

Epidemics in populations with two levels of mixing

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SUMMARY

We consider epidemics with removal ('SIR epidemics') in populations which mix at two levels, 'global' and 'local'. We analyse the conditions under which a large outbreak is possible, the size of such outbreaks when they can occur, and the implications for vaccination strategies; in each case comparing our results with the simpler homogeneous mixing case.

More precisely, we consider models in which each infectious individual i has a 'global' probability p_G for infecting each other individual in the population, plus a 'local' probability p_L , typically much larger, of infecting each other individual among a set of neighbours, $\mathcal{N}(i)$. Our main concern is the case where the population is partitioned into local groups or households, but our approach also applies to cases where neighbourhoods do not form a partition, for instance to spatial models with a mixture of local (*e.g.* nearest-neighbour) and global contacts.

We use a variety of theoretical approaches: a random graph framework for the initial exposition of the simple case where an individual's contacts are independent; branching process approximations for the general threshold result; and an embedding representation for rigorous results on the final size of outbreaks.

From the applied viewpoint, the key result is that, compared with the homogeneous mixing model in which individuals make contacts simply with probability p_G , the local infectious contacts have an 'amplification' effect. The basic reproductive ratio of the epidemic is increased from its value R_0 in the absence of local infections to $R_T = \mu R_0$, where μ is the mean size of an outbreak, started by a randomly chosen individual, in which only local infections count. Where the groups are large, and the within-group epidemics above threshold, this amplification can permit an outbreak in the whole population at very low levels of p_G , for instance for $p_G = O(1/Nn)$ in a population of N divided into groups of size n .

The implication of these results for control strategies is that vaccination should be directed preferentially towards reducing μ ; we discuss the conditions under which the *equalizing strategy*, aimed at leaving unvaccinated sets of neighbours of equal sizes, is optimal.

We also discuss the estimation of our threshold parameter R_T from data on epidemics among households.

1 Introduction

1.1 Mixing at two levels

In the spread of infectious disease, heterogeneities in population behaviour often play a key role in determining whether a major epidemic outbreak occurs and, if it does, its rate of spread and the final size of the epidemic. Here we shall analyse one of the simplest and most basic kinds of heterogeneity, where the probability of infection being transmitted between an infectious individual and a susceptible takes one of two values, a value p_L if they are *neighbours*, and a value p_G (typically much smaller) if they are not. We shall call these *local* and *global* infections respectively.

This kind of model is of application to a wide variety of epidemic situations, and is also of considerable interest in ecology: see, for instance, the reviews by Kareiva (1990) of ‘patch dynamics’, especially the references to ‘island’ and ‘meta-population’ models, and by Hanski and Gilpin (1991).

Perhaps the simplest such model is that of a population partitioned into equal sized groups. That is to say, we have m groups, each of n individuals, giving a total population of size $N = mn$; two individuals are neighbours if and only if they belong to the same group. We shall analyse two cases, that of *households* where n takes a fixed, typically fairly small, value; and the case of *large groups*, where we consider what happens as $n \rightarrow \infty$. In either case, we can generalise the model to allow for unequal group sizes, $\{n_i : 1 \leq i \leq m, \text{ with } \sum_{i=1}^m n_i = N\}$; this level of generality is of course vital in applications (see Section 5).

Possible further generalisations are to models with more than two levels, or with several types of individual with different contact probabilities, which might for instance represent children and adults (see §1.3). An alternative formulation, in which global contacts have a per group rather than per individual probability, will also be discussed briefly (§1.3).

Returning to simple models, another basic case is where individuals are arranged in space (*e.g.* equally spaced around a circle), and the neighbours of an individual are defined as those within a certain distance, in the simplest case as just an individual’s nearest neighbours. Note that in this case the sets of neighbours will overlap, rather than partitioning the population. From the theoretical point of view, this model can be regarded as a kind of limit of a dispersal model with local and long distance interactions, in which the distribution of the latter degenerates into the uniform distribution (for dispersal distributions with extreme behaviour, such as ‘great leaps forward’, or with infinite velocity, see Mollison 1972, Mollison and Levin 1995). Possible applications include the North Sea seal epidemic (Bolker *et al.* 1995), and the spread of infection between pigs in a line of stalls (M de Jong, personal communication).

1.2 Contents

We shall restrict attention to the SIR model, that is where there are just three possible states for an individual, *susceptible* (S), *infected and infectious* (I) and *removed* (R), and the only possible transitions are $S \rightarrow I$ and $I \rightarrow R$. We shall also assume that the sets of contacts made by different individuals are independent of each other. In general, infections made by the same individual will be correlated, if only because of the dependence induced by the variability of the length of the infectious period. [The case where infections made by the same individual *are* independent will be considered in Section 2.]

It is often helpful to begin by considering groups ‘in isolation’, meaning that we consider potential local infections before the global ones. Values for the local infection probability of around $1/n$, *i.e.* $p_L = O(1/n)$, are of interest, since this corresponds to a total of $O(1)$ within-group contacts by an individual; it will turn out that values of $p_G = O(1/N)$ or even $= O(1/Nn)$ are of interest, depending on whether p_L is less or greater than its within-group threshold value of $1/n$.

In the next section we will outline generalisations of these results to populations with two levels of mixing, giving both ‘threshold theorems’, saying whether a large outbreak can occur, and expressions for the size of the outbreak if it can.

Also, in the case of large subgroups it is meaningful to ask whether individual subgroups are above their local threshold. If so, then a global epidemic can occur when p_G is only $O(1/Nn)$.

1.3 Related work

2 Random graphs and the independent contacts case

2.1 Introduction: the random graph framework

We will often not be interested in the time course of the epidemic, but only in which individuals become infected (indeed, we may only be interested in their total number, the *final size* of the epidemic). In that case we can make good use of the representation of the spread of the epidemic by a directed graph, in which we draw an arrow from one individual to another to indicate that the first, if infected, will make an infectious contact with the second (see *e.g.* Barbour and Mollison 1989).

As already mentioned (§1.2), in general infections made by the same individual will be correlated, because of the dependence induced by the variability of the length of the infectious period. We shall later prove results on thresholds and final outbreak size for such more general models. However, the special case where they are independent – the generalisation to two levels of mixing of the well-known Reed-Frost model – is well worth considering first, as then we can use an *undirected graph*, with links rather than arrows (see Barbour and Mollison 1989; also von Bahr and Martin-Löf 1980, Ball 1983a), and analysis is much clearer and simpler. The key idea here is that if an individual's contacts are independent of each other, and if the probability that i infects j is the same as the probability that j infects i , then we can represent both the latter events by the *same*, undirected, link in the contact graph.

An undirected graph can be partitioned into connected components, and the set of those infected during the epidemic will consist precisely of the connected component(s) to which those initially infected belong. In the simple case of homogeneous mixing with contact probability p – the basic Reed-Frost model – the corresponding graph is the simple random graph on a population of size N , $G(N, p)$ (Barbour and Mollison 1989). For large N , this graph has a single ‘giant’ component if and only if $R_0 > 1$, where $R_0 = Np$; it then contains a proportion z of the population, where $z = 1 - e^{-R_0 z}$ (Bollobas 1985). Thus, if there is a large outbreak it will affect approximately this proportion z of the population; and if the initial number of infected $I(0)$ is 1 the probability ζ of a large outbreak is also simply z . [For general values of $I(0)$, $\zeta = 1 - (1 - z)^{I(0)}$.]

In the remainder of this section, we extend the use of undirected random graphs to find the threshold conditions and asymptotic final size for epidemics with two levels of mixing, with particular emphasis on the case of large local groups (§2.4) and on the implications for vaccination strategies (§2.5).

2.2 Local contacts and the clumped Reed-Frost model

We first describe in detail two models in which each individual has a small number of local contacts, and show how they can both be considered as special cases of a ‘clumped Reed-Frost’ model.

The first of these is the households model described above, where we fix the size, or size distribution, of households. Then, if we consider only local contacts, these partition each household into a number of connected components. Once we have done this, these connected components summarise the local interactions – whether two separate components originate from the same household or not is irrelevant when we complete our model by adding the global contacts, since the probability of such contacts is to be the same, independently, for each pair of individuals.

To be precise, we need to allow a pair of individuals in the same group to have both a local probability p_L and a global probability p_G of contacting each other; then their overall probability of contact is $p'_L = 1 - (1 - p_L)(1 - p_G)$. Conversely, if as seems more natural we start with p'_L as the total probability of contact for a pair in the same group, this is equivalent to separate independent contacts of respective probabilities p_L and p_G where $p_L = (p'_L - p_G)/(1 - p_G)$. We of course require $p_G \leq p'_L$ here, which is no problem as our main interest is in the case $p_G \ll p_L$, when $p'_L \approx p_L$.

The probability, π_k say, that an individual chosen at random from the whole population belongs to a component of size k can be calculated – in principle at least – from the distribution of household size and standard methods for the Reed-Frost model (see §3.2). The component sizes will not be exactly independent of each other, because of dependence of sizes within households, but this effect will be negligible provided the number of households is large.

Our second model, the ‘great circle’, is one where the population is not partitioned into households. Instead, we have individuals located in one-dimensional space. For simplicity we shall just consider the case where each individual has two neighbours, one on each side; to avoid boundary problems it is convenient to take the space to be the circumference of a circle. We allow infectious local links, of probability p_L , between each pair of neighbours, and global links, as usual, of equal probability p_G for each pair in the population. When we consider first the local contacts, these again partition the whole population into connected components. In this case the probability π_k of belonging to a component of size k is given by the double geometric distribution of parameter p_L ($\pi_k = kp_L^{k-1}(1 - p_L)^2$, $k \geq 1$). Again the component sizes are not exactly independent, but we can neglect their dependence in what follows provided that the population is large relative to the mean component size.

We note that this ‘neighbours plus global links’ model could be generalised to other isotropic spatial structures, such as a regular toroidal lattice or a tessellation of a Poisson process on a sphere, and that we could allow further than nearest-

neighbour contacts, provided that the local contacts give only relatively small connected components.

2.3 Threshold and final size for the clumped Reed-Frost model

Both the models introduced above are special cases of the following, which we shall call the ‘clumped Reed-Frost’ model. In this, the population consists of clumps, the i th clump having weight w_i . We then run a Reed-Frost type epidemic (that is with independent and symmetric contacts) in this population, with probability $1 - \exp(-cw_iw_j)$ for a contact between clumps i and j . We relate this to our original models by taking a locally connected component containing k individuals to be a clump of weight k ; and by taking $p_G = 1 - \exp(-c)$.

We shall use π_k to denote the probability that a random individual belongs to a clump of size k , and μ to denote the mean clump size, $\sum_k k\pi_k$. For both the household and nearest-neighbour models, in the limit of large total population the clump weights will be chosen independently from the distribution $\{\pi_k\}$. Note that $\{\pi_k\}$ is what is called a *size-biased* distribution for clump size, in distinction from the formulation in which we define the probability h_k that a randomly chosen clump is of size k . The two are simply related, with $\pi_k = kh_k / \sum_j jh_j$; note also that if μ_h and σ_h^2 are respectively the mean and variance of the distribution $\{h_k\}$, then $\mu = \mu_h + \sigma_h^2 / \mu_h$.

Assuming that the number of clumps is large, the probability of a large outbreak can be found by considering the branching process which approximates its early stages (see Section 3.3.1), in which individuals correspond to clumps in the epidemic process and the offspring of a given clump are the clumps that it directly tries to infect in the clumped Reed-Frost epidemic. The approximation (which can be made fully rigorous - see Section 3.3.1) assumes that each new clump contacted in the epidemic process is still susceptible. For large N , the number of clumps contacted by an individual in the epidemic process is Poisson (Np_G), with probability generating function $\exp(Np_G(s - 1))$, and the clump size distribution is $\{\pi_k\}$, with p.g.f. $G_\pi(s)$ say. Thus the number of clumps contacted by a given clump, *i.e.* the offspring distribution for the approximating branching process, has p.g.f. $G_\pi(\exp(Np_G(s - 1)))$. It follows that the offspring distribution for an individual is Poisson(Np_G), with probability generating function $\exp(Np_G(s - 1))$, and the clump size distribution is $\{\pi_k\}$, with p.g.f. $G_\pi(s)$ say; then the probability of a large outbreak is the largest solution z (≤ 1) of $1 - z = G_\pi(\exp(-Np_Gz))$, $= \sum_{k=1}^{\infty} \pi_k \exp(-kNp_Gz)$. Further, z will be > 0 if and only if the mean number of offspring from a clump $Np_G\mu$ is > 1 .

Thus the basic reproductive ratio for the epidemic among clumps is $R_T = \mu Np_G = \mu R_0$, where $R_0 = Np_G$ is the basic reproductive ratio for the ordinary Reed-Frost epidemic - *i.e.* where we only have global contacts so that all clumps are of size 1. [More strictly, we should perhaps use $R_0 = (N - 1)p_G$, but if we

are interested in values of N sufficiently small that this matters, we should be worrying about the correct definition of thresholds in finite populations – see Nåsell 1995.]

The probability z here is that of a large outbreak started by a random individual. If we know that the initial infection(s) is/are in a clump of size k , consideration of the first step shows that the probability of a large outbreak is $z_k = 1 - \exp(-kNp_Gz)$.

In either case, just as for the simple Reed-Frost model, we can argue that the probability of a large outbreak is the same as the probability that an individual belongs to the giant connected component of the contact graph, which in turn is the same as the (proportional) final size of the epidemic conditional on a large outbreak. Thus the final size $\approx zN$, and the probability that an individual in a clump of size k (or equivalently the whole of that clump) is infected during the epidemic is z_k . We may check the consistency of these results: $z = \sum_k \pi_k z_k = \sum \pi_k - \sum \pi_k \exp(-zkNp_G) = 1 - G_\pi(\exp(-zNp_G))$. Also, thinking of $1 - z_k$ as the probability that a clump of size k escapes infection, we note that the number of links from each individual in the clump to the giant component is Poisson(zNp_G), so that the probability of having no such links should indeed be $\exp(-kNp_Gz)$.

Note that for the ‘great circle’ model, $G_\pi(s) = (1 - p_L)^2 s / (1 - p_L s)^2$; in this case R_T is simply a function of the two parameters p_L and p_G .

2.4 Epidemics among giants

We consider here the simple case of a large number (m) of large households, of equal sizes n . For large households the idea of a threshold for local contacts makes sense. When we consider only these local contacts each household has its own local simple Reed-Frost epidemic, with population size n and basic reproductive ratio $R_L = np_L$. It is well-known that the behaviour of these single group models goes through a ‘phase transition’ at around the value $R_L = 1$ (Whittle 1955, von Bahr and Martin-Löf 1980, Nåsell 1995), and it is interesting to examine the implications of this for the present two level model.

If $R_L \leq 1$, the epidemics in individual households are below threshold, and the contact graph within each household consists of components all $\ll n$, *i.e.* of size $O(1)$. Then the analysis of the previous section applies, with R_T being greater than $R_0 = Np_G$ by the factor μ equal to the mean size of these components; but μ is only $O(1)$, so we still require $p_G = O(1/N)$ to get a pandemic – that is, a large outbreak at the inter-household level.

The situation is more interesting when $R_L > 1$, so that the within-household epidemics are above threshold. Then each has its own giant connected component, of size nz_h say, and it is easy to see that the epidemic among the meta-population of giants has $R_T = nNp_Gz_h^2$; and not too difficult to see that the members of households outwith the giants do not significantly affect the probability or size of the overall outbreak.

Since $z_h = O(1)$ in this case, it only requires p_G to be $O(1/Nn)$ for R_T to be > 1 , and thus make possible a large outbreak among the giants; *i.e.* R_0 need only be $O(1/n)$. Then the proportion of giants forming the ‘meta-giant’ component of those involved in this large-scale Reed-Frost epidemic is given by $1 - z_g = \exp(-R_T z_g)$, so that the final proportion of the whole population affected is $z_h z_g$; and, as usual in the independent links case, this is also the probability of a large outbreak arising from an initial infected individual: here z_h represents the probability that the individual belongs to its local giant, and z_g the probability that this giant belongs to the ‘meta-giant’.

In any case the local contacts have an amplifying effect on the global epidemic. But for large households this amplification undergoes a significant change (we might call this a phase transition) from $O(1)$ to $O(n)$ as we reach the local threshold ($R_L = 1$) at which the households go through their individual phase transitions (von Bahr and Martin-Löf 1980).

Finally here, we note the consistency of these essentially asymptotic results with those of the previous section. If in the clumped Reed-Frost model we let the clump distribution tend to that concentrated on nz_h with probability z_h , and 0 with probability $1 - z_h$, then $\mu = nz_h^2$, so that both models agree that $R_T = nNp_G z_h^2$, and $G_\pi(s) = (1 - z_h) + z_h s^{nz_h}$, so that the equation for the final size becomes $1 - z = (1 - z_h)1 + z_h \exp(-Np_G z n z_h)$, which, if we write $z_g = z/z_h$, boils down to $1 - z_g = \exp(-R_T z_g)$ as obtained above for the giant epidemic.

2.5 Vaccination strategies in relation to local thresholds

In a homogeneously mixing population, the minimum proportion v that we need to vaccinate to render the remaining susceptible population sub-threshold is given by $R'_0 = (1 - v)R_0$, *i.e.* we require $v \leq 1 - 1/R_0$.

With our two levels of mixing, we have found that the basic reproductive ratio is $R_T = \mu R_0$. For a population divided into large groups, R_T can take large values, since μ will be a significant proportion of group size if groups are above their individual thresholds ($R_L > 1$). [Essentially, R_T is a parameter describing group to group infection; note that it is therefore not directly comparable with individual to individual reproductive ratios such as R_0 and R_L .]

Now vaccination of a proportion v of the population will still simply reduce R_0 *pro rata*, to $R'_0 = (1 - v)R_0$, but the effect on μ will depend on the distribution of vaccination among the population. We shall consider the question of optimal vaccination strategies in more detail and generality in §2.5; here we simply indicate the practical importance of this question.

For the groups or households model, one strategy is to vaccinate whole groups. Let us assume for simplicity that if they are of different sizes, we choose groups according to the distribution $\{\pi_k\}$. Then μ will be unchanged, so that the overall reproductive ratio will simply become $R'_T = (1 - v)R_T$. However, a strategy in which we vaccinate a proportion of those in each group – for instance the strategy

in which we simply vaccinate members of the overall population chosen at random – can also reduce μ , and thus reduce R_T further. In the case where vaccination changes groups from being above to below their local threshold the difference can be dramatic, as the following simple numerical example illustrates.

Suppose that our population is divided into groups of size $n = 1000$ (perhaps schools or local communities), and that the reproductive ratio R_0 for global contacts is $= 1$ (the exact value is not important for what follows). Suppose also that $p = 0.003$, so that the reproductive ratio for local contacts is $R_L = np_L = 3$. Then $z_h \approx 0.95$, whence (in the notation of the last section) $\mu \approx nz_h^2 \approx 900$, and hence the overall reproductive ratio is $R_T = \mu R_0 \approx 900$.

We now consider two alternative strategies for vaccinating 80% of the population. First note that with any such strategy, R'_0 will be $(1 - 0.8)R_0 = 0.2$. If we have a ‘patchy’ vaccination programme that vaccinates whole groups, we will have $R'_T = \mu R'_0 \approx 900 \times 0.2 = 180$, still far above threshold. However, if we have a uniform vaccination programme, in which approximately 80% of each group are vaccinated, the local reproductive ratio will be brought down to $R'_L \approx (1 - 0.8) \times 3 = 0.6$. The groups will thus be below their local thresholds, and their new mean clump size is easily calculated (from an approximating branching process) to be $\mu' \approx 1/(1 - 0.6) = 2.5$. Thus in this case we will have $R'_T = \mu' R'_0 \approx 2.5 \times 0.2 = 0.5$, so that vaccination will succeed in bringing the infection below threshold.

We can go further: from the practical point of view it is interesting to consider a programme aimed at uniform coverage, but which is inadequate in some groups, meaning that in them there are still enough susceptibles left for the group to be above its local threshold. We find that, where the initial value of R_T is large, a quite small proportion of groups with inadequate coverage suffices to leave the population as a whole above threshold, *i.e.* $R'_T > 1$. Extending our example of groups of size 1000 with $R_0 = 1$, $R_L = 3$, if we have a programme which generally vaccinates 80% within each group, the programme will fail ($R'_T > 1$) if there are just 1% of the groups in which vaccination coverage is only 50%.

3 The model with a general infectious period

3.1 The basic model

We now consider a generalisation of the households model of Section 2, in which the infectious period may follow any arbitrary but specified distribution. Let the population consist of N individuals, subdivided into m groups each of size n . (We shall treat the case of unequal group sizes in §3.5.) The infectious periods of different infectives are independently and identically distributed according to a random variable T_I . Throughout its infectious period a given infective makes contact with a given susceptible in its own group at the points of a homogeneous Poisson process having rate λ_L and with a given susceptible in any other group at the points of a homogeneous Poisson process having rate λ_G/N . The Poisson processes governing contacts between different pairs of individuals are mutually independent. For ease of exposition we shall assume that there is no latent period. However, all our results can be generalised to a model that incorporates a latent period. In particular, the final outcome of the epidemic is invariant to very general assumptions concerning a latent period. This can be seen by considering the random graph associated with the epidemic, in which for any two nodes, i, j say, a directed arc from i to j is present if and only if i will infect j if i is an infective and j is a susceptible. The epidemic is initiated by a number of individuals becoming infected at time $t = 0$. We shall consider the spread of the epidemic in the asymptotic situation where the number of groups m tends to infinity and the group size n is held fixed.

If in the above model we let $T_I \equiv 1$ then the epidemic has the same final outcome as the Reed-Frost model of Section 2 with $p_L = 1 - \exp(-\lambda_L)$ and $p_G = 1 - \exp(-\lambda_G/N)$. If instead we let T_I follow a negative exponential distribution, then our model reduces to the ‘equivalence classes’ model of Watson (1972). Watson studied the deterministic version of the equivalent classes model, and also the branching process approximation as the group size n tend to infinity with the number of groups m fixed and finite. This contrasts sharply with our asymptotic regime outlined above.

The remainder of Section 3 is structured as follows. In §3.2 we summarise several properties of single population SIR stochastic epidemics that will be required in the analysis of our model. In §3.3.1 we show that the early stages of our epidemic can be approximated by a branching process, whose individuals are single group epidemic processes. Moreover, this approximation can be made precise by considering a sequence of epidemics in which the number of groups m tends to ∞ . This enables us to determine a threshold parameter R_T for our epidemic, such that in the limit as m tends to ∞ , global epidemics occur with non-zero probability if and only if $R_T > 1$. Here, a global epidemic is one which affects infinitely many groups as m tends to ∞ . We also determine the probability that a global epidemic occurs and various properties of non-global epidemics.

In §3.3.2 we discuss the threshold parameter R_T . In particular, we compare it with the classical basic reproductive ratio R_0 for our model, and we show that our model displays a similar amplification effect to that described in §2.3 for the clumped Reed-Frost model. In §3.4 we use a heuristic argument to determine the distribution of the total size within a typical group in the event of a global epidemic occurring. A formal proof is provided later in §4.2. Finally, in §3.5, we extend our results to the situation in which the group sizes are not all equal.

We mention here that Bartoszyński (1972) considered a group epidemic model which corresponds to the above limiting branching process. However, his model was described in rather general terms and hence his results are not as explicit as ours.

3.2 Final outcome of a single population SIR stochastic epidemic

Consider now a closed homogeneously mixing population consisting initially of n susceptibles and a infectives, who have just been infected. Suppose, as above, that the infectious period is distributed according to a random variable T_I and that throughout its infectious period a given infective infects a given susceptible at rate λ_L . The epidemic ceases as soon as there are no infectives present in the population. Let T be the total number of initial susceptibles that are ultimately infected by the epidemic, *i.e.* the total size of the epidemic. Let T_A be the severity of the epidemic, *i.e.* the sum of the infective periods of all individuals infected during the course of the epidemic, including the a initial infectives. Note that T_A is equal to the area under the trajectory of infectives, see for example Downton (1972). The joint distribution of (T, T_A) is studied in Ball (1986). More recently, a general framework for analysing the total size and severity of SIR stochastic epidemics has been developed in a series of papers by Lefèvre and Picard, see for example Picard and Lefèvre (1990). A key tool in their framework is a non-standard family of polynomials, first introduced by Gontcharoff (1937), which we now outline.

Let $U = u_0, u_1, \dots$ be a given sequence of real numbers. Then the Gontcharoff polynomials attached to U , $G_0(x|U), G_1(x|U), \dots$, are defined recursively by the triangular system of equations

$$\sum_{j=0}^i \frac{u_j^{i-j}}{(i-j)!} G_j(x|U) = \frac{x^i}{i!}, \quad i = 0, 1, \dots \quad (3.1)$$

For $i = 1, 2, \dots$, the polynomial $G_i(x|U)$ admits the integral representation

$$G_i(x|U) = \int_{u_0}^x \int_{u_1}^{\xi_0} \int_{u_2}^{\xi_1} \dots \int_{u_{i-1}}^{\xi_{i-2}} d\xi_0 d\xi_1 d\xi_2 \dots d\xi_{i-1}, \quad (3.2)$$

see for example Levèvre and Picard (1990), Equation (2.5). Another property of Gontcharoff polynomials, see Equation (2.7) of Lefèvre and Picard (1990), that

we shall require is

$$G_i^{(j)}(x|U) = G_{i-j}(x|E^jU), \quad 0 \leq j \leq i, \quad (3.3)$$

where E^jU is the sequence u_j, u_{j+1}, \dots and $G_i^{(j)}(x|U)$ is the j th derivative of $G_i(x|U)$. Note that $G_i^{(j)}(x|U) = 0$ if $j > i$.

For the single population epidemic model, let $\phi(\theta) = \mathbb{E}[\exp(-\theta T_I)]$, $\theta \geq 0$, be the moment generating function of T_I and let

$$\phi_{n,a}(s, \theta) = \mathbb{E}[s^{n-T} \exp(-\theta T_A)], \quad \theta \geq 0. \quad (3.4)$$

Then it follows from Proposition 3.3 of Picard and Lefèvre (1990), see also Ball and Clancy (1993), that

$$\phi_{n,a}(s, \theta) = \sum_{i=0}^n \frac{n!}{(n-i)!} \phi(\theta + \lambda_L i)^{n+a-i} G_i(s|U), \quad (3.5)$$

where the sequence U is given by $u_i = \phi(\theta + \lambda_L i)$, $i = 0, 1, \dots$.

Let $\mu_{n,a} = \mathbb{E}[T]$ be the mean total size of the above epidemic. Then by differentiating 3.5 with respect to s and setting $s = 1$ and $\theta = 0$, it follows using 3.3 that

$$\mu_{n,a} = n - \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n+a-i} \alpha_i, \quad (3.6)$$

where $q_i = \phi(\lambda_L i)$ and $\alpha_i = G_{i-1}(1|V)$. Here the sequence V is given by $v_i = \phi(\lambda_L(i+1)) = q_{i+1}$ (for $i = 0, 1, \dots$). We may call the q_i s the ‘escape probabilities’, since $q_i = \mathbb{E}[\exp(-i\lambda_L T_I)]$ is the probability that an individual exposed to a set of i infectives in its group is not infected by any of them. From this interpretation it is immediate that the q_i s, and hence the v_i s, are monotone non-increasing:

$$q_i \geq q_{i+1} \quad \text{for all } i \geq 0 \quad (\text{note that } q_0 = 1) \quad (3.7)$$

Note that it is straightforward to compute $\alpha_1, \alpha_2, \dots$ numerically using the recursive definition of the Gontcharoff family of polynomials given in 3.1.

In §s 3.4 and 3.5 we shall require the fact that $\alpha_i > 0$, $i = 1, 2, \dots$, which we now prove. The integral definition of $G_i(x|U)$ given in §3.2 implies $G_i(x|U) > 0$, $i = 0, 1, \dots$, provided that $x > u_0 \geq u_1 \geq \dots \geq 0$. (This gives a new and very elegant proof of a result proved in Gani and Shanbhag (1974).) The strict positivity of the α_i s follows immediately from 3.7 (remembering that $v_i = q_{i+1}$).

We shall need the moment generating function of T_A , $\psi_{n,a}(\theta) = \mathbb{E}[\exp(-\theta T_A)]$ say, which can be obtained by setting $s = 1$ in 3.5.

Consider now an extension of the single population epidemic model, in which susceptibles can also be infected from outside the population. Specifically, suppose that each of the n initial susceptibles has probability π of avoiding infection from outside the population during the course of the epidemic, independently of

other susceptibles in the population. This extended model has been considered by Addy *et al* (1991), who derived recursive expressions for the probability generating function of T and the moment generating function of T_A . The final outcome of the extended model with outside infection has the same distribution as that of the single population model with initial numbers of infectives and susceptibles $a + Y$ and $n - Y$, respectively, where Y is a realisation of a binomial random variable with parameters n and $1 - \pi$. (This follows by considering the random graph associated with the epidemic.)

Let $\tilde{\phi}_{n,a}(s, \theta) = \mathbb{E}[s^{n-T} \exp(-\theta T_A)]$, $\theta \geq 0$, be the joint generating function of (T, T_A) for the model with outside infection. Then conditioning on the value of Y and using 3.5 yields

$$\tilde{\phi}_{n,a}(s, \theta) = \sum_{k=0}^n \binom{n}{k} \pi^k (1 - \pi)^{n-k} \sum_{i=0}^k \frac{k!}{(k-i)!} \phi(\theta + \lambda_L i)^{n+a-i} G_i(s|U), \quad (3.8)$$

which on changing the order of summation gives, after a little algebra,

$$\tilde{\phi}_{n,a}(s, \theta) = \sum_{i=0}^n \frac{n!}{(n-i)!} \phi(\theta + \lambda_L i)^{n+a-i} \pi^i G_i(s|U). \quad (3.9)$$

Let $\tilde{\mu}_{n,a} = \mathbb{E}[T]$ be the mean total size for the epidemic with outside infection. Then arguing as in the derivation of 3.6 yields

$$\tilde{\mu}_{n,a} = n - \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n+a-i} \pi^i \alpha_i. \quad (3.10)$$

We now give expressions for the final size distribution of the single population epidemic model with outside infection. Let $\tilde{P}_k^n = \Pr\{T = k\}$, $k = 0, 1, \dots, n$. Then setting $\theta = 0$ in 3.9, differentiating $n - k$ times with respect to s and using 3.3 yields

$$\tilde{P}_k^n = \frac{1}{(n-k)!} \sum_{i=n-k}^n \frac{n!}{(n-i)!} q_i^{n+a-i} \pi^i G_{i-n+k}(0|E^{n-k}U), \quad k = 0, 1, \dots, n, \quad (3.11)$$

where the sequence U is given by $u_i = q_i = \phi(\lambda_L i)$, $i = 0, 1, \dots$

Addy *et al* (1991) give a similar expression to 3.11, but not using Gontcharoff polynomials. They also show that the total size probabilities can be determined from the following triangular system of linear equations:

$$\sum_{i=0}^k \binom{n-i}{k-i} \tilde{P}_i^n / \{q_{n-k}^{a+i} \pi^{n-k}\} = \binom{n}{k}, \quad k = 0, 1, \dots, n. \quad (3.12)$$

Setting $\pi = 1$ in 3.12 yields a set of linear equations governing the total size distribution of the epidemic without outside infection, see Ball (1986).

The above systems of equations are in principle straightforward to solve numerically, because of their triangular structure. Numerical problems due to rounding

errors can occur even for moderate values of n , say of the order $n = 50$ or 100 . However, in many applications, n will correspond to group, or family, size and will typically be small, say $n \leq 5$ or 10 , permitting the required properties to be calculated accurately.

3.3 Initial stages of a multi-group epidemic

3.3.1 Branching process approximation

Suppose that the total population N , and hence the number of groups m , is large. Then during the early stages of the epidemic, every time a between group infection occurs the contacted individual is likely to be in a previously uninfected group. Thus the initial stages of the epidemic can be approximated by a branching process, in which the units are single group epidemic processes and the offspring of a given unit are those groups that are directly infected by infectives in that unit.

The approximation can be made precise by considering a sequence of epidemics, indexed by the number of groups m , and using the coupling argument of Ball (1983b) and Ball and Donnelly (1995). Specifically, the epidemic processes and the approximating branching process can be constructed on the same probability space $(\Omega, \mathcal{F}, \mathcal{P})$ such that, if $A \subseteq \Omega$ denotes the set on which the branching process goes extinct, then (i) for P -almost all $\omega \in A$ the process of infectives in the epidemic process and the branching process agree over the time interval $[0, \infty)$ for all sufficiently large m , and (ii) for P -almost all $\omega \in \Omega \setminus A$ the epidemic process and the branching process agree over $[0, c \log m]$ for all sufficiently large m , for any $c < (2\alpha)^{-1}$ where α is the Malthusian parameter of the branching process. The result in (ii) is the best possible in the sense that if $c > (2\alpha)^{-1}$ then for all sufficiently large m , the epidemic process and the branching process do not agree over the whole interval $[0, c \log m]$. The Malthusian parameter α can be obtained as follows. For $t \geq 0$, let $Y(t)$ denote the number of infectives at time t in the single group epidemic model of §3.2, when initially there are one infective and $n - 1$ susceptibles. Then, provided that the branching process is supercritical, α is the unique solution in $(0, \infty)$ of the equation

$$\int_0^\infty \lambda_G E[Y(t)] \exp(-\alpha t) dt = 1. \quad (3.13)$$

The total size of the approximating branching process can be obtained by considering its embedded Galton-Watson process, whose offspring distribution can be derived as follows. A typical unit in the branching process commences with one of the susceptibles in the group being infected from outside. That infective will start an epidemic within its own group. Each infective in this single group epidemic independently makes infections outside the group at rate λ_G throughout their infectious period. Hence the total number of outside infections emanating from the group under consideration follows a Poisson distribution with random

mean $\lambda_G T_A$, where T_A is the severity of the single group epidemic. Further, in the branching process approximation, all of these outside infections are with susceptibles in distinct groups, so the offspring distribution, R say, of the embedded Galton-Watson process is also Poisson with random mean $\lambda_G T_A$. Let $R_T = E[R]$. Then, letting T be the total size of the single group epidemic and using the Wald's identity for epidemics proved in Ball (1986), we obtain

$$\begin{aligned} R_T &= \lambda_G E[T_A] \\ &= \lambda_G (1 + E[T]) E[T_I] \\ &= \lambda_G (1 + \mu_{n-1,1}) E[T_I]. \end{aligned} \tag{3.14}$$

Note that, as in the clumped Reed-Frost model, R_T is of the form $R_T = \mu R_0$, where $R_0 = \lambda_G E[T_I]$ is the basic reproductive ratio for the model in which all the groups are of size 1, i.e. $n = 1$, and $\mu = 1 + \mu_{n-1,1}$ is the mean clump size.

To obtain a threshold theorem for the multi-group epidemic process, we say that a global epidemic occurs if in the limit as m tends to ∞ the epidemic infects infinitely many groups. By standard branching process theory, see for example Jagers (1975), global epidemics can occur if and only if $R_T > 1$, so R_T may be viewed as the threshold parameter for the multi-group epidemic. Note that for any given set of parameter values, R_T can be computed using 3.6. Indeed, for small values of the group size m , explicit expressions for α_i , and hence for R_T , can easily be obtained.

The probability of a global epidemic depends on the number and configuration of initial infectives. Consider first the case in which the epidemic is initiated by just one of the susceptibles becoming infected. Then, again by standard branching process theory, the probability of a global epidemic is $1 - \tau$, where τ is the smallest root in $[0, 1]$ of the equation $f(s) = s$. Here $f(s)$ is the probability generating function of R , which, conditioning on the value of T_A , is given by

$$\begin{aligned} f(s) &= E[s^R] \\ &= E[E[s^R | T_A]] \\ &= E[\exp(-\lambda_G T_A (1 - s))] \\ &= \psi_{n-1,1}(\lambda_G (1 - s)), \quad 0 \leq s \leq 1. \end{aligned} \tag{3.15}$$

For $i = 1, 2, \dots, n$, let τ_i be the probability of a non-global epidemic when initially there is one infectious group containing i infectives and $n - i$ susceptibles, so $\tau_1 = \tau$. Let Z be the size of the first generation in the embedded Galton-Watson process, i.e. Z is the total number of outside infections emanating from the initial single group epidemic. Then, again conditioning on the value of T_A ,

$$\tau_i = E[\tau^Z]$$

$$\begin{aligned}
&= \mathbb{E}[\mathbb{E}[\tau^Z | T_A]] \\
&= \mathbb{E}[\exp(-\lambda_G T_A (1 - \tau))] \\
&= \psi_{n-i,i}(\lambda_G (1 - \tau)).
\end{aligned} \tag{3.16}$$

Finally, if initially there are a_i infectious groups with i infectives and $n - i$ susceptibles, $i = 1, 2, \dots, n$, then

$$\Pr\{\text{global epidemic}\} = 1 - \prod_{i=1}^n \tau_i^{a_i}. \tag{3.17}$$

Note that $\psi_{n-i,i}(\theta)$, and hence τ_i , $i = 1, 2, \dots, n$, are straightforward to compute by setting $s = 1$ in 3.5 and using the recursive definition 3.1 for the quantities $G_0(1|U), G_1(1|U), \dots, G_{n-1}(1|U)$.

Other properties of the branching process approximation are straightforward to determine. Suppose that initially there is one infectious group containing just one infective. Let \tilde{N} and \tilde{G} be respectively the total number of individuals and total number of groups infected by the epidemic, where now the initial infective and the initial infectious group are included. As before, let T and T_A be respectively the total size and severity of the single group epidemic in the initial infectious group. Let $h(s_1, s_2) = \mathbb{E}[s_1^{\tilde{N}} s_2^{\tilde{G}}]$ be the joint probability generating function of (\tilde{N}, \tilde{G}) under the branching process approximation. Then, conditioning on (T, T_A) ,

$$\begin{aligned}
h(s_1, s_2) &= \mathbb{E}[\mathbb{E}[s_1^{\tilde{N}} s_2^{\tilde{G}} | T, T_A]] \\
&= \mathbb{E}[\mathbb{E}[s_1^{1+T+\sum_{i=1}^Z \tilde{N}_i} s_2^{1+\sum_{i=1}^Z \tilde{G}_i} | T, T_A]],
\end{aligned} \tag{3.18}$$

where, as above, Z is the size of the first generation in the embedded Galton-Watson process and $(\tilde{N}_1, \tilde{G}_1), (\tilde{N}_2, \tilde{G}_2), \dots, (\tilde{N}_Z, \tilde{G}_Z)$ are independent and identically distributed copies of (\tilde{N}, \tilde{G}) . Now Z is Poisson with mean $\lambda_G T_A$ so

$$\begin{aligned}
h(s_1, s_2) &= s_1 s_2 \mathbb{E}[s_1^T \mathbb{E}[h(s_1, s_2)^Z | T, T_A]] \\
&= s_1 s_2 \mathbb{E}[s_1^T \exp(-\lambda_G T_A (1 - h(s_1, s_2)))] \\
&= s_1 s_2 \hat{\phi}_{n-1,1}(s_1, \lambda_G (1 - h(s_1, s_2))),
\end{aligned} \tag{3.19}$$

where

$$\begin{aligned}
\hat{\phi}_{n-1,1}(s, \theta) &= \mathbb{E}[s^T \exp(-\theta T_A)] \\
&= s^{n-1} \phi_{n-1,1}(s^{-1}, \theta),
\end{aligned} \tag{3.20}$$

is the joint generating function of (T, T_A) . Thus $h(s_1, s_2)$ satisfies the functional equation

$$h(s_1, s_2) = s_1^n s_2 \phi_{n-1,1}(s_1^{-1}, \lambda_G (1 - h(s_1, s_2))). \tag{3.21}$$

Appropriate differentiation of 3.21 yields expressions for the moments of \tilde{N} and \tilde{G} , such as $\mathbb{E}[\tilde{N}]$, $\mathbb{E}[\tilde{G}]$, $\text{var}(\tilde{N})$, $\text{var}(\tilde{G})$ and $\text{cov}(\tilde{N}, \tilde{G})$. Note that 3.3 and

the recursive definition 3.1 of Gontcharoff polynomials enables the derivatives of $\phi_{n-1,1}(s, \theta)$, and hence the above moments to be calculated. When $R_T \geq 1$ the above moments are all infinite. However, if $R_T > 1$ then moments conditional upon the occurrence of a non-global epidemic can be derived from 3.21.

3.3.2 Discussion of threshold parameter R_T

We now discuss the relationship of our threshold parameter R_T to the classical reproduction ratio R_0 (see for example Diekmann *et al* 1990) for the multi-group epidemic. For definiteness of argument, suppose that the infectious period T_I follows a negative exponential distribution with mean γ^{-1} , so our model becomes a multi-group generalisation of the general stochastic epidemic (see for example Bailey 1975, Chapter 6). The deterministic version of our model is then expressed by the differential equations

$$\begin{aligned} \frac{dx_i}{dt} &= -(\lambda_L y_i + N^{-1} \lambda_G \sum_{j \neq i} y_j) x_i, \\ \frac{dy_i}{dt} &= (\lambda_L y_i + N^{-1} \lambda_G \sum_{j \neq i} y_j) x_i - \gamma y_i, \quad i = 1, 2, \dots, m, \end{aligned} \quad (3.22)$$

where the groups are labelled $1, 2, \dots, m$ and $x_i(t)$ and $y_i(t)$ are respectively the numbers of susceptibles and infectives in the i th group at time t .

The reproduction ratio for the above deterministic model, usually defined informally (in a stochastic sense!) as the expected number of infectious contacts made by a single initial infective in an otherwise susceptible population, is $R_0 = \{(n-1)\lambda_L + \lambda_G\}/\gamma$. In the deterministic setting, a major epidemic occurs if and only if $R_0 > 1$. However, as we shall see soon, $R_0 > 1$ does not generally provide a good indication as to whether a global epidemic can occur in our stochastic model. This is because a deterministic model can only be a good approximation to the more realistic stochastic model if all the population sizes are large, *cf* the convergence theorems of Kurtz (1970, 1981), but in the multi-group epidemic the group size n is usually small. Thus the deterministic model 3.22 will not generally provide an adequate description of the multi-group epidemic. Indeed, a more appropriate deterministic model is one described by a system of differential equations for $x_{i,j}(t)$, $0 \leq i, j \leq n$, where $x_{i,j}(t)$ is the number of groups with i susceptibles and j infectives at time t .

It is now convenient to assume that the multi-group epidemic model is parameterised so that the within-group infection rate is $(n-1)^{-1}\lambda_L$ and, for the purpose of illustration, that the time axis is linearly rescaled so that $\gamma = 1$. Under these assumptions, $R_0 = \lambda_L + \lambda_G$ independently of the group size n . The threshold parameter R_T can be calculated using 3.14. Figure 1 shows for various group sizes n the graph of critical values of (λ_L, λ_G) so that $R_T = 1$. The corresponding graph for $R_0 = 1$ is also shown. When the group size $n = 1$ the graph corresponding to $R_T = 1$ is constant at $\lambda_G = 1$, since then there can be no within group spread of

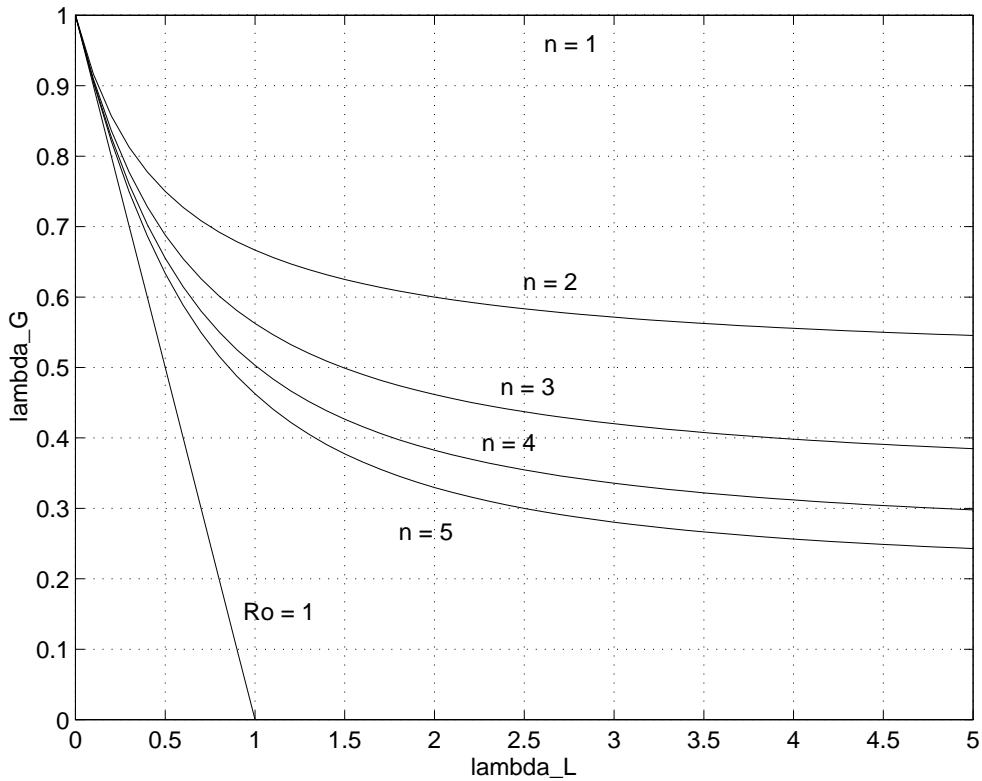


Figure 1. Critical values of (λ_L, λ_G) so that $R_T = 1$.

infection and the value of λ_L is irrelevant. For $n = 1, 2, \dots$, the $R_T = 1$ graph for $n + 1$ lies below that for n and it is shown below that the $R_T = 1$ graph converges to the $R_0 = 1$ graph as n tends to ∞ . As noted above, $R_0 = 1$ does not provide a good indicator as to whether a global epidemic can occur when the group size n is small.

We now return to the model with general T_I and examine the asymptotic behaviour of R_T as n tends to infinity. We still assume without loss of generality that $E[T_I] = 1$ and that the within-group infection rate is $(n - 1)^{-1}\lambda_L$. Thus from 3.14, $R_T = \lambda_G(1 + \mu_{n-1,1})$, so we are interested in the asymptotic behaviour of $\mu_{n-1,1}$ as n tends to ∞ . For large n , the early stages of the single group epidemic process can be approximated by a branching process and Ball (1983b) shows how to make the approximation precise in the limit as n tends to ∞ . Specifically, a sequence of epidemic processes indexed by n and the approximating branching process can be constructed on the same probability space so that, as n tends to ∞ , if the branching process goes extinct then the total size of the epidemic process converges almost surely to the total size of the branching process, and if the branching process does not go extinct then the total size of the epidemic process converges almost surely to ∞ . Moreover, in the latter case von Bahr and Martin-Löf (1980) show that $n^{\frac{1}{2}}(T/n - \rho)$ converges in distribution to a normal random variable with zero mean. Here T is the total size of the single population epidemic and ρ is the largest root in $(0, 1)$ of the equation $1 - x = \exp(-\lambda_L x)$.

Note that ρ is the proportion of initial susceptibles that are ultimately infected in the limiting deterministic epidemic as n tends to infinity.

Suppose first that $\lambda_L < 1$, so that the single group epidemic is below threshold. The mean total size of the approximating branching process is $\lambda_L/(1 - \lambda_L)$, so by the dominated convergence theorem $\lim_{n \rightarrow \infty} \mu_{n-1,1} = \lambda_L/(1 - \lambda_L)$. Thus R_T converges up to $\lambda_G(1 + (1 - \lambda_L))^{-1}\lambda_L = \lambda_G/(1 - \lambda_L)$ as n tends to ∞ . Hence, if $\lambda_G < 1 - \lambda_L$ only non-global epidemics can occur, however large the group size n is, while if $\lambda_G > 1 - \lambda_L$ global epidemics can occur provided that n is sufficiently large. Note that as n tends to ∞ the equation $R_T = 1$ converges to $\lambda_L + \lambda_G = 1$, *i.e.* $R_0 = 1$.

Now suppose that $\lambda_L > 1$ so that the single group epidemic is above threshold. Let q be the probability that the approximating branching process (to the single group epidemic) goes extinct. Recall from Waugh (1958) and Daly (1979) that, conditional upon extinction, a supercritical Galton-Watson process with offspring probability generating function $g(s)$ behaves as a (subcritical) Galton-Watson process with offspring probability generating function $q^{-1}g(qs)$. The number of contacts made by the initial infective in the single population epidemic is Poisson with (random) mean $\lambda_L T_I$, so the offspring probability generating function of the Galton-Watson process embedded in the approximating branching process is $g(s) = \phi(\lambda_L(1 - s))$, where $\phi(\theta) = E[\exp(-\theta T_I)]$. Thus q is the unique solution in $(0, 1)$ of the equation $\phi(\lambda_L(1 - s)) = s$ and the offspring mean for the embedded Galton-Watson process conditioned upon extinction, \tilde{m} say, is given by $\tilde{m} = -\lambda_L \phi^{(1)}(\lambda_L(1 - q))$. Further, conditional upon extinction, the mean total size of the approximating branching process is $\tilde{m}/(1 - \tilde{m})$. Combining all this with the above von Bahr and Martin-Löf limit theorem, and recalling that $R_T = \lambda_G(1 + \mu_{n-1,1})$, yields

$$R_T \sim \lambda_G \left\{ 1 + \frac{q\tilde{m}}{1 - \tilde{m}} + (1 - q)\rho(n - 1) \right\} \quad \text{as } n \rightarrow \infty. \quad (3.23)$$

Thus, in contrast to the situation when $\lambda_L < 1$, for $\lambda_L > 1$ global epidemics can always occur if n is sufficiently large, whatever the value of λ_G (provided it is not zero).

In the critical case, $\lambda_L = 1$, the mean total size of the approximating branching process is infinite, so again global epidemics can always occur provided that n is sufficiently large.

Another way of viewing the above is to assume that λ_L is fixed and examine the behaviour, as n tends to ∞ of the critical value, λ_G^{CRIT} say, of λ_G for global epidemics to be possible. It follows from the preceding arguments that if $\lambda_L < 1$ then $\lambda_G^{\text{CRIT}} = O(1)$ as $n \rightarrow \infty$, whilst if $\lambda_L > 1$ then $\lambda_G^{\text{CRIT}} = O(n^{-1})$ as $n \rightarrow \infty$. This corresponds to the amplification effect discussed for the multi-group Reed-Frost epidemic in Section 2.

We can use our model to study the efficacy of various vaccination strategies. For example, as in §2.5, consider two vaccination policies, a local one in which

a fixed proportion, θ say, of groups is completely vaccinated and a global one in which a proportion θ of susceptibles in every group is vaccinated. For convenience we suppose that θn is an integer. Under both policies the rate at which a given infective makes outside infections is $(1 - \theta)\lambda_G$. However, in the local policy such an infection is with a group having n susceptibles, so $R_T = (1 - \theta)\lambda_G(1 + \mu_{n-1,1})$, but in the global policy it is with a group having $(1 - \theta)n$ susceptibles, so $R_T = (1 - \theta)\lambda_G(1 + \mu_{(1-\theta)n-1,1})$. Clearly $\mu_{n-1,1} > \mu_{(1-\theta)n-1,1}$ so the global policy will be more effective in preventing the spread of a global epidemic.

3.4 Final outcome of a multi-group epidemic

In this subsection we consider the final outcome of the multi-group epidemic as m , the number of groups, becomes large. In §3.3.1 we examined the final outcome of a non-global epidemic; here we shall be concerned with what happens in the event of a global epidemic. Our argument will be heuristic, a formal proof being delayed until §4.2.

Let z be the expected proportion of initial susceptibles that are infected by a global epidemic. Thus z can be interpreted as the probability that a given initial susceptible, who is not in one of the initially infectious groups, is ultimately infected by the epidemic.

Fix attention on a single group that initially contained no infectives. We can decompose the ultimate spread of infection within that group by first determining which of the initial susceptibles are infected from outside the group, and then letting these individuals initiate a single population epidemic amongst the remaining susceptibles in the group. Let \tilde{T} be the total person time units of infection present in the population at large over the whole course of the epidemic. Then for large m , $\tilde{T} \sim NzE[T_I]$. At any time a given susceptible in the group under consideration is being infected from outside the group with intensity $N^{-1}\lambda_G$ per outside infective. Thus, as m tends to ∞ , each given susceptible in the group independently avoids infection from outside with probability $\pi = \exp(-\lambda_G z E[T_I])$. It follows that the ultimate spread of infection within the group has the same distribution as that of the extended model of Addy *et al* (1991) described in §3.2. Hence, the mean total size of the epidemic within the group is given by setting $a = 0$ in 3.10. However, the mean total size also equals zn , since z is the expected proportion of susceptibles that are ultimately infected. Thus we can deduce the following equation

$$nz = n - \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \pi^i \alpha_i, \quad (3.24)$$

which, since $\pi = \exp(-\lambda_G z E[T_I])$, is an implicit equation for z . Clearly $z = 0$ is always a solution of 3.24. We now show that there is a (unique) second solution in $(0, 1)$ if and only if $R_T > 1$.

It is convenient to rearrange 3.24 into

$$n(1 - z) = \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \exp(-\lambda_G z E[T_I] i) \alpha_i. \quad (3.25)$$

We proved in §3.2 that $\alpha_i > 0$, $i = 1, 2, \dots$, so the right hand side of 3.25 is a convex function of z . Thus 3.25 has at most two solutions since its left hand side is linear in z . Further, by examining the values at $z = 0$ of the derivatives with respect to z of the two sides of 3.25, we see that there is a second solution if and only if

$$\lambda_G E[T_I] \sum_{i=1}^n \frac{(n-1)!}{(n-i)!} q_i^{n-i} i \alpha_i > 1. \quad (3.26)$$

Now

$$\begin{aligned} \sum_{i=1}^n \frac{(n-1)!}{(n-i)!} q_i^{n-i} i \alpha_i &= \sum_{i=1}^n \frac{(n-1)!}{(n-i)!} q_i^{n-i} \alpha_i (n - (n-i)) \\ &= \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \alpha_i - \sum_{i=1}^{n-1} \frac{(n-1)!}{(n-i-1)!} q_i^{n-i} \alpha_i. \end{aligned} \quad (3.27)$$

From 3.6, the second sum on the right hand side of 3.27 is $n - 1 - \mu_{n-1,1}$. The first sum can be evaluated by recalling that $\alpha_i = G_{i-1}(1|V)$, where the sequence V is given by $v_i = q_{i+1} = \phi(\lambda_L(i+1))$, $i = 0, 1, \dots$. We obtain

$$\begin{aligned} \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \alpha_i &= \sum_{i=1}^n \frac{n!}{(n-i)!} v_{i-1}^{n-i} G_{i-1}(1|V) \\ &= n \sum_{i=0}^{n-1} \frac{(n-1)!}{(n-1-i)!} v_i^{n-1-i} G_i(1|V) \\ &= n, \end{aligned} \quad (3.28)$$

where in the last step we have used the recursive definition 3.1 of the Gontcharoff polynomials $G_i(x|V)$, $i = 0, 1, \dots$. Putting all this together, we obtain from 3.27 that

$$\sum_{i=1}^n \frac{(n-1)!}{(n-i)!} q_i^{n-i} i \alpha_i = 1 + \mu_{n-1,1}. \quad (3.29)$$

Hence from 3.26 and the expression for R_T given in 3.14, 3.24 has a solution in $(0, 1)$ if and only if $R_T > 1$. When $R_T > 1$ the solution of 3.24 in $(0, 1)$ gives the expected proportion of initial susceptibles ultimately infected by a global epidemic.

As noted earlier, in the event of a global epidemic the total size in a group that did not have initial infectives is distributed as the total size of the extended model of Addy *et al* (1991) with $\pi = \exp(-\lambda_G z E[T_I])$. This distribution may be calculated by using 3.11 or 3.12. Figure 2 illustrates for various values of λ_L and λ_G , the total size distribution in a group when the infectious period T_I follows a negative exponential distribution with mean 1 and the group size $n = 5$. Figure 2

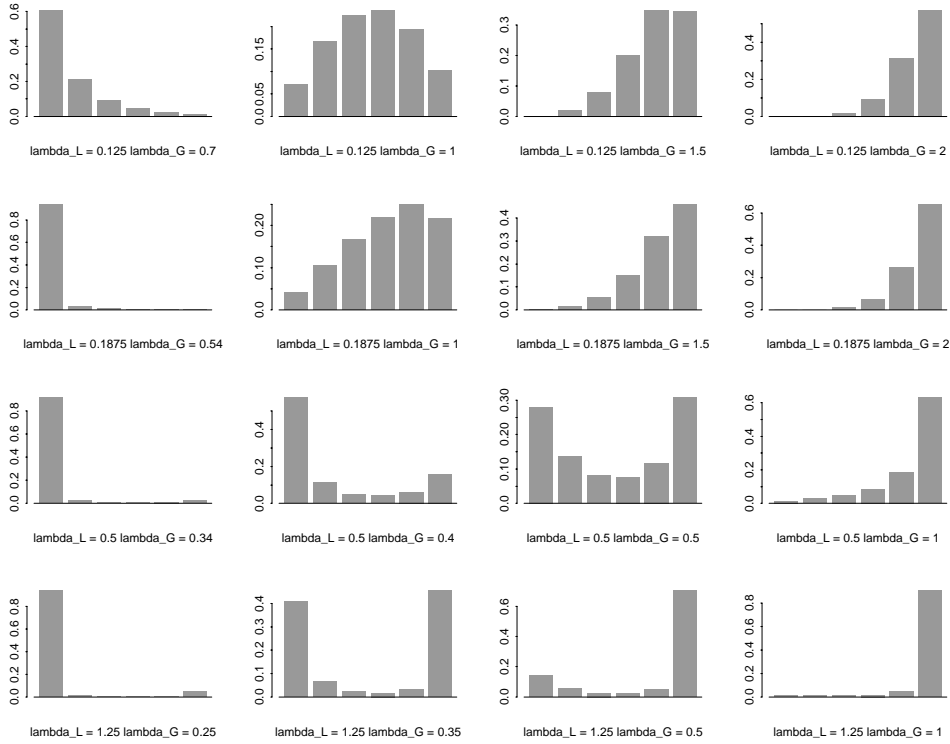


Figure 2. Total size distribution in a group when the infectious period T_I follows a negative exponential distribution with mean 1 and the group size $n = 5$. Note that the critical values of λ_G are (for each row, starting at the top) $\lambda_G^{\text{CRIT}} = .6336, .5321, .3296, .2429$.

also gives for each choice of λ_L the critical value, λ_G^{CRIT} , of λ_G for global epidemics to be possible. Notice the difference in the shape of the distribution according to whether $(n - 1)\lambda_L < 1$ or $(n - 1)\lambda_L > 1$, *i.e.* according to whether the within group epidemic is below or above its threshold. When $(n - 1)\lambda_L < 1$ the distribution is unimodal for all values of $\lambda_G > \lambda_G^{\text{CRIT}}$, with the mode increasing from 0 for values of λ_G just greater than λ_G^{CRIT} to $n (= 5)$ for sufficiently large values of λ_G . When $(n - 1)\lambda_L > 1$ the distribution is initially bimodal as λ_G is increased from λ_G^{CRIT} , but becomes unimodal with the mode either at or close to n for sufficiently large values of λ_G . (In our examples the mode is always at $n = 5$ but this is unlikely to be the case in general.) The shape of the group total size distribution can be explained in terms of the threshold behaviour of the single group epidemic. When $(n - 1)\lambda_L < 1$, only minor epidemics will occur within a group, but as λ_G increases so does the number of group members infected from the population at large, and hence also the size of the epidemic within the group. When $(n - 1)\lambda_L > 1$, the within group epidemic is above threshold, so major epidemics can occur as soon as $\lambda_G > \lambda_G^{\text{CRIT}}$. Thus the distribution is bimodal, being a mixture of two components, one corresponding to a minor epidemic and the other to a major epidemic. Again, as λ_G increases, so does the number of

outside infections, and eventually the minor epidemic component will disappear.

3.5 Unequal group sizes

We now consider the situation in which the group sizes are not all equal. For $n = 1, 2, \dots$, let m_n be the number of groups of size n . Let $m = \sum_{n=1}^{\infty} m_n$ be the total number of groups and $N = \sum_{n=1}^{\infty} nm_n$ be the total number of individuals. As before, the infectious periods of different infectives are independently and identically distributed according to a random variable T_I , and throughout its infectious period a given infective makes contact with a given susceptible in its own group with rate λ_L and with a given susceptible in any other group at rate λ_G/N . We examine the asymptotic situation in which the number of groups m tends to infinity in such a way that $m_n/m \rightarrow h_n$ $n = 1, 2, \dots$, and $\sum_{n=1}^{\infty} h_n = 1$. Thus, for $n = 1, 2, \dots$, h_n is the asymptotic proportion of groups of size n . Let $\mu_h = \sum_{n=1}^{\infty} nh_n$ be the asymptotic mean group size and assume that $\mu_h < \infty$.

The initial stages of the multi-group epidemic can be approximated by a multi-type branching process, in which the units are single group epidemic processes, the offspring of a given unit are those groups that are directly infected by infectives in that unit and type corresponds to group size. Again the approximation can be made precise in the limit as m tends to ∞ by using the coupling argument of Ball (1983b) and Ball and Donnelly (1995). Label the types $1, 2, \dots$, according to group size and let $\Lambda = [\lambda_{ij}]$ be the offspring mean matrix of the embedded multi-type Galton-Watson process. Thus λ_{ij} is the expected number of type j groups infected by infectives from a type i group single population epidemic.

Let $T^{(i)}$ and $T_A^{(i)}$ be respectively the total size and severity of a single population epidemic in which initially there are 1 infective and $i-1$ susceptibles. As in §3.3.1, the total number of outside infections emanating from a type i group follows a Poisson distribution with random mean $\lambda_G T_A^{(i)}$. The probability that a given outside infection is with an individual in a group of size j is $jm_j/N = jh_j/\mu_h$. Hence

$$\begin{aligned} \lambda_{ij} &= \lambda_G \mathbf{E} [T_A^{(i)}] jh_j/\mu_h \\ &= \lambda_G (1 + \mathbf{E} [T^{(i)}]) \mathbf{E} [T_I] jh_j/\mu_h \\ &= \lambda_G (1 + \mu_{i-1,1}) \mathbf{E} [T_I] jh_j/\mu_h, \end{aligned} \tag{3.30}$$

using the Wald's identity for epidemics.

The multiplicative structure of the matrix Λ given by 3.5 implies that its maximal eigenvalue is

$$R_T = \lambda_G \mathbf{E} [T_I] \mu_h^{-1} \sum_{n=1}^{\infty} (1 + \mu_{n-1,1}) nh_n. \tag{3.31}$$

By standard branching process theory a global epidemic (corresponding to non-extinction of the approximating multi-type branching process) has non-zero prob-

ability of occurring if and only if $R_T > 1$. Formulae implicitly giving the probability of a global epidemic and properties of a non-global epidemic can be derived as in §3.3.1.

Note that again R_T is of the form $R_T = \mu R_0$, where $R_0 = \lambda_G E[T_I]$ is the basic reproductive ratio for the model in which all the groups are of size 1, and $\mu = \mu_h^{-1} \sum_{n=1}^{\infty} (1 + \mu_{n-1,1}) n h_n$ is the size-biased mean clump size. The formula for μ uses the fact that if π_i (as in Sections 1 and 2) is the probability that an individual chosen at random from the population is in a group of size i then

$$\pi_i = \mu_h^{-1} i h_i, \quad i = 1, 2, \dots \quad (3.32)$$

(thus $\mu = \sum (\mu_{n-1,1}) \pi_n$). Indeed, using the size-biased sampling, the initial stages of the epidemic can be approximated by a single-type branching process (in which the units are single group epidemic processes) whose offspring distribution is Poisson with random mean, which is a mixture of $T_A^{(1)}, T_A^{(2)}, \dots$ with respective mixing probabilities π_1, π_2, \dots . Note that this second, single-type approximation avoids any difficulties caused by the possibility of there being infinitely many types in the multi-type approximation.

We now turn to the final outcome of a global epidemic. Let z be the probability that a randomly chosen initial susceptible is ultimately infected by the epidemic, and for $n = 1, 2, \dots$, let z_n be the same probability for a randomly chosen initial susceptible in a group of size n . The size biased sampling implies that

$$z = \mu_h^{-1} \sum_{n=1}^{\infty} n z_n h_n. \quad (3.33)$$

Fix attention on a group of size n that did not contain any initial infectives. Arguing as in §3.4, the probability that a given susceptible in that group avoids infection from outside is $\pi = \exp(-\lambda_G z E[T_I])$, and the expected total size of the epidemic within that group is $\tilde{\mu}_{n,0}$. Thus, using 3.10,

$$n z_n = n - \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \pi^i \alpha_i, \quad n = 1, 2, \dots \quad (3.34)$$

Summing 3.34 over n and using 3.33 yields

$$z = 1 - \sum_{n=1}^{\infty} \mu_h^{-1} h_n \sum_{i=1}^n \frac{n!}{(n-i)!} q_i^{n-i} \pi^i \alpha_i, \quad (3.35)$$

which, since $\pi = \exp(-\lambda_G z E[T_I])$, is an implicit equation for z . Clearly, $z = 0$ is always a solution of 3.35 and similar arguments to those used in §3.4 show that there is a (unique) second solution in $(0, 1)$ if and only if $R_T > 1$. When $R_T > 1$, the root of 3.35 in $(0, 1)$ gives the expected proportion of initial susceptibles that are ultimately infected by a global epidemic. As in §3.5, the total spread of infection within a group not having initial infectives has the same distribution as in the extended model of Addy *et al* (1991), with $\pi = \exp(-\lambda_G p E[T_I])$.

4 Embedding representations of the final size of the epidemic

4.1 Embedding and the asymptotic distribution of final size

Showing that the epidemic process and its final size in a population can be constructed by sampling an appropriate ‘embedding’ process at suitably defined stopping times may be of interest in itself since it yields an alternative way of constructing some aspects of the epidemic process, but it also turns out to be an efficient tool for studying the distribution of the final size and related quantities, in particular in asymptotic situations. In the present case, the construction and methods of Scalia-Tomba (1985, 1990) can be used, with minor modifications, to show that the final size of the epidemic, in a large population, is either small, with probabilities related to the approximating branching process, or large, with an approximately normal distribution around the mean expected from the ‘deterministic approximation’.

The general idea of the construction is to create a process describing the number of individuals in the population who would become infected, with infection being considered as coming from outside the population, and then creating the epidemic within the population by letting the infectious individuals in the population define the amount of infection to which the remaining susceptibles will be exposed. The final size of the epidemic will then typically be characterized by a ‘balance equation’ stating that the epidemic stops when the total ‘infection pressure’ generated by those infected in the population (including initial infectives) becomes equal to the infection pressure needed to infect the same individuals. One then proceeds to show that the embedding process is asymptotically Gaussian and that the balance equation translates into a first-crossing problem for the embedding process. Some further calculations are finally needed to clarify the ‘either small or large’ character of the epidemic process.

4.2 The case of distributed infectious period and households

We will first carry out the construction for the situation considered in §3.1, in which the population is composed of *a priori* defined groups or households with given sizes.

4.2.1 The basic household process $(R(t), A(t))$

Let $(R(t), A(t))$ describe what has happened to a household of size n , with no initial infectives, after having been subjected to external infection pressure $t \geq 0$,

i.e. when it has been exposed to t time units of external infection. Here R is the number of household members having had the disease (in the terminology of §3.2, R is the final size when there are 0 initial infectives, and $\pi = \exp(-\lambda_G t/N)$ and A is the cumulative sum of the infectious periods of these individuals. We assume that, as far as the process $(R(t), A(t))$ is concerned, internal (within-household) infections are instantaneous. Thus R and A are constant except for a finite number of (simultaneous) jumps, corresponding to infection from outside of a susceptible individual; they are non-decreasing with $0 \leq R \leq n$ and $0 \leq A \leq \Sigma$, where Σ is the sum of n independent copies of T_I . The R and A components are strongly correlated (as T and T_A in §3.2) and may even be equal if $T_I \equiv 1$ (Reed-Frost case).

It may be useful to have a more concrete construction of (R, A) . Label the individuals in the household $1, 2, \dots, n$. For $k = 1, 2, \dots, n$, let individual k be endowed with random variables $(Q_E^{(k)}, Q_T^{(k)}, T_I^{(k)})$, where Q_E and Q_T are the thresholds for external and internal infections, respectively. Thus Q_E is the total time units of external infection that has to be present before a given individual is externally infected, so Q_E follows a negative exponential distribution with rate λ_G/N . Similarly, Q_T is the total time units of internal infection that has to be present before a given individual is internally infected, so Q_T follows a negative exponential distribution with rate λ_F . All these random variables, whether for the same or different individuals, are assumed to be independent.

To construct the associated realisation of (R, A) , first, the n Q_E -values are marked on the t -axis. The first jump of (R, A) occurs at the smallest of these, i.e. at the least amount of external infection necessary to infect an individual in our previously completely susceptible household. This infected individual will initiate an epidemic among the remaining $n - 1$ susceptibles that is determined by the values of $\{Q_T^{(k)}, T_I^{(k)}\}$ (see, for example, the construction of Sellke (1983) as described in Ball (1986)). Let T and T_A be, respectively, the total size and severity of this epidemic, where T includes the initial infective. Then the size of the first jump of (R, A) is (T, T_A) . Next, the $T - 1$ ‘marks’ corresponding to the individuals who are no longer susceptible should be deleted from the t -axis. The next jump of the process will then occur at the smallest remaining mark, at which point one of the individuals not infected by the epidemic corresponding to the first mark will be externally infected. This individual will initiate an epidemic among the other remaining susceptibles. The total size and severity of this second epidemic is the size of the second jump of (R, A) , and so on. This view of (R, A) yields, for instance, easy estimates of the increments of the process, since these depend on finding at least one of the original marks in the time interval considered.

The results in §3.2 (in particular equations 3.9 and 3.10) are directly interpretable in terms of (R, A) . We have $E[R(t)] = \tilde{\mu}_{n,0}$, with $\pi = \exp(-\lambda_G t/N)$ (we will use the notation $\tilde{\mu}_{n,0}(\pi)$ in the sequel, to make the dependence on π explicit), and $E[A(t)] = E[T_I] E[R(t)]$, since Wald’s identity for epidemics ap-

plies for any fixed number of initial infectives. Let us further, for $t, s \geq 0$, denote $\text{Cov}(R(t), R(s))$ by $c_n^R(t, s)$, $\text{Cov}(A(t), A(s))$ by $c_n^A(t, s)$ and $\text{Cov}(R(t), A(s))$ by $c_n^B(t, s)$. For $t = s$, the covariances can be derived from equation 3.9. For $t \leq s$, say, one may, at least in theory, use the properties of the exponential distributions to derive the covariances: given $(t, R(t), A(t))$, $R(s) - R(t)$ and $A(s) - A(t)$ will have the same distribution as $(R(s - t), A(s - t))$ in a household starting with $n - R(t)$ susceptibles. However, it will be seen in the sequel that explicit determination of the covariance functions is not essential for the derivation of the main results; they will only be needed explicitly for the case $t = s$, for a particular choice of t .

4.2.2 Embedding the epidemic process

Assume that each household in the population has a process $(R_i(t), A_i(t))$, $i = 1, \dots, m$, of the type described above. Let $R_\bullet(t) = \sum R_i(t)$ and $A_\bullet(t) = \sum A_i(t)$. Assume also that an initial amount T_0 of infectious time is applied to the initially totally susceptible population. We can now define a sequence of stochastic times in which to consider $(R_\bullet(t), A_\bullet(t))$ (these correspond roughly to a description of the epidemic by cumulated generations, with ‘anticipated’ local or within household infections):

$$\begin{aligned} T_0 &\rightarrow R_\bullet(T_0), A_\bullet(T_0) \\ T_1 &= T_0 + A_\bullet(T_0) \rightarrow R_\bullet(T_1), A_\bullet(T_1) \\ &\vdots \\ T_{k+1} &= T_0 + A_\bullet(T_k) \rightarrow R_\bullet(T_{k+1}), A_\bullet(T_{k+1}) \\ &\vdots \end{aligned}$$

Thus T_1 is the total amount of infection that has been present in the population after the internal household epidemics initiated by the initial T_0 units of infectious time have occurred. These T_1 units of infection may create further external infections which may in turn give rise to further internal infections, after which there will have been a total of T_2 units of infectious time present in the population. The process continues until the extra infectious time created by a set of internal infections is not enough to give rise to further external infections. Consequently, the above sequence stops at $T_\infty := \min\{t \geq 0 : t = T_0 + A_\bullet(t)\}$ (see Figure 3). Then $R_\bullet(T_\infty)$ represents the final size of the epidemic in the population and $T_\infty = A_\bullet(T_\infty) + T_0$ its severity.

4.2.3 Asymptotic distribution of the embedding process and of the final size of the epidemic

For $n = 1, 2, \dots$, let m_n be the number of households of size n , m the total number of households, $N = \sum nm_n$ the total number of individuals in the population, $\theta_n = m_n/m$ the proportions of households of size n and $\tilde{m}_1 = \sum n\theta_n < \infty$. Then

$E[R_{\bullet}(t)] = \sum m_n \tilde{\mu}_{n,0}(\exp(-\lambda_G t/N))$. In order to handle the bivariate character of $(R_{\bullet}, A_{\bullet})$, let us use the Cramér-Wold device and define, for $(\alpha, \beta) \in \mathbb{R}^2$,

$$Z_m^{(\alpha, \beta)}(t) = \frac{1}{\sqrt{m}} \left(\alpha(R_{\bullet}(Nt) - E[R_{\bullet}(Nt)]) + \beta(A_{\bullet}(Nt) - E[A_{\bullet}(Nt)]) \right).$$

Proceeding as in Scalia-Tomba (1990), under the further condition that $\sum n^2 \theta_n < \infty$, it can be shown that, as $m \rightarrow \infty$, $Z_m^{(\alpha, \beta)}$ converges in distribution, on $D[0, \infty)$ with the Skohorod topology, to a Gaussian process with mean 0 and covariance function

$$\gamma^{(\alpha, \beta)}(t, s) = \sum \theta_n (\alpha^2 c_n^R(t, s) + \alpha\beta(c_n^B(t, s) + c_n^B(s, t)) + \beta^2 c_n^A(t, s)),$$

where π , at times t and s , now equals $\exp(-\lambda_G t)$ and $\exp(-\lambda_G s)$, respectively.

Now let $r(t) = \sum \theta_n \tilde{\mu}_{n,0}(\exp(-\lambda_G t))$, $a(t) = E[T_I]r(t)$, $\tilde{r}(t) = r(t)/\tilde{m}_1$, and $\tilde{a}(t) = a(t)/\tilde{m}_1$. Then, letting $(\alpha, \beta) = (0, 1)$, we have that, as $m \rightarrow \infty$,

$$\tilde{A}_m(t) = \frac{1}{\sqrt{m}} (A_{\bullet}(Nt) - ma(t))$$

converges weakly to a Gaussian process with mean 0 and covariance function $\gamma^{(0,1)}$. Assume now that $T_0/N \rightarrow \mu_0 > 0$ as $m \rightarrow \infty$. Then

$$T_{\infty}/N = \min\{t : t = T_0/N + \tilde{a}(t) + \frac{\sqrt{m}}{N} \tilde{A}_m(t)\},$$

and, since the last term converges uniformly to 0 on any compact subset of $[0, \infty)$, we have that $T_{\infty}/N \rightarrow \tau(\mu_0) := \min\{t : t = \mu_0 + \tilde{a}(t)\}$. We may then conclude that $Z_m^{(\alpha, \beta)}(T_{\infty}/N)$ converges in distribution to $Z_m^{(\alpha, \beta)}(\tau(\mu_0))$ for all (α, β) , which means that the vector

$$\frac{N}{\sqrt{m}} \left(\frac{R_{\bullet}(T_{\infty})}{N} - \tilde{r}(T_{\infty}/N), \frac{A_{\bullet}(T_{\infty})}{N} - \tilde{a}(T_{\infty}/N) \right)$$

converges in distribution to a bivariate normal distribution with mean 0 and covariance matrix $M(\mu_0)$ with elements $M_{11} = \sum \theta_n c_n^R(\tau(\mu_0), \tau(\mu_0))$ ($\pi = \exp(-\lambda_G \tau(\mu_0))$), and $M_{12} = M_{21}$ and M_{22} of similar form, with c_n^B and c_n^A replacing c_n^R . By using the identities satisfied by T_{∞} and by $\tau(\mu_0)$ (see Scalia-Tomba 1990), this result can be recast into the convergence in distribution of the vector

$$\sqrt{m} \left(\frac{R_{\bullet}(T_{\infty})}{N} - \tilde{r}(\tau(\mu_0)), \frac{A_{\bullet}(T_{\infty})}{N} - \tilde{a}(\tau(\mu_0)) \right)$$

to a bivariate normal distribution with mean 0 and covariance matrix $\tilde{m}_1^{-2} (1 - \tilde{a}'(\tau(\mu_0)))^{-2} A M(\mu_0) A^T$, where $A_{11} = 1 - \tilde{a}'(\tau(\mu_0))$, $A_{12} = \tilde{r}'(\tau(\mu_0))$, $A_{21} = 0$ and $A_{22} = 1$.

This is the basic result on asymptotic normality of the final size of the epidemic, around the value predicted by ‘deterministic’ considerations, when the epidemic

is started by a large amount of initial infection (some algebra will show that the definitions of $\tau(\mu_0)$, and consequently, of $\tilde{r}(\tau(\mu_0))$ and $\tilde{a}(\tau(\mu_0))$ agree with equation 3.35, when $\mu_0 = 0$).

The most interesting case to study is, however, when T_0 remains fixed as $m \rightarrow \infty$, corresponding to few initial infectives. One must then combine the branching process approximations of Sections 3.3.1 and 3.5 with the asymptotic normality results shown above. Once again, the strategy in Scalia-Tomba (1985, 1990), of studying the final size distribution in different ranges of values, may be followed. Let us, for simplicity, denote the final size of the epidemic in a population with m households by T_m and assume that the epidemic is above threshold (otherwise, the results in Sections 3.3.1 and 3.5 account for the whole asymptotic distribution). The branching process approximations of Sections 3.3.1 and 3.5 then show that $\Pr\{T_m = k\} \rightarrow p(k)$, for $k = 0, 1, \dots$, where $p(\cdot)$ is the distribution of the total size in the approximating branching process. This distribution has total mass $\tau < 1$, say, corresponding to the event of extinction of the approximating branching process. It therefore remains to show that the remaining probability mass $1 - \tau$ is concentrated around the deterministic solution for a large epidemic (see equation 3.35; the solution corresponds to $\rho = \tilde{r}(\tau(0))$, with the convention that the non-zero solution should be taken when $\mu_0 = 0$). One then starts by studying $\Pr\{k < T_m < a_m\}$, where $\{a_m\}$ satisfies $a_m \rightarrow \infty$ but $a_m/m \rightarrow 0$ as $m \rightarrow \infty$, with the aim of showing that

$$\lim_{k \rightarrow \infty} \lim_{m \rightarrow \infty} \Pr\{k < T_m < a_m\} = 0.$$

The coupling construction of an approximating branching process by Ball and Donnelly (1995) (see Section 3.3.1), combined with an ingenious argument in Andersson (1993) (see also Ball and Clancy (1992)), can be used for this purpose. The approximating branching process $B_U(t)$, say, is always larger than the infectives process $I_m(t)$, since every contact is considered as a new individual in B_U , but some contacts do not yield new infectives in I_m , since contacts may occur with already infected or removed individuals. This mechanism amounts to a thinning of the branching process, with thinning probabilities depending on the total progeny up to the time point considered for the contact. To make things simpler, one can therefore apply thinning to each contact in the branching process, with fixed probability $\epsilon > 0$, which will overestimate the ‘true’ thinning probabilities as long as the total number of individuals ever having been infected is less than ϵN , thus constructing a second branching process $B_L(t)$, for which we will have $B_L(t) \leq I_m(t) \leq B_U(t)$, at least as long as the total epidemic is less than ϵN . If we denote the distribution functions of final size (total progeny) by F_L , F_m , and F_U , respectively, we will then have $F_U(i) \leq F_m(i) \leq F_L(i)$, for all $i \leq \epsilon N$. Thus, $0 \leq F_m(a_m) - F_m(k) \leq F_L(a_m) - F_U(k) \leq \tau(\epsilon) - F_U(k)$, where $\tau(\epsilon)$ is the extinction probability in the ϵ -thinned process. However, since $\tau(\epsilon) \rightarrow \tau$ as $\epsilon \rightarrow 0$ and $F_U(k) \rightarrow \tau$ as $k \rightarrow \infty$, one obtains the desired result.

The remaining range, as long as $\{a_m\}$ is taken so that $a_m/\sqrt{m} \rightarrow \infty$, can be studied using the Gaussian process approximation (see Scalia-Tomba 1985)

to show that the crossing condition, equivalent to achieving the final size, can only be fulfilled in a $O(\sqrt{m})$ -neighbourhood of the 'deterministic' value. Having thus accounted for the whole asymptotic probability mass, one now proceeds by showing that $\Pr\{(T_m - \rho N)/\sqrt{N} \in K\} = \Pr\{(T_m - \rho N)/\sqrt{N} \in K, T_m > a_m\} \Pr\{T_m > a_m\} \approx \Pr\{(T_m - \rho N)/\sqrt{N} \in K, T_m > a_m\}(1 - \tau)$, for large N and $K \subset R$ bounded. The final step consists in showing that the epidemic process, conditioned on $T_m > a_m$, *i.e.* on having a 'large' epidemic, again follows the Gaussian approximation derived above, now with $\mu_0 = 0$. However, the conditioning event involves members from at most a_m households and times, used as arguments in the $Z_m^{(\alpha, \beta)}$ process, of the order $O(a_m/m)$. The effect on the (conditional) limit law of $Z_m^{(\alpha, \beta)}$ will be vanishingly small and the limit law will be unchanged, at least as long as the removal of any set of a_m households from the total set of m households does not affect asymptotic proportions or means. This last requirement is equivalent to the uniform integrability of the sequence $\{\theta(m)\}$ of household size proportions.

4.3 The case of fixed infection probabilities

In the case studied in Sections 2.1 and 2.2, in which the infection probabilities are fixed and independent, it is possible to construct an embedding process directly based on the 'clumps' formed by the local infection process. Let $\{C_k\}$ denote the total number of local components of size $k = 1, \dots, N$ that have been formed by local infection, in a population of size N . Closely following Scalia-Tomba (1985), (1990), we now construct an epidemic between components, with susceptibility and infectivity proportional to size. To each component of size k , we attach a threshold variable with geometric distribution with 'success probability' $= 1 - (1 - p_B)^k$, representing the number of individual infection attempts necessary to infect the component. We denote these variables by $\{Q_{kj}\}$, $1 \leq j \leq C_k$, $k = 1, \dots, N$. We now define processes $X_{kj}(t) = 1_{\{Q_{kj} \leq t\}}$ and $X_k(t) = \sum_j X_{kj}(t)$, which represent the numbers of k -components that have been infected after t infection attempts on the population. Finally, we define $X(t) = \sum_k kX_k(t)$, the total number of individuals infected after t infection attempts. We now construct the 'generations' of the epidemic process by considering $X(t)$ at suitably defined random times. Assuming that the epidemic is started by m_0 initial infectives external to the population, we set $T_1 = m_0$, $T_2 = m_0 + X(T_1)$, and, in general, $T_{k+1} = m_0 + X(T_k)$. These times form an increasing sequence which stops at $T_\infty = \min\{t : t = m_0 + X(t)\}$. The final size of the epidemic in the population is then $X(T_\infty)$.

We would now want to consider the asymptotic situation $N \rightarrow \infty$, $p_B \approx \lambda_G/N$, local infection probabilities fixed and m_0 either fixed or increasing with N . Except for the randomness of $\{C_k\}$, the problem is similar to the situations studied in Scalia-Tomba (1985, 1990). It can therefore be expected that similar results will be valid, modified only by the additional randomness generated by $\{C_k\}$.

However, in models like the great circle (Section 2.1) or the epidemic among giants (Section 2.3), there will potentially be an infinite number of types (sizes) of local components. Work is in progress on how best to resolve the technical problems arising in these situations and the results will be published separately.

5 Applications

5.1 Estimating R_T from household total size data

In this subsection we describe a method for estimating the threshold parameter R_T when the available data are the total number of individuals in each group that are ultimately infected by the epidemic. We shall assume that the number of groups m is large, that a global epidemic has occurred and that the distribution of the infectious period is known. Our method is based on Addy *et al* (1991); see Becker (1989) for alternative approaches.

Consider first the extended model of Addy *et al* (1991) and suppose that the total size of such epidemics in a number of independent groups is known. Addy *et al* (1991) give an algorithm for obtaining maximum likelihood estimates of the local infection rate λ_L and the probability π that a random individual escapes infection. [The likelihood is straightforward to compute numerically using 3.12.] In our situation the epidemic total sizes in different groups are not mutually independent, but if the number of groups is large the total sizes will be approximately independent in the event of a global epidemic. Thus estimates for λ_L and π can be derived using the method of Addy *et al* (1991). An estimate for z can then be obtained using 3.35, allowing λ_G to be estimated from the equation $\pi = \exp(-\lambda_G p E[T_I])$. An estimate for R_T can then be obtained from 3.31.

As a simple example, we consider data on the spread of an influenza epidemic in Tecumseh, Michigan, analyzed in Addy *et al* (1991). The data do not exactly fit our situation since (a) they are combined data over two separate epidemics, (b) only 10% of households are included, and (c) households of 5 or more individuals

No. infected	No. of susceptibles* per household				
	1	2	3	4	5
0	110	149	72	60	13
1	23	27	23	20	9
2		13	6	16	5
3			7	8	2
4				2	1
5					1
Total	133	189	108	106	31

Table 1. Observed distribution of influenza A(H3N2) infections in 1977-1978 and 1980-1981 combined epidemics in Tecumseh, Michigan.

[* Note: the criterion for classifying individuals as susceptible is a pre-season haemagglutination inhibition test detecting no antibody in a dilution of 1 in 128 or less. Households with more than five susceptibles are deleted from all analyses.]

(From Addy *et al* 1991)

are omitted. However, they allow us to illustrate our methodology. The data are shown in Table 1.

Addy *et al* (1991) consider two possible distributions for the infectious period, namely $T_I \equiv 4.1$ days and T_I follows a gamma distribution with probability density function $f(t) = \lambda^2 t \exp(-\lambda t)$, $t > 0$, where $\lambda = 2/4.1 \approx 0.49$. For the model with a constant infectious period, Addy *et al* (1991) obtained the estimates $\hat{\lambda}_L = 0.0423$ and $\hat{\pi} = 0.8677$, from which $p_L = .1592$, $\hat{\lambda}_G = 0.1950$ and $\hat{z} = 0.1775$; from these we can calculate $R_0 = 0.7995$, $\mu = 1.414$, and hence $\hat{R}_T = \mu R_0 = 1.1308$. For the model with a gamma distributed infectious period, Addy *et al* (1991) obtained the estimates $\hat{\lambda}_L = 0.0446$ and $\hat{\pi} = 0.8674$, from which $\hat{z} = 0.1775$, $\hat{\lambda}_G = 0.1955$ and $\hat{R}_T = ??$. Note that the two models give very similar estimates of R_T and other parameters. Also, the observed proportion of initial susceptibles ultimately infected by the disease is $250/1414 = 0.1768$, which is in close agreement with the estimate $\hat{z} = 0.1775$ fitted from both models.

The method of Addy *et al* (1991) also yields approximate confidence sets for (λ_L, π) . Thus an approximate confidence interval for R_T could be obtained, since R_T is a function of λ_L and π . The above method will always yield an estimate of R_T that is larger than one. This is because equation 3.35 is essentially deterministic, and in a deterministic model an initial trace of infection can only lead to a non-zero proportion of the population ultimately being infected if the model is above threshold. Thus the above method of estimating R_T should only be used if there is a good reason to believe that a global epidemic has occurred.

5.2 Vaccination: the equalizing strategy

The fundamental aim of a vaccination programme must be to reduce the basic reproductive ratio R_T to below unity. In §2.5 we examined the implications of this for a simple example of large groups of equal sizes. Now, having seen (Section 3) that the relation $R_T = \mu R_0$ holds for a wider set of models, we return to examine the question of optimal vaccination strategies in more generality. We shall compare different strategies that vaccinate a fixed proportion v of the population.

As noted in §2.5, any vaccination strategy will reduce R_0 simply *pro rata*, so the difference between strategies will lie in how they affect the (size-biased) mean component size μ . In practice, of course, we do not know the component sizes at the time of vaccination, and even for small group sizes the evaluation of the distribution and mean of the component size in general require quite complicated iterative calculation (see §3.2).

Becker and Dietz (1995) get round this problem by restricting attention to the case where $p_L = 1$, *i.e.* where if one individual in a group is infected so is everyone else in their group. The details of their calculations are a little complicated because they work in terms of the non-size-biased distribution $\{h_k\}$ rather than $\{\pi_k\}$ (see §2.3), but it is not difficult to check that their conclusions are consistent

with the optimal strategy being to minimise μ .

When we consider more general within-group distributions, one straightforward strategy that suggests itself is to leave the numbers of susceptibles in each group as nearly equal as possible. We call this the *equalizing strategy*, and conjecture that it is optimal for the groups model for any infectious period distribution.

5.2.1 The equalizing strategy for groups or households

It is easy to see that the equalizing strategy will be optimal if and only if, for all n , two groups of n susceptibles contribute less to μ than a pair of groups of sizes $n-1$ and $n+1$. Because the probability of a global infection hitting a group with n susceptibles is proportional to n , this condition is equivalent to the sequence $(n\mu_n)$ being convex; here $\mu_n = \mu_{1,n-1}$ is the mean size of an outbreak in a group of n susceptibles which is started by just one of them becoming infected. The condition that $(n\mu_n)$ be convex is in turn equivalent to the requirement that the second difference $D_n \equiv n\mu_n - 2(n-1)\mu_{n-1} + (n-2)\mu_{n-2}$ be ≥ 0 for all n .

It is easily shown that the equalizing strategy is optimal for the simple ‘all-or-none’ case where within-group outbreaks are either of size 1, with probability q_1 , or of size n (this arises when the infectious period is either of length 0 or ∞ , with respective probabilities q_1 and $1 - q_1$). For this case, straightforward calculation shows that $D_n = 2 - 2q_1$.

This simple case is one in which the within-group infections by an individual are maximally correlated. The other extreme, for models with a general infectious period, is the independent links or Reed-Frost case considered in Section 2. For this, we have calculated D_n for $n = 2, \dots, 15$ using Maple (see Figure 3), and the conjecture appears to hold for all these values, with a pattern suggesting that it is likely to hold for all n .

Indeed, on the basis of this, and a similar plot for the epidemic with Exponential infectious period, we conjecture that in fact $D_n \geq 2 - 2q_1$ for all n , so that the simple ‘all-or-none’ case is the lower bound.

Our conjecture is further supported by calculations for the model of Gertsbakh (1977), in which each individual makes exactly one (potentially infectious) contact. This does not seem realistic in the context of epidemics, but is of some theoretical interest in that it provides an example with negative correlation between the contacts made by an individual, which is not possible for our basic ‘general infectious period model’ as defined in §3.1. Gertsbakh (1977) also considered the inverse of this model, in which there is exactly one contact *to* each individual, and this inverse model has recently been fitted to data by Islam *et al.* (1995). Both models can be generalized, replacing ‘exactly one contact’ by ‘one contact with probability $(n-1)p$, otherwise none’ (we choose this parametrisation so that p is the probability of contacting any one specific individual; $p \leq 1/(n-1)$).

For the inverse model, with one initial infective in a group of size n , the

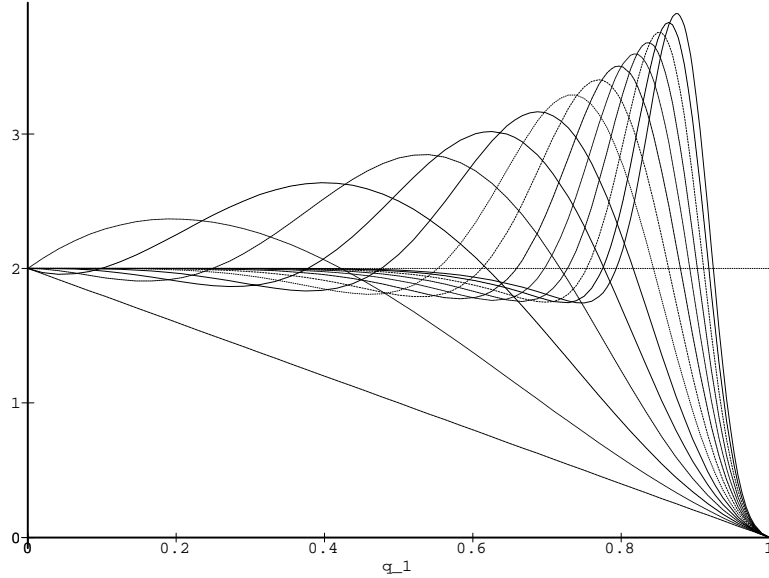


Figure 3. The second difference D_n , conjectured to be $\geq 2 - 2q_1$, plotted against q_1 for $n = 2, \dots, 15$ for the independent links ('Reed-Frost') case.

probability that the total size of the group epidemic will be k is

$$p'_k = \binom{n-1}{k-1} p(kp)^{k-2} (1-kp)^{n-k} \quad (5.1)$$

(Islam *et al.* 1995). It is not easy to calculate the mean outbreak size μ_n from equation 5.1. However, it follows from a simple and general result (see Appendix) that μ_n is the same as for the forward model, for which calculations turn out to be easier. We can write down the corresponding probability that the total size of the group epidemic will be k for the forward model,

$$p_k = \frac{(n-1)!}{(n-k)!} (p^{k-1} - (n-k)p^k). \quad (5.2)$$

From 5.2 it is straightforward to show that (for both the Gertsbakh model and its inverse)

$$\mu_n = \sum_{k=0}^{n-1} \frac{(n-1)!}{(n-k-1)!} p^k. \quad (5.3)$$

From this, matching powers of p in $D_n \equiv n\mu_n + (n-2)\mu_{n-2} - 2(n-1)\mu_{n-1}$, we have that

$$D_n = \sum_{k=1}^{n-1} \frac{(n-2)!}{(n-k-1)!} k(k+1)p^k. \quad (5.4)$$

This is a sum of non-negative terms, and is therefore \geq its first term, $2p = 2 - 2q_1$, so our conjecture holds for both the Gertsbakh model and its inverse.

Our calculations for the independent links and Exponential infectious period models used the techniques of §3.2, particularly equation 3.6. For small values of n , we can work out explicit expressions for D_n for a general infectious period in terms of the sequence (q_k) , where q_k is as before (see following 3.6) the probability of escaping infection from any of a set of k infectives in the same group. Let $d_k \equiv q_k - q_{k+1}$, ≥ 0 because (q_k) is a monotone non-increasing sequence. We find $D_2 = 2d_0$, $D_3 = 2d_0 + 6d_0d_1$, $D_4 = 2d_0 + 12d_0(q_1d_1 + d_0d_2 + 2d_1d_2)$, in each case \geq our conjectured minimum of $2d_0$.

Note that for the different class of models where global infections choose groups with equal probabilities, instead of individuals with equal probabilities, it is easy to show that the equalizing strategy is *not* optimal: it is quite easy to show $D_2 = 1 - 2q_1$, < 0 for $q_1 > 1/2$; and that D_n in general is $= -1/n < 0$ at $q_1 = 1$.

5.2.2 The equalizing strategy for the great circle model

We conclude by proving that the equalizing strategy is optimal for the great circle model: that is, the optimal policy is to spread the vaccinations around the circle as evenly as possible.

We consider then a population of N individuals spaced equally around a circle. If we vaccinate a fixed number m of individuals, so that $v = m/N$, then the (*non-size-biased*) mean length of the intervals of susceptibles between these will be $\tau \equiv (N - m)/m = (1/v) - 1$. Now consider choosing a susceptible at random, and then looking at the numbers of susceptibles T_+, T_- respectively to its right and left between it and the next vaccinated individual; let $T = 1 + T_+ + T_-$. Then $\mathbf{E}[T]$ is the size-biased mean for a group (interval) of susceptibles.

Consider first the case where local contacts always infect, so that $\mathbf{E}[T]$ will also be the mean clump size for the epidemic. That $\mathbf{E}[T]$ is minimal when T is as near constant as possible, that is, it is $= \tau$ when τ is an integer, and has a distribution concentrated on the two integers either side of τ otherwise, is a well-known result for renewal processes: it can be thought of as saying that waiting times for buses will be minimal if they are scheduled at equal intervals.

What we prove is a generalisation of this result that takes account of our actual local infection process. It turns out that we can allow a more general local infection process than the basic great circle model in which infections by different individuals are independent.

Thus, secondly, consider a model in which the local outbreak caused by an individual i , in the absence of vaccination, has an arbitrary distribution on intervals containing that individual. Suppose that it consists of C_+ individuals to the right of i , and C_- individuals to the left, so that its total size is $C = 1 + C_+ + C_-$. Let $p_r = \mathbf{P}(C_+ \geq r)$.

We are now ready to put the vaccination process and the infection process together; we need of course to assume that these are independent. When we include the information on vaccinated intervals, the local outbreak caused by i becomes $D = 1 + R + L$, where $R = \min(T_+, C_+)$, $L = \min(T_-, C_-)$. Our target is to find the distribution of T that minimises $\mu = \mathbf{E}[D]$.

Now $\mathbf{E}[R] = \sum_{r=1}^{\infty} P(R \geq r) = \sum_{r=1}^{\infty} P(C_+ \geq r)P(T_+ \geq r) = \sum_{r=1}^{\infty} p_r P(T_+ \geq r)$. Next comes the crucial step: $P(T_+ < r) = \sum_{j=1}^r P(T_+ = j - 1)$. But $T_+ = j - 1$ only if the individual ‘at j ’ (*i.e.* j steps to the right of individual i) is vaccinated, and this has probability $1/\tau = m/(N - m)$. Hence $P(T_+ = j - 1) \leq 1/\tau$, and therefore $P(T_+ \geq r) \geq 1 - \sum_{j=1}^r 1/\tau = 1 - r/\tau$; of course we also have $P(T_+ \geq r) \geq 0$, so that $\mathbf{E}[R] = \sum_{r=1}^{\infty} p_r P(T_+ \geq r)$ will be minimised by taking $P(T_+ \geq r) = \max(1 - r/\tau, 0)$. A mirror argument for $\mathbf{E}[L]$ leads to the corresponding condition $P(T_- \geq r) = \max(1 - r/\tau, 0)$.

To see that these minima are uniquely attained when the distribution of T is concentrated on $[\tau]$ (the integer part of τ) and $[\tau] + 1$, note that equality in the argument of the last paragraph (turning ‘only if’ into ‘if and only if’, and hence giving $P(T_+ = j - 1) = 1/\tau$) requires that it is impossible to have two vaccinated individuals within the range $j = 0$ to $[\tau] - 1$; hence $T \geq [\tau]$; and $T \leq [\tau] + 1$ because otherwise it would be possible for T_+ (and T_-) to be $= [\tau] + 1$, which would contradict $P(T_+ \geq r) = \max(1 - r/\tau, 0)$.

We have thus shown that the equalizing vaccination strategy is optimal for the generalised great circle model, in which the local outbreak caused by an individual takes an arbitrary distribution on the intervals containing the individual.

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