ROCKY MOUNTAIN
JOURNAL OF MATHEMATICS
Volume 25, Number 1, Winter 1995

MODELS FOR DISEASES WITH EXPOSED PERIODS

FRED BRAUER

ABSTRACT. A general model for a disease without immunity against reinfection having arbitrary distributions of exposed and infective periods was formulated by Hethcote, Stech and van den Driessche [**5**]. They showed that for contact numbers exceeding 1, the endemic equilibrium is asymptotically stable if either the exposed period of the infective period is exponentially distributed or if both exposed and infective period have fixed length, and they conjectured that the endemic equilibrium is always asymptotically stable.

We show that the endemic equilibrium is asymptotically stable if the mean exposed period is less than the mean infective period, or if the contact number is sufficiently large, or if the exposed period distribution function is convex. However, we also show that for a more general type of model in which the infective period distribution can depend on the length of the exposed period it is possible to have instability of the endemic equilibrium and a Hopf bifurcation.

1. There are three main categories of simple models for the spread of communicable diseases, namely, S-I-R models with removal through recovery and immunity against reinfection, S-I-R models with removal through death caused by the disease, and S-I-S models with recovery but with no immunity against reinfection. The formulation of these models goes back to the three fundamental papers of Kermack and McKendrick [**8**]. Descriptions which may be easier to follow may be found in [**1, 2, 7**]. Variations such as an exposed period between infection by the disease and becoming infective, or a period of temporary immunity following recovery from the disease are most readily incorporated into the framework of these three basic categories of models by allowing the infectivity of an individual to depend on the time since infection [**3, 10**].

For each of the basic models there is a basic reproductive number or contact number R_0 depending on the rate of transmission of infection,

Received by the editors on June 19, 1992, and in revised form on November 17, 1992.
1991 AMS *Subject Classification.* 92D30, 45M10.
Key words. Epidemic models, exposed period.

the size of the population, and the mean infective period. If the contact number is less than 1, every solution of the model with nonnegative initial data tends as $t \to \infty$ to the disease-free state in which all members of the population are free of infection. If the contact number exceeds 1, the disease-free state is unstable and there is an endemic equilibrium.

The behaviors of the three models when there is an endemic equilibrium are different. For the S-I-R (recovery) model, the endemic equilibrium is always asymptotically stable, even with variable infectivity [**2, 3**]. Thus, the endemic equilibrium in an S-E-I-R (recovery) model is always asymptotically stable. For the S-I-R (permanent removal) model, instability of the endemic equilibrium is possible even without an exposed period [**3, 10**].

The endemic equilibrium in an S-I-S model with constant infectivity is always asymptotically stable [**2, 6**] but instability is possible in an S-I-S model with variable infectivity, notably in the case of temporary immunity following recovery—an S-I-R-S model [**4, 5**]. However, it is not established whether the endemic equilibrium in an S-E-I-S model need be asymptotically stable. This is the question which we shall study here.

2. Let $S(t)$ denote the number of susceptible members, $E(t)$ the number of exposed (but not yet infective) members, and $I(t)$ the number of infective members of a population at time t. We assume that:

(i) there are no births or deaths, so that total population size is constant,

$$S(t) + E(t) + I(t) = K;$$

(ii) the number of contacts per infective in unit time is constant, so that the rate of new infections in unit time is βSI, with β a constant (bilinear incidence);

(iii) the fraction of exposed members who remain in the exposed class a time s after exposure is a nonincreasing function $Q(s)$, with

$$Q(0+) = 1, \qquad \int_0^\infty Q(s)\,ds = \sigma < \infty; \tag{1}$$

(iv) the fraction of infective members who remain in the infective class a time s after infection is a nonincreasing function $P(s)$, with

$$P(0+) = 1, \qquad \int_0^\infty P(s)\,ds = \tau < \infty; \tag{2}$$

(v) infective members on recovery return to the susceptible class.

The disease is then modeled by the pair of integral equations

$$\begin{aligned} E(t) &= \int_{-\infty}^{t} \beta S(x) I(x) Q(t-x)\,dx \\ I(t) &= \int_{-\infty}^{t} \beta S(x) I(x) U(t-x)\,dx \end{aligned} \tag{3}$$

with

$$U(s) = -\int_0^s Q'(v) P(s-v)\,dv \tag{4}$$

[**6**]. The functions $E_0(t)$ and $I_0(t)$ represent initial data, the number of exposed and infective members, respectively, at time t who were already exposed and infective, respectively, at time $t = 0$. It is convenient to retain the variable S in the model (3), although in the analysis of (3) we replace S by $K - E - I$.

It is known [**6**] that if the contact number $R_0 = \beta\tau K$ exceeds 1, then the disease-free equilibrium $S = K$, $E = 0$, $I = 0$ of (3) is unstable, and there exists an endemic equilibrium

$$\begin{aligned} S &= \frac{1}{\beta\tau} = \frac{K}{R_0}, \\ E &= \frac{\sigma}{\sigma+\tau} \cdot \frac{\beta\tau K - 1}{\beta\tau} = \frac{\sigma}{\sigma+\tau} \cdot \frac{R_0 - 1}{R_0} K, \\ I &= \frac{\tau}{\sigma+\tau} \frac{\beta\tau K - 1}{\beta\tau} = \frac{\tau}{\sigma+\tau} \cdot \frac{R_0 - 1}{R_0} K. \end{aligned} \tag{5}$$

Our purpose in this section is to give some conditions which guarantee the (local) asymptotic stability of this endemic equilibrium.

Theorem. *The endemic equilibrium* (5) *of the* S-E-I-S *model* (3) *is asymptotically stable if any of the following conditions is satisfied.*

$$\text{(6)} \qquad \text{(i)} \quad R_0 > 2 + \sigma/\tau$$

$$\text{(ii)} \quad \sigma < \tau$$

$$\text{(7)} \qquad \text{(iii)} \quad \tau + \int_0^\infty Q(s) \cos ys \, ds > 0, \qquad 0 < y < \infty.$$

Proof. We linearize (3) about the endemic equilibrium and then form the characteristic equation—the condition on the complex parameter λ that the linearization has solutions for which each component is a constant multiple of $e^{\lambda t}$. Then the equilibrium is asymptotically stable if all roots of the characteristic equation have negative real parts [**9**]. This characteristic equation is

$$\text{(8)} \qquad \frac{1}{\tau}\hat{U}(\lambda) = 1 + \frac{R_0 - 1}{\sigma + \tau}[\hat{U}(\lambda) + \hat{Q}(\lambda)]$$

where $\hat{U}(\lambda)$ and $\hat{Q}(\lambda)$ are the Laplace transforms of $U(s)$ and $Q(s)$, respectively. We consider R_0 as a parameter which increases from 1. For $R_0 = 1$, (which implies $E = I = 0$) the characteristic equation (8) reduces to

$$\frac{1}{\tau}\hat{U}(\lambda) = 1$$

which has $\lambda = 0$ as a root because of (2). The root $\lambda(R_0)$ with $\lambda(1) = 0$ obeys

$$\frac{1}{\tau}\hat{U}'(\lambda)\lambda'(R_0) = \frac{1}{\sigma + \tau}[\hat{U}(\lambda) + \hat{Q}(\lambda)] + \frac{R_0 - 1}{\sigma + \tau}[\hat{U}'(\lambda) + \hat{Q}'(\lambda)]\lambda'(R_0)$$

and because

$$\hat{U}'(0) = -\int_0^\infty sU(s) \, ds < 0,$$

$$\lambda'(1) = \frac{(1/(\sigma + \tau))[\hat{Q}(0) + \hat{U}(0)]}{(1/\tau)\hat{U}'(0)} < 0.$$

Thus this root moves into the left half plane as R_0 increases. Because

$$\lim_{|\lambda| \to \infty} \hat{U}(\lambda) = \lim_{|\lambda| \to \infty} \hat{Q}(\lambda) = 0, \qquad R\lambda \geq 0,$$

there are no roots of (8) with $R\lambda \geq 0$ and $|\lambda|$ large; roots cannot appear at infinity as R_0 increases. If $R_0 > 1$, $\lambda = 0$ is not a root of (8). Thus, (8) can have a root with $R\lambda \geq 0$ only if for some value of R_0 there is a pair of complex conjugate roots $\lambda = \pm iy$ with $y > 0$. In order to prove asymptotic stability of the endemic equilibrium, it suffices to show that there is not root $\lambda = iy$ with $0 < y < \infty$ of (8). The condition that $\lambda = iy$ be a root of (8) is

$$\frac{1}{\tau}\hat{U}(iy) = 1 + \frac{R_0 - 1}{\sigma + \tau}[\hat{U}(iy) + \hat{Q}(iy)]$$

and separation into real and imaginary parts gives the pair of conditions

$$\frac{1}{\tau}\int_0^\infty U(s)\cos(ys)\,ds = 1 + \frac{R_0 - 1}{\sigma + \tau}\int_0^\infty [U(s) + Q(s)]\cos(ys)\,ds \tag{9}$$

$$\frac{1}{\tau}\int_0^\infty U(s)\sin(ys)\,ds = \frac{R_0 - 1}{\sigma + \tau}\int_0^\infty [U(s) + Q(s)]\sin(ys)\,ds. \tag{10}$$

Alternate forms of this pair of equations are

$$\left(\frac{1}{\tau} - \frac{R_0 - 1}{\sigma + \tau}\right)\int_0^\infty U(s)\cos(ys)\,ds = 1 + \frac{R_0 - 1}{\sigma + \tau}\int_0^\infty Q(s)\cos(ys)\,ds \tag{11}$$

$$\left(\frac{1}{\tau} - \frac{R_0 - 1}{\sigma + \tau}\right)\int_0^\infty U(s)\sin(ys)\,ds = \frac{R_0 - 1}{\sigma + \tau}\int_0^\infty Q(s)\sin(ys)\,ds \tag{12}$$

and

$$\left(\frac{1}{\tau} - \frac{R_0 - 1}{\sigma + \tau}\right)\int_0^\infty [U(s) + Q(s)]\cos(ys)\,ds = 1 + \frac{1}{\tau}\int_0^\infty Q(s)\cos(ys)\,ds \tag{13}$$

$$\left(\frac{1}{\tau} - \frac{R_0 - 1}{\sigma + \tau}\right) \int_0^\infty [U(s) + Q(s)] \sin(ys)\, ds = \frac{1}{\tau} \int_0^\infty Q(s) \sin(ys)\, ds. \tag{14}$$

Because Q and, as may readily be verified using (4), $U + Q$ are nonnegative, nonincreasing functions,

$$\begin{aligned} \int_0^\infty Q(s) \sin(ys)\, ds &\geq 0, \\ \int_0^\infty [U(s) + Q(s)] \sin(ys)\, ds &\geq 0 \end{aligned} \tag{15}$$

and thus, in order to satisfy (14), we must have

$$\frac{1}{\tau} - \frac{R_0 - 1}{\sigma + \tau} \geq 0.$$

It follows that if (6) is satisfied there can be no root $\lambda = iy$ of (8), and thus the endemic equilibrium is asymptotically stable. Because, as is easily verified, $\int_0^\infty U(s)\, ds \leq \tau$, we have

$$\left| \int_0^\infty U(s) \cos(ys)\, ds \right| \leq \tau.$$

Thus, the left side of (11) is at most $1 - (\tau/(\sigma+\tau))(R_0 - 1)$, and because

$$\left| \int_0^\infty Q(s) \cos(ys)\, ds \right| \leq \sigma,$$

the right side of (11) is at least $1 - (\sigma/(\sigma + \tau))(R_0 - 1)$. If $\sigma < \tau$, (11) cannot be satisfied, and thus the endemic equilibrium is asymptotically stable. If (7) holds and $\lambda = iy$ is a root of (8), by (13) we have

$$\int_0^\infty [U(s) + Q(s)] \cos(ys)\, ds > 0.$$

Then the right side of (9) has absolute value at least 1 while the left side of (9) has absolute value at less than 1. This contradicts (7). Thus, (7) implies the asymptotic stability of the endemic equilibrium and

this completes the proof of the theorem. In particular, convexity of Q implies (7) and thence asymptotic stability of the endemic equilibrium. □

The above theorem complements the result [**6**] that the endemic equilibrium is asymptotically stable in the three cases.

(i) P arbitrary, $Q(s) = e^{-s/\sigma}$,

(ii) Q arbitrary, $P(s) = e^{-\sigma/\tau}$

(iii) $Q(s) = \begin{cases} 1, & 0 \le s \le \sigma \\ 0, & s > \sigma \end{cases}$, $P(s) = \begin{cases} 1, & 0 \le s \le \tau \\ 0, & s > \tau \end{cases}$

with global asymptotic stability for (ii) and lends credence to their conjecture that the endemic equilibrium is always asymptotically stable. However, the general characteristic equation (8) remains intractable, and we can neither confirm nor contradict this conjecture analytically or numerically. This conjecture was made for models with constant total population size and bilinear incidence.

For the more general S-E-I-S model with density-dependent birth and death rates and a contact rate which depends on the total population size, the characteristic equation is identical to (8) except for a removable factor. Thus the assumptions (i) and (ii) made at the beginning of this section can be discarded without affecting any of the results of this paper. Also, the conjecture of [**6**] is equally plausible for this more general model.

3. Models for diseases with an exposed period can be viewed as models with variable infectivity. We think of an infected (rather than infective) class which consists of the classes E and I with exposed members having infectivity 0 and infective members having infectivity 1. The general model for an S-I-S disease with infectivity depending on the time since infection [**3**] is

$$J(t) = J_0(t) + \int_0^t \beta S(xl)\Phi(x)V(t-x)\,dx$$
$$\Phi(t) = \Phi_0(t) + \int_0^t \beta S(x)\Phi(x)U(t-x)\,dx.$$

Here J represents the size of the infected class ($E + I$ in our case) and

Φ represents the total infectivity (I in our case). $V(s)$ represents the function of members of the class J who remain in the class J a time s after becoming infected ($U(s) + Q(s)$ in our case) and $U(s)$ represents the total infectivity of the members of the class J who remain in the class J a time s after becoming infected. If the fraction of infectives who remain infective a time s after becoming infective is $P(s)$, then U is given by (4).

More generally, we could assume that the fraction of infected members whose infectivity was zero for a time v after being infected and who remain infected a time s after being infected is a function $P(s - v, s)$ of both the time $(s - v)$ since becoming infective and the time s since becoming infected. Then it is not difficult to calculate

$$U(s) = -\int_0^s Q'(v)P(s - v, s)\, dv.$$

We may say that a generalized S-E-I-S model is characterized by the conditions (i)–(v) of the previous section, with (iv) replaced by

(iv)* the fraction of infective members who remain in the infective class a time s after becoming exposed is a function $U(s)$.

As before, the assumptions (i) and (ii) may be discarded without producing any essential change in the characteristic equation at the endemic equilibrium.

We now take Q to be an arbitrary function satisfying (1) whose support is contained in the interval $[0, \sigma + \tau]$. Define

$$U(s) = \begin{cases} 1 - Q(s), & 0 \le s \le \sigma + \tau \\ 0, & s > \sigma + \tau. \end{cases} \tag{16}$$

Then, as $U(s) + Q(s)$ is a step function,

$$\hat{U}(\lambda) + \hat{Q}(\lambda) = \frac{1 - e^{-\lambda(\sigma+\tau)}}{\lambda}$$

and the characteristic equation (8) takes the form

$$\frac{1}{\tau}\hat{U}(\lambda) = 1 + \left(\frac{R_0 - 1}{\sigma + \tau}\right)\frac{1 - e^{-\lambda(\sigma+\tau)}}{\lambda} \tag{17}$$

which is precisely the form studied by Diekmann and Montijn [**4**], if time units are chosen to make $\sigma + \tau = 1$. It has been shown in [**4**] that R_0 and $U(s)$ (and hence $Q(s)$) can be chosen so that the characteristic equation (17) has roots in the right half plane. Thus it is possible for the endemic equilibrium in a generalized S-E-I-S model to be unstable; it is indicated in [**4**] that such instability generally leads to a Hopf bifurcation and oscillations about the endemic equilibrium, and this appears to be confirmed by numerical simulations. The particular choice (16) corresponds to a disease with an arbitrary exposed period and an infective period equal to $\sigma + \tau$ less the exposed period, or a fixed infected period of $\sigma + \tau$. The function $P(s - v, s)$ representing the fraction of infected members who became infective a time v after becoming infected and who remain infective a time s after being infected is given by

$$P(s - v, s) = \begin{cases} 1, & 0 \leq v \leq s \leq \sigma + \tau \\ 0, & s > \sigma + \tau. \end{cases}$$

4. We have not been able to settle completely the question of whether the endemic equilibrium of an S-E-I-S disease model must be asymptotically stable. On the one hand, we have extended the cases in which this equilibrium is asymptotically stable; on the other hand, we have shown that instability is possible for a more general type of model. Further stability results would require a more detailed analysis of the pairs of conditions (9)–(14).

Another direction for investigation involves intermediate models, such as diseases which are fatal to some fraction of their victims but for which recovery leads to immunity against reinfection. Such models have not been analyzed in general, even without an exposed period. The broad question of which types of models can support oscillations caused by the delay of an exposed period remains largely open.

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Department of Mathematics, University of Wisconsin, Madison, Wisconsin 53706.