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CALCULATION OF $\mathcal{R}_0$ FOR AGE-OF-INFECTION MODELS

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Abstract. We consider age-of-infection epidemic models to describe multiple-stage epidemic models, including treatment. We derive an expression for the basic reproduction number $\mathcal{R}_0$ in terms of the distributions of periods of stay in the various compartments. We find that, in the model without treatment, $\mathcal{R}_0$ depends only on the mean periods in compartments, and not on the form of the distributions. In treatment models, $\mathcal{R}_0$ depends on the form of the distributions of stay in infective compartments from which members are removed for treatment, but the dependence for treatment compartments is only on the mean stay in the compartments. The results give a considerable simplification in the calculation of the basic reproduction number.

1. **Introduction.** The basic reproduction number is a central concept in the study of disease transmission models. It indicates a threshold for both epidemic models and endemic situations. Diekmann, Heesterbeek and Metz introduced the next-generation operator to give a precise definition of the basic reproduction number [6]. The next-generation operator is a positive linear operator that describes how many secondary cases arise from an infective individual with a general infectivity distribution, and how such cases are distributed over different susceptible classes. $\mathcal{R}_0$ is defined as the spectral radius of this operator [6].

Van den Driessche and Watmough [18] did the same for models in the special case of exponentially distributed periods in each compartment, so that the models are systems of ordinary differential equations. The next-generation operator is described in terms of matrices, and in this case $\mathcal{R}_0$ is the largest eigenvalue of a matrix that describes the next-generation operator.

However, in many situations, models with exponential distributions are poor descriptions of actual disease outbreaks [8, 9, 14], and the calculation of reproduction numbers for general distributions is an important problem. The purpose of this

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paper is to show how to calculate the basic reproduction number for a general class of disease transmission models, namely age-of-infection models. The calculation of the basic reproduction number is applicable to both epidemic models (without demographics) and endemic situations where natural births and deaths are included. In the endemic case, births are not relevant to the calculation of the basic reproduction number but natural deaths are included in the rates of passage between compartments. For simplicity, we confine our attention to epidemic models.

For epidemic models, there is a final size relation connecting the basic reproduction number with the final size of the epidemic [1, 2, 4, 11, 17]. However, quantities such as the peak epidemic size, the duration of the epidemic, and the initial growth rate are not determined by the final size relation and may depend on the nature of the distribution. In addition, it has been noted that in models including treatment, such as quarantine, the basic reproduction number depends on the nature of the infective period distribution and not only on the mean period [7, 8].

2. **Age-of-infection models.** The Kermack-McKendrick age-of-infection SIR epidemic model [4, 15] is a very general compartmental epidemic model. It is formulated in terms of $S(t)$, the number of susceptible members of the population, $\varphi(t)$, the total infectivity of infected members of the population, and $N(t)$, the total population size, but the total infectivity may include contributions from multiple compartments including exposed, asymptomatic and treated compartments. In addition, the model allows arbitrary distributions of time spent in compartments.

EXAMPLE 2.1. *The simplest example is an SIR epidemic model in a population of size N with mass action incidence and a single infective stage in which there are no disease deaths with $P(\tau)$ the fraction of individuals who are still infective a time τ after having become infected. The model is*

$$\begin{aligned} S' &= -\beta S(t)I(t) \\ I(t) &= \int_0^\infty [-S'(t-\tau)]P(\tau)\,d\tau. \end{aligned}$$

In this case, $\varphi(t) = I(t)$ and the method of [6] *gives*

$$\mathcal{R}_0 = \beta N \int_0^\infty P(\tau)\,d\tau.$$

We may see this directly since a single infective causes βN new infections in unit time and $\int_0^\infty P(\tau)d\tau$ is the mean infective period.

Compartmental models, such as the above SIR model, influenza models, and other multiple infective or treatment stage models, can all be unified as age-of-infection models with general distributions of time spent in compartments. Any compartmental model with a sequence of stages can be written as an age-of-infection model. For example, SARS can be viewed as an example of a general class of epidemic diseases for which no treatments were available; only quarantine of those who were suspected of having been infected, and isolation of the diagnosed infectives were the available control measures. A model for SARS with quarantined and isolated compartments can be incorporated into the age of infection structure

Age-of-infection models are general enough to encompass infectious disease models with multiple compartments and with arbitrary distributions of stay in compartments. These are models in which the infectivity of an individual depends on

the time since becoming infected (that is, the time since the initial infection, not the time in the particular stage). Some classes of examples are given in Sections 3 and 4. For this reason, age-of-infection models have been gaining more interest as a real generalization [8, 9, 11, 14].

If there are no disease deaths, the total population size N is constant and $\beta(N)$ is a constant β. In this case, the general age-of-infection epidemic model is

$$\begin{aligned} S'(t) &= -\beta S(t)\varphi(t) \\ \varphi(t) &= \int_0^\infty [-S'(t-\tau)]A(\tau), d\tau. \end{aligned} \tag{1}$$

Here, $A(\tau) = \pi(\tau)B(\tau)$, with $B(\tau)$ representing the fraction of infected individuals still infected at infection age τ and $\pi(\tau)$ representing the infectivity of an infected individual at infection age τ. Thus $A(\tau)$ is the mean infectivity of an individual τ time units after having been infected. In general, the contact rate $\beta(N)$ is a saturating function of total population size $N = S + I + R$. Using the method of Diekmann et al [6], we obtain

$$\mathcal{R}_0 = \beta N \int_0^\infty A(\tau)\, d\tau.$$

However, calculation of the basic reproduction number requires the calculation of $\int_0^\infty A(\tau)\, d\tau$, which presents more difficulty in models with non-exponential distributions.

If the total population size is not constant, the age-of-infection model consists of the pair of equations (1), with the constant β replaced by the function $\beta(N(t))$ together with an equation for $N(t)$.

The number of infective members of the population at time t in the model is given by

$$\begin{aligned} I(t) &= \int_0^\infty \beta(N(t-\tau))S(t-\tau)\varphi(t-\tau)B(\tau)\, d\tau \\ &= \int_{-\infty}^t \beta(N(s))S(s)\varphi(s)B(t-s)\, ds. \end{aligned}$$

To find the rate of departure from the infected class, we differentiate $I(t)$ under the integral sign:

$$I'(t) = \beta(N(t))S(t)\varphi(t) + \int_{-\infty}^t \beta(N(s))S(s)\varphi(s)B'(t-s)\, ds.$$

The first term is the rate of new infections, and the second term is the negative of the rate of recoveries and disease deaths. If a fraction f of infectives recovers from infection while the complementary fraction $(1-f)$ dies of disease,

$$\begin{aligned} N'(t) &= (1-f)\int_{-\infty}^t \beta(N(s))S(s)\varphi(s)B'(t-s)\, ds \\ &= (1-f)\int_{-\infty}^t [-S'(s)]B'(t-s)\, ds. \end{aligned}$$

Thus the general age-of-infection model is

$$\begin{aligned} S'(t) &= -\beta(N(t))S(t)\varphi(t) \\ \varphi(t) &= \int_0^\infty [-S'(t-\tau)]A(\tau), d\tau \\ N'(t) &= (1-f)\int_0^\infty [-S'(t-\tau)]B'(\tau)\, d\tau. \end{aligned}$$

Since the calculation of the basic reproduction number is relative to the initial state and is not affected by disease deaths, the same calculation as was used for (1) gives

$$\mathcal{R}_0 = \beta N \int_0^\infty A(\tau)\, d\tau.$$

3. **Staged progression models.** In epidemic models there is often a sequence of stages of different lengths and infectivities, known as staged progression models [13], where individuals pass from one stage to the next. The simplest example is an $SEIR$ model with an exposed stage, possibly with some infectivity, before the development of symptoms. To describe such a model, we suppose that there is a finite sequence of n infected stages $I_1(t), \ldots, I_n(t)$, with relative infectivity parameters $\varepsilon_1, \ldots, \varepsilon_n$, and infectivity distributions $P_1(\tau), \ldots, P_n(\tau)$. Figure 1 shows the flow chart for such a model with two infected stages. It should be noted that $P_i(\tau)$ represents the fraction of members who were infected initially τ time units earlier who are in the stage I_i.

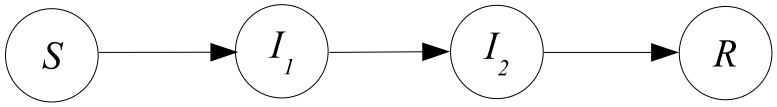

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FIGURE 1. SI_1I_2R model flowchart

The total infectivity at time t is the sum of the infectivities of each infected compartment,

$$\varphi(t) = \sum_{i=1}^{n} \varepsilon_i I_i(t).$$

The general age-of-infection model with a sequence of infected stages is

$$\begin{aligned} S'(t) &= -\beta S(t)\varphi(t) \\ \varphi(t) &= \int_0^\infty [-S'(t-\tau)] \sum_{i=1}^{n} \varepsilon_i A_i(\tau)\, d\tau. \end{aligned}$$

Then

$$\mathcal{R}_0 = \beta N \sum_{i=1}^{n} \varepsilon_i \int_0^\infty A_i(\tau) d\tau,$$

and to calculate $\mathcal{R}_0$ we need to find

$$\int_0^\infty A_i(\tau)\, d\tau.$$

For the first infective stage we have

$$\begin{aligned} I_1(t) &= \int_0^\infty [-S'(t-\tau)]P_1(\tau)\,d\tau \\ &= \int_{-\infty}^t [-S'(u)]P_1(t-u)\,du. \end{aligned}$$

Thus $A_1(\tau) = P_1(\tau)$. Differentiating, we obtain

$$I_1'(t) = -S'(t) + \int_0^\infty [-S'(t-\tau)]P_1'(\tau)\,d\tau.$$

Therefore,

$$\begin{aligned} I_2(t) &= \int_0^\infty \left[\int_0^\infty [S'(t-\tau-\sigma)]P_1'(\tau)\,d\tau\right] P_2(\sigma)\,d\sigma \\ &= \int_0^\infty \left[\int_\sigma^\infty S'(t-u)P_1'(u-\sigma)\,du\right] P_2(\sigma)\,d\sigma \\ &= \int_0^\infty [-S'(t-u)] \int_0^u [-P_1'(u-\sigma)]P_2(\sigma)\,d\sigma\,du \\ &= \int_0^\infty [-S'(t-u)]A_2(u)\,du, \end{aligned}$$

with

$$A_2(u) = \int_0^u [-P_1'(u-\sigma)]P_2(\sigma)\,d\sigma.$$

We have

$$\begin{aligned} \int_0^\infty A_2(u)du &= \int_0^\infty \int_0^u -P_1'(u-\sigma)P_2(\sigma)\,d\sigma\,du \\ &= \int_0^\infty \int_0^\infty -P_1'(\tau)\,d\tau\,P_2(\sigma)\,d\sigma \\ &= \int_0^\infty P_2(\sigma)d\sigma. \end{aligned}$$

We see that, by induction, this holds true for every infective stage. The integral of the kernel will be the sum of the integrals of the infective distribution, where each integral is weighted by the infectivity of each distribution. Thus, the reproduction number is simply

$$\mathcal{R}_0 = \beta N \sum_{i=1}^n \varepsilon_i \int_0^\infty P_i(\tau)\,d\tau.$$

We have established the following result:

THEOREM 3.1. *The basic reproduction number $\mathcal{R}_0$ depends only on the mean period in each infective stage, regardless of its distribution. General epidemic models without treatment behave the same as models with exponentially distributed periods.*

There is no difficulty in extending the approach of this section to models, in which at the end of a stage individuals may proceed to one of two stages, such as the influenza model of [1, 2]. In this model, there is a latent period after which a fraction p of latent individuals L proceeds to an infective stage I, while the remaining fraction $(1-p)$ proceeds to an asymptomatic stage A, with infectivity reduced by a factor δ and a different period $1/\eta$. A flow chart is shown in Figure 2.

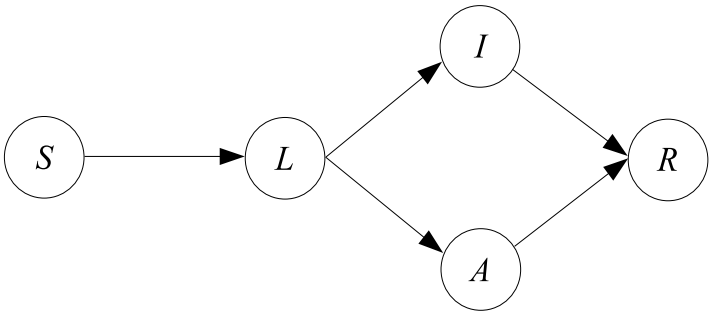

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FIGURE 2. Influenza model flowchart

With exponentially distributed latent, infective and asymptomatic periods, the model is

$$\begin{aligned} S' &= -\beta S[I + \delta A] \\ L' &= \beta S[I + \delta A] - \kappa L \\ I' &= p\kappa L - \alpha I \\ A' &= (1-p)\kappa L - \eta A \end{aligned} \tag{2}$$

and

$$\mathcal{R}_0 = \beta N \left[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta} \right]$$

According to Theorem 3.1, for a model with the same mean periods the basic reproduction number has the same value.

The model (2) is an example of a differential infectivity model. In such models, also used in the study of HIV/AIDS [13], individuals enter a specific group when they become infected and stay in that group over the course of the infection. Different groups may have different parameter values. For example, for influenza infective and asymptomatic members may have different infectivities and different periods of stay in the respective stages. Theorem 3.1 is applicable to such models, and shows that the basic reproduction number depends on the mean stay in each compartment, not on the specific form of the distribution.

In the next section, we examine treatment models that include the rate at which members are removed during a stage and transferred to a treatment stage. Such models differ from staged progression models in that members are removed from a compartment during their stay in the compartment rather than proceeding at the end of their stay in the compartment.

4. **Treatment models as age-of-infection models.** We now take the above age-of-infection model and include a finite sequence of n treatment stages with different treatment distributions. Treatment may be a medical intervention, isolation, or changes in behavior by infectives to reduce contacts. In [12], behavior change is modeled by removal from an infective compartment at a rate that depends on time since infection. We assume a constant removal rate in each infective compartment, which is less general but allows for a simpler model.

We begin with a simple example that has one infective stage and one treatment stage, both with exponentially distributed periods.

4.1. **A simple treatment model.** Consider a treatment model in which a fraction γ per unit time of infectives are selected for treatment, and the treatment reduces infectivity by a fraction δ. Suppose that the rate of removal from infective class is η. The $SITR$ model, where T is the treatment class, is given by

$$\begin{aligned} S' &= -\beta(N)S[I+\delta T] \\ I' &= \beta(N)S[I+\delta T]-(\alpha+\gamma)I \\ T' &= \gamma I-\eta T \\ N' &= -(1-f)\alpha I-(1-f_T)\eta T. \end{aligned} \tag{3}$$

A flow chart is shown in Figure 3.

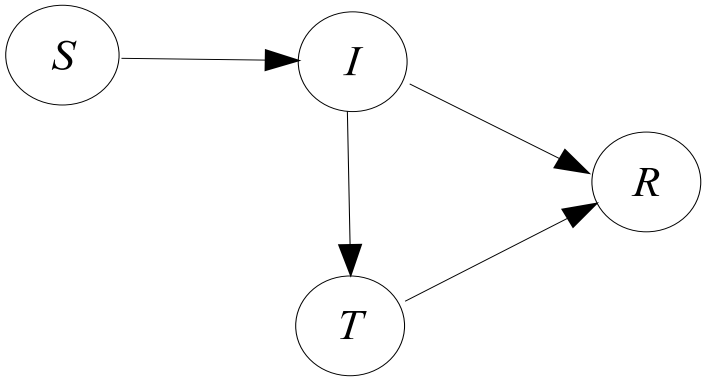

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FIGURE 3. Flow chart for the $SITR$ model

Then $\mathcal{R}_0$, calculated by the method of [18], is

$$\mathcal{R}_0 = \frac{\beta N}{\alpha+\gamma}\left[1+\frac{\delta\gamma}{\eta}\right]. \tag{4}$$

While both the flowcharts shown in Figure 2 and Figure 3 contain bifurcations, there is an important difference. In Figure 2 the splitting between the compartments I and A comes at the end of the stay in the compartment L, while in Figure 3, some individuals are removed from the compartment I during their stay and are sent to the compartment T, while others remain in the compartment I until the end of their stay and then proceed to the compartment R.

We now extend this to an age-of-infection model with general infective and treatment stage distributions. Assume that the distribution of infective periods is given by $P(\tau)$, and the distribution of periods in treatment is given by $Q(\tau)$. Then the $SITR$ model becomes

$$\begin{aligned} S'(t) &= -\beta(N)S(t)[I(t)+\delta T(t)] \\ I(t) &= \int_0^\infty [-S'(t-\tau)]e^{-\gamma\tau}P(\tau)\,d\tau \\ T(t) &= \int_0^\infty \gamma I(t-\sigma)Q(\sigma)\,d\sigma. \end{aligned} \tag{5}$$

Then

$$\varphi(t) = I(t) + \delta T(t).$$

We see from the second equation of (5) that the contribution to $\mathcal{R}_0$ from $I(t)$ is

$$\beta N \int_0^\infty e^{-\gamma\tau} P(\tau)\, d\tau.$$

To find the contribution from $T(t)$, we need to write the equation in the form

$$T(t) = \int_0^\infty [-S'(t-\tau)] Y(\tau)\, d\tau,$$

so that the contribution from $T(t)$ would be

$$\delta\beta N \int_0^\infty Y(\tau)\, d\tau$$

and we would obtain

$$\mathcal{R}_0 = \beta N \left[\int_0^\infty e^{-\gamma\tau} P(\tau)\, d\tau + \delta \int_0^\infty Y(\tau)\, d\tau \right].$$

We rewrite $T(t)$ to find $Y(\tau)$, obtaining

$$\begin{aligned}
T(t) &= \int_0^\infty \gamma I(t-\sigma) Q(\sigma)\, d\sigma \\
&= \int_0^\infty \gamma \left[\int_0^\infty [-S'(t-u-\sigma)] e^{-\gamma u} P(u)\, du \right] Q(\sigma)\, d\sigma \\
&= \int_0^\infty \gamma \left[\int_\sigma^\infty [-S'(t-\tau)] e^{-\gamma(\tau-\sigma)} P(\tau-\sigma)\, d\tau \right] Q(\sigma)\, d\sigma \\
&= \int_0^\infty \gamma [-S'(t-\tau)] \int_0^\tau e^{-\gamma(\tau-\sigma)} P(\tau-\sigma) Q(\sigma)\, d\sigma\, d\tau \\
&= \int_0^\infty [-S'(t-\tau)] B(\tau)\, d\tau,
\end{aligned}$$

with

$$B(\tau) = \gamma \int_0^\tau e^{-\gamma(\tau-\sigma)} P(\tau-\sigma) Q(\sigma)\, d\sigma.$$

Now

$$\begin{aligned}
\int_0^\infty B(\tau)\, d\tau &= \gamma \int_0^\infty \int_0^\tau e^{-\gamma(\tau-\sigma)} P(\tau-\sigma) Q(\sigma)\, d\sigma\, d\tau \\
&= \gamma \int_0^\infty \int_\sigma^\infty e^{-\gamma(\tau-\sigma)} P(\tau-\sigma)\, d\tau\, Q(\sigma)\, d\sigma \qquad (6) \\
&= \gamma \int_0^\infty \int_0^\infty e^{-\gamma\omega} P(\omega)\, d\omega\, Q(v)\, dv \\
&= \gamma \int_0^\infty e^{-\gamma\omega} P(\omega)\, d\omega \int_0^\infty Q(\sigma)\, d\sigma.
\end{aligned}$$

Thus,

$$\begin{aligned}\mathcal{R}_0 &= \beta N \int_0^\infty [A(\tau) + \delta B(\tau)]\, d\tau \\ &= \beta N \left[\int_0^\infty e^{-\gamma\tau} P(\tau)\, d\tau + \delta\gamma \int_0^\infty e^{-\gamma\tau} P(\tau)\, d\tau \int_0^\infty Q(\tau)\, d\tau\right] \qquad (7)\\ &= \beta N \int_0^\infty e^{-\gamma\tau} P(\tau)\, d\tau \left[1 + \delta\gamma \int_0^\infty Q(\tau)\, d\tau\right].\end{aligned}$$

With exponentially distributed infective and treatment periods, $P(\tau) = e^{-\alpha\tau}$, $Q(\tau) = e^{-\eta\tau}$ we use (7) to calculate $\mathcal{R}_0$, obtaining

$$\begin{aligned}\mathcal{R}_0 &= \beta N \int_0^\infty e^{-(\alpha+\gamma)\tau}\, d\tau \left[1 + \delta\gamma \int_0^\infty e^{-\eta\tau}\, d\tau\right] \\ &= \frac{\beta N}{\alpha+\gamma}\left[1 + \frac{\delta\gamma}{\eta}\right],\end{aligned}$$

the same result as (4).

An arbitrary choice of treatment period distribution with mean $1/\eta$ does not affect the quantity $\mathcal{R}_0$, but different infective period distributions may have a significant effect. For example, let us take $\gamma = 1$ and assume the mean infective period is 1. Then, with an exponential distribution, $P(\tau) = e^{-\tau}$,

$$\int_0^\infty e^{-\tau} P(\tau)\, d\tau = \int_0^\infty e^{-2\tau}\, d\tau = \frac{1}{2}.$$

With an infective period of fixed length 1,

$$\int_0^\infty e^{-\tau} P(\tau)\, d\tau = \int_0^1 e^{-\tau}\, d\tau = (1 - e^{-1}) = 0.632.$$

Thus a model with an infective period of fixed length would lead to a basic reproduction number more than 25% higher than a model with an exponentially distributed infective period that has the same mean.

4.2. **Multi-stage treatment models.** We begin by considering a model with two infective stages I_1, I_2 and two treatment stages T_1, T_2. A fraction γ_1 of members of I_1 is transferred to T_1 in unit time and a fraction γ_2 of members of I_2 is transferred to T_2 in unit time. Treated individuals pass from T_1 to T_2. We assume distributions P_i in I_i and Q_i in T_i, and we assume relative infectivity parameters ε_i in the infective stages and δ_i in the treatment stages. Then

$$S'(t) = -\beta S(t)\varphi(t),$$

with

$$\varphi(t) = \sum_{i=1}^{2} [\varepsilon_i I_i + \delta_i T_i].$$

A flow chart is shown in Figure 4.

We have

$$\begin{aligned}I_1(t) &= \int_0^\infty [-S'(t-\tau)] e^{-\gamma_1\tau} P_1(\tau)\, d\tau \\ &= \int_0^\infty [-S'(t-\tau)] A_1(\tau)\, d\tau,\end{aligned}$$

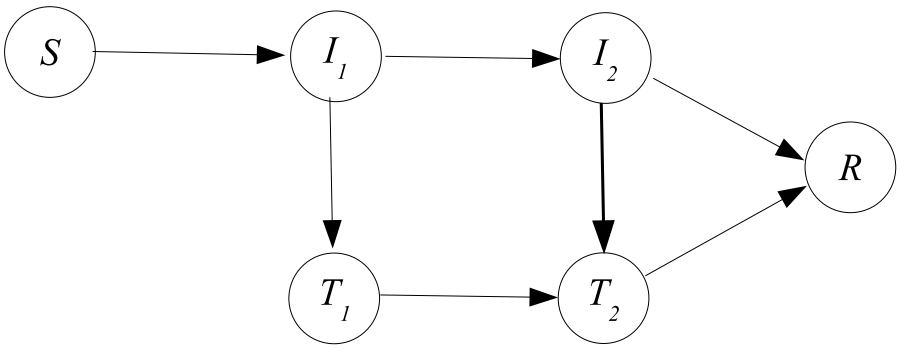

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FIGURE 4. A two-stage treatment model flow chart

with

$$\begin{aligned} A_1(\tau) &= e^{-\gamma_1\tau}P_1(\tau) \\ \int_0^\infty A_1(\tau)\,d\tau &= \int_0^\infty e^{-\gamma_1\tau}P_1(\tau)\,d\tau. \end{aligned} \tag{8}$$

Also,

$$\begin{aligned} T_1(t) &= \int_0^\infty \gamma_1 I_1(t-\sigma)Q_1(\sigma)\,d\sigma \\ &= \int_0^\infty \gamma_1[-S'(t-\tau)]\int_0^\tau e^{-\gamma_1(\tau-\sigma)}P_1(\tau-\sigma)Q_1(\sigma)\,d\sigma\,d\tau \\ &= \int_0^\infty [-S'(t-\tau)]B_1(\tau)\,d\tau, \end{aligned}$$

with, using the same calculation as in (6),

$$\begin{aligned} B_1(\tau) &= \int_0^\tau e^{-\gamma_1(\tau-\sigma)}P_1(\tau-\sigma)Q_1(\sigma)\,d\sigma \\ \int_0^\infty B_1(\tau)\,d\tau &= \gamma_1\int_0^\infty e^{-\gamma_1\omega}P_1(\omega)\,d\omega\int_0^\infty Q_1(\sigma)\,d\sigma. \end{aligned} \tag{9}$$

Again, to find the input from I_1 to I_2, we differentiate I_1, obtaining

$$\begin{aligned} I_2(t) &= -\int_0^\infty\int_0^\infty [-S'(t-\tau-\sigma)]e^{-\gamma_1\tau}P_1'(\tau)\,d\tau\,e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma \\ &= -\int_0^\infty [-S'(t-u)]\int_0^u e^{-\gamma_1(u-\sigma)}P_1'(u-\sigma)e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma\,du \\ &= \int_0^\infty [-S'(t-u)]A_2(u)\,du, \end{aligned} \tag{10}$$

with

$$A_2(u) = -\int_0^u e^{-\gamma_1(u-\sigma)}P_1'(u-\sigma)e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma.$$

Then, using (10) and integration by parts, we have

$$\begin{aligned}\int_0^\infty A_2(\tau)\,d\tau &= -\int_0^\infty \int_0^\tau e^{-\gamma_1(\tau-\sigma)}P_1'(\tau-\sigma)e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma\,d\tau \\ &= -\int_0^\infty e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma\int_0^\infty e^{-\gamma_1\omega}P_1'(\omega)\,d\omega \qquad (11)\\ &= \int_0^\infty e^{-\gamma_2\sigma}P_2(\sigma)\,d\sigma\left[1-\gamma_1\int_0^\infty e^{-\gamma_1\omega}P_1(\omega)\,d\omega\right].\end{aligned}$$

The second treatment stage, T_2, has two inputs: a fraction of people who come from I_2 and a fraction of people who continue treatment from T_1. We have

$$\begin{aligned}T_2(t) &= \int_0^\infty \gamma_2 I_2(t-\sigma)Q_2(\sigma)\,d\sigma \qquad (12)\\ &- \int_0^\infty \gamma_1\int_{-\infty}^t I_1(u)Q'(t-u-\sigma)\,du\,Q_2(\sigma)\,d\sigma.\end{aligned}$$

For simplicity, we let

$$B_2(\tau) = B_{2I}(\tau) + B_{2T}(\tau),$$

with $B_{2I}(\tau)$ coming from the input of I_2, and $B_{2T}(\tau)$, coming from the input of T_1.

To find B_{2I}, we rewrite the first term of(12), We have

$$\begin{aligned}\int_0^\infty \gamma_2 I_2(t-\sigma)Q_2(\sigma)\,d\sigma &= \int_0^\infty [-S'(t-\tau)]\gamma_2\int_0^\tau A_2(\tau-\sigma)Q_2(\sigma)\,d\sigma\,d\tau\\ &= \int_0^\infty -S'(t-\tau)B_{2I}(\tau)\,d\tau.\end{aligned}$$

Now

$$\begin{aligned}\int_0^\infty B_{2I}(\tau)\,d\tau &= \int_0^\infty \gamma_2\int_0^\tau A_2(t-\sigma)Q_2(\sigma)\,d\sigma\,d\tau\\ &= \gamma_2\int_0^\infty Q_2(\sigma)\,d\sigma\int_0^\infty A_2(v)\,dv. \qquad (13)\end{aligned}$$

To find B_{2T}, we rewrite the second term of (12),

$$\begin{aligned}&\int_0^\infty\int_{-\infty}^t -\gamma_1 I_1(u)Q_1'(t-u-\sigma)\,du\,Q_2(\sigma)\,d\sigma\\ =\ &\int_0^\infty\int_0^\infty -\gamma_1 I_1(t-v-\sigma)Q_1'(v)\,dv\,Q_2(\sigma)\,d\sigma\\ =\ &\int_0^\infty \gamma_1\int_\sigma^\infty\int_s^\infty [S'(t-\omega)A_1(\omega-s)]\,d\omega\,Q_1'(s-\sigma)\,ds\,Q_2(\sigma)\,d\sigma\\ =\ &\int_0^\infty S'(t-\omega)\gamma_1\int_0^\omega\int_0^\omega A_1(\omega-s)\,Q_1'(s-\sigma)\,ds\,Q_2(\sigma)\,d\sigma\,d\omega\\ =\ &\int_0^\infty [-S'(t-\omega)]B_{2T}(\omega)\,d\omega,\end{aligned}$$

with

$$B_{2T}(\omega) = -\gamma_1\int_0^\omega A_1(\omega-s)\,Q_1'(s-\sigma)\,ds\,Q_2(\sigma)\,d\sigma.$$

Now,

$$\begin{aligned}\int_0^\infty B_{2T}(\tau)\,d\tau &= -\gamma_1\int_0^\infty\int_0^\tau\int_0^\tau A_1(\tau-s)\,Q_1'(s-\sigma)\,ds\,Q_2(\sigma)\,d\sigma\,d\tau\\ &= -\int_0^\infty \gamma_1 Q_2(\sigma)\int_\sigma^\infty Q_1'(s-\sigma)\int_s^\infty A_1(\tau-s)\,d\tau\,ds\,d\sigma\\ &= \gamma_1\int_0^\infty Q_2(\sigma)\,d\sigma\int_0^\infty A_1(v)\,dv. \qquad (14)\end{aligned}$$

Combining (13) and (14), we obtain

$$\int_0^\infty B_2(\tau)\,d\tau = \int_0^\infty Q_2(\tau)\,d\tau\left[\gamma_2\int_0^\infty A_2(\tau)\,d\tau+\gamma_1\int_0^\infty A_1(\tau)\,d\tau\right]. \qquad (15)$$

We obtain the basic reproduction number for the two-stage treatment model,

$$\mathcal{R}_0 = \beta N\sum_{i=1}^{2}\left[\varepsilon_i\int_0^\infty A_i(\tau)\,d\tau+\delta_i\int_0^\infty B_i(\tau)\,d\tau\right], \qquad (16)$$

with the integrals given by (8),(9), (11) and (15).

For a treatment model with n infective and treatment stages, we assume distributions P_i in I_i and Q_i in T_i, and we assume relative infectivity parameters ε_i in the infective stages and δ_i in the treatment stages. Then

$$S'(t) = \beta S(t)\varphi(t),$$

with

$$\varphi(t) = \sum_{i=1}^{n}[\varepsilon_i I_i+\delta_i T_i].$$

The kernels for both the infective and treatment compartments are formed in the same manner as $A_2(\tau)$ and $B_2(\tau)$ in the two-stage model. Using induction, we see that the basic reproduction number for an age-of-infection model with n infective and treatment stages is given by

$$\mathcal{R}_0 = \beta N\sum_{i=1}^{n}\left[\int_0^\infty \varepsilon_i A_i(\tau)\,d\tau+\delta_i\int_0^\infty B_i(\tau)\,d\tau\right], \qquad (17)$$

with

$$\int_0^\infty A_i(\tau)\,d\tau = \int_0^\infty e^{-\gamma_i\tau}P_i(\tau)\,d\tau\left[1-\int_0^\infty \gamma_{i-1}e^{-\gamma_{i-1}\tau}P_{i-1}(\tau)\,d\tau\right], \qquad (18)$$

and

$$\int_0^\infty B_i(\tau)\,d\tau = \int_0^\infty Q_i(\tau)\,d\tau\left[\int_0^\infty \gamma_i A_i(\tau)\,d\tau+\int_0^\infty \gamma_{i-1}A_{i-1}(\tau)\,d\tau\right], \qquad (19)$$

taking $\gamma_0 = 0$.

The contributions to $\mathcal{R}_0$ of treatment stages depend only on the mean periods of the stages, not on the form of the distribution. The contributions of infective stages, beginning with the first stage from which members are removed for treatment, depend on the form of the distributions as well as the mean periods of these stages.

We have established the following result.

THEOREM 4.1. *For the general age-of-infection treatment model, the basic reproduction number is given by* (17) *with the integrals given recursively by* (18) *and* (19).

This result simplifies the calculation of the basic reproduction number for an age-of-infection treatment model considerably as it eliminates the need to explicitly calculate the age-of-infection kernel $A(\tau)$.

5. **Example: The gamma distribution.** There is ample evidence that exponential distributions of stay in compartments are much less realistic than gamma distributions [7, 8, 16, 19]. A gamma distribution $P(\tau)$ with parameter n and period $1/\alpha$ can be represented as a sequence of n exponential distributions $P_i(\tau)$ with period $1/n\alpha$. Then

$$\begin{aligned} \int_0^\infty P(\tau)d\tau &= \sum_{i=1}^{i=n} \int_0^\infty P_i(\tau)d\tau = \frac{1}{\alpha} \\ \int_0^\infty e^{-\gamma\tau}P(\tau)d\tau &= \sum_{i=1}^{i=n} \int_0^\infty e^{-\gamma\tau}P_i(\tau)d\tau \qquad (20) \\ &= \sum_{i=1}^{i=n} \int_0^\infty e^{-\gamma\tau}e^{-\alpha n\tau}d\tau = \frac{1}{\alpha+\frac{\gamma}{n}}. \end{aligned}$$

The calculation of $\mathcal{R}_0$ for a treatment model requires calculation of integrals of the form

$$\int_0^\infty e^{-\gamma\tau}P(\tau)d\tau.$$

This integral can be calculated explicitly in terms of the mean period and the parameter if $P(\tau)$ is given by a gamma distribution. The value of the parameter depends on the disease being modeled.

For example, for a treatment model (5) if $P(\tau)$ is a gamma distribution with parameter n and $Q(\tau)$ is arbitrary, we see from (7), (20) that

$$\mathcal{R}_0 = \beta N \frac{1}{\alpha+\frac{\gamma}{n}}[1+\delta\gamma\int_0^\infty Q(\tau)\,d\tau].$$

The value of

$$\frac{1}{\alpha+\frac{\gamma}{n}}$$

is obviously an increasing function of the parameter n. The limiting case as $n \to \infty$ of a gamma distribution is a distribution

$$P(t) = 1(0 \le t \le \frac{1}{\alpha}), \quad P(t) = 0(t > \frac{1}{\alpha}),$$

for which

$$\int_0^\infty e^{-\gamma t}P(t)dt = \frac{1-e^{-\gamma/\alpha}}{\gamma}.$$

Then

$$\frac{1}{\alpha+\frac{\gamma}{n}} < \frac{1-e^{-\gamma/\alpha}}{\gamma}. \qquad (21)$$

To prove (21), we let $\gamma = n\alpha x$. Then (21) is equivalent to

$$\frac{x}{1+x} < \frac{1-e^{-nx}}{n}.$$

The function $(1-e^{-nx})/n$ is a decreasing function of n for $x \ge 0$ and thus its minimum is its limit as $n \to \infty$, namely x. Since $x/(1+x) \le x$ if $x \ge 0$, the estimate (21) follows.

6. **Discussion.** We have formulated age-of-infection models, with and without control measures. Our age-of-infection models can encompass a broad range of infectious diseases, and allow a sequence of infective and treatment compartments with general infective and treatment distributions.

In the past, the calculation of the basic reproduction number for age-of-infection models has required direct calculation of the kernel $A(\tau)$ [3, 4]. This is feasible but complicated for ordinary differential equation models with exponentially distributed periods, but is a forbidding task for general distributions. We have shown how to calculate the basic reproduction number of multi-stage age-of-infection and treatment models explicitly in terms of the rates of flow between compartments. Also, we have obtained a result that if the model does not include any treatment compartments into which infectives are moved, then the reproduction number depends only on the mean period in a compartment, not the actual distribution. However, the reproduction number for models with treatment compartments depends both on the mean infective and treatment periods, as well as the infectivity distribution. In other words, one needs detailed information about the mean infective and treatment periods in nontreatment and treatment models alike, but in treatment models, one needs information about the infective period distributions as well.

It has been shown that compartmental models including exposed periods, temporary immunity, and other compartments can be formulated as age-of-infection models [3]. Previous epidemic models can also be interpreted as age-of-infection models with different control measures. For example, in the case of pandemic influenza, vaccination is used before the start of an epidemic and antiviral treatment of infectives is used during the epidemic. SARS can be viewed as an example of a general class of epidemic diseases for which no treatments were available; only quarantine of those who were suspected of having been infected, and isolation of the diagnosed infectives were the available control measures. All of these control measures can be incorporated into the age-of-infection model, and the final size relation can be used to calculate the epidemic size, provided that the models are formulated without demographics so that the final size relation is applicable [2, 5, 10].

Our analyses carry over to endemic diseases such as HIV/AIDS, tuberculosis (TB), or extensively drug resistant tuberculosis (XDR-TB). The nature of such diseases requires the inclusion of multiple compartments. Because of the long time scale, inclusion of demographics is also essential, but this requires only the inclusion of natural death rates in the kernel $B(\tau)$ of the age-of-infection model.

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