Using age of infection models to derive an explicit expression for R_0

by

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Abstract

Using a multiple stage age of infection model, we derive an expression for the basic reproduction number, R_0. We apply this method to find R_0 in analogous treatment models. We find, in the model without treatment, R_0 depends only on the mean infective period, and not on the infective distribution. In treatment models, R_0 depends on the mean infective and mean treatment period, as well as the distribution of the infective period, but not on the distribution of the treatment period. With an explicit formula for R_0 and the final size relation, we provide a practical alternative to evaluating the effect of treatment and other control measures. We compare our models to previous models of SARS and TB.

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Chapter 1

Introduction

Epidemics are defined as sudden disease outbreaks that infect a population and then disappear, leaving a part of the population untouched. Some examples of epidemics include Influenza, Foot-and-Mouth disease and SARS. These are different from endemic situations where a disease becomes established and remains in a population, such as the case with Tuberculosis and HIV/AIDS.

Mathematical modeling of epidemics has been emphasized as an essential tool not only for developing strategies in preparation for an outbreak, but also for evaluating the effect of control policies, as it had during the 2001 outbreak of Foot-and-Mouth disease in the United Kingdom [1]. It has provided insight into the control of SARS [28, 29], and has been discussed a great deal for a possible influenza pandemic. Moreover, epidemic models have been useful in studying endemic diseases such as Tuberculosis and HIV/AIDS, as well as comparing control strategies.

Numerous infectious diseases are well represented by compartmental models such as the Kermack-McKendrick models [12–14], and also by network models [15–17]. In particular, the 1927 Kermack-McKendrick model [12] is an age of infection model in which the infectivity of an individual depends on the time since becoming infected. Although originally designed to study epidemics, age of infection models have also become important in studying endemic situations, as demographics, multiple compartments, and varying infectivity with time–all of which are necessary inclusions for an endemic disease model–can be incorporated [22].

There are two basic properties of epidemic models. First, there is a threshold given by the basic reproduction number R_0 which indicates the likelihood of an epidemic outbreak. R_0 is defined as the number of secondary infections caused by a typical single infective in a wholly susceptible population over the course of an epidemic. Naturally, if $R_0 < 1$ there is no epidemic, and if $R_0 > 1$ there is an epidemic. The second property of such models is that an epidemic eventually dies out, without having infected the entire population.

Simple epidemic models

A simple example that illustrates both of these properties is a special case of the Kermack-McKendrick model. In this model, the population N is divided into three

compartments: the susceptibles ($S(t)$), the infectives ($I(t)$), and the recovered class ($R(t)$). We assume that $R(0) = 0$, that is that there are no recovered individuals at the start of the epidemic. Then the initial population size $N(0) = S(0) + I(0)$. The model is based on three assumptions.

1. An average infective person makes βN contacts sufficient to transmit infection per unit time, if the contact is with a susceptible. N is a function of time if there are disease deaths.

2. A fraction α of infectives leave the infected class, I, per unit time.

3. The population is closed, and the only loss is via disease death. Demographic effects, such as births and natural deaths, are not included.

This produces a simple two dimensional system

$$\begin{aligned} S' &= -\beta SI \\ I' &= (\beta S - \alpha)I, \end{aligned} \tag{1.1}$$

where β is the infectivity parameter and α is the rate of removal from the infective class. The rate of change of R is proportional to I. It is not necessary to include R' as R can be determined when S and I are known.

Let $S(0) \approx K$. Initially, an infected individual makes βK contacts in unit time, all with susceptibles, and thus produces βK new infections in unit time, over a time period $1/\alpha$. Thus the basic reproduction number R_0 is $\beta K/\alpha$ [12].

It can be easily seen that the epidemic dies out as $\lim_{t\to\infty} I(t) = I_\infty = 0$, and a part of the population remains uninfected as $\lim_{t\to\infty} S(t) = S_\infty > 0$ [23]. If $R_0 > 1$, I increases initially and there is an epidemic, whereas if $R_0 < 1$, I decreases to 0 and there is no epidemic. Such simple model provides insight into the disease dynamics and serves as a clear illustration of the two properties of epidemic models.

Calculation of R_0

The basic reproduction number remains an important part of mathematical analysis of disease spread. Diekmann, Heesterbeek and Metz introduced a general framework of the next generation operator to make the calculation of the basic reproduction number feasible [31]. 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. R_0 is defined as the spectral radius of this operator [31].

Van den Driessche and Watmough [30] did the same for models which are systems of ordinary differential equations, with the next generation operator described in terms of matrices. In this case, R_0 is the largest eigenvalue of a matrix that describes the next generation operator. Note that for the above system in Equation (1.1), the matrix is the 1x1 matrix $\beta K/\alpha$.

Final size relation

From the Kermack-McKendrick age of infection model to other models that include horizontal transmission, some vertical transmission, multiple susceptible and infective classes [18, 21], or varying latent or infective periods [21], we are able to obtain R_0 and the final size of the epidemic, $N(0) - S_\infty$ (that is, the number of members of the population who have been infected over the course of an epidemic). More precisely, the expression of R_0 can be used to derive an explicit relation between R_0 and the final size of the epidemic [18]. This is called the final size relation.

If the contact rate is constant (i.e. mass action), as assumed in the simplest form of the Kermack-McKendrick model, the final size relation is an equality. If the contact rate is density-dependent, it only provides bounds. However, if there are no disease deaths so that the total population size is constant, the contact rate is constant and the final size relation is an equality. If the disease death rate is small, then assuming constant contact rate, so that the final size relation is an equality, has been conjectured to yield a good approximation [18]. The final size relation is undoubtedly useful in designing and evaluating control measures of sudden and sometimes unprecedented outbreaks of rapidly spreading infectious diseases [18, 22].

Note that the calculation of the basic reproduction number is not restricted to epidemic models but is applicable to endemic situations in the same manner.

However, a few distinctions should be made regarding the basic reproduction number in epidemic and endemic models (that is, models with and without demographics). R_0 is central to both, but in different ways. In epidemic models, the infection always eventually disappears without infecting the whole population; the reproduction number distinguishes between the event of an epidemic and the infection passing away without building into one. In models that include demographics such as births and natural deaths, the reproduction number distinguishes between a stable disease-free equilibrium and the existence of an endemic equilibrium. In epidemic models, the final size relation gives the size of the epidemic. If births and deaths are included in the model, then there is no final size relation. If there is an endemic equilibrium in this case, it is necessary to find this equilibrium and study its stability.

Goals of this thesis

Since it is not possible, or would be quite inhumane, to do experiments with human subjects, it is useful to apply models to evaluate the effect of control measures. Although it may be possible to draw conclusions about the effect of control measures for past epidemics, models are useful in preparing for an anticipated epidemic. As mentioned before, the Kermack-McKendrick age of infection model is more general in that it can be interpreted to include multiple stages and compartments such as quarantine, isolation, vaccination and treatment.

In this paper, we present an age of infection model that is a slight generalization of the Kermack-McKendrick age of infection model. We formulate models both with and without treatment. We show how to calculate explicitly the basic reproduction number for these multiple stage models, in terms of the parameters of the model given by rates of flow between compartments. We also provide overviews of a few epidemics and discuss the corresponding mathematical modeling efforts.

Chapter 2

Age of Infection Models

Traditional compartmental models include multiple stages and usually assume exponential distributions, which yields systems of ordinary differential equations. Flow diagrams are frequently used to display transitions between compartments and to facilitate the model formulation. For example, we can easily see that the Kermack-McKendrick model from Equation (1.1) corresponds to the flow diagram in Figure 2.1 that displays rates of flow between compartments, based on model assumptions.

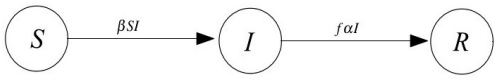

Figure 2.1: Flow diagram for an SIR model as shown in Equation (1.1).

Each disease has its own properties and control measures that lead to a specific flow diagram. Consider influenza. Individuals infected with the influenza virus go through a latent period where they are infected but not infective (represented by class L). We assume that a fraction p will become infective and symptomatic, and move to infective class I at a rate $p\kappa L$ in unit time, while a fraction $(1-p)$ will become infective but not symptomatic and move to an asymptomatic class A. We assume a fraction f of the infective and η of asymptomatic individuals recover. See Figure 2.2 for illustration.

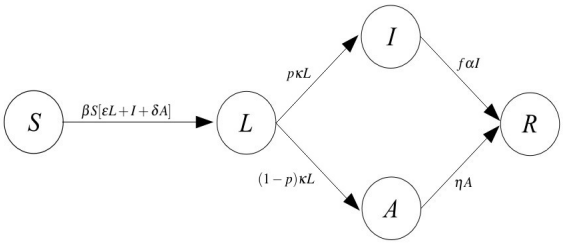

Figure 2.2: Flow diagram for influenza model as shown in Equation (2.1).

With the help of the flow diagram, the basic model can be written as

$$\begin{aligned} S' &= -\beta SQ \\ L' &= \beta SQ - \kappa L \\ I' &= p\kappa L - \alpha I \\ A' &= (1-p)\kappa L - \eta A \\ N' &= -(1-f)\alpha I, \end{aligned} \tag{2.1}$$

with $Q = \varepsilon L + I + \delta A$. The parameters ε and δ allow for infectivity in the latent and asymptomatic stage respectively [20]. β and α are as defined in Equation (1.1). This model comes from [19].

Another example that requires more compartments and complexity due to the nature of the disease is Tuberculosis, which will be introduced later in this paper.

Compartmental models, such as the above *SIR* and 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. Traditional epidemic models with ordinary differential equations and exponential distributions are not sufficiently general to describe many diseases. Age of infection models, however, are general enough to encompass any number of infectious diseases. These are models in which the infectivity of an individual depends on the time since becoming infected. For this reason, age of infection models have been gaining more interest as a real generalization [24–27]. However, unlike the traditional epidemic models, calculating the basic reproduction number for age of infection models is not so obvious.

This work provides means for doing precisely that, in a multi-compartment situation with general distributions. Our purpose is not only to interpret the epidemic process for treatment and non treatment cases using this model, but also to be able to estimate the efficacy of control measures. Our first main result is that for models without treatment, the reproduction number remains unaffected whether we assume exponential or general distributions. Our second main result is that for models with treatment, quarantine, isolation, or anything in which there is a proportional rate of splitting individuals between or among compartments with different parameters, the reproduction number is affected.

2.1 Generalized Epidemic Models as Age of Infection Models: Without Treatment

It has been established that general epidemic models, such as age of infection models, share the same properties as simple epidemic models in that they have

a basic reproduction number which determines whether there will be an epidemic outbreak, and also that the epidemic eventually dies out without infecting the entire population [23]. We introduce a slightly more generalized age of infection model which is based on the 1927 Kermack-McKendrick model, and a practical extension of Brauer's model [12, 23].

In this section, we make the age of infection model more explicit by assuming a sequence of infected stages with different infectivity parameters and infectivity distribution. We start with one infected compartment. Consider a simple *SIR* model, as illustrated in Figure 2.1. We have

$$\begin{aligned} S' &= -\beta(N)SI \\ I' &= \beta(N)SI - \alpha I \\ R' &= f\alpha I, \end{aligned}$$

where S, I and R represent susceptible, infective and recovered classes respectively, and parameters are as previously defined in Equation (1.1). Note that β is now a function of the total population N.

In this simple case, $R_0 = K\beta(K)/\alpha$, where $K = N(0) = S(0) + I(0)$.

Distributed recovery times

Here, we relax the assumption that infected individuals recover and a rate $1/\alpha$, and replace this with assuming a general infective period distribution, $P(t)$, we write this model as the following age of infection model. $P(t)$ is the probability that an infection will have a duration of at least time t in a typical individual, or the probability that an individual will still be infected a time t after having become infected.

$$\begin{aligned} S' &= -\beta(N)SI \\ I(t) &= \int_{-\infty}^{t} \beta(N(s))S(s)I(s)P(t-s)\,ds \\ &= \int_{0}^{\infty} \beta(N(t-u))S(t-u)I(t-u)P(u)\,du \\ &= \int_{0}^{\infty} [-S'(t-u)]P(u)\,du. \end{aligned}$$

This is the sum of new infections at time $(t-u)$ that are still infective u time units after the infection. In this case,

$$R_0 = K\beta(K)\int_0^\infty P(u)\,du,$$

since a single infective causes βK new infections in unit time and $\int_0^\infty P(u)$ is the mean infective period of the single infective over the course of the epidemic.

To get the rate of outflow from the infected population, we differentiate $I(t)$ under the integral sign:

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

where the first term is the rate of new infections, and the latter, the rate of recoveries and disease deaths. Thus the general age of infection model becomes

$$\begin{aligned} S'(t) &= -\beta(N)SI \\ I(t) &= \int_{-\infty}^{t} \beta(N(s))S(s)I(s)P(t-s)\,ds \\ R'(t) &= -f\int_{-\infty}^{t} [-S'(s)]P'(t-s)\,ds. \end{aligned} \tag{2.2}$$

Discrete infected stages

Now 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 2.3 below serves as an example with two infected stages.

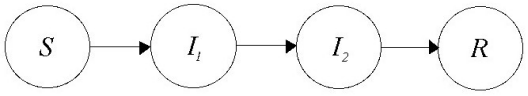

Figure 2.3: Flow diagram with two infective stages, I_1 and I_2.

We define the total infectivity at time t to be

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

Then

$$\phi(t) = \int_0^\infty [-S'(t-\tau)] \sum_{i=1}^{n} \varepsilon_i P_i(\tau)\,d\tau.$$

Thus, the general age of infection model with a sequence of infected stages be-

comes

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

where $X(\tau) = \sum_{i=1}^{n} \varepsilon_i P_i(\tau)\, d\tau$ is the kernel. So $R_0 = K\beta(K)\int_0^\infty X(\tau)d\tau$.

We find the integral of the kernel. For the first infective stage we have

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

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

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

where $A(u) = \int_0^u -P_1'(u-\sigma)P_2(\sigma)\, d\sigma$ is the kernel of I_2 that will contribute to R_0.

We have

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

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

$$R_0 = K\beta(K) \sum_{i=1}^{n} \varepsilon_i \int_0^\infty P_i(\tau)\, d\tau.$$

With this result we pose the following theorem.

Theorem 2.1 *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.*

For example, the R_0 with a fixed length infective period, or any other distribution, is the same as the R_0 with exponentially distributed period.

Chapter 3

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. Again, we start with one infected and one treatment stage.

This is presented in the following flow diagram in Figure 3.1; note that the branchings differ from the SI_1I_2R model.

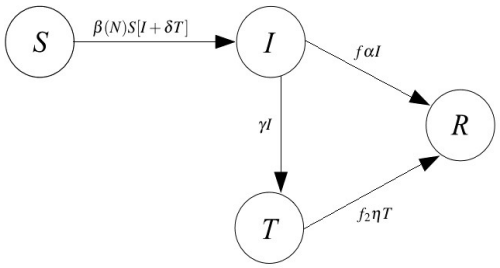

Figure 3.1: Flow diagram for an SITR model as shown in Equation (3.1).

Consider a simple treatment model in which fraction γ per unit time of infectives are selected for treatment, and 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, with exponentially distributed period is given by

$$\begin{aligned} S' &= -\beta(N)S[I+\delta T] \\ I' &= \beta(N)S[I+\delta T] - (\alpha+\gamma)I \\ T' &= \gamma I - \eta T \\ R' &= f\alpha I + f_2\eta T. \end{aligned} \tag{3.1}$$

To calculate R_0, we use the compartmental model approach presented by van den Driessche and Watmough [30], and Diekmann et al [31].

The vector of infected compartments is $\overline{\mathbf{x}} = \begin{pmatrix} I \\ T \end{pmatrix}$. The rate of appearance of new infections is given by $\mathscr{F} = K\beta(K)[I + \delta T]$, and the 2 x 2 Jacobian matrix is

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}\right] = K\beta(K)\begin{pmatrix} 1 & \delta \\ 0 & 0 \end{pmatrix}, \text{ where } 1 \leq i, j \leq 2.$$

Now we need the matrix V describing the rate of transfer into and out of the infected compartments, and its inverse. We have

$$V = \begin{pmatrix} \alpha+\gamma & 0 \\ -\gamma & \eta \end{pmatrix}, \text{ and } V^{-1} = \begin{pmatrix} \frac{1}{\alpha+\gamma} & 0 \\ \frac{\gamma}{\eta(\alpha+\gamma)} & \frac{1}{\eta} \end{pmatrix}.$$

So $FV^{-1} = K\beta(K)\begin{pmatrix} \frac{1}{\alpha+\gamma} + \frac{\delta\gamma}{\eta(\alpha+\gamma)} & \frac{\delta}{\eta} \\ 0 & 0 \end{pmatrix}$. This is called a next generation matrix, whose (i,k) entry represents the expected number of new infections in compartment i, coming from compartment k.

Following Diekmann et al's [31] definition and taking R_0 as the spectral radius of FV^{-1}, we have

$$R_0 = \frac{K\beta(K)}{\alpha+\gamma}\left[1 + \frac{\delta\gamma}{\eta}\right]. \tag{3.2}$$

We now write this as an age of infection model. Assume that the distribution of infective periods given by $P(\tau)$, and distribution of periods in treatment given by $Q(\tau)$. Then the $SITR$ model becomes

$$\begin{aligned} S'(t) &= -\beta(N)S(t)[I(t) + \delta T(t)] \\ I(t) &= \int_0^\infty -S'(t-\tau)e^{-\gamma\tau}P(\tau)\,d\tau \\ T(t) &= \int_0^\infty \gamma I(t-\sigma)Q(\sigma)\,d\sigma. \end{aligned} \tag{3.3}$$

We can calculate the contribution to R_0 from $I(t)$ just as we did for the SIR model, but in order 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 the contribution from $T(t)$ would be $K\beta(K)\int_0^\infty Y(\tau)d\tau$.

Thus, in terms of the age of infection model, this is

$$\begin{aligned} S'(t) &= -\beta(N)S(t)\phi(t) \\ \phi(t) &= I(t) + \delta T(t) \\ &= \int_0^\infty -S'(t-\tau)X(\tau)\,d\tau, \end{aligned}$$

with $R_0 = K\beta(K)\int_0^\infty X(\tau)\,d\tau$ where $X(\tau) = A(\tau) + \delta B(\tau)$. Now we find kernels $A(\tau)$ and $B(\tau)$.

From Equation (3.3), we see that $A(\tau) = e^{-\gamma\tau}P(\tau)$. We rewrite $T(t)$ to find $B(\tau)$. We have

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

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

Now

$$\begin{aligned}
\int_0^\infty B(\tau)\,d\tau &= \gamma\int_0^\infty\int_0^\tau e^{-\gamma(\tau-\sigma)}P(\tau-\sigma)Q(\sigma)\,d\sigma\,d\tau \\
&= \gamma\int_0^\infty\int_\sigma^\infty e^{-\gamma(\tau-\sigma)}P(\tau-\sigma)\,d\tau\,Q(\sigma)\,d\sigma \\
&= \gamma\int_0^\infty e^{-\gamma\omega}P(\omega)\,d\omega\int_0^\infty Q(\sigma)\,d\sigma. \qquad (3.4)
\end{aligned}$$

Thus,

$$\begin{aligned}
R_0 &= K\beta(K)\int_0^\infty [A(\tau)+\delta B(\tau)]\,d\tau \\
&= K\beta(K)\left[\int_0^\infty e^{-\gamma\tau}P(\tau)\,d\tau + \delta\gamma\int_0^\infty e^{-\gamma\omega}P(\omega)\,d\omega\int_0^\infty Q(\sigma)\,d\sigma\right] \\
&= K\beta(K)\int_0^\infty e^{-\gamma\tau}P(\tau)\,d\tau\left[1+\delta\gamma\int_0^\infty Q(\sigma)\,d\sigma\right]. \qquad (3.5)
\end{aligned}$$

Using Equation (3.5), we compute R_0 using exponentially distributed infective and treatment periods, $P(\tau) = e^{-\alpha\tau}$ and $Q(\tau) = e^{-\eta\tau}$. We get

$$\begin{aligned}
R_0 &= K\beta(K)\int_0^\infty e^{-(\alpha+\gamma)\tau}\,d\tau\left[1+\delta\gamma\int_0^\infty e^{-\eta\tau}\,d\tau\right] \\
&= \frac{K\beta(K)}{\alpha+\gamma}\left[1+\frac{\delta\gamma}{\eta}\right].
\end{aligned}$$

This yields the same result as Equation (3.2).

n infective stages

Now suppose we have a finite sequence of n infective stages $I_i(t)$ with distribution $P_i(\tau)$, and a sequence of n treatment stages $T_i(t)$ with distribution $Q_i(\tau)$, for $i = 1,\ldots,n$. We name the kernels of each of the infective and treatment stages $A_i(\tau)$ and $B_i(\tau)$, respectively. We start with two infective and treatment stages. See Figure 3.2.

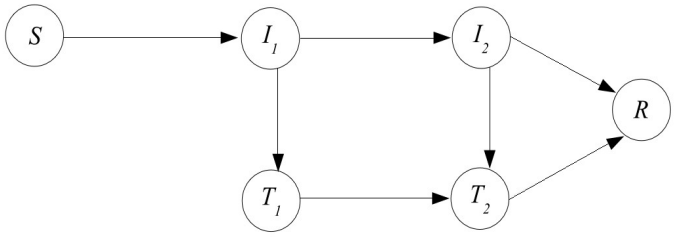

Figure 3.2: Flow diagram with infective stages I_1, I_2, and treatment stages T_1, T_2.

In our treatment model, branching occurs when a fraction γ is removed from the infective class and sent to the treatment class, while in the influenza flow diagram, Figure 2.2, a fraction is transferred each way at the end of the latent period. Although the branchings look the same in flow diagrams, they enter differently into the model equations.

We have

$$\begin{aligned} S' &= -\beta(N)S(t)[I(t)+\delta T(t)] \\ I_1(t) &= \int_0^\infty -S'(t-\tau)e^{-\gamma_1\tau}P_1(\tau)\,d\tau \\ &= \int_0^\infty -S'(t-\tau)A_1(\tau)\,d\tau \qquad (3.6) \\ T_1(t) &= \int_0^\infty \gamma_1 I_1(t-\sigma)Q_1(\sigma)\,d\sigma \\ &= \int_0^\infty \gamma_1[-S'(t-\tau)]\int_0^\tau e^{-\gamma_1(\tau-\sigma)}P_1(\tau-\sigma)Q_1(\sigma)\,d\sigma\,d\tau \\ &= \int_0^\infty -S'(t-\tau)B_1(\tau)\,d\tau. \end{aligned}$$

Again, to find the input from I_1 to I_2, we differentiate I_1. We get

$$\begin{aligned} I_2(t) &= \int_0^\infty \int_0^\infty S'(t-\tau-\sigma)e^{-\gamma_1\tau}P_1'(\tau)\,d\tau\,P_2(\sigma)\,d\sigma \\ &= \int_0^\infty -S'(t-u)\int_0^u -e^{-\gamma_1(u-\sigma)}P_1'(u-\sigma)P_2(\sigma)\,d\sigma\,du \\ &= \int_0^\infty -S'(t-u)A_2(u)\,du. \end{aligned} \tag{3.7}$$

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

$$T_2(t) = \int_0^\infty \gamma_2 I_2(t-\sigma)Q_2(\sigma)\,d\sigma - \int_0^\infty \int_{-\infty}^t \gamma_1 I_1(u)Q'(t-u-\sigma)\,du\,Q_2(\sigma)\,d\sigma. \tag{3.8}$$

In terms of the age of infection model, this is

$$\begin{aligned} S'(t) &= -\beta(N)S(t)\sum_{i=1}^{2}[I_i(t)+\delta_i T_i(t)] \\ \phi(t) &= \sum_{i=1}^{2}[I_i(t)+\delta_i T_i(t)] \\ &= \int_0^\infty -S'(t-\tau)X(\tau)\,d\tau, \end{aligned}$$

where $X(\tau) = \sum_{i=1}^{2}[A_i(\tau)+\delta_i B_i(\tau)]$. Thus,

$$R_0 = K\beta(K)\int_0^\infty X(\tau)\,d\tau.$$

We have the following from Equation (3.6) and Equation (3.4):

$$\int_0^\infty A_1(\tau)\,d\tau = \int_0^\infty e^{-\gamma_1\tau}P_1(\tau)\,d\tau, \tag{3.9}$$

$$\int_0^\infty B_1(\tau)\,d\tau = \gamma_1\int_0^\infty e^{-\gamma_1\omega}P_1(\omega)\,d\omega\int_0^\infty Q_1(\sigma)\,d\sigma. \tag{3.10}$$

Now we calculate the integral of the kernels $A_2(\tau)$ and $B_2(\tau)$. From Equation (3.7), we have

$$\begin{aligned}\int_0^\infty A_2(\tau)\,d\tau &= \int_0^\infty \int_0^\tau -e^{-\gamma_1(\tau-\sigma)}P_1'(\tau-\sigma)P_2(\sigma)\,d\sigma\,d\tau \\ &= \int_0^\infty P_2(\sigma)\,d\sigma \int_0^\infty -e^{-\gamma_1\omega}P_1'(\omega)\,d\omega \\ &= \int_0^\infty P_2(\sigma)\,d\sigma \left[1-\int_0^\infty \gamma_1 e^{-\gamma_1\omega}P_1(\omega)\,d\omega\right]. \end{aligned} \tag{3.11}$$

Last, we find the integral of $B_2(\tau)$ using Equation (3.8). For simplicity, let

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

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

To find B_{2I}, we rewrite the first term from Equation (3.8). 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

$$\begin{aligned}\int_0^\infty B_{2I}(\tau)\,d\tau &= \int_0^\infty \gamma_2 \int_0^\tau A_2(t-\sigma)Q_2(\sigma)\,d\sigma\,d\tau \\ &= \int_0^\infty Q_2(\sigma)\,d\sigma \int_0^\infty \gamma_2 A_2(v)\,dv. \end{aligned} \tag{3.12}$$

To find B_{2T}, we rewrite the second term from Equation (3.8).

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

And

$$\begin{aligned}\int_0^\infty B_{2T}(\tau)\,d\tau &= \int_0^\infty -\gamma_1 \int_0^\tau \int_0^\tau A_1(\tau-s)\,Q_1'(s-\sigma)\,ds\,Q_2(\sigma)\,d\sigma\,d\tau \\ &= \int_0^\infty -\gamma_1 Q_2(\sigma) \int_\sigma^\infty Q_1'(s-\sigma) \int_s^\infty A_1(\tau-s)\,d\tau\,ds\,d\sigma \\ &= \int_0^\infty Q_2(\sigma)\,d\sigma \int_0^\infty \gamma_1 A_1(v)\,dv. \end{aligned} \tag{3.13}$$

Putting Equation (3.12) and Equation (3.13) together, we get

$$\int_0^\infty B_2(\tau)\,d\tau = \int_0^\infty Q_2(\sigma)\,d\sigma \left[\int_0^\infty \gamma_2 A_2(\tau)\,d\tau + \int_0^\infty \gamma_1 A_1(\tau)\,d\tau\right]. \tag{3.14}$$

Thus, R_0 for this two stage model is given by

$$R_0 = K\beta(K)\sum_{i=1}^{2}\left[\int_0^\infty A_i(\tau)\,d\tau + \int_0^\infty \delta_i B_i(\tau)\,d\tau\right], \tag{3.15}$$

where we found the kernels in Equations (3.9), (3.10), (3.11), and (3.14).

We can see that in the following stages, the kernels for both the infective and treatment compartments will behave in a similar manner as $A_2(\tau)$ and $B_2(\tau)$. We generalize, by induction, that the R_0 for an age of infection model with n infective and treatment stages is given by

$$R_0 = K\beta(K)\sum_{i=1}^{n}\left[\int_0^\infty A_i(\tau)\,d\tau + \int_0^\infty \delta_i B_i(\tau)\,d\tau\right], \tag{3.16}$$

where kernels A_i and B_i are represented in terms of the distribution functions:

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

and

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

Note that $\int_0^\infty B_i(\tau)\,d\tau$ is composed only in terms of the distribution functions $P_i(\sigma)$ and $Q_i(\sigma)$. For simplicity, we leave the expression in terms of $A_i(\tau)$.

With this result, we pose the following theorem.

Theorem 3.1 *In the general treatment model, R_0 depends not only on the mean period in each infective and treatment stage, but also on the infectivity distribution.*

Note that R_0 does not depend on the treatment distribution. If control measures are applied to an epidemic model, the above results show how to compute the resulting reproduction number. The final size relation can be calculated from this reproduction number to give the final epidemic size with control measures. Given its simplicity, it may be desirable to use this method to evaluate the effect of a control measure.

For example, consider simple $SI_1I_2T_1T_2R$ models with (1) exponentially distributed infective and treatment stages, (2) exponentially distributed infective and fixed length treatment stages, and finally (3) fixed length infective and exponentially distributed treatment stages.

For part (1), R_0 is given by Equation (3.15) with

$$\begin{aligned}
\int_0^\infty A_1(\tau)\,d\tau &= \frac{1}{a_1} \\
\int_0^\infty A_2(\tau)\,d\tau &= \frac{a_1}{a_2(\gamma_1+a_1)} \\
\int_0^\infty B_1(\tau)\,d\tau &= \frac{\gamma_1}{a_1 b_1} \\
\int_0^\infty B_2(\tau)\,d\tau &= \frac{1}{b_2}\left[\frac{\gamma_2 a_1}{a_2(\gamma_2+a_1)} + \frac{\gamma_1}{a_1}\right].
\end{aligned}$$

For part (2), we find that R_0 is the same as above. Note that the change in treatment distributions does not affect R_0.

Last, for part (3), R_0 is given by Equation (3.15) with

$$\begin{aligned}
\int_0^\infty A_1(\tau)\,d\tau &= \frac{1}{a_1} \\
\int_0^\infty A_2(\tau)\,d\tau &= \frac{1-e^{-\gamma_1/a_1}}{a_2} \\
\int_0^\infty B_1(\tau)\,d\tau &= \frac{\gamma_1}{a_1 b_1} \\
\int_0^\infty B_2(\tau)\,d\tau &= \frac{1}{b_2}\left[\frac{\gamma_2 a_1}{a_2(\gamma_2+a_1)} + \frac{\gamma_1}{a_1}\right].
\end{aligned}$$

Note that changing the infective distribution from exponential (part 1) to fixed length (part 3) does change the value of R_0, while changing the treatment distribution (part 1 to part 2) does not. This is illustrated in Theorem 3.1.

Thus we have derived explicit formulas for R_0 using age of infection models with and without treatment. We found that our R_0 is in accordance with that of the traditional deterministic models. In the case without treatment, the R_0 depends on the mean infective time regardless of its distribution. In the case with treatment, we have found that R_0 depends not only on the mean infective and treatment time, but also on the infectivity distribution.

Chapter 4

Select epidemics of infectious respiratory diseases and their models

In this chapter, we provide a comprehensive overview of SARS, Tuberculosis, and Extensively Drug Resistant Tuberculosis. We discuss different mathematical models designed in efforts to provide optimal public and occupational health measures, or simply to model a disease spread for theoretical purposes.

4.1 Overview of SARS

SARS, an acronym for Severe-Acute Respiratory Syndrome, is a highly contagious, viral disease that first appeared in Southern China in November 2002 [2, 3]. Caused by a novel virus named SARS coronavirus (or SARS-coV), the illness rapidly became an epidemic, spreading over 8000 people worldwide and taking 774 lives [3, 4, 9]. Typical beginning symptoms are similar to a flu and include a feeling of overall discomfort, high fever, head and body aches. After an incubation period of 3 to 17 days, patients develop dry coughs that progress into dyspnea and possibly hypoxia (lack of oxygen in blood); most patients develop pneumonia [6–8]. The disease inflicts a relatively high rate of mortality (15 percent) especially among the elderly (50 percent) [2, 5–8]. SARS is believed to spread through close person-to-person contact; it is most readily transmitted via respiratory droplets caused by coughs or sneezes [11].

In the absence of a rapid diagnostic test, vaccine or other prophylactic drugs, the World Health Organization launched a campaign to stop the spread of SARS through typical means such as isolation and quarantine. Although the implementation of such means has been effective historically, mere isolation and quarantine were not enough to contain the spreading of SARS. Emerging nosocomial infections sustained the epidemic, until finally a sufficiently stringent hygiene protocol was adapted worldwide in approximately in April 2003, to successfully contain the disease. By August 2003, no new cases of SARS were reported, and the WHO

declared the SARS global outbreak to be over [5, 10].

4.1.1 SARS Models

Shortly after the outbreak of SARS, Chowell et al. [28] introduced a model capturing the effect of average infectiousness in a heterogeneous population, and the effect of isolation and diagnostic rates in controlling the epidemic. The model incorporated two susceptible compartments and an isolation compartment. After fitting data available from Hong Kong, Toronto, and Singapore, including the superspreading events, the reproduction number was found to be between 1.1 to 1.2, which is similar to that of Influenza [28].

In 2005, Gumel et al. presented a deterministic model that closely follows the data of four regions of the SARS outbreak: Singapore, Hong Kong, Beijing, and the Greater Toronto Area (GTA) [29], with both quarantine and isolation compartments.

This model ignores social network structure, spatial structure and age structure, as well as superspreading events. It incorporates demographic effects by assuming natural death rate, and includes net inflow of susceptible individuals. It also assumes that due to globalization and increased travel, there is a small rate at which asymptomatic individuals enter the susceptible population.

Both Chowell et al. and Gumel et al. examine the sensitivity of the reproduction number to various parameters that represent quarantine or isolation rate, death or recovery rate, and the rate at which an individual develops clinical symptoms or are diagnosed with an illness.

According to the numerical simulations by Gumel et al., reducing the contact rate of the isolated population by implementing stringent hygienic protocols contains the disease more effectively than reducing that of the quarantined population. The actual data agrees with this model; after introducing stringent hygiene precautions in April, the reported number of new SARS cases plateau until the eventual disappearance of the disease in August.

Chowell et al. similarly find that the reproduction number to be most sensitive to the diagnostic and isolation rate, and thereby assert the importance of prompt isolation and stringent protocols to contain the spread of SARS.

Compartmental models by Chowell et al. and Gumel et al. provide ideas for controlling the epidemic with more efficacy. These models are flexible enough to encompass a variety of respiratory infectious diseases. Both models include demographics, but the parameters are small enough that they could have been given as epidemic models. Since there is no treatment known for SARS, the novel aspects of the models are quarantine of the suspected and isolation of the diagnosed infectives. These models can also be interpreted with an age of infection framework;

using our approach from the previous section, it is possible to calculate the reproduction numbers, and also to find the epidemic size using the final size relation.

4.1.2 Some calculations of R_0

We can apply our method to calculate R_0 using the data from Gumel et al., and ultimately find the final size relation, provided that we have a reasonable estimates of the distribution function for both infective and treatment stages.

Since no expression for $P(\tau)$ and $Q(\tau)$ are available in literature, it is of interest to use available parameter values and find various plausible distributions that would yield a good approximation of R_0 (e.g. those found by Gumel et al.) which follow closely the real data.

Our models ignore demographics, and unlike Gumel et al's model, only have multiple infective and treatment stage compartments. We assign $I_1 = E, I_2 = I, T_1 = Q$, and $T_2 = J$ for our SI_1I_2R and $SI_1I_2T_1T_2R$ models, and estimate the parameters of exponential or fixed length distribution functions. GTA, HK, BJ and SG represent the Greater Toronto Area, Hong Kong, Beijing, and Singapore, respectively.

In the following example, we consider an SI_1I_2R model with exponentially distributed infective periods, where $a_1 = a_2$ for simplicity. Gumel et al. allow the coefficients of exposure and infectivity transmission (ε_E and ε_I, which correspond to our ε_1 and ε_2) to vary in their R_0 calculation; our method yields a linear relationship between R_0 and the ε_i, so we arbitrarily fix both ε_i at the value 0.3 and vary the steepness of the exponential distribution. The average infective period with SARS is approximately 36 days without treatment; generously, we let $0.025 < a_i < 0.03$ where $P_i(\tau) = e^{-a_i\tau}$. See Table 4.1.

Region	R_0 by Gumel et al.	R_0 lower bound	R_0 average	R_0 upper bound
GTA	4.8	4.15	4.53	4.91
HK	3.6	2.97	3.24	3.51
BJ	4.91	4.55	4.96	5.38
SG	5.04	3.96	4.32	4.68

Table 4.1: Lower and Upper bounds for R_0, and R_0 using average infective period for SARS, in comparison with Gumel's

The lower bound assumes $a_i = 0.03$ and upper bound assumes $a_i = 0.025$; R_0 average is calculated using 36 days as the mean infective period. We see that for each region, the R_0 average is slightly below Gumel's, with the exception of Beijing. Different model formulation and insufficient information on infective and

treatment distributions may be few of the causes for discrepancies in estimated values of R_0. As mentioned before, explicit infective and treatment distribution functions are unavailable in literature, but provided that we can approximate them using real data, we should be able to draw conclusions about the disease dynamics.

The following three tables give an illustration as to what plausible distribution functions could yield the values of R_0 presented by Gumel et al. This time, we let infectivity parameters ε_i vary, and approximate the parameter values for different distribution functions. Table 4.2 shows the parameter values for two exponentially distributed infective stages and respective infectivity transmission coefficients, assuming an SI_1I_2R model.

Region	R_0	a_1, in $P_1(\tau) = e^{-a_1\tau}$	a_2, in $P_2(\tau) = e^{-a_2\tau}$	ε_1	ε_2
GTA	4.8	.01	.03	.02	.66
HK	3.6	.01	.03	.02	.66
BJ	4.91	.69	.03	.01	.64
SG	5.04	.01	.03	.02	.66

Table 4.2: Parameter estimation of exponentially distributed infective stages (a_i), and infectivity parameters (ε_i).

Table 4.3 shows parameter values for two exponentially distributed infective and treatment stages. The case where we assume two exponentially distributed infective and two fixed length treatment stages yields the same result as in Table 4.3.

Region	R_0	a_1, in $P_i(\tau) = e^{-a_i\tau}$	a_2	b_1, in $Q_i(\tau) = e^{-b_i\tau}$	b_2
GTA	1.7	.75	.32	.12	.12
HK	2.8	.57	.12	.61	.32
BJ	4.03	.34	.81	.06	.05
SG	1.08	.32	.65	.22	.32

Table 4.3: Parameter estimation of exponentially distributed infective stages (a_i) and treatment stages (b_i).

Now we flip the distributions for infective and treatment stages. Table 4.4 shows parameter values for two fixed length infective stages and two exponentially distributed treatment stages. In both Table 4.3 and Table 4.4, we assume that the transmission coefficient in the first "treatment" compartment (Gumel et al. calls it ε_Q), is $\delta_1 = 0.2$. This is assuming that the transmission coefficient in one treatment stage is very close to that of the next. Gumel et al. gives ε_J, which is our δ_2 to range from .15 to .36.

The purpose of these tables is to illustrate the idea that, first, varying treatment

Region	R_0	a_1, where $P_i(\tau) = 1$ over $[0, 1/a_i]$	a_2,	b_1, where $Q_i(\tau) = e^{-b_i\tau}$	b_2
GTA	1.7	.28	.14	.96	.19
HK	2.8	.13	.26	.03	.40
BJ	4.03	.21	.51	.22	.06
SG	1.08	.44	.14	.81	.14

Table 4.4: Parameter estimation of fixed length infective stages (a_i), and exponentially distributed treatment stages (b_i).

distributions does not change R_0 while varying infective distributions does; and second, given that we can approximate the distribution function using real data, it will be easy to calculate R_0 using our method; and third, using the results, we can approximate the final epidemic size by using the final size relation.

4.2 Tuberculosis and Extensively Drug Resistant Tuberculosis

4.2.1 Overview of Tuberculosis (TB)

Tuberculosis (TB), is an infectious disease caused by a related Mycobacterium that most commonly affects the lungs, but may spread to various parts of the body. After being infected with TB, a patient undergoes a variable latent period in which the bacterium remains dormant, and later develops symptoms such as fever, coughs, dyspnea, caseation, and pleural effusions [32].

Currently, over 2 billion people have the TB bacterium in their bodies, and newly infected cases are arising at a rate of approximately one per second. In 2005, approximately 14 million people had active TB, and there were 8.8 million new cases and 1.6 million deaths, mostly in the South-East Asia Region and sub-Saharan Africa. The 2005 estimated per capita TB incidence was stable or falling in all six WHO regions, but partially offset by the population growth; the number of new infections arising per year is still increasing globally and the WHO regions of Eastern Mediterranean, South-East Asia and Africa [33, 36].

Drug-resistant strains of TB have also emerged and are spreading especially among the population with high HIV prevalence; this will be addressed in more detail in the next section.

In 1993, the WHO declared TB to be a global health emergency, and the Stop TB Partnership proposed a so called Global Plan to Stop Tuberculosis, which aims to save around 14 million lives by 2015, and by the year 2050, eliminate TB as a global health problem by reducing the incidence to less than 1 per million popula-

tion [35].

Transmission

TB is spread by airborne droplets expelled by people with active pulmonary TB via coughing, sneezing, spitting, and talking. It is estimated that a person with untreated, active tuberculosis can infect 10-15 other people every year [33]. People at risk of contracting TB include those from areas where TB is common, patients with HIV/AIDS, residents and employees of high-risk environments, health care workers who serve high-risk patients, low-income populations, and people who share needles injecting drugs.

According to the Center of Disease Control, the probability of transmission depends upon the quantity of the infectious droplets expelled by the patient, the duration of exposure, the quality of ventilation, and the virulence of the Mycobacterium [37]. Thus, transmission can be prevented by isolation and treatment of patients with active TB, by vaccinations for children, and by improving the quality of ventilation in public and private health institutions.

Treatment

The two antibiotics most commonly used to treat TB, also referred to as the first-line drugs, are isoniazid and rifampicin. These require about 6 to 12 months of treatment, which is longer than the duration of regular antibiotic treatments [37]. Once a patient becomes resistant to the first-line drugs, he or she moves to a cocktail drug regime with the second-line drugs, such as fluoroquinolone, amikacin and kanamycin. The second-line drugs are more costly, more toxic, weaker than the first-line drugs, and require at least 18 months of treatment [42]. Patients with Multidrug resistant TB (MDR-TB) show resistance to the most effective and widely used first-line drugs, isoniazid and rifampicin; those with extensively drug resistant TB (XDR-TB) show resistance to both the first and second-line drugs [39]. A detailed definition of XDR-TB follows in the next section.

4.2.2 Overview of Extensively Drug Resistant Tuberculosis (XDR-TB)

On September 1, 2006, the WHO reported that a deadly new strain of XDR-TB had been found in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal. Such 53 cases reportedly represents one sixth of all known XDR-TB cases worldwide, as of January 2007 [38]. XDR-TB has been formally defined to be TB with resistance to at least isoniazid and rifampicin, and at least two of the

second-line drugs (a fluoroquinolone, and one or more of the following injectable drugs: amikacin, kanamycin, capreomycin) [39].

Both MDR-TB and XDR-TB are transmitted in the same manner as regular TB. Primary resistance occurs in patients who are infected with a resistant strain of TB. It is suspected that a patient with fully-susceptible TB develops secondary resistance during TB therapy because of inadequate treatment, failure to adhere strictly to the prescribed regimen, or the use of low quality medication [33, 42]. Drug-resistant TB is a public health issue especially in many developing countries, due to the prolonged length of treatment and high cost of medication.

Current Concern

The current concern with XDR-TB is the high morbidity and mortality (100%) rate coupled with the lack of any active, new classes of drugs to treat the illness. This is a pressing concern in South Africa and other developing countries, as many patients who are infected with tuberculosis are already HIV positive [41, 42]. In a recent study done by Gandhi et al., more than half of the 42 cases who contracted XDR-TB had never been treated with tuberculosis, and an additional third had either been cured or had completed treatment for TB. Gandhi et al. claim that most patients were unlikely to have developed XDR-TB as a consequence of unsuccessful treatment. Instead, they believe that transmission occurred between individuals; nosocomial transmission is also considered a possibility [41].

4.2.3 Prevention and Control Strategies

Several prevention and control strategies, especially pertaining to South Africa, have been suggested in literature. First, resources are needed so that the full extent of MDR-TB and XDR-TB can be assessed. Second, TB treatment programs must be strengthened to improve treatment completion rates (the rates were lower than the WHO standards), and provide treatment for drug resistant TB. Third, simpler tools and more rapid tests for diagnosis should be developed so that resource-limited areas such as South Africa would also gain power and speed in detecting MDR and XDR-TB. Last, improvements in infection control facilities and practices are crucial in order to prevent nosocomial infections. [38, 41, 43].

4.2.4 Mathematical Models of TB

In general, dynamic epidemic models tend not to include birth and death rates, since disease dynamics on the population at large remain unchanged. This is

because the epidemics tend to pass through a population rapidly. Usually Influenza models include control measures such as isolation, quarantine and treatment; SARS models include isolation and quarantine.

However, for diseases such as TB that have a long time scale, it is necessary to include demographics. Also, the structure of TB demands the inclusion of at least a latent compartment. Especially with MDR and XDR-TB, additional compartments are needed as well. TB models can also be written as age of infection models, and our approach can be applied to calculate basic reproduction numbers.

Chapter 5

Discussion

Based on previous models [12, 22], we have formulated slightly more generalized 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.

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 is dependent only on the mean period in a compartment, not the actual distribution. However, the reproduction number for models with treatment compartments is dependent both on the mean infective and treatment periods, as well as the infectivity distribution. In other words, one needs detailed information about the infective and treatment periods in non-treatment and treatment models alike, but in treatment models, one needs information about treatment 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 [22]. 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 if the models are formulated without demographics so that the final size relation is applicable [19, 28, 29].

However, our analyses do not carry over entirely 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. The

final size relation is valid only for models without demographics, but our approach of calculating the basic reproduction number remains applicable.

In conclusion, epidemic models without demographics are simpler because there is a final size relation which provides us with useful information–such as whether there will be an epidemic, if so the size of the epidemic, and the effect of various control measures–in the event of an infectious disease outbreak. Our method of calculating R_0 explicitly by using age of infection models provides more flexibility in dealing with different diseases. This method remains valid for models that include demographics, but we cannot draw further information as the final size relation does not exist.

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