ENDEMIC MODELS WITH ARBITRARILY DISTRIBUTED PERIODS OF INFECTION II: FAST DISEASE DYNAMICS AND PERMANENT RECOVERY[*]

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Abstract. A model for the spread of an infectious disease in a population with constant recruitment of new susceptibles, developed in previous work, is further analyzed in the case that disease survivors are permanently immune and that the disease dynamics are much faster than the demographic dynamics. Though the model allows for arbitrarily many stages of infection, all of which have general length distributions and disease survival functions, the different time scales make it possible to find explicit formulas for the interepidemic period (distance between peaks or valleys of disease incidence) and the local stability or instability of the endemic equilibrium. It turns out that the familiar formula for the length of the interepidemic period of childhood diseases has to be reinterpreted when the exponential length distribution of the infectious period is replaced by a general distribution. Using scarlet fever in England and Wales (1897–1978) as an example, we illustrate how different assumptions for the length distributions of the exposed and infectious periods (under identical average lengths) lead to quite different values for the minimum length of the quarantine period to destabilize the endemic equilibrium.

Key words. many infection stages, arbitrary stage length distributions, stage (or class) age, endemic equilibrium, interepidemic period, average duration, average expectation of remaining duration, isolation (quarantine), scarlet fever, Hopf bifurcation

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1. Introduction. Most epidemic models assume that the infection periods (e.g., latent, infectious, isolation periods) are either exponentially distributed or have fixed durations. The data analyses presented in Bailey (1975, Chapter 15), Gough (1977), and Becker (1989) show various estimates for the latent period of measles. The estimates do somewhat depend on the methods used and the circumstances considered, but they agree on the fact that the standard deviation is not negligible on the one hand but much shorter than the mean duration (about one fifth) on the other hand. Sartwell (1950, 1966) draws a similar picture for the incubation periods of a host of infectious diseases (see also Thieme (to appear) section 1.7).

While this shows that most epidemic models are not realistic in modeling the duration of the various stages, idealization is a genuine feature of any mathematical modeling and not necessarily a reason for concern. Recently, however, Keeling and Grenfell (1997, 1998) demonstrated that infectious periods with small variance give better agreement with persistence data for measles than exponential distributions. In this paper, it is the main concern that, in models with exponentially distributed stage durations, the stage exit rates enter all kinds of important formulas like the *basic reproduction ratio* (or *basic replacement ratio*, the notorious $\mathcal{R}_0$), the formula for the frequency of recurrent outbreaks of childhood diseases (*interepidemic period*), and

conditions for the stability of the endemic equilibrium. In all these cases, stage exit rates have been interpreted as reciprocals of the average stage durations. The concern that this choice may be misleading in specific cases has motivated us to formulate an epidemic model with arbitrarily distributed periods of infection (Feng and Thieme (2000)) which will be analyzed in this paper under the assumption that the disease dynamics are much faster than the demographics, an assumption which holds for most childhood diseases but not for diseases with long incubation and/or infectious periods like HIV/AIDS.

A primer in the mathematics of stage transition. Mathematically the duration of a disease (and any other) stage can be described by a nonincreasing function

$$P : [0, \infty) \to [0, 1], \quad P(0) = 1,$$

with $P(a)$ denoting the probability to be still in the stage after a time units. We call P a *duration function* and the variable a *stage age*. (If the stage is life, P has the more familiar name of a survival function or a survivorship.)

At this point let us ignore that the stage may also be left by death. The *expected (or average, or mean) duration* of the stage, D, is then given by

$$(1.1) \qquad\qquad D = -\int_0^\infty aP(da) = \int_0^\infty P(a)da$$

and its variance V and standard deviation σ by

$$(1.2) \qquad V = \sigma^2 = -\int_0^\infty (a - D)^2 P(da) = 2\int_0^\infty aP(a)da - D^2.$$

(Throughout this paper we assume that all moments of P exist.)

For fixed stage age $b > 0$, $P(a|b) = \frac{P(a+b)}{P(b)}$ is the conditional probability to stay in the stage for a more time units, given that one has already stayed in the stage for b time units. $P(\cdot|b)$ is again a duration function and

$$D(b) = \int_0^\infty P(a|b)da = \frac{\int_b^\infty P(a)da}{P(b)}$$

is the *expected remaining duration* at stage age b. Averaging these expectations we obtain the *average expectation of remaining duration*, $\bar{D}$,

$$(1.3) \qquad\qquad \bar{D} = \frac{\int_0^\infty D(b)P(b)db}{\int_0^\infty P(b)db} = \frac{\int_0^\infty aP(a)da}{D}.$$

The average expectation of remaining duration is somewhat difficult to grasp; if there is a constant input of individuals into the stage, it is equal to the average stage age (Kim and Aron (1989)). Further we have the following relation to D and V from (1.2):

$$(1.4) \qquad\qquad\qquad V = D(2\bar{D} - D)$$

or

$$(1.5) \qquad\qquad\qquad \bar{D} = \frac{1}{2}\left(\frac{V}{D} + D\right) \geq \frac{D}{2}.$$

Notice that, depending on the standard deviation σ, the ratio $\bar{D}/D = (1/2)((\sigma/D)^2 + 1)$ can be any value between $1/2$ and infinity and that $\bar{D} \leq D$ if and only if $\sigma \leq D$. If there is a *maximum stage duration* $D^\bullet$, i.e., $P(a) = 0$ if $a > D^\bullet$ and $P(a) > 0$ if $a < D^\bullet$, then

$$(1.6) \qquad\qquad \bar{D} \leq D^\bullet/2.$$

Most epidemic models assume that individuals leave the stage (progressing to another one) at a constant per capita rate, let us say, θ. This implies that the stage duration is exponentially distributed, $P(a) = e^{-\theta a}$, and has the peculiar consequence that average duration, average expectation of remaining duration, and the standard deviation are all the same,

$$D = \bar{D} = \sigma = \frac{1}{\theta}, \quad D^\bullet = \infty.$$

Another class of epidemic models assume that some of the stages have fixed length, let us say, b,

$$P(a) = \left\{ \begin{array}{ll} 1; & 0 \leq a < b, \\ 0; & a > b \end{array} \right. ,$$

then $D = b = D^\bullet$, $\sigma = 0$, and $\bar{D} = D/2$.

As a bottom line we summarize that, in the most commonly used epidemic models, the reciprocals of the constant stage exit rates are identical to three entities which are quite different in reality: the average duration, the average expectation of remaining duration, and the standard deviation; so it is not clear how they are to be interpreted when they appear in key epidemiologic parameter combinations.

Outline of the paper. This ambiguity has motivated us to develop a general framework for epidemic models with arbitrarily many stages, all durations of which have general distributions (Feng and Thieme (2000)). Our model framework also allows for general disease survival functions at each stage. The demographics in our model are rather special, however, as restricted to constant recruitment of new susceptibles and to a constant natural per capita death rate. Some aspects of this model are presented in section 2 for diseases which lead to complete recovery and immunity for those infected individuals that survive the disease. We will see that average stage durations are the appropriate ingredients for determining $\mathcal{R}_0$.

In section 3 (and the appendix) we further specialize to diseases where the disease dynamics are much faster than the demographic dynamics. Taking advantage of the different time scales (cf. Dietz (1976) and Andreasen (1989a, 1989b, 1993, 1995)) we find an explicit approximation for the leading roots of the characteristic equation associated with the endemic equilibrium. The sign of the real part of these roots (a conjugate pair) determines the local stability of the endemic equilibrium while its imaginary part is the key to the frequency of recurrent outbreaks. Dietz (1976) suggests the following formula for the time between the peaks (or valleys) of two subsequent outbreaks,

$$\tau = 2\pi \sqrt{A(D_E + D_I)},$$

where A is the average age at infection and D_E and D_I are the average durations of the latent (exposed) and infectious stage, respectively. This formula has been

tested against data for childhood diseases by Anderson and May (1982, 1991) who found very good agreement for many childhood diseases, but somewhat less good agreement for Rubella, e.g. While the above formula is completely correct for the models with exponentially distributed disease stages considered by Dietz (1976) and Anderson and May (1982, 1991), we will find (in section 4) that, assuming general length distributions of the latent and infectious stage, it has to be modified as

$$\tau = 2\pi\sqrt{A(D_E + \bar{D}_I)},$$

i.e., for the infectious period, the average duration has to be replaced by the average expectation of remaining duration. See section 7 for some examples of how this modification improves the agreement with disease data. These considerations should be taken with a grain of salt, however, because both formulas for τ are obtained by linearization about the endemic equilibrium fitting a scenario with vanishing or low amplitude oscillations, while it is conceivable that the length of the interepidemic period in recurrent outbreak is influenced by highly nonlinear effects.

In section 5 we consider extensions of standard incidence to several infectious disease stages and a modified standard incidence function which takes into account that the disease may decrease the mixing activity of individuals with disease symptoms. In Feng and Thieme (2000) we show that the endemic equilibrium is locally asymptotically stable under standard incidence, provided there are no disease fatalities. In section 5 we show that this remains valid if the disease dynamics are much faster than the demographic dynamics and the disease mortality is not so severe that almost everybody dies from the disease.

Finally (in sections 6 and 7) we revisit a model where individuals with symptoms completely withdraw (or are withdrawn) from the epidemic scene. We have shown (Feng (1994, dissertation); Feng and Thieme (1995)) that a sufficiently long isolation (or quarantine) period may lead to instability of the endemic equilibrium and, via Hopf bifurcation, to periodic oscillations of the disease dynamics. Lumping the latent and infectious period and assuming exponential stage durations, we have found for scarlet fever that an isolation period of at least 23 days makes the endemic equilibrium unstable. In this paper we separate latent and infectious periods. If both have exponentially distributed durations, an isolation period of at least 18 days average duration will make the endemic equilibrium unstable. If both periods have fixed durations, an isolation period of at least 10 days destabilizes the endemic equilibrium. If we interpolate reported maximum and minimum stage durations by piecewise linear duration functions, an isolation period of at least 11 days is sufficient (see section 7). We mention that Anderson, Arnstein, and Lester (1962) report isolation periods for scarlet fever that last two or three weeks or even longer.

For most other childhood diseases, our analysis rules out that isolation alone is a cause for unstable endemic equilibria. While long isolation periods can theoretically destabilize the endemic equilibrium, the required lengths turn out not to be in a realistic range. It is conceivable, however, that isolation adds to the other factors that have been found to lead to recurrent epidemic outbreaks like seasonal variation in per capita infection rates, stochastic effects, Allee-type effects in the infection rate, and more dynamic demographics than the constant influx of susceptibles that we will assume in this paper (see Dietz and Schenzle (1985), Hethcote and Levin (1989), Feng and Thieme (1995), and Gao, Mena-Lorca, and Hethcote (1995, 1996)).

In this context, our main point consists of illustrating that the required minimum length for an isolation period to destabilize the endemic equilibrium is cut into almost

half, when exponential length distributions of the latent and infectious periods are replaced by realistic distributions with the same average lengths. This may not be of practical relevance for most childhood diseases, because the required minimum length is still not in a realistic range, but should be reason enough to look out for similar phenomena in other situations.

2. Model description and previous results for the case of permanent recovery. We consider an endemic model with arbitrarily many stages of infection. If N denotes the size of the epidemiologically relevant part of the population, we have

$$N = S + \sum_{j=1}^{n} I_j, \tag{2.1}$$

with S denoting the number of the susceptibles and I_j the number of the infected individuals in the jth stage of infection. The incidence (number of new infections per unit of time), B_0, satisfies a functional relation

$$B_0 = f(S, I_1, \ldots, I_n). \tag{2.2}$$

In order to describe the duration of the various stages and the related disease fatalities we introduce nonincreasing functions

$$P_j, \mathcal{F}_j : [0, \infty) \to [0, 1], \qquad P_j(0) = 1, \quad \mathcal{F}_j(0) = 1,$$

with the following interpretation: $P_j(a)$ is the probability that the jth stage of the infection lasts longer than a time units, while $1 - \mathcal{F}_j(a)$ gives the probability to die from disease-related causes during the jth stage before reaching stage age a. P_j is called the *duration function* and $\mathcal{F}_j$ the *disease survival function* of the jth infection period. The average duration of the jth disease stage is

$$D_j = \int_0^\infty P_j(a)\,da, \tag{2.3}$$

while the average sojourn time in the jth stage is

$$T_j = \int_0^\infty e^{-\mu a} \mathcal{F}_j(a) P_j(a)\,da. \tag{2.4}$$

The average sojourn time takes into account that the sojourn may be cut short by dying from the disease, described by $\mathcal{F}_j$, or by dying from disease-unrelated causes. The latter we call natural death and we assume it to occur at the constant per capita mortality rate μ. So the life expectation in absence of the disease is $L = \frac{1}{\mu}$. The following probabilities are also crucial:

$$p_j = (-1) \int_0^\infty \mathcal{F}_j(a) e^{-\mu a} P_j(da) \tag{2.5}$$

is the probability of getting through the jth stage alive;

$$q_1 = 1, \qquad q_j = p_1 \cdots p_{j-1}, \quad j = 2, \ldots, n+1, \tag{2.6}$$

give the probabilities with which an infected individual will survive all the stages 1 to $j-1$. Using these ingredients, a model has been derived in Feng and Thieme (2000);

here we only summarize those parts that are needed for the understanding of this paper.

At an endemic equilibrium we have

$$B_0^* = f(S^*, I_1^*, \ldots, I_n^*), \tag{2.7}$$

where

$$S^* = \frac{\Lambda - B_0^*(1 - q_{n+1})}{\mu}, \qquad I_j^* = B_0^* T_j q_j, \quad j = 1, \ldots, n. \tag{2.8}$$

Λ is the rate at which individuals enter the epidemiologically relevant part of the population; it is also the recruitment rate of new susceptibles.

In this paper we assume that the infected individuals in the last stage have completely recovered from the disease and are completely immune, so there are no disease-related deaths in the last stage and there is no return into the susceptible part of the population. This means that $\mathcal{F}_n \equiv 1$ and $P_n \equiv 1$ and, by (2.4) and (2.5),

$$p_n = q_{n+1} = 0, \quad T_n = \frac{1}{\mu} = L.$$

In particular, infected individuals in the last stage are no longer infective, so we call them recovered individuals and write

$$R = I_n.$$

Further we write $I = (I_1, \ldots, I_{n-1})$ and 0 for I when $I_1 = \cdots = I_{n-1} = 0$. (This notation is different from that in Feng and Thieme (2000), where I includes I_n.) The following is assumed throughout this paper.

H2: The function $f : [0, \infty)^{n+1} \to [0, \infty)$ is continuous. Moreover, for every $S_0, R_0 \geq 0$, $S_0 + R_0 > 0$, there exists a neighborhood V of $(S_0, 0, R_0)$ in $\mathbf{R}^{n+1}$ such that f can be extended to and is three times continuously differentiable on $V \cup (0, \infty)^{n+1}$. Since susceptible and recovered individuals are not infective and there are no infections without infectives or susceptibles, we assume that

$$f(S, 0, R) = 0, \quad f(0, I, R) = 0, \qquad S, I, R \geq 0;$$

further

$$\frac{\partial f}{\partial I_j}(S, 0, R) \geq 0, \qquad S, R \geq 0, \quad S + R > 0,$$

with at least one of the derivatives being strictly positive if $S > 0$.

Recalling that the basic reproduction ratio, $\mathcal{R}_0$, is the number of secondary cases one average freshly infected individual can cause when introduced into an otherwise disease-free population, we find that

$$\begin{aligned}
\mathcal{R}_0 = \mathcal{R}_0(\mu) &= \lim_{B \to 0} \frac{1}{B} f\left(\frac{\Lambda - B}{\mu}, T_1 q_1 B, \ldots, T_n q_n B\right) \\
&= \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(N^\diamond, 0, \ldots, 0) T_j q_j,
\end{aligned} \tag{2.9}$$

$$N^\diamond = \frac{\Lambda}{\mu}.$$

In previous work (Feng and Thieme (2000)) we have shown that the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$. We have also given additional assumptions for the endemic equilibrium not to exist if $\mathcal{R}_0 \leq 1$ and to exist and be unique if $\mathcal{R}_0 > 1$, further for the disease to die out if $\mathcal{R}_0 < 1$ and to be (weakly or strongly) endemic if $\mathcal{R}_0 > 1$.

Recalling that $T_n = \frac{1}{\mu} = L$ is the life expectation (in absence of the disease), the equilibrium equation (2.7) can also be written as

$$(2.10) \qquad \frac{1}{q_n L} R^* = f(S^*, I^*, R^*).$$

Now

$$\frac{f(S^*, I^*, R^*)}{S^*} = \frac{1}{q_n L} \frac{R^*}{S^*}$$

is the per capita rate at equilibrium of a susceptible individual to be infected. Its reciprocal is the average time it takes a susceptible to become infected, i.e., at equilibrium the average age at infection, A, is given by

$$(2.11) \qquad A = \frac{S^*}{R^*} q_n L.$$

3. Fast disease dynamics. We assume that the demographic parameter μ (the natural mortality rate) is small compared to the epidemic parameters and that

$$(3.1) \qquad \Lambda = \mu N^\diamond$$

for some $N^\diamond > 0$ that is kept fixed. $N^\diamond$ is the population size which is approached in the absence of the disease as time tends to infinity.

We also assume that $\mathcal{R}_0^\diamond = \mathcal{R}_0(0) > 1$, where

$$(3.2) \qquad \mathcal{R}_0(\mu) = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(N^\diamond, 0, \ldots, 0) T_j q_j$$

and $\mathcal{R}_0(\mu)$ is the basic reproduction ratio introduced in (2.9). Recalling that T_j and q_j depend on μ, we write

$$(3.3) \qquad T_j = T_j^\diamond, \quad q_j = q_j^\diamond \qquad \text{whenever } \mu = 0.$$

$\mathcal{R}_0^\diamond > 1$ implies that $\mathcal{R}_0(\mu) > 1$ for sufficiently small $\mu > 0$.

In the special case we consider here, $T_n = \frac{1}{\mu} = L$ is the life expectation and, by (2.8), $B_0^* = \frac{\mu}{q_n} R^*$. Set $x = \frac{1}{q_n} R^*$, then, by (2.8),

$$(3.4) \qquad \begin{aligned} S^* &= N^\diamond - x, \qquad I_1^* = \mu T_1 x, \qquad I_j^* = \mu T_j q_j x, \quad j = 2, \ldots, n-1, \\ R^* &= q_n x, \qquad B_0^* = \mu x. \end{aligned}$$

The equilibrium equation (2.7), $B_0^* = f(S^*, I^*, R^*)$, takes the form

$$(3.5) \qquad \mu x = f(N^\diamond - x, T_1 q_1 \mu x, \ldots, T_{n-1} q_{n-1} \mu x, q_n x).$$

Remark. Let us pause for a moment to make precise what it means that the demographic parameters are small compared to the epidemic parameters. Recall that

$L = 1/\mu$ is the life expectation and T_j are the average sojourn times in the infected stages. The first is in the order of decades and the second in the order of a few weeks, so $\mu T_j \ll 1$ for $j = 1, \ldots, n-1$. Let us define

$$\sigma = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(N^\diamond, 0, \ldots, 0).$$

From (3.2), we have that

$$\sigma \min_{j=1,\ldots,n-1} T_j q_j \leq \mathcal{R}_0 \leq \sigma \max_{j=1,\ldots,n-1} T_j q_j.$$

If the $T_j q_j$ do not vary too much between the infection stages, this implies that $\sigma T_j q_j$ is of the same order of magnitude as $\mathcal{R}_0$, which is a number between 2 and 20 for most infectious diseases (Anderson and May (1991), Table 4.1). If the survival probabilities q_j are not too small, this implies that $\delta := \mu/\sigma \ll 1$. Setting $\xi_j = T_j q_j$ and $y = x/N^\diamond$ we can reformulate (3.5) in dimensionless form as

$$\delta y = \frac{1}{\sigma N^\diamond} f(N^\diamond(1-y), N^\diamond \xi_1 \delta y, \ldots, N^\diamond \xi_{n-1} \delta y, N^\diamond q_n y),$$

with $\delta \ll 1$ and ξ_j being neither very small nor very large.

We rewrite (3.5) as a fixed point problem in x for the following function g which is twice continuously differentiable in a neighborhood of $(0,0)$:

$$g(\mu, x) = \frac{1}{\mu} f(N^\diamond - x, T_1 q_1 \mu x, \ldots, T_{n-1} q_{n-1} \mu x, q_n x), \quad \mu \neq 0,$$

$$g(0, x) = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(N^\diamond - x, 0, q_n^\diamond x) T_j^\diamond q_j^\diamond x.$$

By $\mathcal{R}_0^\diamond > 1$, $\frac{\partial f}{\partial I_j}(0, 0, R) = 0$ (see Assumptions H2), and the intermediate value theorem,

$$(3.6) \qquad\qquad 1 = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}\left(N^\diamond - x^\diamond, 0, q_n^\diamond x^\diamond\right) T_j^\diamond q_j^\diamond$$

for some $x^\diamond \in (0, N^\diamond)$. We want to make sure that this is the only solution of (3.6). So we make the following assumptions in addition to the overall Assumptions H2.

H3 (a) For all $S, R > 0$,

$$\frac{\partial^2 f}{\partial S \partial I_j}(S, 0, R) \geq 0 \qquad \text{and} \qquad \frac{\partial^2 f}{\partial S \partial I_j}(S, 0, R) \geq \frac{\partial^2 f}{\partial I_j \partial R}(S, 0, R)$$

with the last inequality being strict for at least one $j \in 1, \ldots, n-1$.

(b) There exists some $\nu > 0$ such that $\int_0^\infty e^{\nu a} P_j(a) da$ and $-\int_0^\infty e^{\nu a} P_j(da)$ are finite for all $j = 1, \ldots, n-1$.

The second inequality in (a) follows from the first if $\frac{\partial^2 f}{\partial I_j \partial R}(S, 0, R) \leq 0$, as it is the case for many incidence functions (see sections 4 and 5). The assumption in (b)

guarantees in particular that all moments of the length distributions of all infected periods but the removed period exist.

With Assumption H3 (a) the right-hand side of (3.6) is strictly decreasing in $x^\diamond$. Further, by the implicit function theorem, (3.5) has a unique solution x in a neighborhood of $x^\diamond$ which is a twice continuously differentiable function of μ such that $x = x^\diamond$ for $\mu = 0$. This implies that the equilibria S^*, I^*, R^* are twice continuously differentiable functions of μ such that, for $\mu = 0$,

$$(3.7) \qquad S^* = S^\diamond := N^\diamond - x^\diamond, \quad I^* = I^\diamond = 0, \quad R^* = R^\diamond := q_n^\diamond x^\diamond.$$

For later use we conclude from (2.11) and note from (3.2) and (3.6) that

$$(3.8) \qquad \frac{A}{L} \approx \frac{S^\diamond}{R^\diamond} q_n^\diamond = \frac{S^\diamond}{x^\diamond}, \quad \mu \to 0,$$

$$\mathcal{R}_0^\diamond = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(N^\diamond, 0, 0) T_j^\diamond q_j^\diamond,$$

$$1 = \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond) T_j^\diamond q_j^\diamond.$$

The stability of the endemic equilibrium is determined by the roots of a characteristic equation (Feng and Thieme (2000), section 7). For $\mu = 0$, $\lambda = 0$ is a double root of the characteristic equation and all other roots have strictly negative real part and are bounded away from the imaginary axis (see the appendix).

Similarly as in Feng and Thieme (1995) the roots of the characteristic equation can be expanded in powers of $\epsilon = \sqrt{\mu}$.

THEOREM 3.1. *Let Assumptions* H2 *and* H3 *hold and consider the characteristic equation associated with the endemic equilibrium. Then there exist numbers* $\mu_0 > 0, \nu > 0$ *such that, for all* $\mu \in (0, \mu_0)$, *the characteristic equation has two complex conjugate roots* λ *in the strip* $|\Re\lambda| < \nu$, *while all other roots satisfy* $\Re\lambda < -\nu$. *Moreover, for the two leading roots, we have* $\Re\lambda \to 0$ *as* $\mu \to 0$ *and the expansion*

$$\lambda = \pm\imath\sqrt{\mu\theta} + \mu\tilde{\lambda}_1 + O(\mu^{3/2}),$$

with $O(\mu^{3/2})$ *indicating a function* $\phi(\mu)$ *such that* $|\phi(\mu)| \leq c\mu^{3/2}$ *for* $\mu \in [0, \mu_0]$.

The proof of this theorem has been relegated to the appendix. There we also show that θ is given by

$$(3.9) \qquad \theta = \frac{\sum_{j=1}^{n-1} \left[\frac{\partial^2 f}{\partial S \partial I_j}(S^\diamond, 0, R^\diamond) - \frac{\partial^2 f}{\partial I_j \partial R}(S^\diamond, 0, R^\diamond) q_n^\diamond \right] T_j^\diamond q_j^\diamond x^\diamond}{\sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond) T_j^\diamond q_j^\diamond c_{1j}},$$

while $\tilde{\lambda}_1$ is given by

$$(3.10) \quad \tilde{\lambda}_1 = -\frac{1}{2} \left(\sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond) T_j^\diamond q_j^\diamond c_{1j} \right)^{-1}$$

$$\times \left[\sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond) \frac{c_{2j} + c_{1j}^2}{2} T_j^\diamond q_j^\diamond \theta + \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond) T_j^\diamond q_j^\diamond c_{1j} \right.$$

$$-\frac{1}{2}\sum_{j,k=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial I_k}(S^\diamond,0,R^\diamond)x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond$$

$$+\sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial R}(S^\diamond,0,R^\diamond)q_n^\diamond T_j^\diamond q_j^\diamond x^\diamond d_1\Bigg].$$

Here

$$(3.11) \qquad c_{mj} = a_{mj} + \sum_{k=1}^{j-1} b_{mk}, \quad j = 2,\dots,n-1, \qquad c_{m1} = a_{m1},$$

$$d_m = \sum_{k=1}^{n-1} b_{mk},$$

where

$$(3.12) \qquad a_{1j} = \int_0^\infty a\frac{\mathcal{F}_j(a)}{T_j^\diamond}P_j(a)da,$$

$$a_{2j} = \int_0^\infty (a-a_{1j})^2\frac{\mathcal{F}_j(a)}{T_j^\diamond}P_j(a)da,$$

and

$$(3.13) \qquad b_{1k} = -\int_0^\infty a\frac{\mathcal{F}_k(a)}{p_k^\diamond}P_k(da),$$

$$b_{2k} = -\int_0^\infty (a-b_{1k})^2\frac{\mathcal{F}_k(a)}{p_k^\diamond}P_k(da).$$

For completeness we remind the reader that

$$(3.14) \qquad T_j^\diamond = \int_0^\infty \mathcal{F}_j(a)P_j(a)da,$$

$$p_j^\diamond = -\int_0^\infty \mathcal{F}_j(a)P_j(da),$$

$$q_1^\diamond = 1, \qquad q_j^\diamond = p_1^\diamond \cdots p_{j-1}^\diamond, \quad j = 2,\dots,n.$$

If $\tilde{\lambda}_1 < 0$, the endemic equilibrium is locally asymptotically stable provided that the demographic dynamics are slow enough compared with the disease dynamics. If the disease dynamics are slightly perturbed away from the endemic equilibrium, they return to the endemic equilibrium in damped oscillations whose quasi-period (distance between two adjacent local maxima), τ, is

$$(3.15) \qquad \tau \approx \frac{2\pi}{\sqrt{\mu\theta}}.$$

τ is sometimes called the *interepidemic period* (cf. Anderson and May (1991), Table 6.1). Notice that the Assumptions H3 guarantee that $\theta > 0$.

In Feng and Thieme (2000, section 8) we discuss whether $\tilde{\lambda}_1$ switching its sign gives rise to periodic solutions via a Hopf bifurcation; periodic solutions that are close to the endemic equilibrium will have periods which are close to τ.

If $\tilde{\lambda}_1 > 0$ the endemic equilibrium is unstable, provided that the demographic dynamics are slow enough compared with the disease dynamics. Instability means that there exists a neighborhood of the endemic equilibrium such that there are solutions that leave this neighborhood though they start arbitrarily close at the endemic equilibrium. Actually it follows from Theorem 3.1 that the roots of the characteristic equation are bounded away from the imaginary axis. As we have discussed in Feng and Thieme (2000, section 7), the semiflow generated by the solutions of the model is continuously differentiable and its derivatives at the equilibrium have their radius of the essential spectral strictly less than 1. This implies that the endemic equilibrium is a hyperbolic fixed point of the semiflow, and so is a saddle with nonempty local stable and unstable C^1-manifolds. Both the local stable and unstable manifold are thin in so far as they do not contain open sets, and actually the local unstable manifold is two-dimensional. (See, e.g., Shub (1987, Theorem III.2, Theorem III.8, and Exercise II.2 in Chapter 5). These invariant manifolds are for maps, but an extension to semiflows is possible.)

Before we start looking at special forms of the incidence function f in the next sections, let us finish with the following general stability result.

THEOREM 3.2. *Let Assumption* H2 *be satisfied. Further, let*

$$\frac{\partial^2 f}{\partial S \partial I_j}(S, 0, R) > \frac{\partial^2 f}{\partial I_j \partial R}(S, 0, R) \geq 0,$$

$$\frac{\partial^2 f}{\partial I_j \partial I_k}(S, 0, R) \leq 0, \quad j = 1, \ldots, n - 1.$$

Then the endemic equilibrium is locally asymptotically stable for sufficiently small $\mu > 0$.

4. Some special cases and the length of the interepidemic period. The formulas in the previous section simplify considerably if only one of the infected stages, let us say stage m, is infectious, $1 \leq m < n$. The stages before this stage can be various exposed stages, while the stages afterward could be various stages where the individuals are removed (e.g., isolated). Mathematically this is reflected in

(4.1)
$$\frac{\partial f}{\partial I_j}(S, 0, R) = 0 \qquad \forall j \neq m,$$

$$\frac{\partial^2 f}{\partial S \partial I_j}(S, 0, R) = 0 = \frac{\partial^2 f}{\partial I_j \partial R}(S, 0, R) \qquad \forall j \neq m,$$

$$\frac{\partial^2 f}{\partial I_j \partial I_k}(S, 0, R) = 0 \qquad \forall j \neq m, k \neq m.$$

It follows from the third equation in (3.8) that

$$\frac{\partial f}{\partial I_m}(S^\diamond, 0, R^\diamond) T_m^\diamond q_m^\diamond = 1.$$

Equations (3.9) and (3.10) simplify to

$$\theta = \left[\frac{\partial^2 f}{\partial S \partial I_m}(S^\diamond, 0, R^\diamond) - \frac{\partial^2 f}{\partial I_m \partial R}(S^\diamond, 0, R^\diamond) q_n^\diamond \right] \frac{T_m^\diamond q_m^\diamond x^\diamond}{c_{1m}}$$

and

$$\tilde{\lambda}_1 = -\frac{1}{2c_{1m}}\left[\frac{c_{2m}+c_{1m}^2}{2}\theta + c_{1m} - \sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial I_m}(S^\diamond,0,R^\diamond)x^\diamond T_j^\diamond T_m^\diamond q_j^\diamond q_m^\diamond\right.$$

$$\left.+\frac{1}{2}\frac{\partial^2 f}{\partial I_m^2}(S^\diamond,0,R^\diamond)x^\diamond(T_m^\diamond)^2(q_m^\diamond)^2 + \frac{\partial^2 f}{\partial I_m \partial R}(S^\diamond,0,R^\diamond)q_n^\diamond T_m^\diamond q_m^\diamond x^\diamond d_1\right].$$

Another type of simplification, at least for θ, can be obtained if

$$(4.2) \qquad \frac{f(S,\cdot)}{S} = f_0(\cdot) \quad \text{does not depend on } S,$$

$$f(\cdot, R) \quad \text{does not depend on } R.$$

Then $\frac{\partial f}{\partial S \partial I_j} = \frac{1}{S}\frac{\partial f}{\partial I_j}$ and (3.6) and (3.9)

$$\theta = \frac{x^\diamond}{S^\diamond}\left(\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}\right)^{-1}.$$

By (3.8), $x^\diamond/S^\diamond \approx L/A$, and $\mathcal{R}_0^\diamond = \frac{N^\diamond}{S^\diamond}$ which implies that

$$\frac{x^\diamond}{S^\diamond} = \frac{N^\diamond - S^\diamond}{S^\diamond} = \mathcal{R}_0^\diamond - 1.$$

So

$$(4.3) \qquad \theta = (\mathcal{R}_0^\diamond - 1)\left(\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}\right)^{-1}$$

$$\approx \frac{L}{A}\left(\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}\right)^{-1}.$$

Let us combine both simplifications.

THEOREM 4.1. *Let f satisfy Assumptions* H2 *and* H3 *and both* (4.1) *and* (4.2). *Then*

$$\theta = \frac{\mathcal{R}_0^\diamond - 1}{c_{1m}}$$

and

$$\tilde{\lambda}_1 = \frac{1}{2c_{1m}}\left[-\frac{1}{2}(\mathcal{R}_0^\diamond - 1)\left(\frac{c_{2m}}{c_{1m}} + c_{1m}\right) - c_{1m}\right.$$

$$\left.+\sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial I_m}(S^\diamond,0,R^\diamond)x^\diamond T_j^\diamond T_m^\diamond q_j^\diamond q_m^\diamond - \frac{1}{2}\frac{\partial^2 f}{\partial I_m^2}(S^\diamond,0,R^\diamond)x^\diamond(T_m^\diamond)^2(q_m^\diamond)^2\right].$$

THEOREM 4.2. *Let f satisfy the assumptions of Theorem* 4.1. *Then the leading root λ of the characteristic equation for the endemic equilibrium satisfies*

$$\Im\lambda \approx \sqrt{\frac{1}{Ac_{1m}}}$$

in the sense that $\Im\lambda\sqrt{Ac_{1m}} \to 1$ *as* $\mu \to 0$.

Proof. This follows from (4.3) and Theorem 3.1 and $L = 1/\mu$. $\quad\square$

In the case that the disease does not cause any fatalities, the parameters c_{1m} also have an easy epidemiological interpretation. After integration by parts

$$
(4.4) \qquad c_{1m} = \bar{D}_m + \sum_{j=1}^{m-1} D_j,
$$

where $\bar{D}_m$ is the expectation of remaining duration of the infective stage and D_j is the expected duration of the jth infected stage (which is an exposed stage),

$$
D_j = \int_0^\infty P_j(a)da, \quad \bar{D}_m = \frac{1}{D_m} \int_0^\infty aP_m(a)da.
$$

This generalizes a formula found by Dietz (1976) (see also Anderson and May (1982)) and clarifies its interpretation. Since Dietz (1976) and Anderson and May considered exponentially distributed durations of the various stages for which the expected duration and the expectation of remaining duration coincide, they were led to formulate (4.4) with D_m replacing $\bar{D}_m$. Recall that a stage with fixed duration (without any variance) has $\bar{D}_m = \frac{D_m}{2}$. As we have already mentioned in the introduction, one can construct distributions for the stage duration such that $\bar{D}_m/D_m$ takes any value between $1/2$ and infinity, but for realistic distributions one expects it to take values between $1/2$ and 1. Anderson and May (1991) have compared $\frac{2\pi}{\Im\lambda}$ with observed interepidemic periods of various childhood diseases. They get very good agreement for diseases with relatively short infectious periods and less good agreement for diseases with longer infectious periods where the calculated values are larger than the observed ones. A possible explanation may be that the mean duration of the infectious stage has to be replaced by the expectation of remaining sojourn. See section 7 for more details.

5. Standard incidence and disease-related reduction in activity levels. In Feng and Thieme (2000) we show that the endemic equilibrium is locally asymptotically stable, if the incidence is of generalized mass action type

$$
f(S, I, R) = S\langle\kappa, I\rangle = S\sum_{j=1}^{n-1} \kappa_j I_j,
$$

or if there are no disease fatalities and the incidence is of generalized standard type

$$
f(S, I, R) = \frac{S}{N}\langle\kappa, I\rangle, \qquad N = S + \sum_{j=1}^{n-1} I_j + R.
$$

Here $I = (I_1, \ldots, I_{n-1})$ and $\kappa = (\kappa_1, \ldots, \kappa_{n-1})$ are nonzero, nonnegative vectors in $\mathbf{R}^{n-1}$ and $\langle\kappa, I\rangle = \sum_{j=1}^{n-1} \kappa_j I_j$ is the inner (or scalar) product on $\mathbf{R}^{n-1}$. In regards to the controversy about whether standard or mass action incidence are more appropriate we refer to Hethcote (1994), Hethcote (1976), Anderson and May (1991, section 12.1), and De Jong, Diekmann, and Heesterbeek (1995). If disease symptoms may cause people to stay in voluntary or enforced isolation, it appears plausible to modify standard incidence to the following functional form:

$$
f(S, I, R) = \frac{S\langle\kappa, I\rangle}{S + \langle\gamma, I\rangle + R}.
$$

The numbers $\gamma_j \in [0, 1]$ give the fraction to which the activity of an infected individual in stage j is reduced and $\gamma = (\gamma_1, \ldots, \gamma_{n-1})$. The numbers κ_j now are of the form $\kappa_j = \gamma_j \tilde{\kappa}_j$, with $\tilde{\kappa}_j$ representing the infectivity of an individual in stage j. In the following we will evaluate θ and $\tilde{\lambda}_1$ in (3.9) and (3.10) for this special case in terms of parameters that are accessible to estimation or educated guess. We will show that the endemic equilibrium is locally asymptotically stable for generalized standard incidence, if the disease dynamics are much faster than the demographics and at least some infected individuals survive the disease. The endemic equilibrium may lose its stability, however, when standard incidence is modified to include disease-reduced activity and infection periods with reduced activity are very long. We start by calculating the various partial derivatives of f:

$$\frac{\partial f}{\partial I_j}(S, I, R) = \frac{S\kappa_j}{S + \langle \gamma, I \rangle + R} - \frac{S\langle \kappa, I \rangle \gamma_j}{(S + \langle \gamma, I \rangle + R)^2}.$$

Hence

$$\frac{\partial f}{\partial I_j}(S, 0, R) = \frac{S\kappa_j}{S + R},$$

$$\frac{\partial f^2}{\partial S \partial I_j}(S, 0, R) = \frac{\kappa_j}{S + R} - \frac{S\kappa_j}{(S + R)^2} = \frac{R\kappa_j}{(S + R)^2},$$

$$\frac{\partial f^2}{\partial I_j \partial R}(S, 0, R) = -\frac{S\kappa_j}{(S + R)^2},$$

$$\frac{\partial f^2}{\partial S \partial I_j}(S, 0, R) - \frac{\partial f^2}{\partial I_j \partial R}(S, 0, R)q_n^\diamond = \frac{\kappa_j}{S + R} + (q_n^\diamond - 1)\frac{S\kappa_j}{(S + R)^2} = \frac{\kappa_j}{(S + R)^2}(R + q_n^\diamond S).$$

From (3.9),

$$\theta = \frac{R^\diamond + q_n^\diamond S^\diamond}{S^\diamond(S^\diamond + R^\diamond)} x^\diamond \frac{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}},$$

and from (3.8),

(5.1)
$$1 = \frac{S^\diamond}{S^\diamond + R^\diamond} \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond.$$

So

(5.2)
$$\theta = \left(\frac{R^\diamond}{S^\diamond} + q_n^\diamond\right) \frac{x^\diamond}{S^\diamond} \frac{1}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}}.$$

Again from (3.8),

(5.3)
$$\mathcal{R}_0^\diamond = \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond,$$

and from (5.1),

(5.4)
$$1 = \frac{S^\diamond}{S^\diamond + R^\diamond} \mathcal{R}_0^\diamond.$$

This implies by (3.7) that

$$(5.5) \qquad \mathcal{R}_0^\diamond - 1 = \frac{R^\diamond}{S^\diamond} = q_n^\diamond \frac{x^\diamond}{S^\diamond}.$$

Substituting this into the formula for θ, (5.2), yields

$$\theta = \frac{\mathcal{R}_0^\diamond - 1}{q_n^\diamond} \frac{\mathcal{R}_0^\diamond - 1 + q_n^\diamond}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}}, \qquad \text{where} \qquad \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond = \mathcal{R}_0^\diamond.$$

We can use (3.8) to tie θ to average age at infection, A, and life expectation, L; with $A \approx \frac{S^\diamond}{x^\diamond} L$ and (5.5) we obtain $\mathcal{R}_0^\diamond - 1 \approx q_n^\diamond \frac{L}{A}$, and

$$\theta \approx \frac{L}{A} q_n^\diamond \frac{L+A}{A} \frac{1}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}}, \qquad \text{where} \qquad \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond = \mathcal{R}_0 \approx q_n^\diamond \frac{L+A}{A}.$$

We notice that, in the case that there is exactly one infective stage, we obtain the same formula for $\Im \lambda$ as in Theorem 4.2.

In order to find out the sign of $\tilde{\lambda}_1$ in (3.10), we look at the following derivatives:

$$\frac{\partial^2 f}{\partial I_j \partial I_k}(S, 0, R) = -(\kappa_j \gamma_k + \kappa_k \gamma_j) \frac{S}{(S+R)^2}.$$

So

$$\frac{1}{2} \sum_{j,k=1}^{n-1} \frac{\partial^2 f}{\partial I_j \partial I_k}(S^\diamond, 0, R^\diamond) x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond = -\frac{S^\diamond}{(S^\diamond + R^\diamond)^2} \left(\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond \right) \left(\sum_{j=1}^{n-1} \gamma_j T_j^\diamond q_j^\diamond \right) x^\diamond$$

$$= -\frac{x^\diamond}{S^\diamond + R^\diamond} \left(\sum_{j=1}^{n-1} \gamma_j T_j^\diamond q_j^\diamond \right).$$

Here we have used (5.1). Similarly

$$\sum_{j=1}^{n-1} \frac{\partial^2 f}{\partial I_j \partial R}(S^\diamond, 0, R^\diamond) q_n^\diamond T_j^\diamond q_j^\diamond x^\diamond d_1 = -\frac{x^\diamond}{S^\diamond + R^\diamond} q_n^\diamond d_1.$$

Substituting these expressions into the formula (3.10) for $\tilde{\lambda}_1$, we find that

$$\tilde{\lambda}_1 \simeq -\frac{\mathcal{R}_0^\diamond - 1}{q_n^\diamond}(\mathcal{R}_0^\diamond - 1 + q_n^\diamond) \frac{S^\diamond}{x^\diamond} \frac{\sum_{j=1}^{n} \kappa_j \frac{c_{2j} + c_{1j}^2}{2} T_j^\diamond q_j^\diamond}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}}$$

$$-\frac{S^\diamond}{x^\diamond} \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j} - \sum_{j=1}^{n-1} \gamma_j T_j^\diamond q_j^\diamond + q_n^\diamond d_1,$$

with $\simeq$ meaning that the two expressions have the same sign. We use (5.5) to eliminate $S^\diamond$,

$$\tilde{\lambda}_1 \simeq -(\mathcal{R}_0^\diamond - 1 + q_n^\diamond) \frac{\sum_{j=1}^{n} \kappa_j \frac{c_{2j} + c_{1j}^2}{2} T_j^\diamond q_j^\diamond}{\sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j}}$$

$$-\frac{q_n^\diamond}{\mathcal{R}_0^\diamond - 1} \sum_{j=1}^{n-1} \kappa_j T_j^\diamond q_j^\diamond c_{1j} - \sum_{j=1}^{n-1} \gamma_j T_j^\diamond q_j^\diamond + q_n^\diamond d_1.$$

It may be tempting to conclude from this formula that the endemic equilibrium is locally asymptotically stable, if $q_n^\diamond = 0$, i.e., if nobody survives to the removed class. But remember that we assumed that $q_n^\diamond$ is not too small, in particular not zero, in the preparatory analysis of section 3. However, we can show that the endemic equilibrium is locally asymptotically stable, if the activity in the various infected classes is not much reduced.

THEOREM 5.1. *Let Assumption* H3(b) *be satisfied and the incidence f be given as generalized standard incidence*

$$f(S, I, R) = S \frac{\langle \kappa, I \rangle}{N}, \qquad N = S + \sum_{j=1}^{n} I_j + R.$$

Then the endemic equilibrium is locally asymptotically stable if the disease dynamics are much faster than the demographic dynamics.

Proof. From the last formula for $\tilde{\lambda}_1$ we see that it is sufficient to show that

$$\Delta := q_n^\diamond d_1 - \sum_{j=1}^{n-1} \gamma_j T_j^\diamond q_j^\diamond \leq 0,$$

if $\gamma_j = 1$ for $j = 1, \ldots, n-1$. By (3.11) and (3.13),

$$\Delta = -q_n^\diamond \sum_{j=1}^{n-1} \frac{1}{p_j^\diamond} \int_0^\infty a \mathcal{F}_j(a) P_j(da) - \sum_{j=1}^{n-1} q_j^\diamond \gamma_j \int_0^\infty \mathcal{F}_j(a) P_j(a) da.$$

Since $\frac{q_n^\diamond}{p_j^\diamond} \leq q_j^\diamond$ by (2.6), we obtain by integration by parts that

$$\Delta \leq \sum_{j=1}^{n-1} (1 - \gamma_j) \int_0^\infty \mathcal{F}_j(a) P_j(a) da \leq \sum_{j=1}^{n-1} (1 - \gamma_j) T_j^\diamond \gamma = 0. \qquad \square$$

We mention a related result by Gao, Mena-Lorca, and Hethcote (1996) for a susceptible-exposed-infectious (SEI) model with exponentially distributed latent and infectious periods, but without assuming different time scales. We also mention that, in an HIV/AIDS model with infection-age dependent infectivity, no recovery from the disease, and high disease fatality, the endemic equilibrium may lose its stability (Thieme and Castillo-Chavez (1993)).

We could use the last estimate in the proof of Theorem 5.1 to figure out how close the γ_j have to be to 1 for the endemic equilibrium to be locally asymptotically stable. We do not go into this, but rather consider the case of a disease that causes no fatalities. Then $q_j = 1$ and

$$d_1 = \sum_{j=1}^{n-1} D_j^\diamond, \quad T_j^\diamond = D_j = \int_0^\infty P_j(a) da.$$

We obtain

$$\tilde{\lambda}_1 \simeq -\mathcal{R}_0^\diamond \frac{\sum_{j=1}^{n-1} \kappa_j \frac{c_{2j} + c_{1j}^2}{2} D_j}{\sum_{j=1}^{n-1} \kappa_j D_j c_{1j}} - \frac{1}{\mathcal{R}_0^\diamond - 1} \sum_{j=1}^{n-1} \kappa_j D_j c_{1j} + \sum_{j=1}^{n-1} (1 - \gamma_j) D_j.$$

Let us assume that there is some k such that the individuals in the stages $k + 1, \ldots, n - 1$ are completely isolated while the individuals in the stages $1, \ldots, k$ have no reduced activity, i.e.,

$$\gamma_j = 1, \quad j = 1, \ldots, k, \qquad \kappa_j = \gamma_j = 0, \quad j = k+1, \ldots, n-1.$$

Then

$$(5.6) \qquad \tilde{\lambda}_1 \simeq -\mathcal{R}_0^\diamond \frac{\sum_{j=1}^{k} \kappa_j \frac{c_{2j}+c_{1j}^2}{2} D_j}{\sum_{j=1}^{k} \kappa_j D_j c_{1j}} - \frac{1}{\mathcal{R}_0^\diamond - 1} \sum_{j=1}^{k} \kappa_j D_j c_{1j} + \sum_{j=k+1}^{n-1} D_j,$$

where

$$\sum_{j=1}^{k} \kappa_j D_j = \mathcal{R}_0^\diamond.$$

In the case that there is exactly one infectious stage, namely $j = k$, then $\kappa_j = 0$ for $j = 1, \ldots, k-1$ and formula (5.6) simplifies to

$$(5.7) \qquad \tilde{\lambda}_1 \simeq -\mathcal{R}_0^\diamond \frac{c_{2k} + c_{1k}^2}{2c_{1k}} - \frac{\mathcal{R}_0^\diamond}{\mathcal{R}_0^\diamond - 1} c_{1k} + \sum_{j=k+1}^{n-1} D_j.$$

We see from (5.6) that increasing the lengths of the stages $k+1, \ldots, n-1$ (the isolated stages) makes the equilibrium less stable or more unstable.

6. A model with an isolated class. We consider a model of $S - E - I - Q - R$ type, with E denoting the size of the exposed part of the population, I the size of the (effectively) infectious class, and Q the size of the isolated (quarantined) part. We assume that there are no disease fatalities and that the disease dynamics are much faster than the demographics. In an earlier work (Feng and Thieme (1995)) we argue (similarly as in section 5) that the incidence should have the functional form

$$f(S, E, I, Q, R) = \kappa \frac{SI}{S + E + I + R}.$$

We could handle this incidence as a special case of section 5. In particular, it follows from Theorem 5.1 that the endemic equilibrium is locally asymptotically stable if f is the standard incidence $\kappa SI/N$ with $N = S + E + I + Q + R$. We have shown in Feng and Thieme (2000) (even without the assumption of different time scales) that the endemic equilibrium is also locally asymptotically stable if the incidence is of mass action type κSI.

Alternatively we base our analysis on the approach in section 4 which is more straightforward in this case. Since we assume that the disease causes no fatalities, we have

$$S(t) + E(t) + I(t) + Q(t) + R(t) \to \frac{\Lambda}{\mu} = N^\diamond.$$

This implies that the endemic equilibrium and its stability remain the same if we consider

$$f(S, I_1, I_2, I_3, R) = \kappa \frac{SI_2}{N^\diamond - I_3}.$$

f satisfies both (4.1) and (4.2) in section 4 with $m = 2$. It follows from Theorem 4.1 that

$$\tilde{\lambda}_1 = \frac{1}{2c_{12}}\left[-\frac{1}{2}(\mathcal{R}_0^\diamond - 1)\left(\frac{c_{22}}{c_{12}} + c_{12}\right) - c_{12} + \frac{\partial^2 f}{\partial I_2 \partial I_3}(S^\diamond, 0, R^\diamond)x^\diamond T_3^\diamond T_2^\diamond q_3^\diamond q_2^\diamond\right].$$

Now

$$\frac{\partial^2 f}{\partial I_2 \partial I_3}(S, 0, R) = \kappa \frac{S}{(N^\diamond)^2}.$$

By (3.8),

$$\mathcal{R}_0^\diamond = \kappa T_2^\diamond q_2^\diamond = \frac{N^\diamond}{S^\diamond} \quad \text{and} \quad \frac{x^\diamond}{N^\diamond} = \frac{N^\diamond - S^\diamond}{N^\diamond} = 1 - \frac{1}{\mathcal{R}_0^\diamond}.$$

So

$$\frac{\partial^2 f}{\partial I_2 \partial I_3}(S, 0, R)T_2^\diamond q_2^\diamond x^\diamond = \frac{\mathcal{R}_0^\diamond - 1}{\mathcal{R}_0^\diamond}$$

and

$$\frac{x^\diamond}{S^\diamond} = \frac{N^\diamond - S^\diamond}{S^\diamond} = \mathcal{R}_0^\diamond - 1.$$

Since the disease is not fatal, $q_j^\diamond = 1$, and

$$\tilde{\lambda}_1 \simeq \frac{1 - \mathcal{R}_0^\diamond}{2}\left(\frac{c_{22}}{c_{12}} + c_{12}\right) - c_{12} + \frac{\mathcal{R}_0^\diamond - 1}{\mathcal{R}_0^\diamond}T_3^\diamond.$$

After reorganizing the terms and realizing that $T_3^\diamond = D_Q$ is the expected duration (mean length) of the isolation (quarantine) period,

$$\tilde{\lambda}_1 \simeq -D_Q^\sharp + D_Q,$$

(6.1) $$D_Q^\sharp = \frac{\mathcal{R}_0^\diamond(\mathcal{R}_0^\diamond + 1)}{2(\mathcal{R}_0^\diamond - 1)}c_{12} + \frac{\mathcal{R}_0^\diamond}{2}\frac{c_{22}}{c_{12}}.$$

This is the same formula as in (5.7). Recall (3.11) to (3.13), $c_{i2} = a_{i2} + b_{i1}, i = 1, 2$. Since $\mathcal{F}_j \equiv 1$,

$$b_{11} = -\int_0^\infty aP_1(da) = D_E, \qquad b_{21} = -\int_0^\infty (a - b_{11})^2 P_1(da) = V_E,$$

with D_E being the expected duration of the exposed stage and V_E its variance, while

$$a_{12} = \frac{\int_0^\infty aP_2(a)da}{T_2} = \bar{D}_I, \qquad a_{22} = \frac{1}{T_2}\int_0^\infty (a - a_{12})^2 P_2(a)da,$$

with D_I being the average duration of the infective stage and $\bar{D}_I$ the average expectation of remaining duration in the infective stage. So

$$c_{12} = \bar{D}_I + D_E, \qquad c_{22} = a_{22} + V_E,$$

and

(6.2) $$D_Q^\sharp = \frac{\mathcal{R}_0^\diamond(\mathcal{R}_0^\diamond + 1)}{2(\mathcal{R}_0^\diamond - 1)}(\bar{D}_I + D_E) + \frac{\mathcal{R}_0^\diamond}{2}\frac{a_{22} + V_E}{\bar{D}_I + D_E}.$$

Stability of the endemic equilibrium. We have the following result from Theorem 3.1.

THEOREM 6.1. *If the expected duration of the isolation period, D_Q, is shorter than $D_Q^\sharp$, then the endemic equilibrium is locally asymptotically stable provided the disease dynamics are fast enough compared to the demographic dynamics.*

If $D_Q > D_Q^\sharp$, then the endemic equilibrium is a saddle provided the disease dynamics are fast enough compared to the demographic dynamics.

$\mathcal{R}_0^\diamond$ and D_E have clear interpretations and reasonable data are available, V_E and $\bar{D}_I$ have clear interpretations but hardly any data are available, while a_{22} is even hard to interpret. We can rewrite it in the following form, however,

$$
a_{22} = \frac{1}{D_I} \int_0^\infty \left[(a - D_I)^2 + 2(a - D_I)(D_I - \bar{D}_I) + (D_I - \bar{D}_I)^2 \right] P_2(a)da
$$
$$
= \frac{1}{D_I} \int_0^\infty (a - D_I)^2 P_2(a)da - (D_I - \bar{D}_I)^2.
$$

Integrating by parts,

$$
(6.3) \qquad\qquad a_{22} = \frac{1}{3} D_I^2 - (D_I - \bar{D}_I)^2 + \frac{1}{3D_I} Z_I^3,
$$

where Z_I^3 is the third central moment of the length distribution of the infectious period. If $Z_I^3 \le 0$ (e.g., if the length of the infectious period is symmetrically distributed about its mean), then

$$
a_{22} \le \left[\frac{\xi^2}{3} - (\xi - 1)^2 \right] \bar{D}_I^2, \qquad \xi = \frac{D_I}{\bar{D}_I} \le 2.
$$

The last estimate follows from (1.5). The expression in the bracket has a global maximum at $\xi = 3/2$, so

$$
(6.4) \qquad\qquad Z_I^3 \le 0 \implies a_{22} \le \frac{1}{3} D_I^2 - (D_I - \bar{D}_I)^2 \le \frac{1}{2} \bar{D}_I^2.
$$

If $Z_3 = 0$, the first inequality is an equality. In particular, if the infectious stage has a fixed duration, then $a_{22} = \frac{1}{3} \bar{D}_I^2$. However, if the duration of the infectious period is exponentially distributed, then $a_{22} = b_{22} = V_I = D_I^2 = \bar{D}_I^2$.

Still, rewriting the equation for $D_Q^\sharp$ as

$$
(6.5) \qquad\qquad D_Q^\sharp = \frac{\mathcal{R}_0^\diamond}{2} (\bar{D}_I + D_E) \left[\frac{\mathcal{R}_0^\diamond + 1}{\mathcal{R}_0^\diamond - 1} + \frac{a_{22} + V_E}{(\bar{D}_I + D_E)^2} \right]
$$

suggests that perhaps the second term in $[\cdot]$ is of little practical importance compared to the first one which is bigger than 1. We will explore this further in the discussion where we also apply this formula to scarlet fever.

Saddle point property of an unstable endemic equilibrium. If $D_Q > D_Q^\sharp$, it follows from Theorem 3.1 and the subsequent remarks that the endemic equilibrium is a saddle of the solution semiflow with a two-dimensional local unstable C^1-manifold. This means in particular that there is a neighborhood of the endemic equilibrium such that all solutions that start in this neighborhood but not on the stable manifold have to leave this neighborhood. Notice that the stable manifold does not contain open sets, so there are plenty of points in this neighborhood that are not in the stable manifold.

Hopf bifurcation of periodic solutions. It is a natural question whether, if the endemic equilibrium is unstable, periodic solutions oscillate around it. One would look for an answer in the framework of Hopf bifurcation. So far the model system shows no explicit parameter. The natural bifurcation parameter is the length of the isolation period. To bring this parameter, $D_Q = D_3$, into the model, we set $\tilde{P}_3(a) = P_3(aD_3)$, $\tilde{\mathcal{F}}_3(a) = \mathcal{F}_3(aD_3)$, and replace $P_3(a)$ by $\tilde{P}_3(a/D_3)$ and $\mathcal{F}_3(a)$ by $\tilde{\mathcal{F}}(a/D_3)$. Notice that $\tilde{D}_3 = \int_0^\infty \tilde{P}_3(a)da = 1$. Then the right-hand side of the characteristic equation (A.1) becomes an analytic function in (D_3, λ) for $D_3 > 0$, $\Re\lambda > -\mu$. It follows from Theorem 3.1 that we can apply the global Hopf bifurcation theory by Fiedler (1986); remember that our model can be reformulated as a system of Volterra integral equations in terms of S, E, I, Q, R (Feng and Thieme (2000), section 2.3).

THEOREM 6.2. *For each sufficiently small $\mu > 0$ we obtain a continuum $\mathcal{C}_\mu$ of pairs $(D_Q, \mathbf{x})$, where $\mathbf{x} = (S, E, I, Q, R)$ is a periodic solution or a center (equilibrium for which the characteristic equation has imaginary roots). The continuum contains both centers and periodic solutions.*

In our special situation we can easily extract the following extra information, namely, that each continuum $\mathcal{C}_\mu$ contains pairs $(D_Q(\mu), \mathbf{x}(\mu))$ with centers $\mathbf{x}(\mu)$ such that $D_Q(\mu) \to D_Q^\sharp$, $\mathbf{x}(\mu) \to (S^\diamond, 0, 0, 0, R^\diamond)$ as $\mu \to \infty$. Recall $S^\diamond, R^\diamond$ from (3.7). Unfortunately, in this context, it is not possible to infer from the global Hopf bifurcation theory how big the continua (connected sets) are. Nor is it possible to say in which direction they extend.

As for the difficulty in applying local Hopf bifurcation theorems we refer to the discussion in Feng and Thieme (2000, section 8).

7. Length distributions of infection periods matter beyond their averages. Exponentially distributed infections periods (where individuals leave the infection stage at constant rates) have the curious feature that the reciprocal exit rate equals three different things at the same time: the average stage duration, the average expectation of remaining duration, and the standard deviation of the stage. So it is not surprising when formulas that have derived for endemic models with exponentially distributed stage duration need to be modified when they are replaced by general distributions.

The length of the interepidemic period. In section 4, we have found that the formula by Dietz (1976) for the length of the interepidemic period,

$$(7.1) \qquad \tau = 2\pi\sqrt{A(D_E + D_I)},$$

derived for a childhood disease model with exponentially distributed latent and infectious periods, has to be modified for general distributions as

$$(7.2) \qquad \tau = 2\pi\sqrt{A(D_E + \bar{D}_I)}$$

with the average expectation of remaining duration replacing the average duration for the infectious period (cf. (4.4)). In order to produce biennial outbreak patterns, Dietz calculated for measles $D_E + D_I$ should not be larger than 9 days (actually about 8.2 days). This seems to be in conflict with an average latent period of about 7.5 days and an infectious period of about 6.5 days. He then argues that this deviation may be due to infectives that are isolated as soon as symptoms show up or to other length distributions of the latent or infectious period. Anderson and May (1991, Table 6.1)

seem to have followed the first suggestion and take $D_E + D_I = 12$ days which is still somewhat larger than 9 days and yields $\tau = 2.41$ years which is rounded to 2 years in Table 6.1.

Let us follow the second of Dietz's suggestions. There seems to be little variation in the length of the infectious period which is between 6 and 7 days, so we may try $\bar{D}_I \approx D_I/2 \approx 3.5$ which gives us $D_E + \bar{D}_I = 11$ days, which is still larger than the required 8.2 days but smaller than Anderson and May's $D_E + D_I = 12$ days. We can combine the two approaches deferring that the average length of the effective infectious period is about 4 days. Assuming that all the variation comes from the latent period, we would end up with $D_E + \bar{D}_I = 7.5 + 2 = 9.5$ days.

Rubella is one of the childhood diseases where formula (7.1) does not give good agreement with the reported average length of the interepidemic period, 3.5 years (Anderson and May (1991), Table 6.1). From Table 6.1 we take $A = 11$ years. Again D_I is only the length of the effective part of the infectious period assuming that children are isolated after symptoms appear. There seems to be almost no variation in the length of the total infectious period of 11 to 12 days. One may infer from the latent period of 7 to 14 days and the incubation period of 14 to 21 days that the length of the effective infectious period is 7 or 8 days. Assuming that there is almost no variation in the length of the effective infectious period, $\bar{D}_I$ is about 4 days yielding $D_E + \bar{D}_I \approx 14$ days, while $D_E + D_I \approx 18$ days as in Anderson and May's (1991) table. Formula (7.1) now provides an interepidemic period of approximately 4.6 years, while formula (7.2) gives approximately 4.1 years. This is still larger than the observed 3.5 years, but considerably closer.

A word of caution is in order at this place. It must be emphasized that formula (7.2) only provides the interepidemic period as long as the endemic equilibrium is stable and the disease dynamics exhibit damped oscillations. The interepidemic periods reported in Anderson and May (1991) refer to undamped recurrent disease outbreaks, however, and the values provided by (7.2) may have no relation whatsoever to the actual values, for (7.2) is obtained by linearization about the endemic equilibrium, while the dynamics of undamped recurrent outbreaks are governed by strong nonlinear effects (see, e.g., Schwartz and Smith (1983), Olsen, Truty, and Schaffer (1988), Grenfell, Bolker, and Kleczkowski (1995)).

Stability of the endemic equilibrium. Continuing the discussion started in Feng and Thieme (1995) whether a long enough isolation (or quarantine) period can destabilize the endemic equilibrium and lead to undamped oscillations, in section 6 we found a threshold $D_Q^\sharp$ such that the endemic equilibrium is locally asymptotically stable if the expected length of the isolation period, D_Q, satisfies $D_Q < D_Q^\sharp$ and unstable if $D_Q > D_Q^\sharp$,

$$(7.3) \qquad D_Q^\sharp = \frac{\mathcal{R}_0^\diamond}{2}(\bar{D}_I + D_E)\left[\frac{\mathcal{R}_0^\diamond + 1}{\mathcal{R}_0^\diamond - 1} + \frac{a_{22} + V_E}{(\bar{D}_I + D_E)^2}\right],$$

where D_E and D_I are the average lengths of the latency (or exposed) period and the (effective) infectious period, respectively, $\bar{D}_I$, the average expectation of the remaining duration of the (effective) infectious period and V_E, the variance of the duration of the latency period. Further $a_{22} > 0$ and

$$(7.4) \qquad a_{22} = \frac{1}{3}D_I^2 - (D_I - \bar{D}_I)^2 + \frac{1}{3D_I}Z_I^3,$$

where Z_I^3 is the third central moment of the (effective) infectious period.

Formula (7.3) yields an estimate from below for $D_Q^\sharp$,

$$D_Q^\sharp > \frac{\mathcal{R}_0^\diamond}{2}(\bar{D}_I + D_E) \geq \frac{\mathcal{R}_0^\diamond}{2}\left(\frac{D_I}{2} + D_E\right).$$

This shows that the average length of the isolation period must be quite long compared to the average length of latency period if the basic reproduction ratio is large, in order to make the endemic equilibrium unstable. This rules out isolation as single cause of periodic outbreaks for quite a few childhood diseases. We mention that recurrent outbreaks of childhood diseases can be caused by seasonal or stochastic fluctuations in the per capita infection rate; see Dietz and Schenzle (1985), Hethcote and Levin (1989), and Grenfell, Bolker, and Kleczkowski (1995) for reviews and references.

If $\frac{\mathcal{R}_0^\diamond}{2}(\bar{D}_I + D_E)$ is not too large, the estimate above may also be a reasonable approximation of (7.3), because the second term in [·] can perhaps be neglected compared to the first one which is bigger than 1.

Let us corroborate this conjecture. If the length of the infectious period is symmetrically distributed about its mean, we have the estimate $a_{22} \leq \bar{D}_I/2$. If the infectious period has fixed duration, $a_{22} = \bar{D}_I/3$. However, if the infectious period has exponential distribution, $a_{22} = D_I = \bar{D}_I$.

The only data for V_E we could find are the ones for measles in Bailey (1975, Chapter 15), Gough (1977), and Becker (1989), all of which suggest $\frac{V_E}{D_E^2} \approx \frac{1}{25}$. In general, for diseases with a maximum latency period, $D_E^\bullet$,

$$V_E \leq D_E^2\left(\frac{D_E^\bullet}{D_E} - 1\right).$$

For all childhood diseases in Anderson and May (1991, Table 3.1) one can safely assume that $\frac{D_E^\bullet}{D_E} \leq \frac{4}{3}$, hence $V_E \leq \frac{D_E^2}{3}$. This, together with the upper estimates for a_{22}, suggests that the term $\frac{a_{22}+V_E}{(\bar{D}_I+D_E)^2}$ may be of minor practical importance in the formula for $D^\sharp$ in (7.3).

Most of the data are of the form that they give a minimum and maximum stage duration, D° and $D^\bullet$. For simplicity we let

$$P(a) = 1, \quad a \leq D^\circ, \qquad P(a) = 0, \quad a \geq D^\bullet,$$

and the graph of P be a line connecting $(D^\circ, 1)$ to $(D^\bullet, 0)$ otherwise. In other words, P is absolutely continuous and

$$P'(a) = 0, \quad a \in (0, D^\circ) \cup (D^\bullet, \infty),$$
$$P'(a) = -\frac{1}{D^\bullet - D^\circ}, \quad a \in (D^\circ, D^\bullet).$$

Then, for $m \in \mathbf{N}_0$,

$$\int_0^\infty a^m P(a)da = -\frac{1}{m+1}\int_0^\infty a^{m+1}P'(a)da = \frac{1}{m+1}\frac{1}{D^\bullet - D^\circ}\int_{D^\circ}^{D^\bullet} a^{m+1}da$$
$$= \frac{1}{(m+1)(m+2)}\frac{(D^\bullet)^{m+2} - (D^\circ)^{m+2}}{D^\bullet - D^\circ}.$$

With $m = 0$,

$$D = \frac{D^\bullet + D^\circ}{2},$$

and we see that the stage length is symmetrically distributed about its mean such that the third central moment is 0. Further,

$$\bar{D} = \frac{1}{3} \frac{(D^\bullet)^3 - (D^\circ)^3}{(D^\bullet)^2 - (D^\circ)^2}.$$

Scarlet fever in England and Wales. For scarlet fever in England and Wales (1897–1978), Anderson and May (1982, Tables 1 and 2; 1991, Table 6.1) report an average age of infection between 10 and 14 years and an average life expectation that rises from 60 to 70 years. We assume $L = 65$ years and $A = 12$ years which leads to a basic reproduction ratio of $\mathcal{R}_0^\diamond \approx 6.4$. Anderson and May (1991, Table 3.1) give a latent period of 1 or 2 days, and infectious period of 14–21 days, and an incubation period of 2 or 3 days.

Assuming that children stay at home as soon as symptoms occur, we assume an effective infectious period of 1 or 2 days and an isolation period between 12 and 20 days. To be specific we assume $D_E = D_I = 1.5$ days. If we assume that the latency period and the effective infectious period are exponentially distributed we obtain

$$D_Q^\sharp = \frac{\mathcal{R}_0^\diamond(\mathcal{R}_0^\diamond + 1)}{2(\mathcal{R}_0^\diamond - 1)}3 + \frac{\mathcal{R}_0^\diamond}{2}1.5 \approx 18 \text{ days}.$$

If we assume fixed latency and effective infectious periods, then

$$D_Q^\sharp \approx 10 \text{ days}.$$

Finally we use the approach of interpolating between minimum and maximum durations by a piecewise linear duration function,

$$D_E^\circ = 1, \quad D_E^\bullet = 2, \qquad D_I^\circ = 1, \quad D_I^\bullet = 2.$$

Then

$$D_E = D_I = 1.5, \quad \bar{D}_E = \bar{D}_I = \frac{7}{9}, \quad V_E = D_E(2\bar{D}_E - D_E) = \frac{1}{12}.$$

Since the length of the infectious period is symmetric about its mean, we can use the first inequality in (6.5) as equality

$$a_{22} = \frac{1}{3}D_I^2 - (D_I - \bar{D}_I)^2 = \frac{37}{162} \approx 0.228,$$

so

$$\frac{a_{22} + V_E}{(\bar{D}_I + D_E)^2} = \frac{0.228 + 0.083}{5.188} \approx 0.06$$

which confirms our previous impression that this term is of minor practical importance in the evaluation of $D_Q^\sharp$. Finally we find

$$D_Q^\sharp \approx 10.4 \text{ days}.$$

We inferred from the data in Anderson and May (1991) that the isolation period should lie between 12 and 20 days. This agrees with Anderson, Arnstein, and Lester (1962) who report isolation periods for scarlet fever that last 2 or 3 weeks or even longer. Formula (7.2) gives an interepidemic period of 1.7 years which is much lower than the observed 3–6 years (Anderson and May (1991), Table 6.1). However, it must be noticed that, for this model, the formula (7.2) which has been obtained by linearization gives the interepidemic period only as long as the endemic equilibrium is stable (and the oscillations are damped) or has just lost its stability such that the oscillations have small amplitudes, i.e., for isolation periods smaller than 11 days. Numerical calculations for the ODE model considered in Feng and Thieme (1995) have shown that the interepidemic period very sensitively increases with the length of the isolation period and that (7.2) can no longer be used for its determination.

Appendix: The roots of the characteristic equation. In Feng and Thieme (2000, section 7) we derived the characteristic equation associated with an equilibrium as

$$1 = -\frac{1 - \prod_{k=1}^{n} K_k(\lambda + \mu)}{\lambda + \mu} \frac{\partial f}{\partial S}(S^*, I^*, R^*) + \frac{\partial f}{\partial I_1}(S^*, I^*, R^*)L_1(\lambda + \mu)$$
$$+ \sum_{j=2}^{n} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*)L_j(\lambda + \mu) \prod_{k=1}^{j-1} K_k(\lambda + \mu),$$

where S^* and I_j^*, R^* give the equilibrium numbers of individuals in the susceptible and the various infected stages and

$$K_j(z) = -\int_0^\infty e^{-za} \mathcal{F}_j(a) P_j(da), \qquad L_j(z) = \int_0^\infty e^{-za} \mathcal{F}_j(a) P_j(a) da$$

are Laplace–Stieltjes and Laplace transforms. Notice that, differently from Feng and Thieme (2000), we now write (I^*, R^*) rather than I^* because we consider the case where infected individuals in the last stage have completely and permanently recovered from the disease. This implies that $\mathcal{F}_n \equiv 1 \equiv P_n$ such that $K_n = 0$ and $L_n(z) = \frac{1}{z}$. So the characteristic equation simplifies to

$$1 = -\frac{1}{\lambda + \mu} \frac{\partial f}{\partial S}(S^*, I^*, R^*) + \frac{\partial f}{\partial I_1}(S^*, I^*, R^*)L_1(\lambda + \mu)$$

(A.1)
$$+ \sum_{j=2}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*)L_j(\lambda + \mu) \prod_{k=1}^{j-1} K_k(\lambda + \mu)$$

$$+ \frac{\partial f}{\partial R}(S^*, I^*, R^*)\frac{1}{\lambda + \mu} \prod_{k=1}^{n-1} K_k(\lambda + \mu).$$

Since it is our aim to expand λ in powers of $\epsilon = \sqrt{\mu}$ with μ being close to 0 (see Theorem 3.1), we may like to convince ourselves that we can reformulate (A.1) in dimensionless ingredients. Recall that the average duration of the jth disease stage is denoted by D_j and given by formula (2.3). As in the remark in section 3 we can argue that $\mu D_j \ll 1$ and that σD_j is neither very small nor very large while $\delta = \mu/\sigma \ll 1$. Define $\tilde{P}_j(s) = P_j(s/D_j)$ and $\tilde{\lambda} = \lambda/\sigma$. Then $\int_0^\infty \tilde{P}(s)ds = 1$ and

$$L_j(\lambda + \mu) = D_j \int_0^\infty e^{-(\lambda+\mu)D_j s} \mathcal{F}_j(D_j s)\tilde{P}_j(s)ds$$

$$= D_j \int_0^\infty e^{-(\tilde\lambda+\delta)\sigma D_j s} \mathcal{F}_j(D_j s)\tilde P_j(s)ds,$$

$$K_j(\lambda+\mu) = -\int_0^\infty e^{-(\lambda+\mu)D_j s}\mathcal{F}_j(D_j s)\tilde P_j(ds)$$

$$= -\int_0^\infty e^{-(\tilde\lambda+\delta)\sigma D_j s}\mathcal{F}_j(D_j s)\tilde P_j(ds).$$

Setting $\breve P_j(r) = \tilde P_j(r/(\sigma D_j))$, we have

$$L_j(\lambda+\mu) = \frac{1}{\sigma}\breve L_j(\tilde\lambda+\delta), \qquad K_j(\lambda+\mu) = \breve K_j(\tilde\lambda+\delta),$$

where $\breve L_j$ and $\breve K_j$ are versions of L_j and K_j with duration and disease survival functions that operate in dimensionless variables. Equation (A.1) now takes the form

$$1 = -\frac{1}{\tilde\lambda+\delta}\frac{1}{\sigma}\frac{\partial f}{\partial S}(S^*, I^*, R^*) + \frac{1}{\sigma}\frac{\partial f}{\partial I_1}(S^*, I^*, R^*)\breve L_1(\tilde\lambda+\delta)$$

$$+\frac{1}{\sigma}\sum_{j=2}^{n-1}\frac{\partial f}{\partial I_j}(S^*, I^*, R^*)\breve L_j(\tilde\lambda+\delta)\prod_{k=1}^{j-1}\breve K_k(\tilde\lambda+\delta)$$

$$+\frac{1}{\sigma}\frac{\partial f}{\partial R}(S^*, I^*, R^*)\frac{1}{\tilde\lambda+\delta}\prod_{k=1}^{n-1}\breve K_k(\tilde\lambda+\delta).$$

We return to (A.1) having convinced ourselves that we can assume that all ingredients are dimensionless and $\mu \ll 1$. We rewrite this equation as

$$(A.2)\quad 0 = -(\lambda+\mu) - \frac{\partial f}{\partial S}(S^*, I^*, R^*) + (\lambda+\mu)\frac{\partial f}{\partial I_1}(S^*, I^*, R^*)L_1(\lambda+\mu)$$

$$+(\lambda+\mu)\sum_{j=2}^{n-1}\frac{\partial f}{\partial I_j}(S^*, I^*, R^*)L_j(\lambda+\mu)\prod_{k=1}^{j-1}K_k(\lambda+\mu)$$

$$+\frac{\partial f}{\partial R}(S^*, I^*, R^*)\prod_{k=1}^{n-1}K_k(\lambda+\mu).$$

For $\mu = 0$, the characteristic equation (A.2) collapses to

$$(A.3)\quad 0 = -\lambda + \lambda\frac{\partial f}{\partial I_1}(S^\diamond, 0, R^\diamond)L_1(\lambda) + \lambda\sum_{j=2}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond, 0, R^\diamond)L_j(\lambda)\prod_{k=1}^{j-1}K_k(\lambda).$$

It follows from (3.8) that $\lambda = 0$ is a double root of (A.3) and that there are no other roots with $\Re\lambda \geq 0$. Notice that $L_j(\lambda) < L_j(0) = T_j^\diamond$ and $K_k(\lambda) < K_k(0) = p_j^\diamond$ whenever $\Re\lambda \geq 0, \lambda \neq 0$. Actually, by the Riemann–Lebesgue lemma, we can conclude that there is some $\nu > 0$ such that all nonzero roots of (A.1) satisfy $\Re\lambda \leq \nu$.

By Assumption H3 (b) and a Riemann–Lebesgue-type argument applied to (A.1) that works uniformly for sufficiently small $\mu > 0$, we see that there exists some $\mu_0 > 0$ and some $\nu > 0, c > 0$ such that, for all $\mu \in (0, \mu_0)$, (A.1) has no roots with $\Re\lambda > -\nu$ and $|\lambda| > c$. Rouché's theorem now implies that, for $\mu \in [0, \mu_0)$, if $\mu_0 > 0$ is chosen small enough, there are exactly two roots of (A.2) with $\Re\lambda > -\nu$ and they lie in the strip $|\Re\lambda| < \nu$. Moreover $\Re\lambda \to 0$ as $\mu \to 0$.

Set $\epsilon = \sqrt{\mu}$. The special case considered in Feng and Thieme (1995) motivates us to look for λ in the form $\lambda = \epsilon\tilde{\lambda}(\epsilon)$ with $\tilde{\lambda}(0) = 0$ and $\tilde{\lambda}$ being continuously differentiable.

In order to facilitate the bookkeeping in our expansion, we use the theory of cumulants (Kendall and Stuart (1958)).

LEMMA A.1. *Let $\mathcal{F}$ be a probability distribution such that the Laplace–Stieltjes transform*

$$\check{\mathcal{F}}(z) = \int_0^\infty e^{-za}\mathcal{F}(da)$$

exists for z in a complex neighborhood U of 0. Then

$$\check{\mathcal{F}}(z) = \exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}a_m z^m\right), \quad z \in U,$$

where a_1 is the mean and a_2 the variance of $\mathcal{F}$,

$$a_1 = \int_0^\infty a\mathcal{F}(da), \quad a_2 = \int_0^\infty (a - a_1)^2\mathcal{F}(da).$$

LEMMA A.2. *For any sequence $(a_m)_{m\geq 1}$,*

$$\exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}a_m z^m\right) = 1 - a_1 z + \frac{1}{2}(a_2 + a_1^2)z^2 + O(z^3)$$

for z in a sufficiently small neighborhood of 0 where convergence holds.

Lemma A.1 implies that

$$L_j(\lambda + \mu) = T_j^\diamond \exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}a_{mj}(\lambda + \mu)^m\right),$$

with

$$a_{1j} = \int_0^\infty a\frac{\mathcal{F}_j(a)}{T_j^\diamond}P_j(a)da, \qquad a_{2j} = \int_0^\infty (a - a_{1m})^2\frac{\mathcal{F}_j(a)}{T_j^\diamond}P_j(a)da.$$

Further

$$K_k(\lambda + \mu) = p_k^\diamond \exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}b_{mk}(\lambda + \mu)^m\right),$$

with

$$b_{1k} = -\int_0^\infty a\frac{\mathcal{F}_k(a)}{p_k^\diamond}P_k(da), \qquad b_{2k} = -\int_0^\infty (a - b_{1k})^2\frac{\mathcal{F}_k(a)}{p_k^\diamond}P_k(da).$$

Substituting these relations in (A.2), we obtain

$$0 = -(\lambda + \mu) - \frac{\partial f}{\partial S}(S^*, I^*, R^*)$$

$$+ (\lambda + \mu)\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^*, I^*, R^*)T_j^\diamond q_j^\diamond \exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}c_{mj}(\lambda + \mu)^m\right)$$

$$+ \frac{\partial f}{\partial R}(S^*, I^*, R^*)q_n^\diamond \exp\left(\sum_{m=1}^\infty \frac{(-1)^m}{m!}d_m(\lambda + \mu)^m\right),$$

where

$$c_{mj} = a_{mj} + \sum_{k=1}^{j-1} b_{mk}, \quad j = 2, \ldots, n-1, \qquad c_{m1} = a_{m1}, \qquad d_m = \sum_{k=1}^{n-1} b_{mk}.$$

By Lemma A.2,

$$\begin{aligned}
0 = &-\frac{\partial f}{\partial S}(S^*, I^*, R^*) + (\lambda + \mu) \left(\sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*) T_j^\diamond q_j^\diamond - 1 \right) \\
&+ (\lambda + \mu) \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*) T_j^\diamond q_j^\diamond \left(-c_{1j}(\lambda + \mu) + \frac{c_{2j} + c_{1j}^2}{2}(\lambda + \mu)^2 \right) \\
&+ \frac{\partial f}{\partial R}(S^*, I^*, R^*) q_n^\diamond \left(1 - d_1(\lambda + \mu) + \frac{d_2 + d_1^2}{2}(\lambda + \mu)^2 \right) \\
&+ (\lambda + \mu)^4 h_1(\lambda, \mu) + (\lambda + \mu)^3 \mu h_2(\lambda, \mu),
\end{aligned}$$

with twice continuously differentiable functions h_1, h_2. By (3.5) and Taylor expansion,

$$\begin{aligned}
&\sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*) T_j^\diamond q_j^\diamond - 1 \\
&= \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I^*, R^*) T_j^\diamond q_j^\diamond - \frac{1}{\mu x} f(N - x, T_1 q_1 \mu x, \ldots, T_{n-1} q_{n-1} \mu x, q_n x) \\
&= \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, 0, R^*)(T_j^\diamond q_j^\diamond - T_j q_j) \\
&\quad + \frac{1}{2} \sum_{j,k=1}^{n-1} \frac{\partial^2 f}{\partial I_j \partial I_k}(S^*, 0, R^*) \mu x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond + \mu^2 h_0(\mu),
\end{aligned}$$

with a generic continuously differentiable function h_0. Now

$$(T_j^\diamond q_j^\diamond - T_j q_j) = -\mu(T_j' q_j^\diamond + T_j^\diamond q_j') + \mu^2 O(\mu),$$

where T_j' and q_j' are derivatives of T_j and q_j with respect to μ evaluated at $\mu = 0$. Hence $-T_j' = T_j^\diamond a_{1j}$, while

$$q_j' = \sum_{k=1}^{j-1} \frac{p_k'}{p_k} q_j = -q_j \sum_{k=1}^{j-1} b_{1k}.$$

So $(T_j^\diamond q_j^\diamond - T_j q_j) = \mu T_j^\diamond q_j^\diamond c_{1j}$, and using these relations we obtain

$$\begin{aligned}
0 = &-\sum_{j=1}^{n-1} \left[\frac{\partial^2 f}{\partial S \partial I_j}(S^*, 0, R^*) - \frac{\partial^2 f}{\partial I_j \partial R}(S^*, 0, R^*) q_n^\diamond \right] \mu^\diamond T_j^\diamond q_j^\diamond x \\
&+ (\lambda + \mu)^2 \sum_{j=1}^{n-1} \frac{\partial f}{\partial I_j}(S^*, I_1^*, \ldots, I_n^*) T_j^\diamond q_j^\diamond \left(-c_{1j} + \frac{c_{2j} + c_{1j}^2}{2}(\lambda + \mu) \right)
\end{aligned}$$

$$+(\lambda+\mu)\mu\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^*,0,R^*)T_j^\diamond q_j^\diamond c_{1j}$$

$$+(\lambda+\mu)\mu\frac{1}{2}\sum_{j,k=1}^{n-1}\frac{\partial^2 f}{\partial I_j\partial I_k}(S^*,0,R^*)x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond$$

$$+(\lambda+\mu)\mu\sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j\partial R}(S^*,0,R^*)q_n^\diamond T_j^\diamond q_j^\diamond x(-d_1)$$

$$+(\lambda+\mu)^4 h_1(\lambda,\mu)+(\lambda+\mu)^2\mu h_2(\lambda,\mu),$$

with continuously differentiable functions h_1, h_2. Substituting $\lambda = \epsilon\tilde{\lambda}$, dividing by $\mu = \epsilon^2$ and expanding further, we obtain

$$0=-\sum_{j=1}^{n-1}\left[\frac{\partial^2 f}{\partial S\partial I_j}(S^\diamond,0,R_n^\diamond)-\frac{\partial^2 f}{\partial I_j\partial R}(S^\diamond,0,R^\diamond)q_n^\diamond\right]T_j^\diamond q_j^\diamond x^\diamond$$

$$+(\tilde{\lambda}^2+2\epsilon\tilde{\lambda})\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond\left(-c_{1j}+\frac{c_{2j}+c_{1j}^2}{2}\epsilon\tilde{\lambda}\right)$$

$$+\epsilon\tilde{\lambda}\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}+\epsilon\tilde{\lambda}\frac{1}{2}\sum_{j,k=1}^{n-1}\frac{\partial^2 f}{\partial I_j\partial I_k}(S^\diamond,0,R^\diamond)x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond$$

$$-\epsilon\tilde{\lambda}\sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j\partial R}(S^\diamond,0,R^\diamond)q_n^\diamond T_j^\diamond q_j^\diamond x^\diamond d_1+\epsilon^2 h(\tilde{\lambda},\epsilon),$$

with a continuously differentiable function h. It follows from (3.8) and the implicit function theorem that this equation has a solution $\tilde{\lambda}$ that is a continuously differentiable function of small $\epsilon > 0$. In order to find the first term in the expansion we set $\epsilon = 0$:

$$0=-\sum_{j=1}^{n-1}\left[\frac{\partial^2 f}{\partial S\partial I_j}(S^\diamond,0,R^\diamond)-\frac{\partial^2 f}{\partial I_j\partial R}(S^\diamond,0,R^\diamond)q_n^\diamond\right]T_j^\diamond q_j^\diamond x^\diamond$$

$$-\tilde{\lambda}^2\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}.$$

Hence $\tilde{\lambda}_0 = \imath\sqrt{\theta}$ with θ being given by (3.9),

$$\theta=\frac{\sum_{j=1}^{n-1}\left[\frac{\partial^2 f}{\partial S\partial I_j}(S^\diamond,0,R^\diamond)-\frac{\partial^2 f}{\partial I_j\partial R}(S^\diamond,0,R^\diamond)q_n^\diamond\right]T_j^\diamond q_j^\diamond x^\diamond}{\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}}.$$

Using the formula for $\tilde{\lambda}_0$, dividing by ϵ, and then setting $\epsilon = 0$ yields

$$0=\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond\left(-2(\tilde{\lambda}_1+1)c_{1j}-\frac{c_{2j}+c_{1j}^2}{2}\theta\right)$$

$$+\sum_{j=1}^{n-1}\frac{\partial f}{\partial I_j}(S^\diamond,0,R^\diamond)T_j^\diamond q_j^\diamond c_{1j}$$

$$+\frac{1}{2}\sum_{j,k=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial I_k}(S^\diamond, 0, R^\diamond)x^\diamond T_j^\diamond T_k^\diamond q_j^\diamond q_k^\diamond$$

$$-\sum_{j=1}^{n-1}\frac{\partial^2 f}{\partial I_j \partial R}(S^\diamond, 0, R^\diamond)q_n^\diamond T_j^\diamond q_j^\diamond x^\diamond d_1.$$

Solving for $\tilde{\lambda}_1$ yields (3.10).

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