SOME EXTENSIONS OF THE CLASSICAL EPIDEMIC MODELS

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AGE OF INFECTION EPIDEMIC MODELS

In 1927 Kermack and McKendrick described a very general epidemic model that included a dependence of infectivity on the time since becoming infected (age of infection). This allows the inclusion of various complicated compartmental structures in the same framework.

We let $\varphi(t)$ be the total infectivity at time t, defined as the sum of products of the number of infected members with each infection age and the mean infectivity for that infection age. We let $P(\tau)$ be the number of individuals who are still infected at infection age τ, and we let $\pi(\tau)$ with $0 \leq \pi(\tau) \leq 1$ be the mean infectivity at infection age τ. Then

$$A(\tau) = \pi(\tau)P(\tau),$$

is the mean infectivity of members of the population with infection age τ. We assume that an average individual makes a contacts sufficient to transmit infection in unit time and that there are no disease deaths, so that the total population size is a constant N.

The age of infection epidemic model is

$$\begin{aligned} S' &= -a\frac{S}{N}\varphi \\ \varphi(t) &= \varphi_0(t) + \int_0^t a\frac{S(t-\tau)}{N}\varphi(t-\tau)A(\tau)d\tau \\ &= \varphi_0(t) + \int_0^t [-S'(t-\tau)]A(\tau)d\tau. \end{aligned}$$

For this model it is known that

- $I(t) \to 0$ and $S(t) \to S_\infty > 0$ as $t \to \infty$.
- The basic reproduction number, defined as the number of secondary infections caused by introducing a single infective individual into an entirely susceptible population, is

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

- There is a *final size relation*, giving a relation between the basic reproduction number and the size of the epidemic,

$$\log\frac{S_0}{S_\infty} = \mathcal{R}_0\left[1 - \frac{S_\infty}{N}\right].$$

The final size relation gives a relation between the basic reproduction number and the size of the epidemic.

In the simplest form of the Kermack-McKendrick epidemic model it is assumed that on average the fraction of infected individuals who remain infective for at least a time τ is $e^{-\gamma\tau}$, so that the mean infective period is $1/\gamma$ and the rate of recovery at time t is $\gamma I(t)$.

These asumptions lead to the simple Kermack-McKendrick model

$$\begin{aligned} S' &= -\frac{a}{N}SI \\ I' &= \frac{a}{N}SI - \gamma I, \end{aligned}$$

together with initial conditions

$$S(0) = S_0, \quad I(0) = I_0, \quad S_0 + I_0 = N.$$

In this special case,

$$\mathcal{R}_0 = \frac{a}{\gamma}.$$

For the simple Kermack-McKendrick model, if $S_0 \approx N$, it is easy to see that if $\mathcal{R}_0 > 1$, the number of infectives increases initially and we have an epidemic, while if $\mathcal{R}_0 < 1$, the number of infectives decreases from the start, and there is no epidemic.

For the general age of infection model, it is necessary to give a more general definition of the meaning of an epidemic. The definition that we will use is that there is an epidemic if and only if the disease-free equilibrium $S = N, \varphi = 0$ is unstable, with respect to initial values for which $\varphi > 0$. It is possible to prove that there is an epidemic if and only if $\mathcal{R}_0 > 1$.

The final size relation assumes that all individuals who are infected at time $t = 0$ have infection age zero at time $t = 0$. If there are initial infectives with infection age greater than zero, the final size relation has the form

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_0 \left(1 - \frac{S_\infty}{N}\right) - \Gamma$$

with

$$0 \leq \Gamma \leq \int_0^\infty (N - S_0) A(t) dt.$$

DIRECT AND INDIRECT TRANSMISSION

Some diseases may be spread in more than one manner. For example, cholera may be spread both by person to person contact and indirectly through a pathogen released by infectives through a medium such as contaminated water. There is a theory of epidemic models for such diseases parallel to the theory of models with direct transmission only. The work described in this section is joint with Z. Shuai and P. van den Driessche.

A Simple Model

We begin with a simple model analogous to the simple SIR model. Consider an epidemic model with direct (person to person) and indirect (through a medium such as contaminated water) transmission. To a simple SIR model we add a pathogen B shed by infectives.

We assume that the infectivity of the pathogen is proportional to its concentration, suggesting mass action transmission. The resulting model is

$$\begin{aligned} S' &= -a\frac{S}{N}I - \beta SB \\ I' &= a\frac{S}{N}I + \beta SB - \gamma I \\ R' &= \gamma I \\ B' &= rI - \delta B, \end{aligned}$$

with initial conditions

$$S(0) = S_0, \quad I(0) = I_0, \quad B(0) = B_0,$$

in a population of constant total size $N = S_0 + I_0$, with $R(0) = 0$. In general, $N = S + I + R$. In this model r represents the rate at which an infectious individual sheds pathogen and δ represents the rate at which the pathogen loses infectivity.

From the sum of the equations for S and I we see that

$$(S + I)' = -\gamma I.$$

This shows that $(S + I)$ decreases to a limit, and since $(S + I)$ is a smooth function it is possible to show that its derivative approaches zero, from which we may deduce that

$$I_\infty = \lim_{t \to \infty} I(t) = 0.$$

Also, integration of this equation gives

$$\gamma \int_0^\infty I(t)dt = N - \lim_{t \to \infty} S(t) = N - S_\infty.$$

This implies $\int_0^\infty I(t)dt < \infty$.

The next generation matrix approach, viewing I, B as disease compartments, gives the basic reproduction number

$$\mathcal{R}_0 = \frac{a}{\gamma} + \frac{r\beta N}{\gamma\delta}.$$

In this expression, the first term represents secondary infections caused directly by a single infective introduced into a wholly susceptible population, infecting a susceptibles in unit time for a time period $1/\gamma$. The second term represents secondary infections caused indirectly through the pathogen since a single infective sheds a quantity r of pathogen in unit time for a time period $1/\gamma$ and this pathogen infects βN susceptibles in unit time for a time period $1/\delta$.

Integration of the equation for S gives

$$\log \frac{S_0}{S_\infty} = \frac{a}{N} \int_0^\infty I(t)dt + \beta \int_0^\infty B(t)dt.$$

Integration of the linear equation for B gives

$$B(t) = B_0 e^{-\delta t} + r \int_0^t e^{-\delta(t-s)} I(s)ds.$$

Next, we must show that

$$\lim_{t\to\infty}\int_0^t e^{-\delta(t-s)}I(s)ds = \lim_{t\to\infty}\frac{\int_0^t e^{\delta s}I(s)ds}{e^{\delta t}} = 0.$$

If the integral in the numerator of this expression is bounded, this is clear, and if the integral is unbounded, L'Hôpital's rule shows that the limit is $\lim_{t\to\infty} I(t)/\delta = 0$. Thus

$$B_\infty = \lim_{t\to\infty} B(t) = 0.$$

Integration now gives

$$\int_0^\infty B(t)dt = \frac{B_0 + r\int_0^\infty I(t)dt}{\delta}.$$

This implies $\int_0^\infty B(t)dt < \infty$, and substitution gives

$$\log\frac{S_0}{S_\infty} = \left[\frac{a}{N} + \beta\frac{r}{\delta}\right]\int_0^\infty I(t)dt + \beta\frac{B_0}{\delta},$$

and now substitution gives the final size relation

$$\begin{aligned}\log\frac{S_0}{S_\infty} &= \left(\frac{a}{N} + \frac{\beta N r}{\gamma\delta}\right)\left[1 - \frac{S_\infty}{N}\right] + \beta\frac{B_0}{\delta} \\ &= \mathcal{R}_0\left[1 - \frac{S_\infty}{N}\right] + \beta\frac{B_0}{\delta}.\end{aligned}$$

This implies $S_\infty > 0$.

An Age of Infection Model

In order to cover such generalizations of the model as multiple infective stages and arbitrary distributions of stay in a stage, we give an age of infection model

$$\begin{aligned} S'(t) &= -S(t)\left[\frac{a}{N}\varphi(t) + \beta B(t)\right] \\ \varphi(t) &= \varphi_0(t) + \int_0^t [-S'(t-\tau)]P(\tau)d\tau \\ B(t) &= B_0(t) + \int_0^t r\varphi(t-\tau)Q(\tau)d\tau. \end{aligned}$$

In this model, $\varphi(t)$ represents the total infectivity of individuals with age of infection t, $\varphi_0(t)$ represents the total infectivity at time t of individuals who were already infected at time $t = 0$, $B_0(t)$ represents the pathogen concentration at time t remaining from pathogen concentration that was already present at time $t = 0$.

$P(\tau)$ represents the mean infectivity of individuals at age of infection τ, normally the product of the fraction of infectives still infective at age of infection τ and the relative infectivity at that infection age, and $Q(\tau)$ represents the fraction of pathogen remaining τ time units after having been shed by an infective. The function Q is monotone non-increasing with $Q(0) = 1, \int_0^\infty Q(\tau)d\tau < \infty$. Since infectivity of an individual may depend on the age of infection of the individual, the function P is not necessarily non-increasing, but we assume $\int_0^\infty P(\tau)d\tau < \infty$.

The basic reproduction number is

$$\mathcal{R}_0 = a \int_0^\infty P(\tau)d\tau + r\beta N \int_0^\infty P(\tau)d\tau \int_0^\infty Q(\tau)d\tau.$$

In this expression, the first term represents new infection transmitted directly by a single infectious individual inserted into a totally susceptible population, while the second term represents secondary infections caused by this individual indirectly through shedding of pathogen.

Integration of the equation for S gives

$$\log \frac{S_0}{S_\infty} = \frac{a}{N} \int_0^\infty \varphi(\tau) d\tau + \beta \int_0^\infty B(\tau) d\tau.$$

Routine calculations involving interchange of the order of integration give

$$\begin{aligned}
\int_0^\infty \varphi(\tau) d\tau &= \int_0^\infty B_0(\tau) d\tau + r \int_0^\infty \varphi(\tau) d\tau \int_0^\infty Q(\tau) d\tau \\
\int_0^\infty B(\tau) d\tau &= \int_0^\infty B_0(\tau) d\tau \\
&\quad + r \int_0^\infty Q(\tau) d\tau \int_0^\infty \varphi_0(\tau) d\tau \\
&\quad + r[S_0 - S_\infty] \int_0^\infty P(\tau) d\tau \int_0^\infty Q(\tau) d\tau.
\end{aligned}$$

Then substitution gives

$$\begin{aligned}
\log \frac{S_0}{S_\infty} &= \mathcal{R}_0 \left[\frac{S_0 - S_\infty}{N} \right] + \frac{a}{N} \int_0^\infty \varphi_0(t) dt \\
&\quad + r\beta \int_0^\infty Q(t) dt \int_0^\infty \varphi_0(t) dt + \beta \int_0^\infty B_0(t) dt.
\end{aligned}$$

If all infections at time zero have infection age zero, then

$$\varphi_0(t) = [N - S_0]P(t), \quad \int_0^\infty \varphi_0(t)dt = [N - S_0] \int_0^\infty P(t)dt,$$

and if the entire pathogen concentration at time zero has infection age zero, then

$$B_0(t) = B_0 Q(t), \quad \int_0^\infty B_0(t)dt = B_0 \int_0^\infty Q(t)dt$$

with some constant B_0. In this case, the final size relation takes the form

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N}\right] + \beta B_0 \int_0^\infty Q(t)dt.$$

The final size relation has a term arising from an initial pathogen concentration that tends to decrease S_∞.

In general, because Q is monotone non-increasing,

$$\int_0^\infty B_0(t)dt \leq B_0 \int_0^\infty Q(t)dt.$$

If P is monotone non-increasing,

$$\int_0^\infty \varphi_0(t)dt \leq [N - S_0] \int_0^\infty P(t)dt.$$

If P is not monotone, this is not necessarily true. However, if there are no infectives initially, so that the epidemic is started by the pathogen, then $\varphi_0(t) = 0$ and $S_0 = N$. Then the final size relation remains valid without the need to assume that P is monotone.

These results have been established only for a constant rate of pathogen shedding. If the rate of pathogen depends on the age of infection, the equation for B in the model should be replaced by an equation

$$B(t) = B_0(t) + \int_0^t r(t-\tau)\varphi(t-\tau)Q(\tau)d\tau.$$

It is not possible to treat the corresponding model as an age of infection model, but we can view it as a staged progression model.

A Staged Progression Model

The age of infection epidemic model is very general, including models with multiple infective stages and treatment. In addition, it allows arbitrary distributions of stay in compartmnets. The drawback of the age of infection model is that it may be difficult to calculate the function $P(\tau)$. The staged progression epidemic model is a fairly general special case of the age of infection model, allowing multiple stages but allowing direct calculation of the function $A(\tau)$.

We consider an epidemic with progression from S through k infected stages $I_1, I_2, \cdots$, but with the addition of a pathogen. We assume that in stage j the relative infectivity is ε_j, the distribution of stay in the stage is given by P_j with $P_j(0) = 1, \int_0^\infty P_j(t)dt < \infty$, and P_j monotone non-increasing, so that the infectivity of an individual in stage j is $A_j(\tau) = \varepsilon_j P_j(\tau)$. There are no disease deaths and the total population size N is constant.

We assume initial conditions

$$S(0) = 0, \quad I_1(0) = I_0, \quad I_2(0) = I_3(0) = \cdots = I_k(0) = 0.$$

The total infectivity is given by

$$\varphi(t) = \sum_{j=1}^{k} \varepsilon_j I_j(t).$$

We let $B_j(t)$ be the quantity of pathogen shed by infectives in the stage I_j and let Q_j denote the distribution of stay of pathogen shed by infectives in this stage, with $Q_j(0) = 1$, $\int_0^\infty Q_j(t)dt < \infty$, and Q_j monotone non-increasing. We let r_j be the shedding rate in this stage. We also define the total quantity of pathogen,

$$B(t) = \sum_{j=1}^{k} B_j(t).$$

Then

$$B_j(t) = B_j^0(t) + \int_0^t r_j I_j(t-\tau) Q_j(\tau) d\tau.$$

A single infective introduced into a wholly susceptible population while in infection stage j causes a secondary infections in unit time directly for a period of $\int_0^\infty P_j(t)dt$. In addition, this individual sheds a quantity r_j of pathogen in unit time for a time period $\int_0^\infty P(t)dt$, and this pathogen causes βN infections in unit time for a time period $\int_0^\infty Q(t)dt$. This shows that the basic reproduction number is

$$\begin{aligned}\mathcal{R}_0 = a\sum_{j=1}^{k}\varepsilon_j\int_0^\infty P_j(t)dt \\ +\beta N\sum_{j=1}^{k} r_j\int_0^\infty P_j(t)dt\int_0^\infty Q_j(t)dt.\end{aligned}$$

We assume that all initial infectives are in the first stage with infection age zero at $t = 0$. Then the equation for I_1 in the model is

$$I_1(t) = I_1^0(t) + \int_0^t [-S'(t-\tau)] P_1(\tau) d\tau,$$

with $I_1^0(t) = I_0 P_1(t)$. Then

$$\begin{aligned}\int_0^\infty I_1(t)dt &= I_0 \int_0^\infty P_1(t)dt + [S_0 - S_\infty] \int_0^\infty P_1(t)dt \\ &= [N - S_\infty] \int_0^\infty P_1(t)dt.\end{aligned}$$

Then

$$\int_0^\infty I_j(t)dt = [N - S_\infty] \int_0^\infty P_j(t)dt, \quad j = 1, 2, \cdots, k.$$

Integration gives

$$\begin{aligned}\int_0^\infty B_j(\tau)d\tau &= \int_0^\infty B_j^0(\tau)d\tau \\ &\quad + r_j \int_0^\infty I_j(\tau)d\tau \int_0^\infty Q_j(\tau)d\tau \\ &= \int_0^\infty B_j^0(\tau)d\tau \\ &\quad + r_j[N - S_\infty] \int_0^\infty P_j(\tau)d\tau \int_0^\infty Q_j(\tau)d\tau.\end{aligned}$$

We have

$$\begin{aligned} S'(t) &= -S(t)[\frac{a}{N}S(t)\varphi(t) + \beta B(t)] \\ &= -S(t)\left[\frac{a}{N}\sum_{j=1}^{k}\varepsilon_j I_j(t) - \beta\sum_{j=1}^{k}B_j(t)\right], \end{aligned}$$

and integration gives

$$\log\frac{S_0}{S_\infty} = \frac{a}{N}\sum_{j=1}^{k}\varepsilon_j\int_0^\infty I_j(t)dt + \beta\sum_{j=1}^{k}\int_0^\infty B_j(t)]dt.$$

For simplicity, we assume that all individuals infected at time zero have infection age zero for $t = 0$, and also that there is a new quantity of pathogen B_0 introduced at time zero, so that $B_0(t) = B_0Q(t)$. Then this relation reduces to the final size relation

$$\log\frac{S_0}{S_\infty} = \mathcal{R}_0\left[1 - \frac{S_\infty}{N}\right] + \beta B_0\int_0^\infty Q(t)dt.$$

MODELS WITH DRUG RESISTANCE

Treatment of a virus with antiviral drugs raises a possibility of development of a drug-resistant strain of the virus. There is some experimental evidence that there are situations in which the treatment may cause development of more drug-resistant cases than it cures, so that treatment may become counter-productive. The work described in this section is joint with S. Moghadas and Y. Xiao.

We will formulate a model for an epidemic in which there is a drug-sensitive strain but treatment may cause some treated individuals to become drug-resistant. We divide a homogeneously mixing population into members who are susceptible (S), infected with the drug-sensitive strain (I_S), infected with the drug-sensitive strain under treatment (I_T), infected with the drug-resistant strain (I_R), and recovered individuals (R). Since treatment is ineffective against the drug-resistant infection, we do not distinguish between treated and untreated individuals in I_R. We begin with a simple treatment model.

A Basic Treatment Model

We add treatment of a fraction of individuals infected with a wild (drug-sensitive) strain of a disease to a simple SIR model,

$$\begin{aligned} S' &= -\beta S[I_S + \delta_T I_T] \\ I_S' &= \beta S[I_S + \delta_T I_T] - (\gamma_S + \eta) I_S \\ I_T' &= \eta I_S - \gamma_T I_S. \end{aligned}$$

Here, S, I_S, I_T are the sizes of the susceptible population, the infective but not treated population size, and the treated population size respectively, β is the contact rate, δ_T is the reduction factor in infectivity of treated members, η the treatment fraction, γ_S the recovery rate, and γ_T the recovery rate for treated members. The basic reproduction number is

$$\mathcal{R}_0 = \frac{\beta N}{\gamma_S + \eta} + \frac{\eta}{\eta + \gamma_S} \frac{\delta_T \beta N}{\gamma_T}.$$

The first term in $\mathcal{R}_0$ represents secondary infections caused by an infective in a wholly susceptible population while the second term represents secondary infections caused by a treated individual.

A Drug Resistance Model

We wish to include the development of drug resistance under antiviral treatment to study whether increasing the treatment rate may do more harm than good by increasing the number of drug-resistant cases. The basic additional assumption is that treated cases may become drug-resistant. We continue to assume that the time scale is short enough that we may neglect births and natural deaths, and that there are no disease deaths, so that the total population size is a constant N.

We assume that:

- resistance may be absent initially, but develops as a result of treatment, and can then be transmitted.
- treatment is effective only against wild infections.
- there is a compartment I_R of members with resistant infection with recovery rate γ_R and δ_R is the corresponding reduction factor for infectivity. We assume $\delta_R < 1$.
- the probability of developing resistance at time τ following the initiation of treatment is $1 - e^{-\kappa\tau}$.

The resulting model is

$$\begin{aligned} S'(t) &= -\beta S(I_S + \delta_T I_T + \delta_R I_R) \\ I'_S(t) &= \beta S(I_S + \delta_T I_T) - (\gamma_S + \eta) I_S \\ I'_T(t) &= \eta I_S(t) - (\gamma_T + \kappa) I_T(t) \\ I'_R(t) &= \delta_R \beta S I_R(t) + \kappa I_T - \gamma I_R(t), \end{aligned}$$

We assume $I_T(0) = 0$, that is, that time is measured from the beginning of treatment. The initial conditions are

$$S(0) = S_0, \quad I_S(0) = I_0, \quad I_T(0) = 0, \quad I_R(0) \geq 0,$$

with $S_0 + I_0 + I_R(0) = N$.

We calculate $\mathcal{R}_S$, the number of secondary sensitive infections caused by a single sensitive infection in a wholly susceptible population, namely

$$\mathcal{R}_S = \frac{\beta N}{\gamma_S + \eta} + \frac{\eta}{\eta + \gamma_S} \frac{\delta_T \beta N}{\kappa + \gamma_T}.$$

Here, the first term is the number of secondary infections caused while this infective is in I_S, $\eta/(\eta+\gamma_S)$ is the fraction of sensitive infectives that are treated, and $\delta_T\beta N/(\kappa+\gamma_T)$ is the number of secondary infections caused while the infective is in I_T. Also, the number of resistant infections caused by a single resistant infective in a wholly susceptible population is

$$\mathcal{R}_R = \frac{\delta_R \beta N}{\gamma_R}.$$

This calculation does not cover the

$$\frac{\eta}{\eta+\gamma_S} \cdot \frac{\kappa}{\kappa+\gamma_T} \cdot \frac{\beta N \delta_R}{\gamma_R}$$

resistant infections that develop from treated sensitive infections when a sensitive infection is introduced into a wholly susceptible population.

Using the next generation matrix method, we calculate

$$\mathcal{R}_0 = \max[\mathcal{R}_S, \mathcal{R}_R],$$

There is an epidemic for the drug resistance epidemic model if and only if $\mathcal{R}_0 > 1$.

Final Size Relations

Summing the equations of the model gives

$$(S + I_S + I_T + I_R)' = -(\gamma_S I_S + \gamma_T I_T + \gamma_R I_R) < 0.$$

Hence, $(S + I_S + I_T + I_R)$ is a decreasing function bounded below by zero, and therefore approaches a limit as $t \to \infty$. It is easy to show that the derivative of this function approaches zero, and this implies, since $I_S,\ I_T,\ I_R$ are non-negative, that each of I_S, I_T, I_R approaches zero as $t \to \infty$. Thus, S approaches a non-negative limit S_∞ as $t \to \infty$.

It is convenient to use the notation $\hat{f}$ for the integral of a non-negative integrable function f,

$$\hat{f} = \int_0^\infty f(t)dt.$$

Integration of the above equation from 0 to ∞ leads to

$$N - S_\infty = \gamma_S \hat{I}_S + \gamma_T \hat{I}_T + \gamma_R \hat{I}_R.$$

Integration of the equation for S in the model gives

$$\log \frac{S_0}{S_\infty} = \beta[\hat{I}_S + \delta_T \hat{I}_T + \delta_R \hat{I}_R].$$

Integration of the equation for I_T in the model gives, since $I_T(0) = \lim_{t\to\infty} I_T(t) = 0$,

$$\eta \hat{I}_S = (\kappa + \gamma_T)\hat{I}_T,$$

and we may use this relation to eliminate $\hat{I}_T$,

$$\begin{aligned} N - S_\infty &= \frac{\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T}{\kappa + \gamma_T}\hat{I}_S + \gamma_R \hat{I}_R \\ \log\frac{S_0}{S_\infty} &= \beta\frac{\kappa + \gamma_T + \eta\delta_T}{\kappa + \gamma_T}\hat{I}_S + \beta\delta_R \hat{I}_R. \end{aligned}$$

This pair of linear equations for $\hat{I}_S, \hat{I}_R$, has solution

$$\begin{aligned} \beta\Delta(\eta)\hat{I}_S &= \beta\delta_R(\kappa + \gamma_T)(N - S_\infty) \\ &\quad -\gamma_R(\kappa + \gamma_T)\log\frac{S_0}{S_\infty} \\ \beta\Delta(\eta)\hat{I}_R &= (\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T)\log\frac{S_0}{S_\infty} \\ &\quad -\beta(\kappa + \gamma_T + \delta_T\eta)(N - S_\infty), \end{aligned}$$

with

$$\Delta(\eta) = \delta_R(\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T) - \gamma_R(\kappa + \gamma_T + \eta\delta_T).$$

It is easy to calculate that $\Delta(\eta) < 0$ is equivalent to

$$\frac{\delta_R \beta N}{\gamma} < \beta N \frac{\kappa + \gamma_T + \eta\delta_T}{\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T},$$

and if we define

$$\mathcal{R}^*(\eta) = \beta N \frac{\kappa + \gamma_T + \eta\delta_T}{\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T},$$

this is equivalent to

$$\mathcal{R}_R < \mathcal{R}^*(\eta).$$

If $\delta_T\gamma_S \leq \gamma_T$, $\delta_T < 1$ it is easy to verify that $\mathcal{R}^*(\eta)$ is a decreasing function of η. Thus

$$\begin{aligned}\mathcal{R}^*(0) &= \beta N \frac{\kappa + \gamma_S}{\gamma_S(\kappa + \gamma_T)} \\ &\geq lim_{\eta\to\infty}\mathcal{R}^*(\eta) = \mathcal{R}^*(\infty) = \beta N \frac{\delta_T}{\gamma_T}.\end{aligned}$$

Since the solutions $\hat{I}_S, \hat{I}_R$ are non-negative, it follows from the expressions for $\hat{I}_S, \hat{I}_R$ that if $\Delta(\eta) < 0$,

$$\mathcal{R}_R \left[1 - \frac{S_\infty}{N}\right] \leq \log \frac{S_0}{S_\infty} \leq \mathcal{R}^*(\eta) \left[1 - \frac{S_\infty}{N}\right].$$

If $\Delta(\eta) > 0$, these inequalities are reversed.

We distinguish three cases, corresponding to the location of $\mathcal{R}_R$ with respect to $\mathcal{R}^*(0)$ and $\mathcal{R}^*(\infty)$.

(i) $\mathcal{R}_R > \mathcal{R}^*(0)$, if

$$\delta_R \gamma_S (\kappa + \gamma_T) > \gamma_R (\kappa + \gamma_T).$$

In this case $\mathcal{R}_R > \mathcal{R}^*(\eta)$ for $0 \leq \eta < \infty$.

$$\mathcal{R}^*(\eta) \left[1 - \frac{S_\infty}{N} \right] < \log \frac{S_0}{S_\infty} < \mathcal{R}_R \left[1 - \frac{S_\infty}{N} \right].$$

(ii) $\mathcal{R}_R < \mathcal{R}^*(\infty)$, if

$$\delta_R \gamma_T < \gamma_R \delta_T.$$

In this case $\mathcal{R}_R < \mathcal{R}^*(\eta)$ for $0 \leq \eta < \infty$.

$$\mathcal{R}_R \left[1 - \frac{S_\infty}{N} \right] < \log \frac{S_0}{S_\infty} < \mathcal{R}^*(\eta) \left[1 - \frac{S_\infty}{N} \right].$$

(iii) $\mathcal{R}^*(0) > \mathcal{R}_R > \mathcal{R}^*(\infty)$, if

$$\delta_R\gamma_S(\kappa+\gamma_T) < \gamma_R(\kappa+\gamma_T), \quad \delta_R\gamma_T > \delta_T\gamma_R.$$

In this case $\mathcal{R}^*(\eta) > \mathcal{R}_R$ for small η and $\mathcal{R}^*(\eta) < \mathcal{R}_R$ for large η. Specifically, there is a value η_c such that $\mathcal{R}^*(\eta_c) = \mathcal{R}_R$, with

$$\eta_c = \frac{\gamma_R(\kappa+\gamma_S) - \delta_R\gamma_S(\kappa+\gamma_T)}{\gamma_T\delta_R - \delta_T\gamma_R -}.$$

$$\mathcal{R}_R\left[1-\frac{S_\infty}{N}\right] < \log\frac{S_0}{S_\infty} < \mathcal{R}^*(\eta)\left[1-\frac{S_\infty}{N}\right] \qquad (0 \le \eta < \eta_c)$$

$$\mathcal{R}^*(\eta)\left[1-\frac{S_\infty}{N}\right] < \log\frac{S_0}{S_\infty} < \mathcal{R}_R\left[1-\frac{S_\infty}{N}\right] \qquad (\eta_c < \eta < \infty).$$

We have two expressions for $\log(S_0/S_\infty)$ and $(N - S_\infty)$. In the analysis of the simple Kermack-McKendrick model the corresponding expressions contained only one term of the form $\hat{I}$, and it was possible to eliminate that term from the two equations. Here, we have two terms $\hat{I}_S$ and $\hat{I}_R$, and elimination is not possible without some additional information or assumption.

In order to establish an equality relating the treatment rate and the epidemic final size, we need to make an additional assumption. We have written $N - S_\infty$, the total number of members who are infected over the course of the epidemic, as the sum of two terms, namely $\gamma \hat{I}_R$, the total number of drug-resistant infections, and

$$\frac{\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T}{\kappa + \gamma_T}\hat{I}_S,$$

the number of cases of drug-sensitive infections that do not develop resistance. We consider the treatment rate η to be a parameter that can be controlled, with all the other parameters of the model fixed. Then the ratio of these two numbers is a function of η, and we define

$$\lambda(\eta) = \frac{\gamma(\kappa + \gamma_T)\hat{I}_R}{(\kappa\gamma_S + \gamma_S\gamma_T + \eta\gamma_T))\hat{I}_S}.$$

We will assume

$$\lambda'(\eta) \geq 0.$$

Simulations indicate that the effect of increasing the treatment rate η is to increase the number of resistant infections and to decrease the number of sensitive infections. If there is no transition from sensitive to resistant infections ($\kappa = 0$), the number of sensitive infections is a decreasing function of the treatment rate, while the number of resistant infections is independent of the treatment rate (except for a decrease because of the decrease in the number of sensitive infections). The effect of adding development of resistance at a given treatment rate is to decrease the number of sensitive infections, because some sensitive infection would develop resistance, and to increase the number of resistant infections. This makes it plausible that the ratio $\lambda(\eta)$ is an increasing function of the treatment rate.

We eliminate $\hat{I}_S$ and $\hat{I}_R$ to obtain a pseudo-final size relation

$$\log \frac{S_0}{S_\infty(\eta)} = E(\eta) \left[1 - \frac{S_\infty(\eta)}{N} \right],$$

where

$$E(\eta) = \frac{\mathcal{R}^*(\eta) + \mathcal{R}_R \lambda(\eta)}{1 + \lambda(\eta)}.$$

For a final size equation of this form, determining S_∞ as a function of η, it is easy to verify that the derivatives of $E(\eta)$ and $S_\infty(\eta)$ with respect to η have opposite sign. This implies that if

$$E'(\eta) = \frac{[1+\lambda(\eta)](R^*(\eta))' + \lambda'(\eta)[\mathcal{R}_R - R^*(\eta)]}{(1+\lambda(\eta))^2} > 0,$$

the effect of increasing the treatment rate η is to decrease S_∞, that is, to make the epidemic more severe. Since $(R^*(\eta))' < 0$, $\lambda'(\eta) > 0$, we see that $E'(\eta) < 0$ if $\mathcal{R}_R < R^*(\eta)]$. However, it is possible to have $E'(\eta) > 0$ if $\mathcal{R}_R > R^*(\eta)]$, and this happens, at least for some values of η, in the cases (ii) $[\delta_R\gamma_T < \gamma_R\delta_T]$ and (iii) $[\delta_R\gamma_S(\kappa+\gamma_T) < \gamma_R(\kappa+\gamma_S)$, $\delta_R\gamma_T > \gamma_R\delta_T]$.

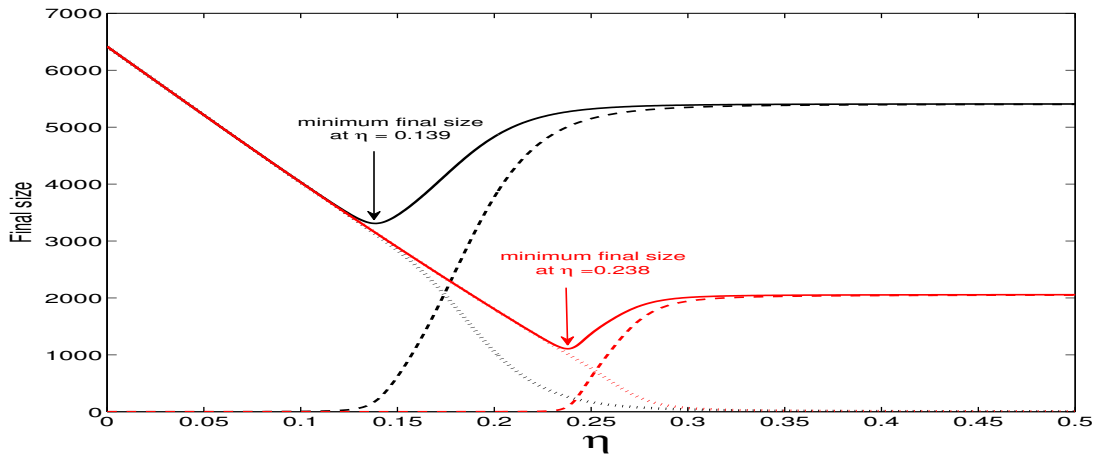
To demonstrate this possibility, we simulated the model, showing optimal treatment rates at which the final size is a minimum for two different levels of resistance transmission, using parameter values

$\beta = 4.5 \times 10^{-5}, \quad N = 10,000, \quad \gamma_S = \gamma_R = 1/4\ day^{-1},$
$\kappa = 0.0002\ day^{-1}, \quad \delta_T = 0.4.$

Initial values are

$$S_0 = 10^4 - 1, \quad I_S(0) = 1, \quad I_T(0) = I_R(0) = 0.$$

For $\delta_R = 0.7$, for which $\eta_c = 0.03$, the optimal rate is $\eta_0 = 0.238$ (red curves). For $\delta_R = 0.9$, which is in case (ii), the optimal treatment rate $\eta = 0.139$. The solid curves are total infections; the dotted curves are the total number of infections without resistance, and the dashed curves are the total number of resistant infections.



CONCLUSIONS

The age of infection epidemic model is a very general form. We have considered extensions in two different directions. For diseases with direct and indirect modes of transmission it is possible to build a parallel development, an age of infection model if the rate of shedding pathogen does not depend on the time since infection, or a stage-structured model if the rate of shedding pathogen depends on the age of infection.

For diseases in which there is a risk of development of drug resistance, experimental evidence indicates a possibility that increasing the treatment rate may be counter-productive. We have formulated a simple model that can exhibit such behavior, but analysis of the model depends on an assumption about the ratio of drug-resistant cases to drug-sensitive cases of disease. Although simulations indicate the validity of this assumption, we have not been able to establish its validity analytically. This remains an open problem, as does the question of describing an age of infection model for a disease with two strains.