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AN EPIDEMIC MODEL WITH INFECTOR-DEPENDENT SEVERITY

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Abstract

A stochastic epidemic model is defined in which infected individuals have different severities of disease (e.g. mildly and severely infected). In the model the severity of an infected individual depends on the severity of the individual he or she was infected by; typically, severe (mild) infectives have an increased tendency to infect others severely (mildly). Large-population properties of the model are derived, using branching process approximations for the initial stages of an outbreak and density dependent population processes in the case when a major outbreak occurs. Effects of vaccination are considered, using two distinct models for vaccine action. The consequences of launching a vaccination program are studied in terms of its effect on reducing the final outbreak size in the event of a major outbreak as a function of the vaccination coverage, and also by determining the critical vaccination coverage above which only small outbreaks can occur.

Keywords: Stochastic epidemic; final size; basic reproduction number; varying severity; branching process; density dependent population process; threshold behaviour

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1. Introduction

Many infectious diseases have the property that the degree of severity of infected individuals varies and where the degree of severity of an infective is also believed to affect potential future spreading, e.g. measles (Morley and Aaby (1997)), varicella (Parang and Archana (2004)) and dengue fever (Mangada and Igarashi (1998)). In the present paper we study a model which attempts to capture this feature within the class of SIR (susceptible \rightarrow infective \rightarrow removed) epidemic models, describing the spread of an infectious disease in a closed finite community (see, for example, Lefèvre (1990) and Andersson and Britton (2000)).

For the same purpose, Ball and Britton (2005) defined an epidemic model for a homogeneously mixing community, where the degree of severity of an infective depended on the amount of “infection force” an individual had been exposed to, and where severe infectives typically exposed more force of infection than mildly infected.

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The new model of the present paper captures the same phenomenon but from a different perspective, also assuming a homogeneously mixing community. Here the severity of an infective depends on who this individual was infected by in that he or she is typically more likely to become severely infected if infected by a severe infective and mildly infective if infected by a mild infective. Contrary to the model in Ball and Britton (2005), an infective always remains the same type and cannot become a severe infective by additional exposure to infection. We denote our model the infector-dependent severity (IDS) model.

For a large community starting with few initial infectives, we show a threshold limit theorem for the IDS model, which states that the epidemic has (strictly) positive chance of becoming established and growing beyond all limits if and only if a suitably defined threshold parameter (reproduction number) is larger than unity. We also show that if the epidemic is initiated by a positive fraction of infectives then the numbers of ultimately mild and severely infected (i.e. the total size of the epidemic) satisfies a law of large numbers. Further, we make plausible that if either (i) the epidemic is initiated by a positive fraction of infectives or (ii) the epidemic is initiated by few infectives but it becomes established, then the total size of the epidemic satisfies a central limit theorem.

We study two different models for the effect of vaccination. In one model the vaccine reduces the severity of disease, in the sense that an individual who would have become severely infected only gets mildly infected if he or she has been vaccinated, and someone who would have become mildly infected avoids getting infected altogether. The other vaccination model is more general and flexible in that it reduces susceptibility and infectivity (if infected) by possibly dependent random factors. For both vaccination models the effect of vaccination on the reproduction number and the final outbreak size are studied, as is the critical vaccination coverage, i.e. the fraction necessary to vaccinate in order to surely prevent a major outbreak.

In what follows, “severity” refers to how infectious an individual is and only indirectly to the degree of illness, in that severity may affect an individual’s social activity. It is the former that is relevant for epidemic spread, which is the focus of the present paper, whereas the latter is of course important from both an individual’s and a national health perspective.

In Section 2 we define the IDS-model, state the main results and also give some heuristic arguments motivating the results. In Section 3 we define the two models for vaccine response and show what effect on outbreak sizes these have as a function of the vaccination coverage. Sections 2 and 3 also contain some numerical examples that illustrate the theory. In Section 4 we give the formal theorems and their proofs, together with heuristic arguments for results that are strongly supported by numerical examples but currently lack fully rigorous proofs. The paper ends with a discussion in Section 5.

2. The IDS epidemic model

2.1. Definition of the model

We now define the infector-dependent severity (IDS) model. In the model an individual can only have one severity but the type of severity may depend on the severity of the infective the individual is infected by.

Consider a closed homogeneously mixing population consisting of n initially susceptible individuals, m_M mildly infectious individuals and m_S severely infectious individuals. An individual who gets mildly infected remains so for a period I_M with distribution F_M . During this period the individual has “close contacts” with other individuals, chosen uniformly among the initial susceptibles, at rate λ_M (i.e. at the points of a homogeneous Poisson process with rate λ_M). If the contacted person is still susceptible he or she becomes a mild case with probability $p_M^{(M)}$ and a severe case with the remaining probability $p_S^{(M)} = 1 - p_M^{(M)}$. Similarly, an individual who gets severely infected remains so for a period I_S with distribution F_S , during which he or she has “close contacts” with others, chosen uniformly among the initially susceptible individuals, at rate λ_S . In this case a contacted person becomes a mild case with probability $p_M^{(S)}$ and a severe case with the remaining probability $p_S^{(S)} = 1 - p_M^{(S)}$. At the end of his or her infectious period an infective individual recovers, becomes immune and plays no further part in the epidemic – a state called removed. All infectious periods, contact processes and uniform “selections” are mutually independent. The infectious period distributions, F_M and F_S , are arbitrary but specified and are assumed to have finite means. The epidemic process continues until there is no mild or severe infective in the population, at which point the epidemic stops. The numbers of individuals who were mild and severely infected during the outbreak specifies the *final size* of the epidemic.

Some special choices of parameter values of the IDS model give rise to models previously studied in the literature. The case where a contacted susceptible necessarily becomes the same type as his or her infector (i.e. $p_M^{(M)} = 1$ and $p_S^{(S)} = 1$) is identical to the so-called competing epidemic model investigated (with exponentially distributed infectious periods) by Kendall and Saunders (1983) and Scalia Tomba and Svensson (2001), see also Scalia-Tomba (2005). The case where the infectious type of an individual is independent of that of his or her infector (i.e. $p_M^{(M)} = p_M^{(S)} = p_M$ and $p_S^{(M)} = p_S^{(S)} = p_S$) has been studied by Ball and Clancy (1995) (see also Picard and Lefevre (1990)), who allow for more than two different infectious states.

Epidemics with $p_M^{(M)} = 1$ or $p_S^{(S)} = 1$, such as the competing epidemic, have a quite different and more complicated asymptotic behaviour than epidemics with other parameter values, since in the early stages of an epidemic in a large population at least one of the mild and severe outbreaks evolves (almost) independently of the other. We exclude such cases from the analysis in this paper and assume throughout that $p_M^{(M)} < 1$ and $p_S^{(S)} < 1$, or equivalently that $p_S^{(M)} > 0$ and $p_M^{(S)} > 0$.

2.2. Main results and ideas

2.2.1. Early stages and minor outbreaks Suppose that the number of susceptibles n is large and that the initial numbers of mild and severe infectives, m_M and m_S , are both small. Then, during the early stages of the epidemic, the probability that a contact is made with an infective or removed individual is very small, so the process of infectives can be approximated by a branching process, in which every infectious contact gives rise to a new infective. The branching process is two-type, with type being either *mild* or *severe*. A typical mild (severe) individual lives for a time having distribution F_M (F_S), during which he or she has offspring at the points of a homogeneous Poisson process with rate λ_M (λ_S). Offspring of a mild (severe) individual are mild independently and

with probability $p_M^{(M)}$ ($p_M^{(S)}$), and severe otherwise.

The approximation of the epidemic process by a branching process is made fully rigorous in Section 4.1 by letting $n \rightarrow \infty$ and using a coupling argument (see Theorem 1). The branching process either goes extinct or it grows unboundedly. A threshold theorem for the epidemic model can be obtained by associating the epidemic becoming established with non-extinction of the branching process.

The mean offspring matrix for the branching process is given by

$$M = \begin{bmatrix} \lambda_M \iota_M p_M^{(M)} & \lambda_M \iota_M p_S^{(M)} \\ \lambda_S \iota_S p_M^{(S)} & \lambda_S \iota_S p_S^{(S)} \end{bmatrix}, \quad (2.1)$$

where $\iota_M = E[I_M]$ and $\iota_S = E[I_S]$ are the mean lengths of mild and severe infectious periods, respectively. The largest eigenvalue of this matrix is denoted by R_0 and called the *basic reproduction number*, see e.g. Heesterbeek and Dietz (1996). It is given by

$$R_0 = \frac{T + \sqrt{T^2 + 4\lambda_M \iota_M \lambda_S \iota_S (1 - p_M^{(M)} - p_S^{(S)})}}{2}, \quad (2.2)$$

where $T = \lambda_M \iota_M p_M^{(M)} + \lambda_S \iota_S p_S^{(S)}$.

By standard branching process theory (e.g. Haccou *et al.* (2005), Chapter 5), the epidemic with few initial infectives has a nonzero probability of becoming established if and only if $R_0 > 1$. The probability that an epidemic becomes established can be determined as follows. For $i, j \in \{M, S\}$, let $R_j^{(i)}$ denote the number of type- j offspring of a typical type- i individual, and define probability generating functions

$$f_M(s_M, s_S) = E \left[s_M^{R_M^{(M)}} s_S^{R_S^{(M)}} \right] \quad \text{and} \quad f_S(s_M, s_S) = E \left[s_M^{R_M^{(S)}} s_S^{R_S^{(S)}} \right].$$

Then, provided $R_0 > 1$, the probability that the epidemic becomes established is given by $1 - \pi_M^{m_M} \pi_S^{m_S}$, where (π_M, π_S) is the unique solution in $(0, 1)^2$ of the equations

$$\pi_M = f_M(\pi_M, \pi_S), \quad \pi_S = f_S(\pi_M, \pi_S). \quad (2.3)$$

(If $R_0 \leq 1$ then $(\pi_M, \pi_S) = (1, 1)$ is the only solution of (2.3) and there is zero probability of an epidemic becoming established.) Note that if $\phi_M(\theta) = E[\exp(-\theta I_M)]$ and $\phi_S(\theta) = E[\exp(-\theta I_S)]$ denote the moment generating functions of typical mild and severe infectious periods, respectively, then

$$f_M(s_M, s_S) = \phi_M \left(\lambda_M \left[p_M^{(M)}(1 - s_M) + p_S^{(M)}(1 - s_S) \right] \right)$$

and

$$f_S(s_M, s_S) = \phi_S \left(\lambda_S \left[p_M^{(S)}(1 - s_M) + p_S^{(S)}(1 - s_S) \right] \right).$$

If the epidemic fails to become established, its final outcome can be approximated by that of the corresponding branching process; explicit results for moments are easily obtained using standard branching process theory.

2.2.2. Large outbreaks We now consider the final outcome of epidemics that become established. Suppose that n is large, and let $\mu_M = m_M/n$ and $\mu_S = m_S/n$. Let r_M and r_S denote the proportions of susceptibles that ultimately become mild and severe infectives, respectively. Then the total force of infection exerted on a given susceptible during the entire epidemic is $\lambda_M \iota_M (\mu_M + r_M) + \lambda_S \iota_S (\mu_S + r_S)$. This follows since $n(\mu_M + r_M)$ is the total number of mild infectives, each of which has contact with a given susceptible at the average accumulated rate $\lambda_M \iota_M/n$; similarly, $n(\mu_S + r_S)$ is the total number of severe infectives, each of which has contact with a given susceptible at the average accumulated rate $\lambda_S \iota_S/n$. It follows that the probability that a given susceptible remains uninfected throughout the epidemic is $\exp[-(\lambda_M \iota_M (\mu_M + r_M) + \lambda_S \iota_S (\mu_S + r_S))]$, since infectious individuals make contacts at the points of independent Poisson processes. Thus, (r_M, r_S) satisfies

$$1 - r_M - r_S = \exp[-(\lambda_M \iota_M (\mu_M + r_M) + \lambda_S \iota_S (\mu_S + r_S))]. \quad (2.4)$$

In general, it is not possible to derive a second balance equation satisfied by (r_M, r_S) and hence to uniquely determine the final outcome of the epidemic. If $\lambda_M \iota_M = \lambda_S \iota_S$ then (2.4) yields an equation for $r_M + r_S$, and hence for the final proportion of susceptibles, but the individual r_M and r_S still need to be determined. In the special case studied by Ball and Clancy (1995), where $p_M^{(M)} = p_M^{(S)} = p_M$ and $p_S^{(M)} = p_S^{(S)} = p_S$, contacted susceptibles become mildly infected independently with probability p_M , irrespective of the type of their infectors, so $r_M/r_S = p_M/p_S$ and the final outcome can be determined. We assume now that the infectious periods follow exponential distributions, with rate γ_M for mild infectives and γ_S for severe infectives, so $\iota_M = \gamma_M^{-1}$ and $\iota_S = \gamma_S^{-1}$. If the numbers of susceptibles and initial infectives are both large, the stochastic model can be approximated by the deterministic model

$$\left. \begin{aligned} \frac{dx}{dt} &= -(\lambda_M y_M + \lambda_S y_S)x, \\ \frac{dy_M}{dt} &= (\lambda_M p_M^{(M)} y_M + \lambda_S p_M^{(S)} y_S)x - \gamma_M y_M, \\ \frac{dy_S}{dt} &= (\lambda_M p_S^{(M)} y_M + \lambda_S p_S^{(S)} y_S)x - \gamma_S y_S, \\ \frac{dz_M}{dt} &= \gamma_M y_M, \\ \frac{dz_S}{dt} &= \gamma_S y_S, \end{aligned} \right\} \quad (2.5)$$

with initial condition

$$(x(0), y_M(0), y_S(0), z_M(0), z_S(0)) = (1, \mu_M, \mu_S, 0, 0). \quad (2.6)$$

Here, $x(t)$, $y_M(t)$, $y_S(t)$, $z_M(t)$ and $z_S(t)$ are respectively the ‘‘proportions’’ of susceptible, mild infective, severe infective, mild removed and severe removed individuals in the population at time t . The final outcome of the deterministic epidemic can be obtained by solving (2.5) numerically. Note that $(r_M, r_S) = (z_M(\infty) - \mu_M, z_S(\infty) - \mu_S)$. The balance equation (2.4) and the above observations concerning (r_M, r_S) are easily verified by analysing the differential equations (2.5).

The approximation of the stochastic epidemic relies on n , the number of initial susceptibles, becoming large, whilst keeping the infection and removal parameters fixed. We study two distinct cases for the initial number of infectives: (i) $n^{-1}m_M \rightarrow \mu_M$ and $n^{-1}m_S \rightarrow \mu_S$, where $\mu_M + \mu_S > 0$, so there are many initial infectives when n is large; and (ii) (m_M, m_S) is fixed, so the numbers of initial infectives of the two types is held fixed as $n \rightarrow \infty$ and consequently there are relatively few initial infectives when n is large.

For case (i), the theory of density dependent population processes described in Ethier and Kurtz (1986), Chapter 11, can be used to show that the stochastic epidemic, suitably normalised, converges as $n \rightarrow \infty$ to the deterministic model (2.5), with fluctuations about the deterministic limit following a zero-mean Gaussian process. The theory also enables a central limit theorem to be derived for the final outcome of the epidemic. Let $R_M^{(n)}$ and $R_S^{(n)}$ denote the number of susceptibles that ultimately become mild and severe infectives, respectively. Then, writing (r_M, r_S) as $(r_M(\mu_M, \mu_S), r_S(\mu_M, \mu_S))$,

$$\sqrt{n} \begin{pmatrix} n^{-1}R_M^{(n)} - r_M(\mu_M, \mu_S) \\ n^{-1}R_S^{(n)} - r_S(\mu_M, \mu_S) \end{pmatrix} \xrightarrow{D} N(\mathbf{0}, \Sigma(\mu_M, \mu_S)) \quad \text{as } n \rightarrow \infty, \quad (2.7)$$

where \xrightarrow{D} denotes convergence in distribution and $N(\mathbf{0}, \Sigma(\mu_M, \mu_S))$ denotes a bivariate normal distribution with mean vector zero and variance-covariance matrix $\Sigma(\mu_M, \mu_S)$. It follows from (2.7) that $(R_M^{(n)}, R_S^{(n)})$ is approximately bivariate normally distributed with mean vector $n(r_M(\mu_M, \mu_S), r_S(\mu_M, \mu_S))^\top$, where \top denotes transpose, and variance-covariance matrix $n\Sigma(\mu_M, \mu_S)$. Of course, the mean vector and variance-covariance matrix depend also on the infection and removal parameters but that dependence is not shown explicitly. A heuristic proof of (2.7) is given in Section 4.2, where calculation of $\Sigma(\mu_M, \mu_S)$ is described. A formal proof that $n^{-1}(R_M^{(n)}, R_S^{(n)})$ converges in probability to (r_M, r_S) as $n \rightarrow \infty$ is given in Section 4.2, see Theorem 3. Note that (2.4) and Theorem 3 also hold for the competing epidemic model.

Consider finally case (ii), in which there are few initial infectives. For $t \geq 0$, let $Y_M(t)$ and $Y_S(t)$ denote respectively the numbers of mild and severe individuals alive at time t in the approximating branching process, and let $T(t)$ be the total number of births (irrespective of type) during $(0, t]$. The theory of exponential growth and asymptotic composition of a branching process (e.g. Haccou *et al.* (2005), Chapter 6) implies that there exists a random variable $W \geq 0$ such that as $t \rightarrow \infty$

$$Y_M(t) \sim We^{\alpha t}v_M, \quad Y_S(t) \sim We^{\alpha t}v_S \quad \text{and} \quad T(t) \sim We^{\alpha t}u_T, \quad (2.8)$$

where α is the Malthusian parameter of the branching process, (v_M, v_S) is the left eigenvector (normalised so that $v_M + v_S = 1$) corresponding to the eigenvalue $e^{\alpha t}$ of an associated mean matrix and $u_T > 0$ is a constant that can be determined. Moreover $W = 0$ if and only if the branching process goes extinct.

Suppose that $R_0 > 1$ and that the branching process does not go extinct. It is shown in Section 4.1 that for large n the process of infectives in the epidemic process and the approximating branching process coincide until order \sqrt{n} susceptibles have been infected in the epidemic, i.e until $T(t)$ is of order \sqrt{n} . Let $t_n = \inf\{t > 0 : T(t) \geq \log n\}$ be the time elapsing until at least $\log n$ individuals have been born in the branching process. Then, using (2.8), for large n the numbers of susceptibles, mild

infectives and severe infectives at time t_n in the epidemic process are approximately $n - \log n$, $v_M u_T^{-1} \log n$ and $v_S u_T^{-1} \log n$, respectively. It is shown in Section 4.3 that if the epidemic infects at least $\log n$ susceptibles then there exists $c^* > 0$ such that the probability that the epidemic infects at least $c^* n$ susceptibles tends to one as $n \rightarrow \infty$; see Lemma 1, in which $c^* = 1 - \epsilon_0$. The above suggests that as $c \downarrow 0$, the ratio of mild to severe infectives when cn susceptibles have been infected is given by v_M/v_S , and hence from (2.7) that, conditional upon the epidemic becoming established,

$$\sqrt{n} \begin{pmatrix} R_M^{(n)} - r_M^{(0)} \\ R_S^{(n)} - r_S^{(0)} \end{pmatrix} \xrightarrow{D} N(\mathbf{0}, \Sigma^{(0)}) \quad \text{as } n \rightarrow \infty, \quad (2.9)$$

where $r_i^{(0)} = \lim_{c \downarrow 0} r_i(c v_M, c v_S)$ ($i \in \{M, S\}$) and $\Sigma^{(0)} = \lim_{c \downarrow 0} \Sigma(c v_M, c v_S)$. Further details and a heuristic proof of (2.9) are given in Section 4.3. The result (2.9) yields a normal approximation for the final outcome of epidemics with few initial cases that become established.

Although this paper is not concerned with the special case of the competing epidemic model, for completeness we outline the behaviour of that model when there are few initial infectives. The processes $Y_M(t)$ and $Y_S(t)$ evolve independently in the branching process approximation. Thus, neither, one or both of the mild and severe outbreaks may become established. Recall that r_M and r_S are the limiting proportions of susceptibles that become mild and severe infectives, respectively, during the course of the epidemic, as $n \rightarrow \infty$. If there are few initial infectives, setting $\mu_M = \mu_S = 0$ in (2.4) shows that (r_M, r_S) satisfies

$$1 - r_M - r_S = \exp \left[- \left(\frac{\lambda_M}{\gamma_M} r_M + \frac{\lambda_S}{\gamma_S} r_S \right) \right]. \quad (2.10)$$

If only one of the mild and severe outbreaks becomes established, say the severe outbreak, then $r_M = 0$ and r_S is the strictly positive root, r_S^* say, of the equation obtained by setting $r_M = 0$ in (2.10). Suppose that both outbreaks become established. Let $\alpha_M = \lambda_M - \gamma_M$ and W_M denote the Malthusian parameter and random variable W for the branching process of mild individuals, and define α_S and W_S similarly for the branching process of severe individuals. If $\alpha_M < \alpha_S$ then $r_S = r_S^*$ and r_M is the largest root of the equation obtained by setting $r_S = r_S^*$ in (2.10). Note that $r_M > 0$ if and only if $(1 - r_S^*)\lambda_M > \gamma_M$. Equivalent results hold if $\alpha_M < \alpha_S$. If $\alpha_M = \alpha_S$ then r_M and r_S depend on the realised values of the independent random variables W_M and W_S , and hence are random. Conditional upon $(W_M, W_S) = (w_M, w_S)$, $r_M = \lim_{c \downarrow 0} r_M(c w_M, c w_S)$ and $r_S = \lim_{c \downarrow 0} r_S(c w_M, c w_S)$. Note that the distribution of (W_M, W_S) depends on the initial numbers of infectives of the two types, as well as on the infection and removal rates. Further details may be found in Scalia Tomba and Svensson (2001), where the above observations are made mathematically precise by proving convergence in distribution of $n^{-1}(R_M^{(n)}, R_S^{(n)})$ to the appropriate limit as $n \rightarrow \infty$.

2.3. Illustrations

In order to see how well our approximations work in finite populations we have performed simulations. Figure 1 below is based on 10 000 simulations of the IDS model for a community consisting of $n = 100\,000$ individuals. The contact parameters

were chosen to be $\lambda_M = 2.5$ and $\lambda_S = 1$, reflecting that severely infected people might not be as socially active as mildly infected people. The duration of the infectious period was modelled by a unit-mean exponential distribution for both mild and severe cases, so $\iota_M = \iota_S = 1$. It was further assumed that both mild and severe cases infected new individuals to the same type as themselves with probability 0.8 implying that $p_M^{(M)} = 0.8$, $p_S^{(M)} = 0.2$, $p_M^{(S)} = 0.2$ and $p_S^{(S)} = 0.8$. Using equation (2.2), the basic reproduction number can be computed as $R_0 = 2.0782$ for this set of parameter values, so the epidemic is clearly above threshold. Each simulation was initiated by 100 mild and 100 severely infectious individuals, thus avoiding minor outbreaks. The figure contains histograms of the final number of mild (upper) and severe (lower) cases from the simulations. The average scaled (i.e. divided by the initial number of susceptibles, n) number of mildly infected in the simulations, including the initially mild infectives, was 0.5878 and the average number of severely infected was 0.2317. The corresponding theoretical values, $r_M + \mu_M$ and $r_S + \mu_S$, were computed as described in Section 2.2.2 and found to be $r_M + \mu_M = 0.5879$ and $r_S + \mu_S = 0.2317$, i.e. (almost) the same as the empirical means. Similarly, the limiting covariance matrix Σ (c.f. equation (2.7)) was computed numerically. The limiting scaled variances (now multiplied by n) for the proportions infected (elements (1,1) and (2,2) of Σ in equation (2.7)) were $\sigma_{11} = 1.2052$ and $\sigma_{22} = 0.3871$. The corresponding empirical variances from the simulations were 1.2186 and 0.3869, respectively, also very close to their asymptotic counterparts. In the histograms we have superimposed the limiting normal distributions having the asymptotic means and variances just mentioned. It is seen that the empirical distributions agree remarkably well with the limiting normal distributions.

Not shown in the figure are the correlations between the proportion mild and severely infected. The asymptotic correlation was computed as $\rho = \sigma_{12}/\sqrt{\sigma_{11}\sigma_{22}} = -0.5534$. The empirical correlation between the proportions mild and severely infected was -0.5478, again close to its theoretical counterpart.

In order to study how quickly the asymptotics kick in, both for the branching process and the final size approximations, we simulated outbreaks starting with few initially infected for different community sizes. We chose the same values for the contact parameters and removal parameters as above (i.e. $\lambda_M = 2.5$, $\lambda_S = \gamma_M = \gamma_S = 1$), and always started with one mild and one severe infective, for community sizes $n = 100, 1000, 10\ 000, 100\ 000$ and $1\ 000\ 000$. It turned out that the speed that the asymptotics kick in depends on how well the two types of infected mix, i.e. on the distance of $p_M^{(M)}$ and $p_S^{(S)}$ from 1. (Recall that when they are equal to 1 we have the competing epidemic model which has a rather different and more complicated asymptotic behaviour). For this reason we list in Table 1 the theoretical and empirical probabilities of major outbreaks for different community sizes and choices of $(p_M^{(M)}, p_S^{(S)})$. We chose to let $p_M^{(M)} = p_S^{(S)} = p$ and varied p from $p = 0.5$, so individuals are equally likely to infect someone mildly or severely (independent of their own state), up to $p = 0.999$ where individuals nearly always create infectives of the same type as themselves. For each p and community size n , the results are based on 10 000 simulations. For the asymptotic values ($n = \infty$), the probability of major outbreak is computed from the branching process approximation. As seen in Table 1, the probability of a major outbreak, computed as the proportion out of the 10 000 simulations resulting in more than 20% getting infected, agrees quite well with

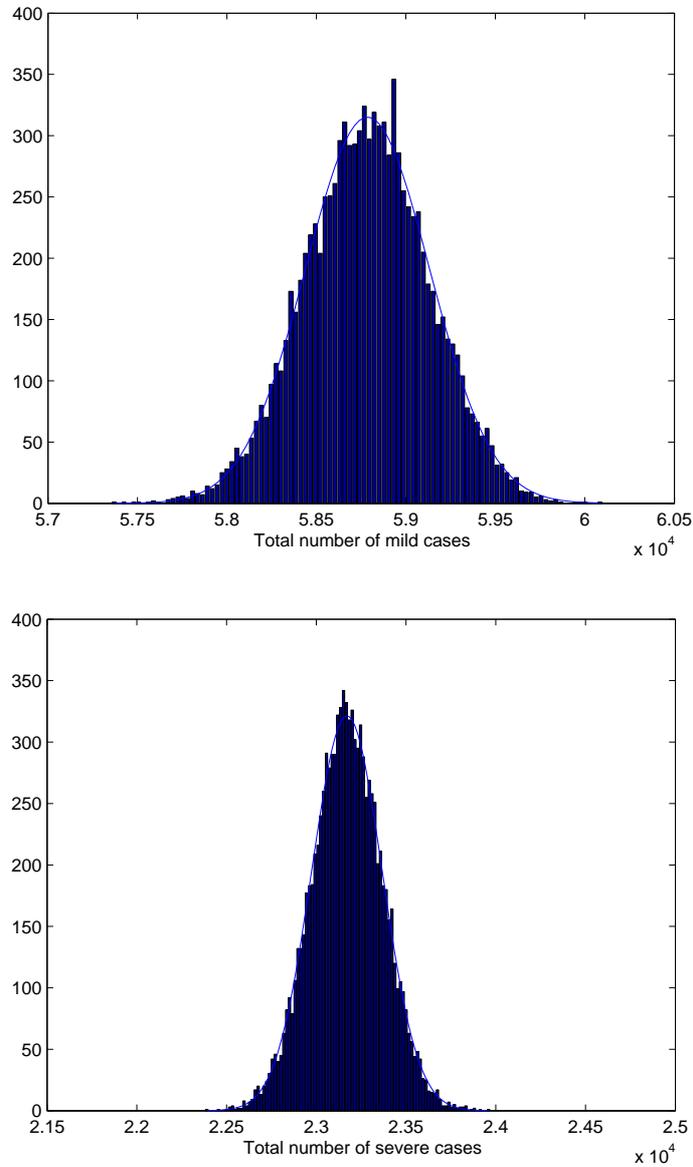


FIGURE 1: Histograms from 10 000 simulations of the number ultimately infected in the IDS model in a community of 100 000 individuals. The number of mild cases is depicted in the upper histogram and the number of severe cases in the lower. Superimposed are the normal approximations obtained from the theoretical approximation.

the branching process approximation. The approximation seems adequate when the community consists of at least a few thousand individuals, more or less irrespective of the value of p .

TABLE 1: Empirical proportions of major outbreaks for different community sizes and values of $p = p_M^{(M)} = p_S^{(S)}$.

n	$P(\text{major outbreak})$				
	$p = 0.5$	$p = 0.8$	$p = 0.9$	$p = 0.99$	$p = 0.999$
100	0.6068	0.6350	0.6332	0.6360	0.6348
1000	0.6354	0.6416	0.6474	0.6239	0.6035
10 000	0.6384	0.6423	0.6496	0.6221	0.6060
100 000	0.6336	0.6446	0.6424	0.6307	0.6139
1 000 000	0.6372	0.6426	0.6427	0.6328	0.6103
∞	0.6307	0.6479	0.6475	0.6247	0.6091

TABLE 2: Empirical mean proportions mild and severe cases among major outbreaks, for different community sizes and values of $p = p_M^{(M)} = p_S^{(S)}$.

Mean prop. mild cases					
n	$p = 0.5$	$p = 0.8$	$p = 0.9$	$p = 0.99$	$p = 0.999$
100	0.3580	0.5655	0.6770	0.7929	0.8074
1000	0.3566	0.5853	0.7199	0.8662	0.8795
10 000	0.3562	0.5871	0.7240	0.8731	0.8899
100 000	0.3563	0.5872	0.7243	0.8744	0.8906
1 000 000	0.3563	0.5872	0.7244	0.8746	0.8908
∞	0.3566	0.5871	0.7246	0.8748	0.8910
Mean prop. severe cases					
n	$p = 0.5$	$p = 0.8$	$p = 0.9$	$p = 0.99$	$p = 0.999$
100	0.3552	0.2384	0.1611	0.0667	0.0547
1000	0.3566	0.2321	0.1369	0.0222	0.0086
10 000	0.3564	0.2299	0.1328	0.0160	0.0024
100 000	0.3563	0.2297	0.1325	0.0149	0.0017
1 000 000	0.3563	0.2297	0.1324	0.0147	0.0015
∞	0.3566	0.2296	0.1324	0.0147	0.0015

Using the same simulations as in Table 1, we also calculated the proportions infected of the two types in the major epidemics. In Table 2 below, we present the means of these proportions for the different community sizes and values of p . The asymptotic ($n = \infty$) proportions infected of the two types are the numerical solutions $r_M^{(0)}$ and $r_S^{(0)}$ obtained as described in Section 2.2.2, for a small value of c . (In practice, c was divided successively by 10 until the change in the total proportion infected was less than 10^{-5} .) It is seen that the mean proportions infected of the two types agree better and better with their asymptotic counterparts as n grows. Unless p is close to 1, the asymptotics provide a good approximation when n is as small as 1000, whereas when p approaches 1 (making the model close to the competing epidemic), the community size has to be considerably larger for the asymptotics to kick in.

3. Vaccination

We study two different models for the effect of a vaccine.

3.1. Reduction in susceptibility and infectivity model

In the first model, which is more general than the second, it is assumed that vaccinated individuals independently have a random reduction in susceptibility and infectivity described by the pair of (possibly dependent) random variables (A, B) , where A is the relative susceptibility and B is the relative infectivity if infected (see e.g. Becker and Starczak (1998) and Becker *et al.* (2006)). For simplicity we assume that the distribution of (A, B) is discrete: $P(A = a_i, B = b_i) = p_i$, $i = 1, \dots$, cf. Becker and Starczak (1998) and Ball and Becker (2006).

By relative susceptibility and relative infectivity we mean the following. A vaccinated, not yet infected, individual having vaccine response (a_i, b_i) that is contacted by an infective, be it a severe or mild contact, avoids becoming infected with probability a_i . A vaccinated individual with vaccine response (a_i, b_i) who still gets infected has a reduced contact rate. If the individual is mildly infected the contact rate is $b_i \lambda_M$ and if the individual is severely infected the contact rate is $b_i \lambda_S$. From this we see that the smaller A is, the more effective is the vaccine in terms of reducing susceptibility and the smaller B is, the more effective is the vaccine in reducing infectivity. Because reduced infectivity only really matters for individuals who do get infected, the product AB is also a relevant measure of vaccine efficacy. Vaccine efficacy is usually defined to equal 1 for perfect vaccines and 0 for completely useless ones. We thus have the following definitions of vaccine efficacies in terms of susceptibility, infectivity and susceptibility-infectivity (also defined in Becker *et al.* (2006)):

$$VE_S = 1 - E[A] \quad VE_I = 1 - \frac{E[AB]}{E[A]} \quad VE_{SI} = 1 - E[AB]. \quad (3.1)$$

Suppose that a proportion v of susceptibles are vaccinated prior to the arrival of the infectious disease, and that the vaccine response is as above. Then the initial stages of the epidemic also admits an approximation by a suitable two-type branching process, in which (mild/severe) individuals correspond to (mild/severe) contacts in the epidemic process and births in the branching process correspond to contacts emanating from the corresponding contact in the epidemic process. Consider a mild contact. This will be with a vaccinated individual having vaccine response (a_i, b_i) with probability vp_i and with an unvaccinated individual with probability $1 - v$. If the contacted individual has response (a_i, b_i) , an infection takes place with probability a_i and, if it does, the expected number of new contacts he or she makes is $b_i \lambda_M \iota_M$. From this it follows that a mild contact, on average, gives rise to $(1 - v + vE[AB])\lambda_M \iota_M$ new contacts, of which a fraction $p_M^{(M)}$ are mild and the remaining fraction $(p_S^{(M)} = 1 - p_M^{(M)})$ are severe. The same reasoning can be applied to severe contacts, implying that the mean offspring matrix has the following form:

$$M^{(AB)}(v) = \begin{bmatrix} (1 - v + vE[AB])\lambda_M \iota_M p_M^{(M)} & (1 - v + vE[AB])\lambda_M \iota_M p_S^{(M)} \\ (1 - v + vE[AB])\lambda_S \iota_S p_M^{(S)} & (1 - v + vE[AB])\lambda_S \iota_S p_S^{(S)} \end{bmatrix}. \quad (3.2)$$

It follows that $M^{(AB)}(v) = (1 - v + vE[AB])M$, where M is the mean offspring matrix without vaccination defined in (2.1). Hence, the largest eigenvalue $R_v^{(AB)}$ of $M^{(AB)}(v)$ satisfies $R_v^{(AB)} = (1 - v + vE[AB])R_0$, where R_0 is the largest eigenvalue without vaccination. Thus, we conclude that, if $1 < R_0 \leq (E[AB])^{-1}$, then the

critical vaccination coverage, above which the entire community is protected from major outbreaks, is given by

$$v_c^{(AB)} = \frac{1}{1 - E[AB]} \left(1 - \frac{1}{R_0}\right) = \frac{1}{VE_{SI}} \left(1 - \frac{1}{R_0}\right), \quad (3.3)$$

cf. Becker and Starczak (1998). If $R_0 > (E[AB])^{-1}$ then vaccination alone cannot protect the community from major outbreaks.

Suppose that the vaccine response is non-random, in that $A \equiv a$ and $B \equiv b$ (i.e. $P(A = a, B = b) = 1$) for some $(a, b) \in (0, 1)^2$. Then the behaviour of large-population epidemics that take off can be approximated by deriving a deterministic model for $(x_U(t), x_V(t), y_{MU}(t), y_{MV}(t), y_{SU}(t), y_{SV}(t), z_M(t), z_S(t))$, where the additional suffices U and V refer to vaccinated and unvaccinated individuals, respectively. We omit the details but the resulting set of ordinary differential equations can be solved numerically to determine the final outcome of the epidemic for any given set of parameter values and initial conditions. This can be extended to the case when there are finitely many vaccine responses by suitably enlarging the set of differential equations. A vaccine response that has received considerable attention in the literature is the so-called *all-or-nothing* model (Halloran *et al.*, 1992), in which a vaccinated individual is rendered completely immune with probability ϵ , otherwise the vaccine has no effect. Thus $P(A = 0, B = 0) = \epsilon = 1 - P(A = 1, B = 1)$, so $VE_S = VE_{SI} = \epsilon$ and $VE_I = 0$. The final outcome of a large-population epidemic that takes off when, prior to the arrival of the disease, a proportion v of susceptibles were vaccinated with an all-or-nothing vaccine having $VE_S = \epsilon$, can be approximated by solving the ordinary differential equations (2.5) with initial condition $(x(0), y_M(0), y_S(0), z_M(0), z_S(0)) = (1 - v\epsilon, \mu_M, \mu_S, 0, 0)$.

3.2. Reduction in severity model

In this model, used in Ball and Becker (2006), vaccination reduces the severity of the disease. By this we mean that an individual who would have become severely infected had he or she not been vaccinated becomes only mildly infected if vaccinated, and a person who would have become mildly infected had he or she not been vaccinated avoids becoming infected when vaccinated. As a consequence, a mild case that has contact with a vaccinated but uninfected individual, infects that person mildly with probability $p_S^{(M)} = 1 - p_M^{(M)}$ and not at all with probability $p_M^{(M)}$. Similarly, a severe infective who has contact with a vaccinated but uninfected individual infects that person mildly with probability $p_S^{(S)} = 1 - p_M^{(S)}$ and not at all with probability $p_M^{(S)} = 1 - p_S^{(S)}$.

Suppose that a fraction v of susceptibles are vaccinated prior to the arrival of the infectious disease. This implies that a fraction v of all contacts are with vaccinated individuals and the remaining fraction, $1 - v$, are with unvaccinated individuals. Just like for the case without vaccination, the initial stages of the epidemic can be approximated by a two-type branching process, but now the mean offspring matrix is as follows:

$$M^{(\text{Sev})}(v) = \begin{bmatrix} \lambda_M \iota_M \left((1-v)p_M^{(M)} + vp_S^{(M)} \right) & \lambda_M \iota_M (1-v)p_S^{(M)} \\ \lambda_S \iota_S \left((1-v)p_M^{(S)} + vp_S^{(S)} \right) & \lambda_S \iota_S (1-v)p_S^{(S)} \end{bmatrix}. \quad (3.4)$$

Starting with few initially infectives a major outbreak can occur if and only if the largest eigenvalue $R_v^{(\text{Sev})}$ of this matrix exceeds unity. Unlike with the first vaccine

response model, there is no simple relationship between $R_v^{(\text{Sev})}$ and R_0 . We omit the details but it is easily shown that $R_v^{(\text{Sev})}$ and the corresponding critical vaccination coverage $v_c^{(\text{Sev})}$ are both given by roots of quadratic equations. Note that vaccination alone cannot protect the community from major outbreaks if $\lambda_M \iota_M p_S^{(M)} > 1$, since then $R_1^{(\text{Sev})} > 1$.

As with the first vaccine-action model, the behaviour of large-population epidemics that become established can be approximated by a deterministic model but now only susceptible individuals need to be classified by their vaccination status.

3.3. Illustrations

We illustrate the two vaccine-action models by studying their application to the example at the beginning of Section 2.3. Thus, in the absence of vaccination, the infectious periods each follow a unit-mean exponential distribution, $\lambda_M = 2.5$, $\lambda_S = 1$, $p_M^{(M)} = 0.8$, $p_S^{(M)} = 0.2$, $p_M^{(S)} = 0.2$ and $p_S^{(S)} = 0.8$. As noted previously, the corresponding reproduction number is $R_0 = 2.078$.

Figure 2 shows the proportions of the population that ultimately become mild and severe cases, for the reduction in susceptibility and infectivity model. The figure studies both an all-or-nothing vaccine response with $P(A = 1, B = 1) = 0.2 = 1 - P(A = 0, B = 0)$ and a leaky vaccine (Halloran *et al.*, 1992) with $A \equiv 0.2$ and $B \equiv 1$. In both cases $VE_S = VE_{SI} = 0.8$ and $VE_I = 0$, thus making the two vaccine models comparable. In the figure, the limiting proportions of mild and severe cases are plotted as a function of the vaccination coverage. It is seen that both vaccine responses have the

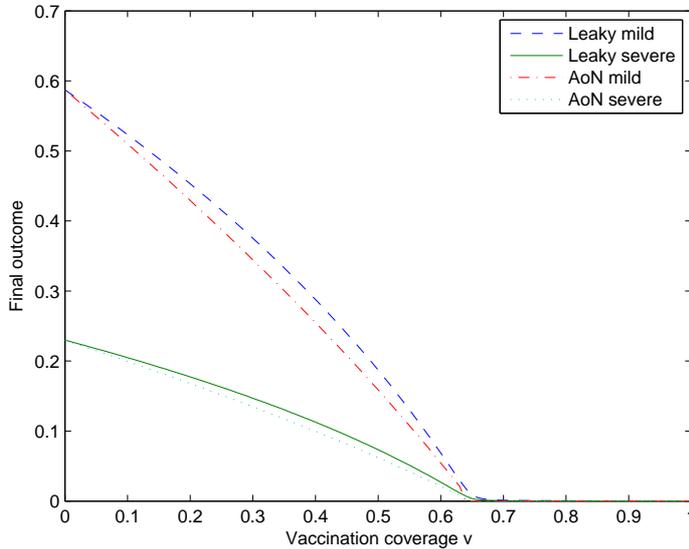


FIGURE 2: Limiting proportions infected as a function of the vaccination coverage under the reduction in susceptibility and infectivity model, for both a leaky vaccine [mild (---) and severe (—) cases] and an all-or-nothing vaccine [mild (- · -) and severe (···) cases].

same critical vaccination coverage $v_c^{(AB)} = 0.649$, which follows from (3.3). However, for sub-critical vaccination coverages, the all-or-nothing vaccine out-performs the leaky vaccine in that fewer people become infected with the all-or-nothing vaccine. This observation holds in general, also for epidemic models without varying severity, and has the following explanation (Ball and Becker (2006)). Among vaccinated individuals the chance that a first infectious contact results in infection is the same in the two models. However, for those who avoid infection at the first contact, the all-or-nothing vaccinated are completely immune whereas the leaky vaccinated only have reduced susceptibility and hence may become infected at a subsequent contact.

For the reduction in severity model the corresponding results are presented in Figure 3. The critical vaccination coverage is $v_c^{(Sev)} = 0.738$. In this example, the

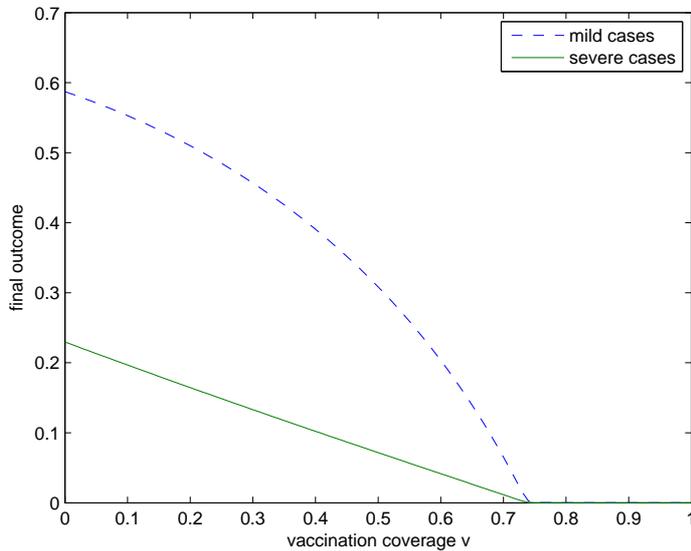


FIGURE 3: Limiting proportions infected as a function of the vaccination coverage for the reduction in severity model; mild (---) and severe (—) cases.

proportions of the population that ultimately become mild and severe cases both decrease with vaccination coverage v . However, this is not always the case. For some parameter values the proportion mildly infected *increases* with v in certain v -regions. This is illustrated in Figure 4, where we have interchanged the contact rates so that $\lambda_M = 1$ and $\lambda_S = 2.5$, keeping all other parameters unchanged. This phenomenon can be explained as follows. In the absence of vaccination there are more severe than mild cases because severe infectives have a higher contact rate and infectives tend to produce subsequent cases having the same type as themselves. When a small proportion of the population is vaccinated, some of the vaccinated individuals, who previously would have become severe cases, will now become mild cases and consequently create further mild cases by contacting unvaccinated individuals. However, the total number of cases will decrease because mild cases make fewer contacts and contacts made by mild cases with

vaccinated individuals are likely not to result in disease transmission. As vaccination coverage increases, the overall reduction in cases dominates the greater proportion of cases being mild, and the total number of mild cases eventually decreases.

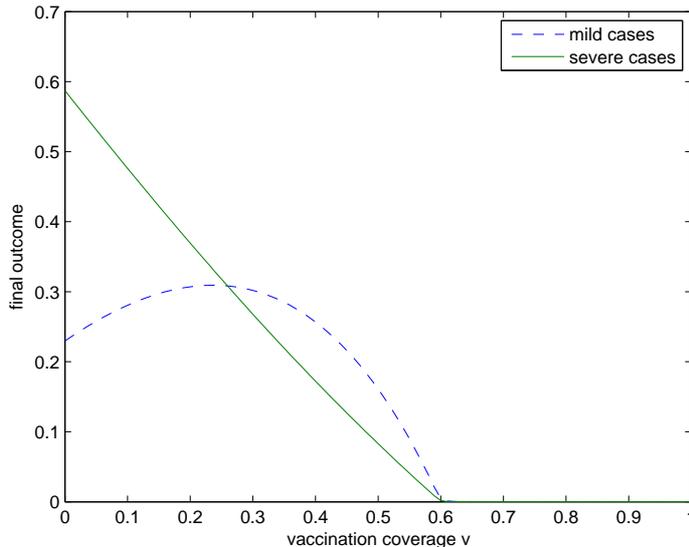


FIGURE 4: Limiting proportions infected as a function of the vaccination coverage for the reduction in severity model with different contact parameters; mild (---) and severe (—) cases.

4. Proofs

4.1. Few initial infectives: branching process approximation

We analyse the initial behaviour of an epidemic with few initial infectives by extending the coupling argument of Ball and Donnelly (1995) to the IDS model. Consider a sequence of IDS epidemics, $\{E^{(n)} : n \geq 1\}$ say, indexed by the initial number of susceptibles n , with each epidemic having m_M initial mild infectives and m_S initial severe infectives. Let $\mathbf{Y} = \{\mathbf{Y}(t) : t \geq 0\}$ denote the branching process described in Section 2.2, where, for $t \geq 0$, $\mathbf{Y}(t) = (Y_M(t), Y_S(t))$, with $Y_M(t)$ and $Y_S(t)$ denoting respectively the numbers of mild and severe individuals at time t , and $\mathbf{Y}(0) = (m_M, m_S)$. Let (Ω, \mathcal{F}, P) be a probability space on which is defined the branching process \mathbf{Y} and, independently of \mathbf{Y} , random variables $\chi_i^{(n)}$ ($i, n = 1, 2, \dots$), where for each n , $\chi_1^{(n)}, \chi_2^{(n)}, \dots$ are independent and uniformly distributed on $\{1, 2, \dots, n\}$.

For $n = 1, 2, \dots$, the epidemic $E^{(n)}$ is constructed on (Ω, \mathcal{F}, P) as follows. Individuals and births in the branching process correspond respectively to infectives and infectious contacts in the epidemic process. Label the initial susceptibles in $E^{(n)}$, $1, 2, \dots, n$. For the k th birth in the branching process, the individual contacted in the epidemic is $\chi_k^{(n)}$. If the contacted individual is susceptible then it becomes infected and adopts

the same type as the corresponding individual, i^* say, in the branching process. If the contacted individual is not susceptible then that contact, and any descendants of i^* in the branching process, are ignored in $E^{(n)}$. The epidemic stops when there is no infective left in the population.

For $n = 1, 2, \dots$, let $\mathbf{Y}^{(n)} = \{\mathbf{Y}^{(n)}(t) : t \geq 0\}$, where, for $t \geq 0$, $\mathbf{Y}^{(n)}(t) = (Y_M^{(n)}(t), Y_S^{(n)}(t))$, with $Y_M^{(n)}(t)$ and $Y_S^{(n)}(t)$ denoting respectively the numbers of mild and severe infectives at time t in $E^{(n)}$. Observe that \mathbf{Y} and $\mathbf{Y}^{(n)}$ coincide up until the first time a contact is made with a previously contacted individual in $E^{(n)}$. For $n = 1, 2, \dots$, let $\eta^{(n)} = \min\{k \geq 2 : \chi_k^{(n)} = \chi_l^{(n)} \text{ for some } l < k\}$ be the number of contacts made in $E^{(n)}$ until a contact is made with a previously contacted individual. Noting the connection with the birthday problem, it is well known (see, for example, Aldous (1985), page 96) that $n^{-1/2}\eta^{(n)} \xrightarrow{D} \eta$ as $n \rightarrow \infty$, where η is a random variable with probability density function $f(x) = x \exp(-\frac{1}{2}x^2)$ ($x > 0$). As in the proof of Theorem 2.1 of Ball and Donnelly (1995), the Skorokhod representation theorem implies that we may assume that $\chi_i^{(n)}$ ($i, n = 1, 2, \dots$) are constructed so that $n^{-1/2}\eta^{(n)} \xrightarrow{a.s.} \eta$ as $n \rightarrow \infty$, where η is also defined on (Ω, \mathcal{F}, P) .

For $n = 1, 2, \dots$, let $Z_M^{(n)}$ and $Z_S^{(n)}$ denote respectively the total numbers of mild and severe infectives removed in the epidemic $E^{(n)}$, and let Z_M and Z_S denote respectively the total mild and severe progeny, including the initial ancestors, in the branching process \mathbf{Y} . Let $A_E \in \mathcal{F}$ denote the set on which \mathbf{Y} becomes extinct, so $Z_M(\omega)$ and $Z_S(\omega)$ are both finite if and only if $\omega \in A_E$, and they are both infinite for P -almost all $\omega \in A_E^c = \Omega \setminus A_E$.

Theorem 1. (a) For P -almost all $\omega \in A_E$, $(Z_M^{(n)}, Z_S^{(n)}) \rightarrow (Z_M, Z_S)$ as $n \rightarrow \infty$.

(b) For P -almost all $\omega \in A_E^c$, $(Z_M^{(n)}, Z_S^{(n)}) \rightarrow (\infty, \infty)$ as $n \rightarrow \infty$.

Proof For P -almost all $\omega \in A_E$, $Z_M(\omega)$ and $Z_S(\omega)$ are both finite, and $\eta^{(n)}(\omega) > \frac{1}{2}\sqrt{n}\eta(\omega)$ for all sufficiently large n . Hence, for such ω and n , every birth in the the branching process yields an infection in $E^{(n)}$, and part (a) follows. Part (b) is proved by noting that for P -almost all $\omega \in A_E^c$, the above argument shows that for any $l \in \mathbb{Z}^+$, if $Z_M + Z_S \geq l$ then $Z_M^{(n)} + Z_S^{(n)} \geq l$ for all sufficiently large n .

The assertions in Section 2.2, concerning the probability that an epidemic with few initial infectives becomes established and the final outcome of an epidemic that does not become established, follow using Theorem 1 and standard properties of branching processes.

4.2. Many initial infectives: law of large numbers and CLT for final outcome

Suppose that the infectious periods follow exponential distributions, with rate γ_M for mild infectives and rate γ_S for severe infectives, and that initially, i.e. at time $t = 0$, there are n susceptibles, $m_M^{(n)}$ mild infectives and $m_S^{(n)}$ severe infectives. For $t \geq 0$, let $X^{(n)}(t)$, $Y_M^{(n)}(t)$, $Y_S^{(n)}(t)$, $Z_M^{(n)}(t)$ and $Z_S^{(n)}(t)$ denote respectively the numbers of susceptible, mild infective, severe infective, mild removed and severe removed individuals at time t . The epidemic is completely specified by the process $\mathbf{X}^{(n)} = \{\mathbf{X}^{(n)}(t) : t \geq 0\}$, where $\mathbf{X}^{(n)}(t) = (X^{(n)}(t), Y_M^{(n)}(t), Y_S^{(n)}(t), Z_M^{(n)}(t))^\top$, since $X^{(n)}(t) + Y_M^{(n)}(t) + Y_S^{(n)}(t) + Z_M^{(n)}(t) + Z_S^{(n)}(t) = n + m_M^{(n)} + m_S^{(n)}$ for all $t \geq 0$. The process $\mathbf{X}^{(n)}$ is a continuous-time

Markov chain with transition intensities

$$q_{(i,j_M,j_S,k_M),(i-1,j_M+1,j_S,k_M)}^{(n)} = n \binom{i}{n} \left[\lambda_M p_M^{(M)} \left(\frac{j_M}{n} \right) + \lambda_S p_M^{(S)} \left(\frac{j_S}{n} \right) \right],$$

for a new mild infection,

$$q_{(i,j_M,j_S,k_M),(i-1,j_M,j_S+1,k_M)}^{(n)} = n \binom{i}{n} \left[\lambda_M p_S^{(M)} \left(\frac{j_M}{n} \right) + \lambda_S p_S^{(S)} \left(\frac{j_S}{n} \right) \right],$$

for a new severe infection,

$$q_{(i,j_M,j_S,k_M),(i,j_M-1,j_S,k_M+1)}^{(n)} = n \gamma_M \left(\frac{j_M}{n} \right),$$

for a mild removal, and

$$q_{(i,j_M,j_S,k_M),(i,j_M,j_S-1,k_M)}^{(n)} = n \gamma_S \left(\frac{j_S}{n} \right),$$

for a severe removal, where (i, j_M, j_S, k_M) is the state of $\mathbf{X}^{(n)}$ at a given time.

The transition intensities are expressed in the above form to indicate that $\mathbf{X}^{(n)}$ is a density dependent population process, as defined by Ethier and Kurtz (1986), Chapter 11. Consider a sequence of epidemics, indexed by n , and suppose that $n^{-1}m_M^{(n)} \rightarrow \mu_M$ and $n^{-1}m_S^{(n)} \rightarrow \mu_S$ as $n \rightarrow \infty$. Throughout this subsection we assume that $\mu_M + \mu_S > 0$. It follows from Theorem 11.2.1 of Ethier and Kurtz (1986) that, as $n \rightarrow \infty$, $n^{-1}\mathbf{X}^{(n)}$ converges almost surely over any finite time interval to $\mathbf{x} = \{\mathbf{x}(t) : t \geq 0\}$, where $\mathbf{x}(t) = (x(t), y_M(t), y_S(t), z_M(t))^\top$ and $(x(t), y_M(t), y_S(t), z_M(t))$ is given by the solution of (2.5) with initial condition (2.6). Theorem 11.2.3 of Ethier and Kurtz (1986) provides a central limit theorem for fluctuations of $\mathbf{X}^{(n)}$ about \mathbf{x} .

Let $\tau^{(n)} = \inf\{t > 0 : Y_M^{(n)}(t) + Y_S^{(n)}(t) = 0\}$ denote the duration of the n th epidemic and let $\tau = \inf\{t > 0 : y_M(t) + y_S(t) \leq 0\}$. Then $\mathbf{X}^{(n)}(\tau^{(n)})$ is the final outcome of the n th epidemic and Theorem 11.4.1 of Ethier and Kurtz (1986) yields a central limit theorem for $\mathbf{X}^{(n)}(\tau^{(n)})$, provided $\tau < \infty$. However, $\tau = \infty$, since τ is clearly greater than the time until all initial infectives have been removed and the latter is infinity in the deterministic model as the number of initial infectives decays exponentially. This difficulty can be overcome by using the following random time scale transformation of $\mathbf{X}^{(n)}$, which is analogous to that suggested by Ethier and Kurtz (1986), page 467, for the general stochastic epidemic.

For $t \geq 0$, let $A^{(n)}(t) = \int_0^t n^{-1}(\lambda_M Y_M^{(n)}(u) + \lambda_S Y_S^{(n)}(u)) du$ be the total force of infection exerted on a given susceptible during $[0, t]$ and let $A^{(n)} = A^{(n)}(\infty) [= A^{(n)}(\tau^{(n)})]$. For $0 \leq t \leq A^{(n)}$, let $U^{(n)}(t) = \inf\{u \geq 0 : A^{(n)}(u) = t\}$ and $\tilde{\mathbf{X}}^{(n)}(t) = \mathbf{X}^{(n)}(U^{(n)}(t))$, and write $\tilde{\mathbf{X}}^{(n)}(t) = (\tilde{X}^{(n)}(t), \tilde{Y}_M^{(n)}(t), \tilde{Y}_S^{(n)}(t), \tilde{Z}_M^{(n)}(t))^\top$. The process $\tilde{\mathbf{X}}^{(n)} = \{\tilde{\mathbf{X}}^{(n)}(t) : 0 \leq t \leq A^{(n)}\}$ is a random time scale transformation of $\mathbf{X}^{(n)}$, obtained by running the clock at rate $n(\lambda_M Y_M^{(n)}(u) + \lambda_S Y_S^{(n)}(u))^{-1}$. Hence, it is a

continuous-time Markov chain with transition intensities

$$\left. \begin{aligned} \tilde{q}_{(i,j_M,j_S,k_M),(i-1,j_M+1,j_S,k_M)}^{(n)} &= \frac{n\left(\frac{i}{n}\right)\left[\lambda_M p_M^{(M)}\left(\frac{j_M}{n}\right)+\lambda_S p_M^{(S)}\left(\frac{j_S}{n}\right)\right]}{\lambda_M\left(\frac{j_M}{n}\right)+\lambda_S\left(\frac{j_S}{n}\right)}, \\ \tilde{q}_{(i,j_M,j_S,k_M),(i-1,j_M,j_S+1,k_M)}^{(n)} &= \frac{n\left(\frac{i}{n}\right)\left[\lambda_M p_S^{(M)}\left(\frac{j_M}{n}\right)+\lambda_S p_S^{(S)}\left(\frac{j_S}{n}\right)\right]}{\lambda_M\left(\frac{j_M}{n}\right)+\lambda_S\left(\frac{j_S}{n}\right)}, \\ \tilde{q}_{(i,j_M,j_S,k_M),(i,j_M-1,j_S,k_M+1)}^{(n)} &= \frac{n\gamma_M\left(\frac{j_M}{n}\right)}{\lambda_M\left(\frac{j_M}{n}\right)+\lambda_S\left(\frac{j_S}{n}\right)}, \\ \tilde{q}_{(i,j_M,j_S,k_M),(i,j_M,j_S-1,k_M)}^{(n)} &= \frac{n\gamma_S\left(\frac{j_S}{n}\right)}{\lambda_M\left(\frac{j_M}{n}\right)+\lambda_S\left(\frac{j_S}{n}\right)}, \end{aligned} \right\} \quad (4.1)$$

and initial condition $\tilde{\mathbf{X}}^{(n)}(0) = (n, m_M^{(n)}, m_S^{(n)}, 0)^\top$.

The possible jumps of $\tilde{\mathbf{X}}^{(n)}$ from a typical state $\mathbf{i} = (i, j_M, j_S, k_M)^\top$ are $\Delta = \{(-1, 1, 0, 0)^\top, (-1, 0, 1, 0)^\top, (0, -1, 0, 1)^\top, (0, 0, -1, 0)^\top\}$. The intensities of these jumps admit the form $n\tilde{\beta}_{\mathbf{l}}(n^{-1}\mathbf{i})$ ($\mathbf{l} \in \Delta$), with the functions $\tilde{\beta}_{\mathbf{l}}$ ($\mathbf{l} \in \Delta$) given by

$$\left. \begin{aligned} \tilde{\beta}_{(-1,1,0,0)}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}) &= \frac{\tilde{x}\left(\lambda_M p_M^{(M)}\tilde{y}_M + \lambda_S p_M^{(S)}\tilde{y}_S\right)}{\lambda_M\tilde{y}_M + \lambda_S\tilde{y}_S}, \\ \tilde{\beta}_{(-1,0,1,0)}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}) &= \frac{\tilde{x}\left(\lambda_M p_S^{(M)}\tilde{y}_M + \lambda_S p_S^{(S)}\tilde{y}_S\right)}{\lambda_M\tilde{y}_M + \lambda_S\tilde{y}_S}, \\ \tilde{\beta}_{(0,-1,0,1)}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}) &= \frac{\gamma_M\tilde{y}_M}{\lambda_M\tilde{y}_M + \lambda_S\tilde{y}_S}, \\ \tilde{\beta}_{(0,0,-1,0)}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}) &= \frac{\gamma_S\tilde{y}_S}{\lambda_M\tilde{y}_M + \lambda_S\tilde{y}_S}. \end{aligned} \right\} \quad (4.2)$$

The processes $\tilde{\mathbf{X}}^{(n)}$ ($n \geq 1$) can be defined on a probability space, (Ω, \mathcal{F}, P) say, by using a special case of a construction given in Ethier and Kurtz (1986), Chapter 11. Let $N_{\mathbf{l}} = \{N_{\mathbf{l}}(t) : t \geq 0\}$ ($\mathbf{l} \in \Delta$) be independent unit-rate Poisson processes defined on (Ω, \mathcal{F}, P) . Then, for each $n \geq 1$, a realisation of the n th epidemic process is given by

$$\tilde{\mathbf{X}}^{(n)}(t) = \tilde{\mathbf{X}}^{(n)}(0) + \sum_{\mathbf{l} \in \Delta} \mathbf{l} N_{\mathbf{l}} \left(n \int_0^t \tilde{\beta}_{\mathbf{l}}(n^{-1}\tilde{\mathbf{X}}^{(n)}(u)) du \right). \quad (4.3)$$

Let

$$\tilde{F}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}) = \sum_{\mathbf{l} \in \Delta} \mathbf{l} \tilde{\beta}_{\mathbf{l}}(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z})$$

and, for $t \geq 0$, let $\tilde{\mathbf{x}}(t) = (\tilde{x}(t), \tilde{y}_M(t), \tilde{y}_S(t), \tilde{z}(t))^\top$ be defined by

$$\tilde{\mathbf{x}}(t) = \tilde{\mathbf{x}}(0) + \int_0^t \tilde{F}(\tilde{\mathbf{x}}(u)) du, \quad (4.4)$$

where $\tilde{\mathbf{x}}(0) = (1, \mu_M, \mu_S, 0)^\top$. Thus $\tilde{\mathbf{x}}(t)$ satisfies the differential equation

$$\left. \begin{aligned} \frac{d\tilde{x}}{dt} &= -\tilde{x}, \\ \frac{d\tilde{y}_M}{dt} &= \frac{\tilde{x}(\lambda_M p_M^{(M)} \tilde{y}_M + \lambda_S p_M^{(S)} \tilde{y}_S) - \gamma_M \tilde{y}_M}{\lambda_M \tilde{y}_M + \lambda_S \tilde{y}_S}, \\ \frac{d\tilde{y}_S}{dt} &= \frac{\tilde{x}(\lambda_M p_S^{(M)} \tilde{y}_M + \lambda_S p_S^{(S)} \tilde{y}_S) - \gamma_S \tilde{y}_S}{\lambda_M \tilde{y}_M + \lambda_S \tilde{y}_S}, \\ \frac{d\tilde{z}_M}{dt} &= \frac{\gamma_M \tilde{y}_M}{\lambda_M \tilde{y}_M + \lambda_S \tilde{y}_S}. \end{aligned} \right\} \quad (4.5)$$

Note that $\tilde{\mathbf{x}}(t)$ is defined for $0 \leq t \leq \tilde{\tau}$, where $\tilde{\tau} = \inf\{t \geq 0 : \tilde{y}_M + \tilde{y}_S \leq 0\}$. Now $\tilde{\tau} < \infty$. For an informal proof, note that $\tilde{\tau}$ is the limit as $n \rightarrow \infty$ of the total force of infection acting on a given individual in the epidemic $\mathbf{X}^{(n)}$, which must be less than the corresponding quantity if everyone were to become infected, which in turn must be less than $(1 + \mu_M + \mu_S) \max(\gamma_M^{-1}, \gamma_S^{-1})$. For a formal proof, the first equation in (4.5) implies that $\tilde{x}(t) = \exp(-t)$, and the second and third equations imply that $(\tilde{y}_M + \tilde{y}_S)'(t) \leq \tilde{x} - \frac{\min(\gamma_M, \gamma_S)}{\max(\lambda_M, \lambda_S)}$, where $'$ denotes derivative with respect to t . Thus there exists $t_0 > 0$ and $a < 0$ such that $(\tilde{y}_M + \tilde{y}_S)'(t) \leq a$ for $t \geq t_0$, whence $\tilde{\tau} < \infty$.

The process $\tilde{\mathbf{X}}^{(n)}$ terminates at time $t = \tilde{\tau}^{(n)}$, where $\tilde{\tau}^{(n)} = \inf\{t > 0 : \tilde{Y}_M^{(n)}(t) + \tilde{Y}_S^{(n)}(t) = 0\}$. In the following theorem we assume that $\tilde{\mathbf{X}}^{(n)}(t) = \tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)})$ for $t > \tilde{\tau}^{(n)}$.

Theorem 2. For $0 \leq t \leq \tilde{\tau}$,

$$\lim_{n \rightarrow \infty} \sup_{0 \leq u \leq t} |n^{-1} \tilde{\mathbf{X}}^{(n)}(u) - \tilde{\mathbf{x}}(u)| = 0 \quad \text{almost surely.} \quad (4.6)$$

Proof For $0 \leq t < \tilde{\tau}$, (4.6) follows directly from Theorem 11.2.1 of Ethier and Kurtz (1986), since $\tilde{F}(\tilde{\mathbf{x}})$ is Lipschitz-continuous in some small neighbourhood of $\{\tilde{\mathbf{x}}(u) : 0 \leq u \leq t\}$. There exists $E \in \mathcal{F}$, with $P(E) = 1$, such that, for $\mathbf{l} \in \Delta, t \geq 0$ and $\omega \in E$, $\lim_{n \rightarrow \infty} \sup_{u \leq t} |n^{-1}(N_{\mathbf{l}}(nu, \omega) - u)| = 0$. (This is a key observation in the proof of Theorem 11.2.1 of Ethier and Kurtz (1986) and it implies that, if $\omega \in E$, the limit in (4.6) holds for all $t < \tilde{\tau}$.) Fix an $\omega \in E$ and an $\epsilon > 0$. The intensity functions $\tilde{\beta}_{\mathbf{l}}$ ($\mathbf{l} \in \Delta$) are bounded on $S = [0, 1) \times (0, \infty)^3$, so $M_{\beta} = \sum_{\mathbf{l} \in \Delta} |\mathbf{l}| \sup_{\tilde{\mathbf{x}} \in S} \tilde{\beta}(\tilde{\mathbf{x}}) < \infty$. There exists $t_1 \in (\tilde{\tau} - \epsilon/(3M_{\beta}), \tilde{\tau})$ such that $|\tilde{\mathbf{x}}(\tilde{\tau}) - \tilde{\mathbf{x}}(t_1)| < \epsilon/3$. Since $\omega \in E$, $|n^{-1} \tilde{\mathbf{X}}^{(n)}(t_1, \omega) - \tilde{\mathbf{x}}(t_1)| < \epsilon/3$ and $|n^{-1} \tilde{\mathbf{X}}^{(n)}(\tilde{\tau}, \omega) - n^{-1} \tilde{\mathbf{X}}^{(n)}(t_1, \omega)| < \epsilon/3$ for all sufficiently large n . Thus, $|n^{-1} \tilde{\mathbf{X}}^{(n)}(\tilde{\tau}) - \tilde{\mathbf{x}}(\tilde{\tau})| < \epsilon$, for all sufficiently large n , and (4.6) follows with $t = \tilde{\tau}$ since $\epsilon > 0$ is arbitrary and $P(E) = 1$.

Note that $\tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)})$ yields the final outcome of the n th epidemic. For $0 \leq t \leq \tilde{\tau}^{(n)}$, let $\tilde{\mathbf{Z}}^{(n)}(t) = (\tilde{Z}_M^{(n)}(t), \tilde{Z}_S^{(n)}(t))$, where $\tilde{Z}_S^{(n)}(t) = n + m_M^{(n)} + m_S^{(n)} - \tilde{X}^{(n)}(t) - \tilde{Y}_M^{(n)}(t) - \tilde{Y}_S^{(n)}(t) - \tilde{Z}_M^{(n)}(t)$ is the number of severe removals in $\tilde{\mathbf{X}}^{(n)}$ during $(0, t]$. For $0 \leq t \leq \tilde{\tau}$, let $\tilde{\mathbf{z}}(t) = (\tilde{z}_M(t), \tilde{z}_S(t))$, where $\tilde{z}_S(t) = 1 + \mu_M + \mu_S - \tilde{x}(t) - \tilde{y}_M(t) - \tilde{y}_S(t) - \tilde{z}_M(t)$. In the notation of Section 2.2.2, $(R_M^{(n)}, R_S^{(n)}) = (\tilde{Z}_M^{(n)}(\tilde{\tau}^{(n)}) - m_M^{(n)}, \tilde{Z}_M^{(n)}(\tilde{\tau}^{(n)}) - m_S^{(n)})$ and $(r_M, r_S) = (\tilde{z}_M(\tilde{\tau}) - \mu_M, \tilde{z}_S(\tilde{\tau}) - \mu_S)$.

Theorem 3. For any $\epsilon > 0$,

$$\lim_{n \rightarrow \infty} P \left(|n^{-1} \tilde{\mathbf{Z}}^{(n)}(\tilde{\tau}^{(n)}) - \tilde{\mathbf{z}}(\tau)| < \epsilon \right) = 1, \quad (4.7)$$

i.e. $n^{-1} \left(R_M^{(n)}, R_S^{(n)} \right) \xrightarrow{P} (r_M, r_S)$ as $n \rightarrow \infty$, where \xrightarrow{P} denotes convergence in probability.

Proof For $0 \leq \xi \leq 1$, let $\mathbf{Y}_\xi = \{(Y_{M\xi}(t), Y_{S\xi}(t)) : t \geq 0\}$ be the two-type linear birth-and-death process having birth-rate matrix

$$\Lambda(\xi) = \xi \begin{bmatrix} \lambda_M p_M^{(M)} & \lambda_M p_S^{(M)} \\ \lambda_S p_M^{(S)} & \lambda_S p_S^{(S)} \end{bmatrix}.$$

and death rates γ_M and γ_S . The process \mathbf{Y}_ξ has basic reproduction number $R_0(\xi) = \xi R_0$, where R_0 is given by (2.2). Note that the elements of $\Lambda(\xi)$ gives the rates that a given mild or severe infective creates further mild and severe infectives when a fraction ξ of the initial susceptibles are still susceptible. Note that there exists $t_0 \in (0, \tilde{\tau})$ such that $R_0(\tilde{x}(t_0)) < 1$. (If this were not the case then the process of infectives in the untransformed deterministic model (2.5) would be bounded below by a deterministic linear two-type birth-and-death process having reproduction number ≥ 1 , and hence $(y_M(t), y_S(t))$ would not tend to $(0, 0)$ as $t \rightarrow \infty$.) For $0 \leq \xi \leq 1$, let $T^{(M)}(\xi)$ be the total progeny in \mathbf{Y}_ξ if $\mathbf{Y}_\xi(0) = (1, 0)$, counting both types and including the initial ancestor, and define $T^{(S)}(\xi)$ similarly when $\mathbf{Y}_\xi(0) = (0, 1)$.

For $0 \leq t \leq \tilde{\tau}^{(n)}$, let

$$\tilde{T}_R^{(n)}(t) = \tilde{Z}_M^{(n)}(\tilde{\tau}^{(n)}) - \tilde{Z}_M^{(n)}(t) + \tilde{Z}_S^{(n)}(\tilde{\tau}^{(n)}) - \tilde{Z}_S^{(n)}(t)$$

be the total number of removals that occur in $\tilde{\mathbf{X}}^{(n)}$ after time t . For $0 \leq \xi \leq 1$ and $i \in \{M, S\}$, let $T_1^{(i)}(\xi), T_2^{(i)}(\xi), \dots$ be independent and identically distributed copies of $T^{(i)}(\xi)$. Observe that $T^{(M)}(\xi)$ and $T^{(S)}(\xi)$ are each stochastically increasing in ξ and, since the birth-and-death process \mathbf{Y}_ξ provides an upper bound for epidemic process after a fraction $1 - \xi$ of susceptibles have been infected,

$$\tilde{T}_R^{(n)}(t) \leq^{\text{st}} \sum_{i=1}^{\tilde{Y}_M^{(n)}(t)} T_i^{(M)} \left(n^{-1} \tilde{X}^{(n)}(t) \right) + \sum_{i=1}^{\tilde{Y}_S^{(n)}(t)} T_i^{(S)} \left(n^{-1} \tilde{X}^{(n)}(t) \right), \quad (4.8)$$

for any $t \in [0, \tilde{\tau}^{(n)})$, where \leq^{st} denotes stochastic ordering. These observations can be proved formally by using the coupling described at the beginning of Section 4.3.

Theorem 2 implies that, for any $t \in (t_0, \tilde{\tau})$,

$$\lim_{n \rightarrow \infty} P \left(\tilde{Y}_M^{(n)}(t) \leq \frac{3}{2} \tilde{y}_M(t) \right) = 1, \quad \lim_{n \rightarrow \infty} P \left(\tilde{Y}_S^{(n)}(t) \leq \frac{3}{2} \tilde{y}_S(t) \right) = 1 \quad (4.9)$$

and

$$\lim_{n \rightarrow \infty} P \left(n^{-1} \tilde{X}^{(n)}(t) \leq \tilde{x}(t_0) \right) = 1. \quad (4.10)$$

For $0 \leq \xi \leq 1$, let $\mu_T^{(M)}(\xi) = E[T^{(M)}(\xi)]$ and $\mu_T^{(S)}(\xi) = E[T^{(S)}(\xi)]$, and note that $\mu_T^{(M)}(\tilde{x}(t_0)) < \infty$ and $\mu_T^{(S)}(\tilde{x}(t_0)) < \infty$ since $R_0(\tilde{x}(t_0)) < 1$. Using, (4.9), (4.10), the

stochastic monotonicity of $T^{(M)}(\xi)$ and $T^{(S)}(\xi)$, and the weak law of large numbers, it follows from (4.8) that, for any $t \in (t_0, \tilde{\tau})$,

$$\lim_{n \rightarrow \infty} P \left(n^{-1} \tilde{T}_R^{(n)}(t) \leq 2 \left[\tilde{y}_M(t) \mu_T^{(M)}(\tilde{x}(t_0)) + \tilde{y}_S(t) \mu_T^{(S)}(\tilde{x}(t_0)) \right] \right) = 1. \quad (4.11)$$

Let $\epsilon > 0$ be given. Since $\tilde{z}(t) \uparrow \tilde{z}(\tilde{\tau})$ and $(\tilde{y}_M(t), \tilde{y}_S(t)) \rightarrow (0, 0)$ as $t \rightarrow \tilde{\tau}-$, there exists $t_1 \in (t_0, \tilde{\tau})$ such that $\tilde{z}_M(\tilde{\tau}) - \tilde{z}_M(t_1) + \tilde{z}_S(\tilde{\tau}) - \tilde{z}_S(t_1) < \frac{\epsilon}{3}$ and $\tilde{y}_M(t) \mu_T^{(M)}(\tilde{x}(t_0)) + \tilde{y}_S(t) \mu_T^{(S)}(\tilde{x}(t_0)) < \frac{\epsilon}{6}$. Then $\lim_{n \rightarrow \infty} P \left(|n^{-1} [\tilde{Z}(\tilde{\tau}^{(n)}) - \tilde{Z}(t_1)]| < \frac{\epsilon}{3} \right) = 1$, using (4.11), and $|\tilde{z}(t_1) - \tilde{z}(\tilde{\tau})| < \frac{\epsilon}{3}$. Further, $\lim_{n \rightarrow \infty} P \left(|n^{-1} \tilde{Z}^{(n)}(t_1) - \tilde{z}(t_1)| < \frac{\epsilon}{3} \right) = 1$, using Theorem 2. The last three facts imply (4.7), as required.

We now seek a central limit theorem for the final outcome of the IDS epidemic. Let $\partial \tilde{F}(\tilde{\mathbf{x}}) = [\partial_j \tilde{F}_i(\tilde{\mathbf{x}})]$ denote the matrix of first partial derivatives of $\tilde{F}(\tilde{\mathbf{x}})$ and, for $0 \leq s \leq t \leq \tilde{\tau}$, let $\tilde{\Phi}(t, s)$ be the solution of the matrix differential equation

$$\frac{\partial}{\partial t} \tilde{\Phi}(t, s) = \partial \tilde{F}(\tilde{\mathbf{x}}(t)) \tilde{\Phi}(t, s), \quad \tilde{\Phi}(s, s) = I, \quad (4.12)$$

where I denotes the 4×4 identity matrix. Let $\tilde{G}(\tilde{\mathbf{x}}) = \sum_{\mathbf{l} \in \Delta} \mathbf{u}^\top \tilde{\beta}_{\mathbf{l}}(\tilde{\mathbf{x}})$. The following theorem is an immediate consequence of Theorem 11.2.3 of Ethier and Kurtz (1986) since $\sum_{\mathbf{l} \in \Delta} |\mathbf{l}|^2 \sup_{\tilde{\mathbf{x}} \in S} \tilde{\beta}(\tilde{\mathbf{x}}) < \infty$.

Theorem 4. For $t \in [0, \tilde{\tau}]$, let $\tilde{\mathbf{V}}^{(n)}(t) = \sqrt{n}(n^{-1} \tilde{\mathbf{X}}^{(n)}(t) - \tilde{\mathbf{x}}(t))$, and suppose that $\lim_{n \rightarrow \infty} \sqrt{n}(n^{-1} m_M^{(n)} - \mu_M) = 0$ and $\lim_{n \rightarrow \infty} \sqrt{n}(n^{-1} m_S^{(n)} - \mu_S) = 0$. Then, for any $t_0 < \tau$,

$$\{\tilde{\mathbf{V}}^{(n)}(t) : 0 \leq t \leq t_0\} \Rightarrow \{\tilde{\mathbf{V}}(t) : 0 \leq t \leq t_0\}, \quad (4.13)$$

where \Rightarrow denotes weak convergence in the space of right-continuous functions from $[0, t_0] \rightarrow \mathbb{R}^4$ with left limits, endowed with the Skorohod topology, and $\{\tilde{\mathbf{V}}(t) : 0 \leq t \leq t_0\}$ is a zero-mean Gaussian process with $\tilde{\mathbf{V}}(0) = \mathbf{0}$ and covariance function given by

$$\text{cov}(\tilde{\mathbf{V}}(t), \tilde{\mathbf{V}}(s)) = \int_0^{\min(t,s)} \tilde{\Phi}(t, u) \tilde{G}(\tilde{\mathbf{x}}(u)) [\tilde{\Phi}(s, u)]^\top du. \quad (4.14)$$

Now $\tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)})$ yields the final outcome of the n th epidemic and, in the notation of Section 2.2.2, $R_M^{(n)} = \tilde{Z}_M^{(n)}(\tilde{\tau}^{(n)}) - m_M^{(n)}$ and $R_S^{(n)} = n + m_M^{(n)} - \tilde{X}^{(n)}(\tilde{\tau}^{(n)}) - \tilde{Z}_M^{(n)}(\tilde{\tau}^{(n)})$. Theorem 11.4.1 of Ethier and Kurtz (1986) would yield a central limit theorem for $\tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)})$ but to apply that theorem as stated requires the processes $\tilde{\mathbf{X}}^{(n)}$ and $\tilde{\mathbf{x}}$ to be defined on the interval $[0, t_1]$, for some $t_1 > \tilde{\tau}$, and that Theorems 2 and 4 hold on that interval.

Suppose that $\theta = \lim_{t \rightarrow \tilde{\tau}-} [\tilde{y}_M(t)/\tilde{y}_S(t)]$ exists. Then, using L'Hôpital's rule,

$$\begin{aligned} \theta &= \lim_{t \rightarrow \tilde{\tau}-} \frac{\tilde{y}'_M(t)}{\tilde{y}'_S(t)} = \lim_{t \rightarrow \tilde{\tau}-} \left[\frac{\tilde{x}(t)(\lambda_M p_M^{(M)} \tilde{y}_M(t) + \lambda_S p_M^{(S)} \tilde{y}_S(t)) - \gamma_M \tilde{y}_M(t)}{\tilde{x}(t)(\lambda_M p_S^{(M)} \tilde{y}_M(t) + \lambda_S p_S^{(S)} \tilde{y}_S(t)) - \gamma_S \tilde{y}_S(t)} \right] \\ &= \frac{\tilde{x}(\tilde{\tau})(\lambda_M p_M^{(M)} \theta + \lambda_S p_M^{(S)}) - \gamma_M \theta}{\tilde{x}(\tilde{\tau})(\lambda_M p_S^{(M)} \theta + \lambda_S p_S^{(S)}) - \gamma_S}, \end{aligned} \quad (4.15)$$

provided $\tilde{x}(\tilde{\tau})(\lambda_M p_S^{(M)} \theta + \lambda_S p_S^{(S)}) - \gamma_S \neq 0$. If this is the case then θ satisfies the quadratic equation

$$\tilde{x}(\tilde{\tau}) \lambda_M p_S^{(M)} \theta^2 + [x(\tilde{\tau})(\lambda_S p_S^{(S)} - \lambda_M p_M^{(M)}) + \gamma_M - \gamma_S] \theta - \tilde{x}(\tilde{\tau}) \lambda_S p_M^{(S)} = 0. \quad (4.16)$$

Now $p_S^{(M)} > 0$ and $p_M^{(S)} > 0$, so the roots of (4.16) have opposite signs and θ is given by the positive root as it clearly cannot be negative. We do not have a proof that the limit θ exists or that $\tilde{x}(\tilde{\tau})(\lambda_M p_S^{(M)} \theta + \lambda_S p_S^{(S)}) - \gamma_S \neq 0$. However, the latter is easily checked numerically for any given case and our numerical studies support the former. We assume that these results both hold. It then follows from (4.5) that $\tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau}))$ is well-defined and thus $\tilde{\mathbf{x}}$ can be extended to an interval of the form $[0, t_1]$ above. The jump intensities (4.2) can be extended similarly, allowing $\tilde{\mathbf{X}}^{(n)}$ to be defined on $[0, t_1]$ but the corresponding drift function \tilde{F} is not Lipschitz-continuous at $\tilde{\mathbf{x}}(\tilde{\tau})$. We proceed on the basis that Theorem 11.4.1 of Ethier and Kurtz (1986) still applies in this setting.

Let $\phi(\tilde{x}, \tilde{y}_M, \tilde{y}_S, \tilde{z}_M) = \tilde{y}_M + \tilde{y}_S$, so $\tilde{\tau}^{(n)} = \inf\{t > 0 : \phi(\tilde{\mathbf{X}}^{(n)}(t)) \leq 0\}$ and $\tilde{\tau} = \inf\{t > 0 : \phi(\tilde{\mathbf{x}}(t)) \leq 0\}$. Now $\nabla \phi(\tilde{\mathbf{x}}) = (0, 1, 1, 0)$ and, using (4.2) and the definition of θ ,

$$\begin{aligned} & \nabla \phi(\tilde{\mathbf{x}}(\tilde{\tau})) \tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau})) \\ &= \frac{[\tilde{x}(\tilde{\tau})(\lambda_M p_M^{(M)} \theta + \lambda_S p_M^{(S)}) - \gamma_M \theta] + [\tilde{x}(\tilde{\tau})(\lambda_M p_S^{(M)} \theta + \lambda_S p_S^{(S)}) - \gamma_S]}{\lambda_M \theta + \lambda_S}. \end{aligned} \quad (4.17)$$

Since $\theta > 0$ and $\tilde{x}(\tilde{\tau})(\lambda_M p_S^{(M)} \theta + \lambda_S p_S^{(S)}) - \gamma_S \neq 0$, the two terms in square brackets in (4.17) are non-zero and have the same sign, which must be negative from the definition of $\tilde{\tau}$. Thus $\nabla \phi(\tilde{\mathbf{x}}(\tilde{\tau})) < 0$, whence Theorem 11.4.1 of Ethier and Kurtz (1986) yields

$$\sqrt{n} \left(n^{-1} \tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)}) - \tilde{\mathbf{x}}(\tilde{\tau}) \right) \xrightarrow{D} \tilde{\mathbf{V}}(\tilde{\tau}) - \frac{(0, 1, 1, 0) \tilde{\mathbf{V}}(\tilde{\tau})}{(0, 1, 1, 0) \tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau}))} \tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau})) \quad \text{as } n \rightarrow \infty. \quad (4.18)$$

Let $\tilde{\Sigma}(t) = \text{cov}(\tilde{\mathbf{V}}(t), \tilde{\mathbf{V}}(t))$ denote the variance-covariance matrix of $\tilde{\mathbf{V}}(t)$, and define matrices B and C by

$$B = I - \frac{\tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau}))(0, 1, 1, 0)^\top}{(0, 1, 1, 0) \tilde{F}(\tilde{\mathbf{x}}(\tilde{\tau}))} \quad \text{and} \quad C = \begin{bmatrix} 0 & 0 & 0 & 1 \\ -1 & 0 & 0 & -1 \end{bmatrix}. \quad (4.19)$$

Then (4.18) implies that

$$\sqrt{n} \left(n^{-1} \tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)}) - \tilde{\mathbf{x}}(\tilde{\tau}) \right) \xrightarrow{D} N(\mathbf{0}, B \tilde{\Sigma}(\tilde{\tau}) B^\top) \quad \text{as } n \rightarrow \infty. \quad (4.20)$$

Hence, the limiting variance-covariance matrix $\Sigma(\mu_M, \mu_S)$ in (2.7) is given by $\Sigma(\mu_M, \mu_S) = C B \tilde{\Sigma}(\tilde{\tau}) B^\top C^\top$.

Note that it follows from (4.12) and (4.14) that $\tilde{\Sigma}(t)$ satisfies the differential equation

$$\frac{d\tilde{\Sigma}}{dt} = \tilde{G}(\tilde{\mathbf{x}}) + \partial \tilde{F}(\tilde{\mathbf{x}}) \tilde{\Sigma} + \tilde{\Sigma} [\partial \tilde{F}(\tilde{\mathbf{x}})]^\top, \quad (4.21)$$

with initial condition $\tilde{\Sigma}(0) = 0$. Thus $\tilde{\Sigma}(\tilde{\tau})$ can be computed by solving numerically the differential equations (4.5) and (4.21) simultaneously.

4.3. Few initial infectives: heuristics for CLT in case of major outbreak

We continue to assume that the infectious periods follow exponential distributions, with rate λ_M for mild infectives and rate λ_S for severe infectives, but, as in Section 4.1, we now consider a sequence of epidemics $\{E^{(n)} : n \geq 1\}$, indexed by the initial number of susceptibles n , with each epidemic having m_M initial mild infectives and m_S initial severe infectives. Let $\mathbf{Y} = \{(Y_M(t), Y_S(t)) : t \geq 0\}$ be the branching process defined in Section 4.1, but with the mild and severe lifetimes following exponential distributions with rates γ_M and γ_S , respectively.

Let (Ω, \mathcal{F}, P) be a probability space, on which is defined the branching process \mathbf{Y} and, independently, a sequence U_1, U_2, \dots of independent and identically distributed random variables that are uniformly distributed on $(0, 1)$. For $\epsilon \in (0, 1)$, let \mathbf{Y}_ϵ denote the branching process obtained from \mathbf{Y} by, for $i = 1, 2, \dots$, deleting the i th birth in \mathbf{Y} and all of its descendants if $U_i \leq \epsilon$. For, $n = 1, 2, \dots$, a realisation of the epidemic $E^{(n)}$ is obtained from \mathbf{Y} , by associating births with infections and, for $i = 1, 2, \dots$, deleting the i th birth in \mathbf{Y} and all of its descendants if $U_i < 1 - n^{-1}X^{(n)}(s-)$, where s is the time of the i th birth in \mathbf{Y} . For $t \geq 0$, let $T(t)$, $Z_M(t)$ and $Z_S(t)$ denote respectively the total number of births, the total number of mild deaths and the total number of severe deaths during $(0, t]$ in \mathbf{Y} . Define $Y_{M\epsilon}(t)$, $Y_{S\epsilon}(t)$ and $T_\epsilon(t)$ for \mathbf{Y}_ϵ in the obvious fashion. Observe that if $\tau_\epsilon^{(n)} = \inf\{t \geq 0 : X^{(n)}(t) < (1 - \epsilon)n\}$, where $\epsilon \in (0, 1)$, then by construction

$$n - T(t) \leq X^{(n)}(t) \leq n - T_\epsilon(t), \quad (4.22)$$

for all $t \in [0, \tau_\epsilon^{(n)}]$.

Consider the branching process \mathbf{Y} . For $t \geq 0$, let $\bar{m}_{ij}(t) = E[Y_j(t)]$ given that initially there is one individual, whose type is i , and let $\bar{M}(t) = [\bar{m}_{ij}(t)]$. The infinitesimal generator of the semigroup $\{\bar{M}(t) : t \geq 0\}$ is

$$\bar{A} = \begin{bmatrix} \lambda_M p_M^{(M)} - \gamma_M & \lambda_M p_S^{(M)} \\ \lambda_S p_M^{(S)} & \lambda_S p_S^{(S)} - \gamma_S \end{bmatrix}. \quad (4.23)$$

Let α denote the maximal eigenvalue of \bar{A} and $\mathbf{v} = (v_M, v_S)$ be the corresponding left eigenvector, normalised so that $v_M + v_S = 1$. The parameter α is called the Malthusian parameter of \mathbf{Y} and $\alpha > 0$ if and only if $R_0 > 1$. Recall that A_E is the set on which the branching process \mathbf{Y} becomes extinct. The branching process \mathbf{Y} is positive regular (as $p_S^{(M)} > 0$ and $p_M^{(S)} > 0$) and nonsingular, so it follows, using Theorem 2 on page 206 of Athreya and Ney (1972) and the theory of asymptotic growth and stabilisation of general multitype branching processes (see e.g. Jagers (1991)), that there exists a random variable $W \geq 0$ such that almost surely

$$\lim_{t \rightarrow \infty} e^{-\alpha t} Y_M(t) = v_M W, \quad \lim_{t \rightarrow \infty} e^{-\alpha t} Y_S(t) = v_S W \quad (4.24)$$

and

$$\lim_{t \rightarrow \infty} e^{-\alpha t} T(t) = \frac{\lambda_M v_M + \lambda_S v_S}{\alpha} W. \quad (4.25)$$

Moreover, $W(\omega) > 0$ if and only if $\omega \in A_E^c$.

Lemma 1. *Suppose that $R_0 > 1$. Then, there exists $\epsilon_0 > 0$ such that*

$$\lim_{n \rightarrow \infty} P\left(X^{(n)}(\infty) \leq (1 - \epsilon_0)n | A_E^c\right) = 1. \quad (4.26)$$

Proof First note that (4.25) implies that, for P -almost all $\omega \in A_E^c$, $t_n = \inf\{t : T(t) > \log n\}$ is well defined and finite for $n = 1, 2, \dots$. Also, by construction, the first $[\log n] + 1$ births in \mathbf{Y} correspond to infections in $E^{(n)}$ if and only if $U_i \geq 1 - (i-1)/n$ for $i = 1, 2, \dots, [\log n] + 1$. Thus,

$$\begin{aligned} & \lim_{n \rightarrow \infty} P \left(X^{(n)}(t_n) = n - T(t_n), Y_M^{(n)}(t_n) = Y_M(t_n), Y_S^{(n)}(t_n) = Y_S(t_n) | A_E^c \right) \\ &= \lim_{n \rightarrow \infty} \prod_{i=1}^{[\log n]+1} \left(1 - \frac{i-1}{n} \right) \\ &\geq 1 - \frac{1}{n} \sum_{i=1}^{[\log n]} i \\ &= 1 - \frac{[\log n]([\log n] + 1)}{2n} \\ &\rightarrow 1 \quad \text{as } n \rightarrow \infty, \end{aligned}$$

so

$$\lim_{n \rightarrow \infty} P \left(X^{(n)}(t_n) = n - T(t_n), Y_M^{(n)}(t_n) = Y_M(t_n), Y_S^{(n)}(t_n) = Y_S(t_n) | A_E^c \right) = 1. \quad (4.27)$$

Now (4.25) implies that $t_n \xrightarrow{a.s.} \infty$ as $n \rightarrow \infty$, so it follows from (4.24) that for P -almost all $\omega \in A_E^c$,

$$\lim_{n \rightarrow \infty} \frac{Y_M(t_n)}{T(t_n)} = c_M \quad \text{and} \quad \lim_{n \rightarrow \infty} \frac{Y_S(t_n)}{T(t_n)} = c_S, \quad (4.28)$$

where $c_M = \alpha v_M / (\lambda_M v_M + \lambda_S v_S)$ and $c_S = \alpha v_S / (\lambda_M v_M + \lambda_S v_S)$. Together with (4.27), (4.28) implies that

$$\lim_{n \rightarrow \infty} P \left(Y_M^{(n)}(t_n) > \frac{c_M}{2} \log n, Y_S^{(n)}(t_n) > \frac{c_S}{2} \log n | A_E^c \right) = 1. \quad (4.29)$$

The branching process \mathbf{Y}_ϵ has mean offspring matrix $M(\epsilon) = (1 - \epsilon)M$ and basic reproduction number $R_0(\epsilon) = (1 - \epsilon)R_0$. For $i = M, S$, let $\pi_i(\epsilon)$ denote the extinction probability of \mathbf{Y}_ϵ given that initially there is one individual, whose type is i . Since $R_0 > 1$, there exists $\epsilon_0 > 0$ such that $R_0(\epsilon_0) > 1$, which implies that $\pi_M(\epsilon_0) < 1$ and $\pi_S(\epsilon_0) < 1$.

For each $n = 1, 2, \dots$, the construction described above (4.22) can be used to define a realisation of $E^{(n)}$, $\hat{E}^{(n)}$ say, and a realisation of \mathbf{Y}_{ϵ_0} , with, in obvious notation, $\hat{Y}_M^{(n)}(0) = Y_{M\epsilon_0}^{(n)}(0) = Y_M(t_n)$, $\hat{Y}_S^{(n)}(0) = Y_{S\epsilon_0}^{(n)}(0) = Y_S(t_n)$ and $\hat{X}^{(n)}(0) = n - T(t_n)$, that are coupled so that $\hat{X}^{(n)}(t) \leq n - T_{\epsilon_0}(t)$ provided $\hat{X}^{(n)}(t) \geq (1 - \epsilon_0)n$. Hence,

recalling (4.27) and (4.29),

$$\begin{aligned}
\lim_{n \rightarrow \infty} P\left(X^{(n)}(\infty) \leq (1 - \epsilon_0)n | A_E^c\right) &= \lim_{n \rightarrow \infty} P\left(\hat{X}^{(n)}(\infty) \leq (1 - \epsilon_0)n\right) \\
&\geq \lim_{n \rightarrow \infty} P(T_{\epsilon_0}(\infty) \geq n\epsilon_0) \\
&\geq \lim_{n \rightarrow \infty} P(T_{\epsilon_0}(\infty) = \infty) \\
&\geq \lim_{n \rightarrow \infty} \left[1 - (\pi_M(\epsilon_0))^{\frac{c_M}{2} \log n} (\pi_S(\epsilon_0))^{\frac{c_S}{2} \log n}\right] \\
&= 1,
\end{aligned}$$

and (4.26) follows.

It is convenient to return now to the construction of $(E^{(n)})$ and \mathbf{Y} given in Section 4.1, but with exponentially distributed infectious periods. As above, let $t_n = \inf\{t : T(t) > \log n\}$. Then, since $n^{-1/2}\eta^{(n)} \xrightarrow{a.s.} \eta$ as $n \rightarrow \infty$, for P -almost all $\omega \in A_E^c$ the process of infectives in $E^{(n)}$ and the branching process \mathbf{Y} coincide over $[0, t_n]$ for all sufficiently large n . Thus, for such n , $X^{(n)}(t_n) = n - T(t_n)$, $Y_M^{(n)}(t_n) = Y_M(t_n)$, $Y_S^{(n)}(t_n) = Y_S(t_n)$ and $Z_M^{(n)}(t_n) = Z_M(t_n)$. It then follows, using (4.24), (4.25) and a similar result for $Z_M(t)$, that for P -almost all $\omega \in A_E^c$,

$$\lim_{n \rightarrow \infty} \frac{Y_M^{(n)}(t_n)}{\log n} = c_M, \quad \lim_{n \rightarrow \infty} \frac{Y_S^{(n)}(t_n)}{\log n} = c_S \quad \text{and} \quad \lim_{n \rightarrow \infty} \frac{Z_M^{(n)}(t_n)}{\log n} = c_{ZM},$$

where $c_{ZM} = \gamma_M v_M / (\lambda_M v_M + \lambda_S v_S)$. Thus, letting $g_n = n^{-1} \log n$, as $n \rightarrow \infty$,

$$\frac{1}{n} \left(X^{(n)}(t_n), Y_M^{(n)}(t_n), Y_S^{(n)}(t_n), Z_M^{(n)}(t_n) \right) \sim (1 - g_n, c_M g_n, c_S g_n, c_{ZM} g_n). \quad (4.30)$$

Let $\hat{\mathbf{X}}^{(n)}$ denote the time-changed process described in Section 4.2, but with $\hat{\mathbf{X}}^{(n)}(0) = \mathbf{X}^{(n)}(t_n)$. Recall that $\tau^{(n)} = \inf\{t > 0 : Y_M^{(n)}(t) + Y_S^{(n)}(t) = 0\}$ and let $\hat{\tau}^{(n)} = \inf\{t > 0 : \hat{Y}_M^{(n)}(t) + \hat{Y}_S^{(n)}(t) = 0\}$. In view of (4.30), let $\hat{\mathbf{x}}^{(n)}$ denote the solution of the deterministic model (4.4) with $\hat{\mathbf{x}}^{(n)}(0) = (1 - g_n, c_M g_n, c_S g_n, c_{ZM} g_n)$, and let $\hat{\mathbf{x}} = \lim_{n \rightarrow \infty} \hat{\mathbf{x}}^{(n)}$. Then it is plausible that $n^{-1} \hat{\mathbf{X}}^{(n)} \Rightarrow \mathbf{x}$ as $n \rightarrow \infty$, and that $n^{-1} \hat{\mathbf{X}}^{(n)}(\hat{\tau}^{(n)}) \xrightarrow{p} \hat{\mathbf{x}}(\hat{\tau})$ as $n \rightarrow \infty$, where $\hat{\tau} = \inf\{t > 0 : \hat{y}_M(t) + \hat{y}_S(t) \leq 0\}$.

Recall that $A^{(n)} = \int_0^\infty n^{-1} \left(\lambda_M Y_M^{(n)}(u) + \lambda_S^{(n)}(u) \right) du$. Note that, since there are few initial infectives, it is possible that $A^{(n)} \rightarrow 0$ as $n \rightarrow \infty$, in which case the time-changed process $\tilde{\mathbf{X}}^{(n)}$, defined in Section 4.2, is defined only for $t = 0$ in the limit as $n \rightarrow \infty$. Indeed, this is what happens if $\omega \in A_E$. However, Lemma 1 implies that there exists $\epsilon_1 > 0$ such that $P(A^{(n)} \geq \epsilon_1 | A_E^c) \rightarrow 1$ as $n \rightarrow \infty$, so, conditional on the epidemic becoming established, the limiting processes $\lim_{n \rightarrow \infty} n^{-1} \tilde{\mathbf{X}}^{(n)}$ and $\lim_{n \rightarrow \infty} n^{-1} \hat{\mathbf{X}}^{(n)}$ do not get stuck at their initial state $(1, 0, 0, 0)$. Further, since $\lim_{n \rightarrow \infty} n^{-\frac{1}{2}} \log n = 0$, it is also plausible that, conditional upon the outbreak becoming established, Theorem 4 and the asymptotic distribution of the final outcome given by (4.20) also hold with obvious modifications. In particular, the asymptotic mean and variance-covariance matrix of $\tilde{\mathbf{X}}^{(n)}(\tilde{\tau}^{(n)})$, given A_E^c occurs, is obtained by setting $\tilde{\mathbf{x}}(0) = (1 - \epsilon, \epsilon c_m, \epsilon c_S, \epsilon c_{ZM})^\top$ in (4.5), (4.19) and (4.20), and letting $\epsilon \downarrow 0$.

The difficulty in making the above heuristic arguments fully rigorous is that the drift function associated with $(\hat{\mathbf{X}}^{(n)}, \hat{F})$ say, is not Lipschitz-continuous at the origin, so the proofs in Ethier and Kurtz (1986), Chapter 11, cannot be directly adapted. For the competing epidemic model, Scalia Tomba and Svensson (2001) use the general theory of counting processes and limit theorems for martingales to obtain rigorously the limiting distribution of the proportions of susceptibles that ultimately become mild and severe infectives, as $n \rightarrow \infty$, though the arguments are quite lengthy. It seems likely that a similar approach will work for the IDS model. However, we do not explore it here and more refined arguments will be required to prove the associated central limit theorem.

5. Discussion

The aim of the paper is to incorporate the fact that many infectious diseases have varying severity of the disease, and this severity often affects an individual's degree of further spreading the disease. In the IDS model we allow for two different severities, mild and severe. It is quite straightforward to generalise the model to allow for an arbitrary number of severities, and the same proof techniques may be used. Another important step to making the model more realistic would be to allow for households, admitting a higher transmission rate and a greater proportion of severe contacts within households. In principle, a household model, e.g. Ball *et al.* (1997), could be combined with the present model for different severities, and this will be the subject of further research.

Concerning vaccination modelling, it could be of interest to study vaccination strategies particularly targeted at reducing the number of severe cases. In particular, if the basic epidemic model was multitype, for example incorporating age-cohorts, it might be of special interest to reduce the number of severe cases in vulnerable groups, such as the very young and the very old.

The IDS model resembles a two-type epidemic model (e.g. Andersson and Britton (2000), Chapter 6) in certain ways, with mild and severe specifying the two types. The difference between the IDS model and a two-type epidemic model is that an individual's type is not decided in advance, but only upon infection, and the probability that an infective becomes a specific type depends on who he or she was infected by. Nevertheless, the initial stages of the IDS model behaves like a two-type epidemic model. It was shown that the IDS model behaves like a two-type branching process, and the same branching process can be used to approximate a two-type epidemic model. By choosing the contact rates in the two-type epidemic suitably, this can be done for arbitrary choice of community proportions of the two types. However, once an epidemic becomes established, the behaviours of the IDS and the two-type epidemic models no longer resemble each other, as is evidenced by the fact that, unlike in the two-type model, there is generally not a system of two equations that determines the asymptotic mean final outcome.

In the IDS model, the infectious state of an individual depends on the type of his or her infector. Ball and Britton (2005) treated a different model for varying severity in which each infected individual was initially mild upon infection, but later may become severely infected if additionally exposed to the disease. Which of the models is more realistic of course depends on the disease of interest, but probably a combination of the

two would be most realistic. That is, where the severity of a given infective depends not only on who he or she was infected by but also on whether or not that infective has been exposed several times.

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