Chapter 1
Introduction: A Prelude to Mathematical Epidemiology

1.1 Introduction

Recorded history continuously documents the invasion of populations by infectious agents, some causing many deaths before disappearing, others reappearing in invasions some years later in populations that have acquired some degree of immunity, due to prior exposure to related infectious pathogens. The "Spanish" flu epidemic of 1918–1919 exemplifies the devastating impact of relatively rare pandemics; this one was responsible for about 50,000,000 deaths worldwide, while on the mild side of the spectrum we experience annual influenza seasonal epidemics that cause roughly 35,000 deaths in the USA each year.

Communicable diseases have played a significant role in shaping human history. The Black Deaths (probably bubonic plague) spread starting in 1346, first through Asia and moving across Europe repeatedly during the fourteenth century. The Black Death has been estimated to have caused the death of as much as one-third of the population of Europe between 1346 and 1350. The disease reappeared regularly in various regions of Europe for more than 300 years, a notable outbreak being that of the Great Plague of London of 1665–1666. It gradually withdrew from Europe afterwards.

Some diseases have become endemic ("permanently" established) in various populations causing a variable number of deaths particularly in countries with inefficient or resource-limited health care systems. Even within the twenty-first century, we see that millions of people die of measles, respiratory infections, diarrhea, and more. Individuals still die in significant numbers from diseases that are no longer considered dangerous, diseases that are easily treated or that have been well managed by resource-rich societies or by nations that invest in public health and prevention systematically. Some highly prevalent old foes include malaria, typhus, cholera, schistosomiasis, and sleeping sickness, endemic diseases in many parts of the world; diseases that have a significant negative impact on the mean life span of a population as well as on the economy of afflicted countries due to their impact

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on the health of the population. The World Health Organization has estimated that in 2011 there were 1,400,000 deaths due to tuberculosis, 1,200,000 deaths due to HIV/AIDS, and 627,000 deaths due to malaria (but other sources have estimated the number of malaria deaths to be more than 1,000,000). In short, HIV, malaria, and TB account for at least 9,000 deaths each day. The impact of vaccines can be dramatic, for example, there were 2,600,000 deaths due to measles in 1980 but only 160,000 by 2011. The development and availability of the measles vaccine led to a reduction in the number of deaths due to this childhood disease of nearly 94%.

Epidemiologists, in response to a health emergency or as a result of systematic surveillance, first obtain and analyze observed data. They use data, observations, science, and theory as they work at identifying a pathogen (when unknown) behind an observed disease outbreak or as they proceed to plan or implement policies that ameliorates its impact. Naturally, understanding the causes and modes of transmission of each disease is central to forecasting or mitigating its impact within and across populations at risk. Mathematical models have played a substantial role in both short and long term planning for controlling the dynamics of a disease.

This volume provides a guided tour of the role that mathematical models have played in epidemiology and public health policy. This tour introduces a wide range of models and tools that have proven useful in the study of disease dynamics and control. This book provides a framework that will position those interested in the use of modeling and computational tools in epidemiology, public health, and related fields, in a position to contribute to the study of the transmission dynamics and control of contagion.

1.2 Some History

The study of infectious disease data began with the work of John Graunt (1620–1674) in his 1662 book "Natural and Political Observations made upon the Bills of Mortality." The Bills of Mortality were weekly records of numbers and causes of death in London parishes. The records, beginning in 1592 and kept continuously from 1603 on, provided the data that Graunt used to begin to understand or identify possible causes of observed mortality patterns. He analyzed the various causes of death and gave a method of estimating the comparative risks of dying from various diseases, giving the first approach to a theory of competing risks.

In the eighteenth century smallpox was endemic and, perhaps not surprisingly, the first model in mathematical epidemiology was tied in to the work that Daniel Bernoulli (1700–1782) carried out on estimating the impact of inoculation against smallpox. Variolation, essentially inoculation with a mild strain, was introduced as a way to produce lifelong immunity against smallpox, but with a small risk of infection and death. There was heated debate about variolation, and Bernoulli was led to study the question of whether variolation was beneficial. His approach was to calculate the increase in life expectancy if smallpox were to be eliminated as a cause of death. His approach to the question of competing risks led to the publication of

a brief outline in 1760 [7] followed in 1766 by a more complete exposition [8]. His work received a mainly favorable reception; research that has become known in the actuarial literature rather than in the epidemiological literature. More recently his approach has been generalized [31].

Another valuable contribution to the understanding of infectious diseases prior to our understanding of disease transmission processes was gained from the study of the temporal and spatial pattern of cholera cases during the 1855 epidemic in London carried out by John Snow. He was able to pinpoint the Broad Street water pump as the source of the infection [54, 71]. In 1873, William Budd was able to gain a similar understanding of the spread of typhoid [17]. Statistical theory also moved forward with William Farr's study of statistical returns in 1840, a study that had as its goal the discovery of the laws that underlie the rise and fall of epidemics [36].

Many of the early developments in the mathematical modeling of communicable diseases are due to public health physicians. The first known result in mathematical epidemiology, as noted before, is a defense of the practice of inoculation against smallpox in 1760 by Daniel Bernoulli, a member of a famous family of mathematicians (eight spread over three generations) who had been trained as a physician. The first contributions to modern mathematical epidemiology are due to P.D. En'ko between 1873 and 1894 [30], and the foundations of the entire approach to epidemiology based on compartmental models were laid by public health physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, and W.O. Kermack between 1900 and 1935, along with important contributions from a statistical perspective by J. Brownlee.

1.2.1 The Beginnings of Compartmental Models

In order to describe a mathematical model for the spread of a communicable disease, it is necessary to make some assumptions about the means of spreading infection. The idea of invisible living creatures as agents of disease goes back at least to the writings of Aristotle (384–322 BC). The existence of microorganisms was demonstrated by van Leeuwenhoek (1632–1723) with the aid of the first microscopes. The first expression of the germ theory of disease by Jacob Henle (1809–1885) came in 1840 and was developed by Robert Koch (1843–1910), Joseph Lister (1827–1912), and Louis Pasteur (1822–1875) in the late nineteenth and early twentieth centuries. The modern view is that many diseases are spread by contact through a virus or bacterium. We focus in this book on the problem of understanding the spread of disease at a population level. Similar modeling approaches can be used to study the dynamics of infection within a host for diseases including HIV. This area is the backbone of the field of mathematical and computational immunology and viral dynamics. An introduction to immunology may be found in the book by Nowak and May [67].

In 1906, W.H. Hamer argued that the spread of infection should depend on the number of susceptible individuals and the number of infective individuals [44]. He

suggested a mass action law for the rate of new infections, and this idea has been basic in the formulation of compartmental models since that time. It is worth noting that the foundations of the entire approach to epidemiology based on compartmental models were laid, not by mathematicians, but primarily by public health physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, and W.O. Kermack between 1900 and 1935.

A particularly instructive example is the work of Ross on malaria. Sir Ronald Ross was awarded the second Nobel Prize in Medicine in 1902 for his demonstration of the dynamics of the transmission of malaria between mosquitoes and humans. He discovered the malarial parasite in the gastrointestinal tract of the *Anopheles* mosquito from which he was able to characterize the life cycle of malaria. He concluded that this vector-borne disease was transmitted by the *Anopheles* mosquito and in the process he developed a program for controlling or eliminating it at the population level.

It was generally believed that, so long as mosquitoes were present in a population, malaria could not be eliminated. Ross introduced a simple compartmental model [69] that included mosquitoes and humans. He showed that reducing the mosquito population below a critical level would be sufficient to eliminate malaria. This was the first introduction of the concept of the basic reproduction number, a central idea in mathematical epidemiology since that time. Field trials supported Ross' conclusion leading sometimes to brilliant successes in malaria control.

The basic compartmental models to describe the transmission of communicable diseases are contained in a sequence of three papers by W.O. Kermack and A.G. McKendrick in 1927, 1932, and 1933 [55–57]. The first of these papers described epidemic models.

The Kermack–McKendrick epidemic model, introduced in Chap. 2 and studied in more detail in Chap. 4, included dependence on age of infection, that is, the time since becoming infected, and can be used to provide a unified approach to compartmental epidemic models.

Various disease outbreaks including the $SARS$ epidemic of 2002–2003, the concern about a possible $H5N1$ influenza epidemic in 2005, the $H1N1$ influenza pandemic of 2009, and the Ebola outbreak of 2014 have reignited interest in epidemic models, with the reformulation of the Kermack–McKendrick model by Diekmann, Heesterbeek, and Metz [27] highlighting the importance of looking at the foundational work. Chapter 4 contains a study of epidemic models.

In the work of Ross and Kermack and McKendrick there is a threshold quantity, the basic reproduction number, which is now almost universally denoted by $\mathscr{R}_0$. Neither Ross nor Kermack and McKendrick identified this threshold quantity or gave it a name. It appears that the first person to name the threshold quantity explicitly was MacDonald [60] in his work on malaria.

The basic reproduction number, $\mathscr{R}_0$ (referred to as the basic reproductive number by some authors), is defined as the expected number of disease cases (secondary infections) produced by a "typical" infected individual in a wholly susceptible population over the full course of the disease outbreak. In an epidemic situation, in which the time period is short enough to neglect demographic effects and all

infected individuals recover with full immunity against reinfection, the threshold $\mathscr{R}_0 = 1$ is the dividing line between the infection dying out and the onset of an epidemic. In a situation that includes a flow of new susceptible individuals, either through demographic effects or recovery without full immunity against reinfection, the threshold $\mathscr{R}_0 = 1$ is the dividing line between an approach to a disease-free equilibrium and an approach to an endemic equilibrium, in which the disease is always present. This situation is studied in detail in Chap. 3.

Since 1933, there has been a great deal of work on compartmental disease transmission models, with generalizations in many directions. In particular, it is assumed in [55–57] that stays in compartments are exponentially distributed. In the generalization to age of infection models in Chap. 4, we are able to assume arbitrary distributions of stay in a compartment.

1.2.2 Stochastic Models

There are serious shortcomings in the simple Kermack–McKendrick model as a description of the beginning of a disease outbreak. Indeed, a very different kind of model is required since the Kermack–McKendrick compartmental epidemic model assumes that the sizes of the compartments are large enough that the mixing of members is homogeneous. However, at the beginning of a disease outbreak, there is a very small number of infective individuals and the transmission of infection is better captured if seen as a stochastic event that depends on the pattern of contacts between members of the population; a more satisfactory description should take such a stochastic pattern into account. We will not study stochastic models in this volume except for two sections at the start of Chap. 4 dealing with the initial stages of a disease outbreak.

The process chosen here to describe it is known as a Galton–Watson process; the result was first given in [39, 77] although there was a gap in the convergence proof. The first complete proof was given much later by Steffensen [72, 73]. The result is now a standard theorem given in many sources on branching processes, for example, [45], but did not appear in the epidemiological literature until later. To the best of the authors' knowledge, the first description in an epidemiological reference is [62] and the first epidemiological book source is the book by O. Diekmann and J.A.P. Heesterbeek [26] in 2000.

A stochastic branching process description of the beginning of a disease outbreak begins with the assumption that there is a network of contacts of individuals, which may be described by a graph with members of the population represented by vertices and with contacts between individuals represented by edges. The study of graphs originated with the abstract theory of Erdös and Rényi of the 1950s and 1960s [33–35], and has become important more recently in many areas, including in the study of social contacts, computer networks, and many other areas, as well as in the spread of communicable diseases. We will think of networks as bi-directional, with disease transmission possible in either direction along an edge. A brief taste of network

models is given at the beginning of Chap. 4. It is however important to stress the fact that this book does not get involved in the study of stochastic models or in the study of epidemics in networks–areas that deserve their own volumes.

We consider a disease outbreak that begins with a single infected individual ("patient zero") who transmits infection to every individual to whom this individual is connected, that is, along every edge of the graph from the vertex corresponding to this individual. In other words, we assume that a disease outbreak begins when a single infective transmits infection to all of the people with whom he or she is in contact. Our development via branching processes is along the lines of that of [26]. Another approach, using a contact network perspective taken in [20, 65, 66] begins with an infected edge, corresponding to a disease outbreak started by an infective individual who passes the infection on to only one contact. This approach is the one taken more commonly in studies of epidemics on networks. It is somewhat more complicated and leads to somewhat different results, although the methods are quite similar.

In a stochastic setting, it is possible to prove that there is also a number called the basic reproduction number denoted by $\mathscr{R}_0$ with the properties that if $\mathscr{R}_0 < 1$ the probability that the infection will die out is 1, while if $\mathscr{R}_0 > 1$ there is a positive probability that the infection will persist leading to an epidemic. However, there is also a positive probability that the infection will increase initially but will produce only a minor outbreak dying out before triggering a major epidemic. This distinction between a minor outbreak and a major epidemic, and the result that if $\mathscr{R}_0 > 1$ there may be only a minor outbreak and not a major epidemic is intrinsic in these stochastic models and is not reflected in deterministic models, the primary theme of this book.

A possible approach to a realistic description of an epidemic would consider the use of a branching process model initially, making a transition to a compartmental model when the epidemic has become established, that is, when there are enough infectives so that the mass action mixing in the population becomes a reasonable approximation. Another approach would be to continue to use a network model throughout the course of the epidemic [63, 64, 76]. It is possible to formulate this model dynamically with the limiting case of this dynamic model, as the population size becomes very large, being the same as the compartmental model.

Past experiences and data have shown that the spread of infection in small populations is better captured in small communities as a random process. For this reason, stochastic models have an important role in disease transmission modeling. The most commonly used stochastic model includes the chain binomial model of Reed and Frost, first described in lectures in 1928 by W.H. Frost but not published until much later [1, 78]. The Reed–Frost model was actually anticipated nearly 40 years earlier by P.D. En'ko [30]. The work of En'ko was brought to public attention much later by K. Dietz [28]. E.B. Wilson and M.H. Burke have given a description of Frost's 1928 lectures with a somewhat different derivation [78]. M. Greenwood introduced a somewhat different chain binomial model in 1931 [40]. The Reed–Frost model has been used widely as a basic stochastic model and many extensions have been formulated. The book [25] by D.J. Daley and J. Gani contains an account

of some of the more recent extensions. Also, a stochastic analogue of the Kermack–McKendrick epidemic model has been described in [6].

1.2.3 Developments in Compartmental Models

In the mathematical modeling of disease transmission, as in most other areas of mathematical modeling, there is always a trade-off between simple, or strategic, models, which omit most details and are designed only to highlight general qualitative behavior, and detailed, or tactical, models, usually designed for specific situations including short-term quantitative predictions. Detailed models are generally difficult or impossible to solve analytically and hence their usefulness for theoretical purposes is limited, although their strategic value may be high.

For example, very simple models for epidemics predict that an epidemic will die out after some time, leaving a part of the population untouched by disease, and this is also true of models that include control measures. This qualitative principle is not by itself very helpful in suggesting what control measures would be most effective in a given situation, but it implies that a detailed model describing the situation as accurately as possible might be useful for public health professionals. The ultimate in detailed models are agent-based models, which essentially divide the population into individuals or groups of individuals with identical behavior [32].

It is important to recognize that mathematical models to be used for making policy recommendations for management need quantitative results, and that the models needed in a public health setting require a great deal of detail in order to describe the situation accurately. For example, if the problem is to recommend what age group or groups should be the focus of attention in coping with a disease outbreak, it is essential to use a model which separates the population into a sufficient number of age groups and recognizes the interaction between different age groups. The development of high speed computing has made it possible to analyze highly detailed models rapidly.

The development of mathematical methods for the study of models for communicable diseases led to a divergence between the goals of mathematicians, who sought broad understanding, and public health professionals, who sought practical procedures for management of diseases. While mathematical modeling led to many fundamental ideas, such as the possibility of controlling smallpox by vaccination and the management of malaria by controlling the vector (mosquito) population, the practical implementation was always more difficult than the predictions of simple models. Fortunately, in recent years there have been determined efforts to encourage better communication, so that public health professionals can better understand the situations in which simple models may be useful and mathematicians can recognize that real-life public health questions are much more complicated than simple models.

In the study of compartmental disease transmission models, the population under study is divided into compartments and assumptions are made about the nature

and time rate of transfer from one compartment to another. For example, in an SIR model, we divide the population being studied into three classes labeled S, I, and R. We let $S(t)$ denote the number of individuals who are susceptible to the disease, that is, who are not (yet) infected at time t. $I(t)$ denotes the number of infected individuals, assumed infectious and able to spread the disease by contact with susceptible individuals. $R(t)$ denotes the number of individuals who have been infected and then removed from the possibility of being infected again or of spreading infection. In an SIS model, infectives recover with immunity against reinfection and the transitions are from susceptible to infective to susceptible.

The rates of transfer between compartments are expressed mathematically as derivatives with respect to time of the sizes of the compartments. Initially, we assume that the duration of stay in each compartment is exponentially distributed, and as a result models are formulated initially as differential equations. Models in which the rates of transfer depend on the sizes of compartments over the past, as well as at the instant of transfer, lead to more general types of functional equations, such as differential–difference equations or integral equations. One way in which models have expressed the idea of a reduction in contacts as an epidemic proceeds is to assume a contact rate of the form $\beta Sf(I)$ with a function $f(I)$ that grows more slowly than linearly in I. Such an assumption, while not really a mechanistic model, may give better approximation to observed data than mass action contact.

In the simple Kermack–McKendrick epidemic model there are two parameters, the rate of new infections and the recovery rate. Often, the recovery rate for a particular disease is known. In compartmental epidemic models with more compartments, the progression rate is more complicated but may also be known. It is possible to estimate the basic reproduction number if these parameters can be estimated, and there is an equation, known as the *final size relation* relating the basic reproduction number to the number of individuals infected over the course of the epidemic. There have been many presentations of this final size relation in various contexts, including models with heterogeneity of mixing [3, 12, 13, 15, 16, 26, 27, 59].

In their later work on disease transmission models [56, 57], Kermack and McKendrick did not include age of infection, and age of infection models were neglected for many years. Age of infection reappeared in the study of HIV/AIDS, in which the infectivity of infected individuals is high for a brief period after becoming infected, then quite low for an extended period, possibly several years, before increasing rapidly with the onset of full-blown AIDS. Thus the age of infection described by Kermack and McKendrick for epidemics became very important in some endemic situations; see, for example, [74, 75]. Also, HIV/AIDS has pointed to the importance of immunological ideas in the analysis on the epidemiological level.

Typically, there is a stochastic phase at the beginning of a disease outbreak, followed by an exponential increase in the number of infectives, and it may be possible to estimate this initial exponential growth rate experimentally. An estimate of the initial exponential growth rate can be used to estimate the rate of new infections, and this enables estimation of the basic reproduction number

The development and analysis of compartmental models has grown rapidly since the early models. Many of these developments are due to H.W. Hethcote [46–50]. We describe only a few of the important developments. While there are three basic compartmental disease transmission models, namely the SIS model, the SIR model without births and deaths, and the SIR model with births and deaths, each disease has its own properties which should be included in a model. We will describe the effects of adding heterogeneity of mixing in several chapters, including heterogeneity of mixing in Chap. 5, age structure in Chap. 13, and spatial heterogeneity in Chaps. 14 and 15. In addition, the chapters on individual diseases (Chaps. 7–12) include modeling aspects of the specific disease being studied.

For influenza, there is a significant fraction of the population which is infected but asymptomatic, with lower infectivity than symptomatic individuals. There are seasonal outbreaks which may be closely related to the strain of the previous year, that is, modified by point mutations, or it may be less closely related or it may be unrelated. The level of relation of two strains, as measured by the response of hosts that have experienced a prior influenza infection, is what we refer to as strain cross-immunity. Cross-immunity measures the level of protection earned by individuals who were infected by a related strain in a previous year. Influenza models may consider the effect that a partially efficacious vaccination may have before an outbreak, as well as the role of antiviral treatment during an outbreak. Considering multiple modes of transmission is critical when the goal is to minimize the impact of a disease in a population. Cholera may be transmitted both by direct contact and by contact with pathogen shed by infectives. In tuberculosis some individuals progress rapidly to active tuberculosis, while others progress much more slowly. Also, active-tuberculosis individuals who fail to comply with long-term treatment schedules become prime candidates for the development of a drug-resistant strain. In HIV/AIDS, the infectivity of an individual depends strongly on the time since infection, while transmission depends on modes of transmission, mixing between individuals and more. In malaria, immunity against infection is boosted by exposure to infection or by genetics (sickle cell anemia).

1.2.4 Endemic Disease Models

The analytic approaches to models for endemic diseases and epidemics are quite different. The analysis of a model for an endemic disease, carried out in Chap. 3, begins with the search for equilibria, which are, by definition, constant solutions of the model. Usually there is a disease-free equilibrium and there are one or more endemic equilibria, with a positive number of infected individuals. The next step is to linearize about each equilibrium and determine the stability of each equilibrium. Usually, if the basic reproduction number is less than 1, the only equilibrium is the disease-free equilibrium and this equilibrium is asymptotically stable. If the basic reproduction number is greater than 1, the usual situation is that the disease-free equilibrium is unstable and there is a unique endemic equilibrium which is

asymptotically stable. This approach also covers diseases in which there is vertical transmission, which is direct transmission from mother to offspring at birth [19].

However, more complicated behavior is possible. For example, if there are two strains of the disease being studied it is common to have regions in the parameter space in which there is an asymptotically stable equilibrium with only one of the strains present and a region in which there is an asymptotically stable equilibrium with both strains coexisting. Another possibility is that there is a unique endemic equilibrium but it is unstable. In this situation, there is often a Hopf bifurcation and an asymptotically stable periodic orbit around the endemic equilibrium. An example of such behavior may be found in an SIRS model, with a temporary immunity period of fixed length following recovery [51] and in an $SVIR$ model [38]. If there is a periodic orbit with large amplitude and a long period, data must be gathered over a sufficiently large time interval to give an accurate picture.

Another possible behavior is a backward bifurcation. As $\mathscr{R}_0$ increases through 1 there is an exchange of stability between the disease-free equilibrium, which is asymptotically stable for $\mathscr{R}_0 < 1$ and unstable for $\mathscr{R}_0 > 1$, and the endemic equilibrium which exists if $\mathscr{R}_0 > 1$. The usual transition is a forward, or transcritical, bifurcation at $\mathscr{R}_0 = 1$, with an asymptotically stable endemic equilibrium and an equilibrium infective population size depending continuously on $\mathscr{R}_0$.

The behavior at a bifurcation may be described graphically by the bifurcation curve, which is the graph of the infective population size I at equilibrium as a function of the basic reproduction number $\mathscr{R}_0$. It has been noted [29, 42, 43, 58] that in epidemic models with multiple groups and asymmetry between groups or multiple interaction mechanisms it is possible to have a very different bifurcation behavior at $\mathscr{R}_0 = 1$. There may be multiple positive endemic equilibria for values of $\mathscr{R}_0 < 1$ and a backward bifurcation at $\mathscr{R}_0 = 1$. The qualitative behavior of a system with a backward bifurcation differs from that of a system with a forward bifurcation and the nature of these changes has been described in [11]. Since these behavioral differences are important in planning how to control a disease, it is important to determine whether a system can have a backward bifurcation. In the presence of two modes of sexually transmitted HIV, it was shown that multiple endemic equilibrium could be supported [53].

1.2.5 Diseases Transmitted by Vectors

Many diseases are transmitted from human to human indirectly, through a vector. Vectors are living organisms that can transmit infectious diseases between humans. Many vectors are bloodsucking insects that ingest disease-producing microorganisms during blood meals from an infected (human) host, and then inject it into a new host during a subsequent blood meal. The best known vectors are mosquitoes for diseases including malaria, dengue fever, chikungunya, Zika virus, Rift Valley fever, yellow fever, Japanese encephalitis, lymphatic filariasis, and West Nile fever, but ticks (for Lyme disease and tularemia), bugs (for Chagas' disease), flies (for

onchocerciasis), sandflies (for leishmaniasis), fleas (for plague, transmitted by fleas from rats to humans), and some freshwater snails (for schistosomiasis) are vectors for some diseases.

Every year there are more than a billion cases of vector-borne diseases and more than a million deaths. Vector-borne diseases account for over 17% of all infectious diseases worldwide. Malaria is the most deadly vector-borne diseases, causing an estimated 627,000 deaths in 2012. The most rapidly growing vector-borne disease is dengue, for which the number of cases has multiplied by 30 in the last 50 years. These diseases are found more commonly in tropical and sub-tropical regions where mosquitoes flourish, and in places where access to safe drinking water and sanitation systems is uncertain.

Some vector-borne diseases such as dengue, chikungunya, and West Nile virus are emerging in countries where they were unknown previously because of globalization of travel and trade and environmental challenges such as climate change. A troubling new development is the Zika virus, which has been known since 1952 but has developed a mutation in the South American outbreak of 2015 [70] which has produced very serious birth defects in babies born to infected mothers. In addition, the current Zika virus can be transmitted directly through sexual contact as well as through vectors. Chapter 6 is an introduction to the modeling of vector-borne diseases. Chapter 11 on malaria and Chap. 12 on dengue fever and the Zika virus describe modeling of specific vector-borne diseases.

Many of the important underlying ideas of mathematical epidemiology arose in the study of malaria begun by Sir R.A. Ross [69]. Malaria is one example of a disease with vector transmission, the infection being transmitted back and forth between vectors (mosquitoes) and hosts (humans). It kills hundreds of thousands of people annually, mostly children and mostly in poor countries in Africa. Among communicable diseases, only tuberculosis causes more deaths. Other vector diseases include West Nile virus, yellow fever, and dengue fever. Human diseases transmitted heterosexually may also be viewed as diseases transmitted by vectors, because males and females must be viewed as separate populations and disease is transmitted from one population to the other.

Vector-transmitted diseases require models that include both vectors and hosts. For most diseases transmitted by vectors, the vectors are insects, with a much shorter life span than the hosts, who may be humans as for malaria or animals as for West Nile virus, although there is malaria (not human malaria) in various animal populations and West Nile virus has infected humans as far as Arizona in the USA.

The compartmental structure of the disease may be different in host and vector species; for many diseases with insects as vectors an infected vector remains infected for life so that the disease may have an SI or SEI structure in the vectors and an SIR or $SEIR$ structure in the hosts.

1.2.6 Heterogeneity of Mixing

In disease transmission models not all members of the population make contacts at the same rate. In sexually transmitted diseases there is often a "core" group of very active members who are responsible for most of the disease cases, and control measures aimed at this core group have been very effective in control [52]. In epidemics there are often "super-spreaders," who make many contacts and are instrumental in spreading disease and in general some members of the population make more contacts than others. Chapter 5 deals with models for diseases with heterogeneous mixing and includes description of a general method (the next generation matrix) for determining the basic reproduction number for models with heterogeneous mixing. To model heterogeneity in mixing we may assume that the population is divided into subgroups with different activity levels. Formulation of models requires some assumptions about the mixing between subgroups. There have been many studies of mixing patterns in real populations, for example, [9, 10, 18, 37, 68].

It has often been observed in epidemics that most infectives do not transmit infections at all or transmit infections to very few others. This suggests that homogeneous mixing at the beginning of an epidemic may not be a good approximation.

The SARS epidemic of 2002–2003 spread much more slowly than would have been expected on the basis of the data on disease spread at the start of the epidemic. Early in the SARS epidemic of 2002–2003 it was estimated that $\mathscr{R}_0$ had a value between 2.2 and 3.6. At the beginning of an epidemic, the exponential rate of growth of the number of infectives is approximately $(\mathscr{R}_0-1)/\alpha$, where $1/\alpha$ is the generation time of the epidemic, estimated to be approximately 10 days for SARS. This would have predicted at least 30,000 cases of SARS in China during the first 4 months of the epidemic. In fact, there were fewer than 800 cases reported in this time. One explanation for this discrepancy is that the estimates were based on transmission data in hospitals and crowded apartment complexes or in the scaling of the model used to estimate parameters [24]. It was observed that there was intense activity in some locations and very little in others. This suggests that the actual reproduction number (averaged over the whole population) was much lower, perhaps in the range 1.2–1.6, and that heterogeneous mixing was a very important aspect of the epidemic.

Age is one of the most important characteristics in the modeling of populations and infectious diseases. Individuals with different ages may have different reproduction and survival capacities. Diseases may have different infection rates and mortality rates for different age groups. Individuals of different ages may also have different behaviors, and behavioral changes are crucial in control and prevention of many infectious diseases. Young individuals tend to be more active in interactions with or between populations, and in disease transmissions. Age-structured models are studied in Chap. 13.

Sexually transmitted diseases (STDs) are spread through partner interactions with pair-formations and the pair-formations process is age-dependent in most cases. For example, most HIV cases occur in the group of young adults.

Childhood diseases, such as measles, chicken pox, and rubella, are spread mainly by contacts between children of similar ages. More than half of the deaths attributed to malaria are in children under 5 years of age due to their weaker immune systems. This suggests that in models for disease transmission in an age-structured population it is necessary to allow the contact rates between two members of the population to depend on the ages of both members. Another important motivation for using age-structured models for childhood diseases is that vaccination is age-dependent (e.g., measles).

The development of age-structured models for disease transmission required development of the theory of age-structured populations. In fact, the first models for age-structured populations [61] were designed for the study of disease transmission in such populations.

1.3 Strategic Models and This Volume

This book is intended for both mathematicians and public health professionals. However, it is a book aimed primarily at practitioners who are quantitatively trained. For readers less familiar with mathematics, we are providing a website that includes notes on calculus, linear algebra, ODEs, and difference equations. We would like to repeat that it is not a book about *mathematics* per se. Hence, *mathematical rigor is not a priority* albeit we have tried to document some assertions. We wish to present the truth and nothing but the truth, but not necessarily the whole truth. Our hope is that public health people will be sufficiently interested to review mathematics if necessary and make use of the book.

We do not cover stochastic models, except for some material in Sects. 4.1 and 4.2. Some presentations of stochastic models may be found in [2, 4, 5, 25, 41].

Also, we do not cover discrete models in the main text. This is a deliberate choice that we have made to limit the size of this volume, despite the fact that a lot can be learned by the appropriate formulation of discrete models, which are unfortunately often seen as a discretization of continuous time models, that is, they are not derived directly from first principles, deviating the focus from the study of disease dynamics to the mathematical question of whether or not it is a proper discretization of a continuous time model. However, there are several projects that could give an introduction to this topic, and some references are [14, 21–23, 79].

The primary goal of this volume is to cover relatively simple models to indicate what qualitative results should be expected from more detailed tactical models. The chapters build on the work that we have done in applying epidemiological models in the context of specific diseases over the past 25 years—including some of our most recent work. It is our hope that the questions and problems highlighted in this introduction may help build collaborations between modelers, epidemiologists, and public health experts.

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