Generality of Endemic Prevalence Formulae

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Abstract

In simple infection models, the susceptible proportion s^* in endemic equilibrium is related to the basic reproduction number R_0 by $s^* = 1/R_0$. We investigate the extent to which this relationship remains valid under more realistic modelling assumptions. In particular, we relax the biologically implausible assumptions that individuals' lifetimes and infectious periods follow exponential distributions; allow a general recruitment process; allow for multiple stages of infection; and consider extension to a multigroup model in which the groups may represent, for instance, spatial heterogeneity, or the existence of super-spreaders. For a homogeneous population, we find that: (i) the susceptible proportion is $s^* = 1/R_0^e$, where R_0^e is a modified reproduction number, equal to R_0 only in certain circumstances; (ii) the proportions of the population in each stage of infection are proportional to the expected time spent by an infected individual in that stage before recovery or death. We demonstrate robustness of the formula $s^* = 1/R_0$ for many human infections by noting conditions under which R_0^e is approximately equal to R_0, while pointing out other circumstances under which this approximation fails. For heterogeneous populations, the formula $s^* = 1/R_0$ does not hold in general, but we are able to exhibit symmetry conditions under which it is valid.

Keywords: endemic equilibrium; basic reproduction number; spatial heterogeneity; super-spreaders

1 Introduction

A key question in infectious disease modelling is the extent to which results derived from highly simplified models remain valid under more realistic modelling assumptions. With this in mind, [23, 24] recently investigated the well-known

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epidemic final size equation of Kermack and McKendrick [17], with a view to understanding the extent to which the original equation remains valid under a range of modelling assumptions. In fact, the original derivation of [17] is already rather general, in that the expected infectivity of an individual is allowed to be an arbitrary function of time since infection, and in particular an individual's infectious period may be drawn from a general distribution. An illuminating discussion of the work of [17] appears in [5]. Sections 9–10 of [23] extend the model to allow for population heterogeneity; the final size equation obtained is a special case of equation (7) of [27]. Ma and Earn [23] discuss conditions under which the form of the original Kermack-McKendrick [17] equation is retained, and note that in the presence of heterogeneities, appropriate modification of the equation is generally required. Further recent discussion of the form of the final size equation, with particular reference to network models, appears in [24].

In the current work, we focus rather upon the prevalence level of an infection in long-term endemic equilibrium. We shall be concerned throughout with deterministic models, which is to say that we study mean behaviour in a large, well-mixed population. Nevertheless, we find it useful to present individual-based stochastic formulations of our models, since this aids intuitive understanding and leads to more transparent derivation of results.

The simplest model for endemic infection is the susceptible-infective-susceptible (SIS) model of [32], the deterministic version of which is represented by the system of differential equations

$$\frac{ds}{dt} = -\beta si + \gamma i,$$
$$\frac{di}{dt} = \beta si - \gamma i,$$

where $s(t), i(t)$ represent the proportions of individuals who are susceptible or infective, respectively, at time t, with $s(t) + i(t) = 1$ for all $t \geq 0$. The constants $\beta > 0$, $\gamma > 0$ are known as the infection rate parameter and recovery rate parameter, respectively. The basic reproduction number (the expected number of secondary cases caused by a typical primary case in an otherwise susceptible population) is here given by $R_0 = \beta/\gamma$. For $R_0 \leq 1$ the only feasible equilibrium point is the disease-free equilibrium $(s, i) = (1, 0)$, whilst for $R_0 > 1$ there is also an endemic equilibrium point $(s^*, i^*) = (1/R_0, 1 - (1/R_0))$.

Clearly the above SIS model is greatly over-simplified. In particular, for any model purporting to describe long-term behaviour, it seems hard to justify the neglect of demographic processes of birth, migration and death. A more plausible model is the susceptible-infective-removed (SIR) model with demography ([26] and references therein). Individuals are recruited (by birth or immigration) into the susceptible category at constant rate $\mu > 0$ and die at per-capita rate μ, and following infection are assumed to become permanently immune. The deterministic version of the model is

$$\frac{ds}{dt} = \mu - \beta si - \mu s, \tag{1}$$

$$\frac{di}{dt} = \beta s i - \gamma i - \mu i, \qquad (2)$$

$$\frac{dr}{dt} = \gamma i - \mu r, \qquad (3)$$

where $s(t), i(t), r(t)$ represent scaled numbers of susceptible, infective and immune ('removed') individuals, respectively. That is, these variables give the numbers of individuals in each category divided by some overall constant scaling factor indicative of population size. Writing $p(t) = s(t) + i(t) + r(t)$, then summing equations (1-3) gives $dp/dt = \mu(1 - p)$ so that $p(t) \to 1$ as $t \to \infty$. Since we are interested in populations in equilibrium we will take $p(0) = 1$, and then $p(t) = 1$ for all t so that s, i, r may be interpreted as proportions of the population. For this model, $R_0 = \beta/(\gamma + \mu)$, and we find that for $R_0 \leq 1$ the only feasible equilibrium point is the disease-free equilibrium $(s, i, r) = (1, 0, 0)$, whilst for $R_0 > 1$ there is also an endemic equilibrium point $(s^*, i^*, r^*) = (1/R_0, (1 - (1/R_0)) \mu/(\gamma + \mu), (1 - (1/R_0)) \gamma/(\gamma + \mu))$.

From these two very simple models, we immediately see some common features emerging. For $R_0 \leq 1$, the only equilibrium point is the disease-free equilibrium. For $R_0 > 1$, in addition to the the disease-free equilibrium there exists a unique endemic equilibrium point with susceptible proportion $s^* = 1/R_0$. Our aim is to investigate the extent to which observations such as these remain valid for more sophisticated and realistic models. It is worth noting that we shall not be concerned with the dynamics of the infection process, but only with the existence, uniqueness, and form of the endemic equilibrium point. In particular we do not consider stability of equilibria, nor whether the infection process displays oscillatory behaviour. These are of course crucial properties, but the objective here is to study the simplest aspects in quite a general context. We discuss issues of stability briefly in section 4.

There are many aspects of the two models presented thus far that are clearly gross simplifications of biological reality. Firstly, the ordinary differential equation formulations imply that individuals' lifetimes and infectious periods are exponentially distributed. These are in general not biologically plausible assumptions. In fact, the early work of Kermack and McKendrick on endemicity [18, 19] already allowed an individual's expected infectivity to be a general function of time since infection, so that in particular, infectious periods need not be exponentially distributed. In terms of individuals' lifetimes, the treatment in [18, 19] is somewhat less satisfactory. In [18] there is no death except due to infection, whereas in [19] natural deaths occur at constant per-capita rates, so that an individual who never becomes infected will live for an exponentially distributed time. More recent work that does not assume exponentially distributed lifetimes and infectious periods has generally fallen into two categories. Firstly, some authors follow the lead of [19] in allowing for a realistic infectious period distribution while assuming that lifetimes are exponentially distributed, for instance [10, 12, 16]. This assumption is clearly unrealistic, but can greatly simplify the analysis. Alternatively, so-called 'age-structured' models ([14, 31, 9] and chapter 22 of [30]) allow for a realistic lifetime distribution, but often not a

realistic infectious period distribution. In such models the rate at which individuals recover from infection is typically allowed to depend upon the individual's age, but not upon the time since infection. This makes the model somewhat difficult to interpret, since the distribution of an individual's infectious period is not straightforward to extract from this framework. For instance, for many infections a reasonable simplifying assumption is that the infectious period is a constant. This means that the rate of recovery depends in the most extreme way upon time since infection, and there is no way to even approximate this within such an age-structured model. Age-structured models in which the recovery rate is allowed to depend upon both age and time since infection are described and studied in [8, 13, 15, 16]. Closer to the spirit of the current work is the recent paper [1], in which the authors study a model based upon that of [18, 19], in that an individual's expected infectivity is allowed to be a general function of time since infection, but allowing a general lifetime distribution.

Rather than follow [1, 18, 19] in modelling infectivity as a continuously varying function, we prefer to treat the infection process as consisting of a sequence of distinct stages of infection. This formulation in terms of multiple stages may be regarded as a special form of time-varying infectivity function; however, we prefer the formulation of stages, which has become standard in modern infection modelling, for the following reasons. Many infections exhibit clinically meaningful stages, such as a latent period or post-infectious period of temporary immunity; and some infections (eg HIV) are commonly modelled as comprising multiple stages of infection. Further, in fitting to data it seems reasonable to estimate a small number of infectivity parameters, whereas to estimate an continuously varying infectivity function would present a much greater challenge.

Another simplifying assumption often made is that recruitment to the population occurs at constant rate μ. This has the desirable effect that the population size stabilises at $p(t) = 1$, providing a simple way to study an infection spreading in a stable population. However, other recruitment rate functions may be more biologically plausible, such as a combination of immigration and linear birth giving rate $\mu + \alpha p(t)$ for some $\mu, \alpha > 0$ [18, 19], or logistic recruitment at rate $\mu\left(1 - (p(t)/K)\right)$ for some $\mu, K > 0$ [20]. We allow quite a general recruitment rate function.

Finally, a variety of heterogeneities may be present in the population; for instance, heterogeneous susceptibility, heterogeneous infectivity, or heterogeneity of mixing. We will allow for heterogeneity by stratifying the population into a finite number of groups. Related previous work includes [11], chapter 23 of [30] and sections 8.5–8.6 of [28]; in each of these references, exponentially distributed lifetimes were assumed.

In summary, we aim to study a model for infection which incorporates a general recruitment rate function; non-exponentially distributed lifetimes and infectious periods; multiple stages of infection; and heterogeneous population structure. In contrast to previous authors, we focus specifically upon the form of the endemic equilibrium point, and the extent to which this form is dependent upon common simplifying assumptions.

2 Endemic infection in a homogeneous population

Consider a population which at time t consists of $P(t)$ individuals. Individuals are recruited into the susceptible population according to an inhomogeneous Poisson process of rate $\Lambda(P(t))$, where $\Lambda(\cdot)$ is some non-negative function. Each individual lives for a time distributed as a non-negative random variable L before being removed from the population (eg by death), and we assume $E[L] < \infty$. We will assume no disease-related mortality (although see discussion in section 4 below), and so total population size $P(t)$ can be analysed separately from the infection process. Denote by P^* the expected equilibrium population level (or quasi-equilibrium level in the case $\Lambda(0) = 0$), and consider the large-population limit in which the process $p(t) = P(t)/P^*$ may be treated as deterministic. We have

$$p(t) \quad = \quad \frac{1}{P^*} \int_{-\infty}^{t} \Lambda(p(u)P^*) \Pr(L > t - u) \, du \quad = \quad \frac{1}{P^*} \int_{0}^{\infty} \Lambda(p(t - v)P^*) \Pr(L > v) \, dv.$$

In equilibrium, $p(t) = 1$ for all t, and so P^* satisfies

$$P^* \quad = \quad \Lambda(P^*) E[L]. \tag{4}$$

We shall assume $\Lambda(\cdot)$ is such that equation (4) has a unique positive solution P^*. The two most commonly used recruitment functions, constant recruitment $\Lambda(P) = \mu$ and logistic recruitment $\Lambda(P) = \mu P(1 - (P/K))$, both satisfy this condition. We consider an infection introduced into a population in demographic equilibrium.

Whenever an individual becomes infected it is assigned an infected life history distributed as $\mathbf{T} = (T_1, T_2, \ldots, T_n)$, independent of its age at infection. Provided the individual has not yet been removed, it spends times $T_1, T_2, \ldots, T_n$ in the successive infected stages before returning to the susceptible state. That is, an individual which becomes infected at age a will be in infected stage j at age $a + u$ provided $\sum_{r=1}^{j-1} T_r \le u < \sum_{r=1}^{j} T_r$ and $L > a + u$. An individual in infected stage j contacts each other individual in the population according to a Poisson process of constant rate $\beta^{(j)}/P^*$. If the contacted individual is susceptible, it becomes infected; otherwise the contact has no effect. Lifetimes L are independent between distinct individuals and independent of the recruitment process; infected life histories $\mathbf{T}$ and infectious contact processes are independent of the lifetimes and the recruitment process, independent between distinct individuals and between successive infections of the same individual; infectious contact processes are independent of each other, of lifetimes, recruitment, and infected life histories. The formulation in terms of stages allows us to model a latent ('exposed') period between an individual being contacted and itself starting to infect others, a period of temporary immunity following infection, and so on. For instance, taking $n = 3$, $\beta^{(1)} = \beta^{(3)} = 0$, and $\Pr(T_3 = \infty) = 1$ yields an SEIR model, while if instead $E[T_3] < \infty$ we obtain an SEIRS model.

The basic reproduction number for this model is given by $R_0 = \sum_{j=1}^{n} \beta^{(j)} E\left[T_j^0\right]$, where T_j^0 is the amount of time that a 'typical' individual will spend in infected stage j before either death or return to the susceptible state. Here 'typical' means that the individual is chosen at random from a wholly susceptible population in demographic equilibrium. In demographic equilibrium the age distribution has probability density $f(a) = \Pr(L > a)/E[L]$, and so

$$
\begin{aligned}
E\left[T_j^0\right] &= \int_{a=0}^{\infty} \int_{u=0}^{\infty} \frac{\Pr(L > a)}{E[L]} \, \Pr\left(\sum_{r=1}^{j-1} T_r \le u < \sum_{r=1}^{j} T_r\right) \Pr(L > a + u \mid L > a) \, du \, da \\
&= \frac{1}{E[L]} \int_{a=0}^{\infty} \int_{u=0}^{\infty} \Pr\left(\sum_{r=1}^{j-1} T_r \le u < \sum_{r=1}^{j} T_r\right) \Pr(L > a + u) \, du \, da. \qquad (5)
\end{aligned}
$$

Defining $A(u) = \sum_{j=1}^{n} \beta^{(j)} \Pr\left(\sum_{r=1}^{j-1} T_r \le u < \sum_{r=1}^{j} T_r\right)$ to be the expected infectivity of an individual infected u time units ago, conditional upon remaining alive, then

$$
R_0 = \frac{1}{E[L]} \int_{a=0}^{\infty} \int_{u=0}^{\infty} A(u) \Pr(L > a + u) \, du \, da. \qquad (6)
$$

Now denote by $s(t), i^{(1)}(t), i^{(2)}(t), \ldots, i^{(n)}(t)$ the (deterministic) proportions of the population in the susceptible state and in each of the infected stages, respectively, at time t, in the limit $P^* \to \infty$. Consider a population initiated from an equilibrium point $\left(s^*, i^{(1)*}, i^{(2)*}, \ldots, i^{(n)*}\right)$ at time $t = -\infty$. Denote by $s^*(a)$ the density of susceptibles of age a, so that the susceptible proportion of the population is $s^* = \int_0^{\infty} s^*(a) \, da$, and denote by $i^{(j)*}(a)$ the density of individuals of age a in infected stage j for $j = 1, 2, \ldots, n$. Writing

$$
\theta = \sum_{j=1}^{n} \beta^{(j)} i^{(j)*} \qquad (7)
$$

for the 'infectious pressure' acting on each susceptible individual, then we have

$$
s^*(a) = \frac{\Pr(L > a) \, \mathrm{e}^{-a\theta}}{E[L]}.
$$

The infected densities are then given by

$$
\begin{aligned}
i^{(j)*}(a) &= \int_0^{a} \theta s^*(a - v) \Pr\left(\sum_{i=1}^{j-1} T_i \le v < \sum_{i=1}^{j} T_i\right) \Pr(L > a \mid L > a - v) \, dv \\
&= \frac{\theta}{E[L]} \int_0^{a} \mathrm{e}^{-(a-v)\theta} \Pr\left(\sum_{i=1}^{j-1} T_i \le v < \sum_{i=1}^{j} T_i\right) \Pr(L > a) \, dv,
\end{aligned}
$$

so that

$$
i^{(j)*} = \int_{a=0}^{\infty} i^{(j)*}(a) \, da = \frac{\theta}{E[L]} \int_{u=0}^{\infty} \int_{v=0}^{\infty} \mathrm{e}^{-u\theta} \Pr\left(\sum_{i=1}^{j-1} T_i \le v < \sum_{i=1}^{j} T_i\right) \Pr(L > u + v) \, dv \, du. \quad (8)
$$

Multiplying equation (8) by $\beta^{(j)}$ and summing over j,

$$\theta \;=\; \frac{\theta}{E[L]} \int_{u=0}^{\infty} \int_{v=0}^{\infty} \mathrm{e}^{-u\theta} A(v) \Pr\left(L > u + v\right) dv\,du.$$

Hence either $\theta = 0$ (disease-free equilibrium) or θ satisfies

$$1 \;=\; \frac{1}{E[L]} \int_{u=0}^{\infty} \int_{v=0}^{\infty} \mathrm{e}^{-u\theta} A(v) \Pr\left(L > u + v\right) dv\,du, \tag{9}$$

similarly to equation (3) of [7]. As noted by [1], the right hand side of equation (9) is a strictly decreasing continuous function of θ, taking the value R_0 at $\theta = 0$, and converging to zero as $\theta \to \infty$. Hence for $R_0 \leq 1$ there is no positive solution to equation (9), while for $R_0 > 1$ there is a unique positive solution.

For the case $R_0 > 1$, denote by T_j^e the time that a typical individual, infected when the population is in endemic equilibrium, will spend in infected stage j before either death or return to the susceptible state. Then

$$E\left[T_j^e\right] \;=\; \int_{a=0}^{\infty} \int_{v=0}^{\infty} \frac{s^*(a)}{s^*} \Pr\left(\sum_{i=1}^{j-1} T_i \leq v < \sum_{i=1}^{j} T_i\right) \Pr\left(L > a + v \mid L > a\right) dv\,da$$

$$\;=\; \frac{\int_{a=0}^{\infty} \int_{v=0}^{\infty} \mathrm{e}^{-a\theta} \Pr\left(\sum_{i=1}^{j-1} T_i \leq v < \sum_{i=1}^{j} T_i\right) \Pr\left(L > a + v\right) dv\,da}{\int_{a=0}^{\infty} \mathrm{e}^{-a\theta} \Pr(L > a)\,da} \tag{10}$$

and we can write equation (8) as

$$i^{(j)*} \;=\; s^* \theta E\left[T_j^e\right] \text{ for } j = 1, 2, \ldots, n. \tag{11}$$

Define the modified reproduction number R_0^e as

$$R_0^e \;=\; \frac{\int_{a=0}^{\infty} \int_{u=0}^{\infty} \mathrm{e}^{-a\theta} A(u) \Pr\left(L > a + u\right) du\,da}{\int_{a=0}^{\infty} \mathrm{e}^{-a\theta} \Pr(L > a)\,da}. \tag{12}$$

Noting that $R_0^e = \sum_{j=1}^{n} \beta^{(j)} E\left[T_j^e\right]$, then R_0^e has a natural interpretation as the expected total number of potentially infectious contacts originating from an infected individual whose age at infection is drawn from the age-distribution of the susceptible individuals in a population in endemic equilibrium. Noting that $E[L] = \int_0^{\infty} \Pr(L > a)\,da$, we see a close parallel between formulae (12) and (6): the formula (6) for R_0 may be recovered from the formula (12) for R_0^e simply by replacing the equilibrium infectious pressure θ with zero, the infectious pressure in a wholly susceptible population.

Multiplying equation (11) by $\beta^{(j)}$ and summing over j yields the balance equation $\theta = s^* \theta R_0^e$, implying that either $\theta = 0$ or $s^* = 1/R_0^e$. From equation (11) we know that $i^{(j)*} \propto E\left[T_j^e\right]$, and so the endemic equilibrium point is given by

$$s^* = \frac{1}{R_0^e}, \quad \left(i^{(1)*}, i^{(2)*}, \ldots, i^{(n)*}\right) = \frac{1 - (1/R_0^e)}{\sum_{r=1}^{n} E\left[T_r^e\right]} \left(E\left[T_1^e\right], E\left[T_2^e\right], \ldots, E\left[T_n^e\right]\right). \tag{13}$$

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Notice the distinction between R_0^e and R_0. The basic reproduction number R_0 is defined in terms of a 'typical' newly-infected individual drawn from the age-distribution of a population in demographic equilibrium; on the other hand, R_0^e is defined in terms of a 'typical' newly-infected individual drawn from the age-distribution of the susceptible individuals in a population in endemic equilibrium. For $R_0 > 1$ we have $\theta > 0$, hence $R_0^e > 1$, and hence the endemic equilibrium point (13) is feasible precisely when $R_0 > 1$, and when feasible it is unique. One would expect the difference between R_0 and R_0^e to be small if either (i) only a small proportion of the population is infected in endemic equilibrium; or (ii) the mean infectious period is short relative to the mean lifetime. We discuss this further in section 4 below.

When modelling an infection in a closed population, the arguments above simplify as follows. We now suppose that $\Pr(L = \infty) = 1$ and $\Lambda(P) \equiv 0$, and we require that $E\left[\sum_{j=1}^n T_j\right] < \infty$. We then have $E\left[T_j^e\right] = E\left[T_j\right]$ for $j = 1, 2, \ldots, n$ and $R_0^e = R_0$, and with these simplifications equation (13) remains valid.

Returning to the model with demography, note that if individuals' lifetimes L are exponentially distributed then the remaining lifetime of a newly-infected individual does not depend upon its current age, so that in this case we again have $R_0^e = R_0$. More generally, from equations (6) and (12) it is straightforward to find a condition upon the lifetime distibution L that implies an ordering between R_0 and R_0^e; specifically,

$$\frac{E\left[1 - \mathrm{e}^{-\psi(L-v)} \mid L > v\right]}{E[L - v \mid L > v]} \geq (\leq) \frac{E\left[1 - \mathrm{e}^{-\psi L}\right]}{E[L]} \text{ for all } \psi > 0, \text{ all } v \text{ with } \Pr(L > v) > 0$$

$$\Rightarrow \quad R_0^e \geq (\leq)R_0. \qquad (14)$$

To understand this result, for any non-negative random variable U define the function

$$M_U(\psi) \quad = \quad \frac{E\left[1 - \mathrm{e}^{-\psi U}\right]}{E[U]} \text{ for } \psi > 0.$$

We can define an ordering of random variables (analogous to the well-known Laplace transform ordering) by writing $U \prec V$ if $M_U(\psi) \geq M_V(\psi)$ for all $\psi > 0$. Noting that the function $\left(1 - \mathrm{e}^{-\psi u}\right)/u$ is decreasing in u for any $\psi > 0$, then it seems reasonable to say that V is in some sense 'greater than' U when $U \prec V$. Denoting by L_v the remaining lifetime of an individual that has already lived v time units, then condition (14) may be written as

$$L_v \prec (\succ)L \text{ for all } v \text{ with } \Pr(L > v) > 0 \Rightarrow R_0^e \geq (\leq)R_0.$$

The condition is reminiscent of the NBUL (New Better than Used in Laplace transform ordering) class of distributions of Yue and Cao [33]. Intuitively, if the remaining lifetime of an individual that has already lived v time units is (in the appropriate stochastic sense) shorter than the lifetime of a newborn individual, then $R_0^e \geq R_0$ because a new case at endemic equilibrium is typically younger

than one in a naïve population, and hence has the opportunity to live longer while infectious and transmit more.

For instance, if the lifetime L is constant, it follows that $R_0^e \geq R_0$. Constant lifetime is a reasonable assumption for a managed livestock population in which animals are to be slaughtered at a specified age. As an example, consider an infection that affects 50% of the population in endemic equilibrium, so that $s^* = 0.5$ and hence $R_0^e = 2$. Further suppose that the lifetime L is constant and the infection is of SI type, so $T_1 = \infty$. We then find that $R_0 = 1.59$. With these assumptions there is thus a substantial discrepancy between R_0 and R_0^e. For an unmanaged population, a constant lifetime does not seem so plausible. Consider the UK life tables for 2011-13 [34]. Since the data are presented separately for males and females, for simple illustrative purposes we consider only the data for males. With this distribution for L, again for an SI infection with $R_0^e = 2$, we find $R_0 = 1.61$, so again we see a substantial difference between R_0 and R_0^e. On the other hand, for an SIR infection with non-random (for simplicity) infectious period $T_I = 1$ year we find $R_0 = 1.99$. That is, the difference between the values of R_0 and R_0^e is now essentially negligible.

The above numerical examples illustrate the point that if the value of s^* is observed (or estimated from data), then whereas $R_0^e = 1/s^*$ may be immediately estimated, to estimate R_0 requires further knowledge (or modelling assumptions) regarding the lifetime distribution L and the infectivity function $A(\cdot)$. Secure vaccination coverage requires that a proportion $\pi = 1 - (1/R_0)$ of the susceptible population be vaccinated, since this has the effect of reducing the basic reproduction number to $\tilde{R}_0 = \pi R_0 = 1$. The relationship between $\tilde{R}_0^e$ for the vaccinated population and the original R_0^e is considerably more complicated, since vaccination reduces the value of the infectious pressure θ, which affects the value of R_0^e, given by (12), in a non-linear manner.

3 Population heterogeneities

A variety of heterogeneous mixing structures may be modelled by supposing the population to be divided into k distinct groups. For instance the groups may represent spatially isolated patches, eg cities (a 'metapopulation' model). We assume for simplicity that the distributions of an individual's lifetime L and of infected life histories $\mathbf{T}$ do not depend upon the group. We allow heterogeneity in the infection rate parameters, and in the birth processes (and hence group sizes), as follows.

For $g = 1, 2, \ldots, k$, group g consists at time t of $P_g(t)$ individuals, with $\mathbf{P}(t) = (P_1(t), P_2(t), \ldots, P_k(t))$. Individuals are recruited into the susceptible population of group g according to an inhomogeneous Poisson process of rate $\Lambda_g(\mathbf{P}(t))$ for some non-negative functions $\Lambda_g(\cdot)$, and we denote $\mathbf{\Lambda}(\mathbf{P}) = (\Lambda_1(\mathbf{P}), \Lambda_2(\mathbf{P}), \ldots, \Lambda_g(\mathbf{P}))$. The expected equilibrium population level $\mathbf{P}^*$ satisfies the balance equation

$$\mathbf{P}^* = \mathbf{\Lambda}(\mathbf{P}^*)E[L]. \tag{15}$$

We assume that equation (15) has a unique non-zero solution with $P_g^* \geq 0$ for $g = 1, 2, \ldots, k$, and that $P_g^* > 0$ for $g = 1, 2, \ldots, k$. Denote $P^* = P_1^* + P_2^* + \cdots P_k^*$ and $f_g = P_g^*/P^*$. We consider an infection introduced into a population in demographic equilibrium.

While in infected stage j $(j = 1, 2, \ldots, n)$, a group g individual makes infectious contacts with each individual in group h at the points of a Poisson process of rate $\beta_{gh}^{(j)}/P^*$. For an individual chosen at random from group g of a wholly susceptible population in demographic equilibrium, the expected number of group h infectious contacts during one infected life history is thus

$$m_{gh}^{(0)} = f_h \sum_{j=1}^{n} \beta_{gh}^{(j)} E\left[T_j^0\right] \tag{16}$$

with $E\left[T_j^0\right]$ being given by equation (5). We assume that the next generation matrix $M^{(0)}$ with entries $\left\{m_{gh}^{(0)}\right\}$ is irreducible, meaning that an infection initiated in any one group can eventually spread to all groups. The basic reproduction number R_0 is given by the maximal eigenvalue of $M^{(0)}$.

Denote by s_g^* the susceptible proportion of group g in endemic equilibrium, and by $i_g^{(j)*}$ the proportion of group g in infected stage j. Denote by $T_j^{e\,(g)}$ the time that a typical group g individual, infected when the population is in endemic equilibrium, will spend in stage j before death or recovery. With

$$\theta_h = \sum_{g=1}^{k} \sum_{j=1}^{n} i_g^{(j)*} f_g \beta_{gh}^{(j)}, \tag{17}$$

then we have

$$E\left[T_j^{e\,(g)}\right] = \frac{\int_{a=0}^{\infty} \int_{v=0}^{\infty} e^{-a\theta_g} \Pr\left(\sum_{i=1}^{j-1} T_i \leq v < \sum_{i=1}^{j} T_i\right) \Pr(L > a + v)\, dv\, da}{\int_{a=0}^{\infty} e^{-a\theta_g} \Pr(L > a)\, da}.$$

In endemic equilibrium, for each group g, by similar arguments to the homogeneous population case we find

$$\left(i_g^{(1)*}, i_g^{(2)*}, \ldots, i_g^{(n)*}\right) = \frac{1 - s_g^*}{\sum_{r=1}^{n} E\left[T_j^{e\,(g)}\right]} \left(E\left[T_1^{e\,(g)}\right], E\left[T_2^{e\,(g)}\right], \ldots, E\left[T_n^{e\,(g)}\right]\right). \tag{18}$$

In order to evaluate $E\left[T_j^{e\,(g)}\right]$ and s_g^*, it remains to determine $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_k)$. Writing $A_{gh}(u) = \sum_{j=1}^{n} \beta_{gh}^{(j)} \Pr\left(\sum_{r=1}^{j-1} T_r \leq u < \sum_{r=1}^{j} T_r\right)$, then from definition (17) and the multigroup version of equation (8) it follows that $\boldsymbol{\theta}$ satisfies the balance equations

$$\theta_h = \sum_{g=1}^{k} \frac{\theta_g f_g}{E[L]} \int_{u=0}^{\infty} \int_{v=0}^{\infty} e^{-u\theta_g} A_{gh}(v) \Pr(L > u + v)\, dv\, du \quad (h = 1, 2, \ldots, k). \tag{19}$$

Clearly (19) admits the solution $\boldsymbol{\theta} = \mathbf{0}$ corresponding to the disease-free equilibrium. For $R_0 \leq 1$ we can show (see appendix) that this is the only feasible solution. In the case $R_0 > 1$, proving existence and uniqueness of a non-zero solution does not seem straightforward. In order to make further progress we restrict to the case that lifetimes L are exponentially distributed, with mean $1/\mu$. We then have

$$s_g^* = \int_{a=0}^{\infty} \frac{\Pr(L > a)}{E[L]} e^{-a\theta_g} \, da = \frac{\mu}{\mu + \theta_g}.$$

Writing $i_g^* = 1 - s_g^*$ and $b_{gh} = \int_{u=0}^{\infty} \int_{v=0}^{\infty} A_{gh}(v) \Pr(L > u + v) \, dv \, du \big/ E[L]$, equation (19) reduces to

$$i_h^* = (1 - i_h^*) \sum_{g=1}^{k} i_g^* f_g b_{gh} \quad (h = 1, 2, \ldots, k). \tag{20}$$

This equation has been previously obtained in the context of a multigroup SIS model, in a closed population [21] and in an open population [28] (with exponentially distributed lifetimes). It follows from theorem 8.2 of [28] that if $M^{(0)}$ is irreducible with $R_0 > 1$ then there exists a unique non-zero solution $(i_1^*, i_2^*, \ldots, i_k^*)$ of equations (20) in $[0, 1]^k$, and that $0 < i_g^* < 1$ for $g = 1, 2, \ldots, k$. Equation (20) is identical to equation (6) of [4], where a multigroup SIS model in a closed population was the object of study. Hence for our current, considerably more general, model we can immediately invoke results from section 5 of [4], and in particular, writing $F = diag\,(f_1, f_2, \ldots, f_k)$, we have the following three important special cases.

(i) *Symmetrical case.* Suppose that the columns of the matrix $FM^{(0)}F^{-1}$ all sum to the same value. That is, the average number of infectious contacts received by a specified susceptible individual from an infected individual chosen uniformly at random from the whole population does not depend upon the group to which the susceptible individual belongs. Then R_0 is equal to this common value, and equations (20) admit the symmetrical solution $i_g^* = 1 - (1/R_0)$ for $g = 1, 2, \ldots, k$. The endemic susceptible proportion is thus $s^* = \sum_{g=1}^{k} f_g s_g^* = 1/R_0$.

(ii) *Heterogeneous infectivity.* If heterogeneity is in infectiousness only, so that $b_{gh} = \lambda_g$ for some $\lambda_1, \lambda_2, \ldots, \lambda_k$, then the columns of $FM^{(0)}F^{-1}$ all sum to the common value $\sum_{g=1}^{k} f_g \lambda_g$, so that $s^* = 1/R_0$ with $R_0 = \sum_{g=1}^{k} f_g \lambda_g$.

(iii) *Separable case.* Suppose now that $b_{gh} = \lambda_g \mu_h$ for some infectivity parameters $\lambda_1, \lambda_2, \ldots, \lambda_k$ and susceptibility parameters $\mu_1, \mu_2, \ldots, \mu_k$. Then the solution to equations (20) is $i_g^* = D\mu_g / (1 + D\mu_g)$ for $g = 1, 2, \ldots, k$, where D is the unique positive value satisfying $\sum_{g=1}^{k} (f_g \mu_g \lambda_g / (1 + D\mu_g)) = 1$. Without loss of generality we can label the groups such that $\mu_1 \leq \mu_2 \leq \cdots \leq \mu_k$. If susceptibility and infectivity are positively correlated, i.e.

$\sum_g \lambda_g \mu_g f_g \geq \left(\sum_g \lambda_g f_g\right)\left(\sum_g \mu_g f_g\right)$, or if $\lambda_1 \mu_1 \leq \lambda_2 \mu_2 \leq \cdots \leq \lambda_k \mu_k$, then $s^* \geq 1/R_0$. Conversely, if $\lambda_1 \mu_1 \geq \lambda_2 \mu_2 \geq \cdots \geq \lambda_k \mu_k$ then $s^* \leq 1/R_0$.

The symmetry condition of (i) above is in essence the same as the condition of Theorem 9.1 of [23], where it is shown that under this condition the final size of a short-lived epidemic outbreak is the same as in the homogeneously mixing case. Heterogeneous infectivity as described in (ii) could, for instance, be used to represent the existence of a group of super-spreaders, via a two-group model with $\lambda_1 \gg \lambda_2$. The existence of super-spreaders has been proposed for a variety of infections, eg severe acute respiratory syndrome (SARS). Result (ii) shows that, under the assumption of exponentially distributed lifetimes, such heterogeneity in infectivity does not affect the endemic prevalence level. Intuitively, if all uninfected individuals have equal susceptibility, then whenever an infectious contact occurs it is equally likely to be directed towards any individual in the population, so that in equilibrium the infected proportion will be the same in every group (and consequently equal to the homogeneous population value). For more general heterogeneous structures, however, numerical examples such as those in figure 3 of [4] show that the endemic prevalence level can be very different from that of a homogeneous population. This is in line with the well-known observation (eg section 10 of [23]) that such social heterogeneities can greatly affect epidemic final size, for a given value of R_0. For the separable case (iii), we have exhibited conditions under which the endemic level may be bounded (either above or below) by the homogeneous population value; case (iii) combines theorems 8 and 9 of [4], where full details of the proof may be found.

In terms of inferring the pattern of heterogeneity from data, the observed values $s_1^*, s_2^*, \ldots, s_k^*$ clearly do not contain enough information to estimate all k^2 of the parameters $\{b_{gh}\}$ from equations (20). Progress can be made if the heterogeneity is known (or assumed) to take some more specific form. For instance, if heterogeneity is in susceptibility only, so that $b_{gh} = \mu_h$, then equations (20) may be solved to give

$$\mu_h = \frac{1 - s_h^*}{s_h^*} \Big/ \sum_{g=1}^{k} \left(1 - s_g^*\right) f_g.$$

On the other hand, if infectiousness and susceptibility are both assumed proportional to the same underlying measure of social activity, so that $b_{gh} = c_g c_h$ (sometimes referred to as proportionate mixing), then we find

$$c_h = \frac{1 - s_h^*}{s_h^*} \Big/ \sqrt{\sum_{g=1}^{k} \frac{\left(1 - s_g^*\right)^2 f_g}{s_g^*}}.$$

That is, either susceptibility μ_h or activity level c_h for group h is found to be proportional to $((1/s_h^*) - 1)$.

4 Discussion

For homogeneous populations (section 2), we have demonstrated two simple general principles. First of all, a balance condition: in order to maintain endemic equilibrium, the effective reproduction number $R(t)$ (expected number of secondary cases caused by a typical primary case at time t) must remain constant at $R(t) = 1$. If individuals' lifetimes are exponentially distributed, then $R(t) = R_0 s(t)$, giving the well-known endemic level formula $s^* = 1/R_0$. When lifetimes are not exponentially distributed, this formula must be modified to $s^* = 1/R_0^e$, with R_0^e defined to allow for the difference between the remaining lifespan of a typical newly-infected individual in endemic equilibrium, and that of a typical newly-infected individual in a wholly susceptible population. This contradicts the conclusion of [12] that 'the asymptotic behaviour of the models with distributed delays is the same as ... the ordinary differential equation models', because their analysis was based throughout upon the assumption that individuals' lifetimes are exponentially distributed. In practice, the difference between R_0^e and R_0 may not be great, in particular if the infection is endemic at a low level, and so has little effect upon the age-distribution of the susceptible part of the population, or if the infectious period is sufficiently short that the chance of natural death during the infectious period may be neglected (note that it has been previously remarked, in proposition 5.2 of [16], that $R_0 \approx 1/s^*$ provided $E[L]$ is short enough). Consequently, for many infectious diseases of humans, our result may be interpreted as demonstrating the robustness of the formula $s^* = 1/R_0$, which would be expected to provide a very good approximation. This is confirmed by a numerical example in section 2 above, in which we deliberately took a high proportion (50%) of the population to be infected, and a long infectious period (1 year), and even under these circumstances found a negligible difference between R_0 and R_0^e. On the other hand, for livestock infections which do not necessarily cause serious symptoms in the livestock but do carry a risk of food poisoning to humans (eg Campylobacter in poultry, Salmonella in pigs), the infectious period may be a substantial fraction of the individual's lifetime, and the difference between R_0 and R_0^e may be significant. Similarly, for some infections of humans the duration of infection can be of the same order as the human lifespan, as for instance in the case of Tuberculosis. The impact of a realistic lifetime distribution upon the behaviour of a Tuberculosis model has recently been studied in [2].

Our second general principle is an ergodic-type result: the proportion of the population in each infected stage in endemic equilibrium is proportional to the expected time spent by an individual in that stage between infection and death or return to susceptibility. This principle is stated as the 'microcosm principle' for a general population process in equilibrium in [25], although without formal justification. Some care is required in evaluating the relevant expectations, since the distribution of the remaining lifespan of a typical infected individual depends upon the prevalence level of infection. Formulae (9,10) make precise the relationship of these expectations to basic parameters of the model.

We have not considered dynamical behaviour of the process, and in par-

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ticular stability of the endemic equilibrium point. The usual situation to be expected is that for $R_0 \leq 1$, the only feasible equilibrium point is the disease-free equilibrium, and this point is globally asymptotically stable; for $R_0 > 1$, there also exists a unique feasible non-zero equilibrium point, the endemic equilibrium, and this point is globally asymptotically stable. It is important to note here that for biologically plausible population sizes, any deterministic model should be regarded as a crude first approximation to a more realistic stochastic formulation, and in stochastic formulations eventual disease extinction typically occurs with probability 1, whatever the value of R_0. Nevertheless, deterministic stability analysis provides valuable information. If the endemic equilibrium point is globally asymptotically stable, this can be interpreted as meaning that provided the infection succeeds in infecting a significant proportion of the population, then it is likely to persist in a state close to the deterministic endemic equilibrium for a long time before stochastic fluctuations lead to eventual extinction. A full stability analysis of our most general model seems challenging. Key existing results include those of [1, 15] for a homogeneous population, and of [21, 22] for heterogeneous populations. The models of [1, 15] differ from our model of section 2 in that recruitment into the population occurs at constant rate, and no distinction is made between stages of infection but rather a general infectivity function $A(u)$ is used. Proposition 6.3 of [15] gives sufficient conditions for local asymptotic stability of the endemic equilibrium point. For the case of exponentially distributed lifetimes L, it is shown in [1] that the endemic equilibrium point is locally asymptotically stable for $R_0 > 1$. Whether this is the case for more general lifetime distributions is left as an open problem. Similarly, [21] provides a full global stability analysis for a multigroup SIS model with exponentially distributed lifetimes and exponentially distributed infectious periods, while [22] give corresponding results for a multigroup SEIR model with exponentially distributed lifetimes and general latent and infectious period distributions.

There are a number of obvious extensions of our model that could be considered. First of all, consider the infection process. For a population containing S susceptible and I infective individuals, we have assumed that new infections arise at average rate βSI. A variety of alternative infection rate functions $\beta(S, I)$ have been proposed in the literature ([3] and references therein). In particular, a popular formulation is that new infections arise at rate $\beta SI / P$, where $P(t)$ is the current population size. Our results remain valid for any infection rate function of the form $\beta(P)SI$ where $\beta(\cdot)$ is a positive function of population size, since we have looked only at populations in demographic equilibrium, i.e. with $P(t)$ remaining constant. Secondly, we have assumed no disease-induced mortality. Denoting by P_0^* the population level in demographic equilibrium in the absence of infection, and by P^* the population level in endemic equilibrium, then one would expect disease-induced mortality to imply that $P^* < P_0^*$. One would anticipate that equations (13) will remain valid, except that now $s^*, i_1^*, \ldots, i_n^*$ represent proportions of a population of size P^*, rather than P_0^*. Finding the level P^* in terms of basic parameters of the model seems likely to be challenging, since the level depends upon the interaction between demographic

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and infection processes. A third possible extension would be to allow an individual's susceptibility to depend upon their age, or for infected life histories $\mathbf{T}$ and infectivity parameters $\beta^{(j)}$ to depend upon the age at which the individual became infected. In particular, so-called 'childhood infections' such as measles, mumps, chicken pox etc. can display rather different symptoms in adults than in children. If susceptibility and the progression of infection are allowed to depend upon the age at infection, these factors will contribute to the distinction between R_0 and R_0^e.

In heterogeneous populations, it becomes more difficult to apply our general balance condition, because precisely what is meant by a 'typical' primary case becomes more complicated. Our ergodic-type result for the proportions in various infected stages remains valid (equation (18)), but evaluating the susceptible proportions s_g^* is not straightforward, and we were obliged to restrict to exponentially distributed lifetimes. In this case, we see that if heterogeneity is only in infectiousness, or under a more general symmetry condition (that the columns of $FM^{(0)}F^{-1}$ all sum to the same value), then the formula $s^* = 1/R_0$ remains valid. In general, however, this is not the case, and instead we have exhibited conditions under which the susceptible proportion may be bounded (either above or below) by $1/R_0$. Establishing existence and uniqueness of a non-zero solution to equations (19) for non-exponentially distributed lifetimes L remains an important open problem. Finally, in dealing with heterogeneous populations we assumed that lifetimes L and infectious life histories $\mathbf{T}$ are identically distributed across all groups. This assumption was made to avoid overly cumbersome notation, and is not unreasonable if the groups represent spatially distinct groupings of an otherwise homogeneous population. If groups represent categories such as male and female, or different species (eg humans and mosquitoes), then this assumption would need to be relaxed.

A   Appendix

We demonstrate that for $R_0 \leq 1$ equation (19) has no non-zero solution.

For $\xi \geq 0$ and $g, h \in \{1, 2, \ldots, k\}$, define

$$c_{gh}(\xi) \quad = \quad \int_{u=0}^{\infty} \int_{v=0}^{\infty} e^{-u\xi} A_{gh}(v) \Pr(L > u + v)\, dv\, du.$$

If $c_{gh}(0) > 0$ then $c_{gh}(\xi)$ is a decreasing function with $c_{gh}(\xi) > 0$ for all $\xi \geq 0$ and $c_{gh}(\xi) \to 0$ as $\xi \to \infty$. Since we have assumed the matrix $M^{(0)}$ is irreducible, it follows that the matrix $C(\boldsymbol{\xi})$ with entries $c_{gh}(\xi_g)$ is irreducible for any $\boldsymbol{\xi} = (\xi_1, \xi_2, \ldots, \xi_k) \geq \mathbf{0}$ (the inequality to be interpreted elementwise). For $\boldsymbol{\xi} \geq \mathbf{0}$, denote by $\rho(\boldsymbol{\xi})$ the dominant eigenvalue of the matrix with elements $f_g c_{gh}(\xi_g) / E[L]$. It follows from the Perron-Frobenius theorem for irreducible matrices (theorem 1.5 of [29]) that if $0 \leq \boldsymbol{\xi}_1 \leq \boldsymbol{\xi}_2$ with $\boldsymbol{\xi}_1 \neq \boldsymbol{\xi}_2$ then $\rho(\boldsymbol{\xi}_2) < \rho(\boldsymbol{\xi}_1)$. Now $\rho(\mathbf{0}) = R_0$, and so if $R_0 \leq 1$ then $\rho(\boldsymbol{\xi}) < 1$ for every non-zero $\boldsymbol{\xi} \geq \mathbf{0}$. Consequently for $R_0 \leq 1$ the disease-free equilibrium provides the only solution of equations (19).

References

[1] D. Breda, O. Diekmann, W.F. de Grallf, A. Pugliese and R. Vermiglio, 2012. On the formulation of epidemic models (an appraisal of Kermack and McKendrick). J. Biol. Dynam. 6, suppl. 2, 103–117.

[2] E. Brooks-Pollock, T. Cohen and M. Murray, 2010. The impact of realistic age structure in simple models of Tuberculosis transmission. PLoS ONE 5(1), e8479.

[3] D. Clancy, 1999. Outcomes of epidemic models with general infection and removal rate functions at certain stopping times. J. Appl. Probab. 36, 799-813.

[4] D. Clancy and C.J. Pearce, 2013. The effect of population heterogeneities upon spread of infection. J. Math. Biol. 67, 963–987.

[5] O. Diekmann, H. Heesterbeek and H. Metz, 1995. The legacy of Kermack and McKendrick. In *Epidemic Models: Their Structure and Relation to Data*, editor D. Mollison, Cambridge University Press, UK.

[6] O. Diekmann and R. Montijn, 1982. Prelude to Hopf bifurcation in an epidemic model: analysis of a characteristic equation associated with a nonlinear Volterra integral equation. J. Math. Biol. 14, 117–127.

[7] K. Dietz and D. Schenzle, 1985. Proportionate mixing models for age-dependent infection transmission. J. Math. Biol. 22, 117–120.

[8] C.P. Farrington, M.N. Kanaan and N.J. Gay,2001. Estimation of the basic reproduction number for infectious diseases from age-stratified serological survey data. Appl. Statist. 50, 251–292.

[9] Z. Feng, W. Huang and C. Castillo-Chavez, 2005. Global behaviour of a multi-group SIS epidemic model with age structure. J. Differential Equations 218, 292–324.

[10] Z. Feng and H.R. Thieme, 2000. Endemic models with arbitrarily distributed periods of infection I: fundamental properties of the model. SIAM J. Appl. Math. 61, 803-833.

[11] H.W. Hethcote and H.R. Thieme, 1985. Stability of the endemic equilibrium in epidemic models with subpopulations. Math. Biosci. 75, 205–227.

[12] H.W. Hethcote and D.W. Tudor, 1980. Integral equation models for endemic infectious diseases. J. Math. Biol. 9, 37–47.

[13] F. Hoppensteadt, 1974. An age dependent epidemic model. J. Franklin Inst. 297, 325–333.

[14] H. Inaba, 1990. Threshold and stability results for an age-structured epidemic model. J. Math. Biol. 28, 411–434.

[15] H. Inaba, 2006. Endemic threshold results in an age-duration-structured population model for HIV infection. Math. Biosci. 201, 15–47.

[16] H. Inaba and H. Nishiura, 2008. The basic reproduction number of an infectious disease in a stable population: the impact of population growth rate on the eradication threshold. Math. Model. Nat. Phenom. 3, 194–228.

[17] W.O. Kermack and A.G. McKendrick, 1927. A contribution to the mathematical theory of epidemics. Proc. R. Soc. Lond. Ser. A 115, 700–721.

[18] W.O. Kermack and A.G. McKendrick, 1932. Contributions to the mathematical theory of epidemics II – the problem of endemicity. Proc. R. Soc. Lond. Ser. A 138, 55–83.

[19] W.O. Kermack and A.G. McKendrick, 1933. Contributions to the mathematical theory of epidemics III – further studies of the problem of endemicity. Proc. R. Soc. Lond. Ser. A 141, 94–122.

[20] I. Krishnarajah, G. Marion and G. Gibson, 2007. Novel bivariate moment-closure approximations. Math. Biosci. 208, 621–643.

[21] A. Lajmanovich and J.A. Yorke, 1976. A deterministic model for gonorrhea in a nonhomogeneous population. Math Biosci. 28, 221–236.

[22] M.Y. Li, Z. Shuai and C. Wang, 2010. Global stability of multi-group epidemic models with distributed delays. J. Math. Anal. Applic. 361, 38–47.

[23] J. Ma and D.J.D. Earn, 2006. Generality of the final size formula for an epidemic of a newly invading infectious disease. Bull. Math. Biol. 68, 679–702.

[24] J.C. Miller, 2012. A note on the derivation of epidemic final sizes. Bull. Math. Biol. 74, 2125–2141.

[25] D. Mollison, 1995. The structure of epidemic models. In *Epidemic Models: Their Structure and Relation to Data*, editor D. Mollison, Cambridge University Press, UK.

[26] I. Nåsell, 1999. On the time to extinction in recurrent epidemics. J. Roy. Statist. Soc. B 61, 309–330.

[27] J. Radcliffe and L. Rass, 1984. The spatial spread and final size of the deterministic non-reducible n-type epidemic. J. Math. Biol. 19, 309–327.

[28] J. Radcliffe and L. Rass, 2003. Spatial Deterministic Epidemics. Mathematical Surveys and Monographs, vol. 102, Amer. Math. Soc.

[29] E. Seneta, 1973. *Non-negative Matrices.* Unwin, London.

[30] H.R. Thieme, 2003. Mathematics in Population Biology. Princeton University Press.

[31] H.R. Thieme, 2011. Global stability of the endemic equilibrium in inifinte dimensions: Lyapunov functions and positive operators. J. Diff. Equations 250, 3772–3801.

[32] G.H. Weiss and M. Dishon, 1971. On the asymptotic behaviour of the stochastic and deterministic models of an epidemic. Math. Biosci. 11, 261–265.

[33] D. Yue and J. Cao, 2001. The NBUL class of life distribution and replacement policy comparisons. Naval Res. Logistics 48, 578–591.

[34] National Life Tables. Office for National Statistics, UK. http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2011-2013/rft-uk.xls