Chapter 1
Introduction

1.1 Preamble

The use of mathematical models to understand infectious disease dynamics has a very rich history in epidemiology. Kermack and McKendrick (1927) is the seminal paper that introduced the equations for the general Susceptible-Infected-Removed model and showed how a set of restrictive assumptions lead to the standard SIR model of ordinary differential equations. During the 1950s and early 1960s stochastic theories of disease dynamics were developed by Bailey (1957) and Bartlett (1960b). Bartlett (1956, 1960a) further pioneered the use of Monte Carlo simulations of epidemics with the aid of "electronic computers" (as opposed to regular human computers), while Muench (1959) proposed the "catalytic" framework for understanding age-incidence patterns.[1] The decades to follow saw broad expansions of theories as well as a surge in real-life application of mathematics to dynamics and control of infectious disease.

There are several excellent textbooks of mathematical epidemiology including Anderson and May (1991) and Keeling and Rohani (2008). The purpose of the current text is not to replicate these efforts but rather use these frameworks as a starting point to discuss practical implementation and analysis. The discussion will be centered around a somewhat haphazard collection of case studies selected to explore various conceptual, mathematical, and statistical issues. The text is designed to be more of a "practicum in infectious disease dynamics."

The dynamics of infectious diseases shows a wide diversity of pattern. Some have locally persistent chains-of-transmission; others persist spatially in "consumer-resource metapopulations." Some infections are prevalent among the young, some among the old, and some are age-invariant. Temporally, some diseases have little

[1] Though, as reviewed by Dietz and Heesterbeek (2002), the original calculations leading to the catalytic model was proposed by Daniel Bernoulli in the late eighteenth century.

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variation in prevalence, some have predictable seasonal shifts, and others exhibit violent epidemics that may be regular or irregular in their timing. Models and "models-with-data" have proved invaluable for understanding and predicting this diversity, and thence help improve intervention and control. The following chapters are an attempt at providing some notes for a "field guide" for working with data, models, and "models-and-data" to understand epidemics and infectious disease dynamics in space and time.

1.2 In-Host Persistence

Infectious diseases can be classified according to their persistence *within* the host and attack rates with respect to age. Some infections result in life-long colonization of a host because the immune system does not clear them. Such "in-host persistence" may be because the immune system permits it—as for the many symbionts that are beneficial to the host (viz. commmensals and mutualists)—or because detrimental symbionts (viz. pathogens) are able to evade clearance. Examples of "in-host persistent" pathogens are retroviruses such as HIV, latent viruses such as, herpes viruses, and a number of bacteria such as the causative agents of tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*M. leprae*).

"Acute" infections, in contrast, result in transient colonization of the host—that in humans can last for days or months depending on the pathogen—followed by clearance. The clearance is usually immune-mediated, though some viruses like canine distemper virus may run out of target cells and some pathogens may have a programmed life cycle within the host. Some coccidian pathogens within the genus *Eimeria*, for example, go through an exact number of replication cycles in the host (as merozoites) before all pathogen cells are expelled into the environment (as oocysts). The more common example of transience is due to immune-mediated clearance. Examples are plentiful and include acute viruses like measles and influenza, bacteria such as many that causes respiratory disease like bacterial meningitis (e.g., *Neisseria meningitidis*) or whooping cough (*Bordetella pertussis* and *B. parapertussis*), and protozoans such as those that cause malaria (*Plasmodium* spp.).

Among the acute infections we further distinguish between those that leave sterilizing immunity following clearance versus those that leave no or short-lived immunity. This can happen via a number of mechanisms including variable gene expression, rapid evolution, co-circulating strain clouds, or other immune evasive maneuvers. *N. meningitidis* and its congener *N. gonorrhoeae* (which cause gonorrhea), for example, are thought to leave little effective immune memory because of the bacteria's ability to express a very variable arsenal of surface proteins (e.g., Stern

et al. 1984; Tettelin et al. 2000). Many influenza subtypes, in contrast, render effective immune memory short-lived because of rapid evolution; high mutation rates lead to "antigenic drift" and viral recombination during coinfection leads to antigenic "shifts." *Plasmodium falciparum* is thought to be comprised of a diverse set of strains with nonoverlapping "antigenic repertoires" (as well as variable antigen expression) that allows repeat reinfection (e.g., Gupta et al. 1998). A number of common viral afflictions of children have a somewhat more limited strain diversity that may allow several reinfection cycles, but the immune system is ultimately able to cover their antigenic space; Examples include rotavirus (Pitzer et al. 2011) and the enterovirus-complex that cause hand-foot-and-mouse disease (Takahashi et al. 2016). Finally, many pathogens have various "anti-immune devices." Respiratory syncytial virus, for example, uses molecular decoys against neutralizing antibodies (Bukreyev et al. 2008) and *Bordetella pertussis* employs the pertussis toxin to, at least transiently, inhibit recruitment of immune effector cells to sites of infection (Kirimanjeswara et al. 2005).

Many of the remaining "acute, immunizing pathogens"—the ones that result in a transient infection followed by life-long sterilizing immunity—are the poster children of mathematical epidemiology. Notable examples are among the classic vaccine-preventable viruses like measles, rubella, and smallpox. From a biological point of view, the complete failure of immune escape of these pathogens is somewhat mysterious (Kennedy and Read 2017), but the resulting simple dynamical clockwork is a joy to anyone hoping to apply mathematics to understand the living world.

From an epidemiological point of view, it is important to make the *functional*—as opposed to taxonomical—classification of pathogens because it allows us to understand the differences in age-specific attack rates and contrasting disease dynamics. The acute, immunizing infections mainly circulate among the young and therefore comprise the many "childhood" infections because most or all older hosts are immune. From the point of view of the compartmental "SIR-like" formalism (Fig. 1.1), it is thus natural to divide the host population in S, I, and R compartments and assume a unidirectional flow from susceptible children through immune ("removed") adults. In contrast, the prevalence of "in-host persistent" infections will tend to accumulate with age. With respect to the SIR formalism, it is thus natural to consider a model with a unidirectional flow from the S class to a terminal I class. The acute but imperfectly immunizing infections should lead to relatively age-invariant attack rates, and $S \to I \to S$ or $S \to I \to R \to S$ flows depending on the duration of immune protection.

The SIR-like framework predicts how the broad expectation for age-prevalence curves will be modulated by factors such as age-specific pattern of mixing and differential mortality between infected and noninfected individuals. Statistical epidemiology can thus be used to probe empirical patterns to discover subtleties in the dynamics of disease transmission that is hard to observe directly.

1.3 Patterns of Endemicity

We can classify the dynamics of infectious disease according to broad "patterns of endemicity." First, there is the distinction between locally persistent *vs* locally non-persistence pathogens. Local persistence fails when a local chain-of-transmission breaks. This can happen for two very different reasons (Fig. 1.1): (i) The transmission bottleneck is when a pathogen is insufficiently transmissible to sustain a chain of transmission; (ii) at the opposite end of the spectrum is the susceptible bottleneck for acute pathogens that are so transmissible that they burn through susceptibles much faster than they are replenished. In measles, for example, prevaccination cities in the USA smaller than a *critical community size* (CCS) of 250k–500k people did not produce enough children to sustain a local chain-of-transmission (Bartlett 1960a) (Fig. 1.2). Recurrence of such pathogens typically involves spatial dynamics and persistence at the metapopulation scale through spread among asynchronous local host communities (Keeling et al. 2004) or core-satellite dynamics in which a few large cities above the CCS serve as persistent sources for spatial dissemination to communities below the CCS (Grenfell and Harwood 1997; Grenfell et al. 2001).

The 1988 and 2002 epidemics of a related morbilli virus, the phocine distemper virus, in European harbor seals is another illustrations of locally non-persistent infections due to high transmission relative to susceptible recruitment rates (e.g., Swinton 1998). Following introduction into each local population ("haul-out"), explosive local epidemics terminated after 1–4 months due to susceptible depletion. When such epidemics happens so fast that recruitment of susceptibles (through birth, immigration, or loss of immunity) is negligible during the course of the outbreak we call it a "closed epidemics." The closed epidemic is the focus of the standard Susceptible-Infected-Recovered model which we will study in Chap. 2. At the opposite end of the transmissibility spectrum, pathogens may bottleneck because transmission is too ineffective. In particular, if the basic reproductive ratio (R_0, the

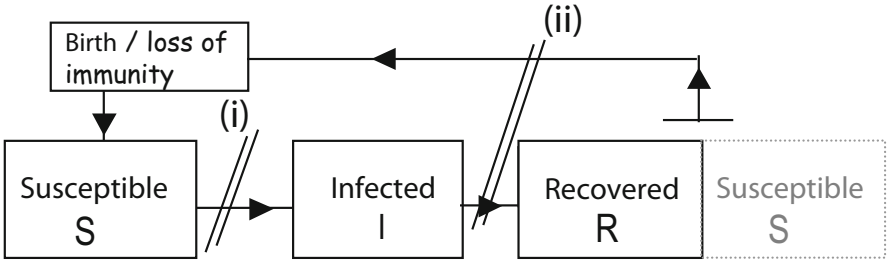

Fig. 1.1 The two bottlenecks for local persistence: (i) the transmission bottleneck for poorly transmitted infections and (ii) the susceptible bottleneck for highly transmissible, acute immunizing (or lethal) pathogens

expected number of secondary cases from a primary case in a completely susceptible population) is smaller than one, we see stuttering ("subcritical") chains of transmission followed by pathogen fade-out. We see this in many zoonoses such as monkey pox and nipah (stage 3 zoonoses in the classification by Lloyd-Smith et al. 2009). Persistent recurrence of these typically involves reservoir host and intermittent zoonotic reintroduction. For example, in their study of Lassa fever in Sierra Leone, Iacono et al. (2015) concluded that about 20% of the human cases were caused by human-to-human transmission (with an average reproductive ratio below one) while the remaining majority was caused by transmission from the multimammate rat (*Mastomys natalensis*) reservoir.

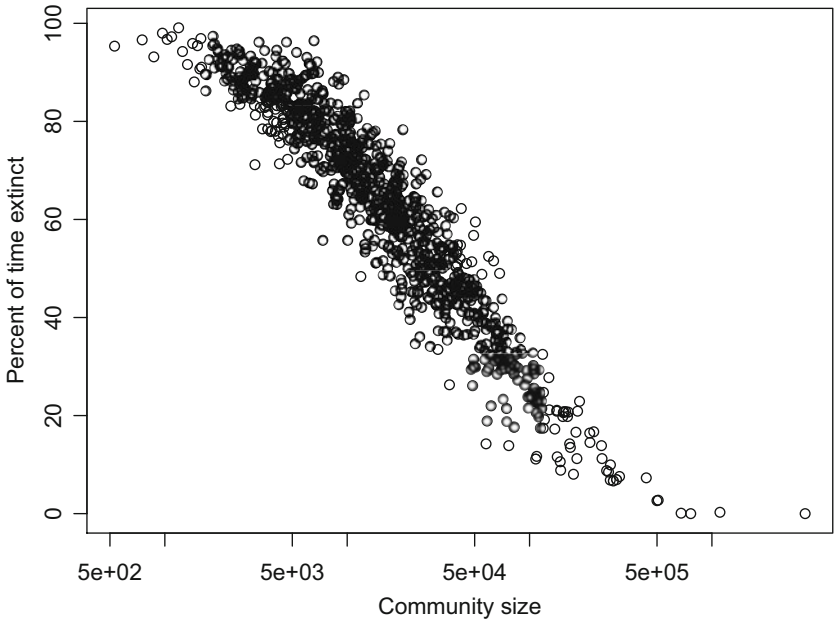

Fig. 1.2 Persistence of measles against population size for 954 cities and villages in prevaccination England and Wales (1944–1964). Communities below 500k exhibited occasional or frequent (depending on size) local extinction of the virus

The locally persistent infections can be classified as: (1) *Stable endemics* that show little variation in incidence through time. Many STDs with SI and SIS-like dynamics like gonorrhea (Fig. 1.3a) and HIV exhibit this pattern. (2) *Seasonal endemics* that show low'ish-level predictable seasonal variation around some mean. Many endemic vector-borne and water-borne infections exhibit this pattern. A classic example is the seasonal two-peaked mortality rate from Cholera in the province

of Dacca, East Bengal (King et al. 2008); The first peak at the beginning of the monsoon season and the second towards the end (Fig. 1.3b). Finally, (3) recurrent epidemics that may be regular or irregular are characterized by violent epidemic fluctuations over time. Many acute, immunizing highly contagious pathogens—measles being the poster-child—follow this pattern (Fig. 1.4).

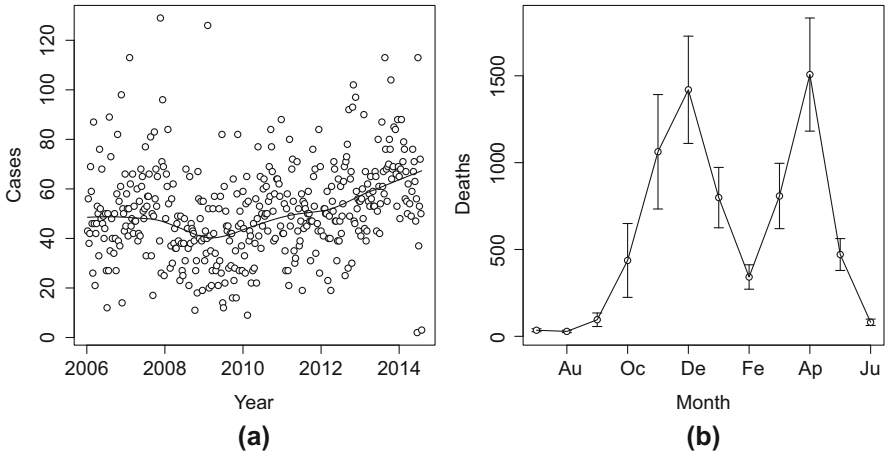

Fig. 1.3 Incidence of (**a**) weekly incidence of gonorrhea in Massachusetts (2006–2015) and (**b**) monthly average (± SE) mortality from cholera in the Dacca district (1891–1940)

1.4 R

To provide a cohesive framework for the practical calculations, all analyses are done in the open-source R-program. The text is written assuming a basic knowledge of this platform. All functions, data, and ShinyApp's discussed in the text are contained in the `epimdr`-package. With the package everything contained herein should be reproducible. The above Figs. 1.2 and 1.4 were for example generated using the following code:

```
#Fig 1.2
data(ccs)
plot(ccs$size, ccs$ext*100, log="x", xlab=
     "Community size", ylab="Percent
     of time extinct")

#Fig 1.3a
plot(magono$time, magono$number, ylab="Cases",
     xlab="Year")
lines(lowess(x=magono$time, y=magono$number, f=.4))
```

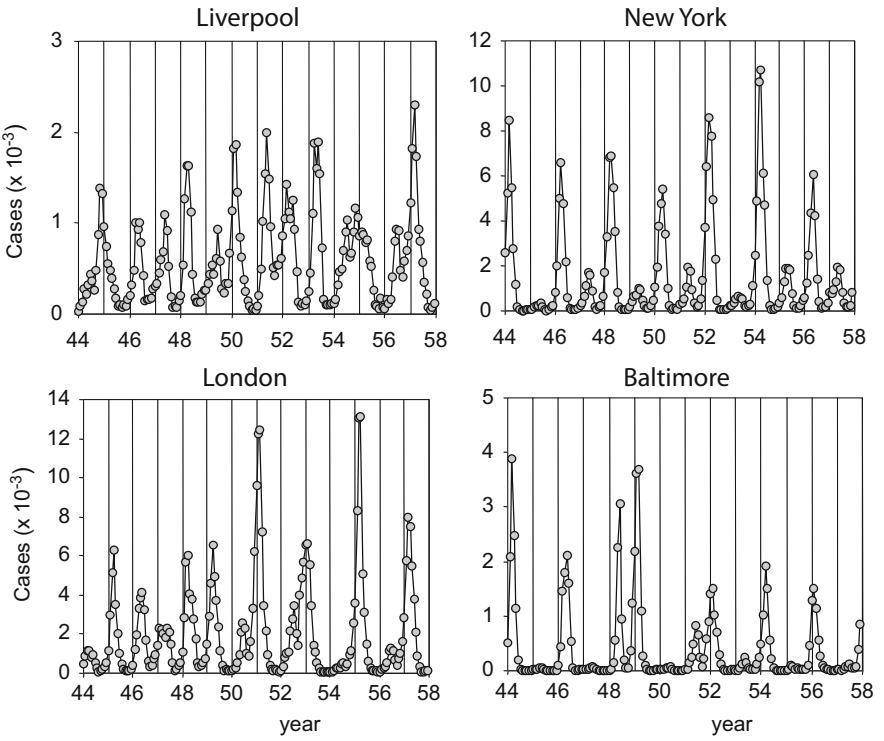

Fig. 1.4 Incidence of measles in various US and UK cities during the pre-vaccination era. The data represent fortnightly incidence (roughly corresponding to the virus' serial interval). The vertical bars mark annual intervals

```
#Fig 1.3b
data(cholera)
ses=sesdv=rep(NA, 12)
ses[c(7:12, 1:6)]=sapply(split(cholera$Dacca,
     cholera$Month), mean, na.rm=TRUE)
sesdv[c(7:12, 1:6)]=sapply(split(cholera$Dacca,
     cholera$Month), sd, na.rm=TRUE)/
     sqrt(length(split(cholera$Dacca, cholera$Month)))
require(plotrix)
plotCI(x=1:12, y=ses, ui=ses+sesdv, li=ses-
     sesdv, xlab="Month", ylab="Deaths")
lines(x=1:12, y=ses)
```

1.5 Other Resources

A 5 min overview of *Patterns of endemicity* can be watched from YouTube: https://www.youtube.com/watch?v=Mf_EZm5amxI. This video is part of the Pennsylvania State University-produced epidemics-MOOC. The entire course is accessible free from https://www.coursera.org/learn/epidemics.