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Transmission and Control of Arbovirus Diseases

K. Dietz* (1975)

Introduction

The present paper is a survey of mathematical models and problems in relation to arbovirus diseases. This class of diseases is caused by arthropod-borne viruses whose primary hosts are vertebrates, but whose development cycle involves multiplication within the vectors by which they are transmitted. Many of these viruses are maintained as endemic in wildlife. But sometimes severe epidemics in human or domestic animal populations may occur. Examples are yellow fever, dengue, St. Louis encephalitis, Japanese encephalitis, tick-borne encephalitis, to name just a few. A concise review is given by Simpson (1972).

Most of the mathematical theory of communicable diseases has been more or less explicitly concerned with those virus infections which produce life-long immunity. The relevant model is usually referred to as the "general epidemic" (Bailey, 1957). Many results of this theory are immediately applicable to arbovirus diseases. In the following we shall deal with some problems that are either peculiar to arbovirus diseases or have not yet been adequately dealt with for any virus disease.

The epidemic threshold

Section 4.4 of Bailey (1957) discusses a model of Kermack and McKendrick for the spread of an epidemic by a vector. Using the same notation, let x, y,z denote the number of susceptibles, infectives and immunes in the human population, respectively. Let x',y', and z' be the number of susceptibles,

* Health Statistical Methodology, World Health Organization, 1211 Geneva 27, Switzerland.

infective and removed vectors, respectively. (The vectors for arboviruses do not develop immunity. Their infective period is terminated by their death.) Bailey gives the following system of differential equations:

$$\frac{dx}{dt} = -\beta xy', \qquad \frac{dx'}{dt} = -\beta' x'y$$

$$\frac{dy}{dt} = \beta xy' - \gamma y, \qquad \frac{dy'}{dt} = \beta' x'y - \gamma' y' \qquad (1)$$

$$\frac{dz}{dt} = \gamma y, \qquad \frac{dz'}{dt} = \gamma' y',$$

where β,β' are contact rates and γ,γ' are removal rates. Let n and n' denote the size of the human and vector population, respectively. Bailey shows that the product nn' has to be greater than the product $\rho\rho'$ of the relative removal rates $\rho = \gamma/\beta$ and $\rho' = \gamma'/\beta'$ in order that a small introduction of infectives (either humans or vectors) into a susceptible population causes an epidemic. A stochastic analogue of this threshold theorem for vector epidemics has been given by Bartlett (1964) and Griffiths (1972).

We shall now discuss the applicability of this model to the spread of arboviruses by mosquitos in one vertebrate host population P. For this we have to examine in some more detail the assumptions with respect to the contact rates between individuals of the two populations involved. Let us take the infection rates of susceptible vertebrates, i.e. $\beta xy'$. This can be rewritten as follows: $\beta n'(y'/n')x$, with the following interpretation: the rate of infection per susceptible is equal to the number of effective contacts with infective vectors per unit of time, which is equal to the number of contacts with vectors per unit of time ($\beta n'$) times the proportion of those contacts which are infective (y'/n'). A similar argument applies to the infection rate for susceptible vectors: $\beta' x'y = \beta' n(y/n)x'$. This way of writing the infection rates reveals the implicit assumption that the number of contacts per unit time per individual with individuals from the other population is propor-

tional to the size of the other population.

The female mosquito requires a blood meal for the maturation of the eggs. The frequency ψ of feeding depends on a number of factors, in particular climatic ones, but can be assumed to be constant as a first approximation. (Moon, 1973, takes into account climatic factors in calculating the infection rates of mosquitos.) Typical values are once every two or three days. Most mosquitos are rather catholic in their host choice. Let m denote the number of alternative hosts available as blood sources, weighed with the preferences of the mosquitos for the different types of blood sources, such that the probability for choosing an individual from P as a host is given by $n/(n + m)$. We assume that the host choices of a mosquito at subsequent feedings are independent of each other. Then an individual from P receives $\psi(n'/n)\{n/(n + m)\}$ bites per unit of time, and the mosquito takes $\psi n/(n + m)$ blood meals from P per unit of time. Hence $\beta = \beta' = \psi/(n + m)$. Thus the threshold condition $nn' > \rho\rho'$ can be written as

$$R = \frac{nn'}{\rho\rho'} = \frac{\beta\beta' nn'}{\gamma\gamma'} = \frac{nn'p^2}{(n+m)^2\gamma\gamma'} > 1. \qquad (2)$$

The quantity R is called the reproduction rate, since it represents the number of secondary cases that one case can produce if introduced to a susceptible population. This can be seen as follows: An infective introduced into P is bitten by $\psi n'/(n + m)$ mosquitos per unit of time each of which distributes $\psi n'/\{(n + m)\gamma'\}$ bites into P during the rest of its life. This number has to be multiplied by the expected duration of the infective period of a case which is $1/\gamma$.

For $m \gg n$, (2) gives a lower bound for the product $n'n$, but for $m \ll n$, we get a lower bound for the ratio n'/n, i.e. a critical density of mosquitos with respect to man. In both cases large vector populations facilitate an

epidemic, whereas large vertebrate populations may or may not be required to cause an epidemic. It all depends on the ratio n/m which determines how many contacts are "wasted" on other populations.

It would be interesting to test experimentally whether the host choices at subsequent feedings of the mosquitos are independent of each other, and to explore theoretically the consequences of some forms of dependence, such as Markov dependence.

Critical population size for maintenance of the virus

In the vertebrate population life-long immunity is usually produced after one infection. Therefore the virus can only be maintained if it is transmitted to new susceptible hosts. This raises the problem of determining the critical size of a vertebrate population which is necessary to maintain a virus population in an endemic state, without the need for immigration of new infectives. In the case of measles, Bartlett (1960 a) arrived at an estimate of 250,000 to 300,000 for U.S. cities using epidemiological records, whereas Black (1966) considered this to be an underestimate on the basis of data from some Pacific islands. For chikungunya virus, de Moor and Steffens (1970) found a critical size of 4,000 individuals (primates) using simulations. An estimate of the critical population size could help in the identification of reservoir populations. For a discussion of this problem in relation to yellow fever in Trinidad see, for example, Spence et al. (1961).

Since we are now interested in stable endemic states, we have to introduce birth and death parameters into (1). We assume that both the vertebrate and the vector populations are stable by setting the birth rates equal to the death rates. The death rate in the vertebrate population is denoted by μ and for symmetry we replace γ' by μ' in the equations for the vector population.

Thus (1) is now replaced by the following set of equations:

$$\frac{dx}{dt} = \mu n-(\beta y' + \mu)x, \qquad \frac{dx'}{dt} = \mu' n'-(\beta y + \mu')x',$$

$$\frac{dy}{dt} = \beta y' x-(\gamma + \mu)y, \qquad \frac{dy'}{dt} = \beta y x' - \mu' y', \tag{3}$$

$$\frac{dz}{dt} = \gamma y - \mu z,$$

where $n = x + y + z$ and $n' = x' + y'$. One equilibrium is given by $(x,y,z,;x',y'):(n,0,0;\ n',0)$ and another one by:

$$x' = n'/(1 + b'y),\ y' = n'b'y/(1 + b'y), \tag{4.1}$$

$$x = \frac{n(1+b'n/M)}{R+b'n/M}, \tag{4.2}$$

$$y = \frac{n(R - 1)}{RM + b'n}, \tag{4.3}$$

$$z = \frac{n(M - 1)(R - 1)}{RM + b'n}, \tag{4.4}$$

where $b' = \beta/\mu'$, $M = (\mu + \gamma)/\mu$ and $R = nn'\beta^2/\{(\mu + \gamma)\mu'\}$.

In order for the second equilibrium to be stable the reproduction rate R has to be greater than one. The infective period has now length $1/(\mu + \gamma)$ instead of γ. Taking this into account, it is justified to use the same symbol for $\leq$ as in (2). The quantity M is the ratio of the average life expectancy of a vertebrate host $(1/\mu)$ to the average duration of the infective period. In order to obtain a rough estimate of the population size required for the maintenance of the virus, we apply the following heuristic argument. The endemic average number of infectives y should be greater than some value y* which would ensure that the time to extinction is "very" long. (In the stochastic analogue of (3) $y = 0$ is an absorbing state, which is reached with probability one. In order to determine y* in a stochastic model, one would have to impose some arbitrary lower bound on the mean time to extinction.) From (4.3) we see that the size of the vertebrate population occurs explicitly

twice. Term in the denominator can be written as follows:

$$b'n = \frac{\beta n}{\mu'} = \frac{\psi n}{\mu'(n + m)}. \tag{5}$$

This quantity is the number of bites which one mosquito takes from individuals in P during its lifetime. We assume this quantity to be a constant, which we denote by a in the following. Hence, the stipulation $y > y^*$ implies

$$n > y^* M \frac{1 + a/RM}{1 - 1/R}. \tag{6}$$

We shall now apply this formula to the simulation study of de Moor and Steffens (1970). Unfortunately, they do not specify in their paper all the parameter values chosen. But one can estimate some of them approximately from the graphs. In their Fig. 7, the proportion of susceptible vertebrates (vervet monkeys, Cercopithecus aethiops, or baboons, Papio ursinus) reaches an endemic level of about 10% (for $\mu' = 0.1$ in our notation). The life expectancy of the vertebrates is assumed to be three years and the infectious period is three days, hence $M = 365$. The quantity a is approximately 1.5. For $x/n \approx 0.1$, it follows from (4.2) that $R \approx 10$. Inserting these values into (6) one can conclude that y* must be approximately equal to 10 if the critical population size is 4,000, as the authors state.

Formula (6) yields immediately the result that the size of a human population, with a life expectancy of 60 years, would have to be 20 times larger, other things being equal. It also suggests that the critical population size is fairly independent of R for $R \gg 1$, but is inversely proportional to $R - 1$ for R close to one.

It would be interesting to determine the relationship between y* and the expected time to extinction in a stochastic model.

Spatial spread of epidemics

Because of immunity or death resulting from a virus infection, the virus has to be transmitted to new susceptibles thus creating a travelling wave. This phenomenon of geographical spread has been treated mathematically by a number of authors: Bartlett (1960b), Kendall (1965), Mollison (1972), Radcliffe (1973) and Noble (1974). The paper by Radcliffe deals with vector-borne infections whereas the others are concerned with epidemic spread by man-to-man contact. A map in Smith (1971) shows the progress of a yellow fever epizootic in Central America which travelled in a linear manner between 1948 and 1954 from the Isthmus of Panama to Guatemala where it burnt out at the northern limit of the habitat of the maintenance host. It would be interesting to apply some of the available models for spatial epidemic spread to actual epidemics in order to relate the observed velocities to the epidemiological parameters of these models as Noble did in the case of plague. Some of these models for the spread of an epidemic along a line may be suitable for the description of the progress of yellow fever in monkey populations which inhabit gallery forests along river beds.

Models for age-specific prevalence of infection and disease

The models discussed so far describe the number of individuals in the various epidemiological states in a cross-sectional way, i.e. they describe averages over all age groups in a population. Since the pathogenicity of an infection is frequently age-dependent, it is important to describe the age-specific distribution of individuals in the various epidemiological states. Another reason for this age-specific approach is the possibility of estimating epidemiological parameters from age-specific data. For simplicity we shall consider the case of man-to-man transmission. Then (3) reduces to

$$\frac{dx}{dt} = n\mu - (\beta y + \mu)x,$$

$$\frac{dy}{dt} = \beta yx - (\gamma + \mu)y, \qquad (7)$$

$$\frac{dz}{dt} = \gamma y - \mu z.$$

We introduce the variables $x(a,t)$, $y(a,t)$, $z(a,t)$, denoting the number of susceptibles, infectives and immunes of age a at time t. The system of ordinary differential equations (7) has now to be replaced by a system of integro-differential equations in an obvious manner:

$$\frac{\partial x}{\partial a} + \frac{\partial x}{\partial t} = -\beta \int_0^\infty y(s,t)ds\, x(a,t) - \mu x(a,t),$$

$$\frac{\partial y}{\partial a} + \frac{\partial y}{\partial t} = \beta \int_0^\infty y(s,t)ds\, x(a,t) - (\gamma + \mu)y(a,t), \qquad (8)$$

$$\frac{\partial z}{\partial a} + \frac{\partial z}{\partial t} = \gamma y(a,t) - \mu z(a,t),$$

with the initial and boundary conditions

$$x(a,0) = x_0(a), y(a,0) = y_0(a),\ z(a,0) = z_0(a),$$
$$x(0,t) = n\mu,\ y(0,t) = 0,\ z(0,t) = 0. \qquad (9)$$

Since we are interested in endemic conditions, we look for stable solutions of (8) which are independent of time, i.e. we want to solve the system

$$\frac{dx}{da} = -\beta \int_0^\infty y(s)ds\, x(a) - \mu x(a),$$

$$\frac{dy}{da} = \beta \int_0^\infty y(s)ds\, x(a) - (\gamma + \mu)y(a), \qquad (10)$$

$$\frac{dz}{da} = \gamma y(a) - \mu z(a),$$

for the initial condition

$$x(0) = n\mu,\ y(0) = 0,\ z(0) = 0. \qquad (11)$$

We introduce the new variables $u = x/K$, $v = y/K$ and $w = z/K$, where $K = x + y + z$. From (10), by adding the equations, we get a differential equation for K.

$$\frac{dK}{da} = -\mu K \tag{12}$$

with $K(0) = n\mu$. Hence $K(a) = n\mu e^{-\mu a}$ and

$$\frac{du}{da} = -\beta n \int_0^\infty v(s)\ \mu e^{-\mu s}\, ds\ u(a),$$

$$\frac{dv}{da} = \beta n \int_0^\infty v(s)\ \mu e^{-\mu s}\, ds\ u(a) - \gamma v(a), \tag{13}$$

$$\frac{dw}{da} = \gamma v(a),$$

with the initial conditions $u(0) = 1$, $v(0) = w(0) = 0$. Let

$$\lambda = \beta n \int_0^\infty v(s)\ \mu e^{-\mu s}\, ds. \tag{14}$$

If (13) has a non-trivial non-negative solution, then λ is a positive constant, and (13) is reduced to a system of linear equations with the solutions

$$u(a) = e^{-\lambda a} \tag{15.1}$$

$$v(a) = \begin{cases} \lambda(e^{-\lambda a} - e^{-\gamma a})/(\gamma - \lambda) & \text{for } \gamma \neq \lambda, \\ \lambda a e^{-\lambda a} & \text{for } \gamma = \lambda, \end{cases} \tag{15.2}$$

$$w(a) = \begin{cases} 1 - (\gamma e^{-\lambda a} - \lambda e^{-\gamma a})/(\gamma - \lambda) & \text{for } \gamma \neq \lambda, \\ 1 - e^{-\lambda a}(1 + \lambda a) & \text{for } \gamma = \lambda. \end{cases} \tag{15.3}$$

Using (14) and (15.2) we can derive a condition for the existence of a positive solution for v. Putting (15.2) into (14) and cancelling the trivial solution $\lambda = 0$, we get

$$\lambda = \mu\left(\frac{\beta n}{\gamma + \mu} - 1\right). \tag{16}$$

If we denote the life expectancy of an individual $1/\mu$ by L and the reproduction rate of the infection $\beta n/(\gamma + \mu)$ by R, then (16) can be rewritten as

$$\lambda = (R - 1)/L, \tag{17}$$

or, if we denote the average age $1/\lambda$ at which an individual contracts the

infection by A, then we have

$$R = 1 + L/A. \tag{18}$$

The condition for λ or v to be positive is naturally $R > 1$. If $\bar{u}$, $\bar{v}$, $\bar{w}$, denote the average proportions of susceptibles, infectives and immunes, we get

$$\bar{u} = 1/R,$$

$$\bar{v} = (1 - 1/R)/M, \tag{19}$$

$$\bar{w} = (1 - 1/R)(1 - 1/M),$$

where $M = (\mu + \gamma)/\mu$, as above. The fact that the average proportion of susceptibles in an endemic equilibrium state equals 1/R is intuitively obvious: At equilibrium, each case should produce on the average one secondary case. If $u = 1$, then one case can produce R secondary cases. If u is less than one, then a proportion of $1 - u$ contacts are "wasted" on non-susceptibles, such that the reproduction rate is actually Ru. At equilibrium, u has therefore to take the value 1/R. From this follows that one can estimate the proportion of susceptibles in the total population and hence the reproduction rate if one only knows the proportion of susceptibles u(a) at a particular age a_o. From (15.1) one determines $A = 1/\lambda$, and (18) yields R, assuming the life expectancy is known. For example, London and Yorke (1973) quote that at the age of 20 years 68% have acquired chickenpox and 50% have acquired mumps. Assuming a life expectancy of 70 years, we get the reproduction rates 5 for chickenpox and 3.4 for mumps. It is to be noted that these calculations assume age-independent death rates, i.e. an exponential age distribution, but they could easily be generalized for arbitrary stable age distributions.

The equations (15) describe not only the age distribution of individuals in the three epidemiological states if they are examined in a cross-sectional survey at a particular time but also the transitions between the states in a cohort followed longitudinally. The variable a is then to be interpreted as

time. Since γ is usually much larger than λ, the proportion of immunes may be approximated by

$$w(a) \simeq 1 - e^{-\lambda a} . \qquad (20)$$

This is the so-called "simple catalytic curve" which is usually fitted to the proportion of immunes. The book of Nuench (1959) contains many examples, including yellow fever.

We now turn to the models for age-specific disease prevalence. Not every infection causes disease and the probability of pathogenesis depends on many factors, including age. Bolshev and Kruopis (1969) propose some kind of queuing model to describe the age-specific disease prevalence of tick-borne encephalitis and fit their model to data collected in the Southern taiga of Western Siberia. They make certain assumptions about temporary immunity which influences the probability that an infection produces symptoms. Fisher and Halstead (1970) compare two models for the pathogenesis of dengue hemorrhagic fever. The basic assumption is that infections of one type of dengue virus sensitize an individual so that subsequent infections with another type may elicit a hypersensitivity reaction causing the disease, provided that the infections occur within a certain interval. One of their models ("the double sequential model") assumes that a person may be sensitized already by one infection, whereas the triple sequential model requires two types of infections. They fit both models to age-specific data collected in Bangkok and find that the double sequential model gives a good fit when it was assumed that primary and secondary infections had to accur within a period of five years.

In this context of interaction of viruses it may also be mentioned that there is some evidence that some viruses may produce protection against yellow fever. (See, e.g. Theiler and Downs, 1973, Chap. 21.) This may have implications on the advisability of vector control. Some simulation models

have already been developed for the interaction of viruses (e.g. Elveback et al., 1971), but the epidemiological consequences of cross-immunity do not seem to have been studied so far mathematically.

In concluding this section we demonstrate by an example that a reduction of infection incidence may cause an increase of disease incidence. (See e.g. Bang, 1974). Let the probability of contracting the disease given infection at age a be determined by a constant w^* times the cumulative distribution function G(a) of the gamma distribution with density $\beta^\alpha a^{\alpha-1} e^{-\beta a}/\Gamma(\alpha)$. Then the proportion D of the population which contracts the disease is given by

$$\begin{aligned} D &= w^* \int_0^\infty e^{-\mu a} \lambda e^{-\lambda a} G(a) da \\ &= \frac{w^* \lambda}{\lambda + \mu} \left(\frac{\beta}{\lambda + \mu + \beta} \right)^\alpha , \end{aligned} \qquad (21)$$

where λ is the infection incidence and μ is the death rate. One can easily verify that D is a unimodal function of λ. Thus, for λ_1 greater than λ_0 with $D'(\lambda_0) = 0$ one would only decrease D if one made λ even greater or by reducing it to a value $\lambda < \lambda_0$ such that $D(\lambda) < D(\lambda_1)$.

Vaccination and vector control

Recently, a number of authors have applied control theory to the general epidemic: Abakuks (1974), Gupta and Rink (1973), Hethcote and Waltman (1973) and Morton and Wickwire (1974). All these papers are concerned with an optimal vaccination strategy to be applied after a certain number of infectives have entered a susceptible population, i.e. they only consider actions to be taken during one isolated outbreak. Very little has so far been done however towards a theory of vaccination strategies in an endemic situation which would have to take into account birth and death rates of hosts, etc. Smith (1970) specifies a critical proportion to be vaccinated in order to control an infection. Let R be the reproduction rate of the infection if the total

population is susceptible. In order to reduce the effective reproduction rate to a value less than one, the proportion of susceptibles has to be less than 1/R, hence if we denote the proportion to be vaccinated by p = 1 - u, then p has to satisfy

$$p > 1 - 1/R. \tag{22}$$

(Fig. 1. in Smith, 1970, plots the inverse relationship R = 1/(1 - p).) Smith proposes to estimate R by $1/u_\infty$, where u_∞ is the proportion of susceptibles after the termination of an epidemic. For example, he quotes reports according to which urban yellow fever epidemic ceased when 65-48% had become immune, i.e. when 35-52% susceptibles remained, from which he gets an estimate of R between about 2 and 3. The theory of the deterministic general epidemic yields however the following relationship between the reproduction rate R and the proportion of susceptibles remaining:

$$R = \frac{1}{1 - u_\infty} \ln \frac{1}{u_\infty}, \tag{23}$$

which can easily be derived from Eq. (4.18) in Bailey (1957) when we set $R = n/\rho = n\beta/\gamma$. Thus, for u_∞ between 35-52% we get from (23) that R has to be between 1.36 and 1.62. If we take the upper limit for R, then (22) implies that a vaccination coverage of 38.3% would have been sufficient to prevent the epidemic, whereas the formula suggested by Smith would require a coverage of 65%.

Many vaccines lose their protective action and thus the need for revaccination has to be taken into account if a certain level of herd immunity is to be maintained. An optimal vaccination strategy could be determined as a solution of the following problem: Let $\pi(a)$ be the rate at which an individual of age a is to be vaccinated. In a stationary situation the equations (13) for the age-specific proportions of susceptibles and infectives are

generalized to include vaccination and loss of protection:

$$\begin{aligned}
\frac{du}{da} &= -\beta n \int_0^\infty v(s)\mu e^{-\mu s}\, ds \cdot u(a) - \pi(a)u(a) + \delta p(a), \\
\frac{dv}{da} &= \beta n \int_0^\infty v(s)\, \mu^{-\mu s}\, ds \cdot u(a) - \gamma v(a), \\
\frac{dp}{da} &= \pi(a)u(a) - \delta p(a), \\
\frac{dw}{da} &= \gamma v(a),
\end{aligned} \tag{24}$$

where p(a) is the proportion protected by vaccination and δ is the rate of loss of protection. The problem is to find $\pi(a)$ such that some cost function which includes costs of vaccination and costs of disease caused by the infection is minimized:

$$\int_0^\infty f(v(a) \cdot G(a),\ \pi(a))\mu e^{-\mu a}\, da.$$

With particular reference to the control of Japanese encephalitis, Wada (1972 a,b) studied the effect of vaccination of pig populations, taking into account maternal antibodies. A more general problem would be to look into the optimal allocation of resources into vaccination and vector control as a combined strategy.

Periodicity of outbreaks

We have to distinguish between populations below and above the critical size for the maintenance of the infection. In the first case, the number of infectives is reduces to zero after an epidemic and the introduction of new infectives is necessary to start a new epidemic. The probability that a new epidemic will occur depends on the number of susceptibles born since the termination of the previous epidemic. Radcliffe (1974 a) has derived an explicit formula for the distribution of the interval between yellow fever epidemics.

The second case refers to regular oscillations around the endemic level with a period of more than one year as it is observed, e.g. for measles in large cities (London and Yorke, 1973), where a two-year period predominates. Other virus diseases in the same places show oscillations of one year period. In Section 8.22 of Bailey (1957) the effect of seasonal variation in the contact rate β is discussed, and it is concluded that this causes forced oscillations of y with the same frequency as the contact rate. If one applies the same approach however to the model described by (7), i.e. with the death rate μ included, then one can show the persistence of a biennial cycle for a certain range of R and for large enough amplitudes. If we linearize (7) around the equilibrium $(\underline{x}_o, \underline{y}_o) = (\underline{n}/\underline{R},\ \underline{n}(1 - 1/\underline{R})/\underline{M})$ by setting

$$x = x_o(1 + \xi),\ y = y_o(1 + \eta), \tag{26}$$

we get the second order differential equation for η:

$$\frac{d^2\eta}{dt^2} + \mu R \frac{d\eta}{dt} + (\gamma + \mu)(R - 1)\eta = 0. \tag{27}$$

The solution of (27) is an oscillation with frequency

$$\omega = \sqrt{\mu(\gamma + \mu)(R - 1) - \mu^2R^2/4} \tag{28}$$

provided that

$$2(M - \sqrt{M(M - 1)}) < R < 2(M + \sqrt{M(M - 1)}). \tag{29}$$

If the contact rate β undergoes a seasonal variation which can be described by $\beta(1 + r \cos \nu t)$, then one could expect a subharmonic resonance of order 2 if ν were close to 2γ. This allows the estimation of the reproduction rate R for which a two-year period is likely for given μ and γ:

$$R \approx 1 + \frac{\nu^2}{4\mu(\gamma + \mu)}. \tag{30}$$

Numerical integration of (7) was carried out with the following parameters values: $n = 10^7$, $\mu = 0.00004$ per day $\approx 1/68.5$ per year and $\gamma = 1/14$ per day. If the contact rate has a period of one year, ν has the value of 0.0172 per

day. Hence (30) yields for R approximately the value 27. Setting the relative amplitude r of β at 10% the ratios of the total number of cases in two successive years had the following values:

R	20	25	30	35	40
	1.0	3.2	8.4	14.2	1.0

For 5% amplitude, these ratios were all close to one. It is surprising to find that for the large reproduction rate 40 the two-year pattern reverts to a one-year pattern. For R around 27 the shape of the epidemic curve showed only one peak in two years, whereas for R = 25 two peaks of different height occurred. A more detailed description of the results will be given elsewhere. It would be interesting to apply the asymptotic methods of nonlinear oscillation theory to a generalization of (7) which includes a vector population. For a simple malaria model, Radcliffe (1974 b) has calculated the eigenfrequency of the system. The interesting phenomena of subharmonic resonance of endemics have not yet been adequately investigated.

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