways. First, it means that in this setting e has a clear and useful interpretation as a measure of the protection vaccination provides against infection, and this is true for a wide range of vaccine responses. In this setting e does not depend on the vaccine's effect on infectivity nor on the distribution of the infection

potential B_0. Secondly, this useful measure of vaccine efficacy is estimated by

$$\hat{e} = 1 - \frac{\text{proportion of cases among vaccinated individuals}}{\text{proportion of cases among unvaccinated individuals}} = 1 - \frac{C_V/v}{C_0/(1-v)},$$

when the vaccination coverage v is known and the eventual numbers of cases among vaccinated and unvaccinated individuals, C_V and C_0, are observed.

In the Appendix an approximate standard error for $\hat{e}$, valid under the assumption that $Z_0 \equiv cd_U$, is shown to be

$$\text{SE}(\hat{e}) = \sqrt{\left\{\frac{(1-\hat{e}(1-v\hat{e})}{C_+}\left(1-\frac{i_0}{C_+}\right)\left(\frac{1-\hat{e}}{1-v}+\frac{1}{v}\right)\right\}},$$

where $C_+ = C_V + C_0 = \sum_{i=0}^{k} C_i$ is the observed total number of cases and i_0 is the initial number of infectious individuals. If i_0 is unknown a conservative estimate is obtained by setting $i_0 = 1$. The derivation of the above standard error requires that $\text{var}(B_0)$ be finite. It is interesting that the standard error, derived using the δ-method, does not depend on $\text{var}(B_0)$ even though the variance-covariance matrix of C does depend on $\text{var}(B_0)$.

5. Combining several different outbreaks

The estimator $\hat{e}$ considered in § 4 is based on one minor outbreak and its variance is inversely proportional to the outbreak size and therefore may not be very small for minor outbreaks. One way of obtaining an estimator with higher precision is to combine data from several separate outbreaks, which we now outline briefly. Separate outbreaks can be distinguished by observing where and when the cases arise, but preferably by means of identifying the virus strain for each case.

Suppose we have data from J different minor outbreaks from a community in which a proportion v are vaccinated with the same type of vaccine. Each such minor outbreak gives an estimate of the vaccine efficacy,

$$\hat{e}_j = 1 - \frac{C_V^{(j)}/v}{C_U^{(j)}/(1-v)} \quad (j = 1, 2, \ldots, J),$$

where $C_V^{(j)}$ and $C_U^{(j)}$ are the numbers of vaccinated and unvaccinated cases in outbreak j. Since these are minor outbreaks it is natural to combine the C_V's and C_U's of different outbreaks by the averages of the different outbreaks. Our combined estimator is hence given by

$$\hat{e}_C = 1 - \frac{\bar{C}_V/v}{\bar{C}_U/(1-v)},$$

where $\bar{C}_V = \sum_{j=1}^{J} C_V^{(j)}/J$ and $\bar{C}_U = \sum_{j=1}^{J} C_U^{(j)}/J$.

A standard error for $\hat{e}_C$ can be derived by the δ-method, using the fact that outbreaks are independent. It turns out to have the form of the standard error for $\hat{e}$ based on only one single outbreak divided by $\sqrt{J}$; that is

$$\text{SE}(\hat{e}_C) = \sqrt{\left\{\frac{(1-\hat{e}_C)(1-v\hat{e}_C)}{J\bar{C}_+}\left(1-\frac{\bar{i}_0}{\bar{C}_+}\right)\left(\frac{1-\hat{e}_C}{1-v}+\frac{1}{v}\right)\right\}},$$

where $\bar{C}_+ = \sum_{j=1}^{J} C_+^{(j)}/J$ is the average total number of cases and $\bar{i}_0 = \sum_{j=1}^{J} i_0^{(j)}/J$ is the average number of initial cases. If unknown, $i_0^{(j)}$, the initial number of infectives in outbreak j, can be set to 1 implying that $\bar{i}_0 = 1$ to provide a conservative standard error.

Example 1. Measles was eliminated in the state of Victoria, Australia, following a statewide campaign of vaccination in 1998. Since then Victoria has practised enhanced surveillance for measles, including identification of the measles strain for each case. Importations of measles infection have led to 33 outbreaks of measles since then, including 14 with secondary infections. The total number of cases was 208, of whom 29 had been vaccinated.

From the Australian Childhood Immunisation Register, serological surveys and past data on immunisation schedules it is estimated that the vaccination coverage in Victoria is 82%, with most susceptible individuals falling into the 15–35 year age group. The vaccination coverage can be assumed constant since 1998, as effective routine vaccination is in place to vaccinate infants at age 12 months. The community is assumed to be homogeneous.

This leads to the estimate $\hat{e}_C = 0{\cdot}964$, with standard error $\text{SE}(\hat{e}_C) = 0{\cdot}0066$. The small standard error indicates that this kind of estimation is of practical value.

6. Community of individuals with inherent differences

Now consider individuals who differ even in the absence of vaccination. In other words, there is an inherent difference between individuals, which may be a biological difference, a difference in social mixing or both. Suppose there are ℓ types of individual, labelled $1, \ldots, \ell$. We refer to them as 'base' types to distinguish them from vaccine-induced differences.

Disease transmission in such a heterogeneous community is described by a multitype epidemic model. In such models the distribution of B_0, the total area under the infectiousness function, may differ between types of individual. The rate of mixing between individuals of different types may also differ; see Andersson & Britton (2000, Ch. 6) for a detailed description of the multitype model.

To introduce our notation, which is analogous to that of § 4, suppose for the moment that no-one has acquired immunity from either vaccination or previous exposure to the infection. Let $m_{rs} = \alpha_r \omega_r \beta_s$ be the mean number of individuals of type r that an initial infective of type s infects, where ω_r is the proportion of individuals of type r. The assumption that each m_{rs} splits into a product of the form

$$(\text{term depending on } r \text{ only}) \times (\text{term depending on } s \text{ only})$$

is known as proportionate, or separable, mixing. In § 4 we saw that our assumption about vaccine response created different types of individual for whom the mean matrix is of the proportionate mixing form. Here we add the proportionate mixing assumption for base types. Strictly speaking, a constraint is needed to make the parameters $\{\alpha_r\}$ and $\{\beta_r\}$ identifiable, but our calculations do not require that this constraint be specified. The proportionate mixing assumption ensures that the basic reproduction number R_0 has the simple form

$$R_0 = \sum_{r=1}^{\ell} \alpha_r \beta_r \omega_r;$$

see Becker & Marschner (1990).

Now suppose that a fraction v_r of base type-r individuals are vaccinated and that individuals may respond differently to vaccination. We introduce k_r possible vaccine responses for individuals of type r. Post-vaccination, we label the types of individual ri, where the first letter indicates the base type and the second letter indicates the type of vaccine response. There are then a total of $\sum_{r=1}^{\ell} k_r$ types of vaccinated individual and ℓ types of unvaccinated individual. The vaccination responses are described by

$$\mathrm{pr}\,(A_r = a_{ri},\, B_r = b_{ri}) = p_{ri} \quad (i = 1,\, 2,\, \ldots,\, k_r,\, r = 1,\, 2,\, \ldots,\, \ell)$$

and $a_{r0} = b_{r0} = 1$, for each r, because 0 refers to unvaccinated individuals. The proportion of type ri individuals is given by

$$\pi_{ri} = \begin{cases} (1 - v_r)\omega_r, & \text{when } i = 0, \\ v_r p_{ri} \omega_r, & \text{otherwise.} \end{cases} \tag{6·1}$$

In this notation, the post-vaccination reproduction number is

$$R_V = \sum_{r=1}^{\ell} \alpha_r \beta_r \left(\sum_{i=0}^{k_r} \pi_{ri} a_{ri} b_{ri} \right), \tag{6·2}$$

which is the multitype analogue of (4·1). Assume that the vaccination coverage is adequate to prevent epidemics, that is $R_V \leqslant 1$. Then the size of an outbreak initiated by a small number of introductory cases can be approximated by the total progeny in a multitype branching process. We are interested in the distribution of the final size vector C, whose typical element gives the eventual number of cases among those of base type r with vaccine response i. As before, $C = Z_0 + Z_1 + Z_2 + \ldots$, where Z_t denotes the vector of the various base and vaccine responses types of infected individuals in generation t. Generation 0 consists of the introductory cases of the outbreak. The individuals infected by direct contact with the introductory cases make up generation 1, and so forth.

The mean $E(C)$ satisfies equation (4·3), but the expressions for the elements of M now reflect inherent heterogeneity as well as heterogeneity due to varying vaccine response. In the present setting the elements of the mean matrix M are given by $m_{ri,sj} = \alpha_r a_{ri} \pi_{ri} \beta_s b_{sj}$.

We may write

$$M = d_{\mathrm{MT}} b_{\mathrm{MT}}^{\mathrm{T}},$$

where the $(\ell + \sum_{r=1}^{\ell} k_r)$-vectors d_{MT} and b_{MT} are given by

$$\begin{aligned} d_{\mathrm{MT}}^{\mathrm{T}} = (&\alpha_1 a_{10} \pi_{10},\, \ldots,\, \alpha_1 a_{1k_1} \pi_{1k_1},\, \alpha_2 a_{20} \pi_{20},\, \ldots,\, \alpha_2 a_{2k_2} \pi_{2k_2},\, \ldots, \\ &\alpha_\ell a_{\ell 0} \pi_{\ell 0},\, \ldots,\, \alpha_\ell a_{\ell k_\ell} \pi_{\ell k_\ell}), \\ b_{\mathrm{MT}}^{\mathrm{T}} = (&\beta_1 b_{10},\, \ldots,\, \beta_1 b_{1k_1},\, \beta_2 b_{20},\, \ldots,\, \beta_2 b_{2k_2},\, \ldots,\, \beta_\ell b_{\ell 0},\, \ldots,\, \beta_\ell b_{\ell k_\ell}). \end{aligned}$$

The subscript in d_{MT} and b_{MT} indicates that this formulation is for multitype individuals. The largest eigenvalue of the matrix $M = d_{\mathrm{MT}} b_{\mathrm{MT}}^{\mathrm{T}}$ is simply $d_{\mathrm{MT}}^{\mathrm{T}} b_{\mathrm{MT}}$ which is exactly R_V, as given in equation (6·2). The assumption $R_V = d_{\mathrm{MT}}^{\mathrm{T}} b_{\mathrm{MT}} < 1$ is equivalent to assuming that the multitype branching process is subcritical.

It is reasonable to assume that $E(Z_0)$ is proportional to d_{MT} thus reflecting both relative susceptibility and relative abundance of the different types. This leads to

$$E(C) = (I - M)^{-1} E(Z_0) = c \left(I + \frac{1}{1 - R_V} d_{\mathrm{MT}} b_{\mathrm{MT}}^{\mathrm{T}} \right) d_{\mathrm{MT}} = \frac{c}{1 - R_V} d_{\mathrm{MT}},$$

provided $R_V = d_{\mathrm{MT}}^{\mathrm{T}} b_{\mathrm{MT}} < 1$.

To obtain $E(C_0)$, the expected number of unvaccinated cases, we sum those elements of $E(C)$ corresponding to unvaccinated individuals of the various types. This gives

$$E(C_0) = \frac{c}{1 - R_V} \sum_{r=1}^{\ell} \alpha_r \pi_{r0}.$$

To obtain $E(C_V)$, the expected number of vaccinated cases, we sum those elements of $E(C)$ corresponding to vaccinated individuals of the various types, which gives

$$E(C_V) = \frac{c}{1 - R_V} \sum_{r=1}^{\ell} \sum_{i=1}^{k_r} \alpha_r a_{ri} \pi_{ri}.$$

Substituting π_{ri}, as given by (6·1), leads to

$$\begin{aligned} e &= 1 - \frac{\text{expected proportion vaccinated individuals to become infected}}{\text{expected proportion unvaccinated individuals to become infected}} \\ &= 1 - \frac{E(C_V)/v}{E(C_0)/(1-v)} \\ &= 1 - \frac{\sum_{r=1}^{\ell} \alpha_r v_r \omega_r E(A_r)/v}{\sum_{r=1}^{\ell} \alpha_r (1 - v_r)\omega_r/(1-v)}, \end{aligned} \tag{6·3}$$

where $v = \sum_{r=1}^{\ell} v_r \omega_r$ is the overall vaccination coverage.

As for a community of homogeneous individuals, e is only affected by the vaccine's reduction of susceptibility and not by the vaccine's effect on infectivity once infected. However, the e in (6·3) also depends on the inherent susceptibility of different types of base individual, their relative abundances and their vaccination coverages. Therefore, the quantity estimated by

$$\hat{e} = 1 - \frac{C_V/v}{C_0/(1-v)}$$

in a multitype setting has an interpretation that is somewhat obscure. The following two examples give an indication of where care is needed.

Example 2. Suppose that the same fraction of each base type of individual is vaccinated, that is $v_r = v$ for all r. This occurs, for example, when vaccinees are selected at random, irrespective of type. Then

$$e = 1 - \sum_{r=1}^{\ell} \gamma_r E(A_r),$$

where $\gamma_r = \alpha_r \omega_r / \sum_{i=1}^{\ell} \alpha_i \omega_i$. The last term is a weighted average of the $E(A_r)$, with weights γ_r reflecting the relative susceptibility and relative abundance of the base types, and therefore $\hat{e}$ estimates a sensible concept of vaccine efficacy. In the particular case when the vaccine induces the same expected reduction in susceptibility for all base types, so that $E(A_r) = E(A)$ for all r, we obtain

$$e = 1 - E(A).$$

Therefore $\hat{e}$ estimates a characteristic that depends only on the vaccine when it induces the same mean reduction in susceptibility for all base types and an equal fraction of each base type is vaccinated. In other words, the estimator is then robust with respect to

differences in the α_r and in the β_r among base types. However, $\hat{e}$ estimates a quantity that depends on the heterogeneity inherent within this community when vaccination coverages v_r differ. Therefore, it is desirable that vaccinees be selected at random when assessing vaccines.

Example 3. Suppose now that there are two types of individual, and that the vaccine responses are the same for both types; that is, $\ell = 2$ and $E(A_1) = E(A_2) = E(A)$. Then equation (6·3) becomes

$$e = 1 - \frac{\alpha_1 v_1 \omega_1 + \alpha_2 v_2 \omega_2}{\alpha_1(1-v_1)\omega_1 + \alpha_2(1-v_2)\omega_2} \frac{1-(v_1\omega_1 + v_2\omega_2)}{v_1\omega_1 + v_2\omega_2} E(A).$$

Without loss of generality assume that $\alpha_1 < \alpha_2$, so type-2 individuals are more susceptible. Then e increases with v_1 and decreases with v_2. This implies that e can take any value between two extremes. For $v_1 = 0$ and $v_2 = 1$ we have $e = 1 - (\alpha_2/\alpha_1)E(A)$, its lowest value, while $v_1 = 1$ and $v_2 = 0$ gives $e = 1 - (\alpha_1/\alpha_2)E(A)$, its highest value. If vaccinees are selected at random, implying that $v_1 = v_2$, then $e = 1 - E(A)$ as in the homogeneous community.

It is seen that e can even attain a negative value, when α_2 is large enough, the vaccine effect is modest and most vaccinations are of type-2 individuals. For example, when $\alpha_2/\alpha_1 = 5$, $E(A) = 0{\cdot}5$, $v_1 = 0$ and $v_2 = 1$ we find $e = -1{\cdot}5$. This negative value for e is misleading since the vaccine is clearly protective; it reduces susceptibility by 50% for both types. The explanation lies in the fact that vaccinees are type-2 individuals who, even after vaccination, are more susceptible than unvaccinated type-1 individuals. The proportion infected among vaccinated individuals will therefore be higher than the proportion infected among unvaccinated individuals, thus giving a negative e. This example shows that e is not always a sensible measure of vaccine efficacy when applied to outbreaks in multitype communities.

A more suitable assessment of vaccine efficacy in the case of multitype outbreaks is to measure e separately for each type, assuming types are distinguishable. This requires that the vaccination coverage for each type be known. The corresponding estimates are then

$$\hat{e}_r = 1 - \frac{C_{Vr}/v_r}{C_{0r}/(1-v_r)} \quad (r = 1, \ldots, \ell),$$

where C_{Vr} and C_{0r} are the numbers of type-r cases among vaccinated and unvaccinated individuals, respectively. The quantity $\hat{e}_r$ estimates $e_r = 1 - E(A_r)$. If a single measure of the vaccine efficacy is desired the weighted average $\hat{e}_C = \sum_r \omega_r \hat{e}_r$ could be used. It estimates $e_C = 1 - \sum_r \omega_r E(A_r)$, the mean reduction in susceptibility in the community.

7. Community of households

Consider homogeneous individuals who reside in a community consisting of a large number of households. A detailed presentation of an epidemic model for a community of households is given by Ball et al. (1997). We outline only the assumptions needed for our focus on estimating vaccine efficacy. Let v_i denote the proportion of households of size i $(i = 1, \ldots, h)$, so that $\bar{v} = \sum_i i v_i$ is the mean household size. Contacts are more frequent between two household members than they are between two individuals who do not share the same household. The transmission assumptions of §§ 2 and 4 are modified for this scenario in the following way. At x time units after infection, an infected individual has infectious contacts with a specific individual outside the household at a rate $\beta(x)/n$.

Additionally, he has contacts with each individual of his household at a rate $\theta_W \beta(x)$, which is independent of the household size. The constant θ_W reflects the enhanced rate of contacts within the household.

Imagine one infected individual in this community when no-one has acquired immunity from either vaccination or previous exposure to the infection. Let $R_c = E(B_0)$ be the expected number of individuals from other households to whom infection is transmitted by this infective. Furthermore, assuming the infective resides in a household of size i, let μ_i denote the expected eventual number of cases in the household neglecting further external infections. Expressions for μ_i can be obtained using certain recursive formulae; see for example Andersson & Britton (2000, § 2.4). Several different basic reproduction numbers can be defined for this initial infective, depending on the way we attribute infections to an individual. Becker & Dietz (1996) define four different basic reproduction numbers for infectives in a susceptible-infectious-removed epidemic model for a community of households. Here we attribute to an infective all of the primary infectives he generates, by direct contact, in other households, as well as all secondary cases arising in those households. In other words, secondary cases are not attributed to the infectives within the household, whose contacts actually caused their infections, but instead to the infective who generated the primary case of their household. This choice is made because the resulting basic reproduction number has an explicit expression, which is

$$R_0 = R_c \sum_{i=1}^{k} \frac{i v_i}{\bar{v}} \mu_i$$

(Hall & Becker, 1996; Ball et al., 1997), and a major outbreak is possible if and only if $R_0 > 1$.

Now suppose that a fraction v of all individuals, chosen from among the households in some specified way, are vaccinated and that individuals may respond differently to vaccination. As before, individuals can then be of type 0, 1, 2, ..., k, where 0 indicates unvaccinated individuals and the proportion of different types of vaccine response is specified by $\{p_r\}$, as in the distribution (3·1) above. We now have types of individual and types of household. Distinguish the type of household by label $n = (n_0, n_1, \ldots, n_k)$, where n_i is the number of type-i individuals in the household. For any given external contact made by an infective, let π_{nr} be the probability that this contact is with a type-r individual from a household of type n. These probabilities depend on the response probabilities $\{p_r\}$ and on the way vaccinations are allocated among households. The probability that the type-r individual is infected by this contact is a_r. Let μ_{nri} denote the mean number of cases of type i that result within the household of kind n, given that the primary household case is of type r and neglecting further external infection. Their expressions can be obtained using recursive formulae for a multitype epidemic model (Andersson & Britton, 2000, § 6.1). In this notation the reproduction number after vaccination is

$$R_V = R_c \sum_{i=0}^{k} b_i \sum_{r,n} a_r \pi_{nr} \mu_{nri}; \tag{7·1}$$

see Becker & Starczak (1998). A major outbreak is possible if and only if $R_V > 1$.

Assume v is large enough to prevent epidemics, that is $R_V > 1$, so that the size of an outbreak initiated by a small number of introductory cases can be approximated by the total progeny in a suitably-defined subcritical branching process. One way to define such a branching process is in terms of the proliferation of infected households, as is done by Bartoszyński (1972). For our purpose it is more appropriate to think in terms of the

proliferation of infected individuals, with infections attributed to infectives as described above. Let C_i denote the eventual number of type-i individuals who are infected. We are interested in $C = Z_0 + Z_1 + Z_2 + \ldots$, where Z_t denotes the vector of the various types of infected individual in generation t. Generation 0 consists of the introductory cases and all secondary cases in their households. Generation 0 cases infect a number of individuals from different households. These newly infected individuals and all secondary cases in their households make up generation 1. Generation 2 consists of all individuals directly infected by generation 1 cases, as well as all cases in the households of those new primary infectives, and so forth.

The mean $E(C)$ satisfies equation (4·3), but the expressions for the elements of $M = (m_{ij})$ now reflect the household structure of the community and the mean sizes of household outbreaks. The element m_{ij} is the expected number of type-i individuals infected, infectives of the next generation, by a single type-j infective. It may be expressed as

$$m_{ij} = b_j R_c \sum_{r,n} a_r \pi_{nr} \mu_{nri}$$

and we may write

$$M = d_{\mathrm{H}} b^{\mathrm{T}},$$

where element $i+1$ of the $(k+1)$-vector d_{H} is $R_c \sum_{r,n} a_r \pi_{nr} \mu_{nri}$ and element $i+1$ of the $(k+1)$-vector b is b_i, for $i = 0, 1, \ldots, k$. The subscript in d_{H} indicates that this formulation is for a community of households. As before, the form of the matrix M implies that its largest eigenvalue is $d_{\mathrm{H}}^{\mathrm{T}} b$, which is exactly R_V, as given in (7·1), so the assumption $R_V < 1$ is identical to saying that this multitype branching process is subcritical.

For this form of M we can easily verify that

$$(I - M)^{-1} = I + \frac{1}{1 - R_V} M,$$

provided that $R_V = d_{\mathrm{H}}^{\mathrm{T}} b < 1$.

Note that Z_0 gives the numbers of type $0, 1, 2, \ldots, k$ individuals in the households infected initially. Assume that the community outbreak is initiated by a few individuals, possibly one, making a contact with an external infective. If external contacts are made randomly it is reasonable to assume that $E(Z_0)$ is proportional to d_{H}. This leads to

$$E(C) = (1 - M)^{-1} E(Z_0) = c \left(I + \frac{1}{1 - R_V} d_{\mathrm{H}} b^{\mathrm{T}} \right) d_{\mathrm{H}} = \frac{c}{1 - R_V} d_{\mathrm{H}},$$

provided $R_V < 1$.

Therefore, $E(C_0) = (1, 0, \ldots, 0) E(C)$ and $E(C_V) = (0, 1, \ldots, 1) E(C)$ lead to

$$e = 1 - \frac{E(C_V)/v}{E(C_0)/(1 - v)} = 1 - \frac{(1 - v) \sum_{r,n} a_r \pi_{nr} \sum_{i=1}^{k} \mu_{nri}}{v \sum_{r,n} a_r \pi_{nr} \mu_{nr0}}. \tag{7·2}$$

Contrary to the community setting of §§ 4 and 6, in the present setting e depends also on the b_i's, the vaccine's effect on infectiousness once infected. This is because μ_{nri}, the expected number of infected type-i individuals in a household of type n, in an outbreak initiated by one primary household infective of type r and neglecting external infection, depends on the b_i's. For a simple illustration of this fact, suppose that $b_r = 0$. Then the primary

case will not spread the disease further, implying that

$$\mu_{nri} = \begin{cases} 1, & \text{for } i = r, \\ 0, & \text{for } i \neq r. \end{cases}$$

Now consider equation (7·2) for some specific examples. The first example merely shows that equation (7·2) reduces to the e of § 4 under appropriate specific assumptions. The next two examples are intended to reveal the extent to which various factors influence expression (7·2), to help us understand what $\hat{e}$ is estimating in this setting. The final example demonstrates that selecting individuals for vaccination at random does not make $\hat{e}$ unbiased for $1 - E(A)$ when the community has a household structure.

Example 4. Suppose all households are of size 1. Then 'household type' coincides with 'individual type', giving

$$\pi_{nr} = \begin{cases} 1 - v, & \text{when } r = 0, \\ vp_r, & \text{otherwise,} \end{cases} \qquad \mu_{nri} = \begin{cases} 1, & \text{when } r = i, \\ 0, & \text{otherwise,} \end{cases}$$

so that e reduces to $1 - E(A)$, as it should since the setting is then equivalent to that considered in § 4, namely a community of homogeneous individuals who mix uniformly.

Example 5. Suppose all households are of size 2, that exactly one individual per household is vaccinated and that the Reed–Frost model applies; see § 2. Denote the household types by $(0, j)$, for $j = 1, 2, \ldots, k$, where 0 refers to the unvaccinated individual and j refers to the type of vaccinated individual in the household. Then

$$\pi_{(0,j)r} = \begin{cases} p_j/2, & \text{when } r = 0 \text{ or } j, \\ 0, & \text{otherwise,} \end{cases}$$

$$\mu_{(0,j)ri} = \begin{cases} 1, & \text{when } r = i = 0 \text{ or } r = i = j, \\ 1 - q_{\mathrm{W}}^{a_j}, & \text{when } r = 0 \text{ and } i = j, \\ 1 - q_{\mathrm{W}}^{b_j}, & \text{when } r = j \text{ and } i = 0, \\ 0, & \text{otherwise,} \end{cases}$$

where q_{W} is the probability that one susceptible avoids infection from his infected household partner when both are unvaccinated individuals. Substituting these quantities and $v = 0{\cdot}5$ into equation (7·2) gives

$$e = 1 - \frac{E\{A + (1 - q_{\mathrm{W}}^{A})\}}{E\{1 + A(1 - q_{\mathrm{W}}^{B})\}} = \frac{E(q_{\mathrm{W}}^{A} - Aq_{\mathrm{W}}^{B})}{E(1 + A - Aq_{\mathrm{W}}^{B})}. \tag{7·3}$$

Under the natural assumption that $A \leqslant 1$ and $B \leqslant 1$, implying that vaccination never increases susceptibility or infectivity, it can be shown that $e \leqslant 1 - E(A)$.

This result may tempt us to use $\hat{e}$ as a conservative estimator of $1 - E(A)$, but this is unwise, first, because the inequality is strict except for some trivial cases. More importantly, e can be substantially less than $1 - E(A)$. For example, with $\mathrm{pr}\,(A = 0{\cdot}9,\ B = 0{\cdot}1) = 1$ and $q_{\mathrm{W}} = 0{\cdot}1$ we obtain $e = -0{\cdot}479$. Not only is this far removed from $1 - E(A) = 0{\cdot}1$, but e is negative although the vaccine reduces both susceptibility and infectivity.

The negative value of e is explained as follows. The stipulated effect of the vaccine's reduction in susceptibility is modest, while the reduction in infectivity is substantial.

Unvaccinated individuals have a slightly higher chance of being infected by an external contact than their vaccinated partners do, but they have a much lower chance of being infected by a within-household contact because of the low infectivity of their vaccinated partner. As a consequence, more vaccinated than unvaccinated individuals tend to be infected in this setting. Therefore, $\hat{e}$ underestimates $e_S = 1 - E(A)$ and the greater the reduction in infectivity, in other words the better the vaccine performs, the more is e_S underestimated to the extent that a negative effect may be indicated. In short, the measure e and its estimator $\hat{e}$ can be misleading when based on data from a structured community.

We now consider more specific versions of (7·3) that help to quantify the extent of any underestimation of e_S.

Case 1. When there is no transmission within households, that is $q_W = 1$, the process behaves like a uniformly mixing community. We indeed obtain $e = 1 - E(A) = e_S$ when we substitute $q_W = 1$.

Case 2. Suppose the vaccine has an all-or-nothing effect, with the probability of vaccine failure being p_F; that is, $\mathrm{pr}(A = B = 1) = p_F = 1 - \mathrm{pr}(A = 0)$. Then (7·3) becomes

$$e = (1 - p_F)\left\{\frac{1}{1 + p_F(1 - q_W)}\right\} \leqslant 1 - p_F = e_S,$$

which is never negative. However, the deflation factor can be as low as $\frac{1}{2}$, tending towards this as $p_F \to 1$ and $q_W \to 0$.

Case 3. Suppose the vaccine affects susceptibility, but not infectivity; that is, A may have any distribution, but $B \equiv 1$. Then (7·3) becomes

$$e = \frac{E(q_W^A) - q_W E(A)}{1 + (1 - q_W)E(A)}.$$

If we also assume that $A \leqslant 1$, so that one cannot become more susceptible from vaccination, then simple calculus gives $0 \leqslant e \leqslant 1 - E(A)$. The two extremes are obtained when $A \equiv 1$ and $A \equiv 0$ respectively.

Case 4. Suppose instead that the vaccine has no effect on susceptibility; that is, B may have any distribution, but $A \equiv 1$. Equation (7·3) then becomes

$$e = \frac{q_W - E(q_W^B)}{2 - E(q_W^B)}.$$

If we also assume that $B \leqslant 1$, so that the vaccine does not increase infectivity, then it is straightforward to show that $-(1 - q_W) \leqslant e \leqslant 1 - E(A) = 0$. The upper bound is attained for $B \equiv 1$, corresponding to no vaccine effect. The lower bound is attained for $B \equiv 0$, corresponding to a vaccine that blocks transmission completely. In other words, $\hat{e}$ estimates a negative quantity, even though the vaccine reduces disease transmission.

Example 6. Again suppose that all households are of size two, but now a proportion v of randomly selected households have both members vaccinated and the remaining households have no vaccinated member. The possible household types are $(0, 0)$ and (i, j), for $1 \leqslant i \leqslant j \leqslant k$, where the two indices refer to the types of the two individuals of the

household, assumed ordered according to vaccine responses. We have

$$\pi_{(i,j)r} = \begin{cases} 1-v, & \text{when } i=j=r=0, \\ vp_i^2, & \text{when } i=j=r=1, 2, \ldots, k, \\ vp_ip_j, & \text{when } 1 \leqslant i < j \leqslant k \text{ and } r=i \text{ or } j, \\ 0, & \text{otherwise,} \end{cases}$$

$$\mu_{(i,j)rs} = \begin{cases} 1+(1-q_{\mathrm{W}}^{a_r b_r}), & \text{when } i=j=r=s=0, 1, 2, \ldots, k, \\ 1, & \text{when } 1 \leqslant i < j \leqslant k \text{ and either } r=s=i \text{ or } r=s=j, \\ 1-q_{\mathrm{W}}^{a_s b_r}, & \text{when } 1 \leqslant i < j \leqslant k \text{ and } r=i,\ s=j \text{ or } r=j,\ s=i, \\ 0, & \text{otherwise.} \end{cases}$$

Substituting these into equation (7·2) gives

$$e = 1 - \frac{E\{A_1(2-q_{\mathrm{W}}^{B_1A_2})\}}{1+p_{\mathrm{W}}},$$

where (A_1, B_1) and (A_2, B_2) are independent and identically distributed random variables with distribution (3·1). Under the natural assumption that $A \leqslant 1$ and $B \leqslant 1$ it can be shown that

$$1 - E(A) \leqslant e \leqslant 1 - \{E(A)/(1+p_{\mathrm{W}})\}.$$

Note that the inequality with respect to $1-E(A)$ here is in the opposite direction to that in Example 5. This means that e not only depends on the effect of the vaccine and on the community structure, but also on how vaccinations are distributed over the community.

In the particular case of an all-or-nothing response we obtain

$$e = 1 - \left(\frac{1+p_{\mathrm{F}}p_{\mathrm{W}}}{1+p_{\mathrm{W}}}\right)p_{\mathrm{F}},$$

which increases with p_{W} and decreases with the failure rate p_{F}. The lower and upper bounds on e are obtained in the limit as p_{F} tends to 1 and 0, respectively.

Example 7. Again suppose that all households are of size two, but now a proportion v of randomly selected individuals are vaccinated. The possible household types are (i, j), for $0 \leqslant i \leqslant j \leqslant k$, where, as before, the indices refer to the types of the two individuals ordered according to vaccine response. We have

$$\pi_{(i,j)r} = \begin{cases} (1-v)^2, & \text{when } i=j=r=0, \\ v(1-v)p_j, & \text{when } 0=i<j \leqslant k \text{ and } r=0 \text{ or } j, \\ v^2p_i^2, & \text{when } i=j=r=1, 2, \ldots, k, \\ v^2p_ip_j, & \text{when } 1 \leqslant i < j \leqslant k \text{ and } r=i \text{ or } j, \\ 0, & \text{otherwise,} \end{cases}$$

$$\mu_{(i,j)rs} = \begin{cases} 1+(1-q_{\mathrm{W}}^{a_r b_r}), & \text{when } i=j=r=s=0, 1, 2, \ldots, k, \\ 1, & \text{when } 0 \leqslant i < j \leqslant k \text{ and either } r=s=i \text{ or } r=s=j, \\ 1-q_{\mathrm{W}}^{a_s b_r}, & \text{when } 0 \leqslant i < j \leqslant k \text{ and } r=i,\ s=j \text{ or } r=j,\ s=i, \\ 0, & \text{otherwise.} \end{cases}$$

Substituting these into equation (7·2) gives

$$e = 1 - \frac{(1-v)E(1-q_{\mathrm{W}}^{A_1} + 2A_1 - A_1 q_{\mathrm{W}}^{B_1}) + vE\{A_1(2-q_{\mathrm{W}}^{B_1 A_2})\}}{1+(1-v)p_{\mathrm{W}} + vE\{A_1(1-q_{\mathrm{W}}^{B_1})\}},$$

where (A_1, B_1) and (A_2, B_2) are independent and identically distributed random variables with distribution (3·1). We do not analyse this e in detail, but point to the important fact that this example demonstrates that random vaccination does not make $\hat{e}$ unbiased for $1 - E(A)$ when the community has a household structure.

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Appendix

Technical details

The total progeny of a multitype branching process. Here we derive a standard error for $\hat{e}$ for a community of homogeneous individuals who mix uniformly. We begin by deriving expressions for the variance-covariance matrix of the total progeny in a multitype branching process, a quantity interesting in its own right. For a single-type branching process the variance for the total progeny is known, see Jagers (1975, p. 39) for example, but we have not found the variance matrix for the total progeny of a multitype Galton–Watson branching process in the literature.

Consider a multitype Galton–Watson process with $k+1$ different types of individual labelled $0, 1, \ldots, k$. Let $p^{(j)}(r)$ denote the offspring distribution of a type-j individual, $j = 0, \ldots, k$, where r is a $(k+1)$-vector. Let $Z_t^{(j)} = (Z_{t0}^{(j)}, \ldots, Z_{tk}^{(j)})^{\mathrm{T}}$ be the vector specifying the numbers of individuals of the different types in generation t assuming the process started with one type-j individual in generation zero; that is $Z_0^{(j)} = 1_j$, the $(k+1)$-vector with its jth element unity and all its other elements zero. The vector $Z_1^{(j)}$ has distribution $p^{(j)}(r)$, so its probability generating function is

$$f^{(j)}(s) = E(s^{Z_1^{(j)}}) = E(s_0^{Z_{10}^{(j)}} \ldots s_k^{Z_{1k}^{(j)}}) = \sum_r p^{(j)}(r) s^r.$$

Define the mean matrix $M = (m_{ij})$ by $m_{ij} = E(Z_{1i}^{(j)}) = f_i^{(j)}(1_A)$, where 1_A is the $(k+1)$-vector with all elements unity and $f_i^{(j)}$ denotes the partial derivative of $f^{(j)}$ with respect to s_i. It is well known, e.g. Jagers (1975, p. 88), that $E(Z_t^{(j)}) = M^t 1_j$. Define also the second-order moments of the offspring distribution

$$c_{uv}^{(j)} = E(Z_{1u}^{(j)} Z_{1v}^{(j)}) - m_{uj} m_{vj} = \begin{cases} f_{uu}^{(j)}(1_A) + f_u^{(j)}(1_A)\{1 - f_u^{(j)}(1_A)\} & (u = v), \\ f_{uv}^{(j)}(1_A) - f_u^{(j)}(1_A) f_v^{(j)}(1_A) & (u \neq v), \end{cases} \tag{A·1}$$

where $f_{uv}^{(j)}(s)$ is the second derivative of $f^{(j)}(s)$ with respect to s_u and s_v.

The total number of individuals, of the various types, up to generation t is defined by the vector $Y_t^{(j)} = \sum_{r=0}^{t} Z_r^{(j)}$. Each component of $Y_t^{(j)}$ is increasing in t, so that $Y_t^{(j)}$ tends to a limit $Y_\infty^{(j)}$ and $t \to \infty$. From standard theory for branching processes (Jagers, 1975) it is known that the largest eigenvalue R of the matrix M determines whether $Y_\infty^{(j)}$ can be infinite or not. For $R < 1$, known as the subcritical case, $Y_\infty^{(j)}$ is finite almost surely and so is its expected value $E(Y_\infty^{(j)})$. From now on assume that we are in the subcritical case $R < 1$, implying that the branching process will surely die out.

Let $h_t^{(j)}(s) = E(s^{Y_t^{(j)}})$, the probability generating function for $Y_t^{(j)}$. By conditioning on what happens in the first generation and using the fact that each of the individuals of the first-generation initiates an independent multitype branching process, we obtain the recursion equation

$$h_t^{(j)}(s) = s_j f^{(j)}\{h_{t-1}(s)\}.$$

This recursion can be used to derive the mean vector and variance-covariance matrix of the total progeny. Taking the partial derivative of $h_t^{(j)}(s)$ with respect to s_i and setting $s = 1_A$ gives recursive formulae whose solution, in vector notation, is $E(Y_t^{(j)}) = (I - M^{t+1})(I - M)^{-1}1_j$. Since the largest eigenvalue of M is less than unity, we can take limits as $t \to \infty$ to obtain $E(Y_\infty^{(j)}) = G1_j$, where the matrix $G = (I - M)^{-1}$ has typical element $= g_{ij} = E(Y_{\infty i}^{(j)})$.

The elements of the variance matrix for $Y_\infty^{(j)}$ are derived in a similar fashion, using second-order partial derivatives of $h_t^{(j)}(s)$. The result is

$$\sigma_{ir}^{(j)} = \operatorname{cov}(Y_{\infty i}^{(j)},\ Y_{\infty r}^{(j)}) = \sum_{u=0}^{k}\sum_{v=0}^{k} c_{uv}^{(j)} g_{ui} g_{vr} + \sum_{u=0}^{k} m_{uj}\sigma_{ir}^{(u)},$$

for all i, j, r, which may be written

$$\sigma_{ir}^{(j)} = \sum_{s=0}^{k}\sum_{u=0}^{k}\sum_{v=0}^{k} g_{js} g_{ui} g_{vr} c_{uv}^{(s)}. \tag{A·2}$$

The variance-covariance matrix for a process started by more than one individual is simply the sum over such elements, one for each ancestor, since all ancestors start independent branching processes.

We now consider some forms for M and $\{c_{uv}^{(j)}\}$ of particular interest in our epidemic context.

Proportionate mixing. All community settings considered in this paper have a mean matrix of the form $M = db^{\mathrm{T}}$. Its largest eigenvalue R, denoted by R_V in previous sections, is then given by $R = d^{\mathrm{T}}b = \sum_{i=0}^{k} d_i b_i$. It is assumed to be less than 1 and then

$$G = (I - M)^{-1} = \frac{1}{1 - R} db^{\mathrm{T}} + I.$$

This means that

$$g_{ij} = E(Y_{\infty i}^{(j)}) = \begin{cases} d_j b_j/(1 - R) + 1 & (i = j), \\ d_i b_j/(1 - R) & (i \neq j). \end{cases}$$

These are the first moments of the total progeny assuming that there was one ancestor of type j. It is often not known who started the epidemic. In previous sections we assume that the expected numbers of initially infected individuals of the different types are given by $E(Z_0) = cd$ for some constant c. Let C denote the vector of total progeny under this assumption. Then the mean vector of C has elements

$$E(C_i) = c\sum_{j=0}^{k} d_j E(Y_{\infty i}^{(j)}) = \frac{cd_i}{1 - R}, \tag{A·3}$$

a result given in previous sections.

To obtain expressions for the variance-covariance terms $\sigma_{ir}^{(j)}$ defined by (A·2) we need to know the variance-covariance terms defined by (A·1). For epidemics these are determined by the model and the distribution of the area under the infectiousness function. For an individual, given his value of B_0 and that, upon vaccination, his response makes him type j, the numbers of infectious contacts this individual has with each of the different types follow independent Poisson distributions. The Poisson number of contacts with type-u individuals has mean $b_j d_u B_0/E(B_0)$ $(u = 0, \ldots, k)$, the denominator coming from the definition that the unconditional expected number of contacts is $b_j d_u$. When we drop the conditioning on B_0 the numbers of contacts with the different types become dependent, unless B_0 is deterministic. It can be shown that the variances and covariances for these

numbers of contacts are

$$c_{uu}^{(j)} = b_j^2 d_u^2 \tau^2 + b_j d_u, \quad c_{uv}^{(j)} = b_j^2 d_u d_v \tau^2 \quad (u \neq v),$$

where $\tau^2 = \mathrm{var}(B_0)/\{E(B_0)\}^2 = \mathrm{var}(B_0)/R_0^2$ is the squared coefficient of variation. Making use of the assumed structure of M in (A·2) we find that

$$\sigma_{ir}^{(j)} = \mathrm{cov}(Y_{\infty i}^{(j)},\ Y_{\infty r}^{(j)}) = \begin{cases} \dfrac{d_i^2 b_j}{(1-R)^3}\left\{(1+\tau^2)z + (1-R)(\tau^2 b_j + 2b_i) + \dfrac{(1-R)^2}{d_i}\right\} & (i = r), \\ \dfrac{d_i d_r b_j}{(1-R)^3}\{(1+\tau^2)z + (1-R)(\tau^2 b_j + b_i + b_r)\} & (i \neq r), \end{cases}$$

where $R = \sum_{u=0}^{k} b_u d_u$ and $z = \sum_{u=0}^{k} b_u^2 d_u$.

These are the variance-covariance terms for the vector $Y_\infty^{(j)}$, that is given that there was one ancestor of type j. In the previous sections we assumed that the expected number of initial infectives of each type is proportional to susceptibility and the abundance of the type. Here we make a slightly stronger assumption by assuming this relationship for the actual numbers rather than the expected numbers, i.e. that $Z_0 \equiv cd$ for some c. Since all ancestors constitute independent branching processes it follows that the covariance terms are then given by

$$\sigma_{ir} = \mathrm{cov}(C_i,\ C_r) = c \sum_{j=0}^{k} d_j \sigma_{ir}^{(j)} = \begin{cases} \dfrac{cRd_i^2}{(1-R)^3}\left\{\left(1 + \dfrac{\tau^2}{R}\right)z + (1-R)2b_i + \dfrac{(1-R)^2}{d_i}\right\} & (i = r), \\ \dfrac{cRd_i d_r}{(1-R)^3}\left\{\left(1 + \dfrac{\tau^2}{R}\right)z + (1-R)(b_i + b_r)\right\} & (i \neq r). \end{cases} \tag{A·4}$$

The classical Reed–Frost and general epidemic models correspond to $\tau^2 = 0$ and $\tau^2 = 1$ respectively.

Standard error of $\hat{e}$ for a homogeneous community. We now derive an approximate standard error for the estimator $\hat{e}$ in the setting of § 4. Recall that $d_i = a_i \pi_i R_0$, where $\pi_0 = 1 - v$ and $\pi_j = v p_j$ $(j = 1, \ldots, k)$, and that the estimator of the vaccine efficacy was defined as

$$\hat{e} = 1 - \frac{1-v}{v}\left(\frac{C_1 + \ldots + C_k}{C_0}\right) = h(C_0, \ldots, C_k),$$

say. We apply the δ-method (Rao, 1973, § 6a.2), to $h(C_0, \ldots, C_k)$ to obtain the approximate expression

$$\mathrm{var}(\hat{e}) \simeq \sum_{i=0}^{k} \sum_{j=0}^{k} h_i(\mu_0, \ldots, \mu_k) h_j(\mu_0, \ldots, \mu_k)\ \mathrm{cov}(C_i,\ C_j),$$

where h_i denotes the partial derivative of $h(c_0, \ldots, c_k)$ with respect to c_i, and $\mu_i = E(C_i)$. Inserting expressions for the partial derivatives we obtain

$$\mathrm{var}(\hat{e}) \simeq \left(\frac{1-v}{v}\right)^2 \left\{\frac{(\mu_1 + \ldots + \mu_k)^2}{\mu_0^4}\ \mathrm{var}(C_0) + \frac{1}{\mu_0^2}\sum_{i=1}^{k} \mathrm{var}(C_i) - 2\frac{\mu_1 + \ldots + \mu_k}{\mu_0^3}\sum_{i=1}^{k} \mathrm{cov}(C_0,\ C_i) + \frac{1}{\mu_0^2}\sum_{i \neq j \geqslant 1}^{k} \mathrm{cov}(C_i,\ C_j)\right\}.$$

The first- and second-order moments of the $C_0, \ldots, C_k$ are given by (A·3) and (A·4), respectively. This gives a variance expression containing c, which comes from assuming $Z_0 \equiv cd$. Let the total number of initial infectives be $i_0 = c \sum_{j=0}^{k} d_j$. Then the variance formula becomes

$$\mathrm{var}(\hat{e}) \simeq \frac{R(1-R)E(A)\{1 - v + vE(A)\}}{i_0}\left\{\frac{E(A)}{1-v} + \frac{1}{v}\right\}.$$

From this expression it is seen that the approximate variance of $\hat{e}$ does not depend on τ, the coefficient of variation of the area under the infectiousness function. In other words, the variance of $\hat{e} = 1 - (1-v)C_V/vC_0$ does not depend on τ even though the variances of C_0 and C_V do. Admittedly, this is only an approximate conclusion because higher-order terms in the Taylor expansion are omitted when applying the δ-method. This result holds more generally, when the variance of B_0 depends on the type of the individual.

In the expression for $\mathrm{var}(\hat{e})$, the quantities $E(A)$ and R are unknown and must be estimated. Naturally, $E(A)$ is estimated by $1-\hat{e}$. We estimate R by replacing $\sum_{j=0}^{k} \mu_j$ in the expression $\sum_{j=0}^{k} \mu_j = i_0/(1-R)$, see (A·3), by the corresponding observed value C_+. This gives the estimator $\hat{R} = 1 - i_0/C_+$ and with these estimates we obtain the standard error

$$\mathrm{SE}(\hat{e}) = \sqrt{\left\{\frac{(1-\hat{e})(1-v\hat{e})}{C_+}\left(1-\frac{i_0}{C_+}\right)\left(\frac{1-\hat{e}}{1-v}+\frac{1}{v}\right)\right\}}.$$

If i_0, the initial number of infectives, is unknown a conservative estimator is obtained by replacing i_0 by 1.

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