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Recurrent Outbreaks of Childhood Diseases Revisited: The Impact of Isolation

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ABSTRACT

The recurrent outbreaks of measles and other childhood diseases have previously been explained by an interaction of intrinsic epidemiologic forces generating dampened oscillations and of seasonal and/or stochastic excitation. We show that isolation (i.e., sick individuals stay at home and have a reduced infective impact) can create self-sustained oscillations provided that the number of per capita contacts is largely independent of the number of individuals present. This means that the bilinear mass action term for disease incidence is modified by dividing it by the number of nonisolated individuals.

1. INTRODUCTION

The recurrent outbreaks of measles and other childhood diseases have fascinated mathematical modelers of infectious diseases for many years, and different mechanisms have been suggested to explain their occurrence. See [1–7] for reviews.

Dietz [8], Hethcote [9], and Anderson and May [10] consider simple models involving three or four epidemic classes that display dynamics that converge to an epidemic equilibrium in damped oscillations with the quasi-periods being surprisingly close (considering the simplicity of the model) to observed values in some of the childhood diseases [6, Table 6.1; 10]. It has been argued that these damped oscillations can be excited to undamped oscillations either by stochastic or periodic deterministic forcing. The impact of stochastic forcing was studied by Bartlett [11, 12] and London and Yorke [13]. The influence of periodic forcing leading to periodic solutions, with the periods being multiples of the period of the forcing, was studied numerically by London and Yorke [14] and Dietz [15], formally by Grossman et al. [16] and Grossman [17],

Dedicated to the memory of Stavros Busenberg.

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and analytically by Smith [18, 19] and Schwartz and Smith [20]. Periodic forcing can even lead to a sequence of period-doubling subharmonic bifurcations and finally chaos [21–25]. See [1] and [5] for more detailed reviews.

Schenzle [2] (see also [1]) convincingly argues that a one-year periodic forcing is provided by the school system where long summer vacations interrupt or weaken the chain of infections and new susceptibles are recruited at the beginning of every school year (with the second being apparently more important than the first). Schenzle's work [2], which also incorporates age structure and mainly consists of numerical simulations, has motivated several authors [26–40] to study the question of whether the introduction of age structure alone can be responsible for undamped oscillations in endemic models that have a stable endemic equilibrium without age structure. Andreasen [30], Enderle [34], and Thieme [40] have shown that this can indeed be the case, but the conditions they have found so far are rather extreme.

Dietz and Schenzle [1] assess that "up to the present day the problem of recurrent epidemics has not been definitely settled" (p. 185) and that there is "reason to think of still another mechanism causing endemic incidence fluctuation to be sustained" (p. 190).

In this article we (partially) rehabilitate the opinion of Hamer [41] and Soper [42] that autonomous internal forces may be responsible for undamped oscillations in childhood diseases. Standard epidemic models have neglected that infected children who become infective at the end of the latency period get severe symptoms at the end of the incubation period that cause them to stay at home. Though they may still infect their relatives when they are at home, their infectious impact is largely reduced because they are kept from making contacts outside their families. Isolation alone would not create oscillations; traditional models simply merge isolated and immune individuals into one class, and the model behavior is, of course, the same as without discriminating isolated individuals. The point is that immune individuals go back into public life, whereas isolated individuals do not. This may have an effect if, as we suspect, the per capita rate of contacts is basically independent of the number of children present unless this number is quite small.

Adding these two features to standard childhood disease models amounts to adding a new class—isolated individuals (those who stay at home because they are too sick to go out)—and modifying the standard bilinear mass action infection term by dividing it by the number of active (i.e., nonisolated) individuals. The importance of this modification has become apparent before in the study of sexually transmitted diseases, and its destabilizing potential was already discovered in an HIV/AIDS model with infection-age-dependent infectivity (see [43] and

references therein). Other infection laws that deviate from the usual bilinear mass action term and can lead to undamped oscillations have been considered by Cunningham [44] and Liu et al. [45, 46]. It is not clear, however, what kind of mechanisms they represent in childhood diseases.

In infectious diseases that are not of the type considered here, undamped oscillations can be excited by other mechanisms; see [5, 7, 43] for surveys and references.

To give a preview of our results, let us first mention that the basic replacement ratio $\mathscr{R}_0$ (or basic reproduction number, number of secondary cases produced by one infective individual in an otherwise completely susceptible population) turns out to be independent of the length of the isolation period. It is more or less proportional to the mean length of the effective infectious period, that is, the part of the infectious period before isolation occurs. As with many other epidemic models, the disease dies out if the basic replacement ratio is smaller than 1 and becomes endemic if $\mathscr{R}_0$ strictly exceeds 1. Further, if $\mathscr{R}_0 > 1$, there exists a uniquely determined endemic equilibrium. As $\mathscr{R}_0$ does not depend on the length of the isolation period, one may fix $\mathscr{R}_0$ at some value strictly bigger than 1 and consider the length of the isolation period as a variable parameter. If the average length of the isolation period is either very long or very short, the disease dynamics always converge to the endemic equilibrium (global stability). Analytically we have found two different parameter values at which periodic solutions bifurcate from the endemic equilibrium via a (presumably supercritical) Hopf bifurcation. Numerical studies using *Auto* [48] show that, for a wide range of the other parameters, there are no other Hopf bifurcation points. This means that for short isolation periods the endemic equilibrium is asymptotically stable and that increasing the length of the isolation period makes the endemic equilibrium less stable and even leads to its instability with a simultaneous rise of stable periodic oscillations. If the length of the isolation period is further increased, however, the endemic equilibrium gains its stability back at long isolation periods. Though there are many data for the length of the latency, incubation, and infection periods of the common childhood diseases, we have not seen any data for the length of the isolation period. Presumably, sick children do not leave home immediately after they stop being infective but spend some more time recovering from the debility caused by the disease. Comparison to data is further hampered by vague knowledge of the key parameter $\mathscr{R}_0$. Most estimates of $\mathscr{R}_0$ determine the force of infection from the mean age of infection assuming a constant infective force in spite of the fact that the observed forces of infection undergo heavy oscillations. We give estimates from below and

above for the time average of periodic forces of infection, which may themselves be of interest. They suggest that the above procedure typically underestimates $\mathscr{R}_0$, but not dramatically. In Section 8, we present some concrete lengths of the isolation period that are associated with sustained oscillations and discuss whether they are realistic.

The paper is organized as follows. In Section 2 we formulate and explain the model. Section 3 contains the relation between the existence of an endemic equilibrium and the basic replacement ratio. Some global results concerning disease extinction or persistence and convergence toward the endemic equilibrium are presented in Section 4. Section 5 contains our bifurcation analysis, and Section 7 presents the numerical results. In Section 6 we present our estimates of the temporal mean of a periodic force of infection from the mean age at infection and compare our findings to scarlet fever data from England and Wales, 1897–1978 [6]. In Section 8 we discuss the relevance of our findings.

This paper is dedicated to Stavros Busenberg—to gratefully remember his friendship and to appreciate his highly contagious agency for the application of mathematics in the biosciences.

2. THE MODEL

We split the population (the size of which we denote by N) into individuals who are susceptible to the disease, S; infective nonisolated individuals, I; isolated individuals Q (Q as in quarantine); and recovered and immune individuals, R. At this point we neglect a latency period (but compare Section 6.2) and assume that immunity is permanent. By $A = S + I + R$ we denote the active, that is, nonisolated, individuals. The basic idea consists in assuming that sick individuals stay at home and so undergo some kind of isolation (or quarantine) that reduces their ability to infect others. For simplicity we assume that they do not infect anybody. We further assume that the disease is basically nonlethal (a realistic assumption for most childhood diseases in developed countries). The model takes the following form:

$$\frac{d}{dt}S = \Lambda - \mu S - \sigma S\frac{I}{A}, \tag{2.1a}$$

$$\frac{d}{dt}I = -(\mu + \gamma)I + \sigma S\frac{I}{A}, \tag{2.1b}$$

$$\frac{d}{dt}Q = -(\mu + \xi)Q + \gamma I, \tag{2.1c}$$

$$\frac{d}{dt}R = -\mu R + \xi Q, \tag{2.1d}$$

$$A = S + I + R. \tag{2.1e}$$

Λ is the rate at which individuals are born into the population; all newborns are assumed to be susceptible. μ is the per capita mortality rate, σ is the per capita infection rate of an average susceptible individual provided that everybody else is infected, and γ and ξ are the rates at which individuals leave the infective and isolated classes; they are all positive constants, $1/\gamma$ and $1/\xi$ give the respective mean lengths of the infective and isolation periods; $1/\mu$ is the average life expectation. I/A gives the probability that a given contact actually occurs with an infective individual.

Notice that we have assumed that the per capita number of contacts is basically independent of the number of active individuals. This assumption is widely accepted for sexually transmitted diseases, but there is growing evidence that it is not a bad assumption for otherwise transmitted diseases either (unless the number of active individuals is very small). See Section 1.1 in [49] or the Introduction in Gao et al. [50]. A possible explanation is that the number of contacts depends on the density of active individuals rather than on their absolute numbers [51]. When there are a few children on a playground or in a schoolyard, for example, they will gather in one part of it, whereas when there are many they will spread out over it; so the per capita number of contacts essentially remains the same unless the number of children becomes very small.

More generally one could replace σ by a contact function $C(A)$ (see [43, 49, 50, 52, 53] and the literature cited there). As far as applications are concerned, this amounts to introducing at least one, but typically several, more parameters that have to be estimated. We know of only one attempt that has been taken in this direction, namely for

$$C(A) = \sigma A^{\alpha}$$

(see [6, Section 12.1] and the reference there). Estimates for five childhood diseases in communities of various sizes provide that α is between 0.03 and 0.07, and our choice $\alpha = 0$ turns out to be a much better approximation than the traditional $\alpha = 1$.

Adding the differential equations in (2.1), we find for the population size $N = A + Q = S + I + Q + R$ that

$$\frac{d}{dt}N = \Lambda - \mu N.$$

Hence $N(t) \to \Lambda / \mu$ as $t \to \infty$. We assume that the size of the population has reached its limiting value, that is,

$$N \equiv \Lambda / \mu \equiv S + I + Q + R = A + Q.$$

Using $A = N - Q$ and $S = A - I - R$ in (2.1) we can eliminate S from the equations. Further we can scale time such that $\sigma = 1$ by introducing a new, dimensionless, time $\tau = \sigma t$. This gives us the system

$$I' = -(\nu + \theta)I + \left(1 - \frac{I + R}{N - Q}\right)I, \tag{2.2a}$$

$$Q' = -(\nu + \zeta)Q + \theta I, \tag{2.2b}$$

$$R' = -\nu R + \zeta Q, \tag{2.2c}$$

where

$$\nu = \frac{\mu}{\sigma}, \qquad \theta = \frac{\gamma}{\sigma}, \qquad \zeta = \frac{\xi}{\sigma}, \tag{2.3}$$

and the prime denotes the derivative in τ.

To transform (2.2) into a system with linear and quadratic relationships only, we introduce the fractions

$$u = \frac{S}{A}, \qquad y = \frac{I}{A}, \qquad q = \frac{Q}{A}, \qquad z = \frac{R}{A} \tag{2.4}$$

and note that

$$A' = -Q' = (\nu + \zeta)Q - \theta I$$

and

$$\Lambda - \mu S = \mu(I + Q + R).$$

Hence, by differentiating (2.4) and using (2.1), we have

$$u' = \nu(y + q + z) - uy + u(\theta y - (\nu + \zeta)q), \tag{2.5a}$$

$$y' = -(\nu + \theta)y + uy + y(\theta y - (\nu + \zeta)q), \tag{2.5b}$$

$$q' = (1 + q)(\theta y - (\nu + \zeta)q), \tag{2.5c}$$

$$z' = \zeta q - \nu z + z(\theta y - (\nu + \zeta)q). \tag{2.5d}$$

The relation $A = S + I + R$ implies that

$$u + y + z = 1. \tag{2.6}$$

Using (2.6) we can eliminate the equation for u' in (2.5) and obtain

$$y' = y[1 - \nu - \theta - y - z + \theta y - (\nu + \zeta)q], \tag{2.7a}$$

$$q' = (1 + q)[\theta y - (\nu + \zeta)q], \tag{2.7b}$$

$$z' = \zeta q - \nu z + z[\theta y - (\nu + \zeta)q]. \tag{2.7c}$$

THEOREM 2.1

Let $u_0, y_0, z_0, q_0 \geqslant 0$, $u_0 + y_0 + z_0 = 1$. *Then there exists a unique solution* u, y, z, q *of* (2.5) *with initial data* u_0, y_0, z_0, q_0 *at time* 0 *that is defined for all forward times.* u, y, q, z *are nonnegative, and* $u + y + z = 1$. *If* $y_0 = 0$, *then* $y \equiv 0$. *If* $y_0 > 0$, *then* $u(t)$, $y(t)$, $q(t)$, $z(t)$ *are strictly positive for* $t > 0$. q *is bounded from above by the maximum of* q_0 *and* $\theta/(\nu + \zeta)$.

Proof. As the right-hand side of (2.7) is locally Lipschitz, there exists a unique local solution y, q, z to (2.7) with initial data y_0, q_0, z_0 that is defined on a maximum forward interval of existence. (See [54], Sections I.1–I.3.) If we set $u = 1 - y - z$, we see that u satisfies the first equation in (2.5). From the form of the y equation we see that if y_0 is nonnegative (positive), so is y. We now sequentially realize that q, z, u are nonnegative (positive for positive times). As $1 = u + y + z$, all of $y, z, y + z$ are bounded by 1. Equation (2.7b) now provides the upper bound for q. Hence the maximum forward interval of existence is $[0, \infty)$.

Remark. Once we have uniquely solved (2.7) we find unique solutions of (2.2) by the relations

$$I = yA = yN\frac{A}{N} = yN\frac{A}{A+Q} = \frac{yN}{1+q}$$

and, similarly,

$$Q = \frac{qN}{1+q}, \qquad R = \frac{zN}{1+q}.$$

3. ENDEMIC EQUILIBRIUM AND BASIC REPLACEMENT RATIO

Looking for nonnegative equilibria of (2.5) and (2.6) we discover that there is always the disease-free equilibrium

$$u^0 = 1, \qquad y^0 = q^0 = z^0 = 0.$$

Any other possible nonnegative equilibrium satisfies

$$\begin{aligned} -(\nu + \theta) + u^* &= 0, \\ \theta y^* - (\nu + \zeta) q^* &= 0, \\ -\nu z^* + \zeta q^* &= 0, \\ u^* + y^* + z^* &= 1. \end{aligned}$$

This system is solved by

$$u^* = \nu + \theta, \qquad y^* = \nu(\nu + \zeta)\kappa, \qquad q^* = \nu\theta\kappa, \qquad z^* = \theta\zeta\kappa$$
$$\kappa = \frac{1 - u^*}{\nu(\nu + \zeta) + \theta\zeta} = \frac{1 - \nu - \theta}{\nu(\nu + \zeta) + \theta\zeta}. \tag{3.1}$$

In order to obtain a nonnegative equilibrium that is different from the disease-free equilibrium, we need to assume that

$$\nu + \theta < 1. \tag{3.2}$$

This condition becomes epidemiologically more meaningful if we introduce

$$\mathscr{R}_0 = \frac{1}{\nu + \theta} = \frac{\sigma}{\mu + \gamma}. \tag{3.3}$$

As $1/(\mu + \gamma)$ is the effective length of the infectious period (also including the possibility of death) and σ is the per capita rate of transmitting the disease, $\mathscr{R}_0$ gives the total number of secondary cases an average infective individual will induce given that the rest of the population is susceptible. $\mathscr{R}_0$ is called the *basic replacement ratio*. The endemic equilibrium makes epidemiological sense only if $\nu + \theta \leqslant 1$.

THEOREM 3.1

If $\mathscr{R}_0 \leqslant 1$, then system (2.5) *has only the disease-free equilibrium $u^0 = 1$, $y^0 = q^0 = z^0 = 0$. If $R_0 > 1$, there is a uniquely determined nonnegative equilibrium that is different from the disease-free equilibrium that is given by* (3.1).

The second equilibrium, if $\mathscr{R}_0 > 1$, is called the *endemic equilibrium*. Theorem 3.1 states that there is an endemic equilibrium if an average infective individual entering a completely susceptible population replaces itself by at least one other infected individual.

4. SOME GLOBAL RESULTS INCLUDING DISEASE EXTINCTION OR PERSISTENCE

The fact that there is an endemic equilibrium only if the basic replacement ratio $\mathscr{R}_0$ strictly exceeds 1 suggests a relation to disease extinction or persistence. Actually, the following holds.

THEOREM 4.1

(a) *Let $\mathscr{R}_0 \leqslant 1$. Then, for any solution of* (2.5) *with nonnegative initial data satisfying $u_0 + y_0 + z_0 = 1$, we have $u(t) \to 1$, $y(t) \to 0$, $q(t) \to 0$, $z(t) \to 0$ as $t \to \infty$.*

(b) *Let* $\mathscr{R}_0 > 1$. *Then there exists some* $\epsilon > 0$ *such that*

$$\liminf_{t\to\infty} y(t) \geqslant \varepsilon, \qquad \liminf_{t\to\infty} q(t) \geqslant \varepsilon,$$

$$\liminf_{t\to\infty} z(t) \geqslant \varepsilon, \qquad \limsup_{t\to\infty} u(t) \leqslant 1-\varepsilon$$

for all solutions to (2.5) *with nonnegative initial data satisfying* $u_0 + y_0 + z_0 = 1$, $y_0 > 0$.

Hence, if an average infective individual does not replace itself, the disease dies out. If the individual replaces itself, the disease persists in the population. Details will be presented by Feng [55] using the approach to persistence of Thieme [52, 53].

As we will see in the next section, if $\mathscr{R}_0 > 1$, the disease dynamics do not always tend to their endemic equilibrium values as time tends to infinity. However, the time average of the ratio of susceptible to active individuals converges toward the equilibrium value. Let

$$\bar{u}(t) = \frac{1}{t}\int_0^t u(s)\,ds.$$

THEOREM 4.2

Let $\mathscr{R}_0 > 1$ *and* $y(0) > 0$. *Then*

$$\bar{u}(t) \to u^*, \qquad t \to \infty.$$

Proof. Let $\mathscr{R}_0 > 1$. Since $I = yA = yNA/N = yN[A/(A+Q)] = yN[1/(1+q)]$, we have that I is bounded away from 0 because q is bounded by Theorem 2.1. From the equation for dI/dt in (2.1) we have

$$\frac{1}{I}\frac{dI}{dt} = \sigma u - \mu - \gamma.$$

This implies that

$$\bar{u}(t) - \nu - \theta = \frac{1}{\sigma}\left(\frac{1}{t}\right)[\ln I(t) - \ln I(0)] \to 0, \qquad t \to \infty,$$

because I is bounded above by N and bounded away from 0. ∎

We notice that the basic replacement ratio $\mathscr{R}_0$ that determines the extinction or persistence of the disease is independent of the length of the quarantine period. Our main interest is in the relation between the

length of the quarantine period and the stability of the endemic equilibrium.

THEOREM 4.3

Let $\mathscr{R}_0 > 1$. If the quarantine period is very short or very long, the endemic equilibrium attracts all solutions of (2.5) *with nonnegative initial data such that $u_0 + y_0 + z_0 = 1$, $y_0 > 0$.*

We give a heuristic argument. A rigorous proof can be found in [55]. Let us first assume that the scaled length of the isolation period $\varepsilon = 1/\zeta$ is short. In (2.7) we introduce the new dependent variable $w = \zeta q$ and obtain the system

$$\begin{aligned} y' &= y[1 - \nu - \theta - y - z + \theta y - (\nu\varepsilon + 1)w], \\ \varepsilon w' &= (1 + \varepsilon w)[\theta y - (\nu\varepsilon + 1)w], \\ z' &= w - \nu z + z[\theta y - (\nu\varepsilon + 1)w]. \end{aligned}$$

As ε is very small, we suspect that this system has the same large-time behavior as the system for $\varepsilon = 0$:

$$\begin{aligned} y' &= y(1 - \nu - \theta - y - z + \theta y - w), \\ 0 &= \theta y - w, \\ z' &= w - \nu z + z(\theta y - w). \end{aligned}$$

We substitute the second relation into the others:

$$y' = y(1 - \nu - \theta - y - z), \qquad z' = \theta y - \nu z. \tag{4.1}$$

The equilibria of (4.1) are $(0,0)$ and $y^* = (\nu/\theta)z^*$, $z^* = [\theta/(\nu + \theta)] \times (1 - \nu - \theta)$, which corresponds to equilibrium (3.1) for $\zeta \to \infty$. Dulac's criterion reveals that the nonzero equilibrium attracts all nonnegative solutions with $y(0) > 0$. Singular perturbation arguments [56] show that the endemic equilibrium of (2.7) attracts all solutions of (2.7) with $y(0) > 0$ provided ε is sufficiently small.

Let us now assume that ζ is small. We first consider (2.7) for $z \equiv 0$, $\zeta = 0$:

$$\begin{aligned} y' &= y(1 - \nu - \theta - y + \theta y - \nu q), \\ q' &= (1 + q)(\theta y - \nu q). \end{aligned}$$

This system has the trivial equilibrium $(0,0)$ and the nonzero equilibrium $q^* = (\theta/\nu)(1 - \nu - \theta)$, $y^* = 1 - \nu - \theta$, which corresponds to the

limiting values of (3.1) for $\zeta \to 0$. Again Dulac's criterion implies that the nonzero equilibrium attracts all nonnegative solutions with $y(0) > 0$. Moreover, it is locally asymptotically stable. In a next step we consider the asymptotically autonomous system

$$y' = y(1 - \nu - \theta - y - z + \theta y - \nu q),$$
$$q' = (1+q)(\theta y - \nu q)$$

with $z(t) \to 0$, $t \to \infty$. A result by Markus [57, Theorem 2] implies that all solutions with $y(0) > 0$, $q(0) \geqslant 0$ converge toward the equilibrium y^*, q^*.

We now consider (2.7) with $\zeta = 0$ or, equivalently, (2.2). In (2.2), $R(t) \to 0$, $t \to \infty$. Hence $z = R/A = (R/N)(N/A) = (R/N)(1+q) \to 0, t \to \infty$, as q is bounded by Theorem 2.1. Hence the endemic equilibrium attracts all nonnegative solutions of (2.7) with $y(0) > 0$ provided $\zeta = 0$. Moreover, it is locally asymptotically stable. As the solutions of (2.7) depend continuously on the parameter ζ (on any finite interval), and as one can show that $\liminf_{t\to\infty} y(t) > \varepsilon > 0$, where $\varepsilon > 0$ can be chosen independently of small ζ, the endemic equilibrium attracts all nonnegative solutions of (2.7) with $y(0) > 0$ provided that $\zeta > 0$ is small enough. For details see [55].

5. STABILITY OF THE ENDEMIC EQUILIBRIUM AND SUSTAINED OSCILLATIONS

To study the stability of the endemic equilibrium and its possible loss due to a Hopf bifurcation (giving rise to sustained oscillations), we linearize our system of ODEs around this equilibrium. Let $U = (y, q, z)^T$, and rewrite (2.7) as $U' = F(U)$. The Jacobian of F at the endemic equilibrium U^* is given by

$$DF(U^*) = \begin{pmatrix} (\theta - 1)y^* & -(\nu + \zeta)y^* & -y^* \\ \theta(1+q^*) & -(\nu+\zeta)(1+q^*) & 0 \\ \theta z^* & \zeta - (\nu+\zeta)z^* & -\nu \end{pmatrix}.$$

The characteristic polynomial has the form

$$|wI - DF(U^*)| = w^3 + aw^2 + bw + c,$$

where

$$a = 2\nu + \zeta + y^*, \tag{5.1a}$$
$$b = (\nu+\zeta)\nu + \nu y^* + \theta z^* y^* + (\nu+\zeta)y^*(1+q^*), \tag{5.1b}$$
$$c = (\nu^2 + \nu\zeta + \theta\zeta)y^*(1+q^*). \tag{5.1c}$$

Note that $\mu = 1/D$ and D is the mean life expectation, whereas $1/\gamma$ and $1/\xi$ are the mean lengths of the effective infective and isolation periods. The mean life expectation is on the order of some decades, whereas the infective and isolation periods are on the order of days or at most weeks. Hence μ is much smaller than γ or ξ, and so ν is much smaller than θ or ζ.

From (3.1) we realize that y^*, q^*, z^* are analytic functions of $\nu > -\delta$ for some $\delta > 0$ and

$$\begin{aligned} y^* &= \nu\frac{1-\theta}{\theta} + O(\nu^2), \qquad q^* = \nu\frac{1-\theta}{\zeta} + O(\nu^2), \\ z^* &= 1 - \theta + O(\nu). \end{aligned} \tag{5.2}$$

Thus the coefficients (5.1) of the characteristic polynomial are analytic functions of $\nu > -\delta$ and have the form

$$a = \zeta + \frac{1+\theta}{\theta}\nu + O(\nu^2), \tag{5.3a}$$

$$b = \left(\frac{\zeta}{\theta} + (1-\theta)^2\right)\nu + O(\nu^2), \tag{5.3b}$$

$$c = \zeta(1-\theta)\nu + O(\nu^2). \tag{5.3c}$$

Note that if U^* exists, then $R_0 > 1$, that is, $\nu + \theta < 1$; so we have $\theta < 1$ and $1 - \theta > 0$. a, b, and c are all positive; hence the characteristic equation has either three negative roots or one negative root and two complex conjugate roots. One easily checks that for small $\nu > 0$ there are three distinct roots.

In the limiting case, $\nu = 0$, the characteristic equation is

$$w^3 + \zeta w^2 = 0.$$

It has the double root 0 and the simple root $w = -\zeta$.

It follows from Rouché's theorem that we have three continuous branches $w_+(\nu)$, $w_-(\nu)$, $w_\diamond(\nu)$ of roots of the characteristic equation that are defined for small $\nu > 0$ and satisfy $w_\pm(0) = 0$, $w_\diamond(0) = -\zeta$.

The analytic version of the implicit function theorem implies that $w_\diamond(\nu)$ is an analytic function of ν and has a series expansion

$$w_\diamond(\nu) = -\zeta + \sum_{j=1}^{\infty} w_j \nu^j.$$

It follows from Kato [58, II, §1, Section 2] that the roots $w_{\pm}(\nu)$ with $w_{\pm}(0) = 0$ have either an expansion

$$w(\nu) = \sum_{j=1}^{\infty} w_j \nu^j$$

or an expansion

$$w(\nu) = \sum_{j=1}^{\infty} w_j \nu^{j/2}. \tag{5.4}$$

Fitting these expansions into the characteristic equation rules out the first possibility, whereas (5.4) with $\varepsilon = \nu^{1/2}$ yields

$$\varepsilon^2\left[\zeta w_1^2 + \zeta(1-\theta)\right] + \varepsilon^3\left[w_1^3 + 2\zeta w_1 w_2 + \left(\frac{\zeta}{\theta} + (1-\theta)^2\right)w_1\right] = O(\varepsilon^4).$$

Hence,

$$w_1^2 = \theta - 1, \qquad w_2 = -\frac{1}{2\zeta}\left[w_1^2 + \frac{\zeta}{\theta} + (1-\theta)^2\right].$$

Note that as $\theta < 1$, we have

$$w_1 = \pm i(1-\theta)^{1/2}, \qquad w_2 = -\frac{1}{2\zeta\theta}(\zeta + \theta^3 - \theta^2).$$

Hence the three roots are

$$w_{\pm} = \pm i(1-\theta)^{1/2}\nu^{1/2} + \frac{1}{2\zeta\theta}(\theta^2 - \theta^3 - \zeta)\nu + O(\nu^{3/2}), \tag{5.5a}$$

and

$$w_{\diamond} = -\zeta + O(\nu). \tag{5.5b}$$

Using ζ as a bifurcation parameter, we see that the roots $w_{\pm}$ cross the imaginary axis from left to right when ζ crosses a number close to $\theta^2(1-\theta)$ from right to left. Analyzing the dependence on ζ more closely and using the implicit function theorem, one can show that this crossing is transversal. As nonresonance holds, we can conclude that there is a Hopf bifurcation close to $\zeta = \theta^2(1-\theta)$.

THEOREM 5.1

There is a function $\zeta_0(\nu)$ *defined for small* $\nu > 0$,

$$\zeta_0(\nu) = \theta^2(1-\theta) + O(\nu^{1/2}),$$

with the following properties:

(a) *The endemic equilibrium is locally asymptotically stable if* $\zeta > \zeta_0(\nu)$ *and unstable if* $\zeta < \zeta_0(\nu)$, *as long as* ζ *does not become too small.*

(b) *There is a Hopf bifurcation of periodic solutions at* $\zeta = \zeta_0(\nu)$ *for small enough* $\nu > 0$. *The periods are approximately*

$$T = \frac{2\pi}{|\Im w_{\pm}|} \approx \frac{2\pi}{(1-\theta)^{1/2}\nu^{1/2}} \approx \frac{2\pi}{\sqrt{\theta y^*}}$$

in the neighborhood of the Hopf bifurcation point.

The second approximation of the period T follows from (5.2). It coincides with the quasi-period found in the model without isolation (see [1], e.g., formula (4.5)).

The global theory of Hopf bifurcation for differential equations (see, e.g., [59–62]) suggests that there is a branch (connected set) of periodic solutions emanating at $\zeta_0(\nu)$ that is global in the following sense. Either the parameter ζ associated with the periodic solutions tends to infinity, or the amplitudes of the solutions tend to infinity, or the periods tend to infinity (in a certain generalized sense), or the branch connects to another Hopf bifurcation point. Our a priori bounds (see Theorem 2.1) preclude that the amplitude tends to infinity. The fact that the endemic equilibrium is globally asymptotically stable for very small and very large positive values of ζ (see Theorem 4.3) excludes that the parameter ζ tends to infinity. Though we cannot rule out that the periods tend to infinity, we may guess the existence of a second Hopf bifurcation point. This second Hopf bifurcation point cannot exist for values of ζ that are large compared to ν, for our previous procedure would have detected it. Hence we suspect that there is a second Hopf bifurcation point for positive ζ that are of the same order of magnitude as ν. (Actually we did not at first find the second Hopf bifurcation point by this reasoning, but by numerical calculations with *Auto* [48].)

We look for ζ in the order of magnitude of ν, i.e., we substitute

$$\zeta = \nu\eta$$

and consider η as a variable parameter. Then, from (3.1),

$$y^* = \nu(1+\eta)\tilde{\kappa}, \qquad q^* = \theta\tilde{\kappa}, \qquad z^* = \theta\eta\tilde{\kappa},$$
$$\tilde{\kappa} = \frac{1-\nu-\theta}{\nu(1+\eta)+\theta\eta},$$

that is,

$$y^* = \nu\left(\frac{1+\eta}{\eta}\right)\left(\frac{1-\theta}{\theta}\right) + O(\nu^2), \tag{5.6a}$$

$$q^* = \frac{1-\theta}{\eta} + O(\nu), \tag{5.6b}$$

$$z^* = 1-\theta+O(\nu). \tag{5.6c}$$

Hence the coefficients (5.1) of the characteristic polynomial take the form

$$a = \left(2+\eta+(1+\eta)\frac{1-\theta}{\theta\eta}\right)\nu + O(\nu^2), \tag{5.7a}$$

$$b = \frac{(1+\eta)(1-\theta)^2}{\eta}\nu + O(\nu^2), \tag{5.7b}$$

$$c = (1+\eta)(1-\theta)\left(1+\frac{1-\theta}{\eta}\right)\nu^2 + O(\nu^3). \tag{5.7c}$$

Thus the characteristic equation takes the form

$$w^3 + \nu A(\nu)w^2 + \nu B(\nu)w + \nu^2 C(\nu) = 0 \tag{5.8}$$

with functions $A(\nu)$, $B(\nu)$, $C(\nu)$ that are analytic in $\nu > -\delta$ for some $\delta > 0$ (which may depend on η) and

$$A(0) = 2+\eta+(1+\eta)\frac{1-\theta}{\theta\eta},$$

$$B(0) = \frac{(1+\eta)(1-\theta)^2}{\eta},$$

$$C(0) = (1+\eta)(1-\theta)\left(1+\frac{1-\theta}{\eta}\right).$$

In the degenerate case $\nu = 0$, the characteristic equation (5.8) has the triple root $w = 0$. The arguments in [58, II, §1, Section 2] suggest

looking for the roots of (5.8) in the form

$$w = \sum_{j=1}^{\infty} \alpha_j \nu^{j/k},$$

with k being either 1, 2, or 3. We first look for roots of the form

$$w = \nu \tilde{w}.$$

Substitution into (5.8) and division by ν^2 yields

$$\nu \tilde{w}^3 + \nu A(\nu)\tilde{w}^2 + B(\nu)\tilde{w} + C(\nu) = 0. \tag{5.9}$$

As $A(0)$, $B(0)$, and $C(0) > 0$, the analytic version of the implicit function theorem (see [63, Theorem 2.3, Section 2.2]) tells us that (5.9) has a unique root $\tilde{w}$ for small $\nu > 0$ that is strictly negative. Moreover, $\tilde{w}$ is an analytic real-valued function of ν. Hence, for small $\nu > 0$, there is a unique root $w = \nu \tilde{w}(\nu)$ of (5.8).

We now look for roots w of the form $w = \varepsilon \hat{w}$, $\varepsilon = \nu^{1/2}$. Substitution into (5.8) and division by ε^3 yields

$$\hat{w}^3 + \varepsilon A(\varepsilon^2)\hat{w}^2 + B(\varepsilon^2)\hat{w} + \varepsilon C(\varepsilon^2) = 0. \tag{5.10}$$

For $\varepsilon = 0$, (5.10) has the three distinct solutions

$$\hat{w} = 0, \pm i\sqrt{B(0)}\,.$$

The analytic version of the implicit function theorem implies that for small $\varepsilon > 0$, there are three distinct roots $\hat{w}_\diamond$, $\hat{w}_\pm$ of (5.10). These roots depend analytically on ε; $\hat{w}_\diamond(0) = 0$, $\hat{w}_\pm(0) = \pm i\sqrt{B(0)}$. The root $\varepsilon \hat{w}_\diamond$ of (5.8) is actually of the form $\nu \tilde{w}$ and so coincides with the strictly negative root we have found before. The roots $w_\pm = \varepsilon \hat{w}_\pm$ of (5.8) have expansions

$$w_\pm(\varepsilon) = \sum_{j=1}^{\infty} \alpha_j^{\pm} \varepsilon^j$$

with

$$\alpha_1^{\pm} = \pm i\sqrt{B(0)} = \pm i\left[\frac{(1+\eta)(1-\theta)^2}{\eta}\right]^{1/2}. \tag{5.11}$$

In order to determine $\alpha_2^{\pm}$ we substitute

$$\hat{w} = \alpha_1^{\pm} + \alpha_2^{\pm}\varepsilon + O(\varepsilon^2)$$

into (5.10). Using (5.11) and noticing that $(\alpha_1^+)^2 = (\alpha_1^-)^2 =: \alpha_1^2$, this yields

$$3\alpha_1^2\alpha_2^{\pm} + \left(2+\eta+\frac{(1+\eta)(1-\theta)}{\theta\eta}\right)\alpha_1^2 + \frac{(1+\eta)(1-\theta)^2}{\eta}\alpha_2^{\pm} + (1+\eta)(1-\theta)\frac{\eta+1-\theta}{\eta} = 0.$$

After some algebra we obtain

$$\alpha_2^{\pm} = \frac{1}{2(1-\theta)\theta\eta}\left[\theta^2\eta^2 + (\theta-1)\eta - (1-\theta)^2\right].$$

Summarizing our calculations, we obtain that

$$\Re w_{\pm}(\varepsilon) = \varepsilon^2\alpha_2 + O(\varepsilon^3) = \frac{\varepsilon^2}{2(1-\theta)\theta\eta} \times\left[\theta^2\eta^2 + (\theta-1)\eta - (1-\theta)^2\right] + O(\varepsilon^3), \tag{5.12a}$$

$$\Im w_{\pm}(\varepsilon) = \pm\varepsilon\left[\frac{(1+\eta)(1-\theta)^2}{\eta}\right]^{1/2} + O(\varepsilon^3) = \sqrt{\theta y^*(1-\theta)} + O(\varepsilon^2). \tag{5.12b}$$

In the last equality we have used the first equation in (5.6). In order to detect a potential Hopf bifurcation point we consider the equation

$$\Re w_{\pm}(\varepsilon) = 0.$$

We see that for small $\varepsilon > 0$, $\Re w_{\pm}(\varepsilon) = 0$ occurs for η being close to

$$\eta_{\pm} = \frac{1-\theta}{2\theta^2}\left(1 \pm \sqrt{1+4\theta^2}\right) + O(\varepsilon),$$

where $\eta_+ > 0$ is the epidemiologically relevant one. Further we see that the roots $w_{\pm}(\varepsilon)$ cross the imaginary axis from left to right when η crosses a number close to $\eta_{\pm}$ from left to right. Analyzing the depen-

dence on η more closely and using the implicit function theorem, one can show that this crossing is transversal. Returning to our original parameterization $\zeta = \nu\eta$, we can formulate the following result concerning a second Hopf bifurcation point.

THEOREM 5.2

There is a function $\zeta_1(\nu)$ defined for small $\nu > 0$,

$$\zeta_1(\nu) = \frac{1-\theta}{2\theta^2}\left(1+\sqrt{1+4\theta^2}\right)\nu + O(\nu^{3/2}),$$

with the following properties:

(a) *The endemic equilibrium is locally asymptotically stable if $\zeta < \zeta_1(\nu)$ and unstable if $\zeta > \zeta_1(\nu)$, as long as ζ does not become too large.*

(b) *There is a Hopf bifurcation of periodic solutions at $\zeta = \zeta_1(\nu)$ for small enough $\nu > 0$. The periods are approximately*

$$T = \frac{2\pi}{|\Im w_-|} \approx \frac{2\pi}{\sqrt{\theta y^*}}\left(\frac{1}{\sqrt{1-\theta}}\right)$$

in the neighborhood of the Hopf bifurcation point.

6. BACK TO THE "REAL" WORLD

The analytical results of Section 5 suggest that there is a wide range of lengths of the isolation periods for which sustained oscillations exist provided that the other parameters are chosen appropriately. In this section we will check what happens for a realistic choice of parameters. Our results in Section 5 are formulated in a scaled time, and going back to real time requires knowledge of the unknown rate σ or, equivalently, of the basic replacement ratio $\mathcal{R}_0 \approx 1/\theta$. In models without an isolation period, the so-called mean age at infection (or mean sojourn time in the susceptible class) has been used to estimate $\mathcal{R}_0$ [8, 10] (see [1] and [6] for more references). This approach requires, however, that the disease dynamics be at their endemic equilibrium. It has also been applied to highly oscillating endemic diseases, nevertheless, and Dietz and Schenzle [1] seem to be only ones who mention that the estimates obtained this way may be biased. In the following we will investigate how far the mean age at infection can be used for parameter estimation if the force of infection is periodic rather than constant.

6.1. *ESTIMATING THE TEMPORAL MEAN OF A PERIODIC INFECTIOUS FORCE*

Following Dietz and Schenzle [1] we consider a cohort of individuals who have been born into the susceptible class at the same time s. Let a denote their age, which coincides with the time they have spent in the susceptible class. Let $p(s,a)$ be the proportion of this cohort that are still susceptible at age a (or equivalently at time $s+a$). Then, in analogy to Equation (2.1a), we have

$$\frac{\partial}{\partial a}p(s,a) = -\sigma p(s,a)y(s+a). \tag{6.1}$$

We have discarded the mortality rate because the data are collected from individuals who leave the susceptible class by infection. Further we have the initial condition

$$p(s,0) = 1. \tag{6.2}$$

Integration yields

$$p(s,a) = \exp\left(-\int_0^a \sigma y(s+b)\,db\right). \tag{6.3}$$

Assume that y is periodic with period T. Then $p(s,a)$ is T-periodic in s for any $a \geqslant 0$. This implies that

$$\bar{p}(a) = \frac{1}{T}\int_0^T p(s+t,a)\,dt = \frac{1}{T}\int_0^T p(t,a)\,dt \tag{6.4}$$

is independent of s and is the temporal mean of the probability of being still susceptible at age a. The mean sojourn time in the susceptible class, D_S (or mean age at infection), is then given by

$$D_S = -\int_0^\infty a\,d\bar{p}(a) = \int_0^\infty \bar{p}(a)\,da. \tag{6.5}$$

If $y = y^*$ is constant, then $\bar{p}(a) = p(s,a) = e^{-\sigma y^* a}$ and $D_S = (\sigma y^*)^{-1}$. If y is T-periodic, let

$$\bar{y} = \frac{1}{T}\int_0^T y(t)\,dt \tag{6.6}$$

such that $\sigma\bar{y}$ is the temporal mean of the periodic infectious force σy. Jensen's inequality, applied to (6.4), (6.3), implies that

$$\bar{p}(a) > e^{-\sigma\bar{y}a}.$$

By (6.5),

$$\frac{1}{D_S} < \sigma \bar{y}. \tag{6.7}$$

To obtain an estimate of $\sigma \bar{y}$ from above, we make the following calculation:

$$\begin{aligned}\int_0^\infty p(s,a)\,da &= \sum_{j=0}^{\infty} \int_{jT}^{(j+1)T} p(s,a)\,da = \sum_{j=0}^{\infty} \int_0^T p(s,a+jT)\,da \\ &= \sum_{j=0}^{\infty} \int_0^T \exp\left(-\int_0^{a+jT} \sigma y(s+b)\,db \right) da \\ &= \sum_{j=0}^{\infty} \int_0^T \exp\left(-j\sigma \bar{y} T - \int_0^a \sigma y(s+b)\,db \right) da \\ &= \frac{1}{1-e^{-\sigma \bar{y} T}} \int_0^T \exp\left(-\int_0^a \sigma y(s+b)\,db \right) da.\end{aligned}$$

Hence, by (6.4) and (6.5),

$$D_S = \frac{1}{1-e^{-\sigma \bar{y} T}} \left(\frac{1}{T} \right) \int_0^T \int_0^T \exp\left(-\int_0^a \sigma y(s+b)\,db \right) da\,ds.$$

This yields the estimate

$$D_S < \frac{T}{1-e^{-\sigma \bar{y} T}}.$$

Combining this estimate with the one in (6.7) we obtain

$$\frac{1}{D_S} < \sigma \bar{y} < -\frac{1}{T} \ln\left(1 - \frac{T}{D_S} \right). \tag{6.8}$$

This shows that

$$\sigma \bar{y} \approx \frac{1}{D_S},$$

provided that T/D_S was small enough, which typically is not the case. No further progress in estimating the parameters can be made unless

we make the plausible, but potentially unrealistic, assumption that the temporal mean of y is roughly the same as its equilibrium value,

$$\bar{y} \approx y^*. \tag{6.9}$$

As pointed out in Section 5, Equation (5.2a) presents a good approximation of y^* in the real situation. Solving for θ yields

$$\theta \approx \frac{\nu}{y^* + \nu} = \frac{\mu}{\sigma y^* + \mu} = \frac{1}{D\sigma y^* + 1}, \tag{6.10}$$

where $D = 1/\mu$ is the life expectation. The results of Section 5 suggest that we have sustained oscillations for $\zeta_1 < \zeta < \zeta_0$. If

$$D_Q = \frac{1}{\xi} = \frac{1}{\sigma\zeta}$$

denotes the mean length of the isolation period, we have sustained oscillations if

$$D_Q^0 < D_Q < D_Q^1,$$

where D_Q^0, D_Q^1 are the necessary minimum and maximum lengths of the isolation period. By Theorems 5.1 and 5.2, they are approximately given by

$$\gamma D_Q^0 \approx \frac{\theta}{\zeta_0} \approx \frac{1}{\theta(1-\theta)}, \qquad \frac{D_Q^1}{D} \approx \frac{2\theta^2}{(1-\theta)\left(1+\sqrt{1+4\theta^2}\right)}. \tag{6.11}$$

6.2. *A MODEL WITH A LUMPED LATENCY PERIOD*

In our original model, $1/\gamma$ is the length of the effective infectious period. This model does not allow comparison to real data, however, because, for mathematical simplicity, we have neglected the latency period (period between moment of infection and moment of becoming infectious), which may be as long or even longer than the infectious period (see [6, Table 3.1]).

Rather than redoing the complete analysis for a model with latency period (though this can be done), we lump the exposed individuals (i.e., those in the latency period) and the infectious individuals by a brute force argument. $1/\gamma$ then becomes the sum of the latency period and the effective infectious period.

The model with latency period takes the form

$$\frac{d}{dt}S = \Lambda - \mu S - \tilde{\sigma} S \frac{I}{A},$$

$$\frac{d}{dt}E = -(\mu + \gamma_1)E + \tilde{\sigma} S \frac{I}{A},$$

$$\frac{d}{dt}I = -(\mu + \gamma_2)I + \gamma_1 E,$$

$$\frac{d}{dt}Q = -(\mu + \xi)Q + \gamma_2 I,$$

$$\frac{d}{dt}R = -\mu R + \xi Q,$$

$$A = S + E + I + R.$$

The notation is the same as in Section 2 except for the following: E denotes the number of exposed individuals, that is, the number of individuals in the latent period, $1/\gamma_1$ is the mean length of the latent period, and $1/\gamma_2$ is the mean length of the effective infectious period. For notational reasons that become apparent later, the per capita rate of infection has been denoted by $\tilde{\sigma}$ rather than σ. We introduce the sum of the exposed and infectious individuals, J,

$$J = E + I.$$

The differential equation for I then takes the form

$$\frac{d}{dt}I = -(\mu + \gamma_1 + \gamma_2)I + \gamma_1 J,$$

whereas by adding the differential equations for E and I we obtain

$$\frac{d}{dt}J = -\mu J - \gamma_2 I + \tilde{\sigma} S \frac{I}{A}.$$

The brute force assumption consists in taking the quasi-steady state for the I differential equation, which could rigorously be justified if γ_1 were large compared with the other parameters:

$$I = \frac{\gamma_1}{\mu + \gamma_1 + \gamma_2} J.$$

Replacing the differential equations for E and I by the equation for J and substituting the last expression for I yields

$$\frac{d}{dt}S = \Lambda - \mu S - \sigma S\frac{J}{A},$$
$$\frac{d}{dt}J = -(\mu+\gamma)J + \sigma S\frac{J}{A},$$
$$\frac{d}{dt}Q = -(\mu+\xi)Q + \gamma J,$$
$$\frac{d}{dt}R = -\mu R + \xi Q,$$
$$A = S + J + R,$$

with

$$\gamma = \frac{\gamma_1\gamma_2}{\mu+\gamma_1+\gamma_2}, \qquad \sigma = \tilde{\sigma}\frac{\gamma_1}{\mu+\gamma_1+\gamma_2}.$$

This system is of the same form as system (2.1), the only difference being that

$$\frac{1}{\gamma} \approx \frac{1}{\gamma_1} + \frac{1}{\gamma_2} = D_E + D_I$$

is approximately the sum of the mean length of the latency (exposed) period D_E and the mean length of the effective infectivity period D_I. Hence $1/\gamma$ is at least as large as the mean length of the incubation period (period from infection to appearance of symptoms). In diseases where symptoms show up in a pronounced and severe form, $1/\gamma$ may more or less correspond to the mean length of the incubation period plus perhaps 1 day. Whatever θ may be in its feasible range between 0 and 1, formula (6.11) provides the estimate

$$D_Q^0 \geqslant 4(D_E + D_I),$$

with this estimate being an equality if and only if $\theta = 1/2$. So the minimum length of the mean isolation period required for sustained oscillation is at least four times as large as the mean length of the incubation period. For some childhood diseases this appears too large to be realistic, but it may still be of the right order of magnitude.

6.3. *COMPARISON TO SCARLET FEVER IN ENGLAND AND WALES, 1897–1978*

Anderson and May [10, Tables 1 and 2; 6, Table 6.1] report an average age of infection between 10 and 14 years, a mean interepidemic

period of 4.4 years, and an average life expectation that rises from 60 to 70 years. Hence we assume

$$D = 65\ \text{yr}, \qquad D_S = 12\ \text{yr}, \qquad T = 4.4\ \text{yr}.$$

We further identify the temporal mean $\bar{y}$ defined in (6.6) with the endemic equilibrium value y^* (which is potentially not justified) and so obtain from the estimates in (6.8) that

$$\frac{1}{D_S} < \sigma y^* < -\frac{1}{T}\ln\left(1 - \frac{T}{D_S}\right). \tag{6.12}$$

In numbers,

$$0.0833 < \sigma y^* \left[\text{yr}^{-1}\right] < 0.1038.$$

The approximate formula (6.10), $\theta \approx (D\sigma y^* + 1)^{-1}$, implies the approximate estimates

$$0.1291 \leqslant \theta \leqslant 0.1559.$$

As

$$\mathscr{R}_0 = \frac{1}{\theta + \nu} = \frac{1}{\theta}\left(\frac{1}{1 + \mu/\gamma}\right) \approx \frac{1}{\theta},$$

we obtain the following lower and upper bounds for the basic replacement ratio $\mathscr{R}_0$:

$$6.4 < \mathscr{R}_0 < 7.7.$$

Our estimate for θ implies $\theta < 1/2$, that is, the formula

$$\gamma D_Q^0 = \frac{\theta}{\zeta_0} \approx \frac{1}{\theta(1-\theta)}$$

in (6.11) is decreasing in θ, whereas the formula

$$\frac{D_Q^1}{D} \approx \frac{2\theta^2}{(1-\theta)\left(1+\sqrt{1+4\theta^2}\right)}$$

in (6.11) is increasing in θ. This makes it possible to give upper and lower bounds for D_Q^0 and D_Q^1:

$$7.6 < \gamma D_Q^0 < 8.9, \qquad 0.0188 < \frac{D_Q^1}{D} < 0.0281.$$

Notice that the lower and upper estimates for $\mathcal{R}_0$ are associated with the lower and upper estimates of γD^0, respectively, whereas the lower estimate for $\mathcal{R}_0$ is associated with the upper estimate for D_Q^1/D, and the upper estimate for $\mathcal{R}_0$ with the lower estimate for D_Q^1/D.

Anderson and May [6, Table 3.1] report a latent period of 1 or 2 days, an infectious period of 14–21 days, and an incubation period of 2 or 3 days. This suggests an effective infectious period that may be as short as 1 or 2 days, a sum of latent and effective period that is $1/\gamma = 3$ days, and an isolation period between 2 and 3 weeks. Anderson et al. [64] report isolation periods of 2 and 3 weeks or even longer. It is possible, however, that there are infections without any symptoms or with slight symptoms such that $1/\gamma$ may be larger than 3 days. We stick to $1/\gamma = 3$ days, which, for the lower estimate $\mathcal{R}_0 = 6.4$, gives us a window

$$22.8 \text{ days} < D_Q < 1.83 \text{ yr}$$

for isolation periods that make the endemic equilibrium unstable and a window

$$26.7 \text{ days} < D_Q < 1.22 \text{ yr}$$

for the upper estimate $\mathcal{R}_0 = 7.7$. So the minimum isolation periods that make the endemic equilibrium unstable are of the right order of magnitude.

The formulas in Theorems 5.1 and 5.2 provide the periods of sustained oscillations in case the length of the isolation period is slightly larger than the necessary minimum length D_Q^0 (Theorem 5.1) or slightly smaller than the required maximum length D_Q^1 (Theorem 5.2). Notice that, with

$$1/\gamma \approx D_E + D_I$$

now being the sum of the lengths of the latency period and the effective infectivity period, the formula in Theorem 5.1 is exactly analogous to the formulas given by Dietz [15] and Anderson and May [10] for a model with latency but without isolation period. In real time, the lengths of the interepidemic periods are given by

$$\frac{T_0}{\sigma} = 2\pi \left(\frac{1/\gamma}{\sigma y^*} \right)^{1/2}$$

if the length of the isolation period is slightly larger than the minimum period and by

$$\frac{T_1}{\sigma} = 2\pi \left(\frac{1/\gamma}{\sigma y^*} \right)^{1/2} \left(\frac{1}{\sqrt{1-\theta}} \right)$$

if the length of the isolation period is slightly smaller than the maximum period. These formulas provide interepidemic periods that are slightly less than 2 yr and so are much shorter than the reported average length of 4.4 yr but still of the right order of magnitude. We emphasize that the above formulas hold only at the bifurcation points, and we refer to the numerical results in the next section for isolation periods that are not close at the bifurcations points.

7. NUMERICAL RESULTS

In this section we study the model equations numerically for the parameters that we believe mimic the scarlet fever situation in England and Wales from 1897 to 1978. As in Section 6, we assume a life expectation of 65 yr and a mean age at infection of 12 yr. We further assume that the sum of the length of the latency period and the effective infectious period (which should be equal to or slightly larger than the length of the incubation period) is 3 days. From these parameters we can calculate ν, once we have estimated θ. Indeed,

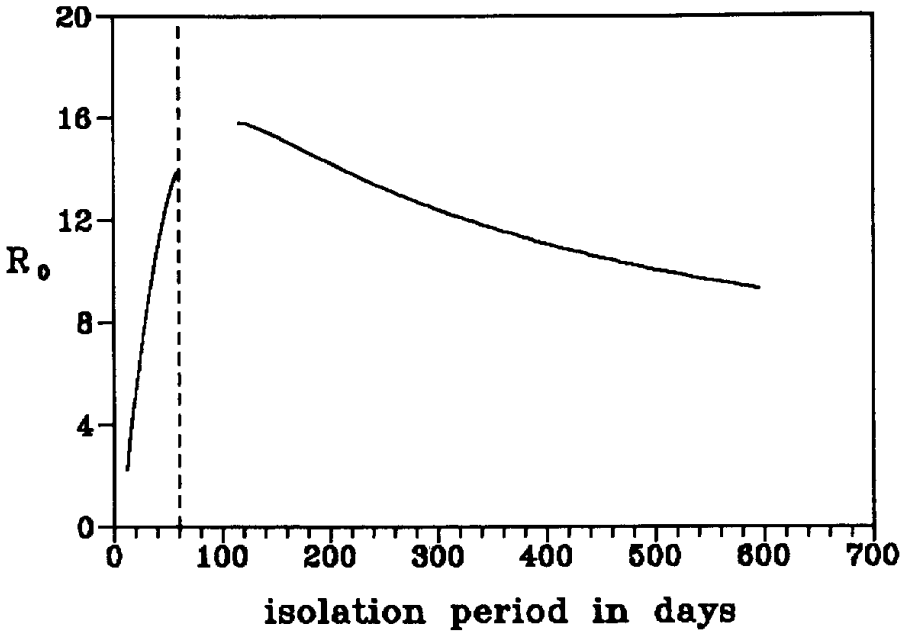
$$\frac{\nu}{\theta} = \frac{\mu}{\gamma} = \frac{3 \text{ days}}{65 \text{ yr}} = 0.000126.$$

In the previous section we estimated the basic replacement ratio $\mathscr{R}_0$ to be between 6.4 and 7.7 and $\theta \approx 1/\mathscr{R}_0$ to be between 0.1291 and 0.1559. These estimates were based on the possibly unrealistic assumption that the temporal mean of a periodic solution equals the endemic equilibrium value.

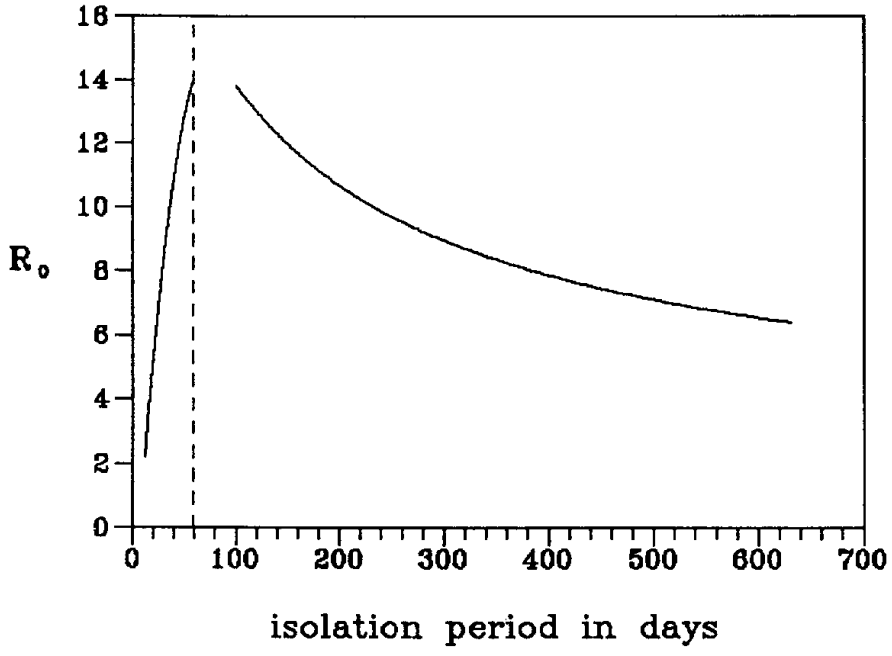
Calculations with Doedel's [48] program *Auto* (see Figure 1) show that the endemic equilibrium loses its stability for some lengths of the isolation period if $\mathscr{R}_0$ is smaller than 14.

The calculations with Auto provide that the endemic equilibrium is unstable for isolation periods whose lengths are between 23.8 and 629.5 days if $\mathscr{R}_0 = 6.4$ is at its lower estimate, and for isolation periods whose lengths are between 28.7 and 419.8 days if $\mathscr{R}_0 = 7.7$ is at its larger estimate. Recall that the approximate formulas in Section 5 suggest an unstable endemic equilibrium when the length of the isolation period is between 22.8 and 667.3 days for $R_0 = 6.4$ and between 26.7 and 447 days for $R_0 = 7.7$.

In the following numerical calculations we have chosen $\mathscr{R}_0$ to be at its lower estimated value, $R_0 = 6.4$. Recall that the lower estimate $R_0 = 6.4$ would be sharp if the endemic were at its (mathematical) equilibrium state. The lower estimate is the one that is typically taken in the literature. Compared to the upper estimate, the lower estimate has the advantage of being independent of the length of the interepidemic



(a)



(b)

FIG. 1. (a) The basis replacement ratio $\mathscr{R}_0$ versus the minimum and maximum lengths of the isolation period between which the endemic equilibrium is unstable. Fig. 1.b. Magnification showing $\mathscr{R}_0$ versus the minimum length.

period (see the derivation of the estimates in Section 6.1). The Auto calculations show that the Hopf bifurcation (with the length of the isolation period being the bifurcation parameter) is supercritical at both bifurcation points (Figure 2). We conjecture that the two bifurcation points are connected by a global branch of periodic solutions, though the Auto calculations do not confirm this.

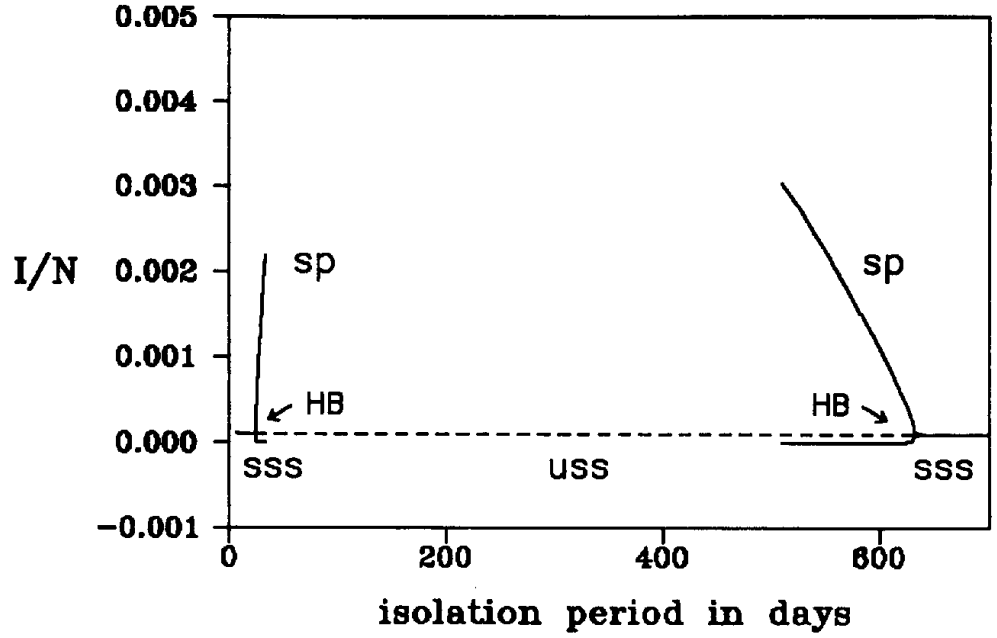
But we guess that this is due to Auto not working properly in the respective parameter region rather than to something fancy going on. Numerical integration according to Gear [65] still provides convergence toward periodic oscillations in parameter regions where Auto does not seem to work.

The periods of the periodic solutions depend rather dramatically on the length of the isolation period (Figure 3). The observed lengths of interepidemic periods (3–6 yr) according to [6, Table 6.1] are feasible with isolation periods between 27 and 57 days. These lengths seems to be unrealistically high, but this may be due to the crudeness of our model (see Discussion). With a model without an isolation period, Anderson and May [6, Table 6.1] can mimic interepidemic periods between 4 and 5 years.

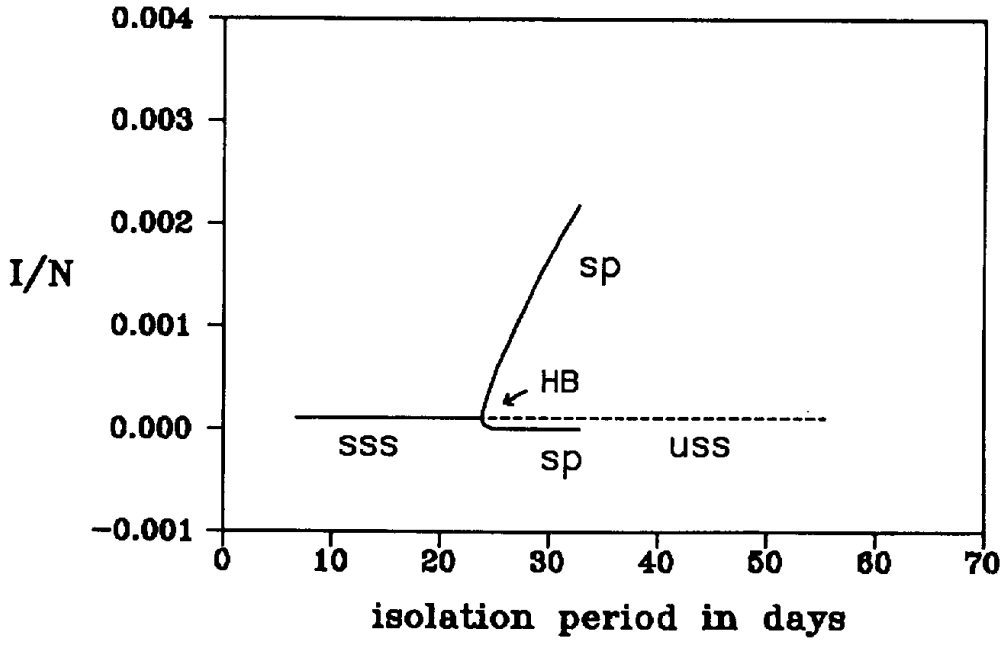
Figures 4 and 5 display numerical solutions (according to [65]) of system (2.5) in terms of I/N, the fraction of infective (nonisolated) individuals, for various lengths of the isolation period (1 day, 15 days, 25 days, 30 days, and 900 days) in order to illustrate how the stability of the endemic equilibrium decreases and is finally lost, as the length of the isolation period increases, and is eventually regained when it becomes very large.

8. DISCUSSION

Hamer [41], in 1906, believed that autonomous internal forces are responsible for the sustained oscillations in childhood diseases. His point of view seemed to be refuted when more precise mathematical models were developed. In 1921, Martini [66] gave an explicit formulation of the standard model for endemic diseases. This model neglects a latency period and is equivalent to the limiting case of our model (2.1) for $\xi \to \infty$. Lotka [67] showed in 1923 that an endemic equilibrium, whenever it exists, is unique and locally asymptotically stable, allowing only dampened oscillations. In 1975, Dietz [8] established the connection between the quasi-periods of these oscillations and the mean age at infection (mean sojourn time in the susceptible class) and extended the model to include a latency period [15] in 1976. Inclusion of the latency period does not change the local stability properties of the endemic equilibrium but gives a more realistic relation between the length of the



(a)



(b)

FIG. 2. (a) An Auto plot of the lower and upper amplitudes of the periodic solutions (in terms of the fraction of infective (nonisolated) individuals) versus the length of the isolation period. $\mathscr{R}_0$ is chosen at its lower estimate, 6.4. HB, Hopf bifurcation point; sss, (locally asymptotically) stable steady state; uss, unstable steady state; sp, (locally asymptotically orbitally) stable periodic solution. (b) Magnification of the left branch.

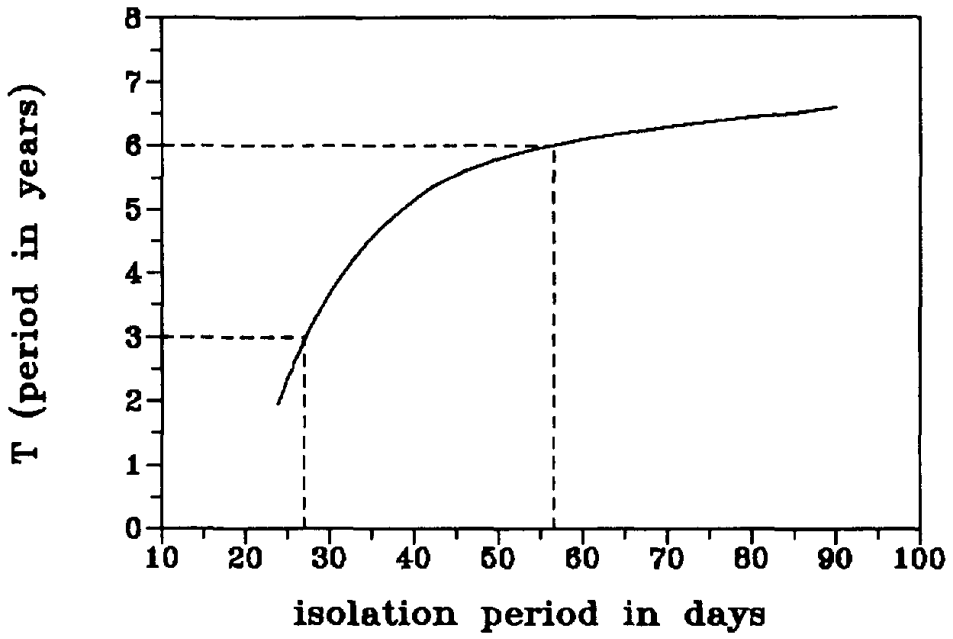


FIG. 3. An Auto plot of the periods of the periodic solutions versus the length of the isolation period. $\mathscr{R}_0$ is chosen at its lower estimate, 6.4.

interepidemic periods (periods between two peaks or valleys of disease prevalence) and the mean age at infection. Global asymptotic stability of the endemic equilibrium was not shown until recently [68]. Thieme and Castillo-Chavez [43, Theorem 5(c)] showed that the introduction of arbitrary (rather than exponential) distributions of the lengths of latency and infection periods and even of infection-age-dependent infectivity cannot destroy the local stability of the endemic equilibrium as long as permanent immunity and nonfatality of the disease are assumed.

Autonomous explanations of recurrent measles outbreaks had a short comeback in the work by Soper [42] in 1929, but his model is structurally unstable and his sustained oscillations are only marginally stable. According to Bailey [69, p. 12], the failure of deterministic models to reproduce undamped oscillations "led to their abandonment in many quarters and consequent replacement by corresponding probability, or stochastic representation." For childhood diseases the replacement was initiated by Bartlett [11, 12] in the late 1950s. In the early 1970s, deterministic explanations of recurrent outbreak were revived, however, in the numerical work by London and Yorke [13, 14], which introduced an external periodic forcing and led Yorke et al. [70] to "believe that stochastic effects play a role, but only one which is secondary to seasonal variation in transmissibility." Their findings were supported by later formal and analytic work by various authors

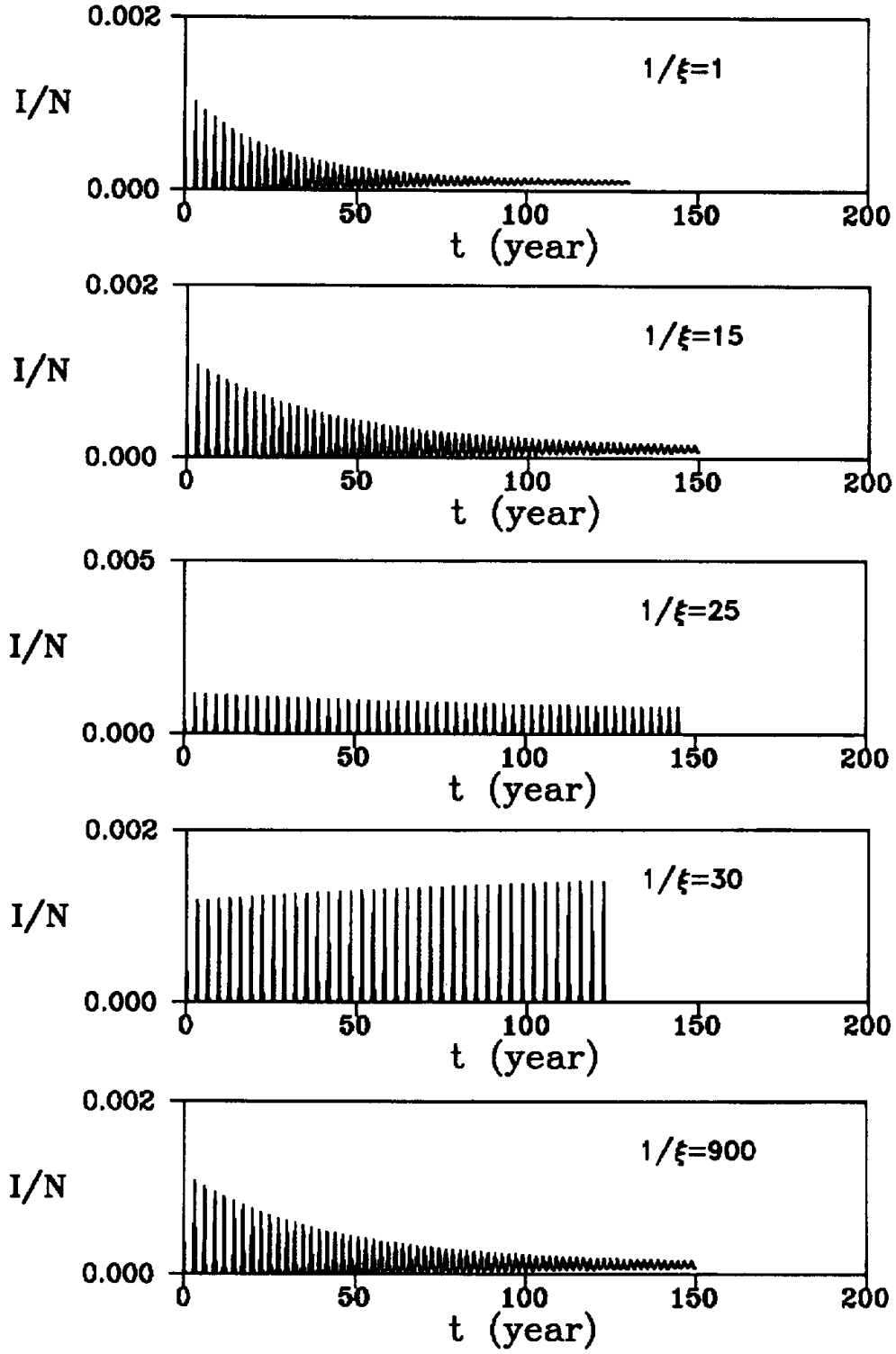


FIG. 4. Numerical integration of the model equations according to Gear. The fraction of infective (nonisolated) individuals is plotted versus time. $\mathcal{R}_0$ is chosen at its lower estimate, 6.4. The length of the isolation period has been chosen (from above to below) to be 1 day, 15 days, 25 days, 30 days, 900 days.

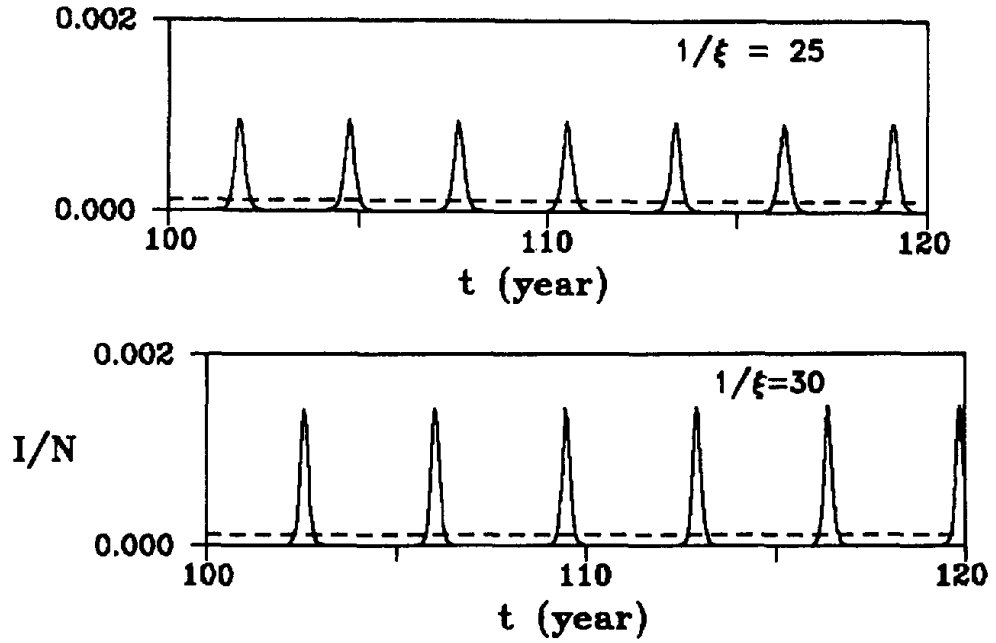


FIG. 5. The fraction of infective (nonisolated) individuals versus time in a time window 100–120 yr after the start. $\mathscr{R}_0$ is chosen at its lower estimate, 6.4. The length of the isolation period has been chosen (from above to below) to be 25 days and 30 days. The dashed lines represent the fractions of infective individuals at the endemic equilibrium. For an isolation period of 25 days, this fraction is 0.000108; for an isolation period of 30 days, it is 0.000112.

(see the Introduction). Other ingredients that have been shown to destabilize the endemic equilibrium are nonlinear incidence rates and age-dependent infection rates (see the Introduction). The nonlinear incidence rates that have been considered so far are difficult to explain for childhood diseases, and the assumptions required for age-dependent infection rates to produce sustained oscillations are rather extreme. Schenzle's [2] complex model that combines seasonal forcing with age dependence by incorporating the school system has led to very good agreements with observations. (For a more detailed historical review, see [1].)

Seasonal variation in the transmission rate does not restore the validity of Hamer and Soper's opinion that autonomous (deterministic) forces can generate sustained oscillations. Yorke et al. [70, p. 114] compare the level of susceptibles in a deterministic model "to a pendulum swinging back and forth past equilibrium. Seasonal variation gives the pendulum a shove every year and these regular shoves are required to keep the pendulum in motion."

In this paper we consider an autonomous mechanism that seems to have been neglected so far: isolation (or quarantine), which takes

account of the fact that sick individuals stay at home after they show sufficiently severe symptoms. Traditional models have merged isolated and immune individuals into one class. We distinguish them because immune individuals, though they do not play an active epidemiological role, may play a very important passive one. Immune individuals act as a buffer, because any contact of an infective with an immune individual is wasted from the infective agent's point of view. The presence of the immune individuals introduces some kind of friction that dampens the oscillations of the endemic pendulum described by Yorke et al. [70]. In contrast to immune individuals, isolated individuals do not act as a buffer because, by their very nature, they are not on the epidemic scene. Splitting off the isolated class reduces the buffering impact of the immune class provided that an individual's rate of contact with other individuals is largely independent of the number of individuals available. We think this is a realistic assumption as long as the number of available individuals is rather large (see the model explanation in Section 2). Mathematically this feature is incorporated by dividing the usual bilinear mass action incidence term by the number of active, that is, nonisolated, individuals. We find that in a suitable range of the other parameters the endemic equilibrium is locally asymptotically stable for small isolation periods and that enlarging the mean length of the isolation period (in a range of a realistic order of magnitude) makes the endemic equilibrium less stable until it loses its stability, giving rise to sustained oscillations. The range of isolation periods for which sustained oscillations exist typically extends from a certain minimum length to a considerably larger maximum length beyond which the endemic equilibrium gains back its stability. Heuristically the destabilizing effect of increasing the mean length of the isolation period can be understood via the decrease in the buffering role of the immune individuals as explained above. Removing this buffer altogether (by making the isolation period extremely long) has a stabilizing effect, however, which seems difficult to explain.

In order to check whether the parameter range for sustained oscillations is realistic, we compare our results with data of the scarlet fever endemic in England and Wales from 1897 to 1978 [6]. Unfortunately, a crucial parameter, the basic replacement ratio $\mathscr{R}_0$, cannot be determined precisely because of the periodic behavior of the scarlet fever endemic. This complication has been neglected in the literature so far. The formulas derived in Section 5 suggest that sustained oscillations are possible for a length of the isolation period between 23 and 668 days at the lower estimate of $\mathscr{R}_0$, $\mathscr{R}_0 = 6.4$, and between 27 and 447 days at the upper estimate of $\mathscr{R}_0$, $\mathscr{R}_0 = 7.7$. The numerical results indicate that the isolation period should have a length between 24 and 630 days for the

lower estimate of $\mathscr{R}_0$ to guarantee undamped oscillations, and a length between 29 and 420 days for the upper estimate of $\mathscr{R}_0$.

The interepidemic periods we have numerically found depend strongly on the length of the isolation period. The empirically observed interepidemic periods stretch from 3 to 6 yr [6, Table 6.1]. We obtain an interepidemic period of 3 yr for an isolation period of about 27 days, and an interepidemic period of 6 yr for an isolation period of about 57 days. In particular, the latter value is unrealistically large. This does not rule out isolation as an explanation for the observed undamped oscillations. To keep the analysis relatively simple, we have chosen a model in which the durations of the various stages of the disease (latency, infectiousness, isolation) and the overall sojourn time in the system are exponentially distributed. Exponentially distributed durations have a standard deviation that is as large as their mean value, a property that is certainly not satisfied in reality. Introducing other than exponentially distributed durations of the various stages typically has a destabilizing effect. It is well known that standard endemic models in which infective individuals become susceptible again (possibly after a period of temporary immunity) have a locally asymptotically endemic equilibrium if the durations of the latency, infectious, and immune periods are all exponentially distributed (see [71], for example) but that the endemic equilibrium can be unstable if some of the periods have durations for which the standard variation is significantly lower than their mean (see [5] for a survey and references; see also [72, 73]). We therefore expect that replacing the exponentially distributed durations of the various disease stages by more realistically distributed durations will presumably push the required parameter values into a more realistic range.

Generalizing our experience with the scarlet fever data, we anticipate that our model will work quite well as an explanation for sustained oscillations for childhood diseases in which the mean age at infection is relatively large (above 10 yr) and the incubation period is short. We found that our model works particularly poorly for measles, where the mean age at infection is about 4.5 yr and the incubation period lasts from 8 to 13 days [6, Tables 6.1, 3.1]. A possible explanation consists in the fact that real populations are split up into various age groups such that the contact rates within these groups are much higher than between these groups, whereas in our model we have assumed homogeneous contact rates. We conjecture that this simplification provides worse quantitative agreements with data the lower the mean age at infection.

To summarize, we can state that our model shows that an isolation period makes the endemic equilibrium less stable and has the potential to lead to sustained oscillations. Whatever the main factor may be in

generating sustained oscillations (if there is a main factor at all), the other factors (seasonal forcing, age-dependent infection or susceptibility rates, stochastic effects, all of which we have neglected in our model) will also play an important role and will change the parameter ranges at which the oscillations occur as well as modify the interepidemic periods. It is obvious from this analysis, however, that the isolation period (in a realistic range) has a destabilizing effect and, if it is not sufficient to induce sustained oscillations by itself, certainly makes it easier for other factors to drive the disease dynamics into undamped oscillations. Hamer and Soper may not be that wrong after all.

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