# Chapter Twelve

# Outbreak Dynamics: From Prediction to Control

## 12.1 INTRODUCTION

On September 26, 2014, the CDC's Ebola Modeling Task Force published an ominous warning: the total number of cases of Ebola virus disease could exceed 1.4 million by January 2015 without large-scale intervention and changes in behavior (Meltzer et al. 2014). Given the high fatality rate, this prediction implied that more than 1M individuals could die from Ebola virus disease over a 4 month period unless large-scale interventions were initiated. This prediction immediately became news and newsworthy. For the public and policy makers, the number - 1.4 million - conveyed an unmistakeable fact: the ongoing Ebola epidemic in West Africa was markedly different than every other Ebola epidemic since the first identification of Ebola virus disease in the 1975 (Chowell and Nishiura 2014). Already by September 2014, more people had been infected over a wide geographic range and more people were dying than in all prior Ebola epidemics combined (Alexander et al. 2015).

The basis for this original CDC forecast was a dynamic epidemiological model of how Ebola virus disease spreads through the three most affected countries: Guinea, Liberia and Sierra Leone. The assumptions of the model, like many other models of infectious outbreaks, were that individuals exposed to the disease eventually become infectious and, only then, could transmit EVD to susceptible individuals (Legrand et al. 2007) Approximately 70% of infected individuals were assumed to subsequently die from the disease. New infections in the model occurred whenever a susceptible individual contracted EVD from an infectious individual through direct contact. A key assumption underlying the CDC model was that individuals within a country had an equally likely chance to interact with anyone else, whether in their village, city or district or in any other village, city, or district, i.e., the model assumed a "well-mixed" population at the country scale.

As is now well known, estimates of the total number of Ebola cases reached nearly 30,000 with greater than 11,000 reported deaths. The true number was likely higher given systemic under-reporting. But the actual case counts remain substantially below that of the September projection by the CDC and subsequent projections by the WHO in October 2014 of monthly cases exceeding 50,000 by November and increasing after that (Team 2014). In reviewing the differences between projections and reported cases it is important to recall that the CDC also included a caveat to the worst-case scenario projection. They

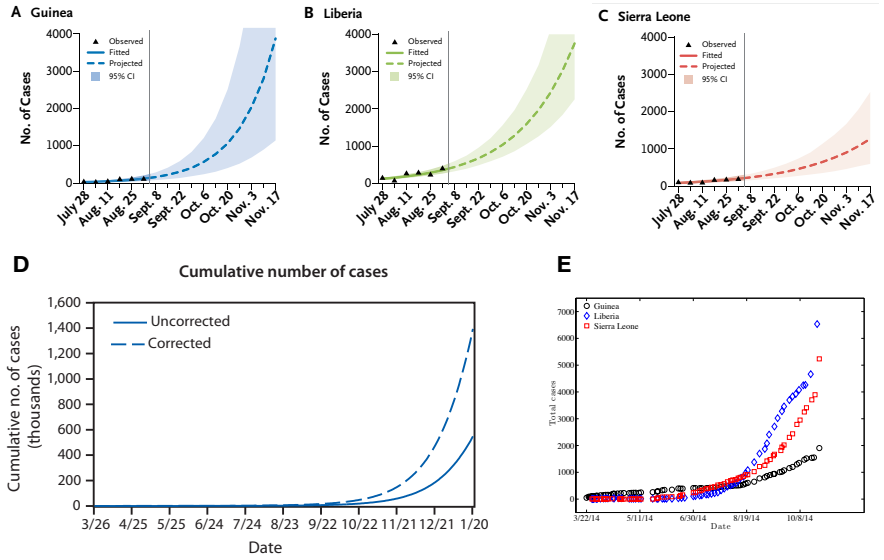


Figure 12.1: Models, data, and predictions in the late 2014 EVD outbreak in West Africa. Panels (A)-(C) denote WHO predictions at the country scale (reproduced from WHO situation reports and (Team 2014)). Panel (D) denotes the CDC prediction of total case count through early 2015 without intervention. Panel (E) denotes actual case count, source: Caitlin Rivers open repository. Panel D reproduced from (Meltzer et al. 2014)

pointed out that as control measures are "rapidly implemented and sustained, the higher projections presented in this report become very unlikely." As of January 2015, the World Health Organization reported that Liberia's new weekly case counts dropped to nearly zero, and Guinea and Sierra Leone saw substantial improvements from late December 2014. Indeed, the 2014-2015 epidemic soon came to a close, even as new outbreaks (in 2018) and threats of transitions to endemicity remain even now.

The difference between worst-case scenarios and outcomes should be a reason for some optimism amidst a challenging situation – particularly to the extent that models helped galvanize the response and shape interventions. Indeed, the purpose of models is not simply to predict, but also to provide a rationale for why intervention is necessary (Rivers 2014; Lofgren et al. 2014). For example, would we blame the person who called the fire department when seeing a house is on fire, if the house was later saved from ruin? Of course not. Yet, some questioned the value of disease forecasts in responding to Ebola, particularly when initial predictions later turned out to have been significant over-estimates of the true scope of the outbreak. Just as there are dangers to inaction when faced with a disease outbreak, there are also costs, trade-offs and dangers to

mis-calibrating response. If models can be used to support the argument to intervene then shouldn't we also expect that they should be used to build the appropriate type, scope and pace of intervention?

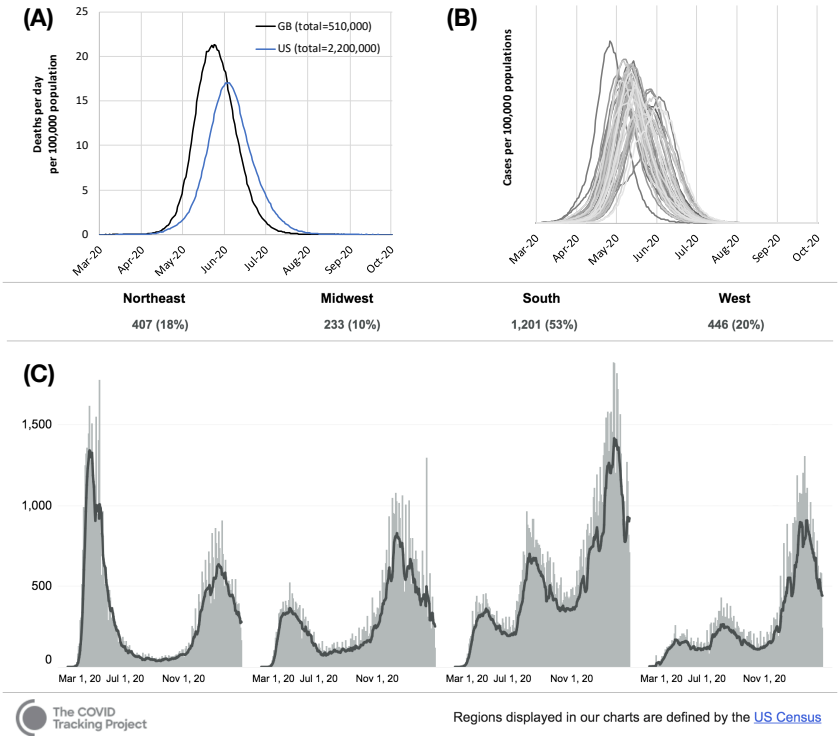


Figure 12.2: Early Covid-19 modeling predictions in the unmitigated case (top, from (Ferguson et al. 2020)) vs. regional fatality data from the USA via covidtracking.com

These questions remain prescient. In January 2020, news reports began to circulate of case clusters of an influenza-like illnes in Wuhan. This emerging infectious disease – Covid-19 – has transformed the health, movement, and fundamental well-being of individuals across the globe. Given prior experiences with the potential rapid spread and severity of SARS-1, the elevated role of modeling in the EVD response, and increased availability of case data (including genomic data (Hadfield et al. 2018)), there has been a rapid, connected response of epidemic response models. One group - the Imperial College of London team - provided a key, influential forecast that, like the CDC work of 2014-5, included both no-intervention forecasts as well as projections of the potential utility of scenarios (Ferguson et al. 2020). The top panels in Figure 12.2 illustrate the key dilemma. In the absence of aggressive non-pharmaceutical interventions (NPIs),

using early case reports from Wuhan to parameterize a compartmental model of spread, the team projected that roughly 80% of a population might become infected and given an infection fatality rate slightly lower than 1% when taking into the age-dependence of severe disease (and fatalities), they concluded that over 2,000,000 individuals in the United States and that over 500,000 individuals in the UK might succumb to this emerging infection.

Yet, unlike EVD, the unmitigated scenario is, unfortunately, far closer to the actual outbreak impact than the mitigated one. The bottom panels of Figure 12.2 show the regional impacts of Covid-19 in the United States, including evidence of plateaus and oscillations in fatalities. As of March 2021, there have been more than 525,000 fatalities in the US alone and over 2.5M globally. Covid-19 has become the leading cause of death in many age groups, rivaling even heart disease amongst the elderly. This widespread impact has emerged despite significant efforts to intervene; guided in part by models that predicted devastating consequences of inaction, as well as the potential impact of NPIs. It is hard to write a textbook about SARS-CoV-2 amidst a response (though other books on virus origins and responses are already in press). Hence, the illustration of impact and contrasting outcomes suggest that diseases that, from a modeling perspective, may have similar large-scale impacts do have, in fact, vastly different outcomes when spreading through populations.

One key difference is that individual and population level outcomes are not equivalent. For those who get infected, EVD is a truly awful disease, with a 70% chance of dying and strikingly few effective treatments – even as new vaccine candidates are being developed. In contrast, the vast majority of individuals infected with SARS-CoV-2 will survive. Notably, although the infection fatality rate of the disease varies with age, increasing to above 5% for individuals above 75, many individuals - especially younger individuals - can have asymptomatic infections. Hence, for many, an infection with SARS-CoV-2 will not be particularly worse than a cold or flu. Yet, at the population scale, the lack of symptoms is precisely one of the reasons that Covid-19 has become so difficult to stop (Du et al. 2020; Wei et al. 2020; Park et al. 2020b): given that asymptomatic and presymptomatic individuals can spread the infection to other, more vulnerable individuals, radiating the impact outwards through partially silent, and then devastating chains.

This chapter is intended to introduce the core concepts of epidemiological models with an eye towards informing the kind of decision making used during an infectious disease outbreak. Whereas many other chapters focus on understanding the core principles of living systems – at whatever scale – here there is an important distinction. The intention of epidemic modeling is to work in Pasteur's Quadrant (Stokes 2011), i.e. developing methods to mitigate and control an outbreak rather than predicting a bad outcome accurately. Hence, the purpose of this chapter is to help advance fundamental understanding of disease transmission that could guide and improve critical interventions. The plural is important. In essence, this chapter takes the persepective that models have a crucial role to play in identifying multi-faceted, rather than a monolithic,

response to epidemic outbreaks. The many facets of such a response may be unconventional, including vaccination, quarantines, and even changes in behavior. The role of each of these responses can be seen by first examining simple dynamic models and then using EVD and SARS-CoV-2 as case studies to put these ideas into practice.

In doing so, this chapter will try to answer the following set of questions. What are the key drivers that determine whether a disease is likely to spread, or not? What are the priorities for intervention that could forestall the spread of disease or to control the spread during an outbreak? How can vaccinatoins make a difference even if not everyone gets vaccinated? And, finally, how certain can we expect to be about the likely spread (without intervention) and the ideal targets of interventions given that estimating outbreaks often takes place at the start, where numbers of infected cases may not necessarily be large and stochasticity may be important, and where behavioural changes in response to disease may be just as important as large-scale interventions.

## 12.2 THE CORE MODEL OF AN OUTBREAK: THE 'SIR' MODEL

### 12.2.1 The premise

The spread of infectious disease requires the spread of the causative agent – an infectious pathogen – from one individual to another. Transmission events may occur through various means, e.g., short- or even long-distance transmissions through the air (e.g., sneezing) physical contact (including sexual transmission), indirect transmission (e.g., through the environment via contact with contaminated surfaces), or via vector-borne transmission (e.g., via mosquitos, ticks, flies, see Figure 12.3). Each transmission is a 'chance' event, yet cumulatively

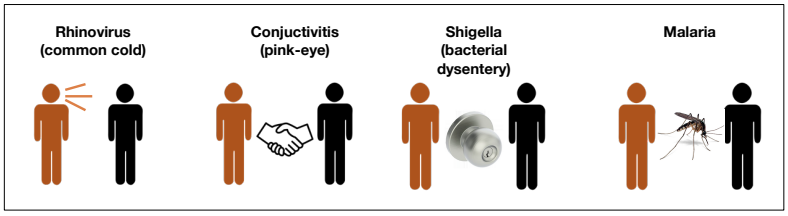


Figure 12.3: Interaction modes for disease transmission, including airborne, contact, environmental, and vector-borne.

outbreak dynamics can exhibit regular features. Part of the reason for this regularity is that for large outbreaks, the factors driving individual transmission events lead to predictable changes in the states of individuals with respect to the pathogen. For example, in the case of an infectious disease from which expo-

sure (and survival) leads to life-long immunity, individuals may be susecptible, infectious, or recovered. The study of epidemiological dynamics aims to connect these microstates of individuals to the macroscopic state of the population, in which there are $S$, $I$, and $R$ individuals that are either susecptible, infectious, or recovered.

To begin, consider a population characterized by $(S(t), I(t), R(t))$ such that $S + I + R = N$, where $N$ is the (fixed) number of individuals in the population. This population might represent a town, county, district, state or country. Imagine one of these susceptible invidiuals who, during the course of a day interacts with $c$ individuals that could potentially lead to disease transmission. Of these individuals, a fraction $I/N$ are infectious. Hence this individual has, on average $cI/N$ potentially infectious contacts. Yet not all contacts lead to transmission. If there is a $p$ probability of transmission for each infectious contact, then one expects the probability of $k$ successful transmission events in one day would be $B(k|c, pI/N)$ where $B$ is the binomial distribution given $c$ trials and $pI/N$ probability of success per trial. Hence, the probability that there are no successful transmission events should be $B(0|c, pI/N)$ or $(1-pI/N)^c$. Likewise, the probability that there is at least one successful transmission event should be $1-(1-pI/N)^c$. Note that when $p \ll 1$ then this reduces to $cpI/N$. We could, in principle build a stochastic model of disease transmission in this way, tracking the stochastic trajectory of an outbreak and its feedback on the underlying numbers of susceptible, infectious, and (eventually) recovered individuals.

Instead, consider a model which keeps track of very small units of time, where we now interpret the value of $c$ to be a *rate* of contact per unit time. In that way, the probability of a transmission event with one focal susceptible individual taking place in a small unit of time is $cp\frac{I}{N}\mathrm{d}t$. For $S$ individuals, the probability of a transmission event in a small unit of time will be $cpS\frac{I}{N}\mathrm{d}t$. Concurrently, infectious individuals can recover at a rate $\gamma$. Altogether, a model of disease dynamics would include transmission events and recovery events, which can be represented as a coupled system of nonlinear differential equations

$$\dot{S} = -\overbrace{\beta S\frac{I}{N}}^{\text{infection}}, \tag{12.1}$$

$$\dot{I} = \overbrace{\beta S\frac{I}{N}}^{\text{infection}} - \overbrace{\gamma I}^{\text{recovery}}, \tag{12.2}$$

$$\dot{R} = \overbrace{\gamma I}^{\text{recovery}} \tag{12.3}$$

where $\beta \equiv cp$. This is the standard 'SIR' model of infectious disease spread (see Figure 12.4). A full derivation beginning with a stochastic model is included in the Technical Appendices.

In practice, the spread of disease in different populations can be compared by re-scaling the dynamics in terms of the fraction of individuals in each of the

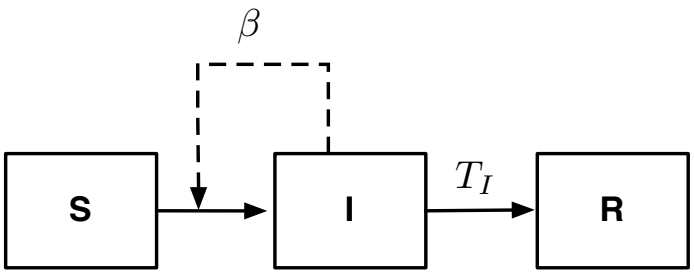


Figure 12.4: The SIR model of disease dynamics.

three states. Hence, consider the normalized variables $\tilde{S} = S/N$, $\tilde{I} = I/N$, and $\tilde{R} = R/N$, such that $\tilde{S} + \tilde{I} + \tilde{R} = 1$. In that case the core model becomes

$$N\frac{\mathrm{d}\tilde{S}}{\mathrm{d}t} = -N^2\beta\tilde{S}\frac{\tilde{I}}{N}, \tag{12.4}$$

$$N\frac{\mathrm{d}\tilde{I}}{\mathrm{d}t} = N^2\beta\tilde{S}\frac{\tilde{I}}{N} - \gamma N\tilde{I}, \tag{12.5}$$

$$N\frac{\mathrm{d}\tilde{R}}{\mathrm{d}t} = \gamma N\tilde{I}, \tag{12.6}$$

Factoring out factors of $N$ and removing the ˜ notation, we can write down the SIR model in terms of the fraction of the population that is susceptive, infectious, or recovered/removed as:

$$\dot{S} = -\beta SI \tag{12.7}$$

$$\dot{I} = \beta SI - \gamma I, \tag{12.8}$$

$$\dot{R} = \gamma I. \tag{12.9}$$

In this model the disease free state corresponds to $(S = 1, I = 0, R = 0)$, although given the fact that $S + I + R = 1$, it is only necessary to focus on two of three state variables. This disease free state is also an equilibrium of the model in Eqs. (12.9). Precisely because it is an equilibrium, we may want to know: what happens then when a small number of infectious individuals are added to the 'disease-free' state?

### 12.2.2 Conditions for disease spread

The fate of a disease can be expressed in multiple ways. Perhaps the most intuitively is to ask: what happens to the fraction of infectious individuals in a population when a very small number (perhaps only one in $N$) of infectious individuals appear in the population. Without loss of generality, the dynamics of the infectious fraction is:

$$\dot{I} = I\left(\beta S - \gamma\right). \tag{12.10}$$

However, when the population is nearly, totally susceptible, i.e, $S \approx 1$, then this equation becomes:

$$\dot{I} \approx I\left(\beta - \gamma\right). \tag{12.11}$$

The fate of the disease depends on the difference between new infections and recovery, or $\beta - \gamma$. This difference is known as the speed of disease spread, $r \equiv \beta - \gamma$. A positive speed implies that an outbreak will occur, with an exponentially increasing number of new cases, at least at first. In contrast, a negative speed implies that the outbreak dissipates, with an exponentially decreasing number of new cases. This difference can also be written in a different way,

$$r = \gamma\left(\mathcal{R}_0 - 1\right) \tag{12.12}$$

where

$$\mathcal{R}_0 \equiv \frac{\beta}{\gamma} \tag{12.13}$$

is known as the basic reproduction number. The basic reproduction number is "arguably the most important number in the study of epidemiology' (sensu (Diekmann et al. 1990; Diekmann and Heesterbeek 2000). It deserves its own box.

$\mathcal{R}_0$: the average number of new infectious caused by a single infectious individual in an otherwise susecptible population.

It is perhaps even more intuitive to understand $\mathcal{R}_0$ by recognizing that $1/\gamma$ is equal to the average infectious period, $T_I$. Hence, if $\beta$ denotes the number of new infections caused by a single individual per unit time, then multiplying by the time of infectiousness yields an average number of new infections over the course of that infection. In essence, $\mathcal{R}_0$ measured disease spread at the individual scale. For example, if $\mathcal{R}_0 = 2$ that implies that a typical infectious individual will generate 2 new cases before they recover. Thoese two new cases will each generate two more (or nearly so), which leads to four caes, then eight, sixteen, and so on. At some point the number of cases may actually deplete the susceptible population and the exponential growth will slow down. Exponentials are not forever. Nonetheless, the strength of the epidemic, as measured in terms of $\mathcal{R}_0$ provides a threshold condition for the spread of the disease. In essence, when $\mathcal{R}_0 > 1$ then the disease will spread, because each infectious invididual leads to 1 or more new infectious individuals (exceeding replacement) (see Figure 12.5).

Yet, you may have a doubt. There is feedback between susceptibles and infecteds. Is it really appropriate to analyze only the $\dot{I}$ equation? The answer, in brief, is yes. Formally this is because $\dot{I}$ is the only infected subsystem of the model. But, if you are still not satisfied then it is worthwhile to take a dynamical systems perspective and ask: what are the conditions in which the disease free equilibrium is unstable? The local stability of a fixed point can be examined by linearizing the model and exploring the growth or decay of small fluctuations.

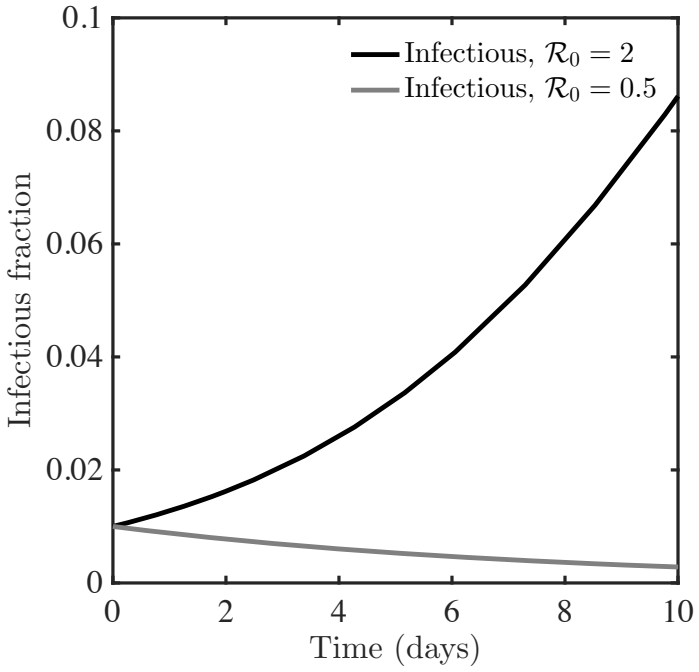


Figure 12.5: Outbreak outcomes depend on the strength of the disease, $\mathcal{R}_0$.

The process of linearizing a nonlinear model was introduced earlier this book, specifically in the context of nonlinear genetic circuits. The same process applies here as demonstrated in the Technical Appendices.

There are two eigenvalues for the SIR model given a disease free equilibrium, $\lambda_1 = 0$ and $\lambda_2 = \beta - \gamma$. Finding a zero eigenvalue implies that there are some perturbations to the fixed point that do not lead to any further change – whether increasing or decreasing – to the state space. It turns out that this corresponds to a particular kind of perturbation, in which a small number of individuals are moved from the $S$ state to the $R$ state, i.e., $(1, 0, 0) \to (1-\epsilon, 0, \epsilon)$. The latter state is also an equilibrium of the model. In fact, there is a *whole line* of equilibria, for any combination of $S$ and $R$ that add up to 1! This pertubration also has a biological interpretation: it is what would happen if one vaccinated a fraction $\epsilon$ of the population. We will return to this concept in a moment to explain precisely why it is possible that vaccinating a fraction of the population can provide 'herd immunity' to nearly everyone, even those who are not vaccinated! Hence, although $\lambda_1$ does not seem to depend on the etiology or transmissability of the disease, $\lambda_2$ does, and it corresponds precisely to the speed inferred from analyzing only the $\dot{I}$ equation. Note that although the analyses coincide, it is preferable to use the linearization approach, or even the next-generation method to find robust answers to the question: what are the conditions in which a disease

will spread, or not.

## 12.3 THE SHAPE OF AN OUTBREAK

### 12.3.1 Outbreak dynamics – basics

In theory, the spread of a disease begins exponentially. As infectious cases increase, even more susceptibles are infected. Some of the infectious individuals begin to recover, leading to the characteristic increase of recovered and infectious individuals while susceptibles decline. Yet the disease does not keep spreading indefiniteily. Instead, at a certain point the infectious case count begins to decrease. It does so not because of any intervention but because there are fewer and fewer susceptibles availble to infect even as the characvteristic recovery rate of the disease remains constant. As is evident in Figure 12.6, there is a critical point at which $\dot{I} = 0$ (corresponding to the peak incidence of the disease), after which the incidence declines. This point must correspond to the condition when

$$\dot{I} = I(\beta S - \gamma) = 0 \tag{12.14}$$

There are two conditions when this holds. The first is when $I = 0$ (i.e., the disease free state) and the secnod is when $S = \frac{\gamma}{\beta} = \frac{1}{\mathcal{R}_0}$. In other words, the disease will begin to die out once the fraction of susceptibles drops below $1/\mathcal{R}_0$. This observation holds the key to multiple facets of epidemiology – both from a prediction and control perspective. Recall that the definition of the basic reproduction number was contextual and assumed that the population was wholly susecptible. Analogously, we can define a state-dependent dimenless number termed the "effective reproduction number", i.e.,

$\mathcal{R}_{eff} = \frac{\beta S}{\gamma}$: the average number of new infectious caused by a single infectious individual in a partially susecptible population, $0 \leq S < 1$.

The connection to the transition between disease spread and disease dissipation is now apparent. The dynamics of $\dot{I}$ can be written as:

$$\dot{I} = \gamma I(\mathcal{R}_{eff} - 1) \tag{12.15}$$

such that the depletion of susceptibles contineus to reduce $\mathcal{R}_0$, and because $\mathcal{R}_{eff}$ scales with $S$, then once $S$ is reduced by a factor of $\mathcal{R}_0$, then the effective reproduction number drops below 1. Once the incident case count starts to decline, it cnotinues to decline until there are no more infectious cases, i.e., the disease has run its course. What is notable is that not everyone gets sick. For the particular example in Figure 12.6 in which $\mathcal{R}_0 = 1.6$ there is still a substantial fraction of the population, 0.35 to be precise, that was never infected. Hence, the final size of the epidemic was 0.65, in the sense that at one point or another

65% of the population had the disease. Notice that $1 - 1/1.6 = 0.375$, which is not equal to the final number of non-infected individuals; because of overshoot after herd immunity is reached. As a reminder herd-immunity is the threshold where cases just replace themselves, this can be a preventative threshold at the outset of an epidemic, but it implies that new cases will continue after incidence starts to decline. In fact, there is a putative relationship between the strength of the disease – as measured by $\mathcal{R}_0$ – and the final size – as measured by $R_\infty$, but that requires more explanation.

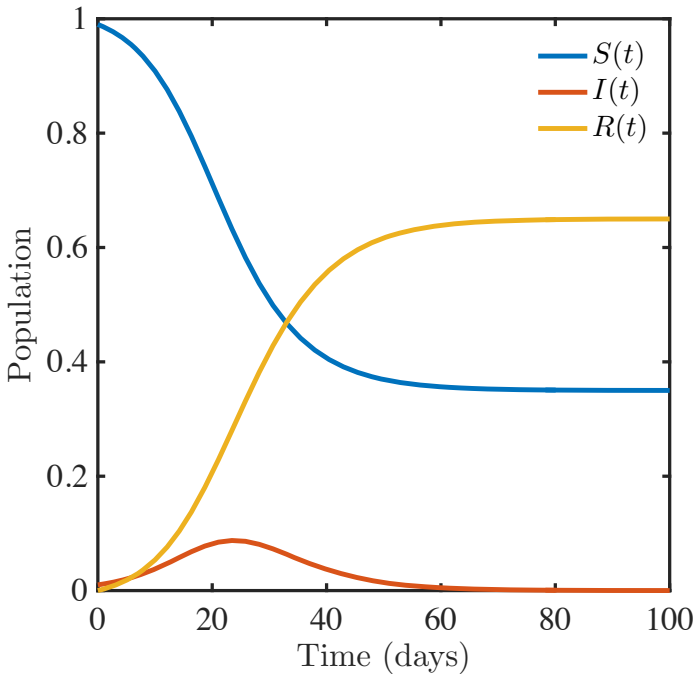


Figure 12.6: Disease outbreak given $\mathcal{R}_0 = 1.6$ and $\gamma = 0.25$ days$^{-1}$.

### 12.3.2 Speed, size and strength

What is the relationshp between the strength of the disease and the final size? It would seem intuitive that if infectious individuals spread the disease more readily at the outset that this would compound, over time, to yield more cases by the end. Such is the power of exponentials. But, diseases spread in finite populations, and so the relationshpi between strength and final size may be more tenous. To understand the problem, consider what would happen if a single infectious individual entered into a population of size $10^4$. As long as $\mathcal{R}_0 > 1$, the disease is expected to spread. But to how many?

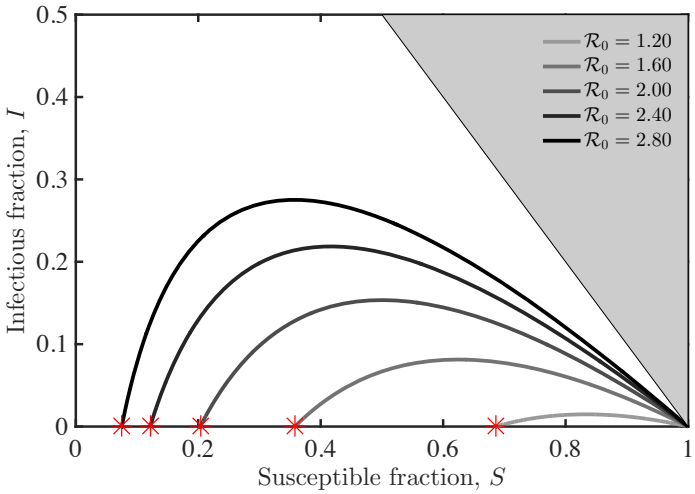


Figure 12.7: Final size dependency on $\mathcal{R}_0$. In each case trajectories begin near a fully susceptible population albeit with different values of $\mathcal{R}_0$. The asterisks denote the expected final size according to theory.

To answer this question, consider a replicate set of populations, e.g., distinct towns, an animal herd, or a crop culture. The strength of a particular pathogen depends both on the etiology of the disease and the connectedness of the population. Hence, the same pathogen could have very different values of $\mathcal{R}_0$ due to the environment in which it spreads. We can determine the final epidemic size by numerically simulating the SIR model. However, there is another way. Note for a moment that the rate of change of infectious and susceptible individuals can be factored, and when taking the ratio of these rates of change yields:

$$\frac{\dot{I}}{\dot{S}} = \frac{-\beta SI + \gamma I}{\beta SI}. \tag{12.16}$$

Because the $I$ variable cancels out, it is possible to integrate these equations, not over time, but respect to the differential change in both infectious and susceptible individuals. The approach, is shown in the Technical Appendices. The result is the following:

$$\mathcal{R}_0 \left(S_\infty - 1\right) = \log\left(S_\infty\right). \tag{12.17}$$

Figure 12.7 compares this final size prediction (red asterisks) to the results of numerical simulations (solid lines), all beginning with the same initial condition but with increasing $\mathcal{R}_0$. The formula works. However, the lack of a closed form implies that the solution requires finding the crossing of the term on the left-hand side with that on the right. Yet, some intuition is possible. Note

that the right-hand side of Eq. (12.17) decreases from 0 to $-\infty$ over the interval $0 \leq S_\infty < 1$. The left-hand side denotes a line from 0 to $-\mathcal{R}_0$ over the same interval. These functions will cross at a single point so long as $\mathcal{R}_0 > 1$, ever closer to 0 as $\mathcal{R}_0$ increases. This single crossing point represents the final size of the epidemic.

Some caveast are important when predicting final sizes from the strength of the disease. Indeed, size-strength predictions may have an elegant mathematical underpinning, but they are often violated, in practice. Critically, models of size-strength coupling assume a well-mixed population with identical risk of exposure, susceptibility, and transmissability. Yet, variation in these levels can lead to fundamental changes in the long-term outcome. For example, given heterogeneity in exposure, it is likely that individuals with more connections may be infected first. However, precisely because they are highly connected, then a pathogen is more likely to 'waste' interactions with highly connected individuals. The gap between predicted size based on $\mathcal{R}_0$ alone and realized size remains one of the key uncertainties in integrating predictions into practice.

### 12.3.3 From epidemics to endemics

The SIR model is one variant of many representations of epidemic dynamics – the variants often depend on the etiology of the disease, in particular the extent to which recovered individuals are immune from subsequent infection (as in measles) or susceptible in the near future (as in many common colds caused by rhinoviruses). For example, consider a SIR model in which recovered individuals eventually become susceptible, e.g., at a rate $\gamma$. Hence, in this case the standard SIR model becomes

$$\dot{S} = -\beta SI + \alpha R \tag{12.18}$$

$$\dot{I} = \beta SI - \gamma I, \tag{12.19}$$

$$\dot{R} = \gamma I - \alpha R. \tag{12.20}$$

where $\alpha$ is the rate of loss of immunity. Now, although an outbreak may temporarily deplete susceptibles, these susceptibles will be replenished by the loss of immunity. This suggests that there may be a new equilibrium outcome: an endemic disease state. This possibility can be analyzed more readily by taking one particular limit, when $\alpha \gg \gamma$. In that case, the dynamics of the recovered are in a quasi-equilibrium, i.e., $\dot{R} = 0$ such that $R^* = \gamma I/\alpha$, and replacing $R(t)$ with this value yields what is termed the 'SI' model:

$$\dot{S} = -\beta SI + \gamma I \tag{12.21}$$

$$\dot{I} = \beta SI - \gamma I, \tag{12.22}$$

The SI model denotes a disease that transmits with a rate $\beta$ and for which infectious individuals recover at a rate $\gamma$ but are then immediately infectious.

In this model, the conditions for the disease outbreak remain precisely the same as in the SIR model. That is there is an outbreak when $\mathcal{R}_0 = \beta/\gamma > 1$.

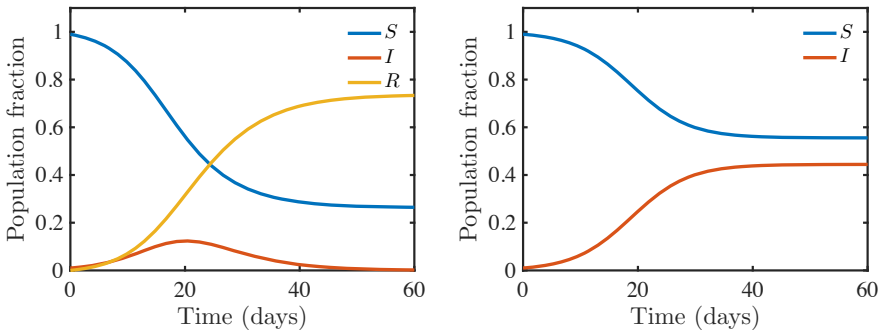


Figure 12.8: From outbreaks in a SIR model (left) to endemics in a SI model (right) both with $\beta = 0.45$ and $\gamma = 0.25$ in units of days.

However, when there is an outbreak, then there is also a different outcome: an endemic disease. Figure 12.8 contrasts the outcomes for a disease with the same values of $\beta$ and $\gamma$, however the case on the left denotes a disease with permanent immunity and that on the right denotes a disease with no immunity. As such, the dynamics do not lead to a new equilibrium with the absence of disease. Instead, the equilibrium endemic state is

$$S^* = \frac{\gamma}{\beta} = \frac{1}{\mathcal{R}_0} \tag{12.23}$$

$$I^* = 1 - \frac{\gamma}{\beta} = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0} \tag{12.24}$$

such that increasing strength also corresponds to a larger final size. It is important to note that the final size of the epidemic in the SIR denotes the number of individuals who ever contracted the disease. In contrast, the SI disease size denotes the disease burden at any given time – it is possible that all will get the disease at one point or another, at least in theory, as long as $\mathcal{R}_0 > 1$. Together these models suggest that controlling a disease depends critically on steps taken to change the dynamics at the very outset, when there are still a small number of infectious individuals in the population.

## 12.4 PRINCIPLES OF CONTROL

The reason for focusing so much attention on the strength $\mathcal{R}_0$ is not only because it is a critical threshold condition for understanding when diseases spread, but it also represents the conceptual basis for understanding how to control and even prevent the spread of an infectious disease. Recall, once again the definition of $\mathcal{R}_0$, this time whil retaining the individual parameters that underlie its definition:

$$\mathcal{R}_0 = c \cdot p \cdot T_I \cdot \left(\frac{S}{N}\right) \tag{12.25}$$

where $c$ is the number of contacts per unit time, $S/N$ is the fraction of such contact that are susceptible, $p$ is the probability that a contact between a susceptible individual leads to transmission. This equation already suggests many of the core strategies necessary, each operating on one or a combination of these contributing factors.

**Hospitalization and treatment - $T_I$:** Hospitalization and treatment has multiple beneficial effects. The most evident effect is that it reduces the period $T_I$ of infectiousness. It may also have secondary effects on $c$, reducing the number of contacts per unit time, however these benefits can be counterbalanced by the repeated interactions with health-care professionals who themselves may be vectors and vulnerable to disease transmission.

**Contact tracing and targeted isolation - $c$:** Contact tracing denotes efforts by public health responders to identify the source of an outbreak. Once an infectious individual is identified, responders will try to work 'backwards' to identify a potential transmission chain, i.e., to find out the potential source of the epidemic, as well as 'forwards' to try and identify those who may have been exposed.

**Vaccination - $S/N$:** Vaccination reduces the pool of susceptible individuals. As a consequence, a random interaction will less often be between a $S$ and an $I$ individual, and as we will show, when enough potential infection events are wasted, then it is possible to control the disease.

**Process engineering or personal protective equipment - $p$:** The last line of defense for stopping a disease is process engineering or the use of PPE (personal protectiv equipment). For EVD this requires extreme measures (the white hamzat-style suits), whereas for other diseases, like SARS, protective measures can include face masks. Finally, hand-washing and other measured are considered standard approaches to reduce $p$ in a preventative sense.

Rather than work through examples of each one, let's focus on a proven approach that has been instrumental in preventing disease outbreaks in the first place: vaccination. Project Tycho recently released a series of data visualizations, one of which I included below. As is apparent, the introduction of a measles vaccine in 1963 lead to a rapid decline in case incidences throughout the United States (see Figure 12.9) Measles can be a deadly disease, pre-vaccine, there were approximately half a million annual cases and 50,000 hospitalizions, and 500 deaths. Measles is also highly transmissable, with an estimated $\mathcal{R}_0 \approx 15$ (see Guerra et al. PID, 2017). How then can vaccines be so effective at stopping it, particularly given that it is unlikely that all will receive them.

One step towards an answer starts with analysis of the SIR model. In practice, a full accounting of a model for measles requires consideration of births, age-dependent susceptibility, transmission, and more. Nonetheless, some insights are possible using the SIR model given the highly contagious nature of the disease.

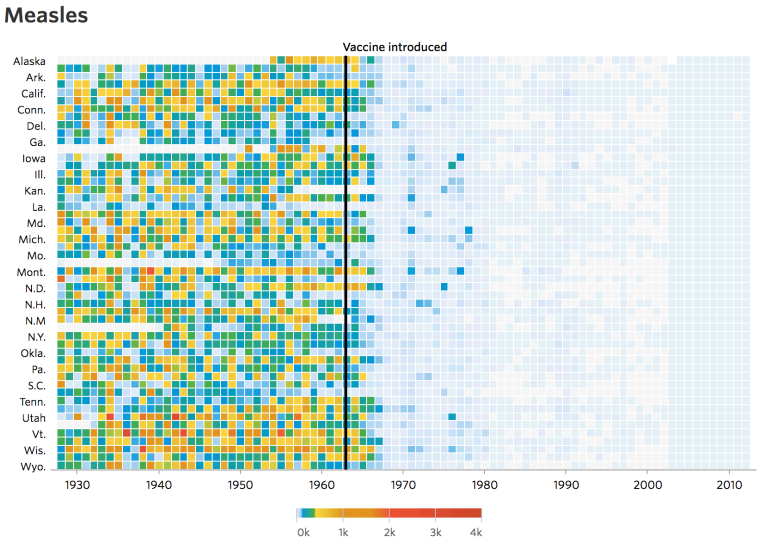


Figure 12.9: Measles incidence per $10^5$ individuals, reproduced from WSJ 2015 Project Tycho data visualization.

To begin, recall that the initial speed of disease (corresponding to the positive eigenvalue) was $\beta S_0 - \gamma$. Now consider if a fraction $0 \le f < 1$ of the population is vaccinatted and therefore already begins in the $R$ class, so that $S_0 = (1 - f)$. The initial (exponential) speed of the outbreak can be written as:

$$r = \gamma \left( \mathcal{R}_0 (1 - f) - 1 \right). \tag{12.26}$$

This speed switches from positive to negative when $\mathcal{R}_0(1 - f) = 1$, or at the critical vaccination level:

$$f_c = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0}. \tag{12.27}$$

Figure 12.10 show that stopping the spread requires that a substantial *fraction* of the population is vaccinated. This fraction increases with increasing strength. The total protection of partial vaccination underlies the concept of *herd immunity*. Imagine a scenario where an infectious individual A moves to a particular population – will such an introduction subsequently lead to the transmission of the disease to individual C? Imagine further that A interacts with B who interacts with C. If B is vaccinated then C will be protected, even if they themselves have not been vaccinated. In essence, interactions are "wasted" on vaccinated individuals. The ideal is to have nearly 100% vaccination, but the imperative becomes more important with increasing disease strength.

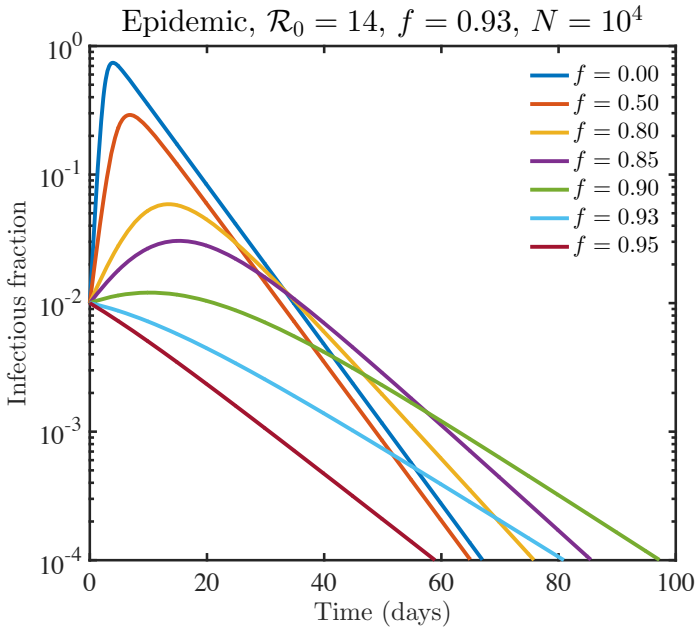


Figure 12.10: Vaccination and outbreaks in epidemic simulations.

## 12.5 EVD: A CASE STUDY IN CONTROL GIVEN UNCERTAINTY

The responses listed in the prior section may seem generic, but they are precisely the kind of responses considered in real outbreaks even when vaccination is not available. For example in the 2014-5 EVD outbreak in West Africa, an influential response model (Pandey et al. 2014) consider a variety of strategies for containing Ebola. These strategies included the following:

- Transmission precautions for healthcare workers
- Reducing general-community transmission
- Sanitary burial
- Isolation of Ebola patients
- Contact tracing and quarantine
- General quarantine

As should be apparent, including this many features requires a more complex model than the SIR model here; this intervention model was informed by datasets and observations of an unfolding crisis. Yet the core concepts stem

from an effort to understand the factors governing $\mathcal{R}_0$. How much effort amd emphasis to place for each factor depends on rogust estimates of the basic reproduction number. Yet that estimate is inherently uncertain, particularly at the start of an outbreak. The extent of this variation sets a lower bound on certainty of the properties of a disease, and should also influence the confidence one has in using a particular, rather than a set of, control mechanisms. Quantifying this stochastic limit to confidence is explained next.

### 12.5.1 Process noise and stochastic outbreaks

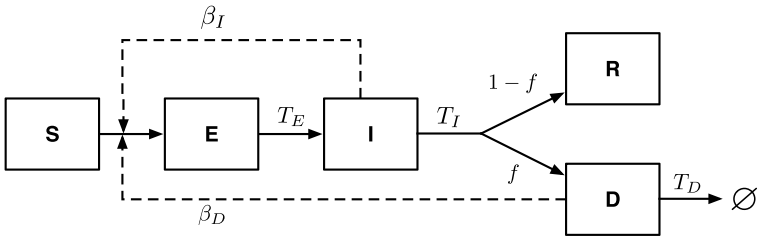


Figure 12.11: SEIRD model of EVD dynamics including post-death transmission; reproduced from (Weitz and Dushoff 2015).

Stochastic variation in the timing of discrete transmission events can generate variation in estimates of the realized growth rate of an epidemic, $r_0$. The amount of variation depends on the particular disease model, disease parameters, and the time-scale over which $r_0$ is estimated. Consider the example of EVD dynamics as modeled using an SEIRD model (see Figure 12.11):

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta_I SI/N - \beta_D SD/N, \tag{12.28}$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta_I SI/N + \beta_D SD/N - E/T_E, \tag{12.29}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = E/T_E - I/T_I, \tag{12.30}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = (1-f)I/T_I, \tag{12.31}$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = fI/T_I - D/T_D. \tag{12.32}$$

in which individuals are suseceptible, exposed (but asymptomatic), infectious, recovered, or dead (but not yet buried). The inclusion of a dead class reflects the fact that post-death transmission was a critical factor in EVD transmission (Weitz and Dushoff 2015) (e.g., in an extreme case the burial of an Imam in Mali led to nearly 100 documented cases). In this model the average latent

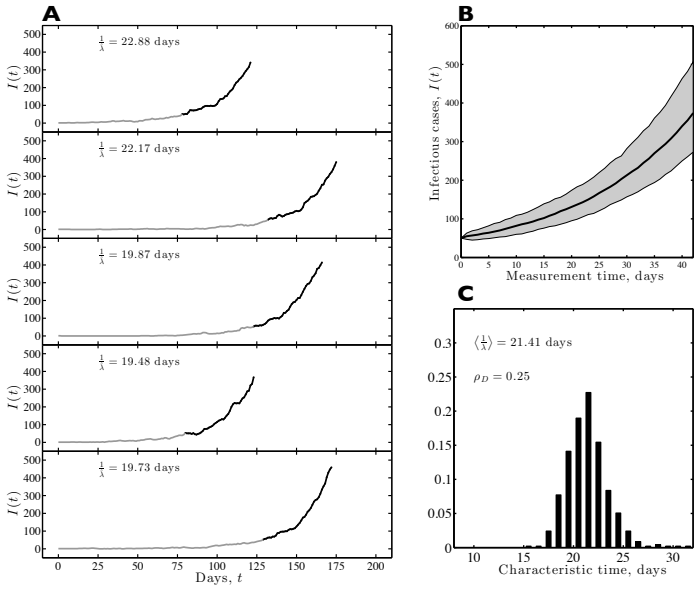


Figure 12.12: Stochastic realizations of a SEIRD epidemic include substantial variability in epidemic growth rate (reprinted from (Taylor et al. 2016)). (A) Each panel denotes a randomly chosen trajectory for which $I(t)$ exceeded 50. The gray period denotes those times for which $I(t) < 50$ and the black period denotes a 42 day measurement period after the first day for which $I(t) \geq 50$. The estimated epidemic growth rate for each trajectory over the fitting period is denoted in the upper left of each panel. (B) Variation in infectious time series once a threshold is reached of 50 cases. The solid line denotes the average number of cases and the shaded region denotes a 95% CI. (C) Variation in the estimated characteristic time, $\tau_c$, of the epidemic. In all cases, simulations correspond to stochastic simulations of a SEIRD model in which $N = 10^6$, $\beta_I = 0.25$, $\beta_D = 0.2$, $\sigma = 1/11$, $\gamma = 1/6$, $f = 0.7$ and $\rho_D = 0.25$. The theoretically expected characteristic time is $\tau_c = 21$ days.

period is $T_E = 11$ days, the average infectious period is $T_I = 6$ days, there is a $f = .7$ chance of an infected individual dying and there is an average time of $T_D = 4$ days before burial. Further, the transmission rates are set to $\beta_D = 0.20$ and $\beta_I = 0.25$, such that a fraction $\rho_D = \frac{\mathcal{R}_0(\text{dead})}{\mathcal{R}_0} = 0.25$ of transmission is attributable to post-death transmission. Resulting simulations using the Gillespie algorithm reveal that at the early stages there can be significant variation in outcomes (a topic explored in the associated computational laboratory). This variation in speed translates directly into uncertainty in $\mathcal{R}_0$ – a theme present in analysis of SARS-CoV-2 as well (Park et al. 2020a).

### 12.5.2 Control strategies given uncertainty

Because of uncertainty, controlling a disease must concede that the strength of the disease is weaker or stronger than it appears via a best-fit approach. In addition, when there are multiple transmission pathways, as in EVD, then there is also lingering uncertainty with respect to the optimal control mechanisms. In EVD, part of the uncertainty had to do with burial transmission. Safe burial teams were deployed to the region early on, a process that could be implemented far more rapidly than Ebola treatment units that took 3 or more months to deploy at scale and within hard-to-access regions. What is the rationale for this choice? For EVD, one estimate of $\mathcal{R}_0$ for a SEIRD model could be written as

$$\mathcal{R}_0 = \frac{1}{M(-\lambda)} \tag{12.33}$$

where

$$M(z) = \int_0^\infty e^{za} g(a) \mathrm{d}a \tag{12.34}$$

is the moment generating function (see the Technical Appendices for more details). As is apparent, given the relatively low value of $\mathcal{R}_0$, models estimate that eliminating post-death transmission would be half of the needed reduction in disease strength to eliminate the outbreak altogether (see Figure 12.13). This result might be surprising, and although burial control was not widely discussed in popular press reports, the inclusion of safe and dignified burials (as per the WHO) became a key to ending the EVD outbreak.

In retrospect, the initial CDC model of Ebola virus disease spread had two central components: a model of infectious transmissions in the absence of interventions and a model for the effect of interventions. In the absence of control, infectious individuals were assumed to cause 1.8 new infected cases. The two types of intervention considered were: (i) hospitalizion; (ii) home/community isolation. The CDC model assumed that the number of new infections for a hostpialized individual was 0.12 and for an individual who was isoalted at home/community to be 0.18. In other words, relative to the no intervention scenario, home isolation was assumed to reduce disease spread by 90Instead, work on extended models with burial associated spread elevated the importance of post-death transmission and its influence on $\mathcal{R}_0$, thereby also raising this new opportunity for control.

## 12.6 ON THE ONGOING CONTROL OF SARS-COV-2

It remains too early to evaluate the aggregate impacts of different NPIs as well as vaccination programs on stopping the ongoing pandemic. The story of SARS-CoV-2 continues to unfold. Epidemic models have played a far larger role in structuring interventions and they remain the subject of ongoing debate. Part of that debate may be warranted, but part of it resembles the very same debate that was triggered in the use of models in the 2014-5 response to EVD.

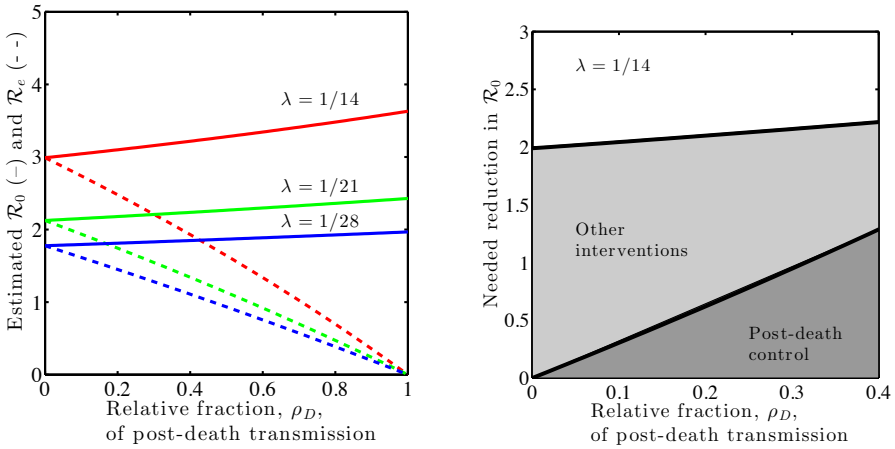


Figure 12.13: The effect of controlling post-death transmission of EVD. (Top-left) Basic reproductive numbers without intervention (solid lines) compared to effective reproductive numbers by eliminating post-death transmission (dashed lines). Reproductive numbers are plotted against the fraction $c_D$ of secondary infections due to dead-to-living transmission. In both panels, $\mathcal{R}_e = (1-p)\mathcal{R}_0$. Estimates are for a SEIRD model given outbreaks with 2, 3 and 4 week characteristic times, i.e., $\lambda = 1/14$, $1/21$ and $1/28$ days$^{-1}$ respectively. (Top-right) Break-down of the needed reduction in $\mathcal{R}_0$ to reach a value of $\mathcal{R}_e = 1$ for one of the characteristic times examined in the top-left panel. The dark-shaded region denotes the reduction in secondary cases due to elimination of post-death transmission as a function of $\rho_D$. The light-shaded region denotes the additional reduction in secondary cases necessary after post-death transmission is eliminated (Weitz and Dushoff 2015).

It is critical to distinguish between models that are meant to highlight the risk of inaction, evaluate the potential benfits of interventions, and to perform short-term forecasts (often in the absence of a mechanistic representation of the transmission of disease). All of these classes of models have been used and continued to be used to respond to SARS-CoV-2. Nonetheless, one of the key gaps in all of these approaches has been the challenge to integrate epidemic spread with the response of individuals and societies in changing behavior.

The link between behavior and epidemics remains one of the most important conceptual challenges for the field (Funk et al. 2010). Yet, in practice, the earliest models used by the Imperial College of London team (and the bulk of models used in forecasting and assessing the value of interventions) combined variants of SEIR models together with strictly exogeneous changes in transmission as a result of policy changes. The policy changes varied, but included a suite of options including generalized lockdowns, restrictions on travel, school closures,

and mask-wearing. Yet, near the outset, the assumptions in such models were that the compliance with these policy changes and the extent to which individuals would comply with travel restrictions and/or mask wearing was set by the timing of the imposition and release of policies. The reality is more complex – and not only becauase populations involved spatially distributed networks of connections – but precisely because individiuals do not have a static suite of reactions to an unfolding pandemic.

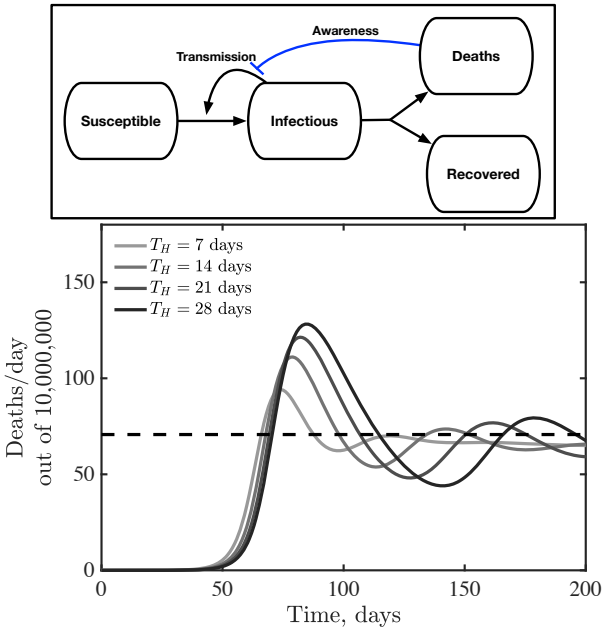


Figure 12.14: SEIR model with awareness-driven feedback (top) and emergent oscillations (bottom) given parameters associated with the transmission of SARS-CoV-2. Reproduced from (Weitz et al. 2020).

In practice, the global awareness of the unfolding SARS-CoV-2 pandemic has elevated the importance of assessing, integrating, and potentially leveraging the feedback between awarness, behavior, and disease spread. In the absence of such feedback, then SARS-CoV-2 transmission should have led to a single peak corresponding to reaching herd immunity and then a rapid decline. Yet, with NPIs, the appearance of peaks in scenario models were connected to the timing of policies, such that a second wave would reflect the fact that early changes in policy led to decreases in transmission in the absence of susceptible depletion. In turn, when policies relaxed, then the disease would rebound. Figure 12.14 reveals that exogeneous changes in transmission are not the only route to generate plateaus and oscillations. Instead, such patterns may be characteristic of feedback between disease and awareness.

In this SEIR model the transmission rate decreases as a function of the awareness of the severity: onsider the extended SEIR model:

$$\dot{S} = -\frac{\beta SI}{\left[1+(\delta/\delta_c)^k\right]} \tag{12.35}$$

$$\dot{E} = \frac{\beta SI}{\left[1+(\delta/\delta_c)^k\right]} - \mu E \tag{12.36}$$

$$\dot{I} = \mu E - \gamma I \tag{12.37}$$

$$\dot{R} = (1-f_D)\gamma I \tag{12.38}$$

$$\dot{H} = f_D\gamma I - \gamma_H H \tag{12.39}$$

$$\dot{D} = \gamma_H H \tag{12.40}$$

where $\beta$ is the transmission rate, $f_D$ is the infection fatality rate, $T_H = 1/\gamma_H$ defines the average time in a hospital stay before a fatality, $\mu$ is the exposure to infectiousness rate $\gamma$ is the average infectious period, $\beta$ is a transmission rate and $\delta =\equiv \dot{D}$ denotes the level of new fatalities, which scales behavior given a critical level $\delta_c$ and a shape exponent $k$. This model variant includes time spent in the hospital in the case of severe illness. As a result the feedback between awareness implies the possibility of oscillatory dynamics. When severity is high, individuals change behavior, but because of time lags between behavior change and the onset of cases that eventually become severe and lead to fatalities, there can be lags before behaviors change again. These cycles drive the system toward a persistent plateau which represents a quasi-stationary state in the disease with $\mathcal{R}_eff \approx 1$. Although such models do exhibit qualitative (and even quantitative) features of joint disease spread and behaviour change, it is evident there remain significant gaps to a full integration. Yet, the absence of such integration always come with peril: neglecting endogeneous behavioural changes will lead to continued missed opportunities to improve the efficacy of planning, control, and intervention efforts.

## 12.7 TAKE-HOME MESSAGES

- Mathematical models of epidemic spread are increasingly utilized in responding to infectious disease outbreals.
- Core epidemic models are driven by interactions that lead to changes in the disease status of individuals.
- The criterion for spread when the bulk of the population is susceptible is that a single infectious individual infects one (or more) new individuals on average.
- Transmission modulates both the the strength and speed of disease.

- The final size of epidemics are linked to the strength (however, caution is needed given the many assumptions use in otherwise, mathematically elegant size-strength formulations).

- Application of epidemic models to the case of EVD interventions suggested the need for interventions, however the absence of certain categories (like post-death transmission) also limited the nature of their recommendations.

- An ongoing challenge arising from SARS-CoV-2 is to integrate behavior change into improved scenario, forecasting, and intervention modeling.

## 12.8 HOMEWORK PROBLEMS

**Problem 1. Nuanced Etiology**

Extend the SIR model of emerging infectious disease to an SEIR model

$$\dot{S} = -\frac{\beta SI}{N} \tag{12.41}$$

$$\dot{E} = \frac{\beta SI}{N} - \eta E \tag{12.42}$$

$$\dot{I} = \eta E - \gamma I \tag{12.43}$$

$$\dot{R} = \gamma I \tag{12.44}$$

Given the parameters $\beta$=1.25/week, $\gamma$ = 1/week calculate the basic reproduction number for the SIR version of this model (i.e., without an exposed state). Then, systematically modulate the value of $\eta$ from 4/week to 0.25/week. Using simulations and other methods, estimate the growth rate of the epidemic and compare it to that expected in the limit where individuals are immediately infectious. Next, assume a mismatch between the real value of $\eta$ and the prior assumption of its value, e.g., $\eta_0$ = 1/week. Infer the estimate value of $\mathcal{R}_0$ from growth data for each pair of true vs. prior value of $\eta$ and discuss how mismatches between the period of infectiousness and actual periods of infectiousness can impact estimates of the strength of an outbreak in terms of $\mathcal{R}_0$.

**Problem 2. Stochastic lift-off**

Extend the SEIR model presented in Problem 1. to a stochastic framework using the techniques developed in the computational laboratories associated with this chapter. Given these parameter sets, simulate 100 outbreaks in a population of size $N = 1000$ beginning with a single individual in the exposed state. What is the final size distribution of these outbreaks? Next, compare and contrast these final size distributions assuming that there are 10 initially exposed individuals. If you have time, use intermediate values and assess the impact of initial infection sizes on outcomes – and assess the potential for 'stochastic liftoff' in this model.

**Problem 3. Cruise ship outbreaks**

Consider a cruise ship with $N = 2200$ individuals in which there is an outbreak of Norwalk disease (equivalent to norovirus), with the following features:

- Infections are highly contagious (approximately 5% chance of infection given an interaction with an infected person)
- Recovery time is typically 5 days. Recovered individuals become immune for 6 months.
- A typical cruise ship passenger interacts with a small percentage of other passengers in a day (usually 1%)

3a. Propose a model for the dynamics, including estimates of all relevant parameters.

3b. The trip is meant to last 3 weeks. One passenger is carrying Norwalk virus and becomes ill on the first day, show the expected dynamics of the disease. Do you think the disease dies-out or does it spread, why or why not?

3c. Using the deterministic SIR model and assumptions, determine how many people got sick, how many people never got sick, and the maximum number of sick people at any given time.

3d. Revisit the two questions above in a stochastic framework: does the disease die-out or does it spread, why or why not? And, in the event that the disease does spread, characterize the features of the outbreak.

3e. Your grandparents invite you to go on a 3 week Alaskan cruise. Sounds fun. You have the option of choosing cruise ships with 1400 people, 800 people, or 200 people. You have heard about Norwalk and are concerned about being on a cruise ship with an epidemic. Assuming that 1 person was infected on any of these cruise-ships, and using the parameter values in part (a), identify which of these ships is susceptible to an outbreak. Show graphs and provide explanations to support your results.

Problem 4. Outbreaks and Behavior

*Caveat: this problem was first utilized in the QBioS course at Georgia Tech in November 2019; it predates the outbreak of SARS-CoV-2.* Thus far we have assumed that interactions remain constant throughout the course of the epidemic. This problem addresses the consequences of feedback between disease spread and behavior, given the following dynamics:

$$\dot{S} = -\frac{\beta(I,R)SI}{N} \tag{12.45}$$

$$\dot{E} = \frac{\beta(I,R)SI}{N} - \eta E \tag{12.46}$$

$$\dot{I} = \eta E - \gamma I \tag{12.47}$$

$$\dot{R} = \gamma I \tag{12.48}$$

where the infection rate $\beta$ is equal to the product of the average number of contacts per unit time and the probability of infection spread per contact; these may depend on the state of the system. In this example, consider dynamics associated with an airborne transmitted disease (like SARS) in a city of size $N = 5\times10^4$ in which individuals usually encounter $\approx 50$ individuals per day (under baseline conditions), with an average incubation duration of 5 days and average infectious period of 5 days. **Warning - this problem set was developed last year, in October 2019, but I recognize that it seems oddly prescient. I hope that working on this problem this year will help reveal new insights that are possible when linking transmission with behavior.**

4a. Simulate the baseline dynamics of the system given the probability of infectious spread given contact of 1%. Given the introduction of a single infectious individual in an otherwise susceptible population, what is the peak time of the epidemic, how many total individuals are infected over the course of the epidemic, and what is the speed of the disease spread? Use visualizations of the epidemic to support your answer.

4b. Given public health campaigns, individuals start to wear masks, which reduce the spread of disease per contact to virtually 0%. However, the compliance with mask wearing scales with disease incidence, such that the fraction of individuals wearing masks scales like $p = \epsilon\frac{I+R}{N}$ where $\epsilon = 0.4$, i.e., representing the maximum fraction of mask mearing. Simulate the expected spread of disease and estimate the strength, speed, and final size of the epidemic? Which of these differ significantly from the baseline case, and why?

4c. Modify the previous model assuming that the campaign targeted all individuals (not just those with symptoms). Is there any difference, why or why not?

4d. If you had to design a public health policy surrounding mask wearing, what level of pre-existing compliance (i.e., what level of pre-existing $p$) would be necessary to prevent an outbreak at the very outset?

## 12.9 TECHNICAL APPENDICES

### 12.9.1 Derivation of the mean field SIR model

The SIR model is often invoked, but rarely derived. Yet, the formal interpretation of the model is that of a continuous disease transmission process where the SIR model equations represent the dynamics of the expected numbers of susceptible, infectious, and recovered. In essence, the SIR are 'mean-field' equations, neglecting fluctuations and correlated changes in population states. Let us show this formally.

To begin, consider the population state in terms of three integers, $(S, I, R)$ such that $S + I + R = N$. A stochastic equation for the change in values of these three states a time step $\Delta t$ in the future is:

$$\begin{aligned} S(t+\Delta t) &= S(t) - \chi(S,I) && (12.49)\\ I(t+\Delta t) &= I(t) + \chi(S,I) - \psi(I) && (12.50)\\ R(t+\Delta t) &= R(t) + \psi(I) && (12.51) \end{aligned}$$

where $\chi$ and $\psi$ are Binomial distributed variables, such that

$$\chi \sim B(S, \beta \frac{I}{N} \Delta t) \tag{12.52}$$

and

$$\psi \sim B(I, \gamma \Delta t). \tag{12.53}$$

There can be at most $S$ new infections and $I$ recovery events in a time period $\Delta t$. However, when $\Delta t \to 0$ that becomes unlikely, indeed, there will be, at most, a single event of either kind per small unit of time. The equations above describe a stochastic process. We are interested in the expected value, i.e.,

$$\begin{aligned} \mathbb{E}\left(S(t+\Delta t)\right) &= \mathbb{E}\left(S(t) - \chi(S,I)\right) && (12.54)\\ \mathbb{E}\left(I(t+\Delta t)\right) &= \mathbb{E}\left(I(t) + \chi(S,I) - \psi(I)\right) && (12.55)\\ \mathbb{E}\left(R(t+\Delta t)\right) &= \mathbb{E}\left(R(t) + \psi(I)\right) && (12.56) \end{aligned}$$

We will 'abuse' notation (to borrow the mathematics term) and use the same letters $S$, $I$, and $R$ for the expected values, such that we can rewrite these equations as:

$$\begin{aligned} S(t+\Delta t) &= S(t) - \beta S \frac{I}{N} \Delta t, && (12.57)\\ I(t+\Delta t) &= I(t) + \beta S \frac{I}{N} \Delta t - \gamma I \Delta t, && (12.58)\\ R(t+\Delta t) &= R(t) + \gamma I \Delta t. && (12.59) \end{aligned}$$

Finally, noting that $\frac{\mathrm{d}x}{\mathrm{d}t} = \lim_{\Delta t \to 0} \frac{x(t+\Delta)-x(t)}{\Delta t}$ we derive the SIR model:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta S \frac{I}{N}, \tag{12.60}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S \frac{I}{N} - \gamma I, \tag{12.61}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I \tag{12.62}$$

### 12.9.2 Local stability analysis of the SIR model

Consider the normalized SIR model and the fixed point $(1,0)$, i.e. $S^* = 1$ and $I^* = 0$ and, by definition, $R^* = 0$ given that $S + I + R = 1$. If $\dot{S} = f(S,I)$ and $\dot{I} = g(S,I)$ then the Jacobian is:

$$J = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix} \tag{12.63}$$

where for this model

$$J = \begin{bmatrix} -\beta I & -\beta S \\ \beta I & \beta S - \gamma \end{bmatrix} \tag{12.64}$$

which evaluated at the fixed point $(1,0)$ becomes

$$J = \begin{bmatrix} 0 & -\beta \\ 0 & \beta - \gamma \end{bmatrix}. \tag{12.65}$$

The eigenvalues can be solved by finding the solution to $\mathrm{Det}\,(J - \lambda \mathbb{I})$ where $\mathbb{I}$ is the identity matrix $\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$. For $2 \times 2$ matrices with a zero off-diagonal term, the eigenvalues can be read off the diagonal of the $J$ matrix. To see this explicitly, note that $\mathrm{Det}\,(J - \lambda \mathbb{I}) = -\lambda\,(\lambda - (\beta - \gamma))$. Hence $\lambda_1 = 0$ and $\lambda_2 = \beta - \gamma$. The interpretation of these eigenvalues is discussed in the main text.

### 12.9.3 Strength-final size relationship

In the SIR model, the final size of the disease $R_\infty$ is related to the strength of the outbreak, $\mathcal{R}_0$. The final size denotes the total number of individuals who were infected by the disease. Because all invididuals eventually recover (or are removed), then $R_\infty = 1 - S_\infty$ represents the quantitity of interest. The final size relationship in the main text can be derived as follows. Recall that in the SIR model, the fraction of susecptible and infectious individuals changes according to

$$\dot{S} = -\beta S I \tag{12.66}$$

$$\dot{I} = \beta S I - \gamma I. \tag{12.67}$$

such that the ratio of the derivatives, $\dot{I}/\dot{S}$, can be written as

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}S} &= \frac{-\beta SI + \gamma I}{\beta SI},\\ \frac{\mathrm{d}I}{\mathrm{d}S} &= \frac{-\beta S + \gamma}{\beta S} = -1 + \gamma/(\beta S).\end{aligned} \tag{12.68}$$

The term on the right-hand side is a function of $S$ only, which means that this equation is separaable and can be solved by multiplying both sides by $\mathrm{d}S$ and integrating, i.e.,

$$\int \mathrm{d}I = \int \mathrm{d}S\left(-1 + \frac{\gamma}{\beta S}\right) \tag{12.69}$$

yielding

$$I = -S + \frac{\gamma}{\beta}\log(S) + C \tag{12.70}$$

where $C$ is an integration constant. This equation can be solved by recalling that at the start of the epidemic, $S = 1$ and $I = 0$ such that $C = 1$. The critical insight to solving this final size prob;lem is to recognize that the relationship between $I$ and $S$ also applies at the end of the epidemic where $S = S_\infty$ and $I_\infty = 0$. Hence, this leads to the following relationship

$$S_\infty - 1 = \frac{\log(S)}{\mathcal{R}_0} \tag{12.71}$$

or

$$\mathcal{R}_0(S_\infty - 1) = \log(S_\infty). \tag{12.72}$$

Note that there is a slightly different size-strength relationship when the population is initially partially susceptible, i.e., $S(t = 0) = S_0$. In that case, the relationship

$$I = -S + \frac{\gamma}{\beta}\log(S) + C \tag{12.73}$$

implies that

$$C = S_0 - \frac{\gamma}{\beta}\log S_0. \tag{12.74}$$

Recall that $\mathcal{R}_{eff} = \mathcal{R}_0 S_0$ where $S_0$ is the initial fraction susceptible. As such, we can rewrite the integration constant as

$$C = S_0\left(1 - \frac{\log S_0}{\mathcal{R}_{eff}}\right). \tag{12.75}$$

Therefore, the final size must satisfy

$$C = S_\infty - \frac{\gamma}{\beta}\log S_\infty \tag{12.76}$$

or

$$\left(1 - \frac{\log S_0}{\mathcal{R}_{eff}}\right) = \frac{S_\infty}{S_0} - \frac{\log S_\infty}{\mathcal{R}_{eff}} \tag{12.77}$$

or finally

$$\mathcal{R}_{eff}\left(1-\frac{S_\infty}{S_0}\right)=\log\frac{S_0}{S_\infty}. \tag{12.78}$$

### 12.9.4 Local stability analysis of the SI model

Consider the normalized SI model and the fixed point $(1,0)$, i.e. $S^*=1$ and $I^*=0$. If $\dot{S}=f(S,I)$ and $\dot{I}=g(S,I)$ then the Jacobian is:

$$J=\begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix} \tag{12.79}$$

where for this model

$$J=\begin{bmatrix} -\beta I & -\beta S+\gamma \\ \beta I & \beta S-\gamma \end{bmatrix} \tag{12.80}$$

which evaluated at the fixed point $(1,0)$ becomes

$$J=\begin{bmatrix} 0 & 0 \\ 0 & \beta-\gamma \end{bmatrix}. \tag{12.81}$$

Using the methods described above, $\lambda_1=0$ and $\lambda_2=\beta-\gamma$. The interpretation of these eigenvalues is discussed in the main text.

### 12.9.5 Stochastic simulations of EVD

This section is adapted from Taylor et al., JTB 2016. Stochastic realizations of the SEIRD model are simulated using the Gillespie framework, given the "reaction" events in the following table: Processes transition individuals who are sus-

| **Process** | **Reaction** | **rate/probability** |
|---|---|---|
| Pre-death infection | $S+I\to E+I$ | $r_1=\beta_I S\frac{I}{N}$ |
| Post-death infection | $S+D\to E+D$ | $r_2=\beta_D I\frac{S}{N}$ |
| Onset of infectiousness | $E\to I$ | $r_3=\sigma=1/T_E$ |
| End of infectiousness (survival) | $I\to R$ | $r_4=(1-f)\gamma=(1-f)/T_I$ |
| End of infectiousness (death) | $I\to D$ | $r_5=f\gamma=f/T_I$ |
| Burial | $D\to B$ | $r_6=\rho=1/T_D$ |

Table 12.1: **Discrete stochastic reactions that transition the state of an individual**

ceptible (S), exposed (E), infected (I), deceased (D), recovered (R), and buried (B). The total population is fixed at $N=S+E+I+R+B$. Epidemics are initiated with one infectious individual in an otherwise susceptible population. Mathematically, the initial state is, in the respective ordering, $\mathbf{y}=(N_0-1,0,1,0,0)$ at $t=0$. The total rate of outbreak-associated events is $r_{tot}=\sum_{i=1}^{6} r_i$. The time until next event is exponentially distributed with rate $r_{tot}$. The probability of

each event is $r_i/r_{tot}$. After selecting an event and updating the discrete number of individuals, the reaction rates are recalculated and the process continues. Trajectories are complete when the epidemic dies out because there are no more infectious individuals.

### 12.9.6 Moment generating functions for EVD

We consider a gamma distributed exposed period with $T_E = 11$ days, and shape parameters $n_E = 6$ and $b_E = n_E/T_E$ whose generating function is:

$$M_E(-\lambda) = \left(\frac{b_E}{b_E + \lambda}\right)^{n_E} \tag{12.82}$$

We also consider two extremal conditions for the infectious periods of the I and D classes: exponentially- and delta-distributed periods. The former is conventionally used while the latter provides on upper bound on the possible inferred values of $\mathcal{R}_0$. The generating functions are, in the first scenario:

$$M_I(-\lambda) = \frac{\gamma}{\gamma + \lambda} \tag{12.83}$$

$$M_D(-\lambda) = \frac{\rho}{\rho + \lambda} \tag{12.84}$$

where $\gamma = 1/T_I$ and $\rho = 1/T_D$ and in the second scenario:

$$M_I(-\lambda) = e^{-\lambda T_I} \tag{12.85}$$

$$M_D(-\lambda) = e^{-\lambda T_D} \tag{12.86}$$

Therefore for the SEIRD model, it is possible to estimate $\mathcal{R}_0$ using the generating function method given observations of an epidemic growth rate and suitable information on epidemiological modes and parameters.