AGE-STRUCTURED EPIDEMIOLOGY MODELS AND EXPRESSIONS FOR R_0

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Demographic models with either continuous age or age groups are developed and then extended to MSEIR and SEIR endemic models for the spread of infectious diseases in populations. Expressions for the basic reproduction number R_0 are obtained and threshold theorems are obtained. Values of R_0 and the contact number σ are estimated for measles in Niger and pertussis in the United States.

Contents

3.1. Introduction

In Chapters 1 and 2 we found that the threshold for many epidemiology models is the basic reproduction number R_0, which determines when an infection can invade and persist in a new host population. In this chapter we extend these results to epidemiology models with age structure based on either continuous age or age groups. The definitions and notation here are the same as in Chapters 1 and 2, as shown in Table 1. For example, the variables M, S, E, I, and R are used for the passively immune, susceptible, exposed (latent), infectious, and removed epidemiological classes, respectively. This chapter is based on the last part of the paper [36].

Realistic infectious disease models include both time t and age a as independent variables, because age is often an important factor in the transmission process. For example, age groups mix heterogeneously, the recovered fraction usually increases with age, risks from an infection may be related to age, vaccination programs often focus on specific ages, and epidemiologic data is often age specific. First, demographic models with either continuous age or age groups are formulated and analyzed. These two demographic models demonstrate the role of the population reproduction numbers in determining when the population grows asymptotically exponentially. Then the MSEIR with continuous age structure is formulated and analyzed. General expressions for the basic reproduction number R_0 and the average age of infection A are obtained. Special expressions for these quantities are found in the cases when the survival function of the population is a negative exponential and a step function. In addition the endemic threshold and the average age of infection are obtained when vaccination occurs at age A_v. Then the SEIR model with age groups is formulated and analyzed. The 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 for the basic reproduction number R_0 are used 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. Estimates of the basic reproduction number R_0 and the contact number σ 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.

3.2. Three threshold quantities: R_0, σ, and R

In Chapters 1 and 2, we defined the basic reproduction number R_0 as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host population [16]. The contact number σ is defined as the average number of adequate contacts of a typical infective during the infectious period [28, 39]. 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 typical infective during the entire period of infectiousness [28]. We noted that these three quantities R_0, σ, and R are all equal at the beginning of the spread of an infectious disease when the entire population (except the infective invader) is susceptible.

Table 1. Summary of notation.

symbol	quantity (number, fraction, rate, or period)
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

Although R_0 is only defined at the time of invasion into a completely susceptible population, σ and R are defined at all times. For most models, the contact number σ remains constant as the infection spreads, so it is then 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 some models such as the pertussis models considered in Section 7, the contact number σ is a function of time and 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, which is the actual number of secondary cases from a typical infective, is always a function of time. After the infection has invaded a population and everyone is no longer susceptible, the replacement number R is always less than the basic reproduction number R_0. Also after the invasion, the susceptible fraction is less than one, 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 we observe that

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

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.

3.3. Two demographic models

Before formulating the age-structured epidemiological models, we present two underlying demographic models, that 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.

3.3.1. *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 [40]. 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

$$\frac{\partial U}{\partial a} + \frac{\partial U}{\partial t} = -d(a)U, \tag{3.3.1}$$

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

$$B(t) = U(0,t) = \int_0^\infty f(a)U(a,t)da. \tag{3.3.2}$$

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 [47] in 1922 for population modeling, by McKendrick [48] in 1926 in conjunction with epidemic models, and by von Foerster [60] 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 [40, 41]. 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 (3.3.2) is subdivided at $a = t$, then substitution of the expressions for $U(a,t)$ on the intervals yields

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

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 (3.3.1) 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 (3.3.2), we obtain the Lotka characteristic equation given by

$$1 = \int_0^\infty f(a)\exp[-D(a) - qa]da. \tag{3.3.3}$$

If the population reproduction number given by

$$R_{\text{pop}} = \int_0^\infty f(a)\exp[-D(a)]da \tag{3.3.4}$$

is less than, equal to, or greater than 1, then the solution q of (3.3.3) 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

$$U(a,t) = \rho e^{qt} e^{-D(a)-qa}, \text{ with } \rho = 1 \Big/ \int_0^\infty e^{-D(a)-qa} da \, . \tag{3.3.5}$$

In this case the birth equation (3.3.2) is equivalent to the characteristic equation (3.3.3).

If the age-specific death rate $d(a)$ is constant, then (3.3.5) 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 are called Type I and Type II mortality, respectively, by Anderson and May [4]. 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 3.6 and 3.7.

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 death is $L = E[a] = \int_0^\infty a[-w'(a)]da = \int_0^\infty w da$. 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.

3.3.2. *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 struc-

tured epidemiologic models for pertussis [34]. 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 (3.3.5), so that the number of individuals in the age bracket $[a_{i-1}, a_i]$ is given by

$$N_i(t) = \int_{a_{i-1}}^{a_i} U(a,t)da = e^{qt}\int_{a_{i-1}}^{a_i} A(a)da = e^{qt}P_i, \tag{3.3.6}$$

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

Substituting $U(a,t) = e^{qt}A(a)$ into (3.3.1) 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

$$A(a) = A(a_{i-1})\exp[-(d_i + q)(a - a_{i-1})]. \tag{3.3.7}$$

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

$$P_i = A(a_{i-1})\{1 - \exp[-(d_i + q)(a_i - a_{i-1})]\}/(d_i + q). \tag{3.3.8}$$

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 (3.3.7) and (3.3.8) to obtain

$$c_i = \frac{A(a_i)}{P_i} = \frac{d_i + q}{\exp[(d_i + q)(a_i - a_{i-1})] - 1}. \tag{3.3.9}$$

Integration of (3.3.1) on the intervals $[a_{i-1}, a_i]$ and (3.3.6) yields

$$\begin{aligned} dN_1/dt &= \sum_{j=1}^{n} f_jN_j - (c_1 + d_1)N_1, \\ dN_i/dt &= c_{i-1}N_{i-1} - (c_i + d_i)N_i, \qquad 2 \le i \le n-1, \\ dN_n/dt &= c_{n-1}N_{n-1} - d_nN_n. \end{aligned} \tag{3.3.10}$$

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

Equations (3.3.7) and (3.3.8) imply $A(a_i) - A(a_{i-1}) = -[d_i + q]P_i$. Substituting $A(a_i) = c_iP_i$ leads to $P_i = c_{i-1}P_{i-1}/(c_i + d_i + q)$ for $i \ge 2$. Iterative use of this equation leads to the following equation for P_i in terms of P_1:

$$P_i = \frac{c_{i-1}\cdots c_1P_1}{(c_i + d_i + q)\cdots(c_2 + d_2 + q)}. \tag{3.3.11}$$

The birth equation $A(0) = \sum_{i=1}^{n} f_i P_i$, $A(0) = (c_1 + d_1 + q)P_1$, and (3.3.11) lead to the age-group form of the Lotka characteristic equation (3.3.3) given by

$$1 = \frac{f_1 + f_2 \dfrac{c_1}{(c_2 + d_2 + q)} + \cdots + f_n \dfrac{c_{n-1} \cdots c_1}{(c_n + d_n + q) \cdots (c_2 + d_2 + q)}}{(c_1 + d_1 + q)}. \tag{3.3.12}$$

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

$$R_{pop} = f_1 \frac{1}{(c_1 + d_1)} + f_2 \frac{c_1}{(c_2 + d_2)(c_1 + d_1)} + \cdots + f_n \frac{c_{n-1} \cdots c_1}{(c_n + d_n + q) \cdots (c_1 + d_1)}. \tag{3.3.13}$$

If the fertility constants f_i and the death rate constants d_i for the age groups are known, then the equation (3.3.12) with each c_i given by (3.3.9) 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 (3.3.12) 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 [34] for more details on the derivation of this demographic model for age groups.

3.4. 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 Chapter 1, both of these methods give the same R_0 for the basic 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 [13]. 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 $R_0 \leq 1$.

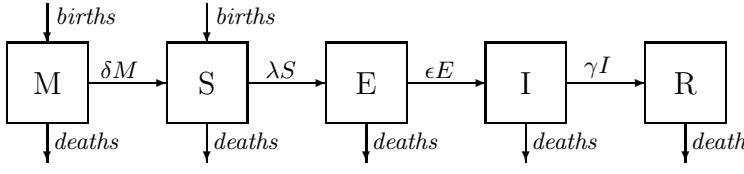

Fig. 1. Transfer diagram for the MSEIR model with the passively-immune class M, the susceptible class S, the exposed class E, the infective class I, and the recovered class R.

This age-structured MSEIR model uses the transfer diagram of Figure 1 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 are 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 later. 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 3.6.

3.4.1. *Formulation of the MSEIR model*

The rate constants δ, ε, and γ are the transfer rates out of the M, E, and I classes. 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 popula-

Table 2. Summary of notation.

symbol	function or parameter
$f(a), f_i$	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

tion size [15, 29, 32, 49]. One example of separable mixing is proportionate mixing, in which the contacts of a person of age are distributed over those of other ages in proportion to the activity levels of the other ages [33, 52]. 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 integro-differential equations for the age distributions are:

$$\begin{aligned}
\partial M/\partial a + \partial M/\partial t &= -(\delta + d(a))M, \\
\partial S/\partial a + \partial S/\partial t &= \delta M - (\lambda(a,t) + d(a))S, \\
\text{with } \lambda(a,t) &= \int_0^\infty b(a)\tilde{b}(\tilde{a})I(\tilde{a},t)d\tilde{a} \Big/ \int_0^\infty U(\tilde{a},t)d\tilde{a}\ , \\
\partial E/\partial a + \partial E/\partial t &= \lambda(a,t)S - (\varepsilon + d(a))E, \\
\partial I/\partial a + \partial I/\partial t &= \varepsilon E - (\gamma + d(a))I, \\
\partial R/\partial a + \partial R/\partial t &= \gamma I - d(a)R.
\end{aligned} \tag{3.4.1}$$

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

$$M(0,t) = \int_0^\infty f(a)[M + E + I + R]da,$$
$$S(0,t) = \int_0^\infty f(a)Sda,$$

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 (3.3.5) 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 (3.4.1) are

$$\begin{aligned}
\partial m/\partial a + \partial m/\partial t &= -\delta m,\\
\partial s/\partial a + \partial s/\partial t &= \delta m - \lambda(a,t)s,\\
\text{with } \lambda(a,t) &= b(a)\int_0^\infty \tilde{b}(\tilde{a})i(\tilde{a},t)\rho e^{-D(\tilde{a})-q\tilde{a}}d\tilde{a},\\
\partial e/\partial a + \partial e/\partial t &= \lambda(a,t)s - \varepsilon e,\\
\partial i/\partial a + \partial i/\partial t &= \varepsilon e - \gamma i,\\
\partial r/\partial a + \partial r/\partial t &= \gamma i,
\end{aligned} \tag{3.4.2}$$

and the boundary conditions at age 0 are zero except for

$$\begin{aligned}
m(0,t) &= \int_0^\infty f(a)[1 - s(a,t)]e^{-D(a)-qa}da,\\
s(0,t) &= \int_0^\infty f(a)s(a,t)e^{-D(a)-qa}da,
\end{aligned} \tag{3.4.3}$$

where $m(0,t) + s(0,t) = 1$ by (3.3.3).

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 (3.4.2) with the time derivatives

set equal to zero. The steady state solutions $m(a)$, $s(a)$, $e(a)$, and $i(a)$ are

$$\begin{aligned}
m(a) &= (1-s_0)e^{-\delta a},\\
s(a) &= e^{-\Lambda(a)}\left[s_0+\delta(1-s_0)\int_0^a e^{-\delta x+\Lambda(x)}dx\right],\\
e(a) &= e^{-\varepsilon a}\int_0^a \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dy,\\
i(a) &= e^{-\gamma a}\int_0^a \varepsilon e^{(\gamma-\varepsilon)z}\\
&\quad\times\int_0^z \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dydz,
\end{aligned}\tag{3.4.4}$$

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.

3.4.2. *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 (3.4.4) into the expression for λ in (3.4.2) yields

$$\begin{aligned}
\lambda(a) &= b(a)\int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}}\int_0^{\tilde{a}}\varepsilon e^{(\gamma-\varepsilon)z}\\
&\quad\times\int_0^z \lambda(y)e^{\varepsilon y-\Lambda(y)}\left[s_0+\delta(1-s_0)\int_0^y e^{-\delta x+\Lambda(x)}dx\right]dydzd\tilde{a}.
\end{aligned}\tag{3.4.5}$$

Using the definition of s_0 and (3.4.4), we find that

$$s_0 = s_0F_\lambda+\delta(1-s_0)F_*,\tag{3.4.6}$$

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

$$F_* = \int_0^\infty f(a)e^{-\Lambda(a)-D(a)-qa}\int_0^a e^{-\delta x+\Lambda(x)}dxda.\tag{3.4.7}$$

Substituting the solution s_0 in (3.4.6) into (3.4.5) and cancelling $\lambda(a)=kb(a)$ yields

$$\begin{aligned}
1 &= \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}}\int_0^{\tilde{a}}\varepsilon e^{(\gamma-\varepsilon)z}\int_0^z b(y)e^{\varepsilon y}\left[\delta F_* e^{-k\int_0^y b(\alpha)d\alpha}\right.\\
&\quad\left.+\delta(1-F_\lambda)\int_0^y e^{-\delta x-k\int_x^y b(\alpha)d\alpha}dx\right]\Big/(\delta F_*+1-F_\lambda)dydzd\tilde{a}.
\end{aligned}\tag{3.4.8}$$

The right side of this equation can be shown to be a decreasing function of k, so that (3.4.8) 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 equation (3.4.8):

$$R_0 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}} \int_0^{\tilde{a}} \varepsilon e^{(\gamma-\varepsilon)z} \int_0^z b(y)e^{\varepsilon y} dy dz d\tilde{a}. \qquad (3.4.9)$$

Note that $R_0 > 1$ implies that (3.4.8) 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 (3.4.4). This expression (3.4.9) 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 [13], but we can construct a Liapunov function to show the global stability of the disease-free steady state when $R_0 \leq 1$. The feasible set for (3.4.2) 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

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

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

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

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 (3.4.9) after changing the order of integration. Thus

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

Hence solutions of (3.4.2) 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 (3.4.1) 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 [50] or Corollary 18.5 in [1] (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 (3.4.2) is uniformly persistent when $R_0 > 1$, as for the ordinary differential equation models in the basic SIR and MSEIR endemic models in Chapter 1, but the assumption of a finite maximum age seems to be necessary to satisfy the condition in Theorem 4.6 in [57] 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 [7] and when $\tilde{b}(\tilde{a})$ is concentrated at a certain age while $b(a)$ is constant [56]. 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 [33]. 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 [14, 43].

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 (3.4.9) for R_0 also works for the MSEIRS, SEIR, SEIRS, and SEIS models, but the equations (3.4.8) 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 (3.4.8) 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

$$1 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}} \int_0^{\tilde{a}} b(y)e^{\gamma y - k\int_0^y b(\alpha)d\alpha} dy d\tilde{a} \tag{3.4.10}$$

and a basic reproduction number given by

$$R_0 = \int_0^\infty \tilde{b}(\tilde{a})\rho e^{-D(\tilde{a})-q\tilde{a}-\gamma\tilde{a}} \int_0^{\tilde{a}} b(y)e^{\gamma y} dy d\tilde{a}. \tag{3.4.11}$$

This expression is similar to previous R_0 expressions for SIR models with constant population size [13, 18]. The expression (3.4.11) 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.

3.4.3. *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 that 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 (3.4.4). Hence the expected age A for leaving the susceptible class is

$$\begin{aligned} A &= E[a] \\ &= \frac{\int_0^\infty a\lambda(a)e^{-D(a)}[\delta F_* e^{-\Lambda(a)} + \delta(1-F_\lambda)\int_0^a e^{-\delta x-\Lambda(a)+\Lambda(x)}dx]da}{\int_0^\infty \lambda(a)e^{-D(a)}[\delta F_* e^{-\Lambda(a)} + \delta(1-F_\lambda)\int_0^a e^{-\delta x-\Lambda(a)+\Lambda(x)}dx]da}. \end{aligned} \tag{3.4.12}$$

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

$$A = E[a] = \frac{\int_0^\infty a\lambda(a)e^{-\Lambda(a)-D(a)}da}{\int_0^\infty \lambda(a)e^{-\Lambda(a)-D(a)}da}. \tag{3.4.13}$$

3.4.4. *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 (3.3.5) 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 (3.4.9) defining the basic reproduction number becomes

$$R_0 = \beta\varepsilon/[(\gamma+d+q)(\varepsilon+d+q)], \tag{3.4.14}$$

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

With the assumptions above, λ is a constant and the equation (3.4.5) for λ becomes

$$1 = \frac{(d+q)R_0}{\lambda+d+q}\left[s_0 + \frac{\delta(1-s_0)}{\delta+d+q}\right]. \tag{3.4.15}$$

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 (3.4.4), we find that $R_0\bar{s} = 1$ is equivalent to the equation (3.4.15). Thus the infective replacement number $R_0\bar{s}$ is one at the endemic equilibrium for this model. This is not generally 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 (3.4.4), we find that

$$s_0 = \frac{\delta-\lambda s_0}{\delta-\lambda}F_\lambda - \frac{\delta(1-s_0)}{\delta-\lambda}F_\delta, \tag{3.4.16}$$

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 (3.4.7) is equal to $(F_\lambda - F_\delta)/(\delta-\lambda)$, so that (3.4.6) is equivalent to (3.4.16). Here the equations (3.4.15) and (3.4.16) are two simultaneous equations in the unknowns R_0, s_0, and λ. One can solve (3.4.16) for s_0 to obtain

$$s_0 = \delta(F_\lambda - F_\delta)/[\delta(1-F_\delta) - \lambda(1-F_\lambda)]. \tag{3.4.17}$$

The right side of (3.4.17) is a decreasing function of λ with $F_\lambda = 1$ and $s_0 = 1$ at $\lambda = 0$. Substituting (3.4.17) into (3.4.15) yields the equation

corresponding to equation (3.4.8) given by

$$1 = \frac{R_0(d+q)\delta\left[F_\lambda - F_\delta + \dfrac{(\delta-\lambda)(1-F_\lambda)}{\delta+d+q}\right]}{(\lambda+d+q)[\delta(1-F_\delta)-\lambda(1-F_\lambda)]}, \tag{3.4.18}$$

which relates R_0 and λ. Because the right side of (3.4.18) is a decreasing function of λ that goes from R_0 at $\lambda = 0$ to zero as $\lambda \to \infty$, the equation (3.4.18) has a positive solution λ if and only if $R_0 > 1$. If $d(a) = d$ and $f(a) = b = d + q$, then equation (3.4.18) reduces to a simple equation for λ in an ordinary differential equations MSEIR model ([36], p. 620). When $R_0 \leq 1$, solutions of (3.4.2) approach the disease-free steady state (3.4.4) with $\lambda = 0$, and for fixed $R_0 > 1$, we expect solutions to approach the endemic steady state (3.4.4) with the constant λ determined by solving either (3.4.18) or the combination of (3.4.15) and (3.4.16).

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 $\lambda s(a) d e^{-da}$, where $s(a)$ is given in (3.4.4). Here the equation for the expected age A for leaving the susceptible class is

$$\begin{aligned} A = E[a] &= \frac{\lambda d \int_0^\infty a[c_1 e^{-(\lambda+d)a} + c_2 e^{-(\delta+d)a}]da}{\lambda d \int_0^\infty [c_1 e^{-(\lambda+d)a} + c_2 e^{-(\delta+d)a}]da} \\ &= \frac{\dfrac{\delta-\lambda s_0}{(\lambda+d)^2} - \dfrac{\delta(1-s_0)}{(\delta+d)^2}}{\dfrac{\delta-\lambda s_0}{(\lambda+d)} - \dfrac{\delta(1-s_0)}{(\delta+d)}}. \end{aligned} \tag{3.4.19}$$

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 (3.4.14). 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 [34]. By not including the death factor e^{-da} when considering the rate

of leaving the susceptible class, one obtains the widely-cited approximate formula $R_0 \approx 1 + L/A$ for the SEIR and SIR models [16]. 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 [4] (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

$$R_0 = \frac{[q + 1/(A-p)](1+pq)}{(q+1/L)(1-p/L)}. \tag{3.4.20}$$

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 naively 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 [4] (p. 79, p. 658), [31], but our careful analysis here shows that this naive formula does not work. Of course, when $q = 0$ and $p = 0$, the expression (3.4.20) reduces to the previous expression $R_0 = L/A$ for the SEIR model with constant population size.

3.4.5. *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 3.6. 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 (3.4.2) 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

$$1 = \frac{R_0(d+q)}{\lambda+d+q}\left[s_0 + \frac{\delta(1-s_0)}{\delta+d+q} - g[c_1 e^{-(\lambda+d+q)A_v} + c_2 e^{-(\delta+d+q)A_v}]\right], \tag{3.4.21}$$

where $c_1 = (\delta - \lambda s_0)/(\delta - \lambda)$ and $c_2 = -\delta(1-s_0)/(\delta-\lambda)$. Note that equation (3.4.21) reduces to (3.4.15) when $g = 0$. The analog here of (3.4.16) is

$$s_0 = c_1 F_\lambda + c_2 F_\delta - g\left[c_1 + c_2 e^{(\lambda-\delta)A_v}\right] F_{A_v}, \tag{3.4.22}$$

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 (3.4.21) and (3.4.22) are two simultaneous equations in the unknowns R_0, s_0, and λ. It is possible to solve (3.4.22) for s_0 and then substitute into (3.4.21), but we do not present the resulting, rather complicated expression, which relates R_0 and λ. For an SEIR and SIR models, $s_0 = 1$, so that (3.4.21) reduces to

$$1 = \frac{R_0(d+q)}{\lambda+d+q}\left[1 - g e^{-(\lambda+d+q)A_v}\right]. \tag{3.4.23}$$

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 $s_0 \to 1$, equation (3.4.21) for the MSEIR model reduces to $\lambda = (d+q)(R_0[1 - g e^{-(\lambda+d+q)A_v}] - 1)$, 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

$$ge^{-(d+q)A_v} \geq 1 - 1/R_0, \tag{3.4.24}$$

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 [30].

If the condition (3.4.24) is satisfied, then we expect solutions of (3.4.2) 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 (3.4.21) and (3.4.22).

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

$$A = \frac{1}{\lambda + d} - \frac{gA_v[c_1e^{-(\lambda+d)A_v} + c_2e^{-(\delta+d)A_v}] + c_2\frac{\delta-\lambda}{(\delta+d)^2}}{c_1[1 - ge^{-(\lambda+d)A_v}] + c_2[\frac{\lambda+d}{\delta+d} - ge^{-(\delta+d)A_v}]}.$$

The analogous expression for an SEIR or SIR model has $c_2 = 0$. The negative signs in the expression for A makes 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.

3.4.6. *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 (3.3.5). 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 (3.4.9) is

$$R_0 = \frac{\beta}{\gamma}\left[1 + \frac{\gamma}{\varepsilon - \gamma}\frac{1 - e^{-\varepsilon L}}{\varepsilon L} - \frac{\varepsilon}{(\varepsilon - \gamma)}\frac{1 - e^{-\gamma L}}{\gamma L}\right]. \tag{3.4.25}$$

An epidemiological interpretation is that the right side of (3.4.25) except for the contact rate β is the average infectious period. For the SEIR model the equation (3.4.8) for the constant λ at the endemic steady state age distribution becomes

$$1 = \beta\varepsilon \left[\frac{1 - e^{-\lambda L}}{(\gamma - \lambda)(\varepsilon - \lambda)\lambda L} + \frac{1 - e^{-\varepsilon L}}{(\varepsilon - \lambda)(\varepsilon - \gamma)\varepsilon L} - \frac{1 - e^{-\gamma L}}{(\gamma - \lambda)(\varepsilon - \gamma)\gamma L} \right]. \tag{3.4.26}$$

For the MSEIR model the integrals in the equation (3.4.8) 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 (3.4.25), 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 (3.4.11) is given by

$$R_0 = \frac{\beta}{\gamma} \left[1 - \frac{1 - e^{-\gamma L}}{\gamma L} \right], \tag{3.4.27}$$

and the equation (3.4.10) for the constant λ at the endemic steady state age distribution is

$$1 = \frac{\beta}{\gamma - \lambda} \left[\frac{1 - e^{-\lambda L}}{\lambda L} - \frac{1 - e^{-\gamma L}}{\gamma L} \right]. \tag{3.4.28}$$

These expressions can also be found heuristically by letting $\varepsilon \to \infty$ in (3.4.25) and (3.4.26), so that the exposed class E disappears.

For the SEIR and SIR models equation (3.4.13) for the average age of attack becomes

$$A = \frac{1}{\lambda} - \frac{Le^{-\lambda L}}{1 - e^{-\lambda L}}. \tag{3.4.29}$$

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

$$\bar{s} = \int_0^L \frac{e^{-\lambda a}}{L} da = \frac{1 - e^{-\lambda L}}{\lambda L}. \tag{3.4.30}$$

It is easy to see from (3.4.25) and (3.4.27) 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 (3.4.25) and (3.4.27), $1 = \beta(1-e^{-\lambda L})/\gamma\lambda L$ from (3.4.26) and (3.4.28), and $A \approx 1/\lambda$ from (3.4.29). 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 ([4], Ch. 4, App. A) are either correct or reasonable approximations.

3.5. 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 1, but there is no class M for passively immune infants. In Sections 3.6 and 3.7 we estimate the basic reproduction number in models with age groups for measles in Niger and pertussis in the United States.

3.5.1. *Formulation of the SEIR model with age groups*

The SEIR model uses the same notation as the MSEIR model. The initial-boundary value problem for this model is given below.

$$\begin{aligned}
\partial S/\partial a + \partial S/\partial t &= -\lambda(a,t)S - d(a)S,\\
\lambda(a,t) &= \int_0^\infty b(a)\tilde{b}(\tilde{a})I(\tilde{a},t)d\tilde{a} \Big/ \int_0^\infty U(\tilde{a},t)d\tilde{a}\ ,\\
\partial E/\partial a + \partial E/\partial t &= \lambda(a,t)S - \varepsilon I - d(a)E,\\
\partial I/\partial a + \partial I/\partial t &= \varepsilon I - \gamma I - d(a)I,\\
\partial R/\partial a + \partial R/\partial t &= \gamma I - d(a)R.
\end{aligned} \tag{3.5.1}$$

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 with age groups. 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 (3.5.1) 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 $s_i'(t) = S_i'(t)/e^{qt} - qs_i$, etc., so that the differential equations for these fractions are

$$\begin{aligned}
ds_1/dt &= (c_1 + d_1 + q)P_1 - [\lambda_1 + c_1 + d_1 + q]s_1, \\
ds_i/dt &= c_{i-1}s_{i-1} - [\lambda_i + c_i + d_i + q]s_i, \qquad i \geq 2, \\
\lambda_i &= b_i \textstyle\sum_{j=1}^{n} \tilde{b}_j i_j, \\
de_1/dt &= \lambda_1 s_1 - [\varepsilon_1 + c_1 + d_1 + q]e_1, \\
de_i/dt &= \lambda_i s_i + c_{i-1}e_{i-1} - [\varepsilon_i + c_i + d_i + q]e_i, \qquad i \geq 2, \\
di_1/dt &= \varepsilon_1 e_1 - [\gamma_1 + c_1 + d_1 + q]i_1, \\
di_i/dt &= \varepsilon_i e_i + c_{i-1}i_{i-1} - [\gamma_i + c_i + d_i + q]i_i, \qquad i \geq 2, \\
dr_1/dt &= \gamma_1 i_1 - [c_1 + d_1 + q]r_1, \\
dr_i/dt &= \gamma_i i_i + c_{i-1}r_{i-1} - [c_i + d_i + q]r_i, \qquad i \geq 2.
\end{aligned} \tag{3.5.2}$$

3.5.2. *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 (3.5.2) is the equilibrium with

$$\begin{aligned}
&s_1 = \hat{c}_1 P_1/\hat{\lambda}_1, \quad s_i = c_{i-1}s_{i-1}/\hat{\lambda}_i, && \text{for } i \geq 2, \\
&e_1 = \lambda_1 s_1/\hat{\varepsilon}_1, \quad e_i = (\lambda_i s_i + c_{i-1}e_{i-1})/\hat{\varepsilon}_i, && \text{for } i \geq 2, \\
&i_1 = \varepsilon_1 e_1/\hat{\gamma}_1, \quad i_i = (\varepsilon_i e_i + c_{i-1}i_{i-1})/\hat{\gamma}_i, && \text{for } i \geq 2,
\end{aligned} \tag{3.5.3}$$

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 (3.5.3) to

obtain $e_1 = \lambda_1\hat{c}_1P_1/(\hat{\varepsilon}_1\hat{\lambda}_1)$, 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 (3.5.3), we obtain $i_1 = \varepsilon_1\lambda_1\hat{c}_1P_1/(\hat{\gamma}_1\hat{\varepsilon}_1\hat{\lambda}_1)$, and for $i \geq 2$,

$$\begin{aligned}\frac{i_i}{C_{i-1}} &= \frac{\varepsilon_i}{\hat{\gamma}_i}\left(\frac{\lambda_i}{\hat{\varepsilon}_i\hat{\lambda}_i\cdots\hat{\lambda}_1} + \frac{\lambda_{i-1}}{\hat{\varepsilon}_i\hat{\varepsilon}_{i-1}\hat{\lambda}_{i-1}\cdots\hat{\lambda}_1} + \cdots + \frac{\lambda_1}{\hat{\varepsilon}_i\cdots\hat{\varepsilon}_1\hat{\lambda}_1}\right)\\ &+ \frac{\varepsilon_{i-1}}{\hat{\gamma}_i\hat{\gamma}_{i-1}}\left(\frac{\lambda_{i-1}}{\hat{\varepsilon}_{i-1}\hat{\lambda}_{i-1}\cdots\hat{\lambda}_1} + \frac{\lambda_{i-2}}{\hat{\varepsilon}_{i-1}\hat{\varepsilon}_{i-2}\hat{\lambda}_{i-2}\cdots\hat{\lambda}_1} + \cdots + \frac{\lambda_1}{\hat{\varepsilon}_{i-1}\cdots\hat{\varepsilon}_1\hat{\lambda}_1}\right)\\ &\quad + \cdots + \frac{\varepsilon_2}{\hat{\gamma}_i\cdots\hat{\gamma}_2}\left(\frac{\lambda_2}{\hat{\varepsilon}_2\hat{\lambda}_2\hat{\lambda}_1} + \frac{\lambda_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{\lambda}_1}\right) + \frac{\varepsilon_1}{\hat{\gamma}_i\cdots\hat{\gamma}_1}\left(\frac{\lambda_1}{\hat{\varepsilon}_1\hat{\lambda}_1}\right). \quad (3.5.4)\end{aligned}$$

From (3.5.2), 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

$$\begin{aligned}1 = \sum_{j=1}^{n}\tilde{b}_j C_{j-1}&\left[\frac{\varepsilon_j}{\hat{\gamma}_j}\left(\frac{b_j}{\hat{\varepsilon}_j\hat{b}_j\cdots\hat{b}_1} + \frac{b_{j-1}}{\hat{\varepsilon}_j\hat{\varepsilon}_{j-1}\hat{b}_{j-1}\cdots\hat{b}_1} + \cdots + \frac{b_1}{\hat{\varepsilon}_j\cdots\hat{\varepsilon}_1\hat{b}_1}\right)\right.\\ &+ \frac{\varepsilon_{j-1}}{\hat{\gamma}_j\hat{\gamma}_{j-1}}\left(\frac{b_{j-1}}{\hat{\varepsilon}_{j-1}\hat{b}_{j-1}\cdots\hat{b}_1} + \frac{b_{j-2}}{\hat{\varepsilon}_{j-1}\hat{\varepsilon}_{j-2}\hat{b}_{j-2}\cdots\hat{b}_1} + \cdots + \frac{b_1}{\hat{\varepsilon}_{j-1}\cdots\hat{\varepsilon}_1\hat{b}_1}\right)\\ &\quad\left. + \cdots + \frac{\varepsilon_2}{\hat{\gamma}_j\cdots\hat{\gamma}_2}\left(\frac{b_2}{\hat{\varepsilon}_2\hat{b}_2\hat{b}_1} + \frac{b_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{b}_1}\right) + \frac{\varepsilon_1}{\hat{\gamma}_j\cdots\hat{\gamma}_1}\left(\frac{b_1}{\hat{\varepsilon}_1\hat{b}_1}\right)\right], \quad (3.5.5)\end{aligned}$$

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

The right side of (3.5.5) 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 below defined by setting $k = 0$ in (3.5.5).

$$\begin{aligned}R_0 = \sum_{j=1}^{n}\tilde{b}_j C_{j-1}&\left[\frac{\varepsilon_j}{\hat{\gamma}_j}\left(\frac{b_j}{\hat{\varepsilon}_j\hat{c}_j\cdots\hat{c}_1} + \frac{b_{j-1}}{\hat{\varepsilon}_j\hat{\varepsilon}_{j-1}\hat{c}_{j-1}\cdots\hat{c}_1} + \cdots + \frac{b_1}{\hat{\varepsilon}_j\cdots\hat{\varepsilon}_1\hat{c}_1}\right)\right.\\ &+ \frac{\varepsilon_{j-1}}{\hat{\gamma}_j\hat{\gamma}_{j-1}}\left(\frac{b_{j-1}}{\hat{\varepsilon}_{j-1}\hat{c}_{j-1}\cdots\hat{c}_1} + \frac{b_{j-2}}{\hat{\varepsilon}_{j-1}\hat{\varepsilon}_{j-2}\hat{c}_{j-2}\cdots\hat{c}_1} + \cdots + \frac{b_1}{\hat{\varepsilon}_{j-1}\cdots\hat{\varepsilon}_1\hat{c}_1}\right)\\ &\quad\left. + \cdots + \frac{\varepsilon_2}{\hat{\gamma}_j\cdots\hat{\gamma}_2}\left(\frac{b_2}{\hat{\varepsilon}_2\hat{c}_2\hat{c}_1} + \frac{b_1}{\hat{\varepsilon}_2\hat{\varepsilon}_1\hat{c}_1}\right) + \frac{\varepsilon_1}{\hat{\gamma}_j\cdots\hat{\gamma}_1}\left(\frac{b_1}{\hat{\varepsilon}_1\hat{c}_1}\right)\right], \quad (3.5.6)\end{aligned}$$

where $\hat{c}_i = c_i + d_i + q$. The expression (3.5.6) for R_0 is the discrete age group analog of the triple integral expression (3.4.9) of R_0 for the SEIR model

with continuous age. As for the continuous age model, the expression (3.5.6) 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 (3.5.5) 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 equation (3.5.5) has a solution with a positive k that gives the forces of infection $\lambda_i = kb_i$, which in turn give the unique endemic equilibrium in the age groups from (3.5.3). 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 $s_i \leq P_i$, we obtain $\dot{V} \leq (R_0 - 1)\sum \tilde{b}_j i_j \leq 0$ if $R_0 \leq 1$. 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 ([25], p. 296). Thus if $R_0 \leq 1$, 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 (3.5.2) can be defined to be uniformly persistent if $\liminf_{t\to\infty} i_j(t) \geq c$ 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 [57] imply that the

system (3.5.2) is uniformly persistent if $R_0 > 1$. The endemic equilibrium (3.5.3) 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

$$1 = \sum_{j=1}^{n} \tilde{b}_j C_{j-1} \left[\frac{b_j}{\hat{\gamma}_j \hat{b}_j \cdots \hat{b}_1} + \frac{b_{j-1}}{\hat{\gamma}_j \hat{\gamma}_{j-1} \hat{b}_{j-1} \cdots \hat{b}_1} + \cdots + \frac{b_2}{\hat{\gamma}_j \cdots \hat{\gamma}_2 \hat{b}_2 \hat{b}_1} + \frac{b_1}{\hat{\gamma}_j \cdots \hat{\gamma}_1 \hat{b}_1} \right], \quad (3.5.7)$$

and the equation for the basic reproduction number is

$$R_0 = \sum_{j=1}^{n} \tilde{b}_j C_{j-1} \left[\frac{b_j}{\hat{\gamma}_j \hat{c}_j \cdots \hat{c}_1} + \frac{b_{j-1}}{\hat{\gamma}_j \hat{\gamma}_{j-1} \hat{c}_{j-1} \cdots \hat{c}_1} + \cdots + \frac{b_2}{\hat{\gamma}_j \cdots \hat{\gamma}_2 \hat{c}_2 \hat{c}_1} + \frac{b_1}{\hat{\gamma}_j \cdots \hat{\gamma}_1 \hat{c}_1} \right]. \quad (3.5.8)$$

These equations can be also derived heuristically from those for the SEIR model by letting $\varepsilon_i \to \infty$ for every i. The R_0 formula (3.5.8) 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.

3.5.3. *Expressions for the average age of infection A*

From Section 3.4.3 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 model with age groups.

$$A = \frac{\sum_{i=1}^n b_i s_i \pi_{i-1}[1 + d_i a_{i-1} - (1 + d_i a_i)e^{-d_i\Delta_i}]/d_i^2}{\sum_{i=1}^n b_i s_i \pi_{i-1}[1 - e^{-d_i\Delta_i}]/d_i}. \quad (3.5.9)$$

3.6. Application to measles in Niger

A deterministic mathematical model has been developed for the study of the effects of heterogeneous mixing and vaccination distribution on disease transmission in Africa [44]. 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 [44]. The fertility rates and the death rates in the 16 age groups are obtained from Niger census data. Using the Lotka equation (3.3.12) 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 [44]. A computer calculation using the demographic and epidemiological parameter values in the formula (3.5.6) for the basic reproduction number yields $R_0 = 18.83$. The average age of infection at the endemic equilibrium found from (3.5.9) is $A = 2.4$ years.

We now consider two methods for finding approximations to R_0, A, and the replacement number R_{end} at the endemic equilibrium. The first method finds approximate values during the computer simulations of the MSEIR measles model. Recall that the replacement number R is the actual number of new cases per infective during the infectious period. At the endemic equilibrium in the basic SIR endemic model, the replacement number R_{end} would be the incidence divided by the quotient of the prevalence and the duration. For this MSEIR model with age groups, R_{end} can be approximated by computing the sum over all age groups of the daily incidence divided by the sum over all age groups of the quotients of the prevalences and the product of the average infectious periods times the fractions surviving the latent periods, so that

$$R_{\text{end}} \cong \frac{\sum_{j=1}^{16} \lambda_j s_j P_j}{\sum_{j=1}^{16} i_j P_j \Big/ \left[\left(\dfrac{1}{\gamma_j + d_j + q}\right)\left(\dfrac{\varepsilon_j}{\varepsilon_j + d_j + q}\right)\right]}. \tag{3.6.1}$$

At the prevaccination endemic equilibrium, this approximation is computed to be $R_{\text{end}} \cong 0.99988$, which is consistent with the concept that the average replacement number is equal to one 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 sum of the daily incidences when all contacts are assumed to be with susceptibles divided by the sum over all age groups of the quotients of the prevalences and the product of the average infectious periods times the fractions surviving the latent periods. When all of the s_j in the numerator in equation (3.6.1) for the replacement number R_{end} are replaced by 1, then we obtain the expression for the contact number σ given by

$$R_0 = \sigma \cong \frac{\sum_{j=1}^{16} \lambda_j P_j}{\sum_{j=1}^{16} i_j P_j \Big/ \left[\left(\frac{1}{\gamma_j + d_j + q}\right)\left(\frac{\varepsilon_j}{\varepsilon_j + d_j + q}\right)\right]}.$$

At the prevaccination endemic equilibrium, this yields $R_0 \cong 18.85$, which is very close to the formula value of 18.83. Note that the expressions for R_0 and R_{end} given here are slightly different from those given in [36]; based on calculations for several pertussis models, the expressions given here are the correct ones.

The average age of infection can be crudely 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 endemic model in Chapter 1, where the model 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 [44]. 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 (3.3.12), 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_{end} is 1 at the endemic equilibrium for this model. Using the values of $d+q$, δ, and λ, the equations (3.4.15) and (3.4.16) can be solved iteratively to obtain a basic reproduction number of $R_0 = 17.4$ and an 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 $s_0 \to 0$, equation (3.4.15) 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 (3.4.12) 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 (3.4.24), 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.

3.7. Application to pertussis in the United States

Previous estimates ([4], p. 70) of 10 to 18 for R_0 for pertussis (whooping cough) are based on the formula $R_0 \approx 1 + L/A$, which is derived in Chapter 1 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 [34, 35], there are 32 age groups. Using fertilities and death rates from United States census information for 1990, the value of q in (3.3.12) 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 [34].

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 [34, 35], the epidemiological classes include a susceptible class S, an infective class I, a class R_4 of those removed people with very high immunity, classes R_3, R_2, and R_1 for those with decreasing immunity. In the two pertussis models, there are 3 or 4 levels of infectivity and 32 age groups, so that not all infectives are equally effective in creating new infectives [35]. 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 one. 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 (3.5.8) for R_0 works for the pertussis models, the formula (3.5.7) 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 [34]. 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 (3.5.8) 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 [34, 35] and 3.7 for the second pertussis model in [35]. 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 4 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 work for the pertussis models. The replacement number R at the pertussis endemic equilibrium depends on the fractions infected in all of the 3 or 4 infective classes. For example, in the first pertussis model

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

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 one, which corresponds to assuming that all contacts are with susceptibles, then we obtain the contact number

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

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, have achieved herd immunity in the pertussis computer simulations [34, 35].

3.8. Discussion

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 [8, 46]. Modern mathematical analysis of age structured models appears to have started with Hoppensteadt [40], 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 [18]. In age-structured epidemiology models, proportionate and preferred mixing parameters can be estimated from age-specific force of infection data [33]. 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 [9, 10, 19], age dependent disease transmission [5, 16, 24, 56], infection class age [55, 61], cross immunity [13], intercohort transmission [11, 12, 14, 42, 43], short infectious period [6, 7], and optimal vaccination patterns [21, 22, 27, 45, 51, 53].

Age structured models have been used in the epidemiology modeling of many diseases [4]. Dietz [16, 17], Hethcote [30], Anderson and May [2, 3], and Rouderfer, Becker, and Hethcote [52] used continuous age structured models for the evaluation of measles and rubella vaccination strategies. Tudor [58] found threshold conditions for a measles model with age groups. Hethcote [31] considered optimal ages of vaccination for measles on three continents. Halloran, Cochi, Lieu, Wharton, and Fehrs [26], Ferguson, Anderson, and Garnett [20], and Schuette and Hethcote [54] used age-structured models to study the effects of varicella (chickenpox) vaccination programs. Grenfell and Anderson [23] and Hethcote [34, 35, 37, 59] have used age-structured models in evaluating pertussis (whooping cough) vaccination programs.

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 (3.4.9) and (3.5.6) 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 (3.4.11) and (3.5.8). 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 (3.5.6) 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 [34, 35], the basic reproduction numbers are estimated 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 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 susceptible. 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 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

[38]. For the pertussis model with four removed groups in [38], the three infective classes with decreasing infectivity are I, I_m,and I_w, where the infective classes I_m and $I_w$are non-empty 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 one. As pointed out in Section 3.2 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.

References

1. H. Amann, Ordinary Differential Equations, Walter de Gruyter, Berlin, 1990.
2. R. M. Anderson and R. M. May, Vaccination against rubella and measles: Quantitative investigations of different policies, J. Hyg. Camb., 90 (1983), pp. 259–325.
3. ———, Age related changes in the rate of disease transmission: Implication for the design of vaccination programs, J. Hyg. Camb., 94 (1985), pp. 365–436.
4. ———, Infectious Diseases of Humans: Dynamics and Control, Oxford University Press, Oxford, 1991.
5. V. Andreasen, Disease regulation of age-structured host populations, Theoret. Population Biol., 36 (1989), pp. 214–239.
6. ———, The effect of age-dependent host mortality on the dynamics of an endemic disease, Math. Biosci., 114 (1993), pp. 29–58.
7. ———, 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, Ltd., Winnipeg, 1995, pp. 3–14.
8. 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.
9. S. Busenberg and K. L. Cooke, Vertically Transmitted Diseases, vol. 23 of Biomathematics, Springer-Verlag, Berlin, 1993.
10. 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.
11. S. N. Busenberg and K. P. Hadeler, Demography and epidemics, Math. Biosci., 101 (1990), pp. 41–62.
12. 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.

13. 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.
14. 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.
15. 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, 1995, pp. 84–94.
16. K. Dietz, Transmission and control of arbovirus diseases, in Epidemiology, K. L. Cooke, ed., SIAM, Philadelphia, 1975, pp. 104–121.
17. ———, 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.
18. K. Dietz and D. Schenzle, Proportionate mixing models for age-dependent infection transmission, J. Math. Biol., 22 (1985), pp. 117–120.
19. M. El-Doma, Analysis of nonlinear integro-differential equations arising in age-dependent epidemic models, Nonlinear Anal., 11 (1987), pp. 913–937.
20. 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.
21. D. Greenhalgh, Analytical threshold and stability results on age-structured epidemic models with vaccination, Theoret. Population Biol., 33 (1988), pp. 266–290.
22. ———, Vaccination campaigns for common childhood diseases, Math. Biosci., 100 (1990), pp. 201–240.
23. 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.
24. G. Gripenberg, On a nonlinear integral equation modelling an epidemic in an age-structured population, J. Reine Angew. Math., 341 (1983), pp. 147–158.
25. J. K. Hale, Ordinary Differential Equations, Wiley-Interscience, New York, 1969.
26. 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.
27. 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.
28. H. W. Hethcote, Qualitative analyses of communicable disease models, Math. Biosci., 28 (1976), pp. 335–356.
29. ———, An immunization model for a heterogeneous population, Theoret. Population Biol., 14 (1978), pp. 338–349.

30. ———, Measles and rubella in the United States, Am. J. Epidemiol., 117 (1983), pp. 2–13.
31. ———, Optimal ages of vaccination for measles, Math. Biosci., 89 (1988), pp. 29–52.
32. ———, A thousand and one epidemic models, in Frontiers in Theoretical Biology, S. A. Levin, ed., vol. 100 of Lecture Notes in Biomathematics, Springer-Verlag, Berlin, 1994, pp. 504–515.
33. ———, 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, 1996, pp. 215–238.
34. ———, An age-structured model for pertussis transmission, Math. Biosci., 145 (1997), pp. 89–136.
35. ———, Simulations of pertussis epidemiology in the United States: Effects of adult booster vaccinations, Math. Biosci., 158 (1999), pp. 47–73.
36. ———, The Mathematics of Infectious Diseases, SIAM Review 42 (2000) 599–653.
37. H. W. Hethcote, P. Horby, and P. McIntyre, Using computer simulations to compare pertussis vaccination strategies in Australia, Vaccine 22 (2004) 2181-2191.
38. H. W. Hethcote, Y. Li, and Z. J. Jing, Hopf bifurcation in models for pertussis epidemiology, Math. Comput. Modelling, 30 (1999), pp. 29–45.
39. 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.
40. F. Hoppensteadt, Mathematical Theories of Populations: Demographics, Genetics and Epidemics, SIAM, Philadelphia, 1975.
41. M. Iannelli, Mathematical Theory of Age-Structured Population Dynamics, vol. 7 of C.N.R. Applied Mathematics Monograph, Giardini Editori, Pisa, 1994.
42. 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.
43. H. Inaba, Threshold and stability results for an age-structured epidemic model, J. Math. Biol., 28 (1990), pp. 411–434.
44. A. V. Kaninda, S. Richardson, and H. W. Hethcote, Influence of heterogeneous mixing on measles transmission in an African context. Preprint, 2000.
45. W. Katzmann and K. Dietz, Evaluation of age-specific vaccination strategies, Theoret. Population Biol., 25 (1984), pp. 125–137.
46. 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.
47. A. J. Lotka, The stability of the normal age distribution, Proc. Nat. Acad. Sci. U.S.A., 8 (1922), pp. 339–345.
48. A. G. McKendrick, Applications of mathematics to medical problems, Proc. Edinburgh Math. Soc., 44 (1926), pp. 98–130.

49. 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.
50. K. Mischaikow, H. Smith and H. R. Thieme, Asymptotically autonomous semiflows: chain recurrence and Lyapunov functions, Trans. A. M. S., 53 (1993), pp. 1447-1479.
51. J. Muller, Optimal vaccination patterns in age-structured populations, SIAM J. Appl. Math., 59 (1998), pp. 222–241.
52. V. Rouderfer, N. Becker, and H. W. Hethcote, Waning immunity and its effects on vaccination schedules, Math. Biosci., 124 (1994), pp. 59–82.
53. V. Rouderfer and N. Becker, Assessment of two-dose vaccination schedules: Availability for vaccination and catch-up, Math. Biosci., 129 (1995), pp. 41–66.
54. 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.
55. 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.
56. ———, 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., vol. 92 of Lecture Notes in Biomathematics, Springer-Verlag, Berlin, 1991, pp. 139-158.
57. ———, Persistence under relaxed point-dissipativity (with an application to an endemic model), SIAM J. Math. Anal., 24 (1993), pp. 407–435.
58. D. W. Tudor, An age-dependent epidemic model with application to measles, Math. Biosci., 73 (1985), pp. 131–147.
59. A. Van Rie and H. W. Hethcote, Adolescent and adult pertussis vaccination: Computer simulations of five new strategies, Vaccine 22 (2004) 3154-3165.
60. H. von Foerster, The Kinetics of Cellular Proliferation, Grune and Stratton, New York, 1959.
61. G. F. Webb, Theory of Nonlinear Age-dependent Population Dynamics, Marcel Dekker, New York, 1985.