SIAM REVIEW
Vol. 42, No. 4, pp. 599–653

The Mathematics of Infectious Diseases*

Herbert W. Hethcote†

Abstract. Many models for the spread of infectious diseases in populations have been analyzed mathematically and applied to specific diseases. Threshold theorems involving the basic reproduction number R_0, the contact number σ, and the replacement number R are reviewed for the classic SIR epidemic and endemic models. Similar results with new expressions for R_0 are obtained for MSEIR and SEIR endemic models with either continuous age or age groups. Values of R_0 and σ are estimated for various diseases including measles in Niger and pertussis in the United States. Previous models with age structure, heterogeneity, and spatial structure are surveyed.

Key words. thresholds, basic reproduction number, contact number, epidemiology, infectious diseases

AMS subject classifications. Primary, 92D30; Secondary, 34C23, 34C60, 35B32, 35F25

PII. S0036144500371907

1. Introduction.

The effectiveness of improved sanitation, antibiotics, and vaccination programs created a confidence in the 1960s that infectious diseases would soon be eliminated. Consequently, chronic diseases such as cardiovascular disease and cancer received more attention in the United States and industrialized countries. But infectious diseases have continued to be the major causes of suffering and mortality in developing countries. Moreover, infectious disease agents adapt and evolve, so that new infectious diseases have emerged and some existing diseases have reemerged [142]. Newly identified diseases include Lyme disease (1975), Legionnaire's disease (1976), toxic-shock syndrome (1978), hepatitis C (1989), hepatitis E (1990), and hantavirus (1993). The human immunodeficiency virus (HIV), which is the etiological agent for acquired immunodeficiency syndrome (AIDS), emerged in 1981 and has become an important sexually transmitted disease throughout the world. Antibiotic-resistant strains of tuberculosis, pneumonia, and gonorrhea have evolved. Malaria, dengue, and yellow fever have reemerged and are spreading into new regions as climate changes occur. Diseases such as plague, cholera, and hemorrhagic fevers (Bolivian, Ebola, Lassa, Marburg, etc.) continue to erupt occasionally. Surprisingly, new infectious agents called prions have recently joined the previously known agents: viruses, bacteria, protozoa, and helminths (worms). There is strong evidence that prions are the cause of spongiform encephalopathies, e.g., bovine spongiform encephalopathy (BSE, "mad cow disease"), Creutzfeldt-Jakob disease (CJD), kuru, and scrapie in sheep [168]. Recent popular books have given us exciting accounts of the emergence and detection of new diseases [82, 168, 170, 183]. It is clear that human or animal invasions

*Received by the editors March 6, 2000; accepted for publication (in revised form) May 7, 2000; published electronically October 30, 2000.
http://www.siam.org/journals/sirev/42-4/37190.html

†Department of Mathematics, University of Iowa, Iowa City, IA 52242 (hethcote@math.uiowa.edu).

of new ecosystems, global warming, environmental degradation, increased international travel, and changes in economic patterns will continue to provide opportunities for new and existing infectious diseases [152].

The emerging and reemerging diseases have led to a revived interest in infectious diseases. Mathematical models have become important tools in analyzing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters; moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modeling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in forecasts [100, 111].

Although a model for smallpox was formulated and solved by Daniel Bernoulli in 1760 in order to evaluate the effectiveness of variolation of healthy people with the smallpox virus [24], deterministic epidemiology modeling seems to have started in the 20th century. In 1906 Hamer formulated and analyzed a discrete time model in his attempt to understand the recurrence of measles epidemics [95]. His model may have been the first to assume that the incidence (number of new cases per unit time) depends on the product of the densities of the susceptibles and infectives. Ross was interested in the incidence and control of malaria, so he developed differential equation models for malaria as a host-vector disease in 1911 [173]. Other deterministic epidemiology models were then developed in papers by Ross, Ross and Hudson, Martini, and Lotka [18, 60, 66]. Starting in 1926 Kermack and McKendrick published papers on epidemic models and obtained the epidemic threshold result that the density of susceptibles must exceed a critical value in order for an epidemic outbreak to occur [18, 136, 157]. Mathematical epidemiology seems to have grown exponentially starting in the middle of the 20th century (the first edition in 1957 of Bailey's book [18] is an important landmark), so that a tremendous variety of models have now been formulated, mathematically analyzed, and applied to infectious diseases. Reviews of the literature [21, 39, 60, 65, 67, 102, 107, 109, 199] show the rapid growth of epidemiology modeling. The recent models have involved aspects such as passive immunity, gradual loss of vaccine and disease-acquired immunity, stages of infection, vertical transmission, disease vectors, macroparasitic loads, age structure, social and sexual mixing groups, spatial spread, vaccination, quarantine, and chemotherapy. Special models have been formulated for diseases such as measles, rubella, chickenpox, whooping cough, diphtheria, smallpox, malaria, onchocerciasis, filariasis, rabies, gonorrhea, herpes, syphilis, and HIV/AIDS. The breadth of the subject is shown in the books on epidemiology modeling [5, 9, 12, 18, 19, 20, 22, 33, 38, 39, 55, 56, 59, 80, 81, 90, 111, 113, 127, 137, 141, 151, 164, 167, 173, 181, 194, 196].

Compartments with labels such as M, S, E, I, and R are often used for the epidemiological classes as shown in Figure 1. If a mother has been infected, then some IgG antibodies are transferred across the placenta, so that her newborn infant has

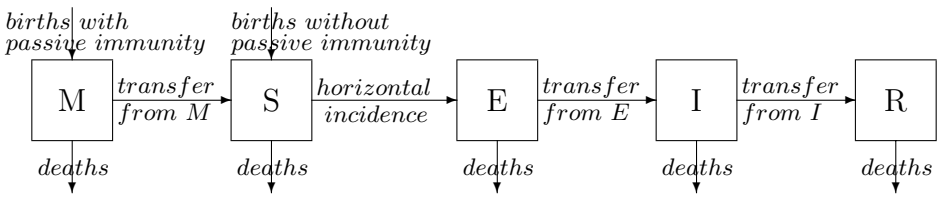

Fig. 1 *The general transfer diagram for the MSEIR model with the passively immune class M, the susceptible class S, the exposed class E, the infective class I, and the recovered class R.*

temporary passive immunity to an infection. The class M contains these infants with passive immunity. After the maternal antibodies disappear from the body, the infant moves to the susceptible class S. Infants who do not have any passive immunity, because their mothers were never infected, also enter the class S of susceptible individuals; that is, those who can become infected. When there is an adequate contact of a susceptible with an infective so that transmission occurs, then the susceptible enters the exposed class E of those in the latent period, who are infected but not yet infectious. After the latent period ends, the individual enters the class I of infectives, who are infectious in the sense that they are capable of transmitting the infection. When the infectious period ends, the individual enters the recovered class R consisting of those with permanent infection-acquired immunity.

The choice of which compartments to include in a model depends on the characteristics of the particular disease being modeled and the purpose of the model. The passively immune class M and the latent period class E are often omitted, because they are not crucial for the susceptible-infective interaction. Acronyms for epidemiology models are often based on the flow patterns between the compartments such as MSEIR, MSEIRS, SEIR, SEIRS, SIR, SIRS, SEI, SEIS, SI, and SIS. For example, in the MSEIR model shown in Figure 1, passively immune newborns first become susceptible, then exposed in the latent period, then infectious, and then removed with permanent immunity. An MSEIRS model would be similar, but the immunity in the R class would be temporary, so that individuals would regain their susceptibility when the temporary immunity ended.

The threshold for many epidemiology models is the basic reproduction number R_0, which is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible [61]. For many deterministic epidemiology models, an infection can get started in a fully susceptible population if and only if $R_0 > 1$. Thus the basic reproduction number R_0 is often considered as the threshold quantity that determines when an infection can invade and persist in a new host population. Section 2 introduces epidemiology modeling by formulating and analyzing two classic deterministic models. The role of R_0 is demonstrated for the classic SIR endemic model in section 2.4. Then thresholds are estimated from data on several diseases and the implications of the estimates are considered for diseases such as smallpox, polio, measles, rubella, chickenpox, and influenza. An MSEIR endemic model in a population without age structure but with exponentially changing population size is formulated and analyzed in section 3. This model demonstrates how exponential population growth affects the basic reproduction number R_0.

Realistic infectious disease models include both time t and age a as independent variables, because age groups mix heterogeneously, the recovered fraction usually increases with age, risks from an infection may be related to age, vaccination pro-

grams often focus on specific ages, and epidemiologic data is often age specific. These epidemiologic models are based on the demographic models in section 4 with either continuous age or age groups. The two demographic models demonstrate the role of the population reproduction numbers in determining when the population grows asymptotically exponentially. The MSEIR with continuous age structure is formulated and analyzed in section 5. New general expressions for the basic reproduction number R_0 and the average age of infection A are obtained. Expressions for these quantities are found in sections 5.4 and 5.6 in the cases when the survival function of the population is a negative exponential and a step function. In section 5.5 the endemic threshold and the average age of infection are obtained when vaccination occurs at age A_v. The SEIR model with age groups is formulated and analyzed in section 6. The new expressions for the basic reproduction number R_0 and the average age of infection A are analogous to those obtained for the MSEIR model with continuous age structure.

The theoretical expressions in section 6 are used in section 7 to obtain estimates of the basic reproduction number R_0 and the average age of infection A for measles in Niger, Africa. These estimates are affected by the very rapid 3.3% growth of the population in Niger. In section 8 estimates of the basic reproduction number R_0 and the contact number σ (defined in section 2.2) are obtained for pertussis (whooping cough) in the United States. Because pertussis infectives with lower infectivity occur in previously infected people, the contact number σ at the endemic steady state is less than the basic reproduction number R_0. Section 9 describes results on the basic reproduction number R_0 for previous epidemiology models with a variety of structures, and section 10 contains a general discussion.

2. Two Classic Epidemiology Models. In order to introduce the terminology, notation, and standard results for epidemiology models, two classic SIR models are formulated and analyzed. Epidemic models are used to describe rapid outbreaks that occur in less than one year, while endemic models are used for studying diseases over longer periods, during which there is a renewal of susceptibles by births or recovery from temporary immunity. The two classic SIR models provide an intuitive basis for understanding more complex epidemiology modeling results.

2.1. Formulating Epidemiology Models. The horizontal incidence shown in Figure 1 is the infection rate of susceptible individuals through their contacts with infectives. If $S(t)$ is the number of susceptibles at time t, $I(t)$ is the number of infectives, and N is the total population size, then $s(t) = S(t)/N$ and $i(t) = I(t)/N$ are the susceptible and infectious fractions, respectively. If β is the average number of adequate contacts (i.e., contacts sufficient for transmission) of a person per unit time, then $\beta I/N = \beta i$ is the average number of contacts with infectives per unit time of one susceptible, and $(\beta I/N)S = \beta Nis$ is the number of new cases per unit time due to the $S = Ns$ susceptibles. This form of the horizontal incidence is called the standard incidence, because it is formulated from the basic principles above [96, 102].

The simple mass action law $\eta IS = \eta(Ni)(Ns)$, with η as a mass action coefficient, has sometimes been used for the horizontal incidence. The parameter η has no direct epidemiological interpretation, but comparing it with the standard formulation shows that $\beta = \eta N$, so that this form implicitly assumes that the contact rate β increases linearly with the population size. Naively, it might seem plausible that the population density and hence the contact rate would increase with population size, but the daily contact patterns of people are often similar in large and small communities, cities, and regions. For human diseases the contact rate seems to be only very weakly dependent

on the population size. Using an incidence of the form $\eta N^v SI/N$, data for five human diseases in communities with population sizes from 1,000 to 400,000 [9, p. 157] [12, p. 306] imply that v is between 0.03 and 0.07. This strongly suggests that the standard incidence corresponding to $v = 0$ is more realistic for human diseases than the simple mass action incidence corresponding to $v = 1$. This result is consistent with the concept that people are infected through their daily encounters and the patterns of daily encounters are largely independent of community size within a given country (e.g., students of the same age in a country usually have a similar number of daily contacts).

The standard incidence is also a better formulation than the simple mass action law for animal populations such as mice in a mouse-room or animals in a herd [57], because disease transmission primarily occurs locally from nearby animals. For more information about the differences in models using these two forms of the horizontal incidence, see [83, 84, 85, 96, 110, 159]. Vertical incidence, which is the infection rate of newborns by their mothers, is sometimes included in epidemiology models by assuming that a fixed fraction of the newborns is infected vertically [33]. Models with population size–dependent contact functions have also been considered [29, 171, 190, 191, 201]. Various forms of nonlinear incidences have been considered [112, 147, 148, 149]. See [107] for a survey of mechanisms including nonlinear incidences that can lead to periodicity in epidemiological models.

A common assumption is that the movements out of the M, E, and I compartments and into the next compartment are governed by terms like δM, ϵE, and γI in an ordinary differential equations model. It has been shown [109] that these terms correspond to exponentially distributed waiting times in the compartments. For example, the transfer rate γI corresponds to $P(t) = e^{-\gamma t}$ as the fraction that is still in the infective class t units after entering this class and to $1/\gamma$ as the mean waiting time. For measles the mean period $1/\delta$ of passive immunity is about six to nine months, while the mean latent period $1/\varepsilon$ is one to two weeks and the mean infectious period $1/\gamma$ is about one week. Another possible assumption is that the fraction still in the compartment t units after entering is a nonincreasing, piecewise continuous function $P(t)$ with $P(0) = 1$ and $P(\infty) = 0$. Then the rate of leaving the compartment at time t is $-P'(t)$, so the mean waiting time in the compartment is $\int_0^\infty t(-P'(t))dt = \int_0^\infty P(t)dt$. These distributed delays lead to epidemiology models with integral or integrodifferential or functional differential equations. If the waiting time distribution is a step function given by $P(t) = 1$ if $0 \le t \le \tau$, and $P(t) = 0$ if $\tau \le t$, then the mean waiting time is τ, and for $t \ge \tau$ the model reduces to a delay-differential equation [109]. Each waiting time in a model can have a different distribution, so there are many possible models [102].

2.2. Three Threshold Quantities: R_0, σ, and R. The basic reproduction number R_0 has been defined in the introduction as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host population [61]. Note that R_0 is also called the basic reproduction ratio [58] or basic reproductive rate [12]. It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix. The contact number σ is defined as the average number of adequate contacts of a typical infective during the infectious period [96, 110]. An adequate contact is one that is sufficient for transmission, if the individual contacted by the susceptible is an infective. The replacement number R is defined to be the average number of secondary infections produced by a

Table 1 *Summary of notation.*

M	Passively immune infants
S	Susceptibles
E	Exposed people in the latent period
I	Infectives
R	Recovered people with immunity
m, s, e, i, r	Fractions of the population in the classes above
β	Contact rate
$1/\delta$	Average period of passive immunity
$1/\varepsilon$	Average latent period
$1/\gamma$	Average infectious period
R_0	Basic reproduction number
σ	Contact number
R	Replacement number

typical infective during the entire period of infectiousness [96]. Some authors use the term reproduction number instead of replacement number, but it is better to avoid the name reproduction number since it is easily confused with the basic reproduction number. Note that these three quantities R_0, σ, and R in Table 1 are all equal at the beginning of the spread of an infectious disease when the entire population (except the infective invader) is susceptible. In recent epidemiological modeling literature, the basic reproduction number R_0 is often used as the threshold quantity that determines whether a disease can invade a population.

Although R_0 is only defined at the time of invasion, σ and R are defined at all times. For most models, the contact number σ remains constant as the infection spreads, so it is always equal to the basic reproduction number R_0. In these models σ and R_0 can be used interchangeably and invasion theorems can be stated in terms of either quantity. But for the pertussis models in section 8, the contact number σ becomes less than the basic reproduction number R_0 after the invasion, because new classes of infectives with lower infectivity appear when the disease has entered the population. The replacement number R is the actual number of secondary cases from a typical infective, so that after the infection has invaded a population and everyone is no longer susceptible, R is always less than the basic reproduction number R_0. Also, after the invasion, the susceptible fraction is less than 1, so that not all adequate contacts result in a new case. Thus the replacement number R is always less than the contact number σ after the invasion. Combining these results leads to

$$R_0 \geq \sigma \geq R,$$

with equality of the three quantities at the time of invasion. Note that $R_0 = \sigma$ for most models, and $\sigma > R$ after the invasion for all models.

2.3. The Classic Epidemic Model. Using the notation in section 2.1, the classic epidemic model is the SIR model given by the initial value problem

$$\begin{aligned} dS/dt &= -\beta IS/N, & S(0) &= S_o \geq 0, \\ dI/dt &= \beta IS/N - \gamma I, & I(0) &= I_o \geq 0, \\ dR/dt &= \gamma I, & R(0) &= R_o \geq 0, \end{aligned} \tag{2.1}$$

where $S(t)$, $I(t)$, and $R(t)$ are the numbers in these classes, so that $S(t)+I(t)+R(t) = N$. This SIR model is a special case of the MSEIR model in Figure 1, in which the

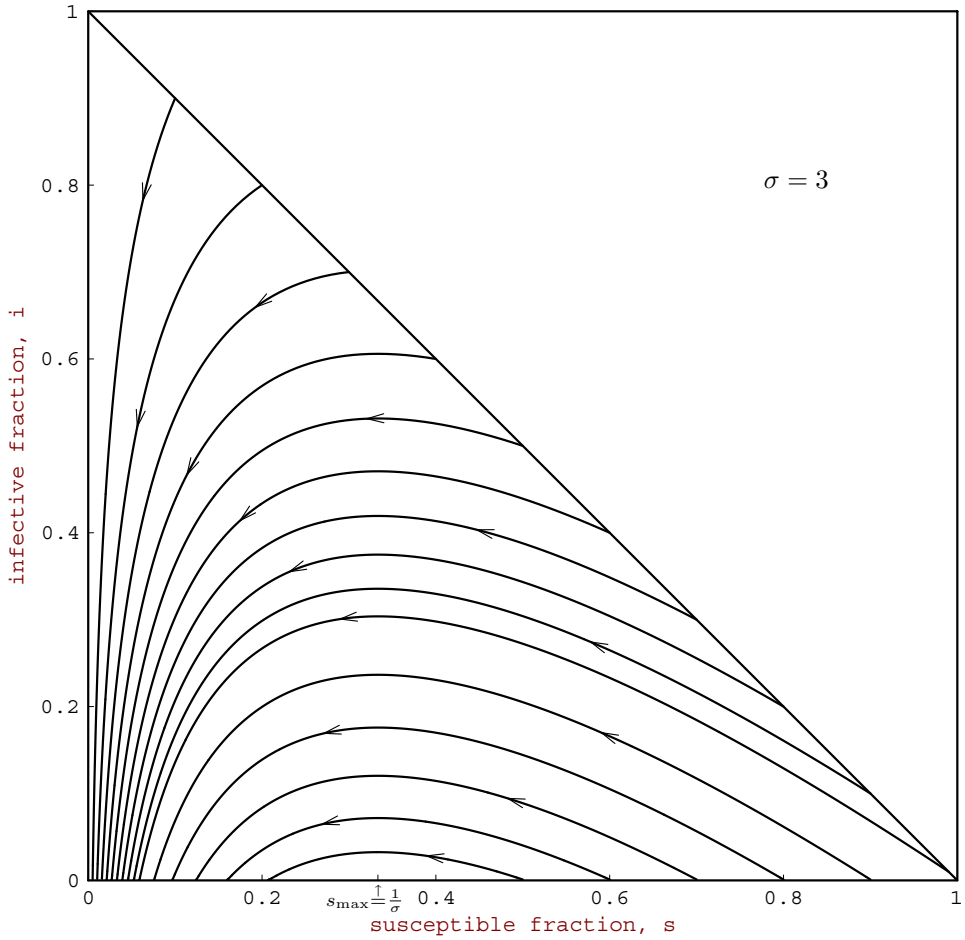

Fig. 2 *Phase plane portrait for the classic SIR epidemic model with contact number* $\sigma = 3$.

passively immune class M and the exposed class E are omitted. This model uses the standard incidence and has recovery at rate γI, corresponding to an exponential waiting time $e^{-\gamma t}$. Since the time period is short, this model has no vital dynamics (births and deaths). Dividing the equations in (2.1) by the constant total population size N yields

$$\begin{aligned} ds/dt &= -\beta is, \qquad & s(0) &= s_o \geq 0, \\ di/dt &= \beta is - \gamma i, \qquad & i(0) &= i_o \geq 0, \end{aligned} \tag{2.2}$$

with $r(t) = 1 - s(t) - i(t)$, where $s(t)$, $i(t)$, and $r(t)$ are the fractions in the classes. The triangle T in the si phase plane given by

$$T = \{(s, i) \,|\, s \geq 0, i \geq 0, s + i \leq 1\} \tag{2.3}$$

is positively invariant and unique solutions exist in T for all positive time, so that the model is mathematically and epidemiologically well posed [96]. Here the contact number $\sigma = \beta/\gamma$ is the contact rate β per unit time multiplied by the average infectious period $1/\gamma$, so it has the proper interpretation as the average number of adequate

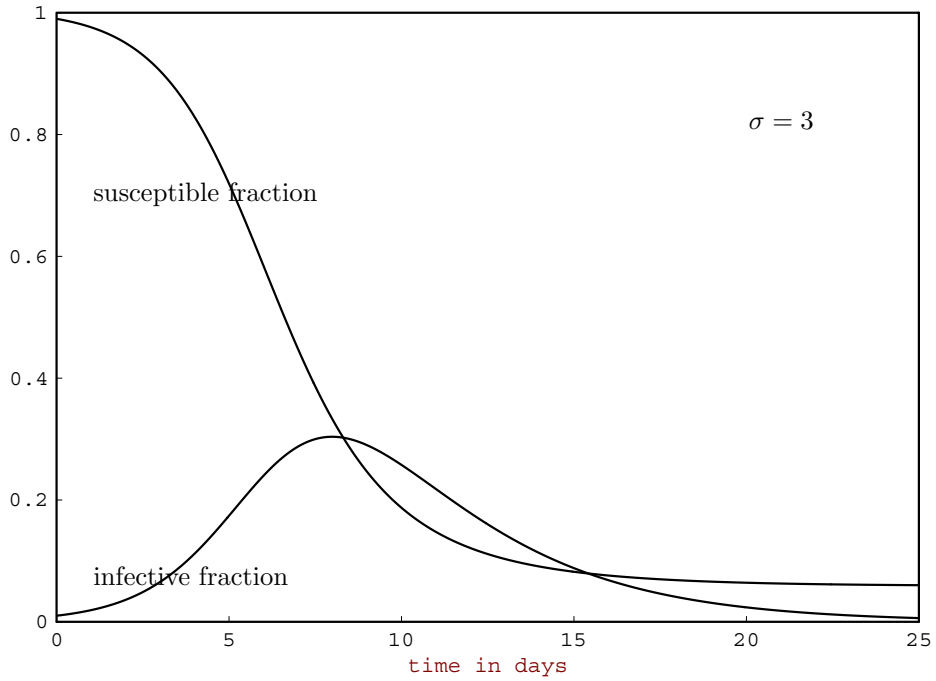

Fig. 3 *Solutions of the classic SIR epidemic model with contact number* $\sigma = 3$ *and average infectious period* $1/\gamma = 3$ *days.*

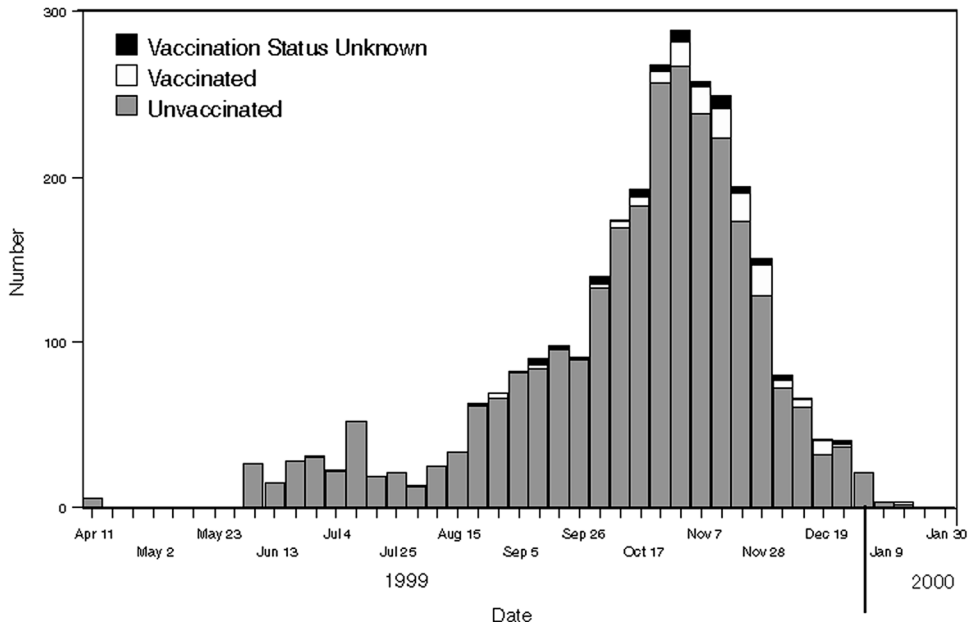

Fig. 4 *Reported number of measles cases in the Netherlands by week of onset and vaccination status during April* 1999 *to January* 2000. *Most of the unvaccinated cases were people belonging to a religious denomination that routinely does not accept vaccination. The* 2,961 *measles cases included* 3 *measles-related deaths. Reprinted from* [52].

contacts of a typical infective during the infectious period. Here the replacement number at time zero is σs_o, which is the product of the contact number σ and the initial susceptible fraction s_o.

THEOREM 2.1. *Let $(s(t), i(t))$ be a solution of (2.2) in T. If $\sigma s_o \leq 1$, then $i(t)$ decreases to zero as $t \to \infty$. If $\sigma s_o > 1$, then $i(t)$ first increases up to a maximum value $i_{max} = i_o + s_o - 1/\sigma - [\ln(\sigma s_o)]/\sigma$ and then decreases to zero as $t \to \infty$. The susceptible fraction $s(t)$ is a decreasing function and the limiting value s_∞ is the unique root in $(0, 1/\sigma)$ of the equation*

$$i_o + s_o - s_\infty + \ln(s_\infty/s_o)/\sigma = 0. \tag{2.4}$$

Typical paths in T are shown in Figure 2, and solutions as a function of time are shown in Figure 3. Note that the hallmark of a typical epidemic outbreak is an infective curve that first increases from an initial I_o near zero, reaches a peak, and then decreases toward zero as a function of time. For example, a recent measles epidemic in the Netherlands [52] is shown in Figure 4. The susceptible fraction $s(t)$ always decreases, but the final susceptible fraction s_∞ is positive. The epidemic dies out because, when the susceptible fraction $s(t)$ goes below $1/\sigma$, the replacement number $\sigma s(t)$ goes below 1. The results in the theorem are epidemiologically reasonable, since the infectives decrease and there is no epidemic, if enough people are already immune so that a typical infective initially replaces itself with no more than one new infective ($\sigma s_o \leq 1$). But if a typical infective initially replaces itself with more than one new infective ($\sigma s_o > 1$), then infectives initially increase so that an epidemic occurs. The speed at which an epidemic progresses depends on the characteristics of the disease. The measles epidemic in Figure 4 lasted for about nine months, but because the latent period for influenza is only one to three days and the infectious period is only two to three days, an influenza epidemic can sweep through a city in less than six weeks. See [100] for more examples of epidemic outbreak curves.

To prove the theorem, observe that the solution paths

$$i(t) + s(t) - [\ln s(t)]/\sigma = i_o + s_o - [\ln s_o]/\sigma$$

in Figure 2 are found from the quotient differential equation $di/ds = -1 + 1/(\sigma s)$. The equilibrium points along the s axis are neutrally unstable for $s > 1/\sigma$ and are neutrally stable for $s < 1/\sigma$. For a complete (easy) proof, see [96] or [100]. One classic approximation derived in [18] is that for small i_o and s_o slightly greater than $s_{\max} = 1/\sigma$, the difference $s_{\max} - s(\infty)$ is about equal to $s_o - s_{\max}$, so the final susceptible fraction is about as far below the susceptible fraction $s_{\max}$ (the s value where the infective fraction is a maximum) as the initial susceptible fraction was above it (see Figure 2). Observe that the threshold result here involves the initial replacement number σs_o and does not involve the basic reproduction number R_0.

2.4. The Classic Endemic Model. The classic endemic model is the SIR model with vital dynamics (births and deaths) given by

$$\begin{aligned} dS/dt &= \mu N - \mu S - \beta IS/N, & S(0) &= S_o \geq 0, \\ dI/dt &= \beta IS/N - \gamma I - \mu I, & I(0) &= I_o \geq 0, \\ dR/dt &= \gamma I - \mu R, & R(0) &= R_o \geq 0, \end{aligned} \tag{2.5}$$

with $S(t) + I(t) + R(t) = N$. This SIR model is almost the same as the SIR epidemic model (2.1) above, except that it has an inflow of newborns into the susceptible class

at rate μN and deaths in the classes at rates μS, μI, and μR. The deaths balance the births, so that the population size N is constant. The mean lifetime $1/\mu$ would be about 75 years in the United States. Dividing the equations in (2.5) by the constant total population size N yields

$$\begin{aligned} ds/dt &= -\beta is + \mu - \mu s, \qquad s(0) = s_o \geq 0, \\ di/dt &= \beta is - (\gamma + \mu)i, \qquad i(0) = i_o \geq 0, \end{aligned} \tag{2.6}$$

with $r(t) = 1 - s(t) - i(t)$. The triangle T in the si phase plane given by (2.3) is positively invariant, and the model is well posed [96]. Here the contact number σ remains equal to the basic reproduction number R_0 for all time, because no new classes of susceptibles or infectives occur after the invasion. For this model the threshold quantity is given by $R_0 = \sigma = \beta/(\gamma + \mu)$, which is the contact rate β times the average death-adjusted infectious period $1/(\gamma + \mu)$.

THEOREM 2.2. *Let $(s(t), i(t))$ be a solution of (2.6) in T. If $\sigma \leq 1$ or $i_o = 0$, then solution paths starting in T approach the disease-free equilibrium given by $s = 1$ and $i = 0$. If $\sigma > 1$, then all solution paths with $i_o > 0$ approach the endemic equilibrium given by $s_e = 1/\sigma$ and $i_e = \mu(\sigma - 1)/\beta$.*

Figures 5 and 6 illustrate the two possibilities given in the theorem. If $R_0 = \sigma \leq 1$, then the replacement number σs is less than 1 when $i_o > 0$, so that the infectives decrease to zero. Although the speeds of movement along the paths are not apparent from Figure 5, the infective fraction decreases rapidly to very near zero, and then over 100 or more years, the recovered people slowly die off and the birth process slowly increases the susceptibles, until eventually everyone is susceptible at the disease-free equilibrium with $s = 1$ and $i = 0$. If $R_0 = \sigma > 1$, i_o is small, and s_o is large with $\sigma s_o > 1$, then $s(t)$ decreases and $i(t)$ increases up to a peak and then decreases, just as it would for an epidemic (compare Figure 6 with Figure 2). However, after the infective fraction has decreased to a low level, the slow processes of the deaths of recovered people and the births of new susceptibles gradually (over about 10 or 20 years) increase the susceptible fraction until $\sigma s(t)$ is large enough that another smaller epidemic occurs. This process of alternating rapid epidemics and slow regeneration of susceptibles continues as the paths approach the endemic equilibrium given in the theorem. At this endemic equilibrium the replacement number σs_e is 1, which is plausible since if the replacement number were greater than or less than 1, the infective fraction $i(t)$ would be increasing or decreasing, respectively.

Theorem 2.2 was proved in [96] and in [100] using phase plane methods and Liapunov functions. For this SIR model there is a transcritical (stability exchange) bifurcation at $\sigma = 1$, as shown in Figure 7. Notice that the i_e coordinate of the endemic equilibrium is negative for $\sigma < 1$, coincides with the disease-free equilibrium value of zero at $\sigma = 1$, and becomes positive for $\sigma > 1$. This equilibrium given by $s_e = 1/\sigma$ and $i_e = \mu(\sigma - 1)/\beta$ is unstable for $\sigma < 1$ and is locally asymptotically stable for $\sigma > 1$, while the disease-free equilibrium given by $s = 1$ and $i = 0$ is locally stable for $\sigma < 1$ and unstable for $\sigma > 1$. Thus these two equilibria exchange stabilities as the endemic equilibrium moves through the disease-free equilibrium when $\sigma = 1$ and becomes a distinct, epidemiologically feasible, locally asymptotically stable equilibrium when $\sigma > 1$. Analogues of the results in the theorem hold for other endemic models. For example, in the SEIR model, the threshold is $R_0 = \sigma = \beta\varepsilon/[(\gamma + \mu)(\varepsilon + \mu)]$, which is the product of the contact rate β, the average fraction $\varepsilon/(\varepsilon + \mu)$ surviving the latent period, and the average infectious period $1/(\gamma + \mu)$. For the

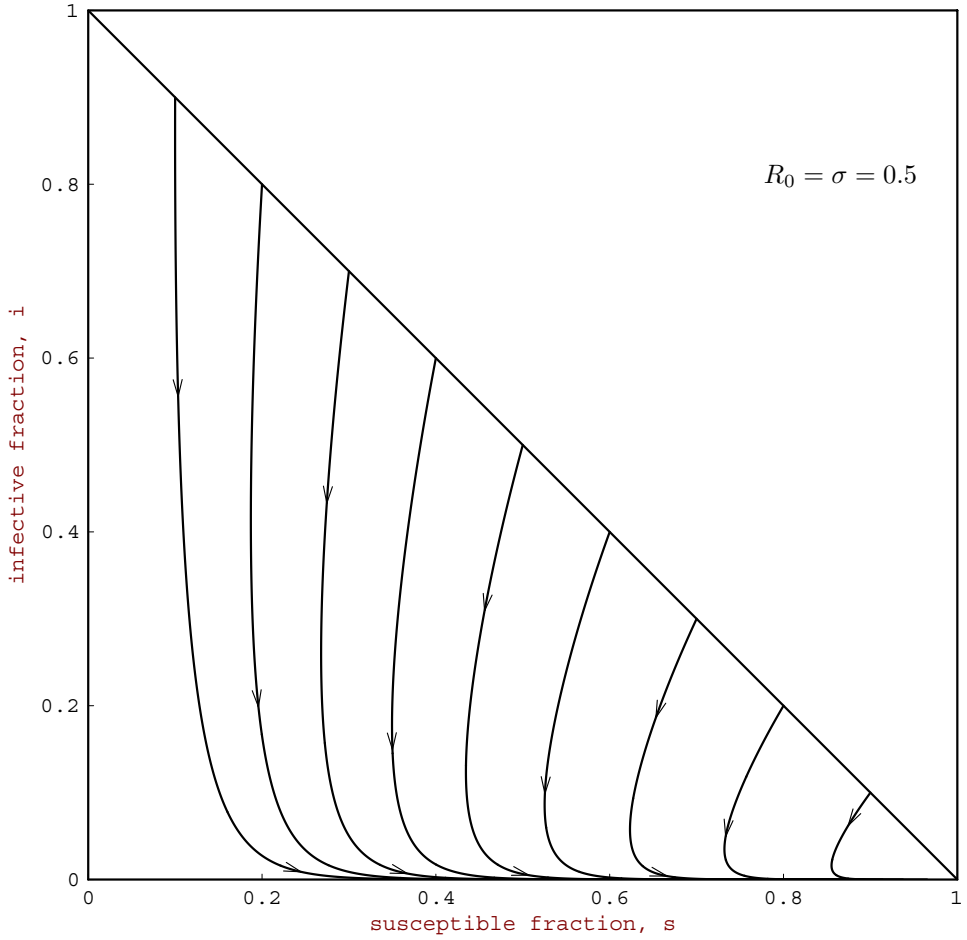

Fig. 5 *Phase plane portrait for the classic SIR endemic model with contact number* $\sigma = 0.5$.

SEIR model the global stability below the threshold was proved in [147] and the global stability above the threshold was recently proved using clever new methods [143]. Results for the MSEIR model are given in section 3.

The following interpretation of the results in the theorem and paragraph above is one reason why the basic reproduction number R_0 has become widely used in the epidemiology literature. If the basic reproduction number R_0 (which is always equal to the contact number σ when the entire population is susceptible) is less than 1, then the disease-free equilibrium is locally asymptotically stable and the disease cannot "invade" the population. But if $R_0 > 1$, then the disease-free equilibrium is unstable with a repulsive direction into the positive si quadrant, so the disease can "invade" in the sense that any path starting with a small positive i_o moves into the positive si quadrant where the disease persists. Thus for this classic SIR endemic model and for many other more complex models [58], the behavior is almost completely dependent on the threshold quantity R_0, which determines not only when the local stability of the disease-free equilibrium switches, but also when the endemic equilibrium enters the feasible region with a positive infective fraction. The latter condition is used to obtain expressions for R_0 in age-structured models in sections 5 and 6.

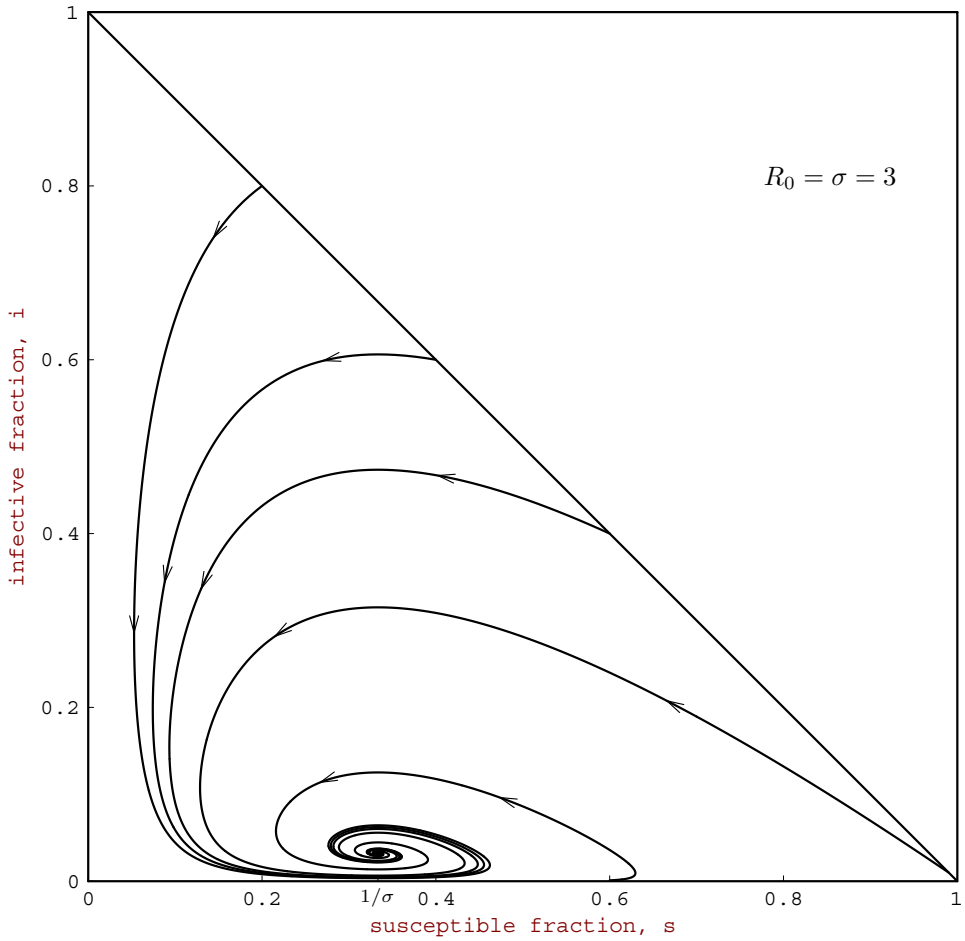

Fig. 6 *Phase plane portrait for the classic SIR endemic model with contact number $\sigma = 3$, average infectious period $1/\gamma = 3$ days, and average lifetime $1/\mu = 60$ days. This unrealistically short average lifetime has been chosen so that the endemic equilibrium is clearly above the horizontal axis and the spiraling into the endemic equilibrium can be seen.*

2.5. Threshold Estimates Using the Classic Models. The classic SIR models above are very important as conceptual models (similar to predator-prey and competing species models in ecology). The SIR epidemic modeling yields the useful concept of the threshold quantity σs_o, which determines when an epidemic occurs, and formulas for the peak infective fraction i_m and the final susceptible fraction s_∞. The SIR endemic modeling yields $R_0 = \sigma$ as the threshold quantity that determines when the disease remains endemic, the concept that the infective replacement number σs_e is 1 at the endemic equilibrium, and the explicit dependence of the infective fraction i_e on the parameters. However, these simple, classic SIR models have obvious limitations. They unrealistically assume that the population is uniform and homogeneously mixing, whereas it is known that mixing depends on many factors including age (children usually have more adequate contacts per day than adults). Moreover, different geographic and social-economic groups have different contact rates. Despite their limitations, the classic SIR models can be used to obtain some estimates and comparisons.

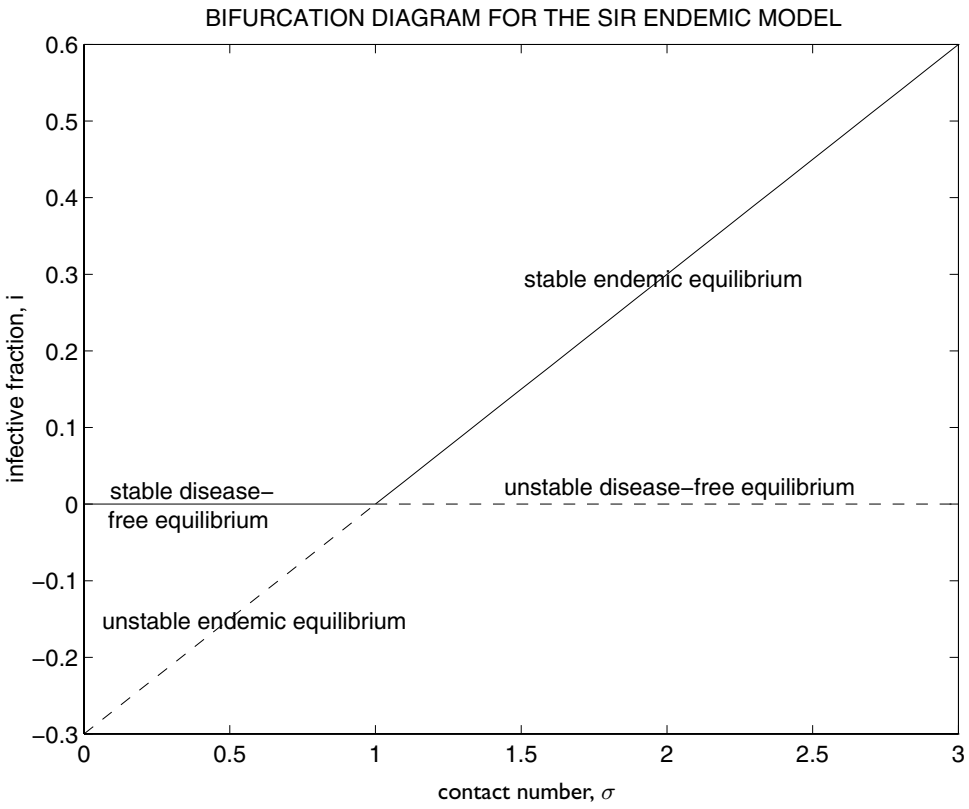

Fig. 7 *The bifurcation diagram for the SIR endemic model, which shows that the disease-free and endemic equilibria exchange stability when the contact number* σ *is* 1.

From (2.4) for s_∞ in the classic SIR epidemic model, the approximation

$$\sigma \approx \frac{\ln(s_o/s_\infty)}{s_o - s_\infty}$$

follows because i_o is negligibly small. By using data on the susceptible fractions s_o and s_∞ at the beginning and end of epidemics, this formula can be used to estimate contact numbers for specific diseases [100]. Using blood samples from freshmen at Yale University [75], the fractions susceptible to rubella at the beginning and end of the freshman year were found to be 0.25 and 0.090, so the epidemic formula above gives $\sigma \approx 6.4$. The fractions $s_o = 0.49$ and $s_\infty = 0.425$ for the Epstein–Barr virus (related to mononucleosis) lead to $\sigma \approx 2.2$, and the fractions $s_o = 0.911$ and $s_\infty = 0.514$ for influenza (H3N2 type A "Hong Kong") lead to $\sigma \approx 1.44$. For the 1957 "Asian Flu" (H2N2 type A strain of influenza) in Melbourne, Australia, the fractions $s_o = 1$ and $s_\infty = 0.55$ from [31, p. 129] yield the contact number estimate $\sigma \approx 1.33$. Thus the easy theory for the classic SIR epidemic model yields the formula above that can be used to estimate contact numbers from epidemic data.

The classic SIR endemic model can also be used to estimate contact numbers. If blood samples in a serosurvey are tested for antibodies to a virus and it is assumed that the SIR model above holds in the population with the disease at an endemic equilibrium, then the contact number can be estimated from $\sigma = 1/s_e$, where s_e is the

fraction of the samples that are not seropositive, since $s_e = 1 - i_e - r_e$. This approach is somewhat naive, because the average seropositivity in a population decreases to zero as the initial passive immunity declines and then increases as people age and are exposed to infectives. Thus the ages of those sampled are critical in using the estimate $\sigma = 1/s_e$. For the SIR model with negative exponential survival in section 5.4, one estimation formula for the basic reproduction number is $R_0 = 1 + L/A$, where L is the average lifetime $1/\mu$ and A is the average age of infection. This estimation formula can also be derived heuristically from the classic SIR endemic model. The incidence rate at the endemic equilibrium is $\beta i_e s_e$, so that βi_e is the incidence rate constant, which with exponential waiting time implies that the average age of infection (the mean waiting time in S) is $A = 1/\beta i_e = 1/[\mu(\sigma - 1)]$. Using $\mu = 1/L$, this leads to $R_0 = \sigma = 1 + L/A$, since $R_0 = \sigma$ for this model.

Data on average ages of infection and average lifetimes in developed countries have been used to estimate basic reproduction numbers R_0 for some viral diseases. These estimates of R_0 are about 16 for measles, 11 for varicella (chickenpox), 12 for mumps, 7 for rubella, and 5 for poliomyelitis and smallpox [12, p. 70], [100]. Because disease-acquired immunity is only temporary for bacterial diseases such as pertussis (whooping cough) and diphtheria, the formula $R_0 = \sigma = 1 + L/A$ cannot be used to estimate R_0 for these diseases (see section 8 for estimates of R_0 and σ for pertussis).

Herd immunity occurs for a disease if enough people have disease-acquired or vaccination-acquired immunity, so that the introduction of one infective into the population does not cause an invasion of the disease. Intuitively, if the contact number is σ, so that the typical infective has adequate contacts with σ people during the infectious period, then the replacement number σs must be less than 1 so that the disease does not spread. This means that s must be less than $1/\sigma$, so the immune fraction r must satisfy $r > 1 - 1/\sigma = 1 - 1/R_0$. For example, if $R_0 = \sigma = 10$, then the immune fraction must satisfy $r > 1 - 1/10 = 0.9$, so that the replacement number is less than 1 and the disease does not invade the population.

Using the estimates above for R_0, the minimum immune fractions for herd immunity are 0.94 for measles, 0.89 for mumps, 0.86 for rubella, and 0.8 for poliomyelitis and smallpox. Although these values give only crude, ballpark estimates for the vaccination-acquired immunity level in a community required for herd immunity, they are useful for comparing diseases. For example, these numbers suggest that it should be easier to achieve herd immunity for poliomyelitis and smallpox than for measles, mumps, and rubella. This conclusion is justified by the actual effectiveness of vaccination programs in reducing, locally eliminating, and eradicating these diseases (eradication means elimination throughout the world). The information in the next section verifies that smallpox has been eradicated worldwide and polio should be eradicated worldwide within a few years, while the diseases of rubella and measles still persist at low levels in the United States and at higher levels in many other countries. Thus the next section provides historical context and verifies the disease comparisons obtained from the simple, classic SIR endemic model.

2.6. Smallpox, Polio, Measles, Rubella, Chickenpox, and Influenza. Smallpox is believed to have appeared in the first agricultural settlements around 6,000 BC. For centuries the process of variolation with material from smallpox pustules was used in Africa, China, and India before arriving in Europe and the Americas in the 18th century. Edward Jenner, an English country doctor, observed over 25 years that milkmaids who had been infected with cowpox did not get smallpox. In 1796 he started vaccinating people with cowpox to protect them against smallpox [168].

This was the world's first vaccine (*vacca* is the Latin word for cow). Two years later, the findings of the first vaccine trials were published, and by the early 1800s, the smallpox vaccine was widely available. Smallpox vaccination was used in many countries in the 19th century, but smallpox remained endemic. When the World Health Organization (WHO) started a global smallpox eradication program in 1967, there were about 15 million cases per year, of which 2 million died and millions more were disfigured or blinded by the disease [77]. The WHO strategy involved extensive vaccination programs (see Figure 8), surveillance for smallpox outbreaks, and containment of these outbreaks by local vaccination programs. There are some interesting stories about the WHO campaign, including the persuasion of African chiefs to allow their tribes to be vaccinated and monetary bounty systems for finding hidden smallpox cases in India. Smallpox was slowly eliminated from many countries, with the last case in the Americas in 1971. The last case worldwide was in Somalia in 1977, so smallpox has been eradicated throughout the world [23, 77, 168]. The WHO estimates that the elimination of worldwide smallpox vaccination saves over two billion dollars per year. The smallpox virus has been kept in U.S. and Russian government laboratories; the United States keeps it so that vaccine could be produced if smallpox were ever used in biological terrorism [182].

Most cases of poliomyelitis are asymptomatic, but a small fraction of cases result in paralysis. In the 1950s in the United States, there were about 60,000 paralytic polio cases per year. In 1955 Jonas Salk developed an injectable polio vaccine from an inactivated polio virus. This vaccine provides protection for the person, but the person can still harbor live viruses in their intestines and can pass them to others. In 1961 Albert Sabin developed an oral polio vaccine from weakened strains of the polio virus. This vaccine provokes a powerful immune response, so the person cannot harbor the "wild-type" polio viruses, but a very small fraction (about one in 2 million) of those receiving the oral vaccine develop paralytic polio [23, 168]. The Salk vaccine interrupted polio transmission and the Sabin vaccine eliminated polio epidemics in the United States, so there have been no indigenous cases of naturally occurring polio since 1979. In order to eliminate the few cases of vaccine-related paralytic polio each year, the United States now recommends the Salk injectable vaccine for the first four polio vaccinations, even though it is more expensive [50]. In the Americas, the last case of paralytic polio caused by the wild virus was in Peru in 1991. In 1988 the WHO set a goal of global polio eradication by the year 2000 [178]. Most countries are using the live-attenuated Sabin vaccine, because it is inexpensive (8 cents per dose) and can be easily administered into a mouth by an untrained volunteer. The WHO strategy includes routine vaccination, National Immunization Days (during which many people in a country or region are vaccinated in order to interrupt transmission), mopping-up vaccinations, and surveillance for acute flaccid paralysis [116]. Polio has disappeared from many countries in the past 10 years, so that by 1999 it was concentrated in the Eastern Mediterranean region, South Asia, West Africa, and Central Africa. It is likely that polio will soon be eradicated worldwide. The WHO estimates that eradicating polio will save about $1.5 billion each year in immunization, treatment, and rehabilitation around the globe [45].

Measles is a serious disease of childhood that can lead to complications and death. For example, measles caused about 7,500 deaths in the United States in 1920 and still causes about 1 million deaths worldwide each year [47, 48]. Measles vaccinations are given to children between 6 and 18 months of age, but the optimal age of vaccination for measles seems to vary geographically [99]. Rubella (also called three-day measles or German measles) is a mild disease with few complications, but a rubella infection

Fig. 8 *Following Jenner's discovery in* 1796, *smallpox vaccination spread throughout the world within decades. But the replacement number R remained above* 1, *so that smallpox persisted in most areas until the mid-*20*th century. In* 1966 *smallpox was still endemic in South America, Africa, India, and Indonesia. After the WHO smallpox eradication program was initiated in* 1967, *the worldwide incidence of the disease decreased steadily. Posters like these motivated people in Africa to get smallpox vaccinations. The last naturally occurring smallpox case was in Somalia in* 1977. *Reprinted from Centers for Disease Control HHS Publication No. (CDC)* 87-8400.

during the first trimester of pregnancy can result in miscarriage, stillbirth, or infants with a pattern of birth defects called congenital rubella syndrome (CRS) [23]. Because the goal of a rubella vaccination program is to prevent rubella infections in pregnant women, special vaccination strategies such as vaccination of 12 to 14-year-old girls are sometimes used [98, 101]. The estimates above based on R_0 values suggest that herd immunity would be achieved if the immune fraction in the population were greater

Fig. 9 *After a measles vaccine was approved in* 1963*, vaccination programs in the United States were very effective in reducing reported measles cases. This* 1976 *photograph shows schoolchildren in Highland Park, Illinois, lining up for measles vaccinations. Because of a major outbreak in* 1989–1991*, the United States changed to a two-dose measles vaccination program. The replacement number R now appears to be below* 1 *throughout the United States, so that measles is no longer considered to be an indigenous disease there. Photo by Thomas S. England, Photo Researchers, Inc.*

than 0.94 for measles and 0.86 for rubella. But the vaccine efficacy for these diseases is about 0.95, which means that 5% of those who are vaccinated do not become immune. Thus to reach the levels necessary to achieve herd immunity, the vaccinated fractions would have to be at least 0.99 for measles and 0.91 for rubella. These fractions suggest that achieving herd immunity would be much harder for measles than for rubella, because the percentages not vaccinated would have to be below 1% for measles and below 9% for rubella. Because vaccinating all but 1% against measles would be difficult to achieve, a two-dose program for measles is an attractive alternative in some countries [50, 98, 99].

Consider the history of measles in the United States. In the prevaccine era, every child had measles, so the incidences were approximately equal to the sizes of the birth cohorts. After the measles vaccine was licensed in 1963 in the United States, the reported measles incidence dropped in a few years to around 50,000 cases per year. See Figure 9. In 1978 the United States adopted a goal of eliminating measles, and vaccination coverage increased, so that there were fewer than 5,000 reported cases per year between 1981 and 1988. Pediatric epidemiologists at meetings at the Centers for Disease Control in Atlanta in November 1985 and February 1988 decided to continue the one-dose program for measles vaccinations instead of changing to a more expensive two-dose program. But there were about 16,000, 28,000, and 17,000 reported measles cases in the United States in 1989, 1990, and 1991, respectively; there were also measles outbreaks in Mexico and Canada during these years [117]. Because of this major measles epidemic, epidemiologists decided in 1989 that the one-dose vaccination program for measles, which had been used for 26 years, should be

replaced with a two-dose program with the first measles vaccination at age 12 to 15 months and the second vaccination at 4 to 6 years, just before children start school [50]. Reported measles cases declined after 1991 until there were only 137, 100, and 86 reported cases in 1997, 1998, and 1999, respectively. Each year some of the reported cases are imported cases and these imported cases can trigger small outbreaks. The proportion of cases not associated with importation has declined from 85% in 1995, 72% in 1996, 41% in 1997, to 29% in 1998. Analysis of the epidemiologic data for 1998 suggests that measles is no longer an indigenous disease in the United States [47]. Measles vaccination coverage in 19 to 35-month-old children was only 92% in 1998, but over 99% of children had at least one dose of measles-containing vaccine by age 6 years. Because measles is so easily transmitted and the worldwide measles vaccination coverage was only 72% in 1998 [48, 168], this author does not believe that it is feasible to eradicate measles worldwide using the currently available measles vaccines.

In the prevaccine era, rubella epidemics and subsequent CRS cases occurred about every 4 to 7 years in the United States. During a major rubella epidemic in 1964, it is estimated that there were over 20,000 CRS cases in the United States with a total lifetime cost of over $2 billion [98, 101]. Since the rubella vaccine was licensed in 1969, the incidences of rubella and CRS in the United States have decreased substantially. Since many rubella cases are subclinical and unreported, we consider only the incidence of CRS. The yearly incidences of CRS in the United States were between 22 and 67 in the 1970s, between 0 and 50 in the 1980s, 11 in 1990, 47 in 1991, 11 in 1992, and then between 4 and 8 from 1993 to 1999 [43]. Although there have been some increases in CRS cases associated with occasional rubella outbreaks, CRS has been at a relatively low level in the United States in recent years. In recent rubella outbreaks in the United States, most cases occurred among unvaccinated persons aged at least 20 years and among persons who were foreign born, primarily Hispanics (63% of reported cases in 1997) [46]. Although it does not solve the problem of unvaccinated immigrants, the rubella vaccination program for children has reduced the incidence of rubella and CRS in the United States to very low levels. Worldwide eradication of rubella is not feasible, because over two-thirds of the population in the world is not yet routinely vaccinated for rubella. Indeed, the policies in China and India of not vaccinating against rubella may be the best policies for those countries, because most women of childbearing age in these countries already have disease-acquired immunity.

The varicella zoster virus (VZV) is the agent for varicella, commonly known as chickenpox. Chickenpox is usually a mild disease in children that lasts about four to seven days with a body rash of several hundred lesions. After a case of chickenpox, the VZV becomes latent in the dorsal root ganglia, but VZV can reactivate in the form of zoster, commonly known as shingles. Shingles is a painful vesicular rash along one or more sensory root nerves that usually occurs when the immune system is less effective due to illness or aging [23]. People with shingles are less infectious than those with chickenpox, but they can transmit the VZV. Indeed, it was found that some isolated Amazon tribes had no antibodies to diseases such as measles, mumps, and rubella, but they did have antibodies to VZV [25]. Thus it appears that the persistence of VZV in these small isolated populations has occurred because VZV can be dormant in people for many years and then be spread in the population by a case of shingles. Because of the transmission by those with both chickenpox and shingles, the expression for R_0 is more complicated than for the MSEIR model [180]. A varicella vaccine was licensed

in the United States in 1995 and is now recommended for all young children. But the vaccine-immunity wanes, so that vaccinated children can get chickenpox as adults. Two possible dangers of this new varicella vaccination program are more chickenpox cases in adults, when the complication rates are higher, and an increase in cases of shingles. An age-structured epidemiologic-demographic model has been used with parameters estimated from epidemiological data to evaluate the effects of varicella vaccination programs [179]. Although the age distribution of varicella cases does shift in the computer simulations, this shift does not seem to be a problem since many of the adult cases occur after vaccine-induced immunity wanes, so they are mild varicella cases with fewer complications. In the computer simulations, shingles incidence increases in the first 30 years after initiation of a varicella vaccination program, because people are more likely to get shingles as adults when their immunity is not boosted by frequent exposures, but after 30 years the shingles incidence starts to decrease as the population includes more previously vaccinated people, who are less likely to get shingles. Thus the simulations validate the second danger that the new vaccination program could lead to more cases of shingles in the first several decades [179].

Type A influenza has three subtypes in humans (H1N1, H2N2, and H3N2) that are associated with widespread epidemics and pandemics (i.e., worldwide epidemics). Types B and C influenza tend to be associated with local or regional epidemics. Influenza subtypes are classified by antigenic properties of the H and N surface glycoproteins, whose mutations lead to new variants every few years [23]. For example, the A/Sydney/5/97(H3N2) variant entered the United States in 1998–1999 and was the dominant variant in the 1999–2000 flu season [51]. An infection or vaccination for one variant may give only partial immunity to another variant of the same subtype, so that flu vaccines must be reformulated almost every year. If an influenza virus subtype did not change, then it should be easy to eradicate, because the contact number for flu has been estimated above to be only about 1.4. But the frequent drift of the A subtypes to new variants implies that flu vaccination programs cannot eradicate them because the target is constantly moving. Completely new A subtypes (antigenic shift) emerge occasionally from unpredictable recombinations of human with swine or avian influenza antigens. These new subtypes can lead to major pandemics. A new H1N1 subtype led to the 1918–1919 pandemic that killed over half a million people in the United States and over 20 million people worldwide. Pandemics also occurred in 1957 from the Asian Flu (an H2N2 subtype) and in 1968 from the Hong Kong flu (an H3N2 subtype) [134]. When 18 confirmed human cases with 6 deaths from an H5N1 chicken flu occurred in Hong Kong in 1997, there was great concern that this might lead to another antigenic shift and pandemic. At the end of 1997, veterinary authorities slaughtered all (1.6 million) chickens present in Hong Kong, and importation of chickens from neighboring areas was stopped. Fortunately, the H5N1 virus did not evolve into a form that is readily transmitted from person to person [185, 198].

3. The MSEIR Model with Exponentially Changing Size. The two classic infectious disease models in section 2 assume that the total population size remains constant. However, constant population size models are not suitable when the natural births and deaths are not balanced or when the disease-related deaths are significant. Infectious diseases have often had a big impact on population sizes and historical events [158, 168, 202]. Infectious diseases that have played a major role in the debilitation and regulation of human populations include plague, measles, scarlet fever, diphtheria, tuberculosis, smallpox, malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, onchocerciasis, hookworm, the gastroenteritises, and the

pneumonias. For example, the black plague caused 25% population decreases and led to social, economic, and religious changes in Europe in the 14th century. Diseases such as smallpox, diphtheria, and measles brought by Europeans devastated native populations in the Americas. AIDS is now changing the population structure in sub-Saharan Africa. Infectious diseases such as measles combined with low nutritional status still cause significant early mortality in developing countries. Indeed, the longer life spans in developed countries seem to be primarily a result of the decline of mortality due to communicable diseases [44].

Models with a variable total population size are often more difficult to analyze mathematically because the population size is an additional variable which is governed by a differential equation [7, 8, 29, 30, 35, 37, 83, 88, 153, 159, 171, 201]. Some models of HIV/AIDS with varying population size have been considered [13, 39, 118, 132, 146]. Before looking at MSEIR models with age structures, we first consider an MSEIR model in a population with an exponentially changing size.

3.1. Formulation of the Differential Equations for the MSEIR Model. The MSEIR model shown in Figure 10 is suitable for a directly transmitted disease such as measles, rubella, or mumps, for which an infection confers permanent immunity. Let the birth rate constant be b and the death rate constant be d, so the population size $N(t)$ satisfies $N' = (b-d)N$. Thus the population is growing, constant, or decaying if the net change rate $q = b - d$ is positive, zero, or negative, respectively. Since the population size can have exponential growth or decay, it is appropriate to separate the dynamics of the epidemiological process from the dynamics of the population size. The numbers of people in the epidemiological classes are denoted by $M(t)$, $S(t)$, $E(t)$, $I(t)$, and $R(t)$, where t is time, and the fractions of the population in these classes are $m(t)$, $s(t)$, $e(t)$, $i(t)$, and $r(t)$. We are interested in finding conditions that determine whether the disease dies out (i.e., the fraction i goes to zero) or remains endemic (i.e., the fraction i remains positive). Note that the number of infectives I could go to infinity even though the fraction i goes to zero if the population size N grows faster than I. Similarly, I could go to zero even when i remains bounded away from zero, if the population size is decaying to zero [83, 159]. To avoid any ambiguities, we focus on the behavior of the fractions in the epidemiological classes.

The birth rate bS into the susceptible class of size S corresponds to newborns whose mothers are susceptible, and the other newborns $b(N-S)$ enter the passively immune class of size M, since their mothers were infected or had some type of immunity. Although all women would be out of the passively immune class long before their childbearing years, theoretically a passively immune mother would transfer some IgG antibodies to her newborn child, so the infant would have passive immunity. Deaths occur in the epidemiological classes at the rates dM, dS, dE, dI, and dR, respectively.

In this MSEIR epidemiological model, the transfer out of the passively immune class is δM, the transfer out of the exposed class is εE, and the recovery rate from the infectious class is γI. The linear transfer terms in the differential equations correspond to waiting times with negative exponential distributions, so that when births and deaths are ignored, the mean passively immune period is $1/\delta$, the mean latent period is $1/\varepsilon$, and the mean infectious period is $1/\gamma$ [109]. These periods are $1/\delta = 6$ months, $1/\varepsilon = 14$ days, and $1/\gamma = 7$ days for chickenpox [179]. For sexually transmitted diseases, it is useful to define both a sexual contact rate and the fraction of contacts that result in transmission, but for directly transmitted diseases spread primarily by aerosol droplets, transmission may occur by entering a room, hallway, building, etc., that is currently or has been occupied by an infective. Since there

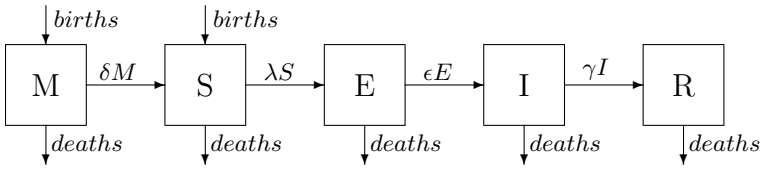

Fig. 10 *Transfer diagram for the MSEIR model with the passively immune class M, the susceptible class S, the exposed class E, the infective class I, and the recovered class R.*

is no clear definition of a contact or a transmission fraction, they are replaced by a definition that includes both. An adequate contact is a contact that is sufficient for transmission of infection from an infective to a susceptible. Let the contact rate β be the average number of adequate contacts per person per unit time, so that the force of infection $\lambda = \beta i$ is the average number of contacts with infectives per unit time. Then the incidence (the number of new cases per unit time) is $\lambda S = \beta i S = \beta SI/N$, since it is the number of contacts with infectives per unit time of the S susceptibles. As described in section 2.1, this standard form $\beta SI/N$ for the incidence is consistent with numerous studies that show that the contact rate β is nearly independent of the population size.

The system of differential equations for the numbers in the epidemiological classes and the population size is

$$\begin{aligned} dM/dt &= b(N - S) - (\delta + d)M, \\ dS/dt &= bS + \delta M - \beta SI/N - dS, \\ dE/dt &= \beta SI/N - (\varepsilon + d)E, \\ dI/dt &= \varepsilon E - (\gamma + d)I, \\ dR/dt &= \gamma I - dR, \\ dN/dt &= (b - d)N. \end{aligned}$$

It is convenient to convert to differential equations for the fractions in the epidemiological classes with simplifications by using the differential equation for N, eliminating the differential equation for s by using $s = 1 - m - e - i - r$, using $b = d + q$, and using the force of infection λ for βi. Then the ordinary differential equations for the MSEIR model are

$$\begin{aligned} dm/dt &= (d + q)(e + i + r) - \delta m, \\ de/dt &= \lambda(1 - m - e - i - r) - (\varepsilon + d + q)e \\ &\qquad \text{with } \lambda = \beta i, \\ di/dt &= \varepsilon e - (\gamma + d + q)i, \\ dr/dt &= \gamma i - (d + q)r. \end{aligned} \tag{3.1}$$

A suitable domain is

$$\mathfrak{D} = \{(m, e, i, r) : m \geq 0, e \geq 0, i \geq 0, r \geq 0, m + e + i + r \leq 1\}.$$

The domain $\mathfrak{D}$ is positively invariant, because no solution paths leave through any boundary. The right sides of (3.1) are smooth, so that initial value problems have unique solutions that exist on maximal intervals [92]. Since paths cannot leave $\mathfrak{D}$, solutions exist for all positive time. Thus the model is mathematically and epidemiologically well posed.

3.2. Equilibria and Thresholds. The basic reproduction number R_0 for this MSEIR model is the same as the contact number σ given by

$$R_0 = \sigma = \frac{\beta\varepsilon}{(\gamma + d + q)(\varepsilon + d + q)}. \tag{3.2}$$

This R_0 is the product of the contact rate β per unit time, the average infectious period adjusted for population growth of $1/(\gamma + d + q)$, and the fraction $\varepsilon/(\varepsilon + d + q)$ of exposed people surviving the latent class E. Thus R_0 has the correct interpretation that it is the average number of secondary infections due to an infective during the infectious period, when everyone in the population is susceptible. The equations (3.1) always have a disease-free equilibrium given by $m = e = i = r = 0$, so that $s = 1$. If $R_0 > 1$, there is also a unique endemic equilibrium in $\mathfrak{D}$ given by

$$\begin{aligned} m_e &= \frac{d+q}{\delta + d + q}\left(1 - \frac{1}{R_0}\right), \\ e_e &= \frac{\delta(d+q)}{(\delta + d + q)(\varepsilon + d + q)}\left(1 - \frac{1}{R_0}\right), \\ i_e &= \frac{\varepsilon\delta(d+q)}{(\varepsilon + d + q)(\delta + d + q)(\gamma + d + q)}\left(1 - \frac{1}{R_0}\right), \\ r_e &= \frac{\varepsilon\delta\gamma}{(\varepsilon + d + q)(\delta + d + q)(\gamma + d + q)}\left(1 - \frac{1}{R_0}\right), \end{aligned} \tag{3.3}$$

where $s_e = 1/R_0 = 1/\sigma$. Note that the replacement number σs_e is 1 at the endemic equilibrium. At the endemic equilibrium the force of infection $\lambda = \beta i_e$ satisfies the equation

$$\lambda = \delta(d+q)(R_0 - 1)/(\delta + d + q), \tag{3.4}$$

so that there is a positive force of infection λ when $R_0 > 1$.

By linearization, the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and is an unstable hyperbolic equilibrium with a stable manifold outside $\mathfrak{D}$ and an unstable manifold tangent to a vector into $\mathfrak{D}$ when $R_0 > 1$. The disease-free equilibrium can be shown to be globally asymptotically stable in $\mathfrak{D}$ if $R_0 \le 1$ by using the Liapunov function $V = \varepsilon e + (\varepsilon + d + q)i$, as follows. The Liapunov derivative is $\dot{V} = [\beta\varepsilon s - (\gamma + d + q)(\varepsilon + d + q)]i \le 0$, since $\beta\varepsilon \le (\gamma + d + q)(\varepsilon + d + q)$. The set where $\dot{V} = 0$ is the face of $\mathfrak{D}$ with $i = 0$, but $di/dt = \varepsilon e$ on this face, so that I moves off the face unless $e = 0$. When $e = i = 0$, $dr/dt = -(d+q)r$, so that $r \to 0$. When $e = i = r = 0$, then $dm/dt = -\delta m$, so $m \to 0$. Because the origin is the only positively invariant subset of the set with $\dot{V} = 0$, all paths in $\mathfrak{D}$ approach the origin by the Liapunov–Lasalle theorem [92, p. 296]. Thus if $R_0 \le 1$, then the disease-free equilibrium is globally asymptotically stable in $\mathfrak{D}$.

The characteristic equation corresponding to the Jacobian at the endemic equilibrium is a fourth-degree polynomial. Using a symbolic algebra program, it can be shown that the Routh–Hurwitz criteria are satisfied if $R_0 > 1$, so that the endemic equilibrium (3.3) is locally asymptotically stable when it is in $\mathfrak{D}$. Thus if $R_0 > 1$, then the disease-free equilibrium is unstable and the endemic equilibrium is locally asymptotically stable. The system (3.1) can be defined to be uniformly persistent if $\liminf_{t\to\infty} i(t) \ge c$ for some $c > 0$ for all initial points such that $e(0) + i(0) > 0$. The properties of the disease-free equilibrium and Theorem 4.5 in [191] imply that

the system (3.1) is uniformly persistent if $R_0 > 1$. Based on results for the SIR and SEIR models, we expect (but have not proved rigorously) that all paths in $\mathfrak{D}$ with some initial latents or infectives go to the endemic equilibrium if $R_0 > 1$. Then we have the usual behavior for an endemic model, in the sense that the disease dies out below the threshold, and the disease goes to a unique endemic equilibrium above the threshold.

Other similar models also have the endemic threshold property above. The MSEIRS model is similar to the MSEIR model, but the immunity after an infection is temporary. This MSEIRS model has a different endemic equilibrium, but it has the same basic reproduction number R_0 given by (3.2). If $\delta \to \infty$, then heuristically the M class disappears (think of people moving through the M class with infinite speed), so that the MSEIR and MSEIRS models become SEIR and SEIRS models [147] with the same basic reproduction number R_0 given by (3.2). If $\varepsilon \to \infty$, then the E class disappears, leading to MSIR and MSIRS models with $R_0 = \beta/(\gamma + d + q)$. If an SEIRS model has an αR transfer term from the removed class R to the susceptible class S and $\alpha \to \infty$, then the R class disappears, leading to an SEIS model with R_0 given by (3.2). If $\varepsilon \to \infty$, then the E class disappears and the SEIS model becomes an SIS model with $R_0 = \beta/(\gamma + d + q)$. If $\delta \to \infty$ and $\varepsilon \to \infty$, then both the M and E classes disappear in the MSEIR model leading to an SIR or SIRS model with $R_0 = \beta/(\gamma + d + q)$. The global stabilities of the endemic equilibria have been proved for the constant population size SEIR model [143], for the SEIRS model with short or long period of immunity [145], and for the SEIR model with exponentially changing population size under a mild restriction [144]. The global stabilities of the SIR, SIRS, and SEIS models with constant population sizes are proved by standard phase plane methods [96, 100]. The SIS model with constant population size reduces to a Bernoulli differential equation, so solutions can be found explicitly [96, 100]. SIRS and SEIR models with exponential population dynamics have also been studied [144, 159].

4. Two Demographic Models. Before formulating the age-structured epidemiological models, we present the underlying demographic models, which describe the changing size and age structure of a population over time. These demographic models are a standard partial differential equations model with continuous age and an analogous ordinary differential equations model with age groups.

4.1. The Demographic Model with Continuous Age. The demographic model consists of an initial-boundary value problem with a partial differential equation for age-dependent population growth [114]. Let $U(a,t)$ be the age distribution of the total population, so that the number of individuals at time t in the age interval $[a_1, a_2]$ is the integral of $U(a,t)$ from a_1 to a_2. The partial differential equation for the population growth is

$$\frac{\partial U}{\partial a} + \frac{\partial U}{\partial t} = -d(a)U, \tag{4.1}$$

where $d(a)$ is the age-specific death rate. Note that the partial derivative combination occurs because the derivative of $U(a(t),t)$ with respect to t is $\frac{\partial U}{\partial a}\frac{da}{dt} + \frac{\partial U}{\partial t}$, and $\frac{da}{dt} = 1$. Let $f(a)$ be the fertility per person of age a, so that the births at time t are given by

$$B(t) = U(0,t) = \int_0^\infty f(a)U(a,t)da. \tag{4.2}$$

The initial age distribution is given by $U(a,0) = U_0(a)$ with $U_0(0) = B(0)$. This model was used by Lotka [150] in 1922 for population modeling, by McKendrick [157] in 1926

in conjunction with epidemic models, and by von Foerster [195] for cell proliferation, so it is sometimes called the Lotka–McKendrick model or the McKendrick–von Foerster model.

We briefly sketch the proof ideas for analyzing the asymptotic behavior of $U(a,t)$ when $d(a)$ and $f(a)$ are reasonably smooth [114, 123]. Solving along characteristics with slope 1, we find $U(a,t) = B(t-a)e^{-\int_0^a d(v)dv}$ for $t \geq a$ and $U(a,t) = u_0(a-t)e^{-\int_{a-t}^a d(v)dv}$ for $t < a$. If the integral in (4.2) is subdivided at $a = t$, then substitution of the expressions for $U(a,t)$ on the intervals yields

$$B(t) = U(0,t) = \int_0^t f(a)B(t-a)e^{-\int_0^a d(v)dv}da + \int_t^\infty f(a)U_0(a)e^{-\int_{a-t}^a d(v)dv}da.$$

This equation with a kernel $K(a)$ in the first integral and $g(t)$ for the second integral becomes the renewal equation $B(t) = \int_0^t K(a)B(t-a)da + g(t)$. To analyze this convolution integral equation for $B(t)$, take Laplace transforms and evaluate the contour integral form of the inverse Laplace transform by a residue series. As $t \to \infty$, the residue for the extreme right pole dominates, which leads to $U(a,t) \to e^{qt}A(a)$ as $t \to \infty$. Thus the population age distribution approaches the steady state $A(a)$, and the population size approaches exponential growth or decay of the form e^{qt}.

To learn more about the asymptotic age distribution $A(a)$, assume a separation of variables form given by $U(a,t) = T(t)A(a)$. Substituting this into the partial differential equation (4.1) and solving the separated differential equations yields $U(a,t) = T(0)e^{qt}A(0)e^{-D(a)-qa}$, where $D(a) = \int_0^a d(v)dv$. Substituting this expression for $U(a,t)$ into the birth equation (4.2), we obtain the Lotka characteristic equation given by

$$1 = \int_0^\infty f(a)\exp[-D(a) - qa]da. \tag{4.3}$$

If the population reproduction number given by

$$R_{pop} = \int_0^\infty f(a)\exp[-D(a)]da \tag{4.4}$$

is less than, equal to, or greater than 1, then the q solution of (4.3) is negative, zero, or positive, respectively, so that the population is decaying, constant, or growing, respectively.

In order to simplify the demographic aspects of the epidemiological models so there is no dependence on the initial population age distribution, we assume that the age distribution in the epidemiology models has reached a steady state age distribution with the total population size at time 0 normalized to 1, so that

$$U(a,t) = \rho e^{qt}e^{-D(a)-qa} \quad \text{with } \rho = 1 \Big/ \int_0^\infty e^{-D(a)-qa}da\ . \tag{4.5}$$

In this case the birth equation (4.2) is equivalent to the characteristic equation (4.3).

If the age-specific death rate $d(a)$ is constant, then (4.5) is $U(a,t) = e^{qt}(d+q)e^{-(d+q)a}$. Intuitively, when $q > 0$, the age distribution is $(d+q)e^{-(d+q)a}$, because the increasing inflow of newborns gives a constantly increasing young population, so that the age distribution decreases with age faster than de^{-da}, corresponding to $q = 0$. Note that the negative exponential age structure may be a reasonable approximation

in some developing countries, but it is generally not realistic in developed countries, where a better approximation would be that everyone lives until a fixed age L such as 75 years and then dies. In this case, $d(a)$ is zero until age L and infinite after age L, so that $D(a)$ is zero until age L and is infinite after age L. These two approximate survival functions given by the step function and the negative exponential were called Type I and Type II mortality, respectively, by Anderson and May [12]. Of course, the best approximation for any country is found by using death rate information for that country to estimate $d(a)$. This approach is used in the models with age groups in sections 7 and 8.

The factor $w(a) = e^{-D(a)}$ gives the fraction of a birth cohort surviving until age a, so it is called the survival function. The rate of death is $-w'(a)$, so that the expected age a of dying is $E[a] = \int_0^\infty a[-w'(a)]da = \int_0^\infty wda$. When the death rate coefficient $d(a)$ is constant, then $w(a) = e^{-da}$ and the mean lifetime L is $1/d$. For a step survival function, the mean lifetime is the fixed lifetime L.

4.2. The Demographic Model with Age Groups. This demographic model with age groups has been developed from the initial boundary value problem in the previous section for use in age-structured epidemiologic models for pertussis [105]. It consists of a system of n ordinary differential equations for the sizes of the n age groups defined by the age intervals $[a_{i-1}, a_i]$, where $0 = a_0 < a_1 < a_2 < \cdots < a_{n-1} < a_n = \infty$. A maximum age is not assumed, so the last age interval $[a_{n-1}, \infty)$ corresponds to all people over age a_{n-1}. For $a \in [a_{i-1}, a_i]$, assume that the death rates and fertilities are constant with $d(a) = d_i$ and $f(a) = f_i$. We also assume that the population has reached an equilibrium age distribution with exponential growth in the form $U(a,t) = e^{qt}A(a)$ given by (4.5), so that the number of individuals in the age bracket $[a_{i-1}, a_i]$ is given by

$$N_i(t) = \int_{a_{i-1}}^{a_i} U(a,t)da = e^{qt}\int_{a_{i-1}}^{a_i} A(a)da = e^{qt}P_i, \tag{4.6}$$

where P_i is the size of the ith age group at time 0.

Substituting $U(a,t) = e^{qt}A(a)$ into (4.1) yields the ordinary differential equation $dA/da = -[d(a) + q]A$, which can be solved on the interval $[a_{i-1}, a_i]$ to obtain

$$A(a) = A(a_{i-1})\exp[-(d_i + q)(a - a_{i-1})]. \tag{4.7}$$

Integrate this $A(a)$ over the interval $[a_{i-1}, a_i]$ to get

$$P_i = A(a_{i-1})\{1 - \exp[-(d_i + q)(a_i - a_{i-1})]\}/(d_i + q). \tag{4.8}$$

For $i = 1, 2, \ldots, n-1$, it is convenient to define the constants c_i by $A(a_i) = c_iP_i$. Use this definition of the constants c_i with (4.7) and (4.8) to obtain

$$c_i = \frac{A(a_i)}{P_i} = \frac{d_i + q}{\exp[(d_i + q)(a_i - a_{i-1})] - 1}. \tag{4.9}$$

Integration of (4.1) on the intervals $[a_{i-1}, a_i]$ and (4.6) yields

$$\begin{aligned} dN_1/dt &= \sum_{j=1}^{n} f_jN_j - (c_1 + d_1)N_1, \\ dN_i/dt &= c_{i-1}N_{i-1} - (c_i + d_i)N_i, \qquad 2 \le i \le n-1, \\ dN_n/dt &= c_{n-1}N_{n-1} - d_nN_n. \end{aligned} \tag{4.10}$$

Thus the constants c_i are the transfer rate constants between the successive age groups.

Equations (4.7) and (4.8) imply $A(a_i) - A(a_{i-1}) = -[d_i + q]P_i$. Substituting $A(a_i) = c_i P_i$ leads to $P_i = c_{i-1}P_{i-1}/(c_i + d_i + q)$ for $i \geq 2$. Iterative use of this equation leads to the following equation for P_i in terms of P_1:

$$P_i = \frac{c_{i-1} \cdots c_1 P_1}{(c_i + d_i + q) \cdots (c_2 + d_2 + q)}. \tag{4.11}$$

The birth equation $A(0) = \sum_{i=1}^{n} f_i P_i$, $A(0) = (c_1 + d_1 + q)P_1$, and (4.11) lead to the age-group form of the Lotka characteristic equation (4.3) given by

$$1 = \frac{f_1 + f_2 \dfrac{c_1}{(c_2 + d_2 + q)} + \cdots + f_n \dfrac{c_{n-1} \cdots c_1}{(c_n + d_n + q) \cdots (c_2 + d_2 + q)}}{(c_1 + d_1 + q)}. \tag{4.12}$$

For this demographic model with n age groups, the population reproduction number is given by

$$R_{pop} = f_1 \frac{1}{(c_1 + d_1)} + f_2 \frac{c_1}{(c_2 + d_2)(c_1 + d_1)} + \cdots + f_n \frac{c_{n-1} \cdots c_1}{(c_n + d_n + q) \cdots (c_1 + d_1)}. \tag{4.13}$$

If the fertility constants f_i and the death rate constants d_i for the age groups are known, then (4.12) with each c_i given by (4.9) can be solved for the exponential growth rate constant q. If the population reproduction number R_{pop} is less than, equal to, or greater than 1, then the q solution of (4.12) is negative, zero, or positive, respectively, so that the population is decaying, constant, or growing, respectively. As in the continuous demographic model, it is assumed that the population starts at a steady state age distribution with total size 1 at time 0, so that the group sizes P_i remain fixed and add up to 1. See [105] for more details on the derivation of this demographic model for age groups.

5. The MSEIR Model with Continuous Age Structure. For many endemic models the basic reproduction number can be determined analytically by either of two methods. One method is to find the threshold condition above which a positive (endemic) equilibrium exists for the model and to interpret this threshold condition as $R_0 > 1$. The second method is to do a local stability analysis of the disease-free equilibrium and to interpret the threshold condition at which this equilibrium switches from asymptotic stability to instability as $R_0 > 1$. As shown in section 2.4, both of these methods give the same R_0 for the classic SIR endemic model, because the two equilibria exchange stability with each other in the sense that as the contact rate increases, the unstable, nontrivial equilibrium with a negative coordinate moves from outside the feasible region through the disease-free equilibrium at $R_0 = 1$ and into the feasible region, where it becomes a positive, stable endemic equilibrium. Similar methods work to obtain the basic reproduction number for age-structured epidemiological models; both are demonstrated for an SIR model with continuous age dependence in [40]. Here we use the appearance of an endemic steady state age distribution to identify expressions for the basic reproduction number R_0, and then show that the disease-free steady state is globally asymptotically stable if and only if $R_0 \leq 1$.

Table 2 *Summary of notation.*

$f(a), f_i$	Fertilities for continuous age, age groups
$d(a), d_i$	Death rate coefficients for continuous age, age groups
L	Average lifetime
R_{pop}	Population reproduction number
q	Population growth rate constant
$U(a,t)$	Distribution of the total population for continuous age
$A(a)$	Steady state age distribution for continuous age
$N_1(t), \ldots, N_n(t)$	Distribution of total population at time t for age groups
$P_1, \ldots, P_n$	Steady state age distribution for age groups
c_i	Rate constant for transfer from ith age class
$\lambda(a,t)$, λ_i	Force of infections on susceptibles of age a, in age group i
$b(a)\tilde{b}(\tilde{a})$	Contact rate between people of ages a and $\tilde{a}$
$b_i\tilde{b}_j$	Contact rate between people in age groups i and j
R_0	Basic reproduction number
A	Average age of infection

This age-structured MSEIR model uses the transfer diagram of Figure 10 and the notation in Tables 1 and 2. The age distributions of the numbers in the classes are denoted by $M(a,t)$, $S(a,t)$, $E(a,t)$, $I(a,t)$, and $R(a,t)$, where a is age and t is time, so that, for example, the number of susceptible individuals at time t in the age interval $[a_1, a_2]$ is the integral of $S(a,t)$ from a_1 to a_2. Because information on age-related fertilities and death rates is available for most countries and because mixing is generally heterogeneous, epidemiology models with age groups are now used frequently when analyzing specific diseases. However, special cases with homogeneous mixing and asymptotic age distributions that are a negative exponential or a step function are considered in sections 5.4 and 5.6. These special cases of the continuous MSEIR model are often used as approximate models. For example, the negative exponential age distribution is used for measles in Niger in section 7.

5.1. Formulation of the MSEIR Model. The rate constants δ, ε, and γ for the transfer rates out of the M, E, and I classes are the same as for the MSEIR model without age structure in section 2. Here it is assumed that the contact rate between people of age a and age $\tilde{a}$ is separable in the form $b(a)\tilde{b}(\tilde{a})$, so that the force of infection λ is the integral over all ages of the contact rate times the infectious fraction $I(\tilde{a},t)/\int_0^\infty U(\tilde{a},t)d\tilde{a}$ at time t. The division by the total population size $\int_0^\infty U(a,t)da$ makes the contact rate $\lambda(a,t)$ independent of the population size, so the contact number is independent of the population size [57, 97, 102, 159]. One example of separable mixing is proportionate mixing, in which the contacts of a person of age a are distributed over those of other ages in proportion to the activity levels of the other ages [103, 174]. If $l(a)$ is the average number of people contacted by a person of age a per unit time, $u(a)$ is the steady state age distribution for the population, and $D = \int_0^\infty l(a)u(a)da$ is the total number of contacts per unit time of all people, then $b(a) = l(a)/D^{1/2}$ and $b(\tilde{a}) = l(\tilde{a})/D^{1/2}$. Another example of separable mixing is age-independent mixing given by $b(a) = 1$ and $\tilde{b}(\tilde{a}) = \beta$.

The system of partial integrodifferential equations for the age distributions is

$$
\begin{aligned}
\partial M/\partial a + \partial M/\partial t &= -(\delta + d(a))M,\\
\partial S/\partial a + \partial S/\partial t &= \delta M - (\lambda(a,t) + d(a))S\\
\text{with } \lambda(a,t) &= \int_0^\infty b(a)\tilde{b}(\tilde{a})I(\tilde{a},t)d\tilde{a} \Big/ \int_0^\infty U(\tilde{a},t)d\tilde{a}\ ,\\
\partial E/\partial a + \partial E/\partial t &= \lambda(a,t)S - (\varepsilon + d(a))E,\\
\partial I/\partial a + \partial I/\partial t &= \varepsilon E - (\gamma + d(a))I,\\
\partial R/\partial a + \partial R/\partial t &= \gamma I - d(a)R.
\end{aligned}
\tag{5.1}
$$

Note that $M+S+E+I+R = U(a,t)$. As in the MSEIR model without age structure, infants born to mothers in the classes M, E, I, and R have passive immunity. Thus the boundary conditions at age 0 are

$$
\begin{aligned}
M(0,t) &= \int_0^\infty f(a)[M + E + I + R]da,\\
S(0,t) &= \int_0^\infty f(a)Sda,
\end{aligned}
$$

while the other distributions at age 0 are zero. Initial age distributions at time 0 complete the initial boundary value problem for this MSEIR model.

For each age a the fractional age distributions of the population in the epidemiological classes at time t are $m(a,t) = M(a,t)/U(a,t)$, $s(a,t) = S(a,t)/U(a,t)$, etc., where $U(a,t)$ is given by (4.5) in the previous section. Because the numerators and denominator contain the asymptotic growth factor e^{qt}, these fractional distributions do not grow exponentially. The partial differential equations for m, s, e, i, and r found from (5.1) are

$$
\begin{aligned}
\partial m/\partial a + \partial m/\partial t &= -\delta m,\\
\partial s/\partial a + \partial s/\partial t &= \delta m - \lambda(a,t)s\\
\text{with } \lambda(a,t) &= b(a)\int_0^\infty \tilde{b}(\tilde{a})i(\tilde{a},t)\rho e^{-D(\tilde{a})-q\tilde{a}}d\tilde{a},\\
\partial e/\partial a + \partial e/\partial t &= \lambda(a,t)s - \varepsilon e,\\
\partial i/\partial a + \partial i/\partial t &= \varepsilon e - \gamma i,\\
\partial r/\partial a + \partial r/\partial t &= \gamma i,
\end{aligned}
\tag{5.2}
$$

and the boundary conditions at age 0 are zero except for

$$
\begin{aligned}
m(0,t) &= \int_0^\infty f(a)[1 - s(a,t)]e^{-D(a)-qa}da,\\
s(0,t) &= \int_0^\infty f(a)s(a,t)e^{-D(a)-qa}da,
\end{aligned}
\tag{5.3}
$$

where $m(0,t) + s(0,t) = 1$ by (4.3).

For this endemic MSEIR model, the steady state age distributions $m(a)$, $s(a)$, $e(a)$, $i(a)$, and $r(a)$ add up to 1 and satisfy the ordinary differential equations corresponding to the equations (5.2) with the time derivatives set equal to zero. The

steady state solutions $m(a)$, $s(a)$, $e(a)$, and $i(a)$ are

$$
\begin{aligned}
m(a) &= (1-s_0)e^{-\delta a},\\
s(a) &= e^{-\Lambda(a)}\left[s_0+\delta(1-s_0)\int_0^a e^{-\delta x+\Lambda(x)}dx\right],\\
e(a) &= e^{-\varepsilon a}\int_0^a \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dy,\\
i(a) &= e^{-\gamma a}\int_0^a \varepsilon e^{(\gamma-\varepsilon)z}\int_0^z \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dydz,
\end{aligned}
\tag{5.4}
$$

where $\Lambda(a)=\int_0^a \lambda(\alpha)d\alpha$ with $\lambda = kb(a)$ for some constant k. At the disease-free steady state, k is zero, $s=1$, and $m=e=i=r=0$. The endemic steady state corresponds to k being a positive constant.

5.2. The Basic Reproduction Number R_0 and Stability. We now use the solutions of the MSEIR model to examine the basic reproduction number R_0. Substituting the steady state solution $i(a)$ in (5.4) into the expression for λ in (5.2) yields

$$
\begin{aligned}
\lambda(a) = b(a)\int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}}\int_0^{\tilde{a}} \varepsilon e^{(\gamma-\varepsilon)z}\\
\times\int_0^z \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dydzd\tilde{a}.
\end{aligned}
\tag{5.5}
$$

Using the definition of s_0 and (5.4), we find that

$$
s_0 = s_0F_\lambda + \delta(1-s_0)F_*, \tag{5.6}
$$

where $F_\lambda=\int_0^\infty f(a)e^{-\Lambda(a)-D(a)-qa}da$ and

$$
F_* = \int_0^\infty f(a)e^{-\Lambda(a)-D(a)-qa}\int_0^a e^{-\delta x+\Lambda(x)}dxda. \tag{5.7}
$$

Substituting the solution s_0 in (5.6) into (5.5) and canceling $\lambda(a)=kb(a)$ yields

$$
\begin{aligned}
1 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}}\int_0^{\tilde{a}} \varepsilon e^{(\gamma-\varepsilon)z}\int_0^z b(y)e^{\varepsilon y}\\
\times\left[\delta F_* e^{-k\int_0^y b(\alpha)d\alpha}+\delta(1-F_\lambda)\int_0^y e^{-\delta x-k\int_x^y b(\alpha)d\alpha}dx\right]\Big/(\delta F_*+1-F_\lambda)dydzd\tilde{a}.
\end{aligned}
\tag{5.8}
$$

The right side of this equation can be shown to be a decreasing function of k, so that (5.8) has a positive solution k corresponding to a positive force of infection $\lambda(a)=kb(a)$ if and only if $R_0>1$, where the basic reproduction number R_0 below is found by setting $k=0$ in the right side of (5.8):

$$
R_0 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}}\int_0^{\tilde{a}} \varepsilon e^{(\gamma-\varepsilon)z}\int_0^z b(y)e^{\varepsilon y}dydzd\tilde{a}. \tag{5.9}
$$

Note that $R_0>1$ implies that (5.8) has a positive solution k, which gives a positive force of infection $\lambda(a)=kb(a)$ and $\Lambda(a)=k\int_0^a b(\alpha)d\alpha$ defining the endemic steady

state solution (5.4). This expression (5.9) for the basic reproduction number in the MSEIR model seems to be new.

Determining the local stability of the disease-free steady state (at which $\lambda = kb(a) = 0$ and $s = 1$) by linearization is possible following the method in [40], but we can construct a Liapunov function to show the global stability of the disease-free steady state when $R_0 \le 1$. The feasible set for (5.2) consists of nonnegative fractions that add to 1. Consider the Liapunov function

$$V = \int_0^\infty [\alpha(a)e(a,t) + \beta(a)i(a,t)]da,$$

where the positive, bounded functions $\alpha(a)$ and $\beta(a)$ are to be determined. The formal Liapunov derivative is

$$\begin{aligned}\dot V &= \int_0^\infty \{\alpha(a)[\lambda s - \varepsilon e - \partial e/\partial a] + \beta(a)[\varepsilon e - \gamma i - \partial i/\partial a]\}da \\ &= \int_0^\infty \{\lambda s\alpha(a) + e[\alpha'(a) - \varepsilon\alpha(a) + \varepsilon\beta(a)] + [\beta'(a) - \gamma\beta(a)]i\}da.\end{aligned}$$

Choose $\alpha(a)$ so that the coefficient of the e term is zero. Then

$$\dot V = \int_0^\infty sb(a)\varepsilon e^{\varepsilon a}\int_a^\infty e^{-\varepsilon z}\beta(z)dzda\int_0^\infty \tilde b(\tilde a)i\rho e^{-D(\tilde a)-q\tilde a}d\tilde a + \int_0^\infty [\beta' - \gamma\beta]ida.$$

Choose $\beta(y)$ so that the last integral is the negative of the next to last integral. Then

$$\begin{aligned}\dot V = &\left[\int_0^\infty sb(a)\varepsilon e^{\varepsilon a}\int_a^\infty e^{(\gamma-\varepsilon)z}\int_z^\infty \tilde b(x)\rho e^{-D(x)-qx-\gamma x}dxdzda - 1\right] \\ &\times \int_0^\infty \tilde b(\tilde a)i(\tilde a,t)\rho e^{-D(\tilde a)-q\tilde a}d\tilde a.\end{aligned}$$

Now $s \le 1$ and the triple integral in the first factor in $\dot V$ above with $s = 1$ is equal to R_0 in (5.9) after changing the order of integration. Thus

$$\dot V \le (R_0 - 1)\int_0^\infty \tilde b(\tilde a)i(\tilde a,t)\rho e^{-D(\tilde a)-q\tilde a}d\tilde a \le 0 \quad \text{if } R_0 \le 1.$$

Hence solutions of (5.2) move downward through the level sets of V as long as they do not stall on the set where $\dot V = 0$. The set with $\dot V = 0$ is the boundary of the feasible region with $i = 0$, but $di(a(t),t)/dt = \varepsilon e$ on this boundary, so that i moves off this boundary unless $e = 0$. If $e = i = 0$ so there are no exposed or infectious people, then (5.1) implies that there would be no removed people or infants with passive immunity after several generations, so everyone would be susceptible. Thus the disease-free steady state is the only positively invariant subset of the set with $\dot V = 0$. If there is a finite maximum age (so that all forward paths have compact closure), then either Corollary 2.3 in [162] or Corollary 18.5 in [4] (Liapunov–Lasalle theorems for semiflows) implies that all paths in the feasible region approach the disease-free steady state.

If $R_0 > 1$, then we have $\dot V > 0$ for points sufficiently close to the disease-free steady state with s close to 1 and $i > 0$ for some age, so that the disease-free steady state is unstable. This implies that the system (5.2) is uniformly persistent when

$R_0 > 1$, as for the ordinary differential equation models in sections 3.2 and 6.2, but the assumption of a finite maximum age seems to be necessary to satisfy the condition in Theorem 4.6 in [191] that there is a compact set that attracts all solutions. Although the endemic steady state would usually be stable, this may not be true in unusual cases. For example, the endemic steady state can be unstable in the age-structured SIR model when $b(a)$ is decreasing and $\tilde{b}(\tilde{a})$ is constant [16] and when $\tilde{b}(\tilde{a})$ is concentrated at a certain age while $b(a)$ is constant [189]. Some types of mixing cannot be written in the separable form $b(a)\tilde{b}(\tilde{a})$. For example, in preferred mixing, certain age groups are more likely to mix with their own age group [103]. For more general mixing, the endemic steady state might not be unique, but some conditions that guarantee existence, uniqueness, and local stability have been given [53, 125].

Because the basic reproduction number for the MSEIR model does not depend on δ or on whether recovered people have no, temporary, or permanent immunity, the expression (5.9) for R_0 also works for the MSEIRS, SEIR, SEIRS, and SEIS models, but the equations (5.8) for k would be different. For example, in the SEIR model all newborns are susceptible, so $s_0 = 1$ and the equation for k is (5.8) with $F_\lambda = 1$. For the SIR model with no passively immune or latent classes, an analysis similar to that above for the MSEIR model leads to an equation for the force of infection constant k given by

$$1 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}} \int_0^{\tilde{a}} b(y)e^{\gamma y - k\int_0^y b(\alpha)d\alpha} dy d\tilde{a} \tag{5.10}$$

and a basic reproduction number given by

$$R_0 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}} \int_0^{\tilde{a}} b(y)e^{\gamma y} dy d\tilde{a}. \tag{5.11}$$

This expression is similar to previous R_0 expressions for SIR models with constant population size [40, 68]. The expression (5.11) for R_0 can also be used for SIRS and SIS models, but the equations for the positive k when $R_0 > 1$ would be different. Proofs of stability and persistence for the models in this paragraph are similar to those for the MSEIR model.

5.3. Expressions for the Average Age of Infection *A*. We now find an expression for the average age of infection for the MSEIR model at the endemic steady state age distribution. Although the steady state age distribution of the population is $\rho e^{-D(a)-qa}$, the age distribution for a specific birth cohort is $e^{-D(a)}/\int_0^\infty e^{-D(a)}da$. Thus the rate at which individuals in a birth cohort leave the susceptible class due to an infection is $\lambda(a)s(a)e^{-D(a)}/\int_0^\infty e^{-D(a)}da$, where $s(a)$ is given in (5.4). Hence the expected age A for leaving the susceptible class is

$$A = E[a] = \frac{\int_0^\infty a\lambda(a)e^{-D(a)}[\delta F_* e^{-\Lambda(a)} + \delta(1-F_\lambda)\int_0^a e^{-\delta x-\Lambda(a)+\Lambda(x)}dx]da}{\int_0^\infty \lambda(a)e^{-D(a)}[\delta F_* e^{-\Lambda(a)} + \delta(1-F_\lambda)\int_0^a e^{-\delta x-\Lambda(a)+\Lambda(x)}dx]da}. \tag{5.12}$$

This expression assumes that the force of infection $\lambda(a) = kb(a)$ at the endemic steady state age distribution has already been determined, so that $\Lambda(a)$, F_λ, and F_* are known. For the SEIR and SIR models, $s(a) = e^{-\Lambda(a)}$, so that the expression for the average age of infection is

$$A = E[a] = \frac{\int_0^\infty a\lambda(a)e^{-\Lambda(a)-D(a)}da}{\int_0^\infty \lambda(a)e^{-\Lambda(a)-D(a)}da}. \tag{5.13}$$

5.4. Expressions for R_0 and A with Negative Exponential Survival. When the death rate coefficient $d(a)$ is independent of the age a, the age distribution (4.5) becomes $U(a,t) = e^{qt}(d+q)e^{-(d+q)a}$. Also, the waiting times in M, E, and I have negative exponential distributions, so that, after adjusting for changes in the population size, the average period of passive immunity, the average latent period, and the average infectious period are $1/(\delta+d+q)$, $1/(\varepsilon+d+q)$, and $1/(\gamma+d+q)$, respectively. Here it is also assumed that the contact rate is independent of the ages of the infectives and susceptibles, so we let $b(a)=1$ and $\tilde{b}(\tilde{a})=\beta$. In this case (5.9) defining the basic reproduction number becomes

$$R_0 = \beta\varepsilon/[(\gamma+d+q)(\varepsilon+d+q)], \tag{5.14}$$

which has the same interpretation as R_0 in the MSEIR model without age structure.

With the assumptions above, λ is a constant and (5.5) for λ becomes

$$1 = \frac{(d+q)R_0}{\lambda+d+q}\left[s_0 + \frac{\delta(1-s_0)}{\delta+d+q}\right]. \tag{5.15}$$

If $\bar{s}$ is the integral average of the susceptible steady state age distribution $s(a)(d+q)e^{-(d+q)a}$ over all ages, then using the endemic steady state solution $s(a)$ given in (5.4), we find that $R_0\bar{s}=1$ is equivalent to (5.15). Thus the infective replacement number $R_0\bar{s}$ is 1 at the endemic equilibrium for this model. However, this is generally not true, so it is not valid to use $R_0 = 1/\bar{s}$ to derive an expression for the basic reproduction number.

Using the definition of s_0 and the solutions (5.4), we find that

$$s_0 = \frac{\delta-\lambda s_0}{\delta-\lambda}F_\lambda - \frac{\delta(1-s_0)}{\delta-\lambda}F_\delta, \tag{5.16}$$

where $F_\lambda = \int_0^\infty f(a)e^{-(\lambda+d+q)a}da$ and $F_\delta = \int_0^\infty f(a)e^{-(\delta+d+q)a}da$. Note that F_* in (5.7) is equal to $(F_\lambda - F_\delta)/(\delta-\lambda)$, so that (5.6) is equivalent to (5.16). Here (5.15) and (5.16) are two simultaneous equations in the unknowns R_0, s_0, and λ. One can solve (5.16) for s_0 to obtain

$$s_0 = \delta(F_\lambda - F_\delta)/[\delta(1-F_\delta) - \lambda(1-F_\lambda)]. \tag{5.17}$$

The right side of (5.17) is a decreasing function of λ with $F_\lambda = 1$ and $s_0 = 1$ at $\lambda = 0$. Substituting (5.17) into (5.15) yields the equation corresponding to (5.8) given by

$$1 = \frac{R_0(d+q)\delta\left[F_\lambda - F_\delta + \dfrac{(\delta-\lambda)(1-F_\lambda)}{\delta+d+q}\right]}{(\lambda+d+q)[\delta(1-F_\delta)-\lambda(1-F_\lambda)]}, \tag{5.18}$$

which relates R_0 and λ. Because the right side of (5.18) is a decreasing function of λ that goes from R_0 at $\lambda=0$ to zero as $\lambda\to\infty$, (5.18) has a positive solution λ if and only if $R_0>1$. If $d(a)=d$ and $f(a)=b=d+q$, then (5.18) reduces to (3.4) for λ in the ordinary differential equation MSEIR model. When $R_0\le 1$, solutions of (5.2) approach the disease-free steady state (5.4) with $\lambda=0$, and for fixed $R_0>1$, we expect solutions to approach the endemic steady state (5.4) with the constant λ determined by solving either (5.18) or the combination of (5.15) and (5.16).

We now find an expression for the average age of infection for this MSEIR model. Here the steady state age distribution of the population is $(d+q)e^{-(d+q)a}$, and the

age distribution for a specific birth cohort is de^{-da}. Thus the rate that individuals in a birth cohort leave the susceptible class due to an infection is $\lambda s(a)de^{-da}$, where $s(a)$ is given in (5.4). Here the equation for the expected age A for leaving the susceptible class is

$$A = E[a] = \frac{\lambda d \int_0^\infty a[c_1 e^{-(\lambda+d)a} + c_2 e^{-(\delta+d)a}]da}{\lambda d \int_0^\infty [c_1 e^{-(\lambda+d)a} + c_2 e^{-(\delta+d)a}]da} = \frac{\dfrac{\delta - \lambda s_0}{(\lambda+d)^2} - \dfrac{\delta(1-s_0)}{(\delta+d)^2}}{\dfrac{\delta - \lambda s_0}{(\lambda+d)} - \dfrac{\delta(1-s_0)}{(\delta+d)}}. \tag{5.19}$$

It is useful to consider limiting cases of the model and the corresponding limiting equations for R_0 and A. If $\delta \to \infty$, the M class disappears, so that the MSEIR model becomes an SEIR model with $s_0 = 1$, and the equations above reduce to $\lambda = (d+q)(R_0 - 1)$ and $A = 1/(\lambda + d)$, where R_0 is still given by (5.14). These same equations also hold for the SIR model, but $R_0 = \beta/(\gamma + d + q)$ for this model. For the SEIR and SIR models it is possible to solve explicitly for R_0 in terms of the average lifetime $L = 1/d$ and the average age of infection A to obtain $R_0 = (q+1/A)/(q+1/L)$. When the population has constant size with $q = 0$, the R_0 expression reduces to $R_0 = L/A$, which is the usual formula for the SEIR and SIR models [105]. By not including the death factor e^{-da} when considering the rate of leaving the susceptible class, one obtains the widely cited approximate formula $R_0 = 1 + L/A$ for the SEIR and SIR models [61]. But the death factor really should be included, since we want to calculate the average age for those who survive long enough to become infected.

As another limiting case, consider the MSEIR model for a very virulent disease in which almost every mother has been infected. In the limiting situation every newborn infant has passive immunity, so that $m_0 \to 1$ and $s_0 \to 0$. In this case $\lambda = (d+q)[R_0\delta/(\delta + d + q) - 1]$ and $A = 1/(\delta + d) + 1/(\lambda + d)$. Note that the formula for λ is for an endemic steady state for a virulent disease, so it does not imply that $R_0\delta/(\delta + d + q) > 1$ is the threshold condition for existence of a positive endemic steady state age distribution; compare with [12, p. 81]. The formula for A is plausible since it is the sum of the average period $p = 1/(\delta + d)$ of passive immunity and the average age of attack $1/(\lambda + d)$ from the SEIR model. Thus for a very virulent disease, adding a passively immune class to a model increases the average age of attack by the mean period of passive immunity. Solving for R_0 in terms of the average period p of passive immunity and the average lifetime $L = 1/d$, we obtain

$$R_0 = \frac{[q + 1/(A-p)](1+pq)}{(q+1/L)(1-p/L)}. \tag{5.20}$$

For a constant population size with $q = 0$, we have $R_0 = L/[(A-p)(1-p/L)]$. For $q = 0$ and $p \ll L$, we obtain the approximation $R_0 \approx (L+p)/(A-p)$. For this MSEIR model with constant size, it seems that one could just subtract off the average period p of passive immunity from the average age A of infection and the average lifetime L to obtain the approximation $R_0 \approx (L-p)/(A-p)$ used in [12, p. 79, p. 658], [99], but our careful analysis here shows that this naive formula does not work. Of course, when $q = 0$ and $p = 0$, the expression (5.20) reduces to the previous expression $R_0 = L/A$ for the SEIR model with constant population size.

5.5. The MSEIR Model with Vaccination at Age A_v. Now we modify the age-structured MSEIR endemic model above with constant coefficients to include vaccination at age A_v. The results using this approximate model for measles in Niger are

compared with the corresponding results for the MSEIR model with age groups in section 7. Let g be the fraction of the population vaccinated successfully at age A_v (i.e., the fraction of the population which has permanent immunity after vaccination). In epidemiological terminology, g is the product of the fraction vaccinated and the vaccine efficacy. This vaccination at age A_v causes a jump discontinuity in the susceptible age distribution given by $s(A_v + 0) = (1 - g)s(A_v - 0)$, where $s(A_v - 0)$ is the limit from the left and $s(A_v + 0)$ is the limit from the right.

With this jump condition, the ordinary differential equations corresponding to (5.2) without time derivatives, but with constant d and λ, are solved first on the interval $[0, A_v]$ and then on the interval $[A_v, \infty)$. The details are omitted, but substituting the steady state solutions $i(a)$ on these intervals into the expression for λ yields

$$1 = \frac{R_0(d+q)}{\lambda+d+q}\left[s_0 + \frac{\delta(1-s_0)}{\delta+d+q} - g[c_1 e^{-(\lambda+d+q)A_v} + c_2 e^{-(\delta+d+q)A_v}]\right], \tag{5.21}$$

where $c_1 = (\delta - \lambda s_0)/(\delta - \lambda)$ and $c_2 = -\delta(1 - s_0)/(\delta - \lambda)$. Note that (5.21) reduces to (5.15) when $g = 0$. The analogue here of (5.16) is

$$s_0 = c_1 F_\lambda + c_2 F_\delta - g\left[c_1 + c_2 e^{(\lambda-\delta)A_v}\right] F_{A_v}, \tag{5.22}$$

where $F_{A_v} = \int_{A_v}^{\infty} f(a)e^{-(\lambda+d+q)a}da$, and F_λ and F_δ are given in the previous subsection. Given g, A_v, and the values for the parameters β, γ, ε, δ, d, and q, the equations (5.21) and (5.22) are two simultaneous equations in the unknowns R_0, s_0, and λ. It is possible to solve (5.22) for s_0 and then substitute into (5.21), but we do not present the resulting, rather complicated expression, which relates R_0 and λ. For SEIR and SIR models, $s_0 = 1$, so that (5.21) reduces to

$$1 = \frac{R_0(d+q)}{\lambda+d+q}\left[1 - ge^{-(\lambda+d+q)A_v}\right]. \tag{5.23}$$

For fixed parameters and $R_0 > 1$, it is interesting to find how large the successfully vaccinated fraction g must be in order to achieve herd immunity. Recall that a population has herd immunity if a large enough fraction is immune, so that the disease would not spread if an outside infective were introduced into the population. To determine this threshold we consider the situation when the disease is at a very low level with λ nearly zero, so that almost no one is infected. Thus the initial passively immune fraction m_0 is very small and the initial susceptible fraction s_0 is nearly 1. In the limit as $s_0 \to 1$, (5.21) for the MSEIR model reduces to $\lambda = (d + q)(R_0[1 - ge^{-(\lambda+d+q)A_v}] - 1)$, which has a positive solution λ if and only if $ge^{-(d+q)A_v} < 1 - 1/R_0$. If the successfully vaccinated fraction g at age A_v is large enough so that

$$ge^{-(d+q)A_v} \geq 1 - 1/R_0, \tag{5.24}$$

then the population has herd immunity and the disease cannot spread in this population. It may seem surprising that this condition is the same for the SEIR and the MSEIR models, but for very low disease levels, almost no newborn children have passive immunity, so that the passively immune class M has no influence on the threshold condition. A similar criterion for herd immunity with vaccination at two ages in a constant population is given in [98].

If the condition (5.24) is satisfied, then we expect solutions of (5.2) to approach the steady state age distribution with $\lambda = 0$, $s(a) = 1$, and all other distributions equal to zero, so that the disease disappears. Intuitively, there are so many immunes that the average infective cannot replace itself with at least one new infective during the infectious period and, consequently, the disease dies out. If the inequality above is not satisfied and there are some infecteds initially, then we expect the susceptible fraction to approach the stable age distribution given by the jump solution with a positive, constant λ that satisfies (5.21) and (5.22).

For an MSEIR model an expression for the average age of infection is

$$A = \frac{1}{\lambda + d} - \frac{gA_v[c_1 e^{-(\lambda+d)A_v} + c_2 e^{-(\delta+d)A_v}] + c_2 \frac{\delta-\lambda}{(\delta+d)^2}}{c_1[1 - ge^{-(\lambda+d)A_v}] + c_2[\frac{\lambda+d}{\delta+d} - ge^{-(\delta+d)A_v}]}.$$

The analogous expression for an SEIR or SIR model has $c_2 = 0$. The negative signs in the expression for A make it seem as if A is a decreasing function of the successfully vaccinated fraction g, but this is not true since the force of infection λ is a decreasing function of g.

5.6. Expressions for R_0 and A for a Step Survival Function. For the demographic model in which everyone survives until age L and then dies, $d(a)$ is zero until age L and infinite after age L, so that $D(a)$ is zero until age L and is infinite after age L. It is assumed that the population is constant, so $q = 0$ and $\rho = 1/L$ in (4.5). Mixing is homogeneous, so $b(a) = 1$ and $\tilde{b}(\tilde{a}) = \beta$. For the MSEIR and SEIR models the basic reproduction number found from (5.9) is

$$R_0 = \frac{\beta}{\gamma}\left[1 + \frac{\gamma}{\varepsilon - \gamma}\frac{1 - e^{-\varepsilon L}}{\varepsilon L} - \frac{\varepsilon}{(\varepsilon - \gamma)}\frac{1 - e^{-\gamma L}}{\gamma L}\right]. \tag{5.25}$$

An epidemiological interpretation is that the right side of (5.25) except for the contact rate β is the average infectious period. For the SEIR model the equation (5.8) for the constant λ at the endemic steady state age distribution becomes

$$1 = \beta\varepsilon\left[\frac{1 - e^{-\lambda L}}{(\gamma - \lambda)(\varepsilon - \lambda)\lambda L} + \frac{1 - e^{-\varepsilon L}}{(\varepsilon - \lambda)(\varepsilon - \gamma)\varepsilon L} - \frac{1 - e^{-\gamma L}}{(\gamma - \lambda)(\varepsilon - \gamma)\gamma L}\right]. \tag{5.26}$$

For the MSEIR model the integrals in (5.8) do not simplify very much, so this equation for the constant λ is not presented. The basic reproduction numbers for the MSEIRS and SEIRS models are also given by (5.25), but the equations for the constant λ at the endemic steady state age distributions would be different for these models.

For the analogous SIR model, R_0 found from (5.11) is given by

$$R_0 = \frac{\beta}{\gamma}\left[1 - \frac{1 - e^{-\gamma L}}{\gamma L}\right], \tag{5.27}$$

and (5.10) for the constant λ at the endemic steady state age distribution is

$$1 = \frac{\beta}{\gamma - \lambda}\left[\frac{1 - e^{-\lambda L}}{\lambda L} - \frac{1 - e^{-\gamma L}}{\gamma L}\right]. \tag{5.28}$$

These expressions can also be found heuristically by letting $\varepsilon \to \infty$ in (5.25) and (5.26), so that the exposed class E disappears.

For the SEIR and SIR models equation (5.13) for the average age of attack becomes

$$A = \frac{1}{\lambda} - \frac{Le^{-\lambda L}}{1 - e^{-\lambda L}}. \tag{5.29}$$

The analogous equation for the MSEIR model does not simplify as much. For the SEIR and SIR models, the average susceptible fraction is

$$\bar{s} = \int_0^L \frac{e^{-\lambda a}}{L} da = \frac{1 - e^{-\lambda L}}{\lambda L}. \tag{5.30}$$

It is easy to see from (5.25) and (5.27) that $R_0\bar{s} \neq 1$ for the SEIR and SIR models, so using $R_0 = 1/\bar{s}$ gives incorrect expressions for R_0. Expressions similar to those in this section can be found for a nonconstant population with $\rho = q/(1 - e^{-qL})$, but they are not presented here.

Typically the lifetime L is larger than the average age of attack $A \approx 1/\lambda$, and both are much larger than the average latent period $1/\varepsilon$ and the average infectious period $1/\gamma$. Thus for typical directly transmitted diseases, λL is larger than 5 and γL, εL, γ/λ, and ε/λ are larger than 50. Hence $R_0 \approx \beta/\gamma$ from (5.25) and (5.27), $1 = \beta(1 - e^{-\lambda L})/\gamma\lambda L$ from (5.26) and (5.28), and $A \approx 1/\lambda$ from (5.29). Thus $R_0 \approx \lambda L/(1 - e^{-\lambda L}) \approx \lambda L \approx L/A$, and $R_0\bar{s} \approx 1$. Hence many of the formulas for Type I mortality in the Anderson and May book [12, Ch. 4, App. A] are either correct or reasonable approximations.

6. The SEIR Model with Age Groups. Here we develop an expression for the basic reproduction number R_0 in an SEIR model with n separate age groups. This SEIR model is similar to the MSEIR model shown in Figure 10, but there is no class M for passively immune infants. In sections 7 and 8 we estimate the basic reproduction number in models with age groups for measles in Niger and pertussis in the United States.

6.1. Formulation of the SEIR Model with Age Groups. The SEIR model uses the same notation as the MSEIR model described in section 5. The initial boundary value problem for this model is given below:

$$\begin{aligned}
\partial S/\partial a + \partial S/\partial t &= -\lambda(a,t)S - d(a)S, \\
\lambda(a,t) &= \int_0^\infty b(a)\tilde{b}(\tilde{a})I(\tilde{a},t)d\tilde{a} \Big/ \int_0^\infty U(\tilde{a},t)d\tilde{a}\ , \\
\partial E/\partial a + \partial E/\partial t &= \lambda(a,t)S - \varepsilon I - d(a)E, \\
\partial I/\partial a + \partial I/\partial t &= \varepsilon I - \gamma I - d(a)I, \\
\partial R/\partial a + \partial R/\partial t &= \gamma I - d(a)R.
\end{aligned} \tag{6.1}$$

The initial conditions are the values of the age distributions at time 0. The boundary values at age 0 are all zero except for the births given by $S(0,t) = \int_0^\infty f(a)U(a,t)da$.

The population is partitioned into n age groups as in the demographic model in section 4.2. The subscripts i denote the parts of the epidemiologic classes in the ith age interval $[a_{i-1}, a_i]$, so that $S_i(t) = \int_{a_{i-1}}^{a_i} S(a,t)da$, etc. Assume that the transfer rate coefficients on the age intervals are ε_i and γ_i. Also assume that the separable

contact rate is constant for the interactions between age groups, so that $b(a) = b_i$ for $a \in [a_{i-1}, a_i]$ and $\tilde{b}(\tilde{a}) = \tilde{b}_j$ for $\tilde{a} \in [a_{j-1}, a_j]$. By integrating the partial differential equations (6.1) on the age intervals $[a_{i-1}, a_i]$, using $\sum_{j=1}^{n} f_i P_i = (c_1 + d_1 + q)P_1$, $S(a_i, t) = c_i S_i$, $E(a_i, t) = c_i E_i$, etc., as in the demographic model, and using the boundary conditions, we obtain an initial value problem for $4n$ ordinary differential equations for the sizes of the epidemiological classes in the ith age group. The total in the four epidemiologic classes for the ith age group is the size $N_i(t) = e^{qt} P_i$ of the ith group, which is growing exponentially, but the age distribution $P_1, P_2, \ldots, P_n$ remains at a steady state and $\sum_{i=1}^{n} P_i = 1$.

Because the numbers are all growing exponentially by e^{qt}, the fractions of the population in the epidemiologic classes are of more interest than the numbers in these epidemiologic classes. These fractions are given by $s_i(t) = S_i(t)/e^{qt}$, etc., so that the fractions s_i, e_i, i_i, and r_i add up to the age group size P_i. The derivatives of these fractions satisfy $s_i'(t) = S_i'(t)/e^{qt} - q s_i$, etc., so that the differential equations for these fractions are

$$
\begin{aligned}
ds_1/dt &= (c_1 + d_1 + q)P_1 - [\lambda_1 + c_1 + d_1 + q]s_1, \\
ds_i/dt &= c_{i-1}s_{i-1} - [\lambda_i + c_i + d_i + q]s_i, \qquad i \geq 2, \\
\lambda_i &= b_i \sum_{j=1}^{n} \tilde{b}_j i_j, \\
de_1/dt &= \lambda_1 s_1 - [\varepsilon_1 + c_1 + d_1 + q]e_1, \\
de_i/dt &= \lambda_i s_i + c_{i-1}e_{i-1} - [\varepsilon_i + c_i + d_i + q]e_i, \quad i \geq 2, \\
di_1/dt &= \varepsilon_1 e_1 - [\gamma_1 + c_1 + d_1 + q]i_1, \\
di_i/dt &= \varepsilon_i e_i + c_{i-1}i_{i-1} - [\gamma_i + c_i + d_i + q]i_i, \quad i \geq 2, \\
dr_1/dt &= \gamma_1 i_1 - [c_1 + d_1 + q]r_1, \\
dr_i/dt &= \gamma_i i_i + c_{i-1}r_{i-1} - [c_i + d_i + q]r_i, \qquad i \geq 2.
\end{aligned}
\tag{6.2}
$$

6.2. The Basic Reproduction Number R_0 and Stability. Here we follow the same procedure used in the continuous model to find an expression for the basic reproduction number R_0. Note that the steady state age distribution for the differential equations (6.2) is the equilibrium with

$$
\begin{aligned}
&s_1 = \hat{c}_1 P_1/\hat{\lambda}_1, \;\; s_i = c_{i-1}s_{i-1}/\hat{\lambda}_i && \text{for } i \geq 2, \\
&e_1 = \lambda_1 s_1/\hat{\varepsilon}_1, \;\; e_i = (\lambda_i s_i + c_{i-1}e_{i-1})/\hat{\varepsilon}_i && \text{for } i \geq 2, \\
&i_1 = \varepsilon_1 e_1/\hat{\gamma}_1, \;\; i_i = (\varepsilon_i e_i + c_{i-1}i_{i-1})/\hat{\gamma}_i && \text{for } i \geq 2,
\end{aligned}
\tag{6.3}
$$

where we use $\hat{\lambda}_i$ for $\lambda_i + c_i + d_i + q$, $\hat{\varepsilon}_i$ for $\varepsilon_i + c_i + d_i + q$, $\hat{\gamma}_i$ for $\gamma_i + c_i + d_i + q$, and $\hat{c}_1$ for $c_1 + d_1 + q$. Substituting s_{i-1} successively, we find that $s_i = C_{i-1}/[\hat{\lambda}_i \cdots \hat{\lambda}_1]$ for $i \geq 2$, where C_{i-1} stands for $c_{i-1} \cdots c_1 \hat{c}_1 P_1$. Next we substitute the s_{i-1} and e_{i-1} successively into the e_i quotient in (6.3) to obtain $e_1 = \lambda_1 \hat{c}_1 P_1/(\hat{\varepsilon}_1 \hat{\lambda}_1)$ and

$$
e_i = \frac{\lambda_i C_{i-1}}{\hat{\varepsilon}_i \hat{\lambda}_i \cdots \hat{\lambda}_1} + \frac{\lambda_{i-1} C_{i-1}}{\hat{\varepsilon}_i \hat{\varepsilon}_{i-1} \hat{\lambda}_{i-1} \cdots \hat{\lambda}_1} + \frac{\lambda_{i-2} C_{i-1}}{\hat{\varepsilon}_i \hat{\varepsilon}_{i-1} \hat{\varepsilon}_{i-2} \hat{\lambda}_{i-2} \cdots \hat{\lambda}_1} + \cdots + \frac{\lambda_1 C_{i-1}}{\hat{\varepsilon}_i \cdots \hat{\varepsilon}_1 \hat{\lambda}_1}
$$

for $i \geq 2$. When the expressions for e_i and i_{i-1} are substituted into the expression for i_i in (6.3), we obtain $i_1 = \varepsilon_1\lambda_1\hat{c}_1P_1/(\hat{\gamma}_1\hat{\varepsilon}_1\hat{\lambda}_1)$, and for $i \geq 2$,

$$\begin{aligned}(6.4)\ \frac{i_i}{C_{i-1}} = {} & \frac{\varepsilon_i}{\hat{\gamma}_i}\left(\frac{\lambda_i}{\hat{\varepsilon}_i\hat{\lambda}_i\cdots\hat{\lambda}_1}+\frac{\lambda_{i-1}}{\hat{\varepsilon}_i\hat{\varepsilon}_{i-1}\hat{\lambda}_{i-1}\cdots\hat{\lambda}_1}+\cdots+\frac{\lambda_1}{\hat{\varepsilon}_i\cdots\hat{\varepsilon}_1\hat{\lambda}_1}\right)\\ & +\frac{\varepsilon_{i-1}}{\hat{\gamma}_i\hat{\gamma}_{i-1}}\left(\frac{\lambda_{i-1}}{\hat{\varepsilon}_{i-1}\hat{\lambda}_{i-1}\cdots\hat{\lambda}_1}+\frac{\lambda_{i-2}}{\hat{\varepsilon}_{i-1}\hat{\varepsilon}_{i-2}\hat{\lambda}_{i-2}\cdots\hat{\lambda}_1}+\cdots+\frac{\lambda_1}{\hat{\varepsilon}_{i-1}\cdots\hat{\varepsilon}_1\hat{\lambda}_1}\right)\\ & +\cdots+\frac{\varepsilon_2}{\hat{\gamma}_i\cdots\hat{\gamma}_2}\left(\frac{\lambda_2}{\hat{\varepsilon}_2\hat{\lambda}_2\hat{\lambda}_1}+\frac{\lambda_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{\lambda}_1}\right)+\frac{\varepsilon_1}{\hat{\gamma}_i\cdots\hat{\gamma}_1}\left(\frac{\lambda_1}{\hat{\varepsilon}_1\hat{\lambda}_1}\right).\end{aligned}$$

From (6.2), we observe that $\lambda_i = kb_i$, where k is a constant given by $k = \sum_{j=1}^{n}\tilde{b}_j i_j$. Now the expressions for i_i and $\lambda_i = kb_i$ can be substituted into this last summation to obtain

$$\begin{aligned}(6.5)\quad 1 = \sum_{j=1}^{n}\tilde{b}_jC_{j-1}\Bigg[& \frac{\varepsilon_j}{\hat{\gamma}_j}\left(\frac{b_j}{\hat{\varepsilon}_j\hat{b}_j\cdots\hat{b}_1}+\frac{b_{j-1}}{\hat{\varepsilon}_j\hat{\varepsilon}_{j-1}\hat{b}_{j-1}\cdots\hat{b}_1}+\cdots+\frac{b_1}{\hat{\varepsilon}_j\cdots\hat{\varepsilon}_1\hat{b}_1}\right)\\ & +\frac{\varepsilon_{j-1}}{\hat{\gamma}_j\hat{\gamma}_{j-1}}\left(\frac{b_{j-1}}{\hat{\varepsilon}_{j-1}\hat{b}_{j-1}\cdots\hat{b}_1}+\frac{b_{j-2}}{\hat{\varepsilon}_{j-1}\hat{\varepsilon}_{j-2}\hat{b}_{j-2}\cdots\hat{b}_1}+\cdots+\frac{b_1}{\hat{\varepsilon}_{j-1}\cdots\hat{\varepsilon}_1\hat{b}_1}\right)\\ & +\cdots+\frac{\varepsilon_2}{\hat{\gamma}_j\cdots\hat{\gamma}_2}\left(\frac{b_2}{\hat{\varepsilon}_2\hat{b}_2\hat{b}_1}+\frac{b_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{b}_1}\right)+\frac{\varepsilon_1}{\hat{\gamma}_j\cdots\hat{\gamma}_1}\left(\frac{b_1}{\hat{\varepsilon}_1\hat{b}_1}\right)\Bigg],\end{aligned}$$

where $\hat{b}_j = b_jk + c_i + d_i + q$ and $C_0 = \hat{c}_1P_1$.

The right side of (6.5) is a decreasing function of k, so that it has a solution for a positive k if and only if $R_0 > 1$, where R_0 is the basic reproduction number defined by setting $k = 0$ in (6.5).

$$\begin{aligned}(6.6)\quad R_0 = \sum_{j=1}^{n}\tilde{b}_jC_{j-1}\Bigg[& \frac{\varepsilon_j}{\hat{\gamma}_j}\left(\frac{b_j}{\hat{\varepsilon}_j\hat{c}_j\cdots\hat{c}_1}+\frac{b_{j-1}}{\hat{\varepsilon}_j\hat{\varepsilon}_{j-1}\hat{c}_{j-1}\cdots\hat{c}_1}+\cdots+\frac{b_1}{\hat{\varepsilon}_j\cdots\hat{\varepsilon}_1\hat{c}_1}\right)\\ & +\frac{\varepsilon_{j-1}}{\hat{\gamma}_j\hat{\gamma}_{j-1}}\left(\frac{b_{j-1}}{\hat{\varepsilon}_{j-1}\hat{c}_{j-1}\cdots\hat{c}_1}+\frac{b_{j-2}}{\hat{\varepsilon}_{j-1}\hat{\varepsilon}_{j-2}\hat{c}_{j-2}\cdots\hat{c}_1}+\cdots+\frac{b_1}{\hat{\varepsilon}_{j-1}\cdots\hat{\varepsilon}_1\hat{c}_1}\right)\\ & +\cdots+\frac{\varepsilon_2}{\hat{\gamma}_j\cdots\hat{\gamma}_2}\left(\frac{b_2}{\hat{\varepsilon}_2\hat{c}_2\hat{c}_1}+\frac{b_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{c}_1}\right)+\frac{\varepsilon_1}{\hat{\gamma}_j\cdots\hat{\gamma}_1}\left(\frac{b_1}{\hat{\varepsilon}_1\hat{c}_1}\right)\Bigg],\end{aligned}$$

where $\hat{c}_i = c_i + d_i + q$. The expression (6.6) for R_0 is the discrete age group analogue of the triple integral expression (5.9) of R_0 for the SEIR model with continuous age. As in section 5.2, the expression (6.6) for R_0 is also valid for the analogous MSEIR, MSEIRS, SEIRS, and SEIS models with age groups, but the equations involving the force of infection constant k would be different from (6.5) for these other models. The equation for k for the MSEIR model could be found by tedious calculations following the method used above.

If $R_0 > 1$ for the SEIR model, then (6.5) can be solved for a positive k to get the forces of infection $\lambda_i = kb_i$, which give the unique endemic equilibrium in the age groups from (6.3). Determining the stability of the disease-free equilibrium (at which everyone is susceptible) by linearization is intractable except for small n, but we can construct a Liapunov function to prove the global stability of the disease-free equilibrium when $R_0 \leq 1$ by taking a linear combination of the exposed and

infectious fractions. Here the feasible region is the subset of the nonnegative orthant in the $4n$-dimensional space with the class fractions in the ith group summing to P_i. Let $V = \sum(\alpha_i e_i + \beta_i i_i)$, where the coefficients are to be determined. In the Liapunov derivative $\dot{V}$, choose the α_i coefficients so that the e_i terms cancel out by letting $\alpha_n = \beta_n \varepsilon_n / \hat{\varepsilon}_n$ and $\alpha_{j-1} = (\beta_{j-1}\varepsilon_{j-1} + c_{j-1}\alpha_j)/\hat{\varepsilon}_{j-1}$ for $\alpha_{n-1}, \ldots, \alpha_1$. Then

$$\dot{V} = \sum \alpha_i b_i s_i \sum \tilde{b}_j i_j - (\beta_1 \hat{\gamma}_1 - \beta_2 c_1) i_1 - \cdots - (\beta_{n-1}\hat{\gamma}_{n-1} - \beta_n c_{n-1}) i_{n-1} - \beta_n \hat{\gamma}_n i_n.$$

Now choose the β_i so that the coefficients of the i_j in the last n terms are $-\tilde{b}_j$ by letting $\beta_n = \tilde{b}_n/\hat{\gamma}_n$ and $\beta_{j-1} = (\tilde{b}_{j-1} + \beta_j c_{j-1})/\hat{\gamma}_{j-1}$ for $\beta_{n-1}, \ldots, \beta_1$. Using $s_i \le P_i$, we obtain $\dot{V} \le (R_0 - 1) \sum \tilde{b}_j i_j \le 0$ if $R_0 \le 1$. The set where $\dot{V} = 0$ is the boundary of the feasible region with $i_j = 0$ for every j, but $di_j/dt = \varepsilon_j e_j$ on this boundary, so that i_j moves off this boundary unless $e_j = 0$. When $e_j = i_j = 0$, $dr_j/dt = -\hat{c}_j r_j$, so that $r_j \to 0$. Thus the disease-free equilibrium is the only positively invariant subset of the set with $\dot{V} = 0$, so that all paths in the feasible region approach the disease-free equilibrium by the Liapunov–Lasalle theorem [92, p. 296]. Thus if $R_0 \le 1$, then the disease-free equilibrium is asymptotically stable in the feasible region. If $R_0 > 1$, then we have $\dot{V} > 0$ for points sufficiently close to the disease-free equilibrium with s_i close to P_i and $i_j > 0$ for some j, so that the disease-free equilibrium is unstable. The system (6.2) can be defined to be uniformly persistent if $\liminf_{t\to\infty} i_j(t) \ge c$ for some $c > 0$ for all j and all initial points such that $e_j(0) + i_j(0) > 0$ for some j. The instability of the disease-free equilibrium and Theorem 4.5 in [191] imply that the system (6.2) is uniformly persistent if $R_0 > 1$. The endemic equilibrium (6.3) corresponding to positive k would usually be asymptotically stable in specific applications, but as for the continuous age model, it could be unstable for unusual or asymmetric choices of b_i and $\tilde{b}_i$.

Using the same methods for an SIR model, the equation for the k in the forces of infection $\lambda_i = kb_i$ is

(6.7)
$$1 = \sum_{j=1}^{n} \tilde{b}_j C_{j-1} \left[\frac{b_j}{\hat{\gamma}_j \hat{b}_j \cdots \hat{b}_1} + \frac{b_{j-1}}{\hat{\gamma}_j \hat{\gamma}_{j-1} \hat{b}_{j-1} \cdots \hat{b}_1} + \cdots + \frac{b_2}{\hat{\gamma}_j \cdots \hat{\gamma}_2 \hat{b}_2 \hat{b}_1} + \frac{b_1}{\hat{\gamma}_j \cdots \hat{\gamma}_1 \hat{b}_1} \right],$$

and the equation for the basic reproduction number is

(6.8)
$$R_0 = \sum_{j=1}^{n} \tilde{b}_j C_{j-1} \left[\frac{b_j}{\hat{\gamma}_j \hat{c}_j \cdots \hat{c}_1} + \frac{b_{j-1}}{\hat{\gamma}_j \hat{\gamma}_{j-1} \hat{c}_{j-1} \cdots \hat{c}_1} + \cdots + \frac{b_2}{\hat{\gamma}_j \cdots \hat{\gamma}_2 \hat{c}_2 \hat{c}_1} + \frac{b_1}{\hat{\gamma}_j \cdots \hat{\gamma}_1 \hat{c}_1} \right].$$

These equations can also be derived heuristically from those for the SEIR model by letting $\varepsilon_i \to \infty$ for every i. The R_0 formula (6.8) also works for the SIRS and SIS models with age groups, but the equations for k would be different. Proofs of stability and persistence for the models in this paragraph are similar to those for the SEIR model.

6.3. Expressions for the Average Age of Infection *A*. From section 5.3 we know that the average age of infection A is given by

$$A = E[a] = \frac{\int_0^\infty a\lambda(a)s(a)e^{-D(a)}da}{\int_0^\infty \lambda(a)s(a)e^{-D(a)}da} = \frac{\sum_{i=1}^n \int_{a_{i-1}}^{a_i} a\lambda(a)s(a)e^{-D(a)}da}{\sum_{i=1}^n \int_{a_{i-1}}^{a_i} \lambda(a)s(a)e^{-D(a)}da}.$$

In each integral above over the interval $[a_{i-1}, a_i]$ of length Δ_i, we have the endemic equilibrium values $s(a) = s_i$, $\lambda(a) = \lambda_i = kb_i$, and $e^{-D(a)} = \pi_{i-1}e^{-d_i(a-a_{i-1})}$, where $\pi_{i-1} = \prod_{j=1}^{i-1} e^{-d_j\Delta_j}$. The integrals over the intervals can be evaluated to obtain the following expression for the average age of infection at the endemic equilibrium for the MSEIR, SEIR, and SIR models with age groups:

$$A = \frac{\sum_{i=1}^{n} b_i s_i \pi_{i-1}[1 + d_i a_{i-1} - (1 + d_i a_i)e^{-d_i\Delta_i}]/d_i^2}{\sum_{i=1}^{n} b_i s_i \pi_{i-1}[1 - e^{-d_i\Delta_i}]/d_i}. \tag{6.9}$$

7. Application to Measles in Niger. A deterministic compartmental mathematical model has been developed for the study of the effects of heterogeneous mixing and vaccination distribution on disease transmission in Africa [133]. This study focuses on vaccination against measles in the city of Naimey, Niger, in sub-Saharan Africa. The rapidly growing population consists of a majority group with low transmission rates and a minority group of seasonal urban migrants with higher transmission rates. Demographic and measles epidemiological parameters are estimated from data on Niger.

Here we consider the MSEIR model with 16 age groups for a homogeneously mixing, unvaccinated population in Niger [133]. The fertility rates and the death rates in the 16 age groups are obtained from Niger census data. Using the Lotka equation (4.12) for the demographic model with age groups, the value of q corresponds to a growth of 3.36% per year. This is consistent with the estimate from 1988 census data of 3.3% growth per year. From measles data, it is estimated that the average period of passive immunity $1/\delta$ is 6 months, the average latent period $1/\varepsilon$ is 14 days and the average infectious period $1/\gamma$ is 7 days. From data on a 1995 measles outbreak in Niamey, the force of infection λ is estimated to be the constant 0.762 per year [133]. A computer calculation using the demographic and epidemiological parameter values in the formula (6.6) for the basic reproduction number yields $R_0 = 18.83$. The average age of infection at the endemic equilibrium found from (6.9) is $A = 2.4$ years.

We now consider two methods for finding approximations to R, R_0, and A. The first method finds approximate values during the computer simulations of the MSEIR measles model. Recall from section 1 that the replacement number R is the actual number of new cases per infective during the infectious period. R can be approximated by computing the sum over all age groups of the daily incidence times the average infectious period times the fraction surviving the latent period, and then dividing by the total number of infectives in all age groups, so that

$$R \cong \frac{\sum_{j=1}^{16} \lambda_j s_j P_j \left(\frac{1}{\gamma + d_j + q}\right)\left(\frac{\varepsilon}{\varepsilon + d_j + q}\right)}{\sum_{j=1}^{16} i_j P_j}.$$

At the prevaccination endemic equilibrium, this approximation is computed to be $R \cong 0.99988$, which is consistent with the concept that the average replacement number is equal to 1 at the endemic equilibrium.

For this MSEIR model there is only one class of infectives, so that the basic reproduction number R_0 is equal to the contact number σ at the prevaccination endemic equilibrium. This contact number σ is approximated by computing the product of the sum of the daily incidences when all contacts are assumed to be with susceptibles times the average infectious period, and dividing by the total number of infectives. When all of the s_j in the numerator in the expression for the replacement number R are replaced by 1, then we obtain the expression for the contact number σ

given by

$$R_0 = \sigma \cong \frac{\sum_{j=1}^{16} \lambda_j P_j \left(\frac{1}{\gamma + d_j + q}\right)\left(\frac{\varepsilon}{\varepsilon + d_j + q}\right)}{\sum_{j=1}^{16} i_j P_j}.$$

At the prevaccination endemic equilibrium, this yields $R_0 \cong 18.85$, which is very close to the formula value of 18.83. The average age of infection can be approximated in the measles computer simulations by the quotient of the sum of the average age in each age group times the incidence in that age group and the sum of the incidences. Hence

$$A \cong \frac{\sum_{j=1}^{16} [\frac{a_{j-1}+a_j}{2}] \lambda_j s_j P_j}{\sum_{j=1}^{16} \lambda_j s_j P_j}.$$

This approach gives $A \cong 2.2$ years, which is slightly less than the formula value of 2.4 years.

The second approximation method is to use the formulas for the MSEIR model in sections 4.4 and 4.5, which has uniform constant mortality and a negative exponential age distribution. This model is plausible because the age distribution of the Niger population is closely approximated by a negative exponential [133]. From census data the death rate for the population is 22 per thousand per year. Using this d value and the fertilities in the Lotka characteristic equation for discrete age groups (4.12), we solve iteratively to obtain $q = 0.02326$ per year. This q value corresponds to a population growth rate of 2.3% per year, which is less than the recent census value of 3.3% growth per year, but this difference may occur because our model is a simplification of the actual demographics. The value $d + q = 0.045$ per year is consistent with the Niger population surviving fraction as a function of age, which is very close to the exponential $e^{-0.045a}$ for age a in years.

Recall that the replacement number R is 1 at the endemic equilibrium for this model. Using the values of $d+q$, δ, and λ, (5.15) and (5.16) can be solved iteratively to obtain a basic reproduction number of $R_0 = 17.4$ and a susceptible fraction at age 0 of $s_0 = 1.6 \times 10^{-6}$. Thus in this population nearly every mother is infected with measles before childbearing age, so almost every newborn child has passive immunity. In the limit as $s_0 \to 0$, (5.15) becomes

$$R_0 = [1 + \lambda/(d+q)][1 + (d+q)/\delta],$$

which also leads to $R_0 = 17.4$. This value is a reasonable approximation to the value of $R_0 = 18.83$ estimated above in the MSEIR model with 16 age groups. The average age of infection of $A = 1.8$ years can be found from either (5.12) or the approximation $A = 1/(\delta+d)+1/(\lambda+d)$. This value is less than the value of $A = 2.4$ years estimated above using the MSEIR model with 16 age groups; this difference may be due to the high infant mortality that occurs in the model with age groups. Using the estimated parameter values and a vaccination age of $A_v = 0.75$ years (9 months) in the herd immunity condition (5.24), we find that to achieve herd immunity the successfully vaccinated fraction g at age 9 months must satisfy $g \geq 0.98$. A measles vaccine efficacy of 0.95 implies that the fraction vaccinated would have to be 1.03, which is impossible to achieve with a program that has at most one vaccination per person. This result is confirmed by the measles computer simulations for Niger, in which herd immunity is not achieved when all children are vaccinated at age 9 months.

8. Application to Pertussis in the United States. Previous estimates [12, p. 70] of 10 to 18 for R_0 for pertussis (whooping cough) are based on the formula $R_0 = 1 + L/A$, which is derived in sections 5.4 or 5.6 for SEIR or SIR models of a disease that confers permanent immunity in a uniform, homogeneously mixing population. However, these estimates of R_0 are not realistic, because pertussis gives only temporary immunity and spreads by heterogeneous mixing. In the age-structured epidemiologic models developed specifically for pertussis [105, 106], there are 32 age groups. Using fertilities and death rates from United States census information for 1990, the value of q in (4.12) corresponds to 0.065% growth per year, which is nearly zero. Thus the age distribution in the pertussis models is assumed to have become stable with a constant population size. More details and graphs of the actual and theoretical age distributions are given in [105].

Immunity to pertussis is temporary, because the agent *Bordetella pertussis* is bacterial, in contrast to the viral agents for measles, mumps, and rubella. As the time after the most recent pertussis infection increases, the relative immunity of a person decreases. When people become infected again, the severity of their symptoms and, consequently, their transmission effectiveness (i.e., their infectivity) depends on their level of immunity at the time of infection. Thus people with lower immunity have more symptoms and higher infectivity. Of course, infected people who were previously fully susceptible are generally the most effective transmitters. In the age-structured pertussis models [105, 106], the epidemiological classes include a susceptible class S, an infective class I, a class R_4 of those removed people with very high immunity, and classes R_3, R_2, and R_1 for those with decreasing immunity. In the two pertussis models, there are three or four levels of infectivity and 32 age groups, so that not all infectives are equally effective in creating new infectives [106]. Infectives in those age groups that mix more with other age groups are more effective transmitters than those in age groups that mix less. Thus it might seem necessary in considering R_0 to define a "typical infective" by using some type of average over all infectivities and age groups, so that R_0 would be the average number of secondary cases produced when a "typical infective" is introduced into a completely susceptible population. In the next paragraph, we explain why averaging over age groups is necessary, but averaging over classes with different infectivities is not appropriate.

The occurrence of the first infection in a fully susceptible population seems to be an unpredictable process, because it depends on random introductions of infectious outsiders into the host population. The probability that a first infection occurs in the host population depends on the infectivity of the outside invader, on how the invader (with a mixing activity level based on its age group) mixes in the host population, and the length of time that the invader is in the population. It is clear that outside invaders from high infectivity classes and high mixing activity age groups are more likely to create a first new infection in a host population, especially if they are in the population for their entire infectious period. We believe that the definition of R_0 should not depend on the circumstances under which an outsider creates a first case, but on whether or not an infection with a first case can persist in a fully susceptible population.

After the first infection in the host population, the infected people in the next generations could be less effective transmitters, so that the infection would die out. Thus the definition of R_0 should be based on the circumstances under which a disease with a first case would really invade a fully susceptible host population more extensively. In order for an infection to survive the first 10 or 20 generations, so that it

really does invade and persist in the new host population, the number of secondary cases produced by infectious members of the host population must exceed 1. Thus R_0 should be the number of secondary cases produced by averaging over all age groups of the infectives that have not been previously infected. Because all of the cases in the first generations of an invasion occur in fully susceptible people, only infectives who were previously fully susceptible are relevant. Thus R_0 is calculated for the SIR_4 part of the pertussis models and it is not necessary to average over the classes with various infectivity levels. Although the SIR model formula (6.8) for R_0 works for the pertussis models, the formula (6.7) for the constant k in the forces of infection $\lambda_i = kb_i$ at the endemic equilibrium does not work, because the pertussis models have temporary immunity and classes with different infectivities.

The fertilities f_j, death rate constants d_j, and transfer rate constants c_j are determined in the demographic model. The average infectious period is 21 days, so that the rate constant γ is 1/21. The form of separable mixing used in the pertussis model is proportionate mixing, which has activity levels l_j in each of the 32 age groups. The activity levels l_j are found from the forces of infection λ_j and the infective fractions i_j, as explained in Appendix C of [105]. Then $b_j = \tilde{b}_j = l_j/D^{1/2}$, where $D = \sum_{j=1}^{32} l_j P_j$ is the total number of people contacted per unit time. Using the SIR model formula (6.8) for R_0 in the pertussis computer simulation programs with the baseline parameter sets, the values of the basic reproduction number R_0 are 5.4 for the pertussis model in [105, 106] and 3.7 for the second pertussis model in [106]. In the first model each pertussis booster moves the individual back up one vaccinated or removed class, but for those in the second model who have had a sequence of at least four pertussis vaccinations or have had a previous pertussis infection, a pertussis booster raises their immunity back up to the highest level. Thus the second model incorporates a more optimistic view of the effectiveness of pertussis booster vaccinations. Note that the R_0 values here of 5.4 and 3.7 are much lower than the estimates of R_0 between 10 and 18 cited above.

Neither of the two methods used to find approximations of R_0 for measles in Niger works for the pertussis models. The replacement number R at the pertussis endemic equilibrium depends on the fractions infected in all of the three or four infective classes. For example, in the first pertussis model

$$R \cong \frac{\sum_{j=1}^{32} \lambda_j (s_j + r_{1j} + r_{2j}) P_j/(\gamma + d_j)}{\sum_{j=1}^{32} (i_j + i_{mj} + i_{wj}) P_j},$$

where i_j, i_{mj}, and i_{wj} are the infective prevalences in the full-, mild-, and weak-disease classes I, I_m, and I_w. In the computer simulations for both pertussis models, R is 1 at the endemic equilibrium. If the expression for R is modified by changing the factor in parentheses in the numerator to 1, which corresponds to assuming that all contacts are with susceptibles, then we obtain the contact number

$$\sigma \cong \frac{\sum_{j=1}^{32} \lambda_j P_j/(\gamma + d_j)}{\sum_{j=1}^{32} (i_j + i_{mj} + i_{wj}) P_j},$$

which gives the average number of cases due to all infectives. At the endemic equilibrium in the pertussis simulations, $\sigma = 3.0$ using the first model and $\sigma = 1.8$ using the second model. Thus the basic reproduction number R_0 is not equal to the contact number σ at the endemic equilibrium, because the forces of infection λ_j in the approximation of σ are due to the contacts of the infectives in the I, I_m, and I_w classes

instead of just the contacts of those in the I class. Thus it is not possible to use the estimate of the contact number σ during the computer simulations as an approximation for R_0 in the pertussis models. Since the age distribution of the population in the United States is poorly approximated by a negative exponential and the force of infection is not constant, the second method used for measles in Niger also does not work to approximate R_0 for pertussis in the United States.

The ultimate goal of a pertussis vaccination program is to vaccinate enough people to get the replacement number less than 1, so that pertussis fades away and herd immunity is achieved. Because the mixing for pertussis is not homogeneous and the immunity is not permanent, we cannot use the simple criterion for herd immunity that the fraction with vaccine-induced or infection-induced immunity is greater than $1 - 1/R_0$. Indeed, the low numerical R_0 values of 5.4 and 3.7 for a disease like pertussis with waning immunity do not indicate that herd immunity for pertussis is easy to achieve. None of the vaccination strategies, including those that give booster vaccinations every five years, has achieved herd immunity in the pertussis computer simulations [105, 106].

9. Other Epidemiology Models with Thresholds. The results presented in this paper provide a theoretical background for reviewing some previous results. In this section we do not attempt to cite all papers on infectious disease models with age structure, heterogeneity, and spatial structure, but primarily cite sources that consider thresholds and the basic reproduction number R_0. The cited papers reflect the author's interests, but additional references are given in these papers and in the books and survey papers listed in the introduction. We refer the reader to other sources for information on stochastic epidemiology models [18, 20, 56, 59, 66, 81, 128, 167], discrete time models [2, 3], models involving macroparasites [12, 59, 90], genetic heterogeneity [12, 90], plant disease models [137, 194], and wildlife disease models [90].

Age-structured epidemiology models with either continuous age or age groups are essential for the incorporation of age-related mixing behavior, fertility rates, and death rates, for the estimation of R_0 from age-specific data, and for the comparison of vaccination strategies with age-specific risk groups and age-dependent vaccination rates. Indeed, some of the early epidemiology models incorporated continuous age structure [24, 136]. Modern mathematical analysis of age-structured models appears to have started with Hoppensteadt [114], who formulated epidemiology models with both continuous chronological age and infection class age (time since infection), showed that they were well posed, and found threshold conditions for endemicity. Expressions for R_0 for models with both chronological and infection age were obtained by Dietz and Schenzle [68]. In age-structured epidemiology models, proportionate and preferred mixing parameters can be estimated from age-specific force of infection data [103]. Mathematical aspects such as existence and uniqueness of solutions, steady states, stability, and thresholds have now been analyzed for many epidemiology models with age structure; more references are cited in the following papers. These SIS and SIR models with continuous age structure have included vertical transmission [33, 34, 72], age-dependent disease transmission [14, 61, 91, 189], infection class age [186, 197], cross immunity [40], intercohort transmission [35, 36, 53, 124, 125], short infectious period [15, 16], and optimal vaccination patterns [86, 87, 94, 135, 165, 175].

Age-structured models have been used in the epidemiology modeling of many diseases [12]. Dietz [61, 64], Hethcote [98], Anderson and May [10, 11], and Rouderfer, Becker, and Hethcote [174] used continuous age-structured models for the evaluation of measles and rubella vaccination strategies. Tudor [192] found threshold conditions

for a measles model with age groups. Hethcote [99] considered optimal ages of vaccination for measles on three continents. Halloran et al. [93], Ferguson, Anderson, and Garnett [78], and Schuette and Hethcote [179] used age-structured models to study the effects of varicella (chickenpox) vaccination programs. Grenfell and Anderson [89] and Hethcote [105, 106] have used age-structured models in evaluating pertussis (whooping cough) vaccination programs. Irregular and biennial oscillations of measles incidences have led to various mathematical analyses including the following seven modeling explanations, some of which involve age structure. Yorke and London [200] proposed SEIR models with seasonal forcing in delay differential equations. Dietz [62] proposed subharmonic resonance in a seasonally forced SEIR model using ordinary differential equations. Schenzle [177] used computer simulations to show that the measles outbreak patterns in England and Germany could be explained by the primary school yearly calenders and entry ages. Olson and Schaffer [169] proposed chaotic behavior in simple deterministic SEIR models. Bolker and Grenfell [27] proposed realistic age-structured models with seasonal forcing and stochastic terms. Ferguson, Nokes, and Anderson [79] proposed finely age-stratified models with stochastic fluctuations that can shift the dynamics between biennial and triennial cycle attractors. Earn et al. [71] proposed a simple, time-forced SEIR model with slow variation in the average rate of recruitment of new susceptibles.

In recent years HIV, which leads to AIDS, has emerged as an important new infectious disease. Many age-structured models have been developed for HIV/AIDS. May and Anderson [154] found R_0 for some simple HIV transmission models. Bongaarts [28] and May, Anderson, and McLean [156] used models with age structure to examine the demographic effects of AIDS in African countries. The book [39] by Castillo-Chavez contains a review of HIV/AIDS modeling papers including single-group models, multiple-group models, and epidemiologic-demographic models. It also contains papers on AIDS models with HIV class age, variable infectivity, distributions for the AIDS incubation period, heterogeneity, and structured mixing. Busenberg and Castillo-Chavez [32] found an R_0 expression for an HIV model with variable infectivity and continuous chronological and HIV class age structure and proportionate mixing. Hyman, Li, and Stanley [120] generalized these results on R_0 to HIV models with nonproportionate mixing and discrete or continuous risk.

For many infectious diseases the transmission occurs in a diverse population, so the epidemiological model must divide the heterogeneous population into subpopulations or groups, in which the members have similar characteristics. This division into groups can be based not only on mode of transmission, contact patterns, latent period, infectious period, genetic susceptibility or resistance, and amount of vaccination or chemotherapy, but also on social, cultural, economic, demographic, or geographic factors. For these models it is useful to find R_0 from the threshold conditions for invasion and endemicity and to prove stability of the equilibria. For the SIS model with n groups, the threshold was first found in terms of whether $s(A) \leq 0$ or $s(A) > 0$, where $s(A)$ is the largest real part of the eigenvalues of the Jacobian matrix A at the disease-free equilibrium. The seminal paper [140] of Lajmanovich and Yorke found this threshold condition and proved the global stability of the disease-free and endemic equilibria using Liapunov functions. This approach has been extended to SIR, SEIR, and SEIRS models with n groups [97, 187, 188]. For these models R_0 can be shown to be the spectral radius of a next generation matrix that is related to the Jacobian matrix A [103, 110]. This next generation operator approach has also been used for epidemiology models with a variety of features such as proportionate mix-

ing, preferred mixing, heterosexual transmission, host-vector groups, multiple mixing groups, vaccination, and age structure [58, 59]. For proportionate mixing models with multiple interacting groups, the basic reproduction number R_0 is the contact number σ, which is the weighted average of the contact numbers in the groups [103, 110, 113]. The sexual transmission of diseases often occurs in a very heterogeneous population, because people with more sexual partners have more opportunities to be infected and to infect others. The basic reproduction number R_0 has been determined for many different models with heterogeneous mixing involving core, social, and sexual mixing groups [113, 129, 131, 138, 139, 184]. It has been shown that estimates of R_0, under the false assumption that a heterogeneously mixing population is homogeneously mixing, are not greater than the actual R_0 for the heterogeneous population [1, 103]. Many models with heterogeneity in the form of competing strains of infectious agents have been considered for diseases such as influenza, dengue, and myxomatosis [17, 40, 41, 42, 63, 70, 73, 74, 76, 155, 160].

HIV/AIDS is spread in a very heterogeneous population by heterosexual intercourse, homosexual intercourse, and sharing of needles by injecting drug users. Because of the great diversity and heterogeneity among those at risk of HIV/AIDS, modeling this disease is a challenging task [6, 12, 39, 104, 115, 118, 119, 126, 130]. For HIV/AIDS models with a continuous distribution of sexual activity levels and with various preference mixing functions, the proportionate mixing has been shown to be the only separable solution, and expressions for the basic reproduction number R_0 in the proportionate mixing case have been found [26, 32]. Expressions for R_0 have also been found for HIV/AIDS models using groups of people based on their sexual behavior, e.g., homosexual men, bisexual men, heterosexual women, and heterosexual men, with further subdivisions based on their numbers of sexual or needle-sharing partners. For staged progression models for HIV/AIDS with many infectious classes with different infectivities, the basic reproduction number R_0 is often the weighted average of the basic reproduction numbers in the infectious classes, where the weights involve the fraction of contacts (or partners) that result in an infection and the probability of reaching that infectious stage [111, 121, 122, 132, 146].

There is clear evidence that infectious diseases spread geographically and maps with isodate spread contours have been produced [12, 55, 158, 166]. Some estimated speeds of propagation are 30–60 kilometers per year for fox rabies in Europe starting in 1939 [166], 18–24 miles per year for raccoon rabies in the Eastern United States starting in 1977 [49], about 140 miles per year for the plague in Europe in 1347–1350 [166], and worldwide in one year for influenza in the 20th century [176]. Epidemiology models with spatial structures have been used to describe spatial heterogeneity [12, 96, 110] and the spatial spread of infectious diseases [38, 54, 59, 90, 166, 193]. There seem to be two types of spatial epidemiology models [163, 193]. Diffusion epidemiology models are formulated from nonspatial models by adding diffusion terms corresponding to the random movements each day of susceptibles and infectives. Dispersal-kernel models are formulated by using integral equations with kernels describing daily contacts of infectives with their neighbors. For both types of spatial epidemiology models in infinite domains, one often determines the thresholds (sometimes in terms of R_0) above which a traveling wave exists, finds the minimum speed of propagation and the asymptotic speed of propagation (which is usually shown to be equal to the minimum speed), and determines the stability of the traveling wave to perturbations [161, 172]. For spatial models in finite domains, stationary states and their stability have been investigated [38]. For stochastic spatial models there is also a threshold condition, so

that the disease dies out below the threshold and approaches an endemic stationary distribution above the threshold [69].

10. Discussion. Mathematical epidemiology has now evolved into a separate area of population dynamics that is parallel to mathematical ecology. Epidemiology models are now used to combine complex data from various sources in order to study equally complex outcomes. In this paper we have focused on the role of the basic reproduction number R_0, which is defined as the average number of people infected when a typical infective enters an entirely susceptible population. We have illustrated the significance of R_0 by obtaining explicit expressions for R_0 and proving threshold results which imply that a disease can invade a completely susceptible population if and only if $R_0 > 1$. Using the SIR endemic model without age structure, the estimates of R_0 for various diseases in section 2.5 show that some diseases are more easily spread than others, so that they are more difficult to control or eradicate. These differences are verified for six diseases in section 2.6.

For the basic endemic models without age structure, the expressions for the basic reproduction number R_0 are intuitively obvious as the product of the contact rate, the average infectious period, and the fraction surviving the latent period (provided there is an exposed class in the model). But for more complicated models, expressions for R_0 must be derived from threshold conditions for the stability of the disease-free equilibrium or the existence of an endemic equilibrium in the feasible region. This approach was used in section 3 for the MSEIR model without age structure, but with an exponentially changing population size. Many epidemiology models now used to study infectious diseases involve age structures, because fertilities, death rates, and contact rates all depend on the ages of the individuals. Thus the basic reproduction number R_0 must be found for these epidemiologic-demographic models. For MSEIR, MSEIRS, SEIR, SEIRS, and SEIS models, expressions for R_0 are given by (5.9) and (6.6) when the demographic structures are continuous age and age groups, respectively. Analogous expressions for R_0 for the SIR, SIRS, and SIS models are given by (5.11) and (6.8). These expressions for R_0 are found by examining when there is a positive (endemic) equilibrium in the feasible region, and then it is verified that the disease persists if and only if $R_0 > 1$.

To illustrate the application of the theoretical formulas for R_0 in models with age groups, two applications have been included in this paper. Based on demographic and epidemiologic estimates for measles in Niger, Africa, the value of the basic reproduction number found from (6.6) in section 7 is $R_0 = 18.8$. The interesting aspect of this measles application is that R_0 is found for a very rapidly growing population. In contrast, the current fertility and death data in the United States suggests that the population is approaching a stable age distribution with constant total size. Using previously developed models for pertussis (whooping cough) in which the immunity is temporary [105, 106], the basic reproduction numbers are estimated in section 8 to be $R_0 = 5.4$ and $R_0 = 3.7$ for two pertussis models. It is interesting that these basic reproduction numbers are found using the R_0 expression derived for an SIR model, even though pertussis immunity is temporary.

Recall from section 2.2 that the contact number σ is the average number of adequate contacts of a typical infective during the infectious period. The interesting aspect of the pertussis calculations is that new types of infectives with lower infectivity occur after the invasion, because infected people who previously had pertussis have lower infectivity when reinfected. Thus typical infectives after the invasion include those who have lower infectivities than the infectives who had been fully suscepti-

ble. Although the contact number σ is equal to R_0 when pertussis first invades the population, the new broader collection of typical infectives implies that $\sigma < R_0$ after the invasion. Using numerical approximations during the computer simulations, the contact numbers at the endemic equilibrium are estimated in section 8 to be $\sigma = 3$ for the first age group pertussis model and $\sigma = 1.8$ for the second pertussis model. This phenomenon that $\sigma < R_0$ at the endemic equilibrium also holds for three relatively simple pertussis models based on ordinary differential equations [108]. For the pertussis model with four removed groups in [108], the three infective classes with decreasing infectivity are I, I_m, and I_w, where the infective classes I_m and I_w are nonempty as soon as pertussis has invaded. For this model the contact number σ satisfies

$$\sigma = R_0[I + \rho_m I_m + \rho_w I_w]/[I + I_m + I_w] < R_0,$$

because the relative infectivities ρ_m and ρ_w are less than 1. As pointed out in section 2.2 the basic reproduction number R_0, the contact number σ, and the replacement number R are all equal at the time when the disease invades the population. For nearly all models $R_0 = \sigma > R$ after the invasion, but for the pertussis models, $R_0 > \sigma > R$ after the invasion. Thus the pertussis models have led to an entirely new way of thinking about the differences between the contact number σ and the basic reproduction number R_0.

Acknowledgments. The author thanks David Greenhalgh, Hal Smith, Horst Thieme, Nick Trefethen, and Pauline van den Driessche for their helpful suggestions and comments, and thanks Brian Treadway for manuscript preparation assistance.

REFERENCES

[1] F. R. Adler, *The effects of averaging on the basic reproduction ratio*, Math. Biosci., 111 (1992), pp. 89–98.
[2] L. J. S. Allen, *Some discrete-time SI, SIR, and SIS epidemic models*, Math. Biosci., 124 (1994), pp. 83–105.
[3] L. J. S. Allen and A. M. Burgin, *Comparison of deterministic and stochastic SIS and SIR models in discrete-time*, Math. Biosci., 163 (2000), pp. 1–33.
[4] H. Amann, *Ordinary Differential Equations*, Walter de Gruyter, Berlin, 1990.
[5] R. M. Anderson, ed., *Population Dynamics of Infectious Diseases*, Chapman and Hall, London, 1982.
[6] R. M. Anderson, ed., *The role of mathematical models in the study of HIV transmission and the epidemiology of AIDS*, J. AIDS, 1 (1988), pp. 241–256.
[7] R. M. Anderson and R. M. May, *Population biology of infectious diseases* I, Nature, 180 (1979), pp. 361–367.
[8] R. M. Anderson and R. M. May, *The population dynamics of microparasites and their invertebrate hosts*, Philos. Trans. Roy. Soc. London Ser. B, 291 (1981), pp. 451–524.
[9] R. M. Anderson and R. M. May, eds., *Population Biology of Infectious Diseases*, Springer-Verlag, Berlin, Heidelberg, New York, 1982.
[10] R. M. Anderson and R. M. May, eds., *Vaccination against rubella and measles: Quantitative investigations of different policies*, J. Hyg. Camb., 90 (1983), pp. 259–325.
[11] R. M. Anderson and R. M. May, eds., *Age related changes in the rate of disease transmission: Implication for the design of vaccination programs*, J. Hyg. Camb., 94 (1985), pp. 365–436.
[12] R. M. Anderson and R. M. May, eds., *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, UK, 1991.
[13] R. M. Anderson, G. P. Medley, R. M. May, and A. M. Johnson, *A preliminary study of the transmission dynamics of the human immunodeficiency virus, the causative agent of AIDS*, IMA J. Math. Appl. Med. Biol., 3 (1986), pp. 229–263.
[14] V. Andreasen, *Disease regulation of age-structured host populations*, Theoret. Population Biol., 36 (1989), pp. 214–239.

[15] V. Andreasen, *The effect of age-dependent host mortality on the dynamics of an endemic disease*, Math. Biosci., 114 (1993), pp. 29–58.
[16] V. Andreasen, *Instability in an SIR-model with age-dependent susceptibility*, in Mathematical Population Dynamics, Vol. 1, O. Arino, D. Axelrod, M. Kimmel, and M. Langlais, eds., Wuerz Publishing, Winnipeg, MB, Canada, 1995, pp. 3–14.
[17] V. Andreasen, J. Lin, and S. A. Levin, *The dynamics of cocirculating influenza strains conferring partial cross-immunity*, J. Math. Biol., 35 (1997), pp. 825–842.
[18] N. T. J. Bailey, *The Mathematical Theory of Infectious Diseases*, 2nd ed., Hafner, New York, 1975.
[19] N. T. J. Bailey, *The Biomathematics of Malaria*, Charles Griffin, London, 1982.
[20] M. Bartlett, *Stochastic Population Models in Ecology and Epidemiology*, Methuen, London, 1960.
[21] N. Becker, *The use of epidemic models*, Biometrics, 35 (1978), pp. 295–305.
[22] N. Becker, *Analysis of Infectious Disease Data*, Chapman and Hall, New York, 1989.
[23] A. S. Benenson, *Control of Communicable Diseases in Man*, 16th ed., American Public Health Association, Washington, DC, 1995.
[24] D. Bernoulli, *Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir*, in Mémoires de Mathématiques et de Physique, Académie Royale des Sciences, Paris, 1760, pp. 1–45.
[25] F. L. Black, W. J. Hierholzer, F. D. P. Pinheiro, et al., *Evidence for the persistence of infectious disease agents in isolated human populations*, Am. J. Epidemiol., 100 (1974), pp. 230–250.
[26] S. P. Blythe and C. Castillo-Chavez, *Like with like preference and sexual mixing models*, Math. Biosci., 96 (1989), pp. 221–238.
[27] B. M. Bolker and B. T. Grenfell, *Chaos and biological complexity in measles dynamics*, Proc. Roy. Soc. London Ser. B, 251 (1993), pp. 75–81.
[28] J. Bongaarts, *A model of the spread of HIV infection and the demographic impact of AIDS*, Stat. Med., 8 (1989), pp. 103–120.
[29] F. Brauer, *Models for the spread of universally fatal diseases*, J. Math. Biol., 28 (1990), pp. 451–462.
[30] H. J. Bremermann and H. R. Thieme, *A competitive exclusion principle for pathogen virulence*, J. Math. Biol., 27 (1989), pp. 179–190.
[31] M. Burnett and D. O. White, *Natural History of Infectious Disease*, 4th ed., Cambridge University Press, Cambridge, UK, 1974.
[32] S. Busenberg and C. Castillo-Chavez, *A general solution of the problem of mixing of subpopulations and its application to risk- and age-structured models for the spread of AIDS*, IMA J. Math. Appl. Med. Biol., 8 (1991), pp. 1–29.
[33] S. Busenberg and K. L. Cooke, *Vertically Transmitted Diseases*, Biomathematics 23, Springer-Verlag, Berlin, 1993.
[34] S. N. Busenberg, K. L. Cooke, and M. Iannelli, *Endemic thresholds and stability in a class of age-structured epidemics*, SIAM J. Appl. Math., 48 (1988), pp. 1379–1395.
[35] S. N. Busenberg and K. P. Hadeler, *Demography and epidemics*, Math. Biosci., 101 (1990), pp. 41–62.
[36] S. N. Busenberg, M. Iannelli, and H. R. Thieme, *Global behavior of an age-structured epidemic model*, SIAM J. Math. Anal., 22 (1991), pp. 1065–1080.
[37] S. N. Busenberg and P. van den Driessche, *Analysis of a disease transmission model in a population with varying size*, J. Math. Biol., 28 (1990), pp. 257–270.
[38] V. Capasso, *Mathematical Structures of Epidemic Systems*, Lecture Notes in Biomath. 97, Springer-Verlag, Berlin, 1993.
[39] C. Castillo-Chavez, ed., *Mathematical and Statistical Approaches to AIDS Epidemiology*, Lecture Notes in Biomath. 83, Springer-Verlag, Berlin, 1989.
[40] C. Castillo-Chavez, H. W. Hethcote, V. Andreasen, S. A. Levin, and W. M. Liu, *Epidemiological models with age structure, proportionate mixing, and cross-immunity*, J. Math. Biol., 27 (1989), pp. 233–258.
[41] C. Castillo-Chavez, W. Huang, and J. Li, *Competitive exclusion in gonorrhea models and other sexually-transmitted diseases*, SIAM J. Appl. Math., 56 (1996), pp. 494–508.
[42] C. Castillo-Chavez, W. Huang, and J. Li, *Competitive exclusion and multiple strains in an SIS STD model*, SIAM J. Appl. Math., 59 (1999), pp. 1790–1811.
[43] Centers for Disease Control and Prevention, *Summary of notifiable diseases, United States*, 1998, MMWR, 47 (1999), pp. 78–83.
[44] Centers for Disease Control and Prevention, *Ten great public health achievements—United States*, 1900–1999, MMWR, 48 (1999), pp. 241–248.

[45] Centers for Disease Control and Prevention, *Progress toward global poliomyelitis eradication*, 1997–1998, MMWR, 48 (1999), pp. 416–421.
[46] Centers for Disease Control and Prevention, *Rubella outbreak—Westchester County, New York*, 1997–1998, MMWR, 48 (1999), pp. 560–563.
[47] Centers for Disease Control and Prevention, *Epidemiology of measles—United States*, 1998, MMWR, 48 (1999), pp. 749–753.
[48] Centers for Disease Control and Prevention, *Global measles control and regional elimination*, 1998–99, MMWR, 48 (1999), pp. 1124–1130.
[49] Centers for Disease Control and Prevention, *Update: Raccoon rabies epizootic—United States and Canada*, 1999, MMWR, 49 (2000), pp. 31–35.
[50] Centers for Disease Control and Prevention, *Recommended childhood immunization schedule—United States*, 2000, MMWR, 49 (2000), pp. 35–47.
[51] Centers for Disease Control and Prevention, *Update: Influenza activity—United States*, 1999–2000 *season*, MMWR, 49 (2000), pp. 53–57.
[52] Centers for Disease Control and Prevention, *Measles outbreak—Netherlands, April* 1999–*January* 2000, MMWR, 49 (2000), pp. 299–303.
[53] Y. Cha, M. Iannelli, and F. A. Milner, *Existence and uniqueness of endemic states for age-structured S-I-R epidemic model*, Math. Biosci., 150 (1998), pp. 177–190.
[54] A. D. Cliff, *Incorporating spatial components into models of epidemic spread*, in Epidemic Models: Their Structure and Relation to Data, D. Mollison, ed., Cambridge University Press, Cambridge, UK, 1996, pp. 119–149.
[55] A. D. Cliff and P. Haggett, *Atlas of Disease Distributions: Analytic Approaches to Epidemiological Data*, Blackwell, London, 1988.
[56] D. J. Daley and J. Gani, *Epidemic Modelling: An Introduction*, Cambridge University Press, Cambridge, UK, 1999.
[57] M. C. M. De Jong, O. Diekmann, and J. A. P. Heesterbeek, *How does transmission depend on population size?*, in Human Infectious Diseases, Epidemic Models, D. Mollison, ed., Cambridge University Press, Cambridge, UK, 1995, pp. 84–94.
[58] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., 28 (1990), pp. 365–382.
[59] O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases*, Wiley, New York, 2000.
[60] K. Dietz, *Epidemics and rumours: A survey*, J. Roy. Statist. Soc. Ser. A, 130 (1967), pp. 505–528.
[61] K. Dietz, *Transmission and control of arbovirus diseases*, in Epidemiology, K. L. Cooke, ed., SIAM, Philadelphia, 1975, pp. 104–121.
[62] K. Dietz, *The incidence of infectious diseases under the influence of seasonal fluctuations*, in Mathematical Models in Medicine, J. Berger, W. Buhler, R. Repges, and P. Tautu, eds., Lecture Notes in Biomath. 11, Springer-Verlag, Berlin, 1976, pp. 1–15.
[63] K. Dietz, *Epidemiologic interference of virus populations*, J. Math. Biol., 8 (1979), pp. 291–300.
[64] K. Dietz, *The evaluation of rubella vaccination strategies*, in The Mathematical Theory of the Dynamics of Populations, Vol. 2, R. W. Hiorns and D. Cooke, eds., Academic Press, London, 1981, pp. 81–97.
[65] K. Dietz, *Density dependence in parasite transmission dynamics*, Parasit. Today, 4 (1988), pp. 91–97.
[66] K. Dietz, *The first epidemic model: A historical note on P. D. En'ko*, Austral. J. Statist., 30A (1988), pp. 56-65.
[67] K. Dietz and D. Schenzle, *Mathematical models for infectious disease statistics*, in A Celebration of Statistics, A. C. Atkinson and S. E. Feinberg, eds., Springer-Verlag, New York, 1985, pp. 167–204.
[68] K. Dietz and D. Schenzle, *Proportionate mixing models for age-dependent infection transmission*, J. Math. Biol., 22 (1985), pp. 117–120.
[69] R. Durrett, *Stochastic spatial models*, SIAM Rev., 41 (1999), pp. 677–718.
[70] G. Dwyer, S. A. Levin, and L. Buttel, *A simulation model of the population dynamics and evolution of myxomatosis*, Ecological Monographs, 60 (1990), pp. 423–447.
[71] D. J. D. Earn, P. Rohani, B. M. Bolker, and B. T. Grenfell, *A simple model for complex dynamical transitions in epidemics*, Science, 287 (2000), pp. 667–670.
[72] M. El-Doma, *Analysis of nonlinear integro-differential equations arising in age-dependent epidemic models*, Nonlinear Anal., 11 (1987), pp. 913–937.
[73] L. Esteva and C. Vargas, *Analysis of a dengue disease transmission model*, Math. Biosci., 150 (1998), pp. 131–151.

[74] L. Esteva and C. Vargas, *A model for dengue disease with variable human population*, J. Math. Biol., 38 (1999), pp. 220–240.
[75] A. S. Evans, *Viral Infections of Humans*, 2nd ed., Plenum Medical Book Company, New York, 1982.
[76] Z. Feng and J. X. Velasco-Hernandez, *Competitive exclusion in a vector-host model for the dengue fever*, J. Math. Biol., 35 (1997), pp. 523–544.
[77] F. Fenner, D. A. Henderson, I. Arita, Z. Jezek, and I. D. Ladnyi, *Smallpox and its Eradication*, World Health Organization, Geneva, 1988.
[78] N. M. Ferguson, R. M. Anderson, and G. P. Garnett, *Mass vaccination to control chickenpox: The influence of zoster*, Rev. Med. Virology, 6 (1996), pp. 151–161.
[79] N. M. Ferguson, D. J. Nokes, and R. M. Anderson, *Dynamical complexity in age-structured models of the transmission of measles virus: Epidemiological implications of high levels of vaccine uptake*, Math. Biosci., 138 (1996), pp. 101–130.
[80] J. C. Frauenthal, *Mathematical Modeling in Epidemiology*, Springer-Verlag Universitext, Berlin, 1980.
[81] J. P. Gabriel, C. Lefever, and P. Picard, eds., *Stochastic Processes in Epidemic Theory*, Springer-Verlag, Berlin, 1990.
[82] L. Garrett, *The Coming Plague*, Penguin, New York, 1995.
[83] L. Q. Gao and H. W. Hethcote, *Disease transmission models with density-dependent demographics*, J. Math. Biol., 30 (1992), pp. 717–731.
[84] L. Gao, J. Mena-Lorca, and H. W. Hethcote, *Four SEI endemic models with periodicity and separatrices*, Math. Biosci., 128 (1995), pp. 157–184.
[85] L. Gao, J. Mena-Lorca, and H. W. Hethcote, *Variations on a theme of SEI endemic models*, in Differential Equations and Applications to Biology and to Industry, M. Martelli, K. Cooke, E. Cumberbatch, B. Tang, and H. Thieme, eds., World Scientific Publishing, Singapore, 1996, pp. 191–207.
[86] D. Greenhalgh, *Analytical threshold and stability results on age-structured epidemic models with vaccination*, Theoret. Population Biol., 33 (1988), pp. 266–290.
[87] D. Greenhalgh, *Vaccination campaigns for common childhood diseases*, Math. Biosci., 100 (1990), pp. 201–240.
[88] D. Greenhalgh and R. Das, *Some threshold and stability results for epidemic models with a density dependent death rate*, Theoret. Population Biol., 42 (1992), pp. 130–151.
[89] B. T. Grenfell and R. M. Anderson, *Pertussis in England and Wales: An investigation of transmission dynamics and control by mass vaccination*, Proc. Roy. Soc. London Ser. B, 236 (1989), pp. 213–252.
[90] B. T. Grenfell and A. P. Dobson, eds., *Ecology of Infectious Diseases in Natural Populations*, Cambridge University Press, Cambridge, UK, 1995.
[91] G. Gripenberg, *On a nonlinear integral equation modelling an epidemic in an age-structured population*, J. Reine Angew. Math., 341 (1983), pp. 147–158.
[92] J. K. Hale, *Ordinary Differential Equations*, Wiley-Interscience, New York, 1969.
[93] M. E. Halloran, S. L. Cochi, T. A. Lieu, M. Wharton, and L. Fehrs, *Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States*, Am. J. Epidemiol., 140 (1994), pp. 81–104.
[94] M. E. Halloran, L. Watelet, and C. J. Struchiner, *Epidemiological effects of vaccines with complex direct effects in an age-structured population*, Math. Biosci., 121 (1994), pp. 193–225.
[95] W. H. Hamer, *Epidemic disease in England*, Lancet, 1 (1906), pp. 733–739.
[96] H. W. Hethcote, *Qualitative analyses of communicable disease models*, Math. Biosci., 28 (1976), pp. 335–356.
[97] H. W. Hethcote, *An immunization model for a heterogeneous population*, Theoret. Population Biol., 14 (1978), pp. 338–349.
[98] H. W. Hethcote, *Measles and rubella in the United States*, Am. J. Epidemiol., 117 (1983), pp. 2–13.
[99] H. W. Hethcote, *Optimal ages of vaccination for measles*, Math. Biosci., 89 (1988), pp. 29–52.
[100] H. W. Hethcote, *Three basic epidemiological models*, in Applied Mathematical Ecology, L. Gross, T. G. Hallam, and S. A. Levin, eds., Springer-Verlag, Berlin, 1989, pp. 119–144.
[101] H. W. Hethcote, *Rubella*, in Applied Mathematical Ecology, L. Gross, T. G. Hallam, and S. A. Levin, eds., Springer-Verlag, Berlin, 1989, pp. 212–234.
[102] H. W. Hethcote, *A thousand and one epidemic models*, in Frontiers in Theoretical Biology, S. A. Levin, ed., Lecture Notes in Biomath. 100, Springer-Verlag, Berlin, 1994, pp. 504–515.
[103] H. W. Hethcote, *Modeling heterogeneous mixing in infectious disease dynamics*, in Models for Infectious Human Diseases, V. Isham and G. F. H. Medley, eds., Cambridge University Press, Cambridge, UK, 1996, pp. 215–238.

[104] H. W. Hethcote, *Modeling AIDS prevention programs in a population of homosexual men*, in Modeling the AIDS Epidemic: Planning, Policy and Prediction, E. H. Kaplan and M. L. Brandeau, eds., Raven Press, New York, 1994, pp. 91–107.
[105] H. W. Hethcote, *An age-structured model for pertussis transmission*, Math. Biosci., 145 (1997), pp. 89–136.
[106] H. W. Hethcote, *Simulations of pertussis epidemiology in the United States: Effects of adult booster vaccinations*, Math. Biosci., 158 (1999), pp. 47–73.
[107] H. W. Hethcote and S. A. Levin, *Periodicity in epidemiological models*, in Applied Mathematical Ecology, L. Gross, T. G. Hallam, and S. A. Levin, eds., Springer-Verlag, Berlin, 1989, pp. 193–211.
[108] H. W. Hethcote, Y. Li, and Z. J. Jing, *Hopf bifurcation in models for pertussis epidemiology*, Math. Comput. Modelling, 30 (1999), pp. 29–45.
[109] H. W. Hethcote, H. W. Stech, and P. van den Driessche, *Periodicity and stability in epidemic models: A survey*, in Differential Equations and Applications in Ecology, Epidemics and Population Problems, S. N. Busenberg and K. L. Cooke, eds., Academic Press, New York, 1981, pp. 65–82.
[110] H. W. Hethcote and J. W. Van Ark, *Epidemiological models with heterogeneous populations: Proportionate mixing, parameter estimation and immunization programs*, Math. Biosci., 84 (1987), pp. 85–118.
[111] H. W. Hethcote and J. W. Van Ark, *Modeling HIV Transmission and AIDS in the United States*, Lecture Notes in Biomath. 95, Springer-Verlag, Berlin, 1992.
[112] H. W. Hethcote and P. van den Driessche, *Some epidemiological models with nonlinear incidence*, J. Math. Biol., 29 (1991), pp. 271–287.
[113] H. W. Hethcote and J. A. Yorke, *Gonorrhea Transmission Dynamics and Control*, Lecture Notes in Biomath. 56, Springer-Verlag, Berlin, 1984.
[114] F. Hoppensteadt, *Mathematical Theories of Populations: Demographics, Genetics and Epidemics*, SIAM, Philadelphia, 1975.
[115] W. Huang, K. L. Cooke, and C. Castillo-Chavez, *Stability and bifurcation for a multiple-group model for the dynamics of HIV/AIDS transmission*, SIAM J. Appl. Math., 52 (1992), pp. 835–854.
[116] H. F. Hull, N. A. Ward, B. F. Hull, J. B. Milstein, and C. de Quatros, *Paralytic poliomyelitis: Seasoned strategies, disappearing disease*, Lancet, 343 (1994), pp. 1331–1337.
[117] S. S. Hutchins, L. E. Markowitz, W. L. Atkinson, E. Swint, and S. Hadler, *Measles outbreaks in the United States,* 1987 *through* 1990, Pediatr. Infect. Dis. J., 15 (1996), pp. 31–38.
[118] J. M. Hyman and E. A. Stanley, *Using mathematical models to understand the AIDS epidemic*, Math. Biosci., 90 (1988), pp. 415–473.
[119] J. M. Hyman and E. A. Stanley, *The effect of social mixing patterns on the spread of AIDS*, in Mathematical Approaches to Problems in Resource Management and Epidemiology, C. Castillo-Chavez, S. A. Levin, and C. Shoemaker, eds., Lecture Notes in Biomath. 81, Springer-Verlag, New York, 1989.
[120] J. M. Hyman, J. Li, and E. A. Stanley, *Threshold conditions for the spread of HIV infection in age-structured populations of homosexual men*, J. Theoret. Biol., 166 (1994), pp. 9–31.
[121] J. M. Hyman, J. Li, and E. A. Stanley, *The differential infectivity and staged progression models for the transmission of HIV*, Math. Biosci., 155 (1999), pp. 77–109.
[122] J. M. Hyman and J. Li, *An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations*, Math. Biosci., 167 (2000), pp. 65–86.
[123] M. Iannelli, *Mathematical Theory of Age-Structured Population Dynamics*, C.N.R. Applied Mathematics Monograph 7, Giardini Editori, Pisa, Italy, 1994.
[124] M. Iannelli, F. A. Milner, and A. Pugliese, *Analytic and numerical results for the age-structured S-I-S model with mixed inter-intracohort transmission*, SIAM J. Math. Anal., 23 (1992), pp. 662–688.
[125] H. Inaba, *Threshold and stability results for an age-structured epidemic model*, J. Math. Biol., 28 (1990), pp. 411–434.
[126] V. Isham, *Mathematical modeling of the transmission dynamics of HIV infection and AIDS: A review*, J. Roy. Statist. Soc. Ser. A, 151 (1988), pp. 5–31.
[127] V. Isham and G. Medley, eds., *Models for Infectious Human Diseases*, Cambridge University Press, Cambridge, UK, 1996.
[128] J. A. Jacquez and C. P. Simon, *The stochastic SI model with recruitment and deaths* I: *Comparison with the closed SIS model*, Math. Biosci., 117 (1993), pp. 77–125.
[129] J. A. Jacquez, C. P. Simon, and J. S. Koopman, *The reproduction number in deterministic models of contagious diseases*, Curr. Topics in Theoret. Biol., 2 (1991), pp. 159–209.
[130] J. A. Jacquez, J. S. Koopman, C. P. Simon, and I. M. Longini, *Role of the primary infection in epidemics of HIV infection in gay cohorts*, J. AIDS, 7 (1994), pp. 1169–1184.

[131] J. A. Jacquez, C. P. Simon, and J. S. Koopman, *Core groups and the R_0's for subgroups in heterogeneous SIS models*, in Epidemic Models: Their Structure and Relation to Data, D. Mollison, ed., Cambridge University Press, Cambridge, UK, 1996, pp. 279–301.
[132] J. A. Jacquez, C. P. Simon, J. S. Koopman, L. Sattenspiel, and T. Perry, *Modeling and analyzing HIV transmission: The effect of contact patterns*, Math. Biosci., 92 (1988), pp. 119–199.
[133] A. V. Kaninda, S. Richardson, and H. W. Hethcote, *Influence of Heterogeneous Mixing on Measles Transmission in an African Context*, preprint, 2000.
[134] M. M. Kaplan and R. G. Webster, *The epidemiology of influenza*, Scientific American, 237 (1977), pp. 88–105.
[135] W. Katzmann and K. Dietz, *Evaluation of age-specific vaccination strategies*, Theoret. Population Biol., 25 (1984), pp. 125–137.
[136] W. O. Kermack and A. G. McKendrick, *Contributions to the mathematical theory of epidemics, part* 1, Proc. Roy. Soc. London Ser. A, 115 (1927), pp. 700–721.
[137] J. Kranz, ed., *Epidemics of Plant Diseases: Mathematical Analysis and Modelling*, Springer-Verlag, Berlin, 1990.
[138] C. M. Kribs-Zaleta, *Structured models for heterosexual disease transmission*, Math. Biosci., 160 (1999), pp. 83–108.
[139] C. M. Kribs-Zaleta, *Core recruitment effects in SIS models with constant total populations*, Math. Biosci., 160 (1999), pp. 109–158.
[140] A. Lajmanovich and J. A. Yorke, *A deterministic model for gonorrhea in a nonhomogeneous population*, Math. Biosci., 28 (1976), pp. 221–236.
[141] H. A. Lauwerier, *Mathematical Models of Epidemics*, Mathematisch Centrum, Amsterdam, 1981.
[142] R. Levins, T. Awerbuch, U. Brinkman, I. Eckardt, P. Epstein, N. Makhoul, C. A. de Possas, C. Puccia, A. Spielman, and M. E. Wilson, *The emergence of new diseases*, American Scientist, 82 (1994), pp. 52–60.
[143] M. Y. Li and J. S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci., 125 (1995), pp. 155–164.
[144] M. Y. Li, J. R. Graef, L. Wang, and J. Karsai, *Global dynamics of an SEIR model with varying population size*, Math. Biosci., 160 (1999), pp. 191–213.
[145] M. Y. Li, J. S. Muldowney, and P. van den Driessche, *Global stability for the SEIRS models in epidemiology*, Canad. Quart. Appl. Math., to appear.
[146] X. Lin, H. W. Hethcote, and P. van den Driessche, *An epidemiological model for HIV/AIDS with proportional recruitment*, Math. Biosci., 118 (1993), pp. 181–195.
[147] W. M. Liu, H. W. Hethcote, and S. A. Levin, *Dynamical behavior of epidemiological models with nonlinear incidence rates*, J. Math. Biol., 25 (1987), pp. 359–380.
[148] W. M. Liu, S. A. Levin, and Y. Iwasa, *Influence of nonlinear incidence rates upon the behavior of SIRS epidemiological models*, J. Math. Biol., 23 (1986), pp. 187–204.
[149] W. P. London and J. A. Yorke, *Recurrent outbreaks of measles, chickenpox and mumps* I: *Seasonal variation in contact rates*, Am. J. Epidemiol., 98 (1973), pp. 453–468.
[150] A. J. Lotka, *The stability of the normal age distribution*, Proc. Nat. Acad. Sci. USA, 8 (1922), pp. 339–345.
[151] D. Ludwig and K. L. Cooke, eds., *Epidemiology*, SIMS Utah Conference Proceedings, SIAM, Philadelphia, 1975.
[152] P. Martens, *How will climate change affect human health?*, American Scientist, 87 (1999), pp. 534–541.
[153] R. M. May and R. M. Anderson, *Population biology of infectious diseases* II, Nature, 280 (1979), pp. 455–461.
[154] R. M. May and R. M. Anderson, *Transmission dynamics of HIV infection*, Nature, 326 (1987), pp. 137–142.
[155] R. M. May and R. M. Anderson, *Parasite-host coevolution*, Parasitology, 100 (1990), pp. S89–S101.
[156] R. M. May, R. M. Anderson, and A. R. McLean, *Possible demographic consequences of HIV/AIDS*, Math. Biosci., 90 (1988), pp. 475–506.
[157] A. G. McKendrick, *Applications of mathematics to medical problems*, Proc. Edinburgh Math. Soc., 44 (1926), pp. 98–130.
[158] W. H. McNeill, *Plagues and People*, Blackwell, Oxford, UK, 1976.
[159] J. Mena-Lorca and H. W. Hethcote, *Dynamic models of infectious diseases as regulators of population sizes*, J. Math. Biol., 30 (1992), pp. 693–716.
[160] J. Mena-Lorca, J. X. Velasco-Hernandez, and C. Castillo-Chavez, *Density-dependent dynamics and superinfection in an epidemic model*, IMA J. Math. Appl. Med. Biol., 16 (1999), pp. 307–317.

[161] J. A. J. Metz and F. van den Bosch, *Velocities of epidemic spread*, in Epidemic Models: Their Structure and Relation to Data, D. Mollison, ed., Cambridge University Press, Cambridge, UK, 1996, pp. 150–186.
[162] K. Mischaikow, H. Smith, and H. R. Thieme, *Asymptotically autonomous semiflows: Chain recurrence and Lyapunov functions*, Trans. Amer. Math. Soc., 53 (1993), pp. 1447–1479.
[163] D. Mollison, *Dependence of epidemic and population velocities on basic parameters*, Math. Biosci., 107 (1991), pp. 255–287.
[164] D. Mollison, *Epidemic Models: Their Structure and Relation to Data*, Cambridge University Press, Cambridge, UK, 1996.
[165] J. Muller, *Optimal vaccination patterns in age-structured populations*, SIAM J. Appl. Math., 59 (1998), pp. 222–241.
[166] J. D. Murray, *Mathematical Biology*, Springer-Verlag, Berlin, 1989.
[167] I. Nasell, *Hybrid Models of Tropical Infections*, Springer-Verlag, Berlin, 1985.
[168] M. B. A. Oldstone, *Viruses, Plagues, and History*, Oxford University Press, New York, 1998.
[169] L. F. Olson and W. M. Schaffer, *Chaos versus noisy periodicity: Alternative hypotheses for childhood epidemics*, Science, 249 (1990), pp. 499–504.
[170] R. Preston, *The Hot Zone*, Random House, New York, 1994.
[171] A. Pugliese, *Population models for diseases with no recovery*, J. Math. Biol., 28 (1990), pp. 65–82.
[172] J. Radcliffe and L. Rass, *Spatial Deterministic Epidemics*, Mathematical Surveys and Monographs, AMS, Providence, RI, 2001.
[173] R. Ross, *The Prevention of Malaria*, 2nd ed., Murray, London, 1911.
[174] V. Rouderfer, N. Becker, and H. W. Hethcote, *Waning immunity and its effects on vaccination schedules*, Math. Biosci., 124 (1994), pp. 59–82.
[175] V. Rouderfer and N. Becker, *Assessment of two-dose vaccination schedules: Availability for vaccination and catch-up*, Math. Biosci., 129 (1995), pp. 41–66.
[176] L. A. Rvachev and I. M. Longini, *A mathematical model for the global spread of influenza*, Math. Biosci., 75 (1985), pp. 3–22.
[177] D. Schenzle, *An age-structured model of pre- and post-vaccination measles transmission*, IMA J. Math. Appl. Med. Biol., 1 (1984), pp. 169–191.
[178] L. Schlien, *Hunting down the last of the poliovirus*, Science, 279 (1998), p. 168.
[179] M. C. Schuette and H. W. Hethcote, *Modeling the effects of varicella vaccination programs on the incidence of chickenpox and shingles*, Bull. Math. Biol., 61 (1999), pp. 1031–1064.
[180] M. Schuette, *Modeling the Transmission of the Varicella-Zoster Virus*, preprint, 2000.
[181] M. E. Scott and G. Smith, eds., *Parasitic and Infectious Diseases*, Academic Press, San Diego, 1994.
[182] D. Shalala, *Bioterrorism: How prepared are we?*, Emerg. Infect. Dis., 5 (1999). Available online from http://www.cdc.gov/ncidod/eid/vol5no4/shalala.htm.
[183] R. Shilts, *And The Band Played On*, St. Martin's Press, New York, 1987.
[184] C. P. Simon and J. A. Jacquez, *Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations*, SIAM J. Appl. Math., 52 (1992), pp. 541–576.
[185] R. Snacken, A. P. Kendal, L. R. Haaheim, and J. M. Wood, *The next influenza pandemic: Lessons from Hong Kong,* 1997, Emerg. Infect. Dis., 5 (1999). Available online from http://www.cdc.gov/ncidod/eid/vol5no2/snacken.htm.
[186] H. R. Thieme, *Asymptotic estimates of the solutions of nonlinear integral equations and asymptotic speeds for the spread of populations*, J. Reine Angew. Math., 306 (1979), pp. 94–121.
[187] H. R. Thieme, *Global asymptotic stability in epidemic models*, in Equadiff 82 Proceedings, H. W. Knobloch and K. Schmitt, eds., Lecture Notes in Math. 1017, Springer-Verlag, Berlin, 1983, pp. 609–615.
[188] H. R. Thieme, *Local stability in epidemic models for heterogeneous populations*, in Mathematics in Biology and Medicine, V. Capasso, E. Grosso, and S. L. Paveri-Fontana, eds., Lecture Notes in Biomath. 97, Springer-Verlag, Berlin, 1985, pp. 185–189.
[189] H. R. Thieme, *Stability change of the endemic equilibrium in age-structured models for the spread of S-I-R type infectious diseases*, in Differential Equations Models in Biology, Epidemiology, and Ecology, S. Busenberg and M. Martelli, eds., Lecture Notes in Biomath. 92, Springer-Verlag, Berlin, 1991, pp. 139–158.
[190] H. R. Thieme, *Epidemic and demographic interaction in the spread of potentially fatal diseases in growing populations*, Math. Biosci., 111 (1992), pp. 99–130.
[191] H. R. Thieme, *Persistence under relaxed point-dissipativity (with an application to an endemic model)*, SIAM J. Math. Anal., 24 (1993), pp. 407–435.
[192] D. W. Tudor, *An age-dependent epidemic model with application to measles*, Math. Biosci., 73 (1985), pp. 131–147.

[193] F. van den Bosch, J. A. J. Metz, and O. Diekmann, *The velocity of spatial population expansion*, J. Math. Biol., 28 (1990), pp. 529–565.
[194] J. E. Vanderplank, *Plant Diseases: Epidemics and Control*, Academic Press, New York, 1963.
[195] H. von Foerster, *The Kinetics of Cellular Proliferation*, Grune and Stratton, New York, 1959.
[196] P. E. Waltman, *Deterministic Threshold Models in the Theory of Epidemics*, Lecture Notes in Biomath. 1, Springer-Verlag, Berlin, 1974.
[197] G. F. Webb, *Theory of Nonlinear Age-dependent Population Dynamics*, Marcel Dekker, New York, 1985.
[198] R. G. Webster, *Influenza: An emerging disease*, Emerg. Infect. Dis., 4 (1998). Available online from http://www.cdc.gov/ncidod/eid/vol4no3/webster.htm.
[199] K. Wickwire, *Mathematical models for the control of pests and infectious diseases: A survey*, Theoret. Population Biol., 11 (1977), pp. 182–238.
[200] J. A. Yorke and W. P. London, *Recurrent outbreaks of measles, chickenpox, and mumps* II, Am. J. Epidemiol., 98 (1973), pp. 469–482.
[201] J. Zhou and H. W. Hethcote, *Population size dependent incidence in models for diseases without immunity*, J. Math. Biol., 32 (1994), pp. 809–834.
[202] H. Zinsser, *Rats, Lice, and History*, Little, Brown and Company, Boston, 1935.