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## "How May Infection-Age-Dependent Infectivity Affect the Dynamics of HIV/AIDS?"

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# HOW MAY INFECTION-AGE-DEPENDENT INFECTIVITY AFFECT THE DYNAMICS OF HIV/AIDS?*

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**Abstract.** Epidemiological and behavioral factors crucial to the dynamics of HIV/AIDS include long and variable periods of infectiousness, variable infectivity, and the processes of pair formation and dissolution. Most of the recent mathematical work on AIDS models has concentrated on the effects of long periods of incubation and heterogeneous mixing in the transmission dynamics of HIV. This paper explores the role of variable infectivity in combination with a variable incubation period in the dynamics of HIV transmission in a homogeneously mixing population. The authors keep track of an individual's infection-age, that is, the time that has passed since infection, and assume a nonlinear functional relationship between mean sexual activity and the size of the sexually active population that saturates at high population sizes. The authors identify a basic reproductive number $R_0$ and show that the disease dies out if $R_0 < 1$, whereas if $R_0 > 1$ the disease persists in the population, and the incidence rate converges to or oscillates around a uniquely determined nontrivial equilibrium. Though conditions are found for the endemic equilibrium to be locally asymptotically stable, undamped oscillations cannot be excluded in general and may occur in particular if the variable infectivity is highly concentrated at certain parts of the incubation period. Whether undamped oscillations can also occur for the reported one early peak and one late plateau of infectivity observed in HIV-infected individuals must be a subject of future numerical investigations.

**Key words.** HIV, AIDS, variable infectivity, infection-age, class-age, population-size-dependent contact rate, basic reproductive number, endemic equilibrium, disease-free equilibrium, disease persistence, stability change, undamped oscillations, characteristic equation, abstract differential equation, Volterra integral equation

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**Introduction.** Most epidemiological models for the transmission of infectious diseases have assumed that all infectious individuals are equally infectious during their period of infectivity. This assumption has proved to be reasonable in the study of the dynamics of communicable diseases such as influenza (see [24], [25], and references therein), as well as in the study of sexually transmitted diseases such as gonorrhea (see [48], and references therein).

In their classical work, Kermack and McKendrick present and analyze both epidemic [60], [72] and endemic models [61], [62] where the infectivity is allowed to depend on infection-age (that is, the time that has passed since the moment of infection). The Kermack and McKendrick model in this general form was largely neglected until the 1970s [52], [53], [79], [88].

The interest in the role played by variable infectivity in disease transmission dynamics has been considerably increased by the HIV/AIDS epidemic. The early infectivity experiments reported in Francis et al. [34] and the measurements of HIV antigen and antibody titers [63], [77], [80] have supported the possibility of an early

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infectivity peak (a few weeks after exposure) and a late infectivity plateau (one year or so before the onset of "full-blown" AIDS) for HIV-infected individuals. Presently, we cannot necessarily identify virus titers and infectivity levels, and we must be aware that alternative patterns of HIV infection have been found [58], [43]. Nevertheless, these findings are reason enough to study the possible effects of variable infectivity on the transmission dynamics of HIV/AIDS.

In this paper, we pursue the question of whether variable infectivity can cause undamped oscillations in AIDS incidence. This possibility is important for the interpretation of incidence data, namely, whether a decline in disease incidence can be attributed to effective behavioral changes and preventive measures, or may be partially due to an oscillatory behavior inherent in the disease dynamics.

Early analyses of models without variable infectivity (see [20]–[23]) have shown that long and variable incubation periods (time from infection to appearance of symptoms) of HIV-infection cannot excite oscillations on their own (at least not by a Hopf bifurcation). Numerical simulations of models that incorporate variable infectivity (see [1], [8], [38], [56], [57], [69]) demonstrate that the initial (transient) dynamics are very sensitive to the shape and timing of the first infectivity peak, but that the long-time dynamics show the same qualitative behavior (even in the presence of heterogeneity in sexual behavior): a steady approach to an endemic equilibrium.

The model in this paper extends the model of Castillo-Chavez et al. [21] by incorporating infection-age-dependent infectivity to study analytically whether convergence to the endemic equilibrium is a general feature or whether undamped oscillations can occur under specific circumstances. Our approach to variable infectivity is different from the one by Simon and Jacquez [83], who assume that an infected individual passes through several discrete stages of the disease with different infectivity. Among other things, they give sufficient conditions for the endemic equilibrium to be globally asymptotically stable. As we point out at the end of §3, these conditions do not apply to our model.

Various mechanisms have been found to cause undamped oscillations in time-autonomous endemic models (see [45] and [46], for surveys). One of the most commonly found reasons is return of infectives into the susceptible class with or without having spent a period of temporary immunity. Anderson et al. [2] have found sustained oscillations in a fox rabies model that were generated by the combined effects of a rapid turnover of the fox population and the relatively long latency period and the high fatality of fox rabies. Models showing similar phenomena have been considered by Brauer [10]–[12] and Pugliese [78]. Liu et al. [65], [66] have shown in their work on influenza that generalized nonlinear incidence rates can also generate sustained oscillations. The work by Chastillo-Chavez et al. [25], [26] and Andreasen [5], [6] on influenza strongly suggests that the interaction between related multiple viral strains of influenza type A, the host immune system (cross-immunity), and age-dependent host mortality are needed to generate sustained oscillations. Diekmann and Kretzschmar [27] find periodic oscillations for the spread of an infectious disease in a population that would grow in the absence of the disease. Their model combines reduced fertility of infective individuals with pair formation. Endemic models that explicitly incorporate infection-age have so far exhibited sustained oscillations only when infective individuals are allowed to return to the susceptible class; it depends on the form of the infection-age-dependent infectivity curve and the distribution of the length of the immunity period whether or not undamped oscillations actually occur (see [28], [29], [35], [36], and [47]).

All these mechanisms that are found to generate sustained oscillations do not

operate in the case of HIV dynamics. Most of the models described above (the rabies model and the models considered by Brauer, Pugliese, and Diekmann and Kretzschmar are the exceptions) assume that the disease is essentially nonfatal and does not reduce fertility and that the population size is constant; assumptions that are not realistic in HIV modeling. Even if we assume a constant recruitment rate into the sexually active population (as we do), the population size will vary with time due to the disease fatalities. This makes it necessary to model the functional relationship between the per capita number of sexual contacts $C = C(T)$ and the number of sexually active individuals $T$. For sexually transmitted diseases, it seems reasonable to assume a saturation effect for partner acquisition, namely, that $C(T)$ becomes largely independent of $T$ if the population size $T$ is large.

In our model, the possible occurrence of undamped oscillations will depend mainly on the interaction of the following epidemiological entities: the saturation of the functional relationship $C$, the length distribution of the sexual activity period of exposed individuals, and the distribution of infectivity over that period. Undamped oscillations (caused by an unstable endemic equilibrium) can be ruled out if the probability that an infected individual is still sexually active is a convex function of infection-age or if the infectivity is sufficiently evenly distributed over the activity period (as it is already suggested by the findings of Castillo-Chavez et al. [20]–[23] or if $C(T)/T$ is close to a constant, i.e., there is not saturation in partner acquisition. Undamped oscillations may occur if all the following conditions are satisfied simultaneously:

(i) The probability that an infected individual is still sexually active is sufficiently far away from being a convex function of infection-age;

(ii) There is sufficient saturation in partner acquisition, i.e., the number $C(T)$ of actual partners per capita is largely independent of slight changes in the number of available partners $T$;

(iii) The period of sexual activity is not too short for infected individuals in relation to uninfected ones;

(iv) The fraction of infected individuals in the sexually active population is neither too low nor too high;

(v) The infection-age-distributed infectivity is highly concentrated at specific parts of the incubation period.

Conditions (i)–(iii) appear to be realistic for AIDS. Condition (v) is rather extreme though several infectivity peaks are allowed (the timing of which must be interrelated in a certain way that presumably is not consistent with reality). We emphasize that this paper completely relies on analytical methods. Future numerical work must show whether undamped oscillations also occur for infection-age distributions with an early peak and a late plateau.

In other respects, we can show the same phenomena as for the model by Castillo-Chavez et al. [21] with constant infectivity. We can identify a basic reproductive number $R_0$ in terms of the model parameters such that, for $R_0 < 1$, the disease dies out and, for $R_0 > 1$, persists in the population. (Similar results have been shown by Simon and Jacquez [83] and by Lin, Hethcote, and van den Driessche [64] for their models with several infectious stages.) If the basic reproductive number exceeds 1, there is a unique endemic equilibrium that is locally asymptotically stable for $R_0$ slightly larger than 1, but that may lose stability if $R_0$ increases.

The work of Castillo-Chavez et al. [22], [23], Huang [54], and Huang, Cooke, and Castillo-Chavez [55] has shown that multiple endemic equilibria may exist in epidemic models (of the type illustrated in this article) for heterogeneously mixing populations, even if the infectivity does not depend on infection-age.

3.

The paper is organized as follows: §1 introduces our model with infection-age-dependent infectivity; §2 discusses the existence of endemic stationary states (in relation to the basic reproductive number); §3 relates the basic reproductive number to disease extinction or persistence; §4 presents the epidemiological content of our stability results; §5 discusses the significance of our results and projects future work. Longer proofs appear in an appendix. The proofs of §3 can be found in Appendix A.1, whereas the proofs of the stability results in §4 are contained in Appendices A.2 and A.3. The examples in §4 are discussed in their mathematical aspects in Appendix A.4. Most of the results of this paper were stated, without proofs and not completely correct, in [87].

**1. A model with infection-age-dependent infectivity.** The transmission dynamics of HIV in a homogeneously mixing, male homosexual population is modeled through the incorporation of the following ingredients:

- A nonlinear functional relationship between mean sexual per capita activity and the size of the sexually active population $T$. We assume that it increases linearly for small population sizes while saturating for large values of $T$.
- A stratification of the infected part of the sexually active population according to infection-age, i.e., time since the moment of being infected.
- An infection-age-dependent rate of leaving the sexually active part of the population by force of the disease.
- An infection-age-dependent infectivity.

The model considered in this paper shares the first three features with the models considered by Castillo-Chavez et al. [20]–[23], though the stratification according to infection-age is not explicit there. The key modification, infection-age-dependent infectivity, has been added to study its effect in combination with the other mechanisms. The model does not include heterogeneities other than infection-age-dependent infectivity. By restricting itself to the homosexual part of a population that is replenished by constant recruitment, it does not reflect the joint effects of HIV dynamics and the demographic dynamics of the population (see [69]–[71], [15]).

We divide the homosexually active population under consideration into three groups: $S$ (uninfected, but susceptible); $I$ (HIV infected with hardly any symptoms); and $A$ (fully developed AIDS symptoms). $A$-individuals are assumed to have been sexually inactivated by the disease. Individuals that are still sexually active ($S$ and $I$) are supposed to choose their partners at random (although the rate of partnership change depends on the size of the active population $T = S + I$).

Furthermore, $t$ denotes time, whereas $\tau$ denotes time since the moment of being infected, i.e., infection-age. As a time unit, we choose the average length of the period of sexual activity for healthy individuals. We assume that individuals are recruited into the sexually active population at a constant rate $\Lambda$ and that the length of the sexually active period is exponentially distributed such that healthy individuals become sexually inactive at a constant rate $\mu$. As we have chosen the average length $1/\mu$ of the activity period to be 1, $\mu = 1$. Infected individuals with infection-age $\tau$ become sexually inactive by force of the disease (and enter the $A$ class) at a rate $\alpha(\tau)$; consequently, the proportion of those individuals that are still sexually active, given that they were infected $\tau$ time units ago, is given by

$$P_{\alpha+1}(\tau) = \exp\left(-\tau - \int_0^\tau \alpha(\rho)d\rho\right).$$

4.

We stratify the infected part of the population $I$ according to age of infection

$$I(t) = \int_0^\infty i(t,\tau)d\tau,$$

where $i(t,\cdot)$ denotes the infection-age density at time $t$.

The proportion of sexually active infected individuals with infection-age $\tau$ in the age-interval $[\tau, \tau+\Delta\tau]$ is $(i(t,\tau)/T(t))\Delta\tau$ with $T = S+I$ being the size of the sexually active population. We assume that a typical susceptible individual (under homogeneous mixing everybody is typical) contracts the disease from an infected partner with age of infection $\tau$ at a mean transmission rate $\lambda(\tau)$. Consequently, the per capita rate at which susceptible individuals are infected at time $t$ (given that they have a sexual contact at that time) is provided by $W(t)/T(t)$, where

$$W(t) = \int_0^\infty \lambda(\tau)i(t,\tau)d\tau.$$

We assume that $C = C(T)$, the mean number of sexual contacts that a typical individual has per unit of time, is a function of the size of the sexually active population $T = S + I$.

Combining these considerations, we arrive at the following expression for the incidence rate of infections (number of new cases of infection per unit of time) $B$:

$$B(t) = C\Big(T(t)\Big)S(t)\frac{W(t)}{T(t)}.$$

The complete dynamical model with infection-age-dependent infectivity can now be formulated as

$$\frac{d}{dt}S(t) = \Lambda - B(t) - S(t), \tag{1}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) i(t,\tau) = -(1+\alpha(\tau))i(t,\tau), \tag{2}$$

$$i(t,0) = B(t) = S(t)C(T(t))\frac{W(t)}{T(t)}, \tag{3}$$

where

$$T = I + S, \tag{4}$$

$$I(t) = \int_0^\infty i(t,\tau)d\tau, \tag{5}$$

$$W(t) = \int_0^\infty \lambda(\tau)i(t,\tau)d\tau, \tag{6}$$

$$\frac{d}{dt}A(t) = \int_0^\infty \alpha(\tau)i(t,\tau)d\tau - \nu A(t),$$

where $\nu$ denotes the rate at which an individual with fully developed AIDS symptoms dies from the disease.

In spite of the fact that the $A$ equation—for the number of individuals with fully developed AIDS symptoms (that are supposed to play no further role in the dynamics

of the disease)—is not needed to make the model well-posed, we include it here because it provides an entity that can be directly compared to data.

Note that, in contrast to earlier models by Anderson and May [3], Blythe and Anderson [7], and Castillo-Chavez et al. [21], [22], this model does not assume that, at the moment of infection, an individual is determined to follow either a severe or a mild course of the disease. By assuming that $\int_0^\infty \alpha(\tau)d\tau < \infty$, however, this model, albeit by a different mechanism, can take into account the possibility that not all individuals will develop "full-blown" AIDS.

Throughout this paper, we make the following mathematical assumptions: $\alpha(\tau)$ is a nonnegative measurable function, $\lambda(\tau)$ is a nonnegative bounded measurable function of infection-age, and $C(T)$ is a nondecreasing function of $T$. Furthermore, we assume that $C(T)$ is continuously differentiable and that $C(T) > 0$ whenever $T > 0$.

Later, we will also assume that

$$M(T) = \frac{C(T)}{T}$$

is a nonincreasing function of $T$; i.e., $C$ increases in a sublinear way that reflects a saturation effect.

There are various ways of handling problems (1)–(6), each of which has its definite advantages. We may deal with this system as an abstract ordinary differential equation (see [85, §7]). This approach provides a dynamical system in terms of $S$ and $i$ and is useful to prove instability of equilibria and persistence of solutions. The same dynamical system can be obtained by integrating (2) along characteristic lines [89]. Otherwise, we use integration along characteristic lines to reduce (1)–(6) to the following system of integral equations:

$$S = \Lambda - B * P_1 + f_1, \tag{7}$$

$$I = B * P_{\alpha+1} + f_2, \tag{8}$$

$$W = B * Q + f_3, \tag{9}$$

$$B = SM(S + I)W. \tag{10}$$

Here we have used the notation

$$P_\alpha(\tau) = \exp\left(-\int_0^\tau \alpha(s)ds\right), \tag{11}$$

$$Q(\tau) = \lambda(\tau)P_{\alpha+1}(\tau), \tag{12}$$

$$(B * P)(t) = \int_0^t B(t-s)P(s)ds, \tag{13}$$

$$f_1(t) = (S(0) - \Lambda)e^{-t}, \tag{14}$$

$$f_2(t) = \int_t^\infty i(0, \tau - t)\frac{P_{\alpha+1}(\tau)}{P_{\alpha+1}(\tau - t)}d\tau, \tag{15}$$

$$f_3(t) = \int_t^\infty i(0, \tau - t)\lambda(\tau)\frac{P_{\alpha+1}(\tau)}{P_{\alpha+1}(\tau - t)}d\tau, \tag{16}$$

$$M(T) = \frac{C(T)}{T}. \tag{17}$$

$P_1$ and $P_{\alpha+1}$ are defined in analogy to $P_\alpha$. We easily observe that

$$f_j(t) \to 0, \quad t \to \infty, \quad j = 1, 2, 3. \tag{18}$$

Some of the expressions defined above have an intuitive biological interpretation. For example, $P_1(s) = e^{-s}$ gives the proportion of healthy individuals that remain sexually active $s$ time units after having entered the active population. $P_{\alpha+1}(\tau)$ can be identified with the proportion of those infected individuals of infection-age $\tau$ that are still sexually active. $Q(\tau) = \lambda(\tau)P_{\alpha+1}(\tau)$ in (12) can be interpreted as the effective infectivity of an individual with infection-age $\tau$. We assume that $Q$ is of bounded variation on $[0, \infty)$.

By substituting (10) into (7)–(9), we obtain a system of convolutional-type Volterra integral equations for which a well-developed theory is available (see [74] or [37]). Alternatively, we can substitute (7)–(9) into (10) and obtain a single integral equation, which is not of the common Volterra type.

From (1) we realize that $S(t)$ remains positive (nonnegative) if $S(0)$ has the corresponding property. It is then easily checked from the various equations that nonnegativity is preserved under the solution flow. Integrating (2) over $\tau$ and combining it with (1) and (4) yields the differential inequality

$$\frac{d}{dt}T \leq \Lambda - T, \tag{19}$$

which provides us with the a priori estimate

$$S(t), I(t) \leq T(t) = S(t) + I(t) \leq \Lambda + (T(0) - \Lambda)e^{-t}. \tag{20}$$

Note that, in the absence of the disease, we have

$$S(t) = T(t) \to \Lambda, \qquad t \to \infty.$$

Using the theory in [89] or [85], or applying standard fixed-point arguments to (7)–(10), we easily show that the model is well-posed; i.e., there is a unique nonnegative solution for nonnegative initial conditions. Furthermore, the mathematical theory shows that the solutions depend continuously on the initial conditions and that the functions $S, I, W, B$ are continuous and satisfy the estimate given by inequality (20).

**2. Stationary states and the basic reproductive number.** In this section, we concentrate on the study of the existence of stationary states, that is, equilibria or time-independent solutions. These special solutions are important because they are candidates for the asymptotic behavior of the disease dynamics. It will turn out that there are only two equilibria: the infection-free state and the endemic state.

Until recently, it was common belief that most epidemic models had at most these two equilibria. Earlier studies (see [48], [25], [24], and references therein) supported this conjecture even for heterogeneously mixing populations. Recent studies (see [22], [23], [54], and Huang, Cooke, and Castillo-Chavez [55]) have shown, however, that multiple endemic equilibria exist.

The existence of endemic equilibria is usually intimately connected to the basic reproductive number $R_0$, which can be determined in terms of the model parameters. We show in this section that the disease-free state is the only equilibrium if $R_0 < 1$. In the next section, we show that, in this case, the disease becomes extinct. When $R_0 > 1$, there exists a unique endemic equilibrium (as we see in this section) that is locally asymptotically stable, provided that $R_0$ is slightly larger than 1, but that may lose stability if $R_0$ increases (see §4). Even if unstable, the endemic equilibrium provides some information about the severity of the disease, as we illustrate in §3.

So, it can serve as a starting point for the development and evaluation of control measures—an approach that has been useful in the management of other diseases, specifically of gonorrhea (see [48], and references therein).

Clearly, system (1)–(6) always has the disease-free equilibrium

$$S_0 = \Lambda, \quad I_0 = 0, \quad W_0 = 0, \quad B_0 = 0, \quad i_0 = 0. \tag{21}$$

To determine the existence of an endemic equilibrium of (1)–(6), we must look for solutions of the following nonlinear system of algebraic equations:

$$S^\star = \Lambda - B^\star, \tag{22}$$

$$I^\star = B^\star \hat{P}_{\alpha+1}(0), \tag{23}$$

$$W^\star = B^\star \hat{Q}(0), \tag{24}$$

$$B^\star = \frac{S^\star}{T^\star} C(T^\star) W^\star, \qquad T^\star = S^\star + I^\star. \tag{25}$$

Equations (23) and (24) are obtained by integrating (2) for time-independent $i$ and substituting the result into (5) and (6), respectively. Alternatively, we can consider time-independent solutions of the limiting equations (for $t \to \infty$) associated with (7)–(10). (Note (18).) In (23), (24), we have used the Laplace transform notation

$$\hat{Q}(z) = \int_0^\infty e^{-za} Q(a) da, \tag{26}$$

$$\hat{P}_{\alpha+1}(z) = \int_0^\infty e^{-za} P_{\alpha+1}(a) da. \tag{27}$$

We substitute (24) into (25) and divide by $B^\star$ (which is supposed to be positive, as otherwise the equilibrium is not endemic) as follows:

$$1 = \frac{S^\star}{T^\star} C(T^\star) \hat{Q}(0), \qquad T^\star = S^\star + I^\star. \tag{28}$$

It will be convenient to formulate the endemic equilibrium equation in terms of the fraction of infected individuals

$$\xi = \frac{I^\star}{T^\star}. \tag{29}$$

Obviously,

$$\frac{S^\star}{T^\star} = 1 - \xi.$$

Furthermore, by (22), (23), and (29),

$$T^\star = S^\star + I^\star = \Lambda - B^\star + I^\star = \Lambda - \left( \frac{1}{\hat{P}_{\alpha+1}(0)} - 1 \right) I^\star = \Lambda - \left( \frac{1}{\hat{P}_{\alpha+1}(0)} - 1 \right) \xi T^\star.$$

We solve this equation for $T^\star$ as follows:

$$T^\star = \frac{\Lambda}{1 + \left( \frac{1}{\hat{P}_{\alpha+1}(0)} - 1 \right) \xi}. \tag{30}$$

8.

We substitute $S^*/T^* = 1 - \xi$ and (30) into (28). This results in the following reformulation of (28) in terms of $\xi$:

$$1 = (1-\xi)C\left(\frac{\Lambda}{1+\left(\frac{1}{\hat{P}_{\alpha+1}(0)}-1\right)\xi}\right)\hat{Q}(0). \tag{31}$$

Alternatively, we can also consider

$$1 = \frac{\Lambda - B^*}{\Lambda - B^*(1-\hat{P}_{\alpha+1}(0))}C(\Lambda - B^*(1-\hat{P}_{\alpha+1}(0)))\hat{Q}(0), \tag{32}$$

which we obtain from (28) by substituting $T^* = S^* + I^*$ and (22), (23).

We realize from (31) that the existence of a unique endemic equilibrium is intimately connected to the properties of $C(T)$. Since $C(T)$ is a monotone nondecreasing function of $T$ and $1 > \hat{P}_{\alpha+1}(0)$, the right-hand side of (31) is strictly decreasing in $\xi \geq 0$ such that there is at most one solution $\xi > 0$. For the same reason, we can conclude that there is no solution $\xi > 0$ if the right-hand side of (31) is smaller than or equal to 1 for $\xi = 0$. We note that the right-hand side of (31) is 0 if $\xi = 1$. The intermediate value theorem implies that there is a solution $\xi, 0 < \xi < 1$ of (31) if the right-hand side of (31) is strictly larger than 1 for $\xi = 0$. We conclude that the right-hand side of (31), evaluated for $\xi = 0$, plays a crucial role for the existence of an endemic equilibrium. Hence we define

$$R_0 = C(\Lambda)\hat{Q}(0). \tag{33}$$

As we see from (33), $R_0$ can epidemiologically be interpreted as the total average number of secondary cases an infective individual can produce if it is introduced into the disease-free population (at its equilibrium size $\Lambda$). ($\hat{Q}(0) = \int_0^\infty Q(\tau)d\tau$ is the total infectivity of an average infective individual.) $R_0$ is called the *basic reproductive number* of the disease.

Consequently, we have proved the following threshold result for the existence of an endemic equilibrium.

THEOREM 1. *If $R_0 \leq 1$, there exists only the disease-free equilibrium. If $R_0 > 1$, there is a unique endemic equilibrium.*

**3. Disease extinction or persistence? The basic reproductive number once more.** Theorem 1 is a static result that does not provide us with a relation between basic reproductive number and the actual disease dynamics. It only gives us information about the existence of a very special state in which the disease persists. In this section, we relate the basic reproductive number to the extinction and persistence of the disease.

Mathematically, we use both the model formulation as an abstract differential equation and as a system of Volterra integral equations of convolution type. For exploiting the second formulation, Fatou's lemma will be an important tool. The following notation will be useful. For a bounded real-valued function $f$ defined on $[0,\infty)$, we set

$$f_\infty = \liminf_{t\to\infty} f(t), \qquad f^\infty = \limsup_{t\to\infty} f(t).$$

The following theorem connects the basic reproductive number to the extinction of the disease.

THEOREM 2. *Let $R_0 < 1$. Then the disease-free equilibrium is globally attractive. In particular, we have*

$$B(t), V(t), W(t) \to 0, \quad S(t) \to \Lambda \qquad \text{for} \quad t \to \infty.$$

*Proof.* We use the model formulation (7)–(10). First, we apply Fatou's lemma to (10) and use estimate (20) and the assumption that $C$ is nondecreasing, below:

$$B^\infty \leq C(\Lambda) W^\infty.$$

Next, we apply Fatou's lemma to (9) as follows:

$$W^\infty \leq B^\infty \hat{Q}(0).$$

We substitute the second inequality into the first and use the definition of $R_0$ in (33) as follows:

$$B^\infty \leq R_0 B^\infty.$$

As $R_0 < 1$, $B^\infty$ must be 0; i.e., $B(t) \to 0, t \to \infty$. The remaining parts of our assertion now follow by applying Lebesgue's theorem of dominated convergence to (7)–(9).

For our model, it is not possible generally to obtain a global convergence result if $R_0 > 1$. The condition for global stability of the endemic equilibrium found by Simon and Jacquez [83] does not apply to our model. Their model can mathematically be considered a discretization of ours with respect to infection-age, and our model, in turn, can be regarded as the limit of their model if the number of infectious stages $m$ goes to infinity and their rate $k$ of transition from one to the next stage equals $k = m\kappa$ with some strictly positive constant $\kappa$. If $k = m\kappa$, the global stability condition (50) in [83] does not hold for $m$ tending to infinity.

We can obtain some global information, however, provided that we make the following assumption:

$$M(T) = \frac{C(T)}{T} \text{ is a monotone nonincreasing function of } T.$$

This assumption is supposed to hold throughout the remainder of this paper.

THEOREM 3. *Let $R_0 > 1$. Then the following holds:*

(i) $B_\infty \leq B^*, I_\infty \leq I^*$;

(ii) *Let $\lambda(a)$ be strictly positive on a nonempty open interval. Let $a_+ \leq \infty$ be the smallest $\tilde{a}$ such that $\lambda(a) = 0$ for almost all $a \geq \tilde{a}$ and assume that*

$$\int_0^{a_+} I(0,a)da \; > 0.$$

*Then*

$$B^\infty \geq B^*, \qquad I^\infty \geq I^*.$$

*In particular, there exist sequences $s_j, t_j \to \infty, j \to \infty$ such that*

$$B(s_j) \to B^*, \quad I(t_j) \to I^*, \quad j \to \infty.$$

Although Theorem 3 does not state the global stability of the endemic equilibrium, it at least guarantees that, infinitely often as time tends to infinity, the number of infected individuals $I(t)$ gets arbitrarily close to its endemic equilibrium value. The

proof of Theorem 3 uses integral equation and comparison techniques and can be found in Appendix A.1.

In particular, Theorem 3(ii) implies that, if the basic reproductive number strictly exceeds 1, the disease does not die out, but persists in the population in a weak, but uniform, sense insofar as $\limsup_{t\to\infty} I(t) \geq I^*$ and the lower asymptotic bound $I^*$ does not depend on the initial condition (with the exception of the requirement that there are secondary cases). It does not settle the questions, however, whether $I$, the total number of infected individuals, will be bounded away from zero (strong disease persistence) if $R_0 > 1$ and whether this bound is independent of the initial conditions (uniform disease persistence). To address these questions, we switch from the Volterra integral formulation (7)–(10) to the abstract differential equation formulation (1)–(6), the solutions of which induce a dynamical system (as follows from the theory developed by Webb [89] and the theory developed by Thieme [85]). Using the persistence theory that Hale and Waltman [42] elaborated for infinite-dimensional dynamical systems or the persistence theory developed by Thieme [86], we can show (see Appendix A.1) that the disease persists in the population in the following strong (and even uniform) sense.

THEOREM 4. *Let $\lambda(a)$ be positive on a nonempty open interval. Furthermore, let $a_+$ be the smallest $\tilde{a}$ such that $\lambda(a) = 0$ for almost all $a \geq \tilde{a}$ and assume that*

$$\int_0^{a_+} I(0,a)da > 0.$$

*Then, if $R_0 > 1$,*

$$\liminf_{t\to\infty} I(t) > \epsilon > 0$$

*with $\epsilon$ not depending on the initial conditions.*

The dynamical systems persistence theory does not give us information, however, as to whether $B$ and $W$ are bounded away from zero, too.

**4. Stability of the endemic equilibrium.** The stability of the endemic equilibrium is of epidemiological interest for at least two reasons: In the case of locally asymptotic stability, in many instances, it is the ultimate state of the epidemic, though only a global stability analysis would provide the definite answer to this question. In our model, this is a definite possibility, as there is only one endemic equilibrium and the disease-free equilibrium becomes a repeller as soon as the endemic equilibrium comes into existence. On the other hand, if an endemic equilibrium is unique and unstable, undamped oscillations of the disease dynamics around this equilibrium are very likely (compare Theorem 3).

Intuitively, local asymptotic stability means that once the course of the disease comes close to the endemic equilibrium it remains close and finally approaches it. The precise definition can be given most nicely in reference to the model formulation (1)–(6).

DEFINITION. (a) The endemic equilibrium $S^*, I^*, W^*, B^*, i^*$ of (1)–(6) with

$$i^*(\tau) = B^* P_{\alpha+1}(\tau)$$

is *locally asymptotically stable* if and only if the following two properties hold:

(i) For any $\epsilon > 0$, there is some $\delta > 0$ such that

$$|S(0) - S^*| + \int_0^\infty |i(0,a) - i^*(a)|da \leq \delta$$

implies that

$$|S(t) - S^*| + \int_0^\infty |i(t,a) - i^*(a)|da \le \epsilon \quad \text{for all} \quad t \ge 0;$$

(ii) There exists $\delta_0 > 0$ with the following property: If

$$|S(0) - S^*| + \int_0^\infty |i(0,a) - i^*(a)|da \le \delta_0,$$

then

$$|S(t) - S^*| + \int_0^\infty |i(t,a) - i^*(a)|da \quad \longrightarrow 0 \quad \text{for } t \to \infty.$$

(b) The endemic equilibrium is called *unstable* if the following holds: There exists a sequence of solutions $S_n, i_n$ to (1)–(6) and a sequence of times $t_n \to \infty$ and a positive number $\epsilon_0 > 0$ such that

$$|S_n(0) - S^*| + \int_0^\infty |i_n(0,a) - i^*(a)|\, da \quad \longrightarrow 0 \quad \text{for} \quad n \to \infty,$$

but

$$|S_n(t_n) - S^*| + \int_0^\infty |i_n(t_n,a) - i^*(a)|da \ \ge \epsilon_0 \quad \text{for all } n \in \mathbf{N}.$$

The discussion of the stability and instability of the endemic equilibrium is facilitated by switching from the original parameters of the model to the following nondimensional ones:

$$\xi = \frac{I^*}{T^*} = \frac{I^*}{S^* + I^*}, \tag{34}$$

$$\gamma := -\frac{T^* M'(T^*)}{M(T^*)}, \tag{35}$$

$$\sigma := \frac{1}{\hat{P}_{\alpha+1}(0)}. \tag{36}$$

Note that $\xi$ gives the fraction of infected individuals in the sexually active population and therefore is a dimensionless parameter satisfying $0 < \xi < 1$. Even though all values of $\xi$ in the interval $0 < \xi < 1$ are feasible (as we can see from (31) and (33) by choosing $R_0 > 1$ accordingly), not all of them may be realistic. Note that $1/\sigma = \hat{P}_{\alpha+1}(0)$ can be interpreted as the average length of the effective sexually active period of infected individuals (relative to the average length of the sexually active period of healthy individuals, our time unit). Hence it is intuitively clear, and follows from the definition of $P_{\alpha+1}$ in (11), that $\sigma > 1$. The average duration of infection has been estimated to be about ten years (see [69], [91], and references therein). If we assume that the mean length of the sexually active period of healthy individuals lies between 15 and 30 years, we obtain values of $\sigma$ in the interval [1.5, 3].

We observe that

$$\gamma = -T^* \frac{M'(T^*)}{M(T^*)} = 1 - T^* \frac{C'(T^*)}{C(T^*)}$$

12.

is a dimensionless parameter, also. As $M(T) = C(T)/T$ is nonincreasing and $C$ is nondecreasing, we have that $0 \leq \gamma \leq 1$. The following choices for $C(T)$ may give us a feeling for a reasonable range for $\gamma$.

**4.1. Mass action type contact law.** The classical epidemiological contact law is $C(T) = \beta T$. This implies that $M = \text{const}$; hence $\gamma = 0$.

This contact law is more appropriate for communicable diseases such as influenza (see [24] and [25]), but not for sexually transmitted diseases.

**4.2. C = const.** This may be a good approximation if the number of available partners is large enough and everybody could make more contacts than is practically feasible. In this case, $\gamma = 1$.

**4.3. Michaelis–Menten type contact law.** The Michaelis–Menten type contact law (or Holling functional response type 2) combines the two previous approaches by assuming that, if the number of available partners $T$ is low, the number of actual per capita partners $C(T)$ is proportional to $T$, whereas, if the number of available partners is large, there is a saturation effect that makes the number of actual partners constant. Specifically, it has the form

$$C(T) = \frac{\beta T}{1 + \kappa T}.$$

This law was first formulated by Michaelis and Menten [73] for enzyme-catalyzed reactions. It was used by Monod [76] to describe the nutrient uptake by bacteria. Later, Holling [51, p. 11] derived it to model the functional response of an invertebrate predator to the available amount to prey. A similar derivation can be made relating the number of sexual contacts to the number of available partners (compare [30] and [27]).

For the Michaelis–Menten contact law, we obtain from definition (35) that

$$\gamma = \frac{\kappa T^*}{1 + \kappa T^*}.$$

Consequently, $\gamma$ covers the whole range from 0 to 1 when $T^*$ covers the range from 0 to $\infty$. From (30), we have that

$$T^* = \frac{\Lambda}{1 + (\sigma - 1)\xi},$$

such that any value of $T^*$ between 0 and $\infty$, i.e., any value of $\gamma$ between 0 and 1, is possible (though not necessarily realistic) by choosing $\Lambda$ accordingly.

**4.4. Contact by formation of short-term pairs.** The Michaelis–Menten contact law neglects competition in partner acquisition. This is taken into account by Heesterbeek and Metz [44], who model the formation of short-term pairs to derive a contact function $C$ of the form

$$C(T) = \frac{2\theta T}{1 + 2\theta T + \sqrt{1 + 4\theta T}}.$$

Definition (35) provides that

$$\gamma = 2\theta T^* \frac{1 + (1 + 4\theta T^*)^{-1/2}}{1 + 2\theta T^* + (1 + 4\theta T^*)^{1/2}}.$$

13.

As for the Michaelis–Menten contact law, we find that $\gamma$ covers the whole range from 0 to 1, as $T^*$ covers the range from 0 to $\infty$.

In view of this discussion, we call $\gamma$ the *saturation index* of the number of partners at the endemic equilibrium. If $\gamma = 0$, there is no saturation at all because the number of actual partners is proportional to the number of available partners. If $\gamma = 1$, there is complete saturation because the number of actual partners hardly changes if the number of available partners does.

After introducing this terminology, we can formulate the following stability result.

THEOREM 5. *The endemic equilibrium is locally asymptotically stable if one of the following holds:*

(a) $\xi$ *is sufficiently close to* 0 *or to* 1;
(b) $\sigma$ *is sufficiently large*;
(c) $\gamma$ *is sufficiently close to* 0;
(d) $\lambda = \text{const}$;
(e) $P_{\alpha+1}$ *is convex.*

Assumptions (d) and (e) are special cases of the considerably more general, but very technical, condition (d) in Proposition 2 (Appendix A.3).

Apparently, the endemic equilibrium is locally asymptotically stable if the fraction of infected individuals is either low or high, if the mean length of the sexually active period of infected individuals is short compared with the length of the sexually active period of susceptible individuals, or if the saturation index is low. Furthermore, we have local stability if the infectivity is evenly distributed over the period of sexual activity. $P_{\alpha+1}$ may be convex, for example, if the length of the sexually active period of infected individuals is exponentially distributed (particularly if the inactivation rate $\alpha$ is constant), but this is presumably not the case for AIDS.

The fact that constant infectivity implies the stability of the endemic equilibrium has already been proved in [21]. In the model with variable infectivity, we can specify how much the infectivity may deviate from its mean value without destroying the stability of the endemic equilibrium. To this end, we first must introduce an appropriate mean infectivity. We recall that $\lambda(\tau)$ is actually the potential infectivity at infection-age $\tau$ because it does not come into effect if an individual has already retired from sexual activity. Remember that $P_{\alpha+1}(\tau)$ gives the proportion of individuals that are still sexually active at time $\tau$ after infection. We make it a probability density by setting

$$p(\tau) = \frac{P_{\alpha+1}(\tau)}{\int_0^\infty P_{\alpha+1}(0)}.$$

Hence

$$\bar{\lambda} = \int_0^\infty \lambda(\tau)p(\tau)d\tau$$

can be interpreted as the *effective mean infectivity*. Note that $\lambda = \bar{\lambda}$ if $\lambda$ is constant. As a measure for the deviation from the effective mean infectivity, we introduce

$$\int_0^\infty \frac{|\lambda(\tau) - \bar{\lambda}|}{\bar{\lambda}} p(\tau)d\tau.$$

Note that this expression does not change if $\lambda$ is replaced by a constant multiple of itself.

THEOREM 6. *The endemic equilibrium is locally asymptotically stable if*

$$\int_0^\infty \frac{|\lambda(\tau) - \bar{\lambda}|}{\bar{\lambda}} p(\tau)d\tau \le 1.$$

14.

Theorems 5 and 6 list so many different sufficient conditions for the endemic equilibrium to be locally asymptotically stable that we question whether the endemic equilibrium can ever lose its local stability. Theorem 6, in particular, tells us that stability loss may only occur if the infectivity distribution is sufficiently spiky. This can indeed happen if the spikes are properly located.

THEOREM 7. *Let* $0 < \gamma \leq 1$ *and*

$$\frac{1}{1+y^2}(1-\gamma) + \gamma \int_0^\infty \cos(sy) P_{\alpha+1}(s) ds < 0$$

*for some* $y > 0$. *Then there exists an infectivity distribution* $\lambda$ *with arbitrarily many peaks such that the endemic equilibrium is unstable.*

*Remark.* It is actually only the multiplicative combination $Q$ of $\lambda$ and $P_{\alpha+1}$ in (12) that is required to have a peaked distribution. The peaks are concentrated at points of the form $\tau_0, \ldots, \tau_m$, where $0 < \tau_0 < \pi/2y$ must be chosen appropriately and $\tau_j = \tau_0 + 2k_j/y$ with arbitrary numbers $k_j \in \mathbf{N}$.

The condition in Theorem 7 concerning $P_{\alpha+1}$ is easier to satisfy the closer $\gamma$ is to 1. So, apparently, the saturation index has a destabilizing effect. The requirement that $\lambda$ is concentrated at certain parts of the incubation period, i.e., that the infectivity occurs in peaks, emphasizes the importance of an infection-age-dependent infectivity. The remark shows that the endemic equilibrium can be unstable for infectivity distributions with an early peak if the condition in Theorem 7 can be satisfied for large $y$. This is the case for the following example of an inactivation rate $\alpha$ (see Appendix A.4 for mathematical details):

$$\alpha(\tau) = \begin{cases} \rho_1, & 0 \leq \tau \leq \tau_\circ, \\ \rho_2, & \tau > \tau_\circ, \end{cases} \tag{37}$$

with $0 \leq \rho_1 < \rho_2, \tau_\circ > 0$. $\rho_1$ can be interpreted as the rate at which infected individuals stop sexual activity because they have tested HIV-positive, whereas the larger rate $\rho_2$ also incorporates inactivation by AIDS symptoms. $\tau_\circ$ is the infection-age at which symptoms start appearing. By (11), the proportion $P_{\alpha+1}(\tau)$ of infected individuals that are still sexually active at infection age $\tau$ is given by

$$P_{\alpha+1}(\tau) = \begin{cases} e^{-(1+\rho_1)\tau}, & 0 \leq \tau \leq \tau_\circ, \\ e^{-(1+\rho_1)\tau_\circ} e^{-(1+\rho_2)(\tau-\tau_\circ)}, & \tau \geq \tau_\circ. \end{cases} \tag{38}$$

Hence, in view of Theorem 5(e), $P_{\alpha+1}$ consists of two convex parts, but is not convex itself.

*Example* 1. Let the inactivation rate $\alpha$ be given by (37). If $\rho_2 - \rho_1$ is sufficiently large and $\gamma, 0 < \gamma \leq 1$, is sufficiently close to 1, then there exists an infectivity distribution $\lambda$ with arbitrarily many peaks, including early peaks, such that the endemic equilibrium is unstable.

The peaks of $\lambda(\tau)$ are concentrated at points of the form $\tau_0, \ldots, \tau_m$ with

$$0 < \tau_0 < \frac{\tau_\circ}{2s+4n}, \qquad 1 < s < 2,$$

$$\tau_j = \tau_0 + \frac{2k_j}{s+2n}\tau_\circ, \qquad k_j \in \mathbf{N},$$

where $n \in \mathbf{N}$ must be chosen sufficiently large.

In this example, the time moments at which the infectivity is concentrated satisfy some kind of resonance relation among each other and also to the time $\tau_\circ$ after infection at which symptoms start to appear. It is doubtful whether this mathematical relation is compatible with the biological relation between the time at which AIDS symptoms occur for the first time and the time at which the second infectivity rise occurs. Moreover, the empirical data suggest that the second infectivity rise has the form of a plateau rather than of a peak. Though the multiplicative combination $Q$ in (12) of the infectivity distribution $\lambda$ with the probability $P_{\alpha+1}$ of being still sexually active brings the plateau-like shape of $\lambda$ finally down again, the "effective infectivity" $Q$ is presumably too spread out to be of the form described in Theorem 7 and the subsequent remark.

To illustrate the possible effect of a physiologically sensible coupling between the infectivity distribution and the inactivation rate, we consider the following example of variable infectivity without a first peak, but with a late plateau. We assume that the infectivity is zero until the moment where symptoms occur and a positive constant thereafter; see the example below:

$$\lambda(\tau) = \begin{cases} 0, & 0 \le \tau < \tau_\circ, \\ \lambda_\circ, & \tau > \tau_\circ. \end{cases} \tag{39}$$

It is suggestive that the moments where the symptoms start to appear and the infectivity rises are related in time because both effects are caused by the breakdown of the immune system. The above choice, which identifies these two moments, is the easiest way to mimic this relation. It is certainly an extreme idealization, but not totally artificial. Note that the "effective infectivity" $Q$, the product of $\lambda$ and $P_{\alpha+1}$, has a rather sharp peak at $\tau_\circ$ if $\rho_2$ is large. Nevertheless, the endemic equilibrium is stable.

*Example* 2. Let $\alpha$ and $\lambda$ be given by (37) and (39). Then the endemic equilibrium is locally asymptotically stable.

In a next step, we would like to combine a late infectivity plateau as described in Example 2 with an early peak as in Example 1. If the early peak alone would destroy the local stability, the combined distribution will have an unstable endemic equilibrium as well, provided that the early peak dominates the late plateau. Conversely, if the late plateau dominates the early peak, the endemic equilibrium will be stable. Further (presumably numerical) investigations would clarify how much the early peak must dominate the late plateau for instability to be possible.

**5. Conclusions.** Several mathematical studies of epidemic models have identified mechanisms that are both capable and incapable of generating sustained oscillations (see [46] and [45] for surveys), and as discussed in the Introduction of this paper, most of these mechanisms are inadequate in the case of HIV.

In our model, the saturation of mean per capita sexual activity interacts with an infection-age-dependent removal rate (from sexual activity by the disease) and an infection-age-dependent infectivity. We have shown in this paper that the unique endemic equilibrium can lose its stability (thus presumably generating sustained oscillations) by a rather unique combination of conditions (see the Introduction and §4). The endemic equilibrium is locally asymptotically stable if any of the reasonable conditions (i)–(iv) in the Introduction are not satisfied. Condition (v)—the infection-age-distributed infectivity is highly concentrated at certain parts of the incubation period—emphasizes the possible relevance of variable infectivity on the dynamics of an HIV epidemic. Whereas the endemic equilibrium is locally asymptotically stable

as long as the infectivity is sufficiently evenly distributed over the activity period (Theorem 6), we have shown the possibility of sustained oscillations if the infectivity distribution has sufficiently sharp peaks that are suitably situated. Example 1, in §4, suggests that the first peak can be early. Example 2 shows, however, that, if we restrict to infectivity distributions with one late peak or one late plateau, the endemic equilibrium may be stable if the peak (or plateau) is related to the inactivation rate in an epidemiologically sensible way. This leaves the stability question open for distribution with one early peak and one late plateau when the late plateau is realistically linked with the inactivation rate. Undamped oscillations may occur if the early peak sufficiently dominates the late plateau, whereas the endemic equilibrium is stable if the plateau is the dominating part.

Though these results show that the stability of the endemic state definitely cannot be taken for granted, they allow the cautious conjecture that the endemic equilibrium is locally asymptotically stable for realistic inactivation rates and infectivity distributions. This conjecture is supported by the numerical simulations of models that incorporate variable infectivity by Anderson and May [3], Hyman and Stanley [56], [57], Blythe and Anderson [8], Anderson et al. [1], and Gupta and Anderson [38]. Our model ignores the fact that not only the infectivity, but also the timing of the first infectivity peak and of the late infectivity plateau, may be highly variable. This variability has the effect that, on the average, the early peak and the late plateau are spread out; this presumably increases the odds that the endemic equilibrium is locally stable.

Whereas the results in this paper completely rely on analytical techniques, we plan to numerically clarify how much the early peak must dominate the late plateau for undamped oscillations to occur. Our stability criterion can be used to determine numerically in which parameter range the endemic equilibrium is unstable. Although simulations of the full model will be indispensable for showing whether the amplitudes of the oscillations are large enough to be epidemiologically significant, we feel that they need to be guided by the previous exploration of the critical parameter range.

The uncertainty of whether the endemic equilibrium is stable raises the question of whether it should be discarded as some kind of measure of the severity of the disease when unstable. It provides some information, however, because we show that the number of infected individuals, for example, gets infinitely often arbitrarily close to its endemic equilibrium value as time tends to infinity. Of course, it would be more useful to know whether the time averages converge (as time tends to infinity) toward the endemic equilibrium.

We remark that variable infectivity is just one of the important factors involved in HIV dynamics. Other important factors are the following:

- Heterogeneity in sexual behavior and resistance to HIV infection (see [9], [13], [14], [18], [19], [26], [49], [50], [59], [75], [81], [84], [90], and references therein);
- Pair formation (particularly in heterosexual populations) (see [31], [32], [39], and [41]).

The analytical study of a model that incorporates variable infectivity and heterogeneous mixing and/or pair formation looks like a formidable task (see [40]). However, mathematical studies of submodels of this general model are central to the execution of extensive numerical simulations of more detailed models.

We conclude with a not very optimistic view of the predictive value of mathematical models for HIV transmission. The recent literature in HIV modeling reveals a *potentially* very complex picture: multiple endemic equilibria and the possibility of oscillations. This dynamic behavior is not observed in less-detailed versions of these

models (see [20] and [21]), indicating that very aggregated versions of these models may not be adequate. Unfortunately, detailed models require more data (most of which are available but not of sufficient quality). As [67], [68], have shown, these demands put very severe limits on our ability to generate accurate predictions. The theoretical value of these models is nevertheless very important.

**Appendix A.1. Disease extinction or persistence. Proof of the results in §3.** In the proof of Theorem 3, we use the following inequality several times.

LEMMA. *For* $0 < S_1 < S_2, I_1 \geq I_2 \geq 0$,

$$S_1 M(S_1 + I_1) < S_2 M(S_2 + I_2).$$

*Proof.* As $C$ is nondecreasing, we have

$$S_1 M(S_1 + I_1) = \frac{S_1 C(S_1 + I_1)}{S_1 + I_1} < \frac{S_2 C(S_2 + I_1)}{S_2 + I_1} = S_2 M(S_2 + I_1).$$

As $M(T) = C(T)/T$ is nonincreasing, the assertion follows.

*Proof of Theorem* 3. (i) From (10) it holds that

$$B^\infty \leq \limsup_{t\to\infty} \frac{S(t)C\Big(S(t) + I(t)\Big)}{S(t) + I(t)} W^\infty.$$

By the lemma,

$$B^\infty \leq \frac{S^\infty C(S^\infty + I_\infty)}{S^\infty + I_\infty} W^\infty.$$

We apply Fatou's lemma to (9) as follows:

$$W^\infty \leq B^\infty \hat{Q}(0).$$

We substitute this inequality into the previous one and divide by $B^\infty$. Note that we can assume $B^\infty$ to be strictly positive (otherwise, $B_\infty \leq B^\infty = 0$, and the proof would be finished). It follows that

$$(\heartsuit) \qquad 1 \leq \frac{S^\infty C(S^\infty + I_\infty)}{S^\infty + I_\infty} \hat{Q}(0).$$

We apply Fatou's lemma to (7) and (8) and use (18) as follows:

$$S^\infty \leq \Lambda - B_\infty, \qquad I_\infty \geq B_\infty \hat{P}_{\alpha+1}(0).$$

We now suppose that $B_\infty > B^\star$ and derive a contradiction. First, by (22) and (23), $S^\infty < S^\star, I_\infty > I^\star$. By the lemma, we can substitute these inequalities into ($\heartsuit$) as follows:

$$1 < \frac{S^\star C(S^\star + I^\star)}{S^\star + I^\star} \hat{Q}(0) = \frac{S^\star C(T^\star)}{T^\star} \hat{Q}(0).$$

By (28), however, the right-hand side of this inequality is 1, a contradiction.

(ii) From the lemma, we have

$$(\diamondsuit) \qquad \liminf_{t\to\infty} S(t)M(T(t)) \geq S_\infty M(S_\infty + I^\infty).$$

We apply Fatou's lemma to (7) and (8) and use (18) as follows:

$$S_\infty \geq \Lambda - B^\infty, \qquad I^\infty \leq B^\infty \hat{P}_{a+1}(0).$$

We suppose that $B^\infty < B^*$ and derive a contradiction. First, we obtain from the last inequality and (22), (23) that

$$S_\infty > S^*, \qquad I^\infty < I^*.$$

By the lemma, we can substitute these inequalities into ($\diamondsuit$) and obtain

$$\liminf_{t\to\infty} S(t)M(T(t)) > S^*M(S^* + I^*).$$

Hence we find $\tilde{s} \geq 0$ and $\beta > S^*M(S^* + I^*)$ such that

$$S(t+s)M(T(t+s)) \geq \beta, \qquad s \geq \tilde{s}, t \geq 0.$$

By (28),

$$\beta\hat{Q}(0) > 1.$$

From (10) and (9),

$$B(t+s) \geq \beta\left(\int_0^t B(t+s-a)Q(a)da + \int_0^s B(s-a)Q(a+t)da\right)$$

for $t \geq 0, s \geq \tilde{s}$. It follows from the assumption in Theorem 3(ii) that the initial infectives produce secondary cases. Actually, we can show that there is some $\tilde{t}$ such that $B(t) > 0$ for $t \geq \tilde{t}$. Hence by choosing $s$ large enough we can achieve that

$$g(t) = \beta\int_0^s B(s-a)Q(a+t)da > 0 \quad \text{for some } t > 0.$$

We fix $s$ and set $u(t) = B(t+s)$. This way we obtain the following renewal inequality for $u$:

$$u(t) \geq \beta\int_0^t u(t-a)Q(a)da + g(t)$$

with

$$\beta\hat{Q}(0) > 1, \quad g \geq 0, \quad g \not\equiv 0.$$

We now apply a standard comparison argument for Volterra integral equations. See [37, p. 344] and the celebrated renewal theorem formulated by Sharpe and Lotka [82], first rigorously proved by Feller [31]. (See [89, Thm. 4.10] for a proof and further references.) This yields that $u(t)$ and hence $B(t)$ tend to infinity as $t \to \infty$, in contradiction to our assumption that $B^\infty < B^*$.

Analogous statements for $B$ can now be derived for $S, I, W$ by using Fatou's lemma and the equilibrium equations.

*Proof of Theorem* 4. It follows from Webb [89] and Thieme [85] that the solutions to system (1)–(6) induce a dynamical system to which we can apply Theorem 4.2 of Hale and Waltman [42]. In checking the assumptions of this theorem, we use the terminology by Hale and Waltman. Our state space $X$ is given by elements $(S, i)$, where $S$ is a nonnegative number and $i$ a nonnegative integrable function on $[0, a_+)$, where $a_+$ is the number specified in our Theorem 3(ii). We choose the "boundary" $\partial X$ of

our state space to be formed by the elements of the form $(S,0)$. In our case, the flow on $\partial X$ is extremely simple: All solutions in $\partial X$ converge to the state $(\Lambda,0)$. This is a much stronger property than assumption (iv) in Theorem 4.2. It follows from our Theorem 3(ii) that $I^\infty > I^*$. This means in particular that the distance from $\partial X$ to any solution starting outside $\partial X$ does not converge to zero. Thus assumption (4.2) by Hale and Waltman is satisfied. From our estimate (20), we see that the dynamical system induced by (1)–(6) has a bounded attractor; i.e., it is point dissipative (assumption (ii) in Theorem 4.2). From (20) we realize as well that the orbit of any bounded set is bounded (assumption (iii) in Theorem 4.2). Assumption (i), where the dynamical system is asymptotically smooth (i.e., the trajectory of every forward invariant bounded set is attracted by a compact set), can be proved in the same way as Proposition 3.16 by Webb [89].

**Appendix A.2. Stability of the endemic equilibrium via a characteristic equation.** Using results from the theory of evolution equations (abstract differential equations), specifically, Corollary 4.3 and §7 in Thieme [85] or Theorem 4.13 in Webb [89], it is possible to approach the stability of the endemic equilibrium for the infinite-dimensional system (1)–(6) in the same way as for a finite system of ordinary differential equations. Hence we set

$$S = S^* + s, \quad i = i^* + u, \quad I = I^* + v, \quad W = W^* + w$$

and consider the variational equations for $s, u, v, w$ related to (1)–(6). In other words, we linearize (1)–(6) around the endemic equilibrium as follows:

$$\frac{d}{dt}s(t) = -u(t,0) - s(t), \tag{40}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)u(t,a) = -(\alpha(a)+1)u(t,a), \tag{41}$$

$$u(t,0) = s(t)M(T^*)W^* + (s+v)S^*M'(T^*)W^* + wS^*M(T^*), \tag{42}$$

where

$$v(t) = \int_0^\infty u(t,a)da, \tag{43}$$

$$w(t) = \int_0^\infty \lambda(a)u(t,a)da. \tag{44}$$

To study the stability of this linear system we look for solutions to (40)–(44) of the exponential form

$$s(t) = e^{zt}\tilde{s}, \qquad u(t,a) = e^{zt}\tilde{u}(a) \tag{45}$$

with a complex number $z$ and $\tilde{s} \neq 0$ or $\tilde{u} \not\equiv 0$.

The endemic equilibrium will be locally asymptotically stable, provided that, for all solutions of this form, the real part of $z$ is strictly negative. It will be unstable if there is at least one such solution with the real part of $z$ being strictly positive.

Substituting (45) into (40)–(44) yields

$$z\tilde{s} = -\tilde{u}(0) - \tilde{s}, \tag{46}$$

$$z\tilde{u}(a) + \frac{d}{da}\tilde{u}(a) = -(\alpha(a) + 1)\tilde{u}(a), \tag{47}$$

$$\tilde{u}(0) = \tilde{s}W^*M(T^*) + (\tilde{s} + \tilde{v})S^*M'(T^*)W^* + \tilde{w}S^*M(T^*), \tag{48}$$

$$\tilde{v} = \int_0^\infty \tilde{u}(a)da, \tag{49}$$

$$\tilde{w} = \int_0^\infty \lambda(a)\tilde{u}(a)da. \tag{50}$$

From (46) we obtain

$$\tilde{s} = -\frac{\tilde{u}(0)}{1+z}. \tag{51}$$

We solve (47) for $\tilde{u}$ and fit the result into (49) and (50) as follows:

$$\tilde{v} = \tilde{u}(0)\hat{P}_{\alpha+1}(z), \tag{52}$$

$$\tilde{w} = \tilde{u}(0)\hat{Q}(z). \tag{53}$$

Note that $\tilde{u}(0)$ must be different from zero because otherwise both $\tilde{s} = 0, \tilde{u} \equiv 0$. Fitting (51)–(53) into (48) and dividing by $\tilde{u}(0) \neq 0$ yields the *characteristic equation*

$$1 = -\frac{W^*}{1+z}(M(T^*) + S^*M'(T^*)) + S^*M'(T^*)W^*\hat{P}_{\alpha+1}(z) + S^*M(T^*)\hat{Q}(z). \tag{54}$$

We note that the same characteristic equation is obtained by linearizing the limiting equations associated with (7)–(10) around the endemic equilibrium and looking for solutions of exponential form.

Finally, we arrive at the following relation between the stability of the endemic equilibrium and the roots of the characteristic equation (54).

PROPOSITION 1. (a) *The endemic equilibrium is locally asymptotically stable if all the roots $z$ of the characteristic equation* (54) *have strictly negative real parts.*

(b) *The endemic equilibrium is unstable if the characteristic equation* (54) *has at least one root $z$ with strictly positive real part.*

**Appendix A.3. Analysis of the characteristic equation. Proofs of Theorems 5–7.** The difficulty in analyzing (54) along the lines proposed by Proposition 1 consists in the fact that $W^*, S^*, T^*$ are related by the steady state equations (22)–(25). We incorporate these relations into (54) and reformulate (54) with epidemiologically meaningful parameters that can be modified independently of each other.

From (25), (17), (23), and (29), we obtain

$$W^*M(T^*) = \frac{B^*}{S^*} = \frac{I^*}{S^*}\frac{1}{\hat{P}_{\alpha+1}(0)} = \frac{\xi}{1-\xi}\frac{1}{\hat{P}_{\alpha+1}(0)}.$$

From (24), (28), (17), (23), and (29), we obtain

$$S^*W^* = S^*B^*\hat{Q}(0) = \frac{B^*}{M(T^*)} = \frac{I^*}{M(T^*)\hat{P}_{\alpha+1}(0)} = \frac{T^*}{M(T^*)}\frac{\xi}{\hat{P}_{\alpha+1}(0)}$$

and from (28)

$$S^*M(T^*) = \frac{1}{\hat{Q}(0)}.$$

We substitute these relations into the characteristic equation (54) as follows:

$$1 = -\frac{1}{1+z}\frac{\xi}{\hat{P}_{\alpha+1}(0)}\left(\frac{1}{1-\xi} + \frac{T^*M'(T^*)}{M(T^*)}\right) + \xi\frac{T^*M'(T^*)}{M(T^*)}\frac{\hat{P}_{\alpha+1}(z)}{\hat{P}_{\alpha+1}(0)} + \frac{\hat{Q}(z)}{\hat{Q}(0)}. \tag{55}$$

To simplify the characteristic equation further, we define the probability densities

$$p(s) = \frac{P_{\alpha+1}(s)}{\hat{P}_{\alpha+1}(0)} \tag{56}$$

and

$$q(s) = \frac{Q(s)}{\hat{Q}(0)} \tag{57}$$

and reintroduce the parameter

$$\gamma := -\frac{T^*M'(T^*)}{M(T^*)}. \tag{58}$$

As $P_{\alpha+1}(0) = 1$ by (11), we see from (56) that

$$\frac{1}{\hat{P}_{\alpha+1}(0)} = p(0) = \sigma \tag{59}$$

(cf. (36)). With these definitions, (55) takes the form

$$1 = -\frac{p(0)\xi}{1+z}\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\hat{p}(z) + \hat{q}(z). \tag{60}$$

Recall from §4 that

$$0 < \xi < 1, \quad 0 \le \gamma \le 1, \quad \sigma = p(0) > 1.$$

To study the position of the roots $z \in \mathbf{C}$ of (60), we let $z = x + iy$ and separate (60) into real and imaginary parts as follows:

$$1 - \int_0^\infty e^{-xs}\cos(sy)q(s)ds = -\frac{(1+x)p(0)\xi}{(1+x)^2+y^2}\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty e^{-xs}\cos(sy)p(s)ds \tag{61}$$

and

$$\int_0^\infty e^{-xs}\sin(sy)q(s)ds = \frac{yp(0)\xi}{1+x^2+y^2}\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty e^{-xs}\sin(sy)p(s)ds. \tag{62}$$

We can solve for $\xi$ by multiplying (61) by $y$ and (62) by $1+x$ and adding the two equations together as follows:

$$\xi = \frac{y\left(1 - \int_0^\infty e^{-sx}\cos(sy)q(s)ds\right) + (1+x)\int_0^\infty e^{-sx}\sin(sy)q(s)ds}{\gamma\left((1+x)\int_0^\infty e^{-sx}\sin(sy)p(s)ds - y\int_0^\infty e^{-sx}\cos(sy)p(s)ds\right)}. \tag{63}$$

As $q$ is a probability density, we see that the left-hand side of (61) is strictly positive. Furthermore, by the Riemann and Lebesgue Lemma,

$$\int_0^\infty e^{-sx}\sin(sy)p(s)ds \to 0, \qquad \int_0^\infty e^{-sx}\sin(sy)q(s)ds \to 0, \ |y|+x \to \infty, x \geq 0, \tag{64}$$

as $p$, $q$ are of bounded variation. Of course, the same holds if sine is replaced by cosine. Note further that

$$\int_0^\infty e^{-sx}\sin(sy)p(s)ds > 0, \quad x \geq 0, \quad y > 0 \tag{65}$$

because $p$ is nonincreasing.

As we show later, there exist no roots with $x \geq 0, y = 0$. Furthermore, there are no roots with $x \geq 0, y \in \mathbf{R}$ if $\xi > 0$ is small enough.

Taking this for granted for a moment, suppose that there exists some $0 < \xi < 1$ such that (61) and (62) can be solved by $x, y > 0$. Since the roots of the characteristic equation depend continuously on $\xi$ by Rouché's theorem and do not lie in the right half-plane for small $\xi > 0$, they must cross the imaginary axis (without passing through 0) as $\xi$ decreases. Note that $y \to \infty$ is excluded by (64). Hence, for some $0 < \xi < 1$ (different from the one we started with), (61) and (62) are solved with $x = 0, y > 0$, i.e.,

$$1 - \int_0^\infty \cos(sy)q(s)ds = -\frac{1}{1+y^2}p(0)\xi\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty \cos(sy)p(s)ds \tag{66}$$

and

$$\int_0^\infty \sin(sy)q(s)ds = \frac{y}{1+y^2}p(0)\xi\left(\frac{1}{1-\xi} - \gamma\right) + \xi\gamma\int_0^\infty \sin(sy)p(s)ds. \tag{67}$$

In this case (see (63)),

$$\xi = \frac{y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds}{\gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right)}. \tag{68}$$

Taking into account that $0 < \xi < 1, 0 \leq \gamma \leq 1$, and that $p(0) > 1$, we have the following result, which, together with Proposition 1, implies Theorem 5.

PROPOSITION 2. *There are no roots of* (61), (62) *with* $x \geq 0$ *if one of the following holds*:

(a) $\xi$ *is sufficiently close to* 0 *or to* 1;

(b) $p(0)$ *is sufficiently large*;

(c) $\gamma$ *is sufficiently close to* 0;

(d) *There is no $y > 0$ satisfying the following simultaneously:*

$$\int_0^\infty \cos(sy)q(s)ds > 0,$$

$$\int_0^\infty \sin(sy)q(s)ds > 0,$$

$$\int_0^\infty \cos(sy)p(s)ds < 0,$$

$$0 < y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds$$
$$< \gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right);$$

(e) $\lambda = \text{const}$;

(f) *$p$ convex.*

*Proof.* We first note that $1/(1-\xi) - \gamma > 0$ because $0 < \xi < 1$ and $0 \le \gamma \le 1$. Equation (61) implies that there are no roots with $x \ge 0$, $y = 0$, because the right-hand side of (61) is nonnegative, whereas the left-hand side is strictly negative.

(a) If (a) does not hold, we have sequences $\xi_j, x_j, y_j$ satisfying (61) and (62) with $0 < \xi_j < 1$, $x_j, y_j \ge 0$ and $\xi_j \to 0$ or $\xi_j \to 1$ for $j \to \infty$. As we have argued above, we actually have $y_j > 0$.

We first consider the case where $\xi_j \to 0, j \to \infty$. As the left-hand side of (61) is strictly positive for $y > 0$ and bounded away from 0 for $y \to \infty$ by (64), this can only occur if $x_j, y_j \to 0$. We now divide (62) (with $y = y_j$) by $y_j > 0$. Taking the limit for $j \to \infty$, we obtain $\int_0^\infty sq(s)ds > 0$ on the left-hand side, whereas, on the right-hand side, we obtain zero. This contradicts (62).

In the case where $\xi_j \to 1, j \to \infty$, the left-hand side remains nonnegative, whereas the right-hand side of (61) converges toward $-\infty$ (at least for a subsequence), unless $y_j \to \infty$. In the case where $y_j \to \infty, j \to \infty$, we have from (64) that the left-hand side of (61) converges to 1 for $j \to \infty$, whereas the right-hand side is nonpositive in the limit. Hence (61) cannot hold for large $j$, a contradiction.

The statements (b) and (c) follow from (61), (62), and (64) in a similar way as (a).

(d) We recall that, at the start of this proof, we have shown that there are no roots with $x \ge 0$, $y = 0$. After having proved (a), we can now argue as we did between formulas (65) and (66). Hence the existence of a root with $x \ge 0$ for some $\xi, 0 < \xi < 1$ implies the existence of a root with $x = 0$, $y > 0$ for some (presumably different) $\xi, 0 < \xi < 1$. For such a root, it follows from (67) and (65) that $\int_0^\infty \sin(sy)q(s)ds > 0$. As the left-hand side of (66) is strictly positive, it follows that $\int_0^\infty \cos(sy)p(s)ds < 0$. If $\int_0^\infty \cos(sy)q(s)ds \le 0$, the left-hand side of (66) is larger than 1, whereas the right-hand side is strictly smaller than 1. Recall that $p$ is a probability density and $0 \le \gamma \le 1$. The last inequality in (d) now follows from (68) and $0 < \xi < 1$.

Statements (e) and (f) are consequences of (d). If $\lambda = \text{const}$, then $q(s) = \lambda p(s)$, so the relative integrals cannot have different signs. If $p$ is convex, then $-p'$ is nonnegative and nonincreasing (recall that $p$ is nonincreasing). Hence $\int_0^\infty \cos(sy)p(s)ds = \int_0^\infty (1 - y)\sin(sy)(-p'(s))\,ds \ge 0$.

The following result implies Theorem 6 via Proposition 1.

PROPOSITION 3. *All roots $z$ of the characteristic equation* (60) *have strictly negative real parts, provided that*

$$\int_0^\infty \frac{|\lambda(\tau) - \bar{\lambda}|}{\bar{\lambda}} p(\tau) d\tau \leq 1.$$

*Proof.* Let us suppose that there is a root $z$ with nonnegative real part. As we have argued before, we then have a purely imaginary root for some $\xi, 0 < \xi < 1$. In particular, (66) holds. By (57), (12), (56), and the definition of $\bar{\lambda}$, we have

$$q(\tau) = \frac{Q(\tau)}{\hat{Q}(0)} = \frac{\lambda(\tau) P_{\alpha+1}(\tau)}{\int_0^\infty \lambda(s) P_{\alpha+1}(s) ds} = \frac{\lambda(\tau) p(\tau)}{\bar{\lambda}}.$$

From (66), we now obtain

$$0 > 1 - \int_0^\infty \cos(sy) \frac{\lambda(s)}{\bar{\lambda}} p(s) ds + \xi\gamma \int_0^\infty \cos(sy) p(s) ds.$$

By the proof of Proposition 2(d), we can assume that

$$\int_0^\infty \cos(ys) p(s) ds < 0.$$

As $\xi\gamma < 1$, we can continue the above inequality by

$$0 > 1 - \int_0^\infty \cos(sy) \frac{\lambda(s) - \bar{\lambda}}{\bar{\lambda}} p(s) ds \geq 1 - \int_0^\infty \frac{|\lambda(s) - \bar{\lambda}|}{\bar{\lambda}} p(s) ds.$$

This inequality contradicts our assumption.

Propositions 2 and 3 list so many constraints for a root of the characteristic equation to have nonnegative or even positive real parts that we might conjecture that there are none with this property. It is indeed difficult to show that, for given probability densities $p, q$, the characteristic equation has roots with positive real part. This task is facilitated by considering a family of probability densities $q_c$ rather than a specific density $q$. We will give conditions for a fixed probability density $p$ and a family of probability densities $q_c$ that guarantee that the characteristic equation has a root with positive real part for at least one member of the family. Actually, to apply these conditions, it is convenient to formulate them for probability measures.

*Assumptions.* (a) Let $p$ be a nonincreasing probability density. Assume that there is some $y > 0$ such that

$$\frac{1}{1+y^2} p(0)(1-\gamma) + \gamma \int_0^\infty \cos(sy) p(s) ds < 0.$$

Further assume that $q_c, c_1 \leq c \leq c_2$ is a family of probability measures with the following properties:

(b) $\hat{q}_c(z)$ is continuous in $c, c_1 \leq c \leq c_2$, for every $z \in \mathbf{C}$ with nonnegative real part;

(c) $\hat{q}_c(z)$ is continuous in $z \in \mathbf{C}, \Re z \geq 0$ uniformly in $c, c_1 \leq c \leq c_2$;

(d) The integral $\int_{[0,\infty)} \sin(sy) q_c(ds)$ is strictly positive for $c > c_1$, $c$ close to $c_1$, and is 0 for $c = c_1$;

(e) $$\frac{1 - \int_{[0,\infty)} \cos(sy) q_c(ds)}{\int_{[0,\infty)} \sin(sy) q_c(ds)} \to 0, \qquad c \to c_1;$$

(f) If $\xi_c$ is defined by (68) with $q = q_c$, then $0 < \xi_c < 1$ for $c_1 < c < c_2$ and $\xi_c = 1$ for $c = c_2$.

PROPOSITION 4. *Let the assumptions be satisfied. Then the characteristic equation* (60) *has roots* $z = x \pm \sqrt{-1}y$ *with* $x > 0$ *for at least one* $\xi \in (0,1)$ *and one probability measure* $q = q_c$, $c_1 < c < c_2$.

*Proof.* The strategy of the proof follows. We consider (61) with $\xi$ being given by (63), where $q$ is replaced by $q_c$. We show that, for some $\tilde{c}_1$ close to $c_1$, the left-hand side of (61) is smaller than the right-hand side, whereas, for some $\tilde{c}_2$ close to $c_2$, the left-hand side of (61) is larger than the right-hand side. Furthermore, for all values of $c$ between $\tilde{c}_1$ and $\tilde{c}_2$, the number $\xi$ given by (63) is strictly between 0 and 1. Then we apply the intermediate value theorem. This provides some $c$, $\tilde{c}_1 < c < c_2$, such that $0 < \xi_c < 1$ for $\xi_c$ given by (63) and that (61) holds with $\xi = \xi_c$. Equivalently, (61), (62) are satisfied with $\xi = \xi_c$, and so is (60).

In a first step, we consider (66) and (68) rather than (61) and (63). This amounts to looking for purely imaginary roots $z$. It follows from assumptions (d) and (e) that $\xi_c \to 0$, $c \to c_1$ and that the following limit exists:

$$\lim_{c \to c_1} \frac{\int_{[0,\infty)} \sin(sy) q_c(ds)}{\xi_c} \in (0, \infty). \tag{69}$$

We divide (66) by $\xi_c$ as follows:

$$\frac{1 - \int_{[0,\infty)} \cos(sy) q_c(ds)}{\xi_c} = -\frac{1}{1+y^2} p(0) \left( \frac{1}{1-\xi_c} - \gamma \right) - \gamma \int_0^\infty \cos(sy) p(s) ds. \tag{70}$$

By assumption (e) and (69), the left-hand side of (70) tends to 0 for $c \to c_1$, while the right-hand side converges toward

$$-\frac{1}{1+y^2} p(0)(1-\gamma) - \gamma \int_0^\infty \cos(sy) p(s) ds.$$

This expression is positive because of assumption (a). Therefore, we find some $\tilde{c}_1$ close to $c_1$ such that the right-hand side of (70), or equivalently of (66), is strictly larger than the left-hand side. If $c \to c_2$, $\xi_c \to 1$, hence the right-hand side of (66) goes to $-\infty$, whereas, by assumption (b), the left-hand side of (66) tends to some finite limit. Hence we find some $\tilde{c}_2$ between $\tilde{c}_1$ and $c_2$ such that the right-hand side of (66) is strictly smaller than the left-hand side.

In summary, let $\xi_c$ be given by (68). We have found $\tilde{c}_1, \tilde{c}_2$, $c_1 \le \tilde{c}_1 < \tilde{c}_2 \le c_2$ such that $0 < \xi_c < 1$ for all $\tilde{c}_1 \le c \le \tilde{c}_2$, and the right-hand side of (66) is strictly larger than the left-hand side if $c = \tilde{c}_1$ and $\xi = \xi_{\tilde{c}_1}$, whereas the right-hand side of (66) is strictly smaller than the left-hand side if $c = \tilde{c}_2$ and $\xi = \xi_{\tilde{c}_2}$.

By assumption (c) we have the same situation if (66) is replaced by (61) with $\xi = \xi_c(x)$ being given by (63), provided that $x > 0$ is sufficiently close to 0. Assumption (b) and the intermediate value theorem imply that, for any $x > 0$ which is sufficiently close to 0, there is some $c$ between $\tilde{c}_1$ and $\tilde{c}_2$ such that (61) is satisfied with $\xi = \xi_c(x)$ being given by (63), $0 < \xi < 1$. Equivalently, (60) with $\xi = \xi_c(x)$ has a root $z = x + \sqrt{-1}y$.

We can use Proposition 4 to show that the characteristic equation can have roots with positive real part indeed. The following result implies Theorem 7 (recall (56) and (59)) via Proposition 1.

PROPOSITION 5. *Let $p$ be a decreasing probability density. Assume there is some $y > 0$ such that*

$$\frac{1}{1+y^2}p(0)\,(1-\gamma)+\gamma\int_0^\infty \cos(sy)p(s)ds < 0.$$

*Then there exists a probability density $q$ with arbitrarily many peaks such that the characteristic equation (60) has a root $z$ with strictly positive real part.*

*Remark.* The peaks of $q$ are concentrated at points of the form $c, cs_1, \ldots, cs_m$, $0 < c < \pi/2y$, such that

$$s_j = 1 + \frac{2k_j\pi}{cy}$$

with $k_j \in \mathbf{N}, k_j > 0, j = 1, \ldots, m$.

*Proof.* Let $q_c, c \geq 0$, be a probability measure that is concentrated at the points $cs_j$, as indicated in the remark, $s_0 = 1$. In other words,

$$q_c = \sum_{j=0}^{m} \kappa_j \delta_{cs_j}$$

with $\kappa_j > 0, \sum_{j=0}^m \kappa_j = 1$ and $\delta_s$ denoting the Dirac measure concentrated at the point $s$. The choice of the points $cs_j$ implies that

$$\int_{[0,\infty)} \cos(sy)q_c(ds) = \cos(cy), \qquad \int_{[0,\infty)} \sin(sy)q_c(ds) = \sin(cy).$$

By (68)

$$\xi_c = \frac{y\Big(1-\cos(cy)\Big)+\sin(cy)}{\gamma\Big(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\Big)}.$$

For $c = \pi/2y$, we have

$$\xi_c = \frac{y+1}{\gamma\Big(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\Big)} \geq \frac{1}{\gamma} \geq 1,$$

as $0 < \int_0^\infty \sin(sy)p(s)ds, -\int_0^\infty \cos(sy)p(s)ds \leq 1$. So we find some $c_2, 0 < c_2 \leq \pi/2y$, such that, with $c_1 = 0$, assumption (f) is satisfied. The other parts are now checked easily. Hence, by Proposition 3, there exists some $c \in (c_1, c_2)$ such that the characteristic equation (60)—with $q = q_c$—has a root $z$ with strictly positive real part. By Rouché's theorem, there exists a probability density $q$ with peaks at $c, cs_1, \ldots, cs_m$ such that (60) has a root with $z$ with strictly positive real part.

**Appendix A.4. Examples 1 and 2 in §4.** Let $\alpha$ be given by (37). By (38), the Laplace transform of $P_{\alpha-1}$ is given by

$$\hat{P}_{\alpha-1}(z) = \frac{1}{1+\rho_1+z}\left(1-e^{-(1+\rho_1+z)\tau_0}\right) + \frac{1}{1+\rho_2+z}e^{-(1+\rho_1+z)\tau_0}.$$

To check the assumption of Proposition 5, we set $z = \sqrt{-1}y$ and take the real part as follows:

(71)
$$\int_0^\infty \cos(sy)P_{\alpha+1}(s)ds = \frac{1+\rho_1}{(1+\rho_1)^2+y^2}\left(1 - e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond)\right) + \frac{1+\rho_2}{(1+\rho_2)^2+y^2}e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond) + y\left(\frac{1}{(1+\rho_1)^2+y^2} - \frac{1}{(1+\rho_2)^2+y^2}\right)e^{-(1+\rho_1)\tau_\diamond}\sin(y\tau_\diamond).$$

If we pick $1 < s < 3/2$, set

$$y\tau_\diamond = (s+2n)\pi,$$

and choose $\rho_2 - \rho_1$ and $n$ sufficiently large, we can arrange that

$$\int_0^\infty \cos(sy)P_{\alpha+1}(s)ds < 0.$$

By (59) the condition in Proposition 5 takes the form

$$\frac{1}{1+y^2}(1-\gamma) + \gamma\int_0^\infty \cos(sy)P_{\alpha+1}(s)ds < 0$$

and thus is satisfied if we choose $s$, $y$, $\rho_1$, $\rho_2$, and $n$ as before and $\gamma, 0 < \gamma \leq 1$ close enough to 1. Hence Proposition 5 has the following corollary, which, together with Proposition 1, provides Example 1 in §4.

COROLLARY. *Let the inactivation rate $\alpha(\tau)$ be given by* (37) *with $\rho_2 - \rho_1$ being sufficiently large. If $\gamma, 0 < \gamma \leq 1$, is sufficiently close to* 1, *then there exists a probability density $q$ with arbitrarily many peaks such that the characteristic equation* (60) *has roots $z$ with strictly positive real part.*

The position of the peaks in Example 1 follows from $y\tau_\diamond = (s+2n)\pi$ and the remark after Proposition 5.

*Proof of Example* 2. Let $\alpha, \lambda$ be given by (37) and (39). By (57) and (12),

$$q(\tau) = \begin{cases} 0, & 0 \leq \tau \leq \tau_\diamond, \\ (1+\rho_2)e^{-(1+\rho_2)(\tau-\tau_\diamond)}, & \tau > \tau_\diamond. \end{cases}$$

Hence

$$\hat{q}(z) = \frac{1+\rho_2}{1+\rho_2+z}e^{-z\tau_\diamond}.$$

We set $z = \sqrt{-1}y$ and separate into real and imaginary parts as follows:

$$\int_0^\infty \cos(sy)q(s)ds = \frac{1+\rho_2}{(1+\rho_2)^2+y^2}\left((1+\rho_2)\cos(y\tau_\diamond) - y\sin(y\tau_\diamond)\right),$$

$$\int_0^\infty \sin(sy)q(s)ds = \frac{1+\rho_2}{(1+\rho_2)^2+y^2}\left(y\cos(y\tau_\diamond) - (1+\rho_2)\sin(y\tau_\diamond)\right).$$

Let us suppose that the characteristic equation (60) has a root with nonnegative real part. From Proposition 2(d), we can conclude that

(72)
$$(1+\rho_2)\cos(y\tau_\diamond) - y\sin(y\tau_\diamond) > 0.$$

$$y\cos(y\tau_\diamond) + (1+\rho_2)\sin(y\tau_\diamond) > 0 \tag{73}$$

for some $y > 0$. Equations (72) and (73) imply that

$$\cos(y\tau_\diamond) > 0.$$

From (73),

$$\sin(y\tau_\diamond) > -\frac{y}{1+\rho_2}\cos(y\tau_\diamond).$$

We substitute this inequality into (71), recalling $\rho_2 > \rho_1$,

$$\begin{aligned}
&\int_0^\infty \cos(sy)P_{\alpha+1}(s)ds \\
&> \frac{1+\rho_1}{(1+\rho_1)^2+y^2}\left(1 - e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond)\right) + \frac{1+\rho_2}{(1+\rho_2)^2+y^2}e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond) \\
&\quad - y\left(\frac{1}{(1+\rho_1)^2+y^2} - \frac{1}{(1+\rho_2)^2+y^2}\right)e^{-(1+\rho_1)\tau_\diamond}\frac{y}{1+\rho_2}\cos(y\tau_\diamond) \\
&= \frac{1+\rho_1}{(1+\rho_1)^2+y^2}\left(1 - e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond)\right) \\
&\quad + \frac{1}{1+\rho_2}\left(1 - \frac{y^2}{(1+\rho_1)^2+y^2}\right)e^{-(1+\rho_1)\tau_\diamond}\cos(y\tau_\diamond).
\end{aligned}$$

As $\cos(y\tau_\diamond) > 0$, this implies that

$$\int_0^\infty \cos(sy)P_{\alpha+1}(s)ds \geq 0,$$

in contradiction to Proposition 2(d) and (56).

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