Applied Probability Trust (6 October 2009)

ASSESSING THE IMPACT OF INTERVENTION DELAYS ON STOCHASTIC EPIDEMICS

SIMON E. F. SPENCER,*

PHILIP D. O'NEILL,* *University of Nottingham*

Abstract

A stochastic model of disease transmission among a population partitioned into groups is defined. The model is of SEIR (Susceptible-Exposed-Infective-Removed) type and features intervention in response to the progress of the disease, and moreover includes a random delay before the intervention occurs. A threshold parameter for the model, which can be used to assess the efficacy of the intervention, is defined. The threshold parameter can be calculated for a number of different choices of exposed, infectious and delay period distributions, both for the epidemic model itself and also a large-group approximation. It is found that the mean length and distribution of the random delay time can have a material impact on the value of the threshold parameter, as illustrated by numerical examples.

Keywords: Epidemic; stochastic epidemic; emerging disease; intervention; vaccination; intervention delay; branching process; reproduction number

2000 Mathematics Subject Classification: Primary 92D30

Secondary 60K99

1. Introduction

Mathematical models of infectious disease transmission are routinely used to describe and analyse real-life disease outbreaks [1, 12]. A key aspect of such modelling is the ability to assess the efficacy of interventions and control measures, ranging from pre-outbreak strategies such as vaccination to during-outbreak responses such as case isolation, prophylactic treatment, travel restrictions etc. In this paper we use the term

* Postal address: School of Mathematical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK

Email address: simon.spencer@nottingham.ac.uk

dynamic intervention to mean one that is taken in response to a particular trigger event, such as the observation of a new case or a certain number of cases. Such intervention strategies are often applied to diseases for which pre-vaccination of a population is infeasible or undesirable, for example novel strains of influenza, emerging diseases such as SARS, or foot-and-mouth disease. Dynamic interventions can be extremely cost-effective if successful since they typically only involve a small part of the at-risk population. Obviously, the speed with which a dynamic intervention can be carried out in response to a trigger event is of considerable importance.

Several previous studies have considered epidemic models in which dynamic interventions occur following a delay [8, 10, 14, 15, 17, 19], although in all these cases the model behaviour is explored via simulation or the numerical solution of differential equations. Three of these studies specifically consider the impact of a delay in intervention, and all three conclude that the length of the delay strongly influences the effectiveness of the intervention. Eubank *et al.*[8] simulate a smallpox outbreak on a realistic social network. The authors consider three different lengths of time taken for infected individuals to withdraw to the home (self-isolation) and find that this delay is "by far the most important factor" in determining the outcome of the epidemic. Keeling *et al.*[15] consider several proposed intervention strategies that could have been used in the 2001 UK foot-and-mouth outbreak. It is found that a (dynamic) 'prompt cull' with only a 24/48-hour delay would have reduced cases by almost a half. The authors conclude that "the delay between the decision to vaccinate and protection from the infection... means that it is very difficult to get 'in front' of the disease and prevent its spread." Longini *et al.*[17] simulate an influenza outbreak with a dynamic intervention using antiviral agents. The authors find that as the intervention delay is increased from one to five days, the number of cases steadily increases. When the delay length is one day 79% of epidemics are prevented, however when the delay length is 3 days only 19% of epidemics are prevented. Such findings highlight the need for a better understanding of the reduction in effectiveness caused by delaying an intervention.

Simulation studies, such as those described above, are often unavoidable when seeking to understand complex models, and permit a broad exploration of the likely consequences of different interventions. However, such methods can make it hard to gain a precise understanding of model behaviour. In contrast, in this paper our focus

is towards explicit calculations within the setting of simpler models, with a view to understanding such models in greater detail.

The paper is structured as follows. In Section 2 an epidemic model for a population partitioned into homogeneously mixing groups is defined. The effectiveness of interventions is assessed through the reproduction number, and in Sections 3 and 4 the procedure for calculating the reproduction number is described for two important special cases: when the model is Markovian, and when the intervention delay has a constant distribution. Section 5 explores the numerical properties of some of the results obtained and Section 6 considers the effect of the distribution of the intervention delay length.

2. Model and threshold behaviour

2.1. Model definition

Ball *et al.* [5] describes an epidemic model of SEIR (Susceptible-Exposed-Infective-Removed) type featuring dynamic interventions that occur with no delay. We here describe a broadly similar model which also features delays, and in which the scaling of within-group infection rates is different.

Consider a population of N individuals partitioned into groups of various sizes and let $p(g)$ $(g = 1, 2, \ldots)$ denote the proportion of groups containing g individuals. We assume that $\sum_{g\geq 1} gp(g) < \infty$. At any point in time, each individual in the population can be in one of four states, namely susceptible, exposed, infective or removed. It is typically assumed that initially one or a few individuals are exposed or infective, and the remainder susceptible.

When infected, a susceptible enters the exposed category and remains there for a period of time distributed according to a specified random variable T_E. During this time the individual is infected but not infectious. Once the exposed period is over, the individual becomes an infective for a period of time distributed according to a random variable T_I. During their infectious period, an infective makes local contacts with each individual in their own group at times given by the points of a Poisson process with rate β/n, where n is the initial number of susceptibles in the group. In addition, infectives also make global contacts with all individuals in the population at

times given by the points of a Poisson process with rate λ/N. Each such contact that is made with a susceptible immediately results in the susceptible becoming exposed. All of the Poisson processes, exposed periods and infectious periods are assumed to be mutually independent. At the end of their infectious period, an infective becomes removed and plays no further part in the spread of the disease. The epidemic ends as soon as there are no more exposed or infective individuals remaining in the population.

A dynamic intervention takes place as follows. We assume that the intervention operates on a group basis, meaning that the intervention is applied to an entire group some period of time after a trigger event. The trigger event is assumed to be the vth removal in the group, $v = 1, 2, \ldots$. For many diseases, the removed category corresponds to the appearance of symptoms, and so the trigger amounts to observing v symptomatic individuals within a group. Denote by D the random delay time between the trigger and the intervention itself. We do not specify the exact nature of the intervention, but it is assumed to be completely effective in the sense that no further infections occur either within the group or from the group following the intervention. Finally, note that the intervention itself need not necessarily occur, since the trigger event is not always certain to occur if $v > 1$.

2.2. Threshold and effective severity

The stochastic epidemic model described above exhibits threshold behaviour which we now briefly recall; for full details see [5, 3]. Suppose that the population size N becomes large such that the group proportions $p(g)$ remain unchanged, and for $g = 1, 2, \ldots$, define $\alpha(g) = \frac{gp(g)}{\sum_{h\geq 1} hp(h)}$ to be the proportion of individuals in a group of size g. In this setting, with high probability each global contact made will be with an individual residing in a group that has not previously been infected. It follows that the initial stages of the epidemic can be approximated by a multitype branching process in which the individuals correspond to groups in the epidemic, consisting initially of one exposed individual, types correspond to the size of the group, and in which offspring correspond to infections made by global contacts. Due to the assumptions of the epidemic model, the number of global contacts produced by a group of size g has a Poisson distribution with random mean $\lambda T_A(g)$, where $T_A(g)$ denotes the total number of infected-individual time units within the group. By standard branching

process theory, this branching process has a threshold parameter R, where

$$R = \lambda \sum_{g \geq 1} \alpha(g) \mathrm{E}[T_A(g)],$$

with the property that if $R \leq 1$ the branching process dies out almost surely, while if $R > 1$ then there is a non-zero probability that the process becomes infinite in size.

The threshold parameter can be translated into the setting of the epidemic model as follows. We define a *within-group epidemic* as an epidemic within a single group comprising one initially exposed individual and n initially susceptible individuals, in which no susceptible individuals in the group can be infected by global contacts from outside the group. Denote the numbers of susceptible, exposed, infective and removed individuals within the group at time $t \geq 0$ by $S(t)$, $E(t)$, $I(t)$ and $R(t)$ respectively, where $t = 0$ corresponds to the time at which the initially exposed individual becomes infective.

Let $U_v = \inf\{t \geq 0 : R(t) \geq v\}$ be the time of the vth removal in the group and let $T_v = U_v + D$ denote the time at which the intervention becomes effective. Recall that no global infections can be caused by the group after time T_v. If v removals do not occur we set $U_v = T_v = \infty$.

Since the intervention in a group prevents any future global contacts from that group, we have that

$$\mathrm{E}[T_A(n+1)] = \mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| (S(0), E(0), I(0), R(0)) = (n, 0, 1, 0)\right].$$

It follows that

$$R_* = \lambda \sum_{n \geq 0} \alpha(n+1) \mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| (S(0), E(0), I(0), R(0)) = (n, 0, 1, 0)\right]$$

is a threshold parameter for the epidemic model, in the sense that as $N \to \infty$, there is a non-zero probability of an infinitely large epidemic only when $R_* > 1$.

Following [5] we refer to the expectation $\mathrm{E}[T_A(n+1)]$ as the expected effective severity. Calculating this quantity in various settings is the main objective of the remainder of the paper. For brevity, the condition $(S(0), E(0), I(0), R(0)) = (n, 0, 1, 0)$ will henceforth be suppressed in our notation. Calculating $\mathrm{E}[T_A(n+1)]$ in general is complicated due to the fact that the intervention is dependent on the progress of

the within-group epidemic. However, in certain special cases progress can be made, specifically when the within-group epidemic is Markovian, or when the intervention delay D is constant.

For some settings we shall also calculate $\mathrm{E}[T_A(n+1)]$ in the limiting case as $n \to \infty$. In practice, this provides an approximation for large n. Following standard theory (e.g. [1], Chapter 3), as $n \to \infty$ the within-group epidemic converges to a single-type continuous-time branching process in which an individual's lifetime is comprised of a childhood period distributed according to T_E followed by a reproductive period distributed according to T_I. During the reproductive period, an individual gives birth to new offspring according to a Poisson process of rate β, each of whom behave independently of each other and their parent.

3. Markovian models

Suppose that T_E, T_I and D have Erlang distributions with parameters $(K_E,\ \gamma_E)$, $(K_I,\ \gamma_I)$ and $(K_D,\ \gamma_D)$ respectively, where an Erlang distribution with parameters $(K,\ \gamma)$ has probability density function $f(x) = \frac{\gamma^K x^{K-1} \exp(-\gamma x)}{(K-1)!}$ for $x > 0$ and $K \in \mathbb{N}$. Thus by the method of stages [2, 11], the within-group epidemic can be represented by a Markov process. The state of this process can be represented by a vector of non-negative integers of the form $(s, e_1, \ldots, e_{K_E}, i_1, \ldots, i_{K_I}, d)$, where s is the number of susceptible individuals in the group, e_k is the number of exposed individuals in the kth stage of their exposed period, i_k is the number of infectives in the kth stage of their infectious period and d is the stage of the delay period. Define $e = \sum_{k=1}^{K_E} e_k$ and $i = \sum_{k=1}^{K_I} i_k$ and note that $r = n + 1 - s - e - i$ gives the number of removed individuals in the group. Since the delay period starts when v individuals have been removed, we have that $d = 0$ if and only if $r < v$. The state space of the process, Ω, is given by all possible vectors of the above form that satisfy the following conditions:

1. $0 \leq s \leq n$,

2. $0 \leq r \leq n + 1$,

3. $0 \leq d \leq K_D$,

4. $d = 0$ if and only if $r < v$.

However, for our purposes it is sufficient to restrict Ω to contain only the transient states (those in which $s + r < n + 1$) plus a single absorbing state denoted by $\mathbf{0}$. This is because once $e + i = 0$, the within-group epidemic has finished and so the severity cannot increase. We now give two methods for obtaining the expected effective severity.

3.1. Recurrence relation method

Let $\boldsymbol{X}(t)$ denote the state of the process at time $t \geq 0$ and for $\boldsymbol{\omega} \in \Omega$ define $x(\boldsymbol{\omega}) = \mathrm{E}[\int_0^{T_v} I(u)\,\mathrm{d}u | \boldsymbol{X}(0) = \boldsymbol{\omega}]$. By conditioning on the time and type of the first event given that the process starts in state $\boldsymbol{\omega}$, we obtain that if $\rho(\boldsymbol{\omega}) > 0$,

$$\rho(\boldsymbol{\omega})x(\boldsymbol{\omega}) = \iota(\boldsymbol{\omega}) + \sum_{\boldsymbol{\nu} \in \Omega \setminus \boldsymbol{\omega}} \rho(\boldsymbol{\omega}, \boldsymbol{\nu})x(\boldsymbol{\nu}), \tag{1}$$

where $\iota(\boldsymbol{\omega})$ is the number of infectives in state $\boldsymbol{\omega}$, $\rho(\boldsymbol{\omega})$ is the rate out of state $\boldsymbol{\omega}$ and $\rho(\boldsymbol{\omega}, \boldsymbol{\nu})$ is the rate from state $\boldsymbol{\omega}$ to state $\boldsymbol{\nu}$. There are five kinds of transition in this process: infections, progressions, removals, intervention progressions and the intervention itself. Infections are transitions from state $\boldsymbol{\omega}$ to state $\boldsymbol{\omega} + (-1, 1, 0 \ldots, 0)$ and occur at rate $\beta si/n$. Progressions move individuals into the next stage of their exposed/infectious period, and so take $\boldsymbol{\omega}$ to $\boldsymbol{\omega} + (0, \ldots, -1, 1, \ldots, 0)$, with rate $\gamma_E e_k$ or $\gamma_I i_k$ appropriate to the category of the individual. Removals take state $\boldsymbol{\omega}$ to $\boldsymbol{\omega} + (0, \ldots, 0, -1, 0)$ unless it is the vth removal, in which case they reach $\boldsymbol{\omega} + (0, \ldots, 0, -1, 1)$, both occurring at rate $\gamma_I i_{K_I}$. Intervention progressions can only occur once $d > 0$ and take $\boldsymbol{\omega}$ to $\boldsymbol{\omega} + (0, \ldots, 0, 1)$ at rate γ_D. The intervention maps states with $d = K_D$ to the absorbing state $\mathbf{0}$ at rate γ_D. Combining all of these events yields $\rho(\boldsymbol{\omega}) = \frac{\beta}{n} si + \gamma_E e + \gamma_I i + \gamma_D 1_{\{d>0\}}$, where 1_A denotes the indicator function of an event A.

When coupled with the boundary condition for the end of the epidemic $x(s, 0, \ldots, 0, d) = 0$, recurrence relation (1) can be applied finitely many times to yield a solution for $x(n, 1, 0, \ldots, 0)$, as there can be at most $(n + 1)(K_E + K_I) + n + K_D - 1$ transitions before an absorbing state is reached.

3.2. Random time-scale transformation method

Alternatively, it is possible to use the random time-scale transformation originally due to Watson[20] to express the expected effective severity in a more explicit manner. Construct a new Markov process $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$ from the relation $\widetilde{\boldsymbol{X}}(u) = \boldsymbol{X}(A(u))$, where $A(u) = \inf\{u \geq 0 : \int_0^t I(s)\,\mathrm{d}s = u\}$. Thus, when $I(t) > 0$ in $\{\boldsymbol{X}(t) : t \geq 0\}$, the clock in $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$ runs at rate $I(t)^{-1}$; and when $I(t) = 0$ the clock stops in $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$ – restarting once $I(t) > 0$. When $\{\boldsymbol{X}(t) : t \geq 0\}$ spends time t in state $\boldsymbol{\omega}$, then $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$ will spend $\iota(\boldsymbol{\omega})t$ in state $\boldsymbol{\omega}$. This means that the time at which the new process enters the absorbing state corresponds to the severity generated in the original process. Consequently, the expected effective severity is equal to the expected time to absorption in the new process $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$. Let T_A denote this absorption time. Since T_A has a phase-type distribution, proposition 4.1 in [2] implies that $\mathrm{E}[T_A] = -\boldsymbol{\alpha}\widetilde{Q}^{-1}\mathbf{1}$, where the row vector $\boldsymbol{\alpha}$ is the initial distribution of the process and $\widetilde{Q}$ is the submatrix of the generator matrix of $\{\widetilde{\boldsymbol{X}}(u) : u \geq 0\}$ that features only the transient states. In practice, both methods perform the same calculation, although the random time-scale transformation is harder to implement because to form the generator matrix, one must choose an ordering of the state space.

4. Non-Markovian models

4.1. D constant; T_E, T_I Erlang

Lemma 1. *When D is constant, $T_E \sim$ Erlang(K_E, γ_E) and $T_I \sim$ Erlang(K_I, γ_I),*

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \boldsymbol{\alpha}\widetilde{Q}^{-1}\mathbf{1} + \int_0^D \boldsymbol{\alpha}_v e^{(D-u)Q}\Delta e^{uQ}\mathbf{1}\,\mathrm{d}u,$$

where the row vector $\boldsymbol{\alpha}$ is the initial distribution, Q is the generator matrix of the within-group epidemic process without intervention, $\widetilde{Q}$ is the submatrix of transient states of the random time-scaled within-group epidemic process without intervention, Δ is a diagonal matrix with δ_{ii} equal to the number of infectives in state i, $\mathbf{1}$ is a column vector of ones and $\boldsymbol{\alpha}_v$ is a row vector with ith component being the probability that the within-group epidemic is in state i just after the vth removal.

Proof. First, recall that U_v is the time of the vth removal and so,

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] + \mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right], \tag{2}$$

where we define the second of these expectations to be zero if v removals do not occur, as in this case $T_v = U_v = \infty$. Since the epidemic process without intervention is Markovian, the methods described in Section 3 can be used to calculate both of these expectations. Two modifications are required. Firstly, it is no longer necessary to keep track of the intervention or the stage of the intervention delay; and secondly, in the first expectation, the vth removal event must cause the process to enter the absorbing state (which generates no severity). Thus, the first expectation becomes $\mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] = \boldsymbol{\alpha}\widetilde{Q}^{-1}\mathbf{1}$.

Since D is a constant and $T_v = U_v + D$, the expression $\mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right]$ in equation (2) is the expected reward between times 0 and D of the Markov Reward Process[6] $\{\boldsymbol{X}(t) : t \geq 0\}$, in which reward accumulates at rate $\iota(\boldsymbol{\omega})$ when $\boldsymbol{X}(t) = \boldsymbol{\omega}$. The expected reward up to time t for a Markov Reward Process is $\int_0^t \boldsymbol{\alpha} e^{(t-u)Q}\Delta e^{uQ}\mathbf{1}\,\mathrm{d}u$ [4, 18], where Q is the generator matrix of $\{\boldsymbol{X}(t) : t \geq 0\}$, the row vector $\boldsymbol{\alpha}$ is the initial distribution, $\mathbf{1}$ is a column vector of ones with length equal to the size of the state space and Δ is a diagonal matrix with δ_{ii} equal to the reward rate of state i. Such integrals can be evaluated numerically. All that remains is to find the distribution of the process at time U_v, as this forms the initial distribution of the Markov reward process. This can be done by conditioning on the type of the first jump from every state and solving the resulting set of equations.

Remark 1. For the special case in which $T_I \sim \mathrm{Exp}(\gamma)$, Ball *et al.* [5] use the random time-scale transformation to show that the amount of severity generated between removal events has an exponential distribution with rate γ_I. Thus, given that v removals actually occur, the expected severity generated by time U_v is equal to v/γ_I. This yields the surprising result that the severity until the vth removal is related to the final size distribution of the epidemic, specifically $\mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] = \sum_{k=1}^{n} \frac{1}{\gamma_I}\min\{k, v\}\mathrm{P}(F = k)$, where F is the final number of individuals in the group infected, including the initial infective.

Remark 2. For the special case in which $T_E \equiv 0$, infections transfer individuals

directly from the susceptible category into the infective category. Lemma 1 still holds, but with the state space reduced to only those states that have zero exposed individuals.

Lemma 1 allows the expected effective severity generated by a group to be computed, which in turn yields R_* for the model with a constant intervention delay. However, as the group size increases so does the computation time, and so for large groups the branching process approximation is useful.

4.2. D constant, $T_E \equiv 0$, $T_I \sim \text{Exp}(\gamma)$

Lemma 2. *For the branching process approximation to the within-group epidemic with D constant, $T_E \equiv 0$ and $T_I \sim \text{Exp}(\gamma)$,*

$$\text{E}\left[\int_0^{T_v} I(u)\,\text{d}u\right] = \begin{cases} \frac{1}{\gamma} + \frac{\beta}{\gamma}x_1(D) & v = 1, \\ \frac{v}{\gamma} + \sum_{k=1}^{v-1} \frac{(k-v)}{k\gamma}\left(\frac{\beta}{\beta+\gamma}\right)^{k-1}\left(\frac{\gamma}{\beta+\gamma}\right)^{k}\binom{2k-2}{k-1} + C_v x_1(D) & v > 1, \end{cases}$$

where

$$\begin{aligned} x_1(t) &= \begin{cases} t & \beta = \gamma, \\ \frac{1}{\beta-\gamma}\left(e^{(\beta-\gamma)t} - 1\right) & \beta \neq \gamma, \end{cases} \\ C_v &= 2 + v(\beta-\gamma)\left(\tfrac{1}{\gamma} - \tfrac{1}{\beta}\right) - \frac{v\gamma}{\beta}\left(\frac{\gamma}{\beta+\gamma}\right)^{v-1} \\ &\quad - \sum_{k=0}^{v-1}(1+k-v)\left(\frac{\beta}{\beta+\gamma}\right)^{k}\left(\frac{\gamma}{\beta+\gamma}\right)^{v}\left[\binom{k+v-1}{v-1} - \binom{k+v-1}{v-2}\right]. \end{aligned}$$

Proof. Again we use decomposition (2):

$$\text{E}\left[\int_0^{T_v} I(u)\,\text{d}u\right] = \text{E}\left[\int_0^{U_v} I(u)\,\text{d}u\right] + \text{E}\left[\int_{U_v}^{T_v} I(u)\,\text{d}u\right].$$

However, using the same random time-scale transformation as in Remark 1, we again find that the severity generated between removals has an exponential distribution with rate γ. Thus, given that v removals occur, the expected severity up to the vth removal is v/γ. Theorem 2.11.2 of [13] implies that if Z is the total progeny of the branching process (including the initial ancestor), then $\text{P}(Z = k) = \left(\frac{\gamma}{\beta+\gamma}\right)^{k}\left(\frac{\beta}{\beta+\gamma}\right)^{k-1}\frac{1}{k}\binom{2k-2}{k-1}$ for $k \geq 1$. Conditioning on Z yields

$$\text{E}\left[\int_0^{U_v} I(u)\,\text{d}u\right] = \frac{v}{\gamma} + \sum_{k=1}^{v-1}\frac{(k-v)}{k\gamma}\left(\frac{\gamma}{\beta+\gamma}\right)^{k}\left(\frac{\beta}{\beta+\gamma}\right)^{k-1}\binom{2k-2}{k-1},$$

where the empty sum is zero.

To find the second component of (2), we condition on $I(U_v)$.

$$\begin{aligned}\mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right] &= \sum_{k=0}^{\infty} \mathrm{E}\left[\int_{U_v}^{U_v+D} I(u)\,\mathrm{d}u \middle| I(U_v)=k\right] \mathrm{P}(I(U_v)=k) \\ &= \sum_{k=0}^{\infty} \mathrm{E}\left[\int_{0}^{D} I(u)\,\mathrm{d}u \middle| I(0)=k\right] \mathrm{P}(I(U_v)=k).\end{aligned}$$

Define $x_k(t) = \mathrm{E}\left[\int_0^t I(u)\,\mathrm{d}u \middle| I(0)=k\right]$, and notice that the offspring from different ancestors are independent, so that $x_k(t) = kx_1(t)$. Thus,

$$\begin{aligned}\mathrm{E}\left[\int_{U_v}^{T_v} I(u)\,\mathrm{d}u\right] &= \sum_{k=1}^{\infty} kx_1(D)\mathrm{P}(I(U_v)=k) \\ &= x_1(D)\mathrm{E}[I(U_v)].\end{aligned}$$

For this branching process model we have $\mathrm{E}[I(t)|I(0)=1] = e^{(\beta-\gamma)t}$ so by Fubini's Theorem,

$$\begin{aligned}x_1(t) &= \int_0^t \mathrm{E}[I(u)]\,\mathrm{d}u \\ &= \begin{cases} t & \beta=\gamma, \\ \frac{1}{\beta-\gamma}(e^{(\beta-\gamma)t}-1) & \beta\neq\gamma. \end{cases}\end{aligned}$$

It remains to find $\mathrm{E}[I(U_v)]$, the expected number of individuals alive after the vth death. We begin by conditioning on the path that the embedded discrete time branching process takes. This process is a random walk on $\mathbb{N}\cup\{0\}$ with probability of an upward jump $\beta/(\beta+\gamma)$ and an absorbing barrier at zero. Thus, $\mathrm{E}[I(U_v)] = \sum_{w\in W} I(U_v;w)\mathrm{P}(\text{the process takes path } w)$, where $I(U_v;w)$ is the number of individuals alive just after the vth death in path w and W is the set of valid paths in which v deaths occur, the last event is a death and $I(U_v;w) > 0$. Paths with equal values of $I(U_v;w)$ can be grouped together since the number of births before U_v determines $I(U_v;w)$ and for this model each of these paths has equal probability. Thus,

$$\mathrm{E}[I(U_v)] = \sum_{j=v}^{\infty}(1+j-v)\left(\frac{\beta}{\beta+\gamma}\right)^j\left(\frac{\gamma}{\beta+\gamma}\right)^v N_{1,j,v} \tag{3}$$

where $N_{a,j,v}$ is the number of paths from a containing j births and v deaths that end with a death. The reflection principle[9] gives $N_{a,j,v} = \binom{j+v-1}{v-1} - \binom{j+v-1}{v-a-1}$.

The infinite sum in (3) can be reduced to a finite sum with the application of two identities. Let X be a random variable that counts the number of successes in a sequence of independent Bernoulli(p) trials before $r \geq 1$ failures and let $q = 1 - p$. Then for $l \geq 0$, $\mathrm{P}(X = l) = p^l q^r \binom{l+r-1}{r-1}$ and $\mathrm{E}[X] = r(\frac{1}{q} - 1)$. Thus $\sum_{l=0}^{\infty} p^l q^r \binom{l+r-1}{r-1} = 1$ and $\sum_{l=0}^{\infty} l p^l q^r \binom{l+r-1}{r-1} = r(\frac{1}{q} - 1)$. This implies that for $r > 0$,

$$a + r(\tfrac{1}{q} - 1) - r = \sum_{l=0}^{\infty} (a + l - r) p^l q^r \binom{l + r - 1}{r - 1} \tag{4}$$

which, after the transformation $(a, l, r) \mapsto (-1, k+1, v-1)$ and a little rearrangement, gives that for $v > 1$,

$$\frac{v(p-q)}{p} - 1 = \sum_{k=-1}^{\infty} (1 + k - v) p^k q^v \binom{k + v - 1}{v - 2}. \tag{5}$$

Applying (4) and (5) to (3) with $p = \frac{\beta}{\beta+\gamma}$ gives

$$\mathrm{E}[I(U_v)] = \begin{cases} \frac{\beta}{\gamma} & v = 1, \\ 2 + v(\beta - \gamma)\left(\frac{1}{\gamma} - \frac{1}{\beta}\right) - \frac{v\gamma}{\beta}\left(\frac{\gamma}{\beta+\gamma}\right)^{v-1} & \\ \quad - \sum_{k=0}^{v-1} (1 + k - v)\left(\frac{\beta}{\beta+\gamma}\right)^k \left(\frac{\gamma}{\beta+\gamma}\right)^v \left[\binom{k+v-1}{v-1} - \binom{k+v-1}{v-2}\right] & v > 1. \end{cases}$$

4.3. T_E, T_I and D constant

When T_E, T_I and D are fixed constants we can calculate the expected effective severity for the special case in which only the initial infective and the individuals infected by them contribute to the effective severity. We define $t = 0$ to be the beginning of the infectious period of the initial infective. First, we will assume that $v = 1$, so that the intervention is certain to occur at time $T_v = T_I + D$. To prevent the second generation of infection contributing to the severity, they must not begin their infectious periods before the intervention, and so the intervention time must be less than two exposed periods, ie. $T_I + D \leq 2T_E$. In addition, we will make the simplifying assumption that infections from the initial infective have ceased before infections from the first generation of infection can begin, ie. $T_E \geq T_I$. This assumption allows us to separate infections from the initial infective and the first generation, and therefore calculate the distribution of the number of infectious contacts in the time interval $(0, T_I)$.

Lemma 3. *If $v = 1$, $T_I + D \leq 2T_E$ and $T_E \geq T_I$ then*

$$\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = T_I + \sum_{c=1}^{\infty} \frac{(\frac{\beta T_I}{n})^c e^{-\beta T_I/n}}{c!} \sum_{j=1}^{c} p_j T_I \Big[\mathrm{P}(B_{j,c} < \tfrac{t_1}{T_I}) + (T_I + D + T_E)\mathrm{P}(\tfrac{t_1}{T_I} < B_{j,c} < \tfrac{t_2}{T_I}) - \tfrac{j}{c+1}\mathrm{P}(\tfrac{t_1}{T_I} < A_{j,c} < \tfrac{t_2}{T_I})\Big],$$

where $t_1 = \min\{D - T_E, T_I\}$, $t_2 = \max\{0, T_I + D - T_E\}$, $A_{j,c} \sim Beta(j+1, c+1-j)$, $B_{j,c} \sim Beta(j, c+1-j)$ and $p_j = \left(\frac{n-1}{n}\right)^{j-1}$, where $Beta(a,b)$ denotes a Beta random variable with probability density function $f(x) \propto x^{a-1}(1-x)^{b-1}1_{\{0<x<1\}}$.

Proof. Let C_1 denote the number of infectious contacts made by the initial infective, recall that these contacts will result in an infection if and only if the individual contacted is susceptible. From the definition of the infection process, C_1 has a Poisson distribution with mean βT_I. Given that C_1 infectious contacts occur in the interval $(0, T_I]$, the (unordered) contact times have independent uniform distributions on $(0, T_I]$ since the contacts occur at the points of a homogeneous Poisson process. The jth contact occurs at the jth order statistic of these C_1 uniform distributions, say $U_{(j),C_1}$. Note that $U_{(j),C_1} \sim T_I\mathrm{Beta}(j, C_1 + 1 - j)$. Next, let p_j denote the probability that the jth contact results in an infection. An infection occurs if the individual has not been contacted by the initial infective before, and so p_j is the probability that the first $j-1$ contacts avoid the individual chosen for the jth contact, ie. $p_j = \left(\frac{n-1}{n}\right)^{j-1}$.

Our aim is to find $\mathrm{E}[\int_0^{T_v} I(u)\,\mathrm{d}u | C_1 = c]$. Contributions to the effective severity can be split into four parts. Assume that if $a \geq b$ then $(a, b] = \emptyset$.

1. The initial infective contributes T_I to the effective severity. If the next generation do not begin their infectious periods before the intervention ($T_E > T_I + D$) then this is the only contribution to the severity.

2. In addition, individuals in the first generation infected in the time interval $(0, t_1]$, where $t_1 = \max\{0, D - T_E\}$, complete their infectious period before the intervention, and therefore contribute T_I to the effective severity. The jth infectious contact will create one of these individuals with probability $p_j\mathrm{P}(U_{(j),C_1} < t_1)$.

3. Individuals infected in $(t_2, T_I]$, where $t_2 = \max\{0, T_I + D - T_E\} \geq t_1$ do not begin their infectious period and therefore do not contribute anything to the severity.

4. Individuals infected at time $x \in (t_1, t_2]$ begin their infectious period, but do not complete it before the intervention, and therefore contribute $T_I + D - T_E - x$ to the effective severity. The jth infectious contact will create one of these individuals with probability $p_j \mathrm{P}(t_1 < U_{(j),C_1} < t_2)$.

Thus,

$$\begin{aligned}\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u \middle| C_1 = c\right] &= T_I + \sum_{j=1}^{c} p_j \mathrm{P}(U_{(j),c} < t_1) T_I \\ &\quad + p_j \int_{\max\{0,t_1\}}^{\min\{t_2,T_I\}} (T_I + D - T_E - x) f_{(j),c}(x)\,\mathrm{d}x,\end{aligned}$$

where $f_{(j),c}$ is the density function for $U_{(j),c}$.

Using the fact that $U_{(j),c} \sim T_I \mathrm{Beta}(j, c+1-j)$ and $\frac{B(j+1,c+1-j)}{B(j,c+1-j)} = \frac{j}{c+1}$, we can solve the integral to obtain

$$\begin{aligned}\int_{\max\{0,t_1\}}^{\min\{t_2,T_I\}} (T_I + D - T_E - x) f_{(j),c}(x)\,\mathrm{d}x &= (T_I + D - T_E)\mathrm{P}(\tfrac{t_1}{T_I} < B_{j,c} < \tfrac{t_2}{T_I}) \\ &\quad - \tfrac{j}{c+1}\mathrm{P}(\tfrac{t_1}{T_I} < A_{j,c} < \tfrac{t_2}{T_I}),\end{aligned}$$

where $B_{j,c} \sim \mathrm{Beta}(j, c+1-j)$ and $A_{j,c} \sim \mathrm{Beta}(j+1, c+1-j)$. The result follows, after removing the conditioning on C_1.

Remark 3. For $c \geq j > 0$ integers and $t \in [0,1]$, $\mathrm{P}(\mathrm{Beta}(j, c+1-j) < t)$ represents the probability that the jth order statistic of c independent uniform distributions is below t, this probability can be expressed in terms of a Binomial distribution with c trials and success probability t, ie. $\mathrm{P}(\mathrm{Bin}(c,t) \geq j)$.

Lemma 4. *For the branching process approximation to the within-group epidemic we have that for $t > 0$,*

$$\mathrm{E}\left[\int_0^t I(u)\,\mathrm{d}u\right] = \int_0^t \mathrm{E}[I(t)]\,\mathrm{d}t, \tag{6}$$

for $t \in (0, T_I) \cup (T_I, \infty)$,

$$\frac{\mathrm{dE}[I(t)]}{\mathrm{d}t} = \beta \mathrm{E}[I(t - T_E)] - \beta \mathrm{E}[I(t - T_E - T_I)], \tag{7}$$

for $t < 0$, $I(t) = 0$ and at the discontinuity at $t = T_I$, $\mathrm{E}[I(T_I-)] = \mathrm{E}[I(T_I+)] + 1$. If $v = 1$ then $\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right]$ is the solution to (6) evaluated at $t = T_v = T_I + D$.

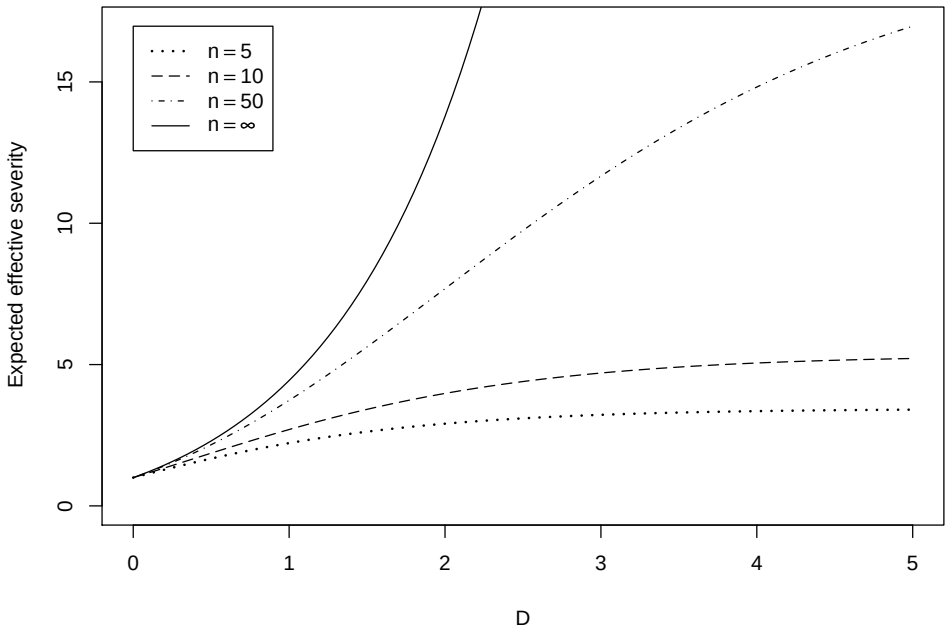

FIGURE 1: The expected effective severity as the intervention delay is increased for various values of n. The branching process approximation (in which the supply of susceptibles is never exhausted) is used to calculate $n = \infty$. For all curves $\beta = 2$, $T_I \sim \text{Exp}(1)$ and $T_E \equiv 0$.

Proof. First note that by Fubini's Theorem equation (6) holds. A single initial infective is introduced into the population at $t = 0$, and this individual becomes removed at time T_I. Thus, $I(t) = 0$ for $t < 0$ and $I(T_I-) = I(T_I+) + 1$ almost surely. Since the holding times T_E and T_I are non-random, infectives are produced at time t at rate $\frac{\beta}{n} I(t - T_E)$ and removed at rate $\frac{\beta}{n} I(t - T_E - T_I)$, which yields (7). Finally note that since D is also non-random, when $v = 1$ we have that $T_v = T_I + D$.

5. Numerical results

Figure 1 demonstrates the effect of increasing D and group size on the expected effective severity with constant delays. When the delay length is zero the intervention occurs at the first removal, and irrespective of the group size the expected effective

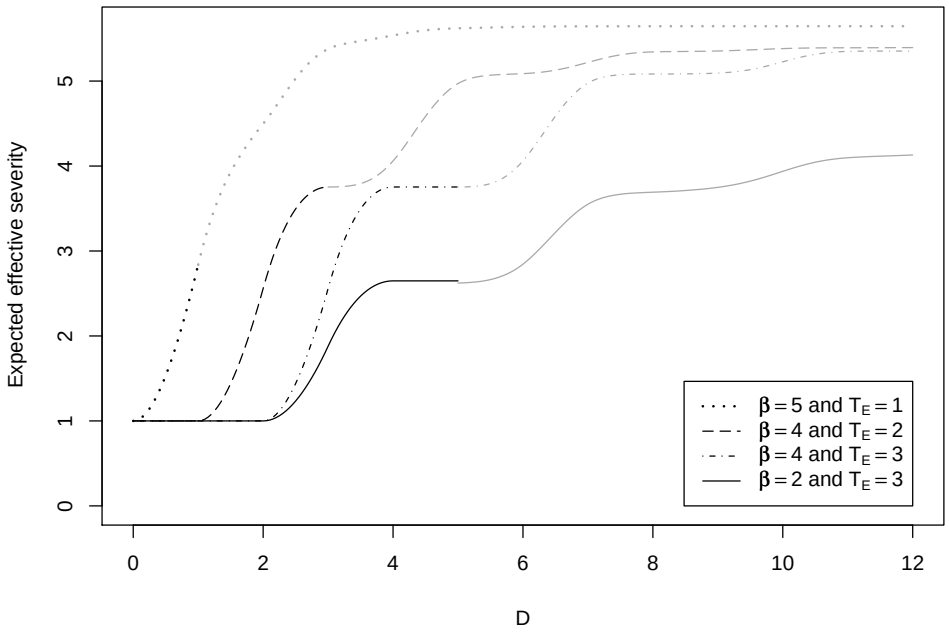

FIGURE 2: The expected effective severity as the expected intervention delay is increased for the model with constant exposed, infectious and intervention delay lengths. For all curves $T_I = 1$ and $n = 5$. The grey parts of the curve have been produced via simulation, as in these regions the conditions imposed in Section 4.3 are not met.

severity is one for this model. This is because the infectious periods are exponentially distributed and so when additional infectives are created the time to intervention is reduced in proportion to the increase in the rate that severity is accumulated. This leads to the surprising result that the reproduction number R_* is independent of the exposed period distribution, the within-group infection rate and the group size.

Once D is increased above zero we see that in large groups, the length of the intervention delay strongly influences the effectiveness of the intervention. For smaller, household-sized groups more realistic in human epidemics, the decrease in effectiveness is more subtle but still important. For example in a group with $n = 5$, delaying the intervention by the length of the infectious period increases the reproduction number by a factor of 2.22. This highlights the need to include an intervention delay in any

epidemic model attempting to realistically capture disease transmission.

Figure 2 demonstrates the interaction between the exposed period and the intervention delay for the model with constant exposed, infectious and intervention delay periods. Long exposed periods like the ones shown separate the generations of infection in the early stages. Consequently there are some regions (for example when D is very small) in which changing the exposed period does not affect the effective severity, and other regions where a small change in the intervention delay causes a sharp change in effective severity. This demonstrates that if the length of the intervention delay in the model does not accurately reflect the delay in practice, then there is the potential to obtain very different results when the intervention being modelled is put into practice.

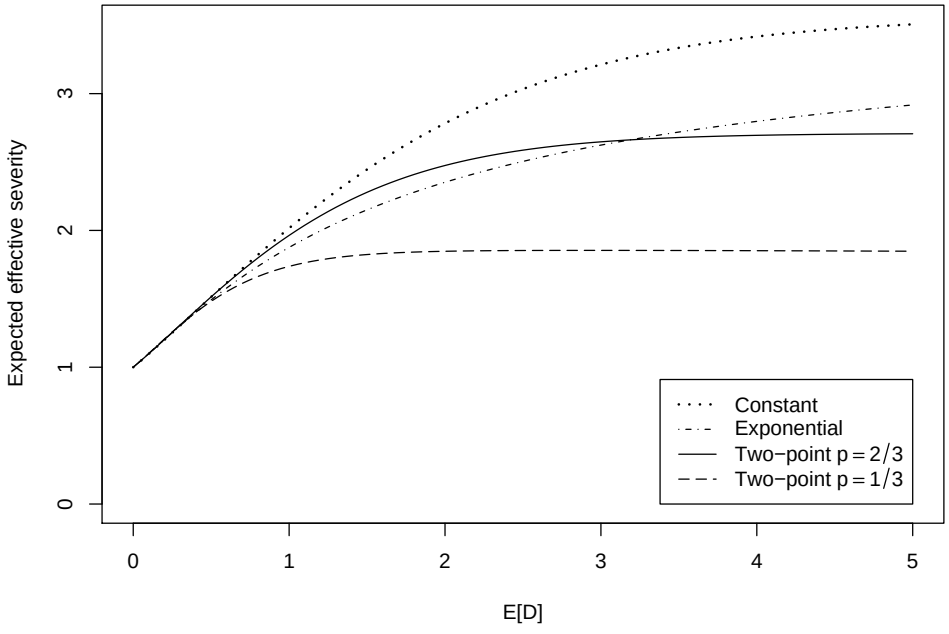

FIGURE 3: The expected effective severity as the expected intervention delay is increased for various delay distributions. For all curves $\beta = 3$, $n = 4$, $T_I \sim \text{Exp}(1)$ and $T_E \sim \text{Exp}(2)$.

6. Effect of delay distribution

By considering a specific model for an epidemic with a delayed dynamic intervention we have demonstrated a method of quantifying the reduction in effectiveness of the intervention caused by its delay. Numerical exploration of these results highlights the need to include such a delay in any epidemic model attempting to realistically capture dynamic interventions and that the length of the intervention delay must be chosen carefully if the results are to have a realistic interpretation.

As we shall see, there is also the potential for the *distribution* of the intervention delay to cause surprising changes in the effectiveness of the intervention. First, we will demonstrate that a constant delay 'often' reduces the effectiveness of the intervention by the most and then we will go on to find best distribution for the intervention delay.

For our most general model we have that $\mathrm{E}\left[\int_0^{T_v} I(u)\,\mathrm{d}u\right] = \mathrm{E}\left[\int_0^{U_v} I(u)\,\mathrm{d}u\right] + \mathrm{E}\left[f(D)\right]$, where $f(t) = \mathrm{E}\left[\int_{U_v}^{U_v+t} I(u)\,\mathrm{d}u\right]$, since the within-group epidemic process is independent of D. Denote by C the subinterval of $\mathbb{R}$ on which D takes values. Jensen's inequality implies that if f is concave on C then the constant delay gives rise to the highest value of R_* for a given value of $\mathrm{E}[D]$, ie. $\mathrm{E}[f(D)] \leq f(\mathrm{E}[D])$. A constant delay is used in figures 1 and 2, and so we can determine the shape of f. Notice that f is concave when the within-group epidemic is dying out, for example when D is large or the group size is small.

When we look at the branching process approximation for the within-group epidemic with exponential infectious periods and zero exposed period, we have from the proof of lemma 2 that $f(D) = \mathrm{E}[I(U_v)]x_1(D)$. The definition of $x_1(t)$ then implies that the constant intervention delay produces the largest value of R_* if and only if $\beta \leq \gamma$. These results tie in with the analogous result for the infectious period distribution, where the constant infectious period gives rise to the most severe epidemic in all cases [7, 16, 18]. Surprisingly however, for $\beta \geq \gamma$ in this model we find the opposite result: $\mathrm{E}[f(D)] \geq f(\mathrm{E}[D])$. This stems from the assumption that, for the branching process approximation of the within-group epidemic, the supply of susceptibles is never exhausted.

Next, we transfer our attention to the best possible delay distribution with a given mean for the finite-group epidemic model. Consider the random variable W_p, which

is zero with probability $1-p$ and μ/p with probability p. Now W_p is an optimal intervention delay distribution with mean μ if for an arbitrary D with $\mathrm{E}[D] = \mu$, we have that $\mathrm{E}[f(W_p)] \leq \mathrm{E}[f(D)]$. However, f is a non-decreasing function which is bounded above by $(n+1-v)\mathrm{E}[T_I]$, as there are at most $n+1-v$ infective individuals at U_v. Thus,

$$\mathrm{E}[f(W_p)] = (1-p)f(0) + pf(\mu/p) \leq p(n+1-v)\mathrm{E}[T_I] \to 0 \text{ as } p \to 0.$$

These results have some interesting implications. Imagine a situation during an influenza pandemic in which the quantity of the anti-viral stockpile that can be used is constrained by the ability of the health authority to distribute it to the population. The fairest system, in which infected households join a waiting list for treatment, might ensure that each household waits approximately the same time (a constant intervention delay) and the least effective intervention occurs. Instead, the most recent household to join the list should be treated first, (which may result in an approximately two-point distributed delay) as this prevents the most future infections.

Figure 3 shows the effect that the distribution of the intervention delay has on the expected effective severity for the model with exponential exposed and infectious periods. In this example the constant intervention delay usually gives rise to the most severe epidemics. Of those shown, the curve for the exponential distribution has the smallest expected effective severity for small delays. However, the curves for the two-point distribution demonstrate that as p is decreased, the expected effective severity can be made closer and closer to $\mathrm{E}[T_I]$.

Acknowledgement

Simon Spencer was supported by an EPSRC Doctoral Training grant.

References

[1] Andersson, H. and Britton, T. (2000). *Stochastic Epidemic Models and Their Statistical Analysis*, Springer Verlag, New York.

[2] Asmussen, S. (2003). *Applied Probability and Queues*, second ed., Springer, New York.

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

[4] Ball, F. G., Milne, R. K. and Yeo, G. F. (1994). Continuous-time Markov chains in a random environment, with applications to ion channel modelling. *Adv. Appl. Prob.* **26**, 919–946.

[5] Ball, F. G., O'Neill, P. D. and Pike J. (2007). Stochastic epidemic models in structured populations featuring dynamic vaccination and isolation. *J. Appl. Prob.* **44**, 571–585.

[6] Bhatt, U. N. (1972). *Elements of applied stochastic processes*, John Wiley and Sons, New York.

[7] Daley, D. J. (1990). The size of epidemics with variable infectious periods. Technical report SMS–012–90, Statistics Research Section, School of Mathematical Sciences, Australian National University.

[8] Eubank, S., Guclu, H., Kumar, V. S. A., Marathe, M. V., Srinivasan, A., Toroczkai, Z. and Wang, N. (2004). Modelling disease outbreaks in realistic social networks. *Nature* **429**, 180–184.

[9] Feller, W. (1971). *An introduction to probability theory and its applications.* Volume I, 3rd edition.

[10] Halloran, M. E., Longini, I. M., Nizam, A. and Yang, Y. (2002). Containing bioterrorist smallpox. *Science* **298**, 1428–1432.

[11] Isham, V. (1993) Stochastic models for epidemics with special reference to AIDS. *Ann. Appl. Prob.* **3**, 1–27.

[12] Isham, V. and Medley, G. (eds). (1996) *Models for Infectious Human Diseases: Their structure and relation to data*. Cambridge University Press.

[13] Jagers, P. (1975). *Branching Processes with Biological Applications.* John Wiley and Sons, London.

[14] Kaplan, E. H., Craft, D. L. and Wein, L. M. (2002). Emergency response to a smallpox attack: The case for mass vaccination. *Proc. Natl. Acad. Sci.* **99** (16), 10935–10940.

[15] Keeling, M., Woolhouse, M. E. J., Shaw, D. J., Matthews, L., Chase-Topping, M., Haydon, D. T., Cornell, S. J., Kappey, J., Wilesmith, J. and Grenfell, B. T. (2001). Dynamics of the 2001 UK foot and mouth epidemic: Stochastic dispersal in a heterogeneous landscape. *Science* **294**, 813–817.

[16] Lefèvre, C. P. and Picard, P. (1993). An unusual stochastic order relation with some applications in sampling and epidemic theory. *Adv. Appl. Prob.* **25** 63–81.

[17] Longini, I. M., Halloran, M. E., Nizam, A. and Yang, Y. (2004). Containing pandemic influenza with antiviral agents. *Am. J. Epidemiol.* **159**, 623–633.

[18] Spencer, S. E. F. (2007). Stochastic epidemic models for emerging diseases. PhD Thesis, University of Nottingham School of Mathematical Sciences.

[19] Tildesley, M. J., Savill, N. J., Shaw, D. J., Deardon, R., Brooks, S. P., Woolhouse, M. E. J., Grenfell, B. T. and Keeling, M. J. (2006). Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. *Nature* **440**, 83–86.

[20] Watson, R. K. (1980). A useful random time-scale transformation for the standard epidemic model. *J. App. Prob.* **17**, 324–332.