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"Models for the spread of universally fatal diseases"

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Models for the spread of universally fatal diseases

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Abstract. In the formulation of models of *S-I-R* type for the spread of communicable diseases it is necessary to distinguish between diseases with recovery with full immunity and diseases with permanent removal by death. We consider models which include nonlinear population dynamics with permanent removal. The principal result is that the stability of endemic equilibrium may depend on the population dynamics and on the distribution of infective periods; sustained oscillations are possible in some cases.

Key words: Epidemiology — Stability of endemic equilibrium — Distributed delays — AIDS

1. Introduction

The classical model (Kermack and McKendrick 1927) for the spread of an infectious disease with removal in a closed population displays a threshold phenomenon. If a dimensionless quantity, often called the contact or reproductive number, is less than 1 the infection will die out but if the contact number is greater than 1 there is an epidemic (the number of infectives first increases to a maximum and then decreases to zero). If births and deaths are incorporated into the model, even keeping the total population size constant, there is a change in the threshold phenomenon. The infection still dies out if the contact number is less than 1, but if it is greater than 1, the model typically displays the existence of a unique endemic equilibrium (Hethcote 1974).

For a disease in which the removal is through death caused by the disease, the total population size cannot be constant because members of the removed class cannot be counted in the population. This forces us to formulate models for such diseases differently from models for diseases in which the removal is through recovery with permanent full immunity. We shall consider only simple models with a single susceptible class, and a single infective class. To make

quantitative predictions for specific diseases it may be necessary to subdivide these classes into sub-classes with different contact rates because of dependence on such factors as age structure or differences in behavior. However, this is not the object of this paper. Our purpose is to formulate and analyze models for infectious diseases with removal by death in which nonlinear population dynamics and transmission rates more general than the bilinear transmission rates of classical models are included.

In Sect. 2 we describe basic models for diseases in closed populations and in Sect. 3 we incorporate nonlinear contact rates and population dynamics as well as differences in the distribution of infective periods to formulate a simple general model for a universally fatal disease. This model is analyzed in Sect. 4; the principal result is that the stability of endemic equilibrium for some kinds of population dynamics may depend on the distribution of infective periods; sustained oscillations are possible in some cases.

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2. Models for diseases in closed populations

We let $S(t)$ denote the number of members of a population susceptible to a disease, $I(t)$ the number of infective members, and $R(t)$ the number of members who have been removed from the possibility of infection either through immunity or through death caused by the disease. Then the classical model (Kermack and McKendrick 1927) is

$$\begin{aligned} S' &= -\beta SI, \\ I' &= \beta SI - \frac{1}{\tau} I, \\ R' &= \frac{1}{\tau} I, \end{aligned} \tag{1}$$

where $'$ denotes the derivative with respect to time. This model is based on three fundamental assumptions:

(i) The population is closed, with no births, no deaths except from the disease, and no migration.
(ii) The rate at which members become infective is proportional to the product of the number of susceptibles and the number of infectives.
(iii) The rate of passage from infective to removed class through recovery or death is proportional to the number of infectives.

It follows immediately from the assumption (i) that $S + I + R$ is a constant K; this is reflected in the system (1) by the fact that $(S + I + R)' = 0$. For a disease in which the class R consists of members removed through recovery with immunity, the total population size is constant. For such a disease, it is sometimes assumed that the average number of contacts sufficient to transmit

infection per infective in unit time is a constant λ (Hethcote 1976). Then the number of such contacts in unit time is λI, and the probability that each contact is with a susceptible is S/K. Thus the infection rate is βSI, with $\beta = \lambda/K$.

For a disease in which the class R consists of members removed through death, the total population, which we shall denote by N, is $S + I$. In general, for such a disease the total population size cannot be constant. If it is assumed that the average number of contacts sufficient to transmit infection per infective in unit time is a constant λ, we would obtain a transmission rate $\lambda SI/(S + I)$, and the model would be

$$\begin{aligned} S' &= -\frac{\lambda SI}{S+I}, \\ I' &= \frac{\lambda SI}{S+I} - \frac{1}{\tau} I, \\ R' &= \frac{1}{\tau} I. \end{aligned} \tag{2}$$

The qualitative behavior of the system (2) is not the same as that of the system (1). In order to obtain the model (1) for a fatal disease, it is necessary to assume a contact rate proportional to population density.

We will generalize the assumption (ii) by assuming that the number of contacts in unit time per infective is a function $C(N)$ of total population size, with

$$C(N) > 0, \qquad C'(N) \geqslant 0, \qquad \left[\frac{C(N)}{N}\right]' \leqslant 0 \tag{3}$$

for $N > 0$. This assumption may be appropriate for sexually transmitted diseases (Castillo-Chavez et al. 1989) as well as for virally transmitted diseases. It may be reasonable to assume a contact rate proportional to population size when the population size is small but that the contact rate saturates for larger population sizes. The hypothesis (3) includes such behavior, and leads to a transmission rate $C(N)SI/N$. It is convenient to define the per capita contact rate.

$$\hat{C}(N) = C(N)/N,$$

so that $C(N) = N\hat{C}(N)$, $\hat{C}'(N) \leqslant 0$, and the transmission rate is $\hat{C}(N)SI$. We now have the following model for a fatal disease in a closed population

$$\begin{aligned} S' &= -\hat{C}(S+I)SI, \\ I' &= \hat{C}(S+I)SI - \frac{1}{\tau} I. \end{aligned} \tag{4}$$

The model (1) is the special case $C(N) = \beta N$ while the model (2) is the special case $C(N) = \lambda$, and in each case $N = S + I$.

Theorem 1. *Under the hypotheses* (3) *on the function C, if there exists* $\bar{S} > 0$ *with* $\tau C(\bar{S}) = 1$ *then the model* (4) *displays a threshold phenomenon. For small positive* $I(0)$, *the infection dies out* [$I(t)$ *decreases monotonically to zero*] *if* $S(0) < \bar{S}$ *and an*

epidemic occurs [$I(t)$ *increases to a maximum and then decreases to zero*] *if* $S(0) > \bar{S}$.

Proof. It is clear from (4) that $S(t)$ decreases monotonically for every solution of (4). Since $S(t) \geqslant 0$, $S(t)$ tends to a limit as $t \to \infty$. The equilibria of (4) are the points $(S_\infty, 0)$ with $S_\infty \geqslant 0$, and thus every orbit tends to a point on the S-axis. There is a maximum of I on an orbit if the orbit crosses the curve Γ in the S-I plane given implicitly by

$$\tau S\hat{C}(S + I) = 1;$$

the intersection of Γ with the S-axis is given by $\tau S\hat{C}(S) = 1$, or $\tau C(S) = 1$, and is therefore the point $(\bar{S}, 0)$. It is easy to verify by implicit differentiation that $dS/dI > 0$ on Γ, and thus the curve Γ has positive slope. If $S(0) < \bar{S}$, the orbit cannot cross Γ and $I(t)$ decreases monotonically. If $I(0)$ is small and $S(0) > \bar{S}$, $I(t)$ increases until the orbit crosses Γ and then decreases. Because C is a monotone increasing function, $\tau C(S) < 1$ if $S < \bar{S}$ and $\tau C(S) > 1$ if $S > \bar{S}$. Thus the threshold quantity is $\tau C(S)$.

For the Kermack–McKendrick model (1), with $C(N) = \beta N$, the threshold quantity is $\beta\tau S$, and an epidemic occurs if and only if $S(0) > 1/\beta\tau$. For the model (2), with $C(N) = \lambda$, there is no positive solution $\bar{S}$ of $\tau C(S) = 1$ and the hypothesis of Theorem 1 is not satisfied. In fact, the curve Γ is the straight line $I = (\lambda\tau - 1)S$ through the origin. It is not difficult to verify that if $\lambda\tau < 1$ every orbit of the system (2) starting in the interior of the first quadrant of the phase plane tends monotonically to the S-axis, while if $\lambda\tau > 1$ every such orbit crosses the line $I = (\lambda\tau - 1)S$ in the first quadrant and then tends to the origin.

Just as for the special case (1) it is possible to relate S_∞, the limiting value of S on an orbit of (4) to S_0, the initial value of S on that orbit, where $I(0)$ is sufficiently small that $S_0 + I(0) \approx S_0$. On an orbit of (4),

$$\frac{dI}{dS} = -1 + \frac{I}{\tau SI\hat{C}(S + I)} = -1 + \frac{1}{\tau S\hat{C}(S + I)}.$$

If we let $N = I + S$, we obtain

$$\frac{dN}{dS} = \frac{1}{\tau S\hat{C}(N)}$$

and separation of variables gives, using $N(0) \approx S_0$ and $N(\infty) = S_\infty$,

$$\tau \int_{S_0}^{S_\infty} \hat{C}(u)\, du = \int_{S_0}^{S_\infty} \frac{dv}{v} = \log \frac{S_\infty}{S_0}.$$

For the Kermack–McKendrick model (1), where $C(N) = \beta N$, this becomes

$$\beta\tau(S_\infty - S_0) = \log \frac{S_\infty}{S_0}$$

(Hethcote 1970).

3. A model with nonlinear population dynamics

If births and deaths are included in the Kermack–McKendrick model, with a constant birth rate and an equal death rate distributed proportionally among the classes, the behavior of the model is quite different from that of a model for a closed population (Hethcote 1974). If the contact number is less than 1 the infection dies out, but if the contact number is greater than 1 there is an asymptotically stable endemic equilibrium, with a positive number of infectives. It should be noted, however, that this model is inappropriate for universally fatal diseases because it assumes deaths in the removed class. In this section we shall formulate a model for universally fatal diseases which extends the model (4) in two directions, including nonlinear population dynamics and generalizing the assumption that the rate of passage from infective to removed class is proportional to the number of infectives.

If t is large enough for all members who were infective at time $t = 0$ to have been transferred to the removed class, the differential equation

$$I' = \hat{C}(S + I)SI - \frac{1}{\tau} I$$

governing the number of infectives in the model (4) is equivalent to the integral equation

$$I(t) = \int_0^t \hat{C}\{S(x) + I(x)\}S(x)I(x)\, e^{-(t-x)/\tau}\, dx\,.$$

In this integral equation we interpret $e^{-s/\tau}$ as the proportion of individuals at time t that if alive are still infective at time $(t + s)$, with an average infective period τ. Thus the assumption (iii) of a transition rate from infective to removed class which is proportional to the number of infectives is equivalent to the assumption of exponentially distributed infective periods.

Instead of assuming an exponential distribution of infective periods, we shall assume more generally that $P(s)$ is the proportion of individuals infected at time t that if alive are still infective at time $(t + s)$, where $P(s)$ is a non-increasing function with $P(0) = 1$ and $\int_0^\infty P(s)\, ds = \tau < \infty$. This gives the integral equation

$$\begin{aligned} I(t) &= \int_0^t \hat{C}\{S(x) + I(x)\}S(x)I(x)P(t-x)\, dx \\ &= \int_0^t \hat{C}\{S(t-y) + I(t-y)\}S(t-y)I(t-y)P(y)\, dy\,. \end{aligned} \tag{5}$$

An interesting special case is the choice

$$P(s) = \begin{cases} 1, & 0 \leqslant s \leqslant \tau \\ 0, & s > \tau \end{cases} \tag{6}$$

corresponding to an infective period of fixed length τ. In this case, (5) is equivalent to the differential-difference equation

$$I'(t) = \hat{C}\{S(t) + I(t)\}S(t)I(t) - \hat{C}\{S(t-\tau) + I(t-\tau)\}S(t-\tau)I(t-\tau),$$

together with appropriate initial data on the interval $(-\tau, 0]$.

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The other modification in the assumptions of the Kermack–McKendrick model which we shall make is to include density-dependent population dynamics. We will assume that all new births are in the susceptible class, thus ruling out vertical disease transmission. We will also assume that the infective class does not contribute to the birth rate, so that the birth rate of susceptibles depends on the number of susceptibles. This assumption is biologically reasonable for debilitating animal diseases (Anderson et al. 1981). For human diseases such as AIDS, instead of a birth rate there is a rate of recruitment of newcomers into a behavioral class of susceptibles, and this also may reasonably be assumed independent of the size of the infective class (Castillo-Chavez et al. 1989). The analysis of models in which the birth rate depends on total population size is considerably more complicated; however, this direction will not be pursued here.

We assume that the death rate in the susceptible class depends on the number of susceptibles. As $1 - P(s)$ is the proportion of individuals infected at time t but no longer infective at time $(t + s)$, whether because of death from the disease and death from other causes, our model allows the possibility that the infection may make victims more subject to other fatal diseases. We now have the following model for a universally fatal disease:

$$\begin{aligned} S'(t) &= g\{S(t)\} - \hat{C}\{S(t) + I(t)\}S(t)I(t), \\ I(t) &= \int_0^t \hat{C}\{S(x) + I(x)\}S(x)I(x)P(t-x)\,dx\,. \end{aligned} \tag{7}$$

This model is based on the following assumptions.

(a) All births are in the susceptible class and the birth and death rates in the susceptible class depend only on the size of this class.
(b) In the absence of disease, the population has a carrying capacity K.
(c) The average number of contacts sufficient to transmit infection per infective in unit time is a function $C(S + I)$ of total population size $S + I$.
(d) The proportion of individuals remaining in the infective class of time $(t + s)$ after becoming infective at time t is $P(s)$, with average infective period τ.

As $g(S)$ is the rate of change of population size in the absence of disease, the assumption (b) is expressed analytically by the conditions

$$g(K) = 0, \quad g(S) > 0\ [0 < S < K], \quad g(S) \leqslant 0\ [S \geqslant K], \quad g'(K) < 0. \tag{8}$$

In many cases $g(0) = 0$, but this need not be assumed. It is convenient to define the constant β by

$$\beta = \hat{C}(K) = C(K)/K. \tag{9}$$

The contact rate C is assumed to satisfy (3), and the condition on P are

$$P(0) = 1, \quad \int_0^\infty P(s)\,ds = \tau < \infty, \quad P \text{ non-increasing.} \tag{10}$$

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4. Analysis of the model

Asymptotic equilibria of the system (7), that is, equilibria of the limit system

$$S'(t) = g\{S(t)\} - \hat{C}\{S(t) + I(t)\}S(t)I(t),$$
$$I(t) = \int_{-\infty}^{t} C\{S(x) + I(x)\}S(x)I(x)P(t-x)\,dx$$

are given by the conditions

$$g(S) = \hat{C}(S+I)SI, \qquad I = \tau\hat{C}(S+I)SI. \tag{11}$$

Thus either $I=0$ or $\tau S\hat{C}(S+I)=1$. If $I=0$, then $g(S)=0$ and $S=K$, the disease-free equilibrium. If $g(0)=0$, there is an additional equilibrium $S=0$, but it is easy to show that this equilibrium is always unstable. If $\tau S\hat{C}(S+I)=1$, we have an endemic equilibrium which is clearly unique. Because C is assumed increasing, $C(S+I) \leqslant C(K) = \beta K$; thus for an endemic equilibrium, $S+I = \tau SC(S+I) \leqslant \tau\beta SK$, and

$$\beta\tau K \geqslant 1 + I/S > 1. \tag{12}$$

It follows from (11) that at an endemic equilibrium $I = \tau g(S)$, and S is given implicitly by

$$\tau S\hat{C}\{S + \tau g(S)\} = 1.$$

If the contact number $\beta\tau K$ is viewed as a parameter, then $I \to 0+$ and $S \to K-$ as $\beta\tau K \to 1+$. The quantity $\beta\tau K$ is the basic reproductive number R_0, the number of secondary infections generated on the average by an infective individual in a population of susceptibles. If the basic reproductive number exceeds one it is possible for the disease to invade a susceptible population.

To linearize (7) about an asymptotic equilibrium (S_∞, I_∞), we let $S = S_\infty + u$, $I = I_\infty + v$. It is convenient to write

$$M(S_\infty, I_\infty) = \hat{C}(S_\infty + I_\infty) + S_\infty\hat{C}'(S_\infty + I_\infty),$$
$$N(S_\infty, I_\infty) = \hat{C}(S_\infty + I_\infty) + I_\infty\hat{C}'(S_\infty + I_\infty).$$

The assumptions (3) imply that

$$M(S_\infty, I_\infty) = \frac{I_\infty C(S_\infty + I_\infty) + S_\infty(S_\infty + I_\infty)C'(S_\infty + I_\infty)}{(S_\infty + I_\infty)^2} > 0,$$
$$N(S_\infty, I_\infty) = \frac{S_\infty C(S_\infty + I_\infty) + I_\infty(S_\infty + I_\infty)C'(S_\infty + I_\infty)}{(S_\infty + I_\infty)^2} > 0.$$

The linearization at (S_∞, I_∞) is

$$u' = [g'(S_\infty) - I_\infty M(S_\infty, I_\infty)]u - S_\infty N(S_\infty, I_\infty)v,$$
$$v(t) = \int_0^t [I_\infty M(S_\infty, I_\infty)u(t-y) + S_\infty N(S_\infty, I_\infty)v(t-y)]P(y)\,dy. \tag{13}$$

For the equilibrium $S = K$, $I = 0$, (13) becomes

$$\begin{aligned} u' &= g'(K)u - K\hat{C}(K)v = g'(K)u - \beta Kv, \\ v(t) &= \int_0^t K\hat{C}(k)v(t-y)P(y)\,dy = \beta K \int_0^t v(t-y)P(y)\,dy. \end{aligned} \tag{14}$$

It is known (Feller 1940) that all solutions of the second equation in (14) tend to zero as $t \to \infty$ if and only if

$$\beta K \int_0^\infty P(y)\,dy = \beta K\tau < 1,$$

and since $g'(K) < 0$ because of (8), if $v(t) \to 0$ then $u(t) \to 0$ as $t \to \infty$. Thus the disease-free equilibrium is asymptotically stable if and only if $R_0 = \beta\tau K < 1$, that is, if and only if it is the only equilibrium.

At the endemic equilibrium, the characteristic equation is

$$\det \begin{bmatrix} g'(S_\infty) - I_\infty M(S_\infty, I_\infty) - \lambda & -S_\infty N(S_\infty, I_\infty) \\ I_\infty M(S_\infty, I_\infty) \int_0^\infty P(s)\,e^{-\lambda s}\,ds & S_\infty N(S_\infty, I_\infty) \int_0^\infty P(s)\,e^{-\lambda s}\,ds - 1 \end{bmatrix} = 0$$

which reduces to

$$[g'(S_\infty) - \lambda]\left[S_\infty N(S_\infty, I_\infty) \int_0^\infty P(s)\,e^{-\lambda s}\,ds - 1\right] = -I_\infty M(S_\infty, I_\infty).$$

This has the form

$$b \int_0^\infty P(s)\,e^{-\lambda s}\,ds = \frac{\lambda + a}{\lambda + c} \tag{15}$$

with

$$a = I_\infty M(S_\infty, I_\infty) - g'(S_\infty), \quad b = S_\infty N(S_\infty, I_\infty), \quad c = -g'(S_\infty). \tag{16}$$

Then

$$\begin{aligned} b\tau &= \tau S_\infty[\hat{C}(S_\infty + I_\infty) + I_\infty \hat{C}'(S_\infty + I_\infty)] \\ &\leqslant \tau S_\infty \hat{C}(S_\infty + I_\infty) = 1, \end{aligned}$$

because of (11) and the negativity of $\hat{C}'(S_\infty + I_\infty)$. Also, $a > c$, because $M(S_\infty I_\infty) > 0$. The characteristic equation (15) has been analyzed (Hethcote et al. 1981); a partial stability result can be derived directly

Lemma 1. *If* $\tau < 0$, $|b|\tau \leqslant 1$, $a > |c| \geqslant 0$, *then all roots of* (15) *are in the left half plane.*

Proof. If $\Re\lambda \geqslant 0$, then

$$\left| b \int_0^\infty P(s)\,e^{-\lambda s}\,ds \right| \leqslant |b| \int_0^\infty |P(s)|\,ds = |b|\tau \leqslant 1.$$

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If $a > |c| > 0$ and $\mathscr{R}\lambda \geqslant 0$, then

$$\left|\frac{\lambda + a}{\lambda + c}\right| > 1.$$

Thus the two sides of (15) cannot be equal for $\mathscr{R}\lambda \geqslant 0$.

It follows immediately from Lemma 1 that if $a > |c| \geqslant 0$, in particular if $g'(S_\infty) < 0$ so that $c > 0$, the endemic equilibrium of (7) is asymptotically stable. If $\beta\tau K$ is sufficiently close to 1, then S_∞ is sufficiently close to K that $g'(S_\infty) < 0$. We have now established the following result.

Theorem 2. *Under the assumptions* (3), (8), (9), (10), *the disease-free equilibrium of the model* (7) *is asymptotically stable if the reproductive number* $\beta\tau K$ *is less than* 1. *If the contact number is greater than* 1 *the disease-free equilibrium is unstable but there is an endemic equilibrium which is asymptotically stable at least if the contact number is sufficiently close to* 1, *and for all contact numbers if* $g'(S) < 0$ *for* $0 < S < K$.

In models for AIDS (Castillo-Chavez et al. 1989) it is assumed that there is a constant rate of recruitment of new-susceptibles and that there is a death rate proportional to the number of susceptibles. Then $g(S)$ has the form $p - qS$ with $p > 0$, $q > 0$ and $g'(S) < 0$ for all S. Thus the endemic equilibrium is always stable. For animal diseases, $g(S)$ accounts for births and non-disease-related deaths, and usually there exists $\varrho < K$ such that $g'(S) < 0$ for $\varrho < S < K$ but $g'(S) > 0$ if $S < \varrho$. Then if the contact number is large enough it may be possible to have $g'(S_\infty) > 0$ and this could lead to a situation in which the condition $a > |c|$, or $I_\infty M(S_\infty, I_\infty) > 2g'(S_\infty)$ is violated and the endemic equilibrium might be unstable. A related result has been established for models incorporating age of infection (Thieme and Castillo-Chavez 1989).

To explore the possibility of instability of the endemic equilibrium, we consider two different choices of $P(s)$.

Example 1. If $P(s) = e^{-s/\tau}$, corresponding to an exponentially distributed infective period and an ordinary differential equation model,

$$\int_0^\infty P(s)\, e^{-\lambda s}\, ds = \frac{\tau}{\lambda\tau + 1},$$

and the characteristic equation (15) becomes

$$\tau\lambda^2 + [(a - b)\tau + 1]\lambda + [a - bc\tau] = 0. \tag{17}$$

The condition that all roots of (17) have negative real part is

$$(a - b)\tau + 1 > 0, \qquad a - bc\tau > 0.$$

Using (11) and (16) we may calculate

$$(a - b)\tau + 1 = \tau\left[\frac{g(S_\infty)}{S_\infty} - g'(S_\infty)\right],$$

and thus under the reasonable hypothesis

$$g(S) > Sg'(S), \quad S > 0,$$

we have $(a-b)\tau + 1 > 0$. The condition $a - bc\tau > 0$ is an immediate consequence of $a > c$, $0 < b\tau \leqslant 1$. Thus for this choice of P, the endemic equilibrium remains asymptotically stable for all contact numbers.

Example 2. For the choice (6) of P, corresponding to an infective period of fixed length and a differential-difference equation model,

$$\int_0^\infty P(s)\, e^{-\lambda s}\, ds = \frac{1 - e^{-\lambda\tau}}{\lambda},$$

and the characteristic equation (15) becomes

$$\lambda + a = b(\lambda + c)\left(\frac{1 - e^{-\lambda\tau}}{\lambda}\right). \tag{18}$$

It is known (Hethcote et al. 1981) that if $a > 0$, $0 < b\tau \leqslant 1$, $c < 0$ and $|c|$ is sufficiently large then (18) has roots in the right half plane.

For the logistic population growth model, with $g(S) = rS(1 - S/K)$ and the contact rate $C(N) = \beta N$, it is not difficult to calculate

$$a = \frac{r}{\beta\tau K}, \qquad b = \frac{1}{\tau}, \qquad c = -r + \frac{2r}{\beta\tau K}.$$

Thus $a > 0$, $b\tau = 1$, and $a + c < 0$ if $\beta\tau K > 3$. As $\beta\tau K \to +\infty$, $a \to 0$ and $c \to -r$. The condition that (18) with $b\tau = 1$ has a pure imaginary root $\lambda = iy$ is

$$a = \frac{2}{\tau} - y \cot\frac{\tau y}{2}, \qquad c = \frac{-y(\tau y - \sin\tau y)}{1 - \cos\tau y},$$

and $a \to 0$, $c \to 0$ as $y \to 0+$. Thus if a is close to zero and c is negative and bounded away from zero, the endemic equilibrium is unstable. This will occur if $\beta\tau K$ is sufficiently large. In fact, as the contact number $\beta\tau K$ increases there is a bifurcation to a periodic solution. It is not known whether further increase of the contact number leads to period-doubling and chaotic behavior. It is plausible to conjecture that other choices of $g(S)$ and $C(N)$ will exhibit similar behavior.

Qualitative behavior like that indicated by Example 2 has been suggested by studies of fox rabies in Europe and predicted by a four-dimensional ordinary differential equation model (Anderson et al. 1981). This model assumes an exposed period and a natural death rate in each class. Similar behavior is predicted by a model of the form (7) (Brauer 1989).

Examples 1 and 2 show that (7) is a disease model for which the endemic equilibrium is not necessarily stable. While instability of the endemic equilibrium is a possibility in populations divided into sub-populations with different characteristics, this is the first example of a simple model in which the behavior depends on the distribution of infective periods. Exponentially distributed infective periods have commonly been used for infectious disease models because they lead to relatively tractable ordinary differential equation models whose behavior

has been considered to be shared by more complicated models. Diseases which are universally fatal do not conform to this notion, and more study of the dependence of the behavior at endemic equilibrium on the form of the function P is needed. There is reason to believe that convexity or lack of convexity of P is relevant to this question (Thieme and Castillo-Chavez 1989).

5. Discussion

We have noted that in modelling infectious diseases it is essential to distinguish between members removed through recovery with immunity and members removed through death from disease. This distinction is necessary both for describing contact rates which depend on total population size and for incorporating realistic population dynamics. For diseases which are invariably fatal, total population size cannot remain constant, and the simple classical models are therefore inappropriate.

Two classes of fatal diseases which are currently of interest are animal diseases such as rabies and human immunodeficiency virus diseases (AIDS). We have established the possibility of a significant difference in the behavior of models for such diseases because of differences in the shape of the recruitment curves. By allowing contact rates more general than those of the classical models we have also made it possible to study simple AIDS models in the same framework.

It is possible to formulate models for diseases without immunity and diseases with recovery and full immunity which incorporate nonlinear population dynamics and contact rates which depend on total population size. Preliminary investigations indicate that for such models the endemic equilibrium is always asymptotically stable. A more difficult modelling problem is the description of diseases in which there are some fatalities and some recoveries. This is relevant for measles and some strains of influenza in underdeveloped countries.

Another question calling for further study is whether any changes in behavior are produced by the inclusion of an exposed period. Is is known (Hethcote and Tudor 1980) that for a disease with recovery with immunity in a population with constant birth and death rates and constant total population size, the inclusion of an exposed period with arbitrary distribution does not change the qualitative behavior. For a disease without immunity in a closed population, if either the infective or exposed period has exponential distribution the inclusion of an exposed period does not change the behavior, but it is not known whether this extends to models with both exposed and infective periods having arbitrary distribution.

A question of particular importance in the study of AIDS modelling is the formulation and analyses of models in which the transmission of infection depends on the time since becoming infective. Such models will necessarily be more complicated than the simple model considered here and may well have different qualitative behavior. A partial answer has been given (Thieme and Castillo-Chavez 1989).

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