the model describes as closely as possible the characteristics of the disease being transmitted. In this paper, we are interested in the transmission of Dengue hemorrhagic fever (DHF).

Dengue hemorrhagic fever is one of the emerging viral diseases spreading throughout the tropical regions of the world. From its first appearance in the Philippines in 1953, it has become the most important arthropod-borne viral diseases of humans [4]. It has been estimated that there are between 50 and 100 million cases of Dengue fever (DF) a year, over 250,000 cases of Dengue hemorrhagic fever (DHF) with approximately 10,000 infant deaths due to the latter form of this disease. The classical Dengue fever is a disease of older children and adults. DHF on the other hand is primarily a disease of children under the age of 15, see [5]. DHF differs from DF by the manifestation of plasma leakage in DHF. DF and DHF are illnesses arising through an infection by any one of the four serotypes of a virus belonging to the genus *Flavirus*, in the family *Flavicidae*. Immunity to one serotype does not confer immunity to the others. Since two of the transmitting vectors, *Aedes aegypti* and *Aedes albopictuus* mosquitoes, exist in the Americas, it has been possible for DHF and its benign precursor, DF, to become endemic in the New World, see [6]. The first severe outbreak of DHF in the Americas occurred in 1981 in Cuba with 116,000 hospitalized patients, 34,000 documented DHF cases, and 158 deaths. Important outbreaks of DHF have also occurred in Mexico, see [7].

In hopes of understanding the mechanisms that allow the invasion and persistence of a serotype of the Dengue virus in a region, Esteva and Vargas [8–10] introduced a mathematical model to provide a qualitative assessment for the problem. The model they used is based on the susceptible-infected-recovered (SIR) model often used to model the dynamics of transmission of some diseases. They showed that the endemic state was globally stable whenever a parameter R_o called the basic reproduction number is greater than one. Application of an ultra low volume (ULV) amount of insecticides (the standard method used to control the spread of Dengue fever and other arthroped-borne disease) could reduce the value of R_o to below one. The value of R_o would return to the above one value once the application is stopped and since the endemic state is globally stable, the disease would return. Therefore, the eradication program would have to be a continuing one.

In the SIR model used by Esteva and Vargas, no age structure was incorporated into the models. While the lack of an age structure may be appropriate for describing the 1981 DHF epidemic in Cuba [11] and the DHF outbreak in Santiago de Cuba in 1997 [12], it is not appropriate for Thailand. Most DHF cases in Thailand occur in children less than 15 years old, in agreement with the remark made by Gubler [5]. Feng and Velasco-Hernandez [13] have pointed to the need for a model that incorporates age structure into the Dengue population dynamics. It is the purpose of this paper to report on a DHF transmission model, which includes an age structure in the human population. In our model, the human population is divided into two classes, a juvenile class and an adult class. In Section 2, we introduce a mathematical model describing the transmission of DHF in a two class age structure of the human population. A mathematical analysis of this model is done in Section 3. In Section 4, we perform a complete analysis of a simplified model, one in which no further infection occurs in the adult population. Numerical solutions of the simplified model are presented in Section 5.

2. MATHEMATICAL MODEL

The simplest way to incorporate an age structure into a disease model is to divide up the human population into two classes, juveniles (J) and adults (A). Another way is to divide the population into N cohorts and then divide up the cohorts into the three subcategories, susceptible, infected, and recovered. This latter approach (leading to what is known as a realistic age structure (RAS) approach) would make an analytical analysis difficult and one would have to resort to simulations [14]. We have chosen the first method since it allows us to establish the conditions leading to the disease free state and the endemic state. We have allowed infection to occur in both classes but with rate of infection in the adult class being much lower than that in

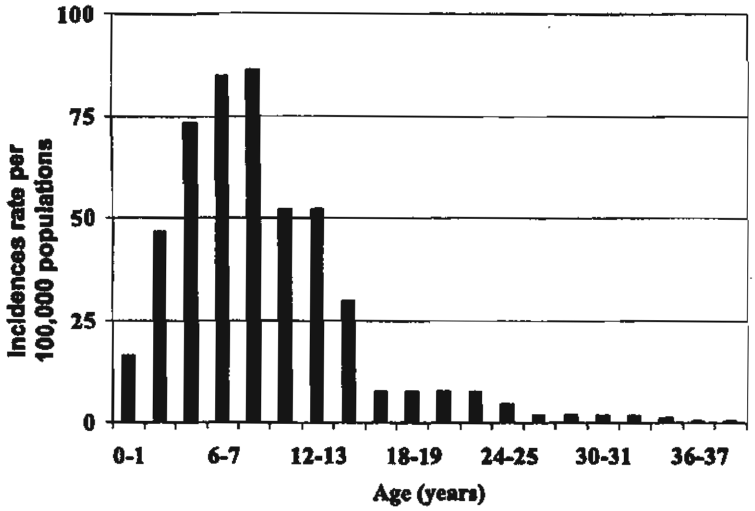


Figure 1. Age distribution of the 1998 Dengue fever incidence rates in Mukdahan, a province in central Thailand.

the juvenile class. In Figure 1, we show the age distribution of the incidence rates in one province in Thailand during the 1998 DHF epidemic [15]. As we see, most cases occur in children under the age of 15. However, a small number of cases do occur in older people. Similar distributions are seen in the other provinces in the country.

Most adults in the population have been exposed to the infection even though they are not aware of it. Burke *et al.* [16] reported that 87% of the infected children in his study (done in Bangkok, Thailand in 1980–1981) were either asymptomatic or minimally symptomatic. Antibodies against the virus will still develop in these infected children. This silent population will enter into adulthood, immune to further infections. The adult population will then be composed of people who are known to have been infected, members of the silent population and people who were never infected as a juvenile. We have initially classified all the adults as susceptible adults S_A, because of the uncertainty of which group the adult comes from. Treating all adults as being the same leads to the rate of transmission of the virus from a mosquito to a susceptible adult to be the average of the transmission rates to the different subclasses the adults came from. This leads the transmission rates of the virus to a (average) susceptible adult to be much lower than that to a susceptible juvenile.

In our SIR model with age structure, the dynamics of each component of the human is given by

$$\frac{dS'_J}{dt} = \lambda' N_T - \frac{b\beta_J}{N_T + m} S'_J I'_v - (\mu_h + \delta) S'_J, \tag{1a}$$

$$\frac{dR'_J}{dt} = rI'_J - (\mu_h + \delta) R'_J \frac{dI'_J}{dt} = \frac{b\beta_J}{N_T + m} S'_J I'_v - (\mu_h + \delta + r) I'_J, \tag{1b}$$

$$\frac{dS'_A}{dt} = \delta(S'_J + I'_J + R'_J) - \varepsilon\beta_J \frac{b}{N_T + m} S'_A I'_v - \mu_h S'_A, \tag{1c}$$

$$\frac{dR'_A}{dt} = rI'_A - \mu_h R'_A, \tag{1d}$$

and

$$\frac{dI'_A}{dt} = \varepsilon\beta_J \frac{b}{N_T + m} S'_A I'_v - (\mu_h + r) I'_A, \tag{1e}$$

where $S'_{J(A)}$, $I'_{J(A)}$, and $R'_{J(A)}$ are the numbers of susceptible juveniles (adults), infected juveniles (adults), and recovered juveniles (adults), respectively; N_T, the total population (taken to be constant); m, the number of other animals the mosquitoes can bite; b, the average number of bites a mosquito takes per day; λ', the birth rate; μ_h, the death rate (assumed to be the same for all categories); δ, the rate at which the juveniles pass into adulthood, and r is the rate at which the infected juveniles recover. I'_v is the number of infected mosquitoes; β_J, the probability of the virus surviving in the juvenile after being bitten by an infected mosquito [8], and $\varepsilon\beta_J$ is the probability of the virus surviving in a susceptible adult after being bitten by an infected mosquito. ε is the ratio between the probability that an adult becomes infected and the probability that a juvenile becomes infected by the bite of an infected mosquito and is assumed to be less than one.

If we add equations (1a)–(1f) together, we get

$$\frac{d(S'_J + I'_J + R'_J + S'_A + I'_A + R'_A)}{dt} = \lambda N_T - \mu_h \left(S'_J + I'_J + R'_J + S'_A + I'_A + R'_A\right). \tag{2a}$$

For the total human population to be constant, i.e., $\frac{dN_T}{dt} = 0$, the birth rate would have to be equal to the death rate, $\lambda = \mu_h$. If we now add only equations (1a)–(1c) together, we get

$$\frac{dN_J}{dt} = \lambda N_T - (\mu_h + \delta) N_J, \tag{2b}$$

where $N_J (= S'_J + I'_J + R'_J)$ is the total number of juveniles. Assuming that the total number of juveniles is also constant, equation (2b) would give us the ratio between the number of adults and the number of juveniles, i.e.,

$$\frac{N_A}{N_J} = \frac{\delta}{\mu_h},$$

where N_A is the total number of adults and is equal to $S'_A + I'_A + R'_A$.

The dynamics of the mosquitoes is described by

$$\frac{dS'_v}{dt} = A - \frac{b\beta_v}{N_T + m} S'_v \left(I'_J + I'_A\right) - \mu_v S'_v \tag{3a}$$

and

$$\frac{dI'_v}{dt} = \frac{b\beta_v}{N_T + m} S'_v \left(I'_J + I'_A\right) - \mu_v I'_v, \tag{3b}$$

where S'_v and I'_v the number of susceptible and infected mosquitoes, respectively; μ_v, the death rate of the mosquitoes; A, the carrying capacity of the environment (for the mosquitoes) and β_v is the probability that a Dengue virus transmitted to the mosquito from an infected human, be it a juvenile or adult. If we add equations (3a) and (3b) together, we get

$$\frac{d(S'_v + I'_v)}{dt} = A - \mu_v N_v, \tag{3c}$$

where N_v is the number of mosquitoes and is equal to $S'_v + I'_v$. If the number of mosquitoes is also constant, equation (3c) gives $N_v = A/\mu_v$.

Introducing the normalized parameters $S_{J(A)} = S_{J(A)'}/N_{J(A)}$, $I_{J(A)} = I'_{J(A)}/N_{J(A)}$, $R_{J(A)} = R'_{J(A)}/N_{J(A)}$, and $I_v = I'_v/(A/\mu_v)$, we find that equations (1a)–(1f) and equation (3b) can be rewritten as

$$\frac{dS_J}{dt} = (\mu_h + \delta)(1 - S_J) - \gamma_h S_J I_v, \tag{4a}$$

$$\frac{dI_J}{dt} = \gamma_h S_J I_v - (\mu_h + \delta + r) I_J, \tag{4b}$$

$$\frac{dS_A}{dt} = \mu_h - \varepsilon\gamma_h S_A I_v - \mu_h S_A, \tag{4c}$$

$$\frac{dI_A}{dt} = \varepsilon\gamma_h S_A I_v - (\mu_h + r) I_A, \tag{4d}$$

and

$$\frac{dI_v}{dt} = \gamma_{vJ}(1 - I_v)I_J + \gamma_{vA}(1 - I_v)I_A - \mu_v I_v, \tag{4e}$$

where

$$\gamma_h = \frac{b\beta_J(A/\mu_v)}{N_T + m} \tag{5a}$$

and

$$\gamma_{vJ(A)} = \frac{b\beta_v N_{J(A)}}{N_T + m}. \tag{5b}$$

The dynamical equations for $R_{J(A)}$ and S_v are not needed, since $S_{J(A)} + I_{J(A)} + R_{J(A)} = 1$ and $S_v + I_v = 1$.

3. MATHEMATICAL ANALYSIS

3.a. Equilibrium States

The equilibrium states (S_J, I_J, S_A, I_A, I_v) are obtained by setting the RHS of equations (4a)–(4e) to zero. Doing this, we get two equilibrium states, the disease free state $E_o = (1, 0, 1, 0, 0)$ and the endemic state $E_1 = (S_J*,\ I_J*,\ S_A*,\ I_A*,\ I_v*)$ where

$$S_J* = \frac{1}{1 + (\gamma_h/(\mu_h + \delta))I_v*}, \tag{6a}$$

$$I_J* = \frac{b\beta_J(A/\mu_v)}{(N_T + m)(\mu_h + r)} S_J * I_v*, \tag{6b}$$

$$S_A* = \frac{1}{1 + \varepsilon(b\beta_J(A/\mu_v))/(\mu_h(N_T + m))} I_v*, \tag{6c}$$

and

$$I_A* = \varepsilon \frac{b\beta_J(A/\mu_v)}{(\mu_h + r)(N_T + m)} S_A * I_v*, \tag{6d}$$

with I_v* being the solution of

$$A_1(I_v*)^2 + A_2 I_v * + A_3 = 0, \tag{7a}$$

with

$$A_1 = \varepsilon\gamma_h^2 \left[\frac{\gamma_{vJ}}{\mu_h(\mu_h + r + \delta)} + \frac{\gamma_{vA}}{(\mu_h + r)(\mu_h + \delta)} + \frac{\mu_v}{\mu_h(\mu_h + \delta)}\right], \tag{7b}$$

$$A_2 = \frac{\gamma_h\gamma_{vJ}}{\mu_h + r + \delta} + \frac{\gamma_h\mu_v}{\mu_h + \delta} + \varepsilon\gamma_J \left[\frac{\mu_v}{\mu_h} + \frac{\gamma_{vA}}{\mu_h + r} - \frac{\gamma_h\gamma_{vJ}}{\mu_h(\mu_h + r + \delta)} - \frac{\gamma_h\gamma_{vA}}{(\mu_h + r)(\mu_h + \delta)}\right], \tag{7c}$$

and

$$A_3 = \mu_h - \gamma_h \left[\frac{\gamma_{vJ}}{\mu_h + r + \delta} + \varepsilon\frac{\gamma_{vA}}{\mu_h + r}\right], \tag{7d}$$

with γ_h, γ_{vA}, and γ_{vJ} defined by equations (5a) and (5b).

3.b. Local Asymptotical Stability

The local stability of an equilibrium state is determined from the Jacobian (gradient) matrix of the RHS of the above set of differential equations evaluated at the equilibrium state.

3.b.1. Disease free state

For the system defined by equation (4a)–(4e), the Jacobian matrix evaluated at E_o is the 5×5 matrix given by

$$\begin{vmatrix} -(\mu_h+\delta) & 0 & 0 & 0 & -\gamma_h \\ 0 & -(\mu_h+r+\delta) & 0 & 0 & \gamma_h \\ 0 & 0 & -\mu_h & 0 & -\varepsilon\gamma_h \\ 0 & 0 & 0 & -(\mu_h+r) & \varepsilon\gamma_h \\ 0 & \gamma_{vJ} & 0 & \gamma_{vA} & -\mu_v \end{vmatrix}. \tag{8}$$

The eigenvalues are obtained by solving the matrix equation, $\det|\lambda I - J| = 0$. Using the program MATHEMATICA, (Wolfram Research, Champaign, IL) to evaluate the determinant, we get the following characteristic equation:

$$(\lambda+\mu_h+\delta)(\lambda+\mu_h)\left(\lambda^3+A\lambda^2+B\lambda+C\right)=0, \tag{9}$$

where

$$A = (\mu_h+r)+(\mu_h+r+\delta)+\mu_v, \tag{10}$$

$$B = (\mu_h+r)(\mu_h+r+\delta)+\mu_v(\mu_h+r+\delta)(1-R_1)+\mu_v(\mu_h+r)(1-\varepsilon R_2), \tag{11}$$

and

$$C = \mu_v(\mu_h+r)(\mu_h+r+\delta)\left(1-R_o'\right), \tag{12}$$

with

$$R_1 = \frac{b^2\beta_v\beta_J N_J(A/\mu_v)}{\mu_v(N_T+m)^2(\mu_h+r+\delta)},$$

$$R_2 = \frac{b^2\beta_v\beta_J N_A(A/\mu_v)}{\mu_v(N_T+m)^2(\mu_h+r)},$$

and

$$R_o' = R_1 + \varepsilon R_2. \tag{13}$$

Looking at the characteristic equation, equation (9), we see that two of the eigenvalues are

$$\lambda_1 = -(\mu_h+\delta) \quad \text{and} \quad \lambda_2 = -(\mu_h+r+\delta). \tag{14}$$

Both of these are negative. The signs of the other three eigenvalues can be ascertained by the use of the Routh-Hurwitz conditions [18]

$$\begin{aligned} &\text{(i)} && A > 0, \\ &\text{(ii)} && C > 0, \quad \text{and} \\ &\text{(iii)} && AB > C. \end{aligned} \tag{15}$$

Looking at equation (10), we see that Condition (i) is always satisfied. Condition (ii) is satisfied if $R_o' < 1$. To see when Condition (iii) is satisfied, we note that the cross product AB will be the sum of positive terms if $R_1 < 1$ and $R_2 < 1$. Given that the sum of positive numbers is greater than any individual number, we have $AB > \mu_v(\mu_h+r)(\mu_h+r+\delta)(2-R_o')$ (this being the sum of the product of the first term in A and the second term in B and the product of the second term in A and the third term in B). $\mu_v(\mu_h+r)(\mu_h+r+\delta)(2-R_o') > C$. We therefore have $AB > C$. From the definition of R_o', $R_o' < 1$ implies $R_1 < 1$ and $R_2 < 1$. Thus, the real parts of the three eigenvalues determined from

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0$$

will be negative. Combining this with the signs of the first two eigenvalues, equation (14), we see that all the real parts of all eigenvalues are negative. Thus, the disease free state will be a locally asymptotically stable state when $R_o < 1$.

3.b.2. Endemic state

The stability of the epidemic state, E_1, like that of E_o, is determined by looking at the eigenvalues of the Jacobian evaluated at E_1. The Jacobian for this state is

$$\begin{vmatrix} -(\mu_h+\delta)-\gamma_h I_v* & 0 & 0 & 0 & -\gamma_h S_J* \\ \gamma_h I_v* & -(\mu_h+r+\delta) & 0 & 0 & \gamma_h S_J* \\ 0 & 0 & -\mu_h-\varepsilon\gamma_h I_v* & 0 & \varepsilon\gamma_h S_J* \\ 0 & 0 & \varepsilon\gamma_h I_v* & -(\mu_h+r) & -\varepsilon\gamma_h S_J* \\ 0 & \gamma_{vJ}(1-I_v*) & 0 & \gamma_{vA}(1-I_v*) & -\mu_v-\gamma_{vA}I_A*-\gamma_{vJ}I_J* \end{vmatrix}, \tag{16}$$

where S_J*, I_J*, S_A*, I_A*, and I_v* are given by equation (5a)–(5d) and equation (6). The 5×5 matrix equation, $\det|\lambda I - J| = 0$, can again be solved by MATHEMATICA. MATHEMATICA can also diagonalize the above Jacobian. The characteristic equation will be a fifth-order polynomial in λ and the expressions for the eigenvalues will be very long and complicated, preventing an easy analysis. We find out that an easy analysis can be made if we make a further simplifying assumption, no adults become sick with DHF.

4. SIMPLIFIED MODEL

Looking at the medical records of Department of Pediatrics, Siriraj Hospital, the largest health care hospital in Bangkok, Thailand, out of the 318 patients with confirmed DHF who were admitted in 1998, only two were above the age of 15; of the 137 patients admitted in 1999, only one was above 15 years old; out of 84 patients admitted in 2000, again only one was above 15 years old and out of 332 patients admitted in 2001, none were above 15 years old. From these records, it appears that in Bangkok, the adults have only a small or no chance of becoming sick with DHF. To overcome the untractable mathematical nature of the analysis of the epidemic state encountered in our original model, we have looked at a model in which adults do not become sick with the disease. Such a model can be obtained by setting ε to be zero. Doing this, the 5×5 Jacobian matrix given by equation (16) takes on a much simplified form. But before we find the eigenvalues of the new Jacobian, let us review some additional modifications we will have made.

We now assume that the reason for the adults not becoming sick with DHF is that they are immune to the infections. The categories I'_A and R'_A would no longer exist and all the adults fit into one category, S'_A. The dynamics of the human population is given by

$$\frac{dS'_J}{dt} = \lambda' N_T - \frac{b\beta_J}{N_T+m} S'_J I'_v - (\mu_h+\delta)S'_J, \tag{17a}$$

$$\frac{dI'_J}{dt} = \frac{b\beta_J}{N_T+m} S'_J I'_v - (\mu_h+\delta+r)I'_J, \tag{17b}$$

$$\frac{dR'_J}{dt} = rI'_J - (\mu_h+\delta)R'_J, \tag{17c}$$

and

$$\frac{dS'_A}{dt} = \delta(S'_J + I'_J + R'_J) - \mu_h S'_A. \tag{17d}$$

In the absence of infected adults, the dynamics of the mosquitoes are now given by

$$\frac{dS'_v}{dt} = A - \frac{b\beta_v}{N_T+m} S'_v I'_J - \mu_v S'_v \tag{18a}$$

and

$$\frac{dI'_v}{dt} = \frac{b\beta_v}{N_T+m} S'_v I'_J - \mu_v I'_v. \tag{18b}$$

Introducing the new set of normalized parameters $S = S'_J/N_T$, $I = I'_J/N_T$, $R = R'_J/N_T$, $S_A = S'_A/N_T$, and $I_v = I'_v/(A/\mu_v)$, equations (17a)–(18b) reduce to

$$\frac{dS}{dt} = \lambda - \gamma_h I_v S - (\mu_h + \delta)S, \tag{19a}$$

$$\frac{dI}{dt} = \gamma_h S I_v - (\mu_h + r + \delta)I, \tag{19b}$$

$$\frac{dR}{dt} = rI - (\mu_h + \delta)R, \tag{19c}$$

and

$$\frac{dI_v}{dt} = \gamma_v(1 - I_v)I - \mu_v I_v, \tag{19d}$$

$$\gamma_v = \frac{b\beta_v N_T}{(N_T + m)}. \tag{19e}$$

It should be noted that γ_v differs from γ_{vJ} in that it has an N_T instead in the numerator. The dynamical equations for S_A and S_v are not needed since $S + I + R + S_A = 1$ and $S_v + I_v = 1$. The requirement that N_T be a constant leads to the condition that the birth rate, λ is equal to the death rate, μ_h.

4.a. Endemic Equilibrium States

Setting the RHS of equations (19a)–(19d), we obtain endemic equilibrium state $E_1 = (S*, I*, R*, I*_V)$, where

$$S* = \frac{\beta + M}{((\mu_h + \delta)/\mu_h)(\beta + MX_o)}, \tag{20a}$$

$$I* = \frac{(X_o - 1)}{\beta + MX_o}, \tag{20b}$$

$$R* = \left(\frac{r}{\mu_h + \delta}\right)\left(\frac{X_o - 1}{\beta + MX_o}\right), \tag{20c}$$

and

$$I_v^* = \beta\left(\frac{X_o - 1}{X_o[M + \beta]}\right), \tag{20d}$$

where

$$X_o = \frac{\mu_h \gamma_h \gamma_v}{\mu_v(\mu_h + \delta)(\mu_h + \delta + r)}, \tag{21a}$$

$$M = \frac{\mu_h + \delta + r}{\mu_h}, \tag{21b}$$

and

$$\beta = \frac{\gamma_v}{\mu_v}. \tag{21c}$$

For the endemic state to be meaningful, $X_o > 1$. Equations (20a), (20b), and (20d) have the same form as those in Esteva and Vargas's paper [8] except for the definitions of X_o (the basic reproduction number (R_o) in [8]) M and the presence of some prefactors. In the limit, δ goes to zero and there is no differentiation between adults and juveniles, they are the same.

4.b. Local Asymptotical Stability

For the system defined by equation (19a)–(19d), the Jacobian matrix evaluated at E_1 is the 4×4 matrix given by

$$\begin{vmatrix} -(\mu_h+\delta)-\gamma_h I_v* & 0 & 0 & -\gamma_h S* \\ 0 & -(\mu_h+\delta+r) & 0 & \gamma_h S* \\ 0 & r & -(\mu_h+\delta) & 0 \\ 0 & \gamma_v(1-I_v*) & 0 & -\mu_v-\gamma_h I* \end{vmatrix}. \tag{22}$$

Using MATHEMATICA to diagonalize this matrix, we obtain the following characteristic equation;

$$(\lambda+\mu_h+\delta)\left(\lambda^3+A\lambda^2+B\lambda+C\right)=0, \tag{23}$$

where

$$A=(\mu_h+\delta)\left(\frac{\beta+MX_0}{\beta+M}\right)+\mu_h M+\mu_v X_0\left(\frac{\beta+M}{\beta+MX_0}\right), \tag{24}$$

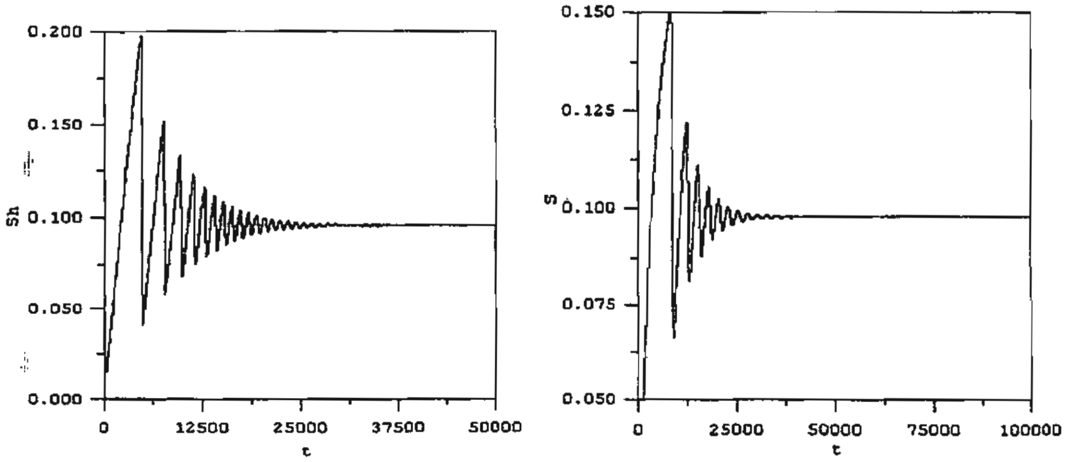
$$B=\mu_h(\mu_h+\delta)M\left(\frac{\beta+MX_0}{\beta+M}\right)+\mu_v(\mu_h+\delta)X_0+\mu_v\mu_h M\beta\left(\frac{X_0-1}{\beta+MX_0}\right), \tag{25}$$

and

$$C=\mu_v(\mu_h+r)(\mu_h+r+\delta)(X_o-1), \tag{26}$$

where X_0, M, and β are given by equations (21a)–(21c). The real parts of the eigenvalues are negative when the coefficients A, B, and C satisfy the Routh-Hurwitz condition given by equation (15). Looking at equation (23), we see that Condition (i) is always satisfied. Conditions (ii) and (iii) are satisfied when $X_0 > 1$. (To see that Condition (iii) is satisfied when $X_0 > 1$, we note that the cross product $AB > \mu_v\mu_h(\mu_h+\delta)MX_o$ (this being the product of the second terms in A and B). This term is larger than C. We thus have $AB > C$.)

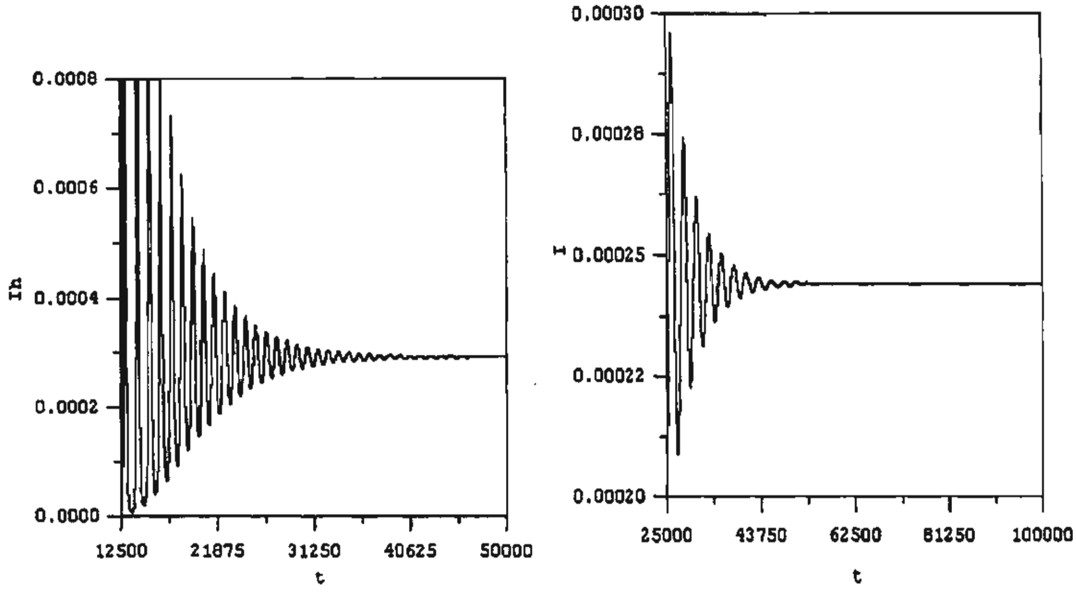
This shows that if $X_0 > 1$, the real parts of all the eigenvalues of the Jacobian evaluated at the endemic state are negative. Thus, the equilibrium state $E_1(S*, I*, R*, I_v*)$ given by equations (20a)–(20d) is a locally asymptotically stable state. Since the simplified model is obtained



(a) Solution of equation (2) in [7] for an SIR model of Dengue fever transmission with no age structure.

(b) Solution of equation (3a) of the present text for a SIR model having an age structure. The values of the parameters are given in the text.

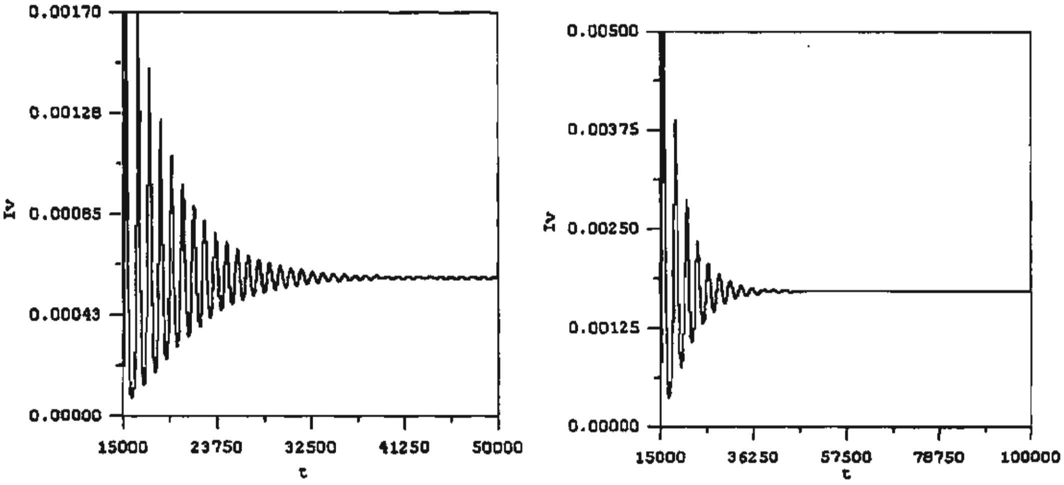
Figure 2. Number of susceptible humans as a function of time.



(a) Solution of equation (2) in [7].

(b) Solution of equation (3b) for a SIR model having an age structure.

Figure 3. Number of infected humans as a function of time.



(a) Behavior in a nonage structured SIR model.

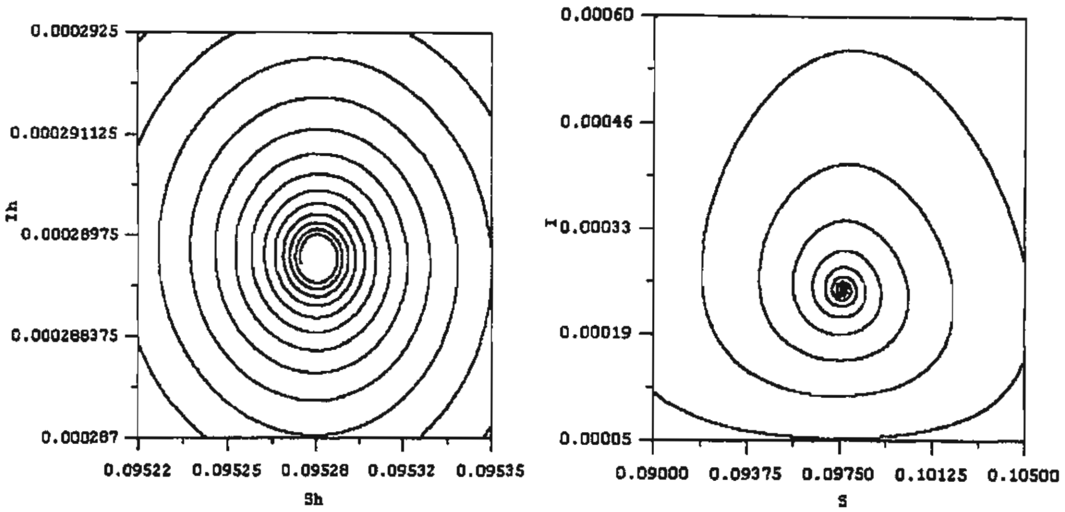
(b) Behavior in an age structured model.

Figure 4. Number of infected mosquitoes as a function of time.

from equations (1a)–(1f) by setting ε to zero and dropping the categories I_A, R_A, one would expect that an analysis similar to the one done in Section 3.b.1 would yield the same results (except that ε would be equal to 0). When ε in R_0' is set to zero, we find that $R_0' = R_1$, which is the same as X_0 after N_J has been replaced by $\mu_h N_T/(\mu_h + \delta)$ (this being what N_J is equal to) in the definition of R_1. We can therefore conclude that when $X_0 < 1$, the equilibrium state is the disease free state and that this state is locally asymptotically stable.

4.c. Numerical Studies

The main effect of introducing an age structure into the model is to change the definition of the basic reproduction rate. Using the values of the parameters similar to those used by Esteva and Vargas ($\mu_h = 0.0000456$, $\mu_v = 0.23$, $b = 0.3$, $\beta_h = 0.75$, $\beta_v = 1.0$, $m = 0.0$, $r = 0.343$, $N_T =$



(a) Behavior in a nonage structured SIR model.

(b) Behavior in an age structured model. The equilibrium states in both cases are stable spiral nodes.

Figure 5. Plot of number of susceptible and infected humans.

10,000, $A = 5000$), the value of the basic reproduction number defined in [8] would be 10.3. Numerically solving the set of equations given by Esteva and Vargas [8, equation (2)], we obtain the time development of the susceptible humans as seen in Figure 2a. In Figure 2b, we show the solution to equation (3a). The values of some of the parameters have been changed (i.e., $\delta = 0.000283$, $A = 200$, and $r = 0.0713$, with the others staying the same). Substituting these values into equation (16), we get $R_0 = 1.8$. In Figures 3 and 4, we show the time development of the infected humans and infected mosquitoes for the case of no age structure and an age structure model. In Figure 5, we plot the number of infected humans versus the number of susceptible humans in both a nonage structure population and age structure population. The values of the parameters are such that for both populations, the equilibrium state is the endemic state. The endemic state is the stable spiral state. As we see, the periods of fluctuations in the number of individuals in each class are much shorter in the absence of any age structure. The spiraling in is much more severe in the absence of the age structure. The age structure appears to calm down the fluctuations.

5. DISCUSSION

The square of the basic reproduction number is the number of secondary infections, which can result from one primary infection. For a disease to be capable of invading and establishing itself in a host population, this must be greater than one. If the number is less than one, then every successive generation will diminish in size until its number approaches zero. To determine what this number is, we note that an infected juvenile (adult) will be bitten by

$$\frac{b(A/\mu_v)}{(N_T + m)(\mu_h + r + \delta)} \left(\frac{b(A/\mu_v)}{(N_T + m)(\mu_h + r)} \right) \tag{27}$$

mosquitoes during the time juvenile (adult) is infectious. Of these mosquitoes, a portion of them will become infected (the above numbers multiplied by β_v). One of these infected mosquitoes will in turn bite

$$\frac{bN_J}{(N_T + m)\mu_v} \text{ juveniles and } \frac{bN_A}{(N_T + m)\mu_v} \text{ adults}$$

during its lifetime. Multiplying the first number by β_J and the second by $\epsilon\beta_J$, we get the number of juveniles and adults infected by an infectious mosquito. Multiplying the number of juveniles infected by the number of mosquitoes infected during the lifetime of the infectious juvenile, we get

$$\frac{\mu_h b^2 \beta_v \beta_J N_J (A/\mu_v)}{\mu_v (N_T + m)^2 (\mu_h + \delta + r)}. \tag{28}$$

If we multiply the number of infectious adults infected by the number of mosquitoes infected during the lifetime of the infectious adults, we get

$$\varepsilon \frac{\mu_h b^2 \beta_v \beta_h N_A (A/\mu_v)}{\mu_v (N_T + m)^2 (\mu_h + r)}. \tag{29}$$

Adding these two numbers together, we obtain the basic reproduction number. The sum of equation (28) and (29) is the R_0' given by equation (21).

The different models for disease transmission have yielded expressions for the basic reproduction number. These expressions have provided insights into the control of the various diseases. One of the first expressions obtained was the basic reproduction number for the spread of malaria. It is given by

$$R_o = \frac{b^2 \beta_v \beta_h m}{\mu_v (\mu_h + r)}, \tag{30}$$

where m is the ratio between the mosquito population and the human population. Based on the epidemiological data, Molineaux and Gramiccia [18] estimated R_0 to be 80 for the malaria epidemic in northern Nigeria. The implication of this (each infective person infects 80 other people) points to possible shortcoming of the model. It was pointed out by MacDonald that the malaria transmission model did not take into account an incubation period during which mosquito is not infectious. Taking this period into account, MacDonald obtained a new expression for the basic reproduction number

$$R_o = \frac{b^2 \beta_v \beta_h m}{\mu_v (\mu_h + r)} e^{-\mu_v \tau}, \tag{31}$$

where τ is the incubation period of the malaria parasite in the mosquito [19]. Equation (31) points to the fact that if the incubation period is longer than the life expectancy of the mosquito, the disease will not be established since the mosquito will die before it becomes infectious. The appearance of an exponential factor containing the life expectancy of the mosquito has led to the changes in the strategy for controlling malaria, exterminate the mosquito during its adult state and not in its larva stage.

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Cannibalism in an age-structured predator–prey system

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Abstract

The effect of cannibalism on an age-structured predator–prey system is studied. Three stable equilibrium states are found. Using a Hopf bifurcation analysis, it is found that the non washout steady state looses its stability as the cannibalism attack rate increases past a bifurcation point S_c. The dependence of the bifurcation point on the other parameters in the model is found. It is shown that the trajectory of the solution spirals in for attack rates $S < S_c$ and exhibits limit cycle behavior for $S > S_c$.

Keywords: Predator–prey; Cannibalism; Hopf bifurcation; Limit cycle

1. Introduction

Under what circumstances is cannibalism adaptive? For evolutionary games being played on a small part of nature's stage, one could measure the rewards of the games in terms of expected future reproductive success, i.e. by seeing whether the species goes extinct or not. To win the game, one looks for an evolutionary stable strategy (ESS) (Maynard-Smith, 1982). An ESS is a population strategy that yields a higher reward than any other feasible mutant strategies. The nature of the strategy depends on the values of the ecological parameters, which are present at the time. Change the time and the ESS may be different, e.g. it may be one of the mutant strategies or it could be a completely new one.

An intuitive belief of biologists is that evolution should favor behaviors with the lowest cost to the species practicing them (Mesterton-Gibbons and Adams, 1998). Because it costs energy to breed and because cannibalism would waste this energy, evolution would not select cannibalism as a desirable trait. Another reason is that intraspecific feeding facilitates the spread of prion proteins (abnormal protein growth in the brain and other internal organs) among the individuals within the species. The presence of these proteins in the brains leads to fatal diseases such as bovine spongiform encephalopathy (BSE) in cows, trans-missible spongiform encephalopathy (TSE) in sheep and kuru in the Fore people of New Guinea. The first two diseases are not due to cannibalism per se, but are the result of eating feed meal made from ground up diseased animals of the same species. The much dreaded disease vCJD (variant Creutzfeldt–Jakob disease) is due to the interspecific transmission of bovine prion proteins from the cow to the human. Because the bovine prion is foreign to humans, the efficacy of the transmission would be much less than that of intraspecific transmission. This is one of the reasons for the incidence of vCJD not being as wide spread as that of BSE. Cannibalism, thus leads to a higher mor-

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tality rate and animals that practice it would then be at a competitive disadvantage with those who do not.

Having said the above, it was surprising when two recent mathematical studies of cannibalism showed that cannibalism could stabilize a predator–prey system. Kohlmeier and Ebenhöh (1995) found that the cannibalism of the predator could lead to an increase of the standing stocks of both the prey and predator. The authors were surprised by this result since as they pointed out, it is contrary to intuitive expectation. Van den Bosch and Gabriel (1997) have pointed out that in the absence of cannibalism, the system of equations used in by Kohlmeier and Ebenhöh (KE) has for certain parameter combinations an unstable internal steady state. For these parameter combinations, predator–prey cycles occur. Cannibalism suppresses these cycles since increasing cannibalism attack rates causes the internal steady state to change from being unstable to being stable. We would like to point out that the model of KE employs a Holling type II functional response. This means that they are using a model that contains predatory switching. The reason for pointing this out is that several studies (see for instance, Pelletier, 2000) have shown that prey switching has a strong stabilizing effect on a multi-species ecosystem.

In their paper, Van der Bosch and Gabriel went on to improve the predator–prey model by incorporating an age structure in the predator population. It was reasoned that cannibalism usually involves larger (adult) predators eating smaller (juvenile) predators and so an age structure would be required to properly describe the predator–prey relation. The predator–prey cycles in their study are generated by the age structure while the cycles seen in KE's study are due to the interaction between the logistic prey growth and the hyperbolic functional response. Increasing the cannibalism attack rate would diminish the effects of the age structure. The fluctuations (cycles) would, therefore, be suppressed implying that cannibalism stabilized the predator–prey system.

Recently, Magnusson (1999) has reexamined the effects of cannibalism on the predator–prey system. He found that cannibalism has a destabilizing effect. For the case of large prey carrying capacity of the environment, Magnusson finds that as the cannibalism attack rate is increased, the non washout equilibrium point (a stable spiral point) becomes unstable via a Hopf bifurcation. He goes on to state that the loss of stability is not possible without a high juvenile mortality rate and a low adult recruitment rate. We have studied cannibalism in an age-structured predator–prey system described by the same set of basic equations as those used by Magnusson but with a different set of scaling parameters. The new set of equations allows us to follow the loss of stability for all values of the parameters in the model (not just those for large carrying capacity, high juvenile mortality rates and low adult recruitment rate) as the cannibalism attack rate is changed continuously. Like Magnusson, we use an analysis based on the Hopf bifurcation theory. We have found the dependence of the bifurcation point on the values of the other parameters in the system.

In this study, we have ignored any structure, which may occur in the juvenile population. In their study, Van den Bosch and Gabriel proposed that only juveniles of an age within the "cannibalism window" would be vulnerable to cannibalism by adults. Juveniles of age below this window would be too small to satisfy the hunger of the adults or would be protected by their mothers. Older juveniles would be active enough to get away from the adults. This brings up the question of whether the old juveniles should be reclassified as young (immature) adults. In this type of population structure, it is not the age, which counts, but the size. The population model should, therefore, be called a size-structured population model (Cushing, 1992).

A true age-structured population model is achieved when the juvenile population or, the adult population or the whole population is divided into discrete age groups regardless of other distinctions. The division of the juvenile population is often done in the study of the transmission of childhood diseases (Anderson and May, 1992). These studies are often referred to as being realistic age-structured population model studies. The division of the adult population has been used in a study of fishery management (Allen and Miranda, 1998). The erratic recruitment of a specie of fish (crappie) year to year has caused difficulties in the development of management strategies of this fish. Allen and Miranda divided the adult population into cohorts of fishes entering into the population each year and followed the progression of each cohort as they are subjected to various life and death factors. Many population studies (Roughgarden, 1979) divide up the whole population into different age groups and see what the age distribution would be under different circumstances.

It has been noted that cannibalism in certain species are often directed at the egg or larvae of the specie. This would necessitate the division of the juveniles into different developmental stages. Yang et al. (1997) divided the citrus rust mite population into four populations: egg, protonymph, deutonymph and adults in their studies of the population dynamics of fruit mite–fungal pathogen system. Krivan and Havelka (2000) divided the gall-midge juvenile population into three sub populations: egg, larvae and pupae, in their study of the use of gall-midge for biological control of pests. This type of division leads to what would be better called a stage-structured population model.

Having pointed out that "juvenile" (nonadult) population often has an internal structure, we will nevertheless assume that the juvenile population is a single group. Cushing (1991) remarked that even a simple two-age class population model with appropriate negative and positive feedbacks due to cannibalism can account for several important phenomena concerning cannibalistic populations. Cushing's study differs from ours in that it uses discrete time, while this work is based on a continuous time development. In Section 2, we introduce the model and obtain the equilibrium states, while in Section 3, we perform a stability analyses of both washout and non washout equilibrium states. In Section 4, we study the effects of cannibalism on the stability of the non washout state. We present the numerical solutions, which show the transition from a steady state behavior to a limit cycle behavior as the attack rate increases past the critical attack rate. In Section 5, we present some conclusions.

2. The model

The ecosystem in our model consists of a single predator species, a prey population and the vegetation. The predator population is divided into juvenile predators (denoted by Y) and adult predators (denoted by X). The prey population may consist of several herbivore species, but since we use only one set of parameters to describe their interaction with each other and the rest of the ecosystem, the prey population is treated as being a single species (denoted by Z). We assume that the prey population is subjected to a logistic growth condition. Magnusson makes the implicit assumption that there is a second prey species present. The second species is required since Magnusson allows for the possibility that the predator population can exist when the primary prey species becomes extinct. The equations describing their ecosystem do not contain any reference to the second prey population. The second species would, therefore, be invisible to the predator species, meaning that the predators could not feed on them when the primary prey species becomes extinct. The fourth steady state (x_0, y_0, 0) obtained by Magnusson would, therefore, be impossible. In our ecosystem, the different species interact via some sort of mass action inaction. This leads to the time rate of change of the prey population density to be given by

$$\frac{dZ}{dt} = (T - UZ)Z - VZX \qquad (1)$$

where T is the net rate of growth; T/U, the prey carrying capacity and VX is the increase in the prey's mortality rate due to predation by the adult predator. As we have pointed out, Kohlmeier and Ebenhöh use a Holling type II functional response to describe the predation. Its use means that the predation will change depending on whether the population density of the prey or predator is high or low. This is probably a better description of the actual predation seen in nature. Since we are interested in this paper on the effects of cannibalism, we have used the simplest description, i.e. predation is described by a constant value. In writing Eq. (1), we have assumed that juvenile predators do not eat any prey. They obtain their subsistence from their parents.

The time rates of change of the predator populations are given by

$$\frac{dX}{dt} = AY - \mu_a X + \gamma SXY + CXZ \qquad (2)$$

and

$$\frac{dY}{dt} = \lambda X - AY - \mu_j Y - SXY \qquad (3)$$

where A is the recruitment rate (rate at which juveniles mature into adults); μ_a (μ_j), mortality rate of the adult (juvenile) predator; S, the cannibalism attack rate; γSY and CZ, the increases in the adult mortality rate due to being better fed through eating juveniles and prey, respectively, and λ is the birth rate of the predators.

Looking at Eqs. (2) and (3), we see that there are five (plus the two mortality rates) parameters whose values have to be assigned. There are three additional parameters in Eq. (1). We can reduce the number of parameters by making the following change of variables (a rescaling):

$$x = \frac{V}{\mu_a}X,\quad z = \frac{C}{\mu_a}Z,\quad y = \frac{VA}{\mu_a}Y$$

and

$$\tau = \mu_a T. \tag{4}$$

Making these changes, Eqs. (1)–(3) assume the much simpler form

$$\frac{dx}{d\tau} = y - x + xz + \gamma' sxy,\quad \frac{dy}{d\tau} = rx - my - sxy$$

and

$$\frac{dz}{d\tau} = (t - uz - x)z \tag{5}$$

where $s = S/V$, $\gamma' = \gamma\mu_a/A$, $t = T/\mu_a$, $r = RA/\mu_a^2$, $u = U/C$ and $m = (A + \mu_j)/\mu_a$. The rescaling here is different from those introduced by Magnusson. We believe that they are better since they allow for the role of the cannibalism attack rate to be followed more closely (s is directly proportional to the cannibalism attack rate).

The equilibrium (or steady state) points are obtained by setting the LHS of Eq. (5) to zero. Doing this, we get the following equilibrium points $E(x,y,z)$;

$$E_1 = (0, 0, 0), \tag{6a}$$

$$E_2 = \left(0, 0, \frac{t}{u}\right) \tag{6b}$$

and

$$E_3 = (x^*, y^*, z^*) \tag{6c}$$

where

$$x^* = \frac{\delta + \sqrt{\delta^2 - 4s(mu - ru - tm)}}{2s}, \tag{7a}$$

$$y^* = \frac{rx^*}{m + sx^*} \tag{7b}$$

and

$$z^* = \frac{t - x^*}{u} \tag{7c}$$

with $\delta = st - su - m + \gamma' sru$. It can be shown that the term appearing in the square root in Eq. (7a) is always positive. The requirement that $x^* > 0$, places certain restrictions on the values of the parameters. Their values must be such that $st - su - m + \gamma' sru > 0$ and $mu - ru - tm < 0$. We will discuss the stability of the three equilibrium points in the next section. We do not find a fourth equilibrium point E_4. As we have mentioned, the existence of the equilibrium point at $(x_0, y_0, 0)$ would imply that it would be possible for the predators to exist in the absence of food to eat.

3. Stability analysis

The stability of the equilibrium points is determined by first linearizing the system of first-order differential equations and then assuming that the solutions vary as $\exp\{\lambda t\}$ where the λs are the eigenvalues of the Jacobian matrix evaluated at the equilibrium point. The equilibrium point is a stable point if all the eigenvalues are real and negative; unstable point if they are real and positive and is a saddle point if two of them are real and of opposite signs. If the eigenvalues are complex, the equilibrium points are stable spiral points or unstable spiral points if the real parts of the eigenvalues are negative or positive.

3.1. Predator washout states (0, 0, 0) and (0, 0, t/u)

The Jacobian matrix for the present set of differential equations is

$$\begin{pmatrix} -1 + z' + \gamma' sy' & 1 + \gamma' sx' & x' \\ r - sy' & -m - sx' & 0 \\ -z' & 0 & t - x' - 2uz' \end{pmatrix} \tag{8}$$

where x', y' mad z' are the values of rescaled variables at the equilibrium point. For the first predator washout state, the diagonalization of the Jacobian matrix yields the following characteristic equation

$$(\lambda - t)(\lambda^2 + (m + 1)\lambda + (m - r)) = 0. \tag{9}$$

The eigenvalues for the washout state (0, 0, 0) are

$$\lambda_1 = t > 0$$

and

$$\lambda_{2.3} = \frac{-(m + 1) \pm \sqrt{(m + 1)^2 - 4(m - r)}}{2}. \tag{10}$$

For $m > r$ and $m > -1$, $\lambda_{2,3}$ are both negative. Therefore, the washout equilibrium state is a saddle point.

Evaluating the Jacobian matrix at the second washout point (0, 0, t/u), we find that the eigenvalues for this equilibrium point are

$$\lambda_1 = -t$$

and

$$\lambda_{2,3} = \frac{-(1+m-(t/u)) \pm\sqrt{(1+m-(t/u))^2-4(m-r-(t/u)m)}}{2}. \tag{11}$$

It can be shown that all of these eigenvalues will be negative if

$$1-\frac{t}{u} > \frac{r}{m}. \tag{12}$$

If the values are the parameters satisfy condition (11), then (0, 0, t/u) is a stable equilibrium. If the opposite is true, then (0, 0, t/u) will be an unstable saddle point.

3.2. *Non washout predator state (x^*, y^*, z^*)*

The eigenvalues of the Jacobian evaluated at the non washout equilibrium point are the roots of the following cubic equation

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0 \tag{13}$$

where

$$a_0 = z^*\left[mu\left(z^*+\frac{r}{m}-1\right)+x^*(m+sx^*)\right],$$

$$a_1 = uz^*\left(\frac{y^*}{x^*}+r\frac{x^*}{y^*}\right)+x^*z^*-m\left(1-z^*-\frac{r}{m}\right)$$

and

$$a_2 = \frac{y^*}{x^*}+r\frac{x^*}{y^*}+uz^* \tag{14}$$

where x^*, y^* and z^* are given by Eqs. (7a)–(7c).

Given a_0, a_1 and a_2, we now define

$$q = \tfrac{1}{3}a_1 - \tfrac{1}{9}a_2^3, \quad r = \tfrac{1}{6}(a_1a_2-3a_0) - \tfrac{1}{27}a_2^3.$$

$$S_{1,2} = [r \pm (q^3+r^2)^{1/2}]^{1/3}. \tag{15}$$

If $q^3 + r^2 > 0$, λ_1 and λ_2 would be the complex conjugate of each other and λ_3 would be real.

In terms of the above constants, the three eigenvalues of the Jacobian matrix are

$$\lambda_{1,2} = -\frac{1}{2}(S_1+S_2) - \frac{a_3}{3} \pm \mathrm{i}\frac{\sqrt{3}}{2}(S_1-S_2)$$

and

$$\lambda_3 = (S_1+S_2) = \frac{a_2}{3}. \tag{16}$$

Now if the values of the parameters are such that

$$\frac{-2a_2}{3} < S_1+S_2 < \frac{a_2}{3},$$

the real parts of all three eigenvalues would be negative and the non washout state E_3 would be stable.

4. Effect of cannibalism on stability of non washout state

4.1. *Bifurcation point*

A Hopf bifurcation occurs (see Marsden and McCracken, 1976) when for some critical value of the bifurcation parameter (which we take in this study to be the cannibalism attack rate), the following are true

(a) $Re\,\lambda_{1,2}(s^*) = 0$
(b) $Re\,\lambda'_{1,2}(s^*) \neq 0$
(c) $Im\,\lambda_{1,2}(s^*) \neq 0$
(d) The real parts of all other eigenvalues of the Jacobian evaluated at the steady state point negative.

From the above conditions, it can be shown that for Hopf bifurcation to occur, we need

$$a_0 > 0, \quad a_1a_2 < a_0$$

with

$$a_2 < 0.$$

If we define s_1^* as the critical value where $a_1(s_1^*)a_2(s_1^*) = a_0(s_1^*)$, we get

$$s > s_1^* \equiv \frac{r}{y^*}\left(1+\frac{ru}{y^*}\right)+\frac{1}{z^*(x^*)^2} \times\left[a\left(\frac{rx^*}{y^*}+\frac{y^*}{x^*}\right)+z^*(b+cxc^*+y^*)\right] \tag{17}$$

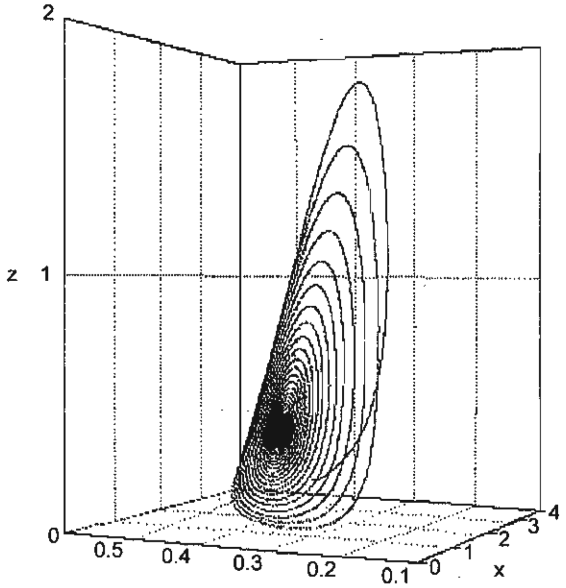

Fig. 1. Trajectory of the solution of Eq. (5) for values of the parameters lying in region II. X denotes the adult predator; Y, the juvenile predator and Z, the prey. The non washout steady state point is a stable spiral point. The values of the parameters are $s = 0.9$, $m = 1$, $\gamma' = 1.5$, $r/m = 0.5$ and $u = 0.1$.

where

$$a = m(z^* - 1) + (uz^*)^2 + r, \quad b = 2ru + \frac{u(y^*)^2}{(x^*)^2}$$

and

$$c = uz^* - m.$$

Next we define another critical value s_2^* as the value where $a_0(s_2^*) = 0$. This give us

$$s > s_2^* \equiv \frac{mu}{(x^*)^2}\left[1 - \frac{r}{m} - z^* - \frac{x^*}{u}\right]. \tag{18}$$

Since $s > s_1^* > s_2^*$, we can pick the bifurcation point s^* to be s_1^*.

4.2. Description of parametric space

To study the effect of increasing the (rescaled) cannibalism attack rate 's', we introduce a hyperspace Ω in which each point is designated by the values of s, r, m, t, u and γ', i.e. (s', r', m', t', u', γ''). In this hyperspace, there are families of hypersurfaces on which

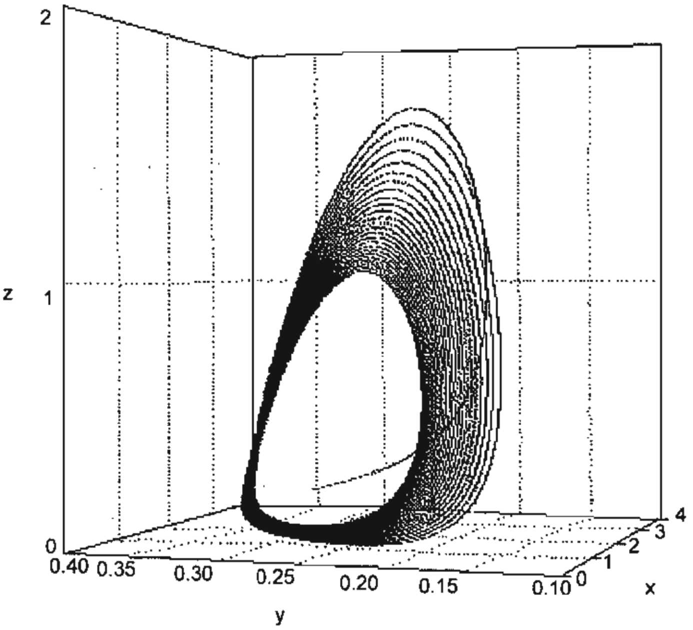

Fig. 2. Trajectory of the solution of Eq. (5) when s is changed to 1.0 which is greater than the critical bifurcation point $s^* = 0.98$. X denotes the adult predator; Y, the juvenile predator and Z, the prey. The values of all other parameters are the same as those used for Fig. 1. The bifurcation is a supercritical one.

the parameters have the values satisfying the relationship $a_2 > 0$. Each of the hypersurfaces are divided into three regions by the hypercurves $a_0 = 0$ and $a_1a_2 = a_0$. In region I of the hypersurface, the values of the parameters are such that $a_0 < 0$ and $a_1a_2 > a_0$; in region II, the values are such that $a_0 > 0$ and $a_1a_2 > a_0$; while in region III, the values are such that $a_0 > 0$ and $a_1a_2 < a_0$. Only the two washout states (0, 0, 0) and (0, 0, t/u) would be possible for values of the parameters in region I. The first would be a saddle point while the second would be a stable or unstable point depending on the initial conditions. The values of the parameters in region II would produce a phase solution trajectory which would spiral into the non washout steady state (x^*, y^*, z^*) given by Eqs. (7a)–(7c). For values of parameters in region III, the non washout steady state would lose its stability and the trajectory of the solution in phase space would jump to a limit cycle behavior.

4.3. Numerical solutions

Given Eq. (14), we can calculate the value of the bifurcation point. Picking $m = 1$, $\gamma' = 1$, $r/m = 0.5$ and $t = 1.3$, we have calculated s^* to be 0.98. Picking $s = 0.9$, we have a set of parameters belonging to region II. Numerically solving Eq. (5), we obtain the three-dimensional trajectory shown in Fig. 1. As we see, the trajectory spirals into the stable point (x^*, y^*, z^*). If we change s (only) to 1.0, we would then be in region III. Now solving, Eq. (5), we get the limit cycle behavior seen in Fig. 2. Further increasing the value of s, yields limit cycle trajectories. All the bifurcations appear to be supercritical.

5. Conclusion

Our numerical studies show that the predator non washout steady state solution of a predator–prey system looses its stability as the cannibalism attack rate increases beyond a critical value s^*. Whether or not this is adaptive depends on whether or not the predator species becomes extinct. Passage into a limit cycle behavior means that during some time in its life cycle, the predator will experience harshness in its life. This would cause nature to select those traits that would allow future descendants to have the ability to adapt to changes in the environment. Many species who have reached the pinnacle of their food chain have become over specialized and have become extinct when nature changed; witness of the fate of the dinosaurs.

Magnusson has obtained results similar to ours. However, he restricts his conclusions to the case where there is high juvenile mortality and/or low recruitment rate and high conversion efficiency. One of the reasons for this is the nature of the rescaling he introduced. The only parameter appearing in his equations that depends on the cannibalism attack rate, depends on the inverse of attack rate. As the attack rate increases, its influence on the dynamics would decrease. Also, he assumes that the carrying capacity for the prey is high. This allows him to drop a very important factor in his predator–prey model (limitations due to logistic growth of the prey).

The appearance of oscillations in the populations in certain cannibalistic ecosystems has also been explained by Diekmann et al. (1986). Their approach is somewhat different from the one used in this study. They used integrodifferential equations to model their predator–prey interaction. Cushing (1991) has used difference equations to study the predator prey system. He finds that if the environmental resources are low and the net reproductive number is below replacement, then cannibalism might insure the survival of the species. All of this shows that the predicted outcome of cannibalism on a predator–prey system depends on the model used to model the system.

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Dengue Haemorrhagic Fever in Thailand, 1998-2003: Primary or Secondary Infection

by

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Abstract

The pathogenesis of dengue haemorrhagic fever (DHF) is looked for in the serological records of DHF patients (mainly children between the ages of one month and 16 years) at Siriraj Hospital in Thailand over a six-year period beginning 1998 (covering two three-year cycles). Based on the primary and secondary infections by both the haemagglutination-inhibition assay (HI) test and the IgM capture enzyme-linked immunosorbent assay (ELISA) test, it was found that in 1998, 14 of the cases for which paired sera specimens were tested using both HI and ELISA (or 9.6% of 146 cases) had resulted from primary infections. In 1999, 2000, 2001, 2002 and the first half of 2003, three out of 57 cases (5.3%), six out of 48 cases (12.5%), 85 out of 293 cases (29%), 23 out of 90 cases (25.6%) and 16 out of 56 cases (28.6%), respectively, resulted from primary infections. The percentages of primary infections during the last three years are well above 14.0% reported for cases occurring in Bangkok between 1988 and 2003.

Keywords: Dengue haemorrhagic fever, serological tests, primary-secondary infection.

Introduction

Dengue fever (DF) is a rather benign febrile disease, afflicting mainly older children and adults[(1)] and often remaining unapparent in young children[(2)]. The sudden onset of fever and a variety of non-specific signs and symptoms characterize DF. The high fever lasts for two or three days, followed by additional symptoms. Its clinical presentations are similar to those of several other diseases, meaning thereby that many of the reported cases of DF could be due to other febrile illnesses and also that many

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[#] **For correspondence**: *scimt@mahidol.ac.th* dengue infections are not recognized. During the 1977 epidemic in Santiago de Cuba(3), only 3,012 out of 9,747 people who developed febrile illnesses and whose sera were tested, turned out to be infected with dengue fever. DF is caused by the dengue virus which belongs to the genus, *Flavivirus,* in the *Flaviviridae* family. There are four serotypes of this virus known as DEN-1, DEN-2, DEN-3 and DEN-4. Infection by any of the four serotypes causes similar clinical presentations, and confers permanent immunity to that particular serotype, but only a temporary one to the others.

The dengue virus is transmitted by the *Aedes* mosquitoes, i.e. *Aedes aegypti* and *Aedes albopictus,* in countries of South-East Asia. Introduction of the dengue virus by just one individual into a susceptible population residing in a locality where the above mosquitoes are prevalent can quickly lead to an epidemic. In many tropical countries, DF has now emerged as a major public health problem(4).

The pathogenesis of dengue haemorrhagic fever (DHF) is still a matter of controversy. According to one school of thought(5), pre-existing heterologous dengue antibodies recognize the infecting virus and form an antigen-antibody complex, which then binds the virus to the cell membrane of some leukocyctes. Since the antibodies are only heterologous, the virus is not neutralized and is free to replicate once inside the cell. It is then thought that these cells secrete vasoactive mediators in response to dengue infection. These mediators cause an increased vascular permeability, which leads to hypovolemia and shock. Since the antibodies have to be pre-existing, this hypothesis terms it as the secondary infection or immune enhancement.

A cautionary note should be added here. It appears that the occurrence of DHF after a second infection depends on the strain of the serotype. During the 1996-1997 dengue epidemic in Belem Para, Brazil, none of the 24 patients who had been previously infected by the DEN-1 virus developed DHF after they had been re-infected by the DEN-2 virus(6). Watts et al(7) observed the same pattern during the 1995 epidemic in Iquitos, Peru. No cases of DHF/DSS were reported even though it was expected that between 887 to 10,247 cases would have occurred. The DEN-2 isolates were found to be of the American genotype (strain). Kochel et al(8), attributed the non-occurrence of DHF/DSS to the presence of common envelope epitopes in both the American strain of the DEN-2 virus and the DEN-1 virus and the absence of these epitopes in the Asian strain of the DEN-2 virus. The common epitopes could have been acquired through the recombination between the American DEN-2 and the DEN-1 virus co-circulating in the Americas or through genetic drift (mutation).

The other school of thought(5) maintains that the mutation of the viruses could have produced viruses with greater virulence and therefore greater epidemic potential. DHF would then be due to the appearance of these mutant strains among the circulating virus. This second hypothesis does not pre-suppose the presence of pre-existing antibodies and so the DHF/DSS infection would be the result of a primary infection. In an attempt to contribute to this debate, we reviewed the serological status of children suffering from DHF who were admitted to the Paediatrics ward of Siriraj Hospital (a tertiary-care medical centre with a 300-bed facility in Bangkok, Thailand) between 1998 and mid-2003. A similar review of children admitted to the Department of Paediatrics, Chulalongkorn Hospital, Bangkok, between 1985 and 1995 was made recently(9).

Materials and methods

Criteria for primary and secondary infections

The World Health Organization (WHO)(4) has established a set of criteria to determine whether a case of dengue fever is due to primary or a secondary infection. The determination is based on the results of either HI tests or ELISA tests or both, done on a paired set of sera taken at least seven days apart, one in the acute phase and the other in the convalescence phase. The criteria for primary infection are that, for a paired set of sera specimens there should be a fourfold increase in the IgM antibody response and HI titers of any of the DEN serotypes and the IgM/IgG ratio should be ≥1.8 and/or the HI titers in the convalescence phase should be <1,280. The criteria for determining secondary infection are that the IgM/IgG ratio should be <1.8 and/or the HI titers in the convalescence phase should be ≥2,560.

Patients

Admission to the ward was based on the clinical presentation of DHF as per the case definition of WHO(4). Serological tests, i.e. haemagglutination inhibition (HI) assay(10) and IgM/IgG enzyme-linked immunosorbent assay (ELISA)(11), were used to determine whether the patients had dengue virus infection. Attempts were made to isolate the virus on *Toxorhynchites* mosquito to identify the serotype of the virus responsible for the illness.

Results

The results of the laboratory survey are given in the Table. Of the 1,183 patients admitted, the serological tests established that 1,082 of them were confirmed as of DHF. A total of 214 patients were determined to be due to primary infections, 291 due to secondary infection and 577 remained undetermined. One hundred and one patients turned out not to be sick with DHF. The virus responsible for the infection was isolated in 373 cases. The predominant virus was DEN-1 (162), followed by DEN-2 (121), DEN-3 (70) and DEN-4 (17). Multiple viruses were found in three patients (not included in the table). On the basis of the serological tests and using the WHO criteria for primary and secondary infections, our study found that in 1998, 14 of the cases for which paired sera specimens were tested by both tests (or 9.6% of 146 cases) had resulted from primary infection. In 1999, 2000, 2001, 2002 and the first half of 2003, three out of 57 cases (5.3%), six out of 48 cases (12.5%), 85 out of 293 cases (29%), 23 out of 90 cases (25.6%) and 16 out of 56 cases (28.6%), respectively, had resulted from primary infection.

Table. *Summary of the serological records of DHF patients admitted to Siriraj Hospital, 1998-2003*

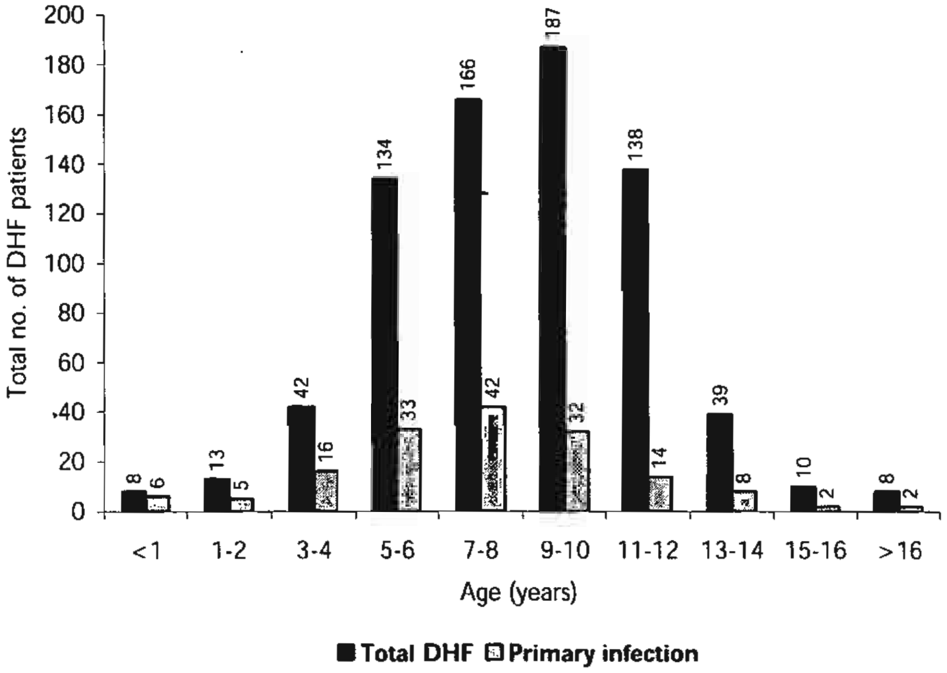
Year	Number of patients admitted	Number sick with DHF	Number of cases where virus were isolated				
			DEN-1	DEN-2	DEN-3	DEN-4	Total
1998	318	281	51	28	41	1	121
1999	137	112	9	13	3	4	29
2000	84	71	13	13	5	0	31
2001	334	334	49	36	17	8	110
2002	186	186	23	22	4	1	50
2003*	121	121	17	9	0	3	29

*From January – June 2003

Regarding the results of virus isolation, of the 121 cases where virus was isolated in 1998, 40.0% were of DEN-1, 24.2% were of DEN-2, 34.2% were of DEN-3 and 1.7% were of DEN-4. In 1999, the respective percentages were 31.0, 44.8, 10.3 and 13.8. In 2000, the percentages changed to 42, 42, 16.1 and 0, respectively. In 2001, they were 44.5, 32.7, 15.5 and 14.1. In 2002, they were 46.0, 44.0, 8.0 and 2.0 respectively. For the first half of 2003, the percentages were 58.6, 31.0, 0 and 10.3 respectively. Comparing the percentages year by year, we can quantify the relative amount of the virus in circulation during that year. The relative abundance of DEN-1 virus appears to be increasing year after year, while that of DEN-3 appears to be decreasing. Overall, DEN-2 appeared to be the second-most abundant serotype in circulation throughout the study period.

The age distribution of the patients suffering from DHF is given in the Figure. This looks similar to the one of the DHF/DSS patients admitted to Yangon Children's Hospital, Myanmar, between 1995 and 1996, but is different from that of the children admitted to the Children's Hospital in Bangkok between 1995 and 1998(12). The age distribution pattern for the latter hospital shows a bimodal distribution, with the second maximum in infants below the age of one year. Halstead et al(12) proposed that this group should be the one to study for understanding primary infections. They found that infants with DHF/DSS constituted 4.9% of the patients in their study group. Only eight infants were recorded in our study group. A similarly small number of infants was seen in the study group of Pancharoen et al(9). Also shown in the Figure is the age distribution of the DHF cases resulting from primary infection. In all the three studies, DHF infections in infants were primary infections.

Figure. ***Age distribution of primary infection and total DHF patients (1998-2003) The numbers listed are for the patients whose ages are known and include those whose diagnoses are based on either single sera test or clinical presentations***



Discussion

The period covered in the present study spans two complete three-year cycles in the month of incidence of DHF in Bangkok, Thailand, between January 1998 and June 2003. Hays et al[13] carried out a spectral density analysis of the data and found an annual variation and a super-annual variation (of three years). The 1998 epidemic was one of the peak years in the annual occurrence of DHF in Thailand. Based on this, Hays predicted during a dengue fever conference held in December 2000 in Chiang Mai that 2001 would be a peak year for DHF. This was borne out by the increase observed in the incidence of DHF in Bangkok in that year. Many of us also made similar predictions[14]. As observed in this study, the incidence of DHF peaked in 1998 and then decreased in 1999 and again went down in 2000. It rose sharply in 2001 (a peak year in the three-year cycle) and then dropped in 2002. The decrease appeared to be continuing in 2003. Based on the previous trends, it is expected that there will be a rise in the incidence of DHF in 2004.

In the present study, dengue virus was isolated only in 34.5% of the 1,082 DHF patients confirmed by serological examinations. This is far below the percentage isolated by Vaughn et al(15), who were able to isolate the virus in 98% of their patients. Their study was done in 1994. The difference in the percentages is due to the fact that Vaughn et al carried out their isolation within three days of the beginning of the high fever. Using similar criteria for differentiating between primary and secondary infections as the cause of the DHF illness, Vaughn et al established that only 8% of the acute dengue illnesses were due to primary infections (92% were due to secondary infections).

The relative abundance of the four serotypes observed by Vaughn et al, in 1994 was DEN-1 (20.3%), DEN-2 (28.8%), DEN-3 (16.9%) and DEN-4 (33.9%). Combining these numbers with the relative abundance observed in our study and in 1960(16), we observed that there was permanent circulation of the four serotypes in Thailand. This is likely to be the cause of the short intervals between the high epidemic peaks, compared to what is observed, for example, in Polynesia where mono-serotype epidemics occur at an interval of at least six-to-seven years(17). Looking at the relative abundance of all the four serotypes on a year-to-year basis, we found that the relative abundance of DEN-4 was fluctuating the most, followed by DEN-3. No significant differences ($p<0.05$) were observed between confirmed primary and secondary infections for any serotype during any year.

The percentages of primary infections during the last three years are well above 14.0 reported for cases occurring in Bangkok between 1988 and 1995(9). This raises the question: Does the fact that the percentages of DHF/DSS arising from primary infections have almost doubled during the last three years signify that the dengue viruses have become more virulent or are there other factors at play?

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H.Nishiura et al. / Journal of Medical Safety 1(1) 2003 (Details explanation by authors)

The impact of initial attack size on SARS epidemic for SARS free countries: Possible reason for Japan without a domestic transmission.

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Background: The newly identified coronavirus has caused an epidemic of severe acute respiratory syndrome (SARS) to appear worldwide, particularly in parts of Asia. Although Japan has experienced the entry of a SARS-CoV infected person, the virus has so far not succeeded in invading the community.

Method: A mathematical model based on Kermack & McKendrick epidemic model, was recently developed to be used, is applied for evaluating the effect of interventions such as quarantine and isolation. An analysis centered on initial attack size has been done to estimate the conditions needed for the successful invasion of SARS.

Results: The possible trajectories of SARS epidemics are obtained for different initial attack sizes, i.e., the number of infectious persons who are first introduced into a specific community having a susceptible population. It was demonstrated that the successful invasion of SARS would largely dependent on the initial attack size under certain assumptions. Mathematical analyses were performed to prove that the maximum number of susceptible humans who would be infected could be estimated on the basis of the initial attack size, using simple formulas.

Conclusion: The initial attack size is one of the most important determinants of whether a SARS epidemic can occur or not. Under an effective quarantine (which would lead to $R_0 < 1$) regime, it would be difficult to generate secondary cases through the entry of only a few infectious individuals into large populace. The method was considered to also be useful when we estimate the degree of quarantine required.

Keywords: Severe Acute Respiratory Syndrome (SARS); Mathematical Model; Initial Attack Size; Japan

1. Introduction

Since November 2002, SARS (Severe Acute Respiratory Syndrome)-associated coronavirus (SARS-CoV) has caused outbreaks of an atypical pneumonia worldwide, particularly in parts of Asia[1]. Since the average overall case-fatality rate for all countries has ranged from 10.4 to 14.7 %[2], growing fears for SARS among public as well as health-care workers have spread dramatically. The spread of SARS stopped when public health measures such as quarantine and

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isolation were imposed on the public. Riley et al3) believed that the reduction in the contact rate between the infectious individual and the rest of the susceptible population was the main reason for the end of the SARS crisis. By the time of the last report of someone becoming sick with SARS, 8457 individuals had been afflicted with the illness, 813 of who died4).

From the beginning of the epidemics, SARS has been a worry to Japan because of its close proximity to Hong Kong and other SARS affected Southeast-Asian countries5). Many Japanese and foreign travelers have traveled to these countries and have returned to Japan after their visits. The Japanese government has therefore drawn up contingency plans for the possibility of SARS-infected individuals entering into Japan. Medical doctors of national hospitals have been dispatched to each airport quarantine office around the country. In addition, thermometers has been put in place, and all passengers from countries where SARS infections are presently occurring have been subject to a temperature check upon their arrival at each airport. Although strengthened quarantine has been carried out at each international airport, Japan has experienced the entry of a SARS-CoV (SARS associated coronavirus) infected person in mid May, 2003. He traveled to western Japan for a vacation and was later confirmed to be suffering from SARS6). Fortunately, Japan with its highly concentrated population has so far not experienced a domestic spread of SARS.

One of the greatest concerns and questions, among Japanese experts as well as public, is why SARS epidemic or domestic transmission has not occurred in Japan. Recently, we proposed possible reasons, through the use of mathematical model, for why ‘the introduction of only a few cases into the communities in Japan can not easily lead to an epidemic7)’. Here we present further mathematical analysis centered on the impact of initial attack size on SARS epidemic in order to clarify the reason and to determine the optimal level of quarantine that can break the transmission cycle of SARS-CoV.

2. Materials and Methods

Here, we employ a mathematical model for SARS epidemic to determine properties of disease invasion, spread and persistence of the disease. The model is based on a simple modification of the Kermack & McKendrick epidemic model8). The new model is a *SEIR* (Susceptible–Exposed–Infectious–Recovered (or Dead) type model9)) and is described by a set of ordinal differential equations. Fig. 1 illustrates the simple flow diagram about our model. We incorporated the effects of quarantine and isolation into our model. It is assumed those who were quarantined and isolated would not contribute to the spread of SARS-CoV. Detailed descriptions of model structure and parameter assumptions are beyond the scope of this paper, and are given elsewhere7). The equations describing the new model is given by the following approximately parameterized set of differential equations:

$$\frac{dS}{dt} = -\zeta(q-\beta(q+\kappa-1))SI+\sigma T$$
$$\frac{dT}{dt} = (1-\beta)q\zeta SI-\sigma T$$
$$\frac{dEq}{dt} = \beta q(1-\kappa)\zeta SI-\phi Eq$$
$$\frac{dE}{dt} = \beta(1-q)(1-\kappa)\zeta SI-\phi E \qquad [1]$$
$$\frac{dQ}{dt} = \phi Eq-(\gamma_2+\delta)Q$$
$$\frac{dI}{dt} = \phi E-(\gamma_1+\delta)I$$
$$\frac{dIq}{dt} = \delta(I+Q)-\gamma_1 Iq$$
$$\frac{dR}{dt} = \gamma_1(I+Iq)+\gamma_2 Q$$

The basic reproductive number, R_0 is given by:

$$R_0 = \frac{1}{\delta+\gamma_1}\zeta\beta(1-q)(1-\kappa)N \quad [2]$$

Here, $1/(\delta+\gamma_1)$ is the mean duration of infectious period. $\zeta\beta$ represents the infection rate because ζ and β are the probability of transmission per contact and the daily number of contacts per capita, respectively. The fraction of those who undertook 100% effective precaution and those whose contacts were traced and removed would be described by κ and q respectively. Both κ and q are the function of precaution and quarantine. N is the size of the population in which the epidemic occurs.

The values of the biological variables for Japan will be assumed to be not much different from those for Hong Kong[10], although this is clearly a rough assumption. We have used the values given in the epidemiologic reports[11] and analyses[12][13] of the epidemics in Hong Kong in our analyses. Secondly, we have assumed that there is homogenous mixing among the infectious and susceptible, so that every infectious person would transmit the virus to exactly R_0 susceptible individuals within an infectious period. This means that the cases of "super-spreading" events (SSEs), those arising from individuals who generate much more than the average number of secondary cases, and which has been described as a rare heterogenous events[13][14], are not taken into consideration. This is done since the purpose of this report is to understand the role of initial attack size and interventions with the commonest transmission route as a possible scenario in Japan. The degree of quarantine is assumed to be 75%, the number for the epidemic occurring case in Hong Kong. This is a pessimistic values given that the Japanese government has traced approximately 2500 persons among 2600 suspected contacts. Further description of the principal parameters in the model and of their assigned value is presented elsewhere[7].

In this study, two important analyses are performed. First, simulations have been done using different basic reproductive numbers. We then perform a linear regression analyses to establish the linear correlation that can be approximated by a simple mathematical formula. Secondly, further mathematical analyses were carried out in order to investigate the role of initial attack size in SARS epidemic. The model has been programmed using Turbo Pascal Version 1.5 (Borland International Inc. Scotts Valley, CA, USA) working on Microsoft WindowsTM® platform. All data from the program were analyzed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA, USA) except regression analysis performed using Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

3. Results

Fig. 2 shows the model generated maximum number of newly infected generated over the time period examined for different values for R_0. Linear correlations between the initial attack size and the maximum number of infected are seen when the values of R_0 are less than 1 because of the level of public health interventions. Based on this finding, we propose that the coefficient of initial attack size could be represented as the function of basic reproductive number by:

$$(E(t)+Eq(t))_{max} = (\frac{R_0}{2}-0.167)I(0) \quad [3]$$

This result was found in the previous study[7]. It should

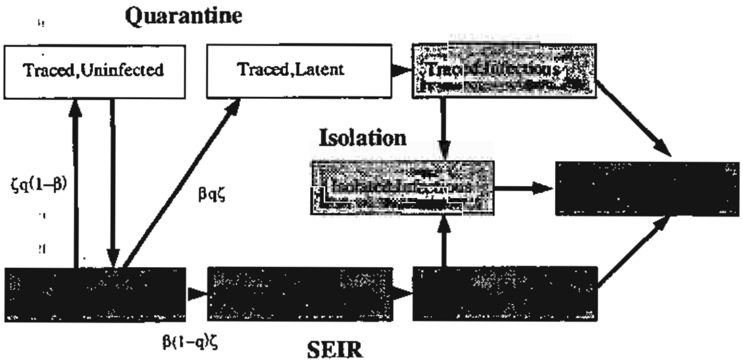

Figure 1. The transmission dynamics of the SARS taking into account the impact of precautionary measures and quarantine system. The new infection would be quarantined or not with a proportion *q*. A proportion, *κ*, of the potentially infected contacts is protected.

be noted that the simulations were done under the condition that the initial attack size is small compared to the susceptible population. When the susceptible population is small in comparison to the 'traced and uninfected' population, equations [1] can be simply described (for the purpose of analysis) to

$$\frac{dS}{dt} = -\zeta\beta(\kappa - 1)SI$$
$$\frac{dE}{dt} = \beta(1-q)(1-\kappa)\zeta SI - \phi E \quad [4]$$
$$\frac{dI}{dt} = \phi E - (\gamma_1 + \delta)I$$

According to analyses by Kendall who applied phase portrait into simple epidemic model[15], there should be an equilibrium point at which the number of susceptible at infinite time is given by

$$\lim_{t\to\infty} S(t) = S(+\infty) \quad [5]$$

and $I(t)$ and $E(t)$ are zero. The epidemic curve would always start at an unstable equilibrium point and end up at the stable equilibrium point described above. It can be shown that the function given by

$$V(S,E,I) = S^{\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}} e^{[(1-q)S+E+I]} \quad [6\text{-}1]$$

would be constant for every *S*, *E*, and *I* (see Appendix 1). *V* is called as Liapunov function that would always give us the constant solutions. Taking the time $t = t_{max}$, to be one at which

$$\frac{dE}{dt} = \frac{dI}{dt} = 0 \quad [6\text{-}2]$$

we can obtain E_{max} and I_{max}, the values of *E* and *I* at the peak of epidemic curve. The value of S_{max} is given by

$$S_{\max} = S(t_{\max}) = \frac{\gamma_1 + \delta}{\zeta\beta(1-\kappa)(1-q)} \quad [7]$$

S_{max} is often denoted as N_{cr}, a proportionality constant, whose inverse would be the sum of all the biological, social, and environmental aspects of transmission. Independent from the time after onset of epidemic, *V* would be constant due to equation [6]. Hence

$$V(S_{\max}, E_{\max}, I_{\max}) = V(S_0, E_0, I_0) \quad [8]$$

Performing a logarithmic manipulation in expression [8] gives

$$-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}\log S_0 + (1-q)S_0 + E_0 + I_0$$
$$= -\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}\log S_{\max} + (1-q)S_{\max} + E_{\max} + I_{\max} \quad [9]$$

Substituting E_{max} by I_{max} since $E_{\max} = \frac{\gamma_1+\delta}{\phi} I_{\max}$, we get

$$\left(\frac{\gamma_1+\delta}{\phi} + 1\right) I_{\max}$$
$$= (1-q)(S_0 - S_{\max}) + E_0 + I_0 + (1-q)S_{\max}\log\frac{S_{\max}}{S_0} \quad [10]$$

Therefore, I_{max} can be seen as being a function of initial attack size under the assumptions used in our model. Clearly, one could obtain the same result for the maximum number of infected, using an analysis similar to one given above.

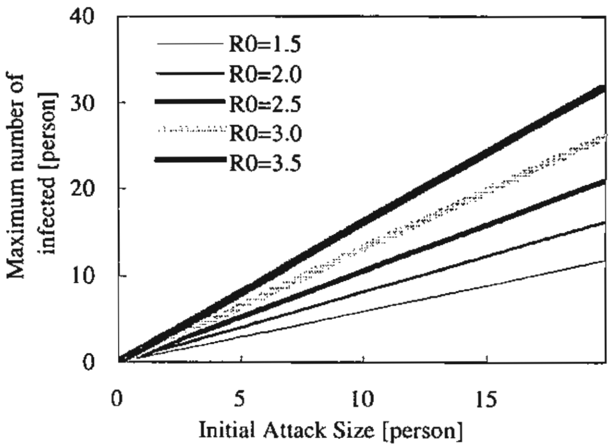

Figure 2. Maximum number of newly infected SARS cases according to different basic reproductive numbers, R_0. The linear correlation can be seen for whole values drawn here.

4. Discussion

It has been demonstrated that the maximum number of newly infected, or the crude size of epidemic, could be estimated on the basis on initial attack size in the presence or in the absence of any public health interventions. In this study, we provided both a mathematical analyses and numerical solutions of the equations describing the model. Our analysis shows that it would be possible to predict the fate of epidemic whenever SARS infected persons enter into any communities having approximately the same transmissibility and employing the same control strategy. In spite of the fact that our theoretical framework did not take into account stochastic effects and that conditions such as such as $I(0)N < 1$ does not exist in real situations, we obtained a simple formula which showed that the introduction of only a few cases into a given community would not necessarily lead to an epidemic. The fact that number of infected individuals entering into Japan is below the number to succeed invasion might be one of the reasons for Japan not experiencing the SARS epdemic so far. In addition, by taking into account the initial attack size and transmission potential of pathogen, the formula might be generalized for it to estimating the degree of quarantine required.

Homogenous mixing may not be a correct depiction of actual population interactions of SARS transmission. Although we are still presented with many unknowns including the role of SSEs, the small number of transmissions in most of the countries that experienced SARS occurrences suggests that the daily contact among the populace is not sufficient for transmission did not occur(16). For instance, an index case, not a SSEs, caused the epidemic in one hospital in Toronto(17). Secondly, the fact that 76% of the infections in Singapore were acquired in a health-care facility(14) points to the easy spread of SARS in only certain settings. Therefore, it is too optimistic to apply the assumption that every infected person will pass the disease to exactly R_0 susceptible individuals to the real world. It would be necessary to incorporate probability theory and contact patterns into the research since the epidemic threshold parameters are based on approximating the infection process during its initial stages as a branching process(18). It should be possible to apply network theory when it comes to the story of SARS, since the thesis of transmission dynamics on scale-free networks is well fitted to several epeidemiologic findings of SARS. Complex systems of transmission dynamics of SARS are not based upon random networks as has been thought for the last 40 years, but are governed by power laws, and that only a few hubs dominate the whole network(19). We must apply these thoughts by considering models, which are most realistic, as well as ones that include variance in reproductive number.

One approach to overcome the problem of risk management is to model the potential episodes with mathematical modeling. SARS is believed to recur in this winter because of the viral ecology(20). In order to prepare the possible recurrence of SARS, much more studies in ecological aspects are required as well.

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Appendix 1.

Let us look for a V that will always be a constant. We begin by considering the ordinary differential equation of V 0 ($\frac{dV}{dt}=0$). That is, we start by considering

$$\frac{dV}{dt}=\frac{\partial V}{\partial S}\frac{dS}{dt}+\frac{\partial V}{\partial E}\frac{dE}{dt}+\frac{\partial V}{\partial I}\frac{dI}{dt}$$

Here, each solution can be written as follows:

$$\frac{\partial V}{\partial S}\frac{dS}{dt}=-\beta\zeta(1-\kappa)SI\begin{bmatrix}-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}S^{-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}-1}e^{[(1-q)S+E+I]}\\+(1-q)S^{-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}}e^{[(1-q)S+E+I]}\end{bmatrix}$$

$$\frac{\partial V}{\partial E}\frac{dE}{dt}=S^{-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}}e^{[(1-q)S+E+I]}(\beta\zeta(1-\kappa)(1-q)SI-\phi E)$$

$$\frac{\partial V}{\partial I}\frac{dI}{dt}=S^{-\frac{\gamma_1+\delta}{\beta\zeta(1-\kappa)}}e^{[(1-q)S+E+I]}\left[\phi E-(\gamma_1+\delta)I\right]$$

Putting everything together, we have

$$\frac{dV}{dt}=0$$

This completes the proof.

INFECTION RISK TO TRAVELERS GOING TO DENGUE FEVER ENDEMIC REGIONS

by

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Abstract:

The risk of dengue virus infection to travelers visiting dengue fever endemic regions is studied through the use of mathematical modelling. A Susceptible-Infected-Recovered (SIR) model is used to describe the transmission of Dengue Fever (DF) in an endemic region into which tourists enter. The dynamics of a new class of humans, the travelers, is incorporated into the systems of first order differential equations in the SIR describing the dynamics of the transmission in the host region. Using standard dynamic analysis methods, the numbers of travelers who become infected with the dengue virus are calculated as a function of the length of time the tourist stays in the region.

Keywords: Disease Transmission, Dengue Fever, SIR Model, and Foreign Travel.

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I. Introduction.

Dengue fever (DF) is an illness that is characterized by a moderately high fever, extreme pain in and stiffness in the joints, a rash and a reduction in the white blood cells (Gubler 1998). These symptoms are caused by the toxins produced by one of the four serotypes of a virus belonging to the genus *Flavivirus*, in the family *Flaviviridae*. In many cases, the illness is asymptomatic and an infection can only be determined through serologic tests. It has been estimated that there are between 50 and 100 million cases of dengue fever (DF) a year. Some 40% of the world's population live in the endemic areas of this disease. Areas which are potential endemic region for this disease are those in which the transmitting vectors *Aedes aegypti* and *Ae. albopictuus* mosquitoes thrive and where the climate is right for the development of the virus. In 1990, almost 30% of the world population lived in regions where the risk of dengue transmission was greater than 50% (Hales *et al.*, 2002).

As air travel becomes less expensive, people from non-endemic countries in Europe and the United States are increasingly traveling to countries where the disease is endemic. The travelers (tourists) should be aware of the risk of dengue virus infection and so many governmental health organization (such as Center for Disease Control and Prevention (CDC), 2003) issue out travel warnings. Dengue infections are the second most common infections (after malaria) among travelers who go aboard (Schwartz *et al.*, 1996). Because there are no prophylaxis or vaccine against the dengue virus, the travelers to the dengue-endemic regions are at special risk. The only defense is not to be bitten by the mosquitoes. Awareness of the risk then becomes the best defense.

Recently there have been reports of increased number of travelers to Thailand who are being infected with the dengue virus. A special report issued by the surveillance net TropNetEurop (2002) point out that during 2002, 61.4% of the 68 reported cases (among German or Swiss tourists) had become infected while they were visiting Ko Phangan and Ko Samui, two islands in the Gulf of Thailand. During the previous three years, only 20.4%

of the imported dengue cases among this group of tourists originated in Thailand. In a study of Swedish tourists (Lindback *et al.*, 2003), 71% of the imported dengue cases during 1998-99 were infected in Thailand. A similar preponderance was seen among Israeli tourists during 1994-1995, i.e., 14/18 confirmed infections originated on the island of Ko-Pangan (Schwartz *et al.*, 1996). The average duration of the visits in these three studies was three to four weeks. A prospective study of Israeli travelers to tropical countries who stay a long time (at least three months) indicate that the incident rate of dengue infection for these travelers may be as high as 600 per 100,000 travelers (Potasman *et al.*, 1999).

To study the risk of travelers (tourists) becoming infected while they are visiting an endemic area, we have set up a mathematical model to describe the transmission of the dengue virus in a host population in which B numbers of travelers visit per unit time and stay for a length of time, τ_1. We are interested in this study on what the risk increases with the time spent in the endemic area. It is assumed that the conditions are such that the disease is endemic in the host population and that none of the travelers carry the virus when they enter into the country. In Section II. we introduce the mathematical model. The results of dynamical analyses of the system of equations are presented in Section III. In Section IV. we present the results of our numerical solutions of the equations and discuss their implications.

II. Mathematical Model.

To formulate a mathematical model for the transmission of dengue virus in the system of interest, we need to introduce different population groups. The time rate of change in the number of subjects in each group is equal to the number of subjects entering into the group minus the number leaving the group. For our system, we have two human populations, host and travelers, and one mosquito population. Each human population is divided into three classes, susceptible, infected and recovered, i.e., S'_h, I'_h and R'_h (S'_t, I'_t and R'_t), respectively. The mosquito population is divided into two classes, S'_v and I'_v. To see how the rate of change of the numbers in each population, let us consider in detail the rate of change of the number of susceptible travelers, i.e.,

$$\frac{dS'_t}{dt} = B - \frac{b\beta_h'}{N_T + c} S'_t I'_v - (\mu_h + (1/\tau_1))S_t' \tag{1}$$

where N_T is the total host population (taken to be constant); μ_h, the death rate (assumed to be the same for all categories); b, the biting rate of the mosquito; c, the total number of other animals which can also be bitten by the mosquito and β_h is the probability that the dengue virus will survive in the human after it is transmitted from the mosquito. The first term on the RHS is the number of travelers entering into the region. The next term is the number of travelers lost by them becoming infected. To get this term, we note that bI'_v is the total number of bites, which could transmit the virus. $S'_t/(N_T+c)$ is the fraction of the bites which are delivered to susceptible travelers and β_h is the probability that these virus transmitted by the bite survive in the human and begin to reproduce there. The next two terms are the losses due to natural death and to the traveler leaving the region. The other equations are obtained by similar considerations (Esteva and Vargas, 1998).

The number of equations we need to consider would be reduced to five if we assume that the total numbers of host, travelers and mosquitoes remain constant. It can be easily established the total number of travelers is $B/(\mu_h + (1/\tau_1))$ and the total mosquito population is A/μ_v, where A is the recruitment rate of the mosquitoes and μ_v is the death rate of the mosquitoes. Dividing S'_h, I'_h, and R'_h by N_T; S'_t, I'_t and R'_t by the total number of travelers and S'_v and I'_v by the total number of mosquitoes, we obtain the population densities and the conditions $S_h + I_h + R_h = 1$, $S_t + I_t + R_t = 1$ and $S_v + I_v = 1$. The differential equations for the time rate of change of the population densities are

$$\frac{dS_t}{dt} = \mu_h + (1/\tau_1) - \gamma_h S_t I_v - (\mu_h + (1/\tau_1))S_t \tag{2a}$$

$$\frac{dS_h}{dt} = \lambda - \gamma_h S_h I_v - \mu_h S_h \quad , \qquad (2b)$$

$$\frac{dI_h}{dt} = \gamma_h S_h I_v - (\mu_h + r) I_h \quad , \qquad (2c)$$

$$\frac{dI_t}{dt} = \gamma_h S_t I_v - (\mu_h + (1/\tau_1) + r) I_t \qquad (2d)$$

and

$$\frac{dI_v}{dt} = \gamma_{v,h} S_v I_h + \gamma_{v,t} I_t - \mu_v I_v \qquad (2e)$$

with

$$\gamma_h = b\beta_h m \quad , \qquad (3a)$$

$$\gamma_{v,t} = b\beta_h m_o \quad , \qquad (3b)$$

and

$$\gamma_{v,h} = b\beta_v \qquad (3c)$$

where β_v is the probability that the virus after it is transmitted to the mosquito will survive; r, the rate at which the infected recover; m and m_o are the ratios between the total number of mosquitoes and total number of host humans and between the total number of travelers and total number of host humans. Eqn. (2a) is obtained by dividing eqn. (1) by $B/(\mu_h+)1/\tau_1))$, the total number of visitors. We have also assumed that $N_T >> B/(\mu_h+)1/\tau_1))$, i.e., the number of people permanently living in the area is greater than the number of visitors.

III. Analytical Results.

III.a Equilibrium States.

The equilibrium states are obtained by setting the RHS of eqns. (2a) to (2e) to zero. Doing this, we get two equilibrium states, the disease free state, $E_o = (1, 0, 1, 0, 0)$ and the endemic equilibrium state, $E_1 = (S_h^*, I_h^*, S_t^*, I_t^*, I_v^*)$ where

$$S_h{}^* = \frac{1}{1+\beta_1 I_v{}^*} \quad , \qquad (4a)$$

$$I_h{}^* = \frac{\beta_2 I_v{}^*}{1+\beta_1 I_v{}^*} \quad , \qquad (4b)$$

$$S_t{}^* = \frac{1}{1+\beta_3 I_v{}^*} \quad . \qquad (4c)$$

$$I_t{}^* = \frac{\beta_4 I_v{}^*}{1+\beta_3 I_v{}^*} \qquad (4d)$$

with $\beta_1 = \gamma_h/\mu_h$, $\beta_2 = \gamma_h/(\mu_h+r)$, $\beta_3 = \gamma_h/(\mu_h+(1/\tau_1))$, $\beta_4 = \gamma_h/(\mu_h+(1/\tau_1)+r)$ and $I_v{}^*$ is the positive solution of a quadratic equation obtained by substituting eqns. (4a) to (4d) into the RHS of eqn. (2e) and setting it equal to zero. The algebraic expression for $I_v{}^*$ is quite complicated and therefore will not be written down.

III.b Local Asymptotical Stability.

The local stability of an equilibrium state is determined from the Jacobian (gradient) matrix of the RHS of the set of differential equations evaluated at the equilibrium state. If all the eigenvalues (obtained by diagonalizing the Jacobian matrix) have negative real parts, then the equilibrium state in question is locally asymptotically stable. Performing the necessary calculations for the *disease free state*, we find that the characteristic equation is a product of three polynomials, two of order one and the remaining of order three. The eigenvalues given by the two polynomials of order one are negative. Using the Routh-Horwitz criterion (May, 1973) for the eigenvalues determined by a third order characteristic equation to have negative real parts, we find that the conditions would be satisfied if $R_{0,1} < 1$ and $R_{0,2} < 1$ where $R_{0,1}$ and $R_{0,2}$ are defined as

$$R_{0,1} = \frac{b^2\beta_v\beta_h m}{\mu_v(\mu_h + r)} \quad \text{and} \quad R_{0,2} = \frac{b^2\beta_v\beta_h m m_o}{\mu_v(\mu_h + r)(\mu_h + (1/\tau_1))} \qquad (5)$$

The disease free state will occur since the basic reproduction number $R_0 = R_{0,1} < 1$, and since $m_0 << 1$, the second condition will also be met. The disease free state will arise whenever the number of mosquitoes falls below $\mu_v(\mu_h + r)/b^2\beta_h\beta_v$.

The determination of the stability of the endemic state is more difficult. This is due to the fact that the Jacobian matrix evaluated at endemic equilibrium state E_1 is much more complicated than that for the disease free state. Diagonalizing this 5×5 matrix is quite difficult and so we have used the computer program MATHEMATICA™ to perform this task. The program yields a fifth order characteristic equation of the form

$$\lambda^5 + K_4\lambda^4 + K_3\lambda^3 + K_2\lambda^2 + K_1\lambda + K_0 = 0 \tag{6}$$

where the coefficients K_0, K_1, K_2, K_3 and K_4 are extremely complicated expressions. In some cases, they have up to 45 terms. The Routh-Hurwitz stability criterion for fifth orders polynomials to use to determine whether all the eigenvalues determined from eqn. (6) have negative real parts. Again, this is done by MATHEMATICA™. The program shows that the Routh-Hurwitz criterions are met when $R_{0,1} > 1$ and $R_{0,2} < 1$. The endemic equilibrium state $E_1 = (S_h^*, I_h^*, S_t^*, I_t^*, I_v^*)$ will therefore be locally asymptotically stable when these two conditions are met. In the next section, we show numerically that this is indeed true.

III. Numerical Results and Discussion.

In this paper, we are interested in the transmission of the dengue virus, not whether a person is sick or not. Therefore, we should only be interested in whether a person has immunity to the virus or not and whether the person is infectious or not. A susceptible person is one who is both not immune and not infectious. An infected person should be one who is infectious. This occurs only during the period of viremia which last for approximately three days. After that, the infected person still suffers from the presence of the toxins produced by the virus and is classified as still being sick. He has immunity to new infections during both stages of the illness. Once the toxin disappears, the person becomes well and is classified as being recovered. For dengue infection, he keeps his immunity after he has recovered. For the purpose of transmission, there is no difference between the infected person after the viremia stage and a recovered person (provided we do not consider the presence of more than one strain of the dengue virus) since both will have immunity to the virus and not be infectious. This means that the recovery rate r should be 1/3 per day.

The values of the other parameters used are: $\mu_h = 0.0000456$ per day, corresponding to a life expectancy of 70 years; $\mu_v = 0.071$ per day, corresponding to a mean life of 14 days: b = 0.33, one bite providing enough bloodmeal for three days; $\beta_h = 0.5$, $\beta_v = 0.75$, which are arbitrarily chosen; r = 0.33, the reciprocal of the viremia period. The length of stay is varied from one week to three months while the two ratios m and m_0 are adjusted to have $R_{0,1}$ and $R_{0,2}$ have the values for the endemic state to be locally asymptotically stable and were taken to be 0.17 and 0.0007. These values yielded a $R_{0,1}$ equal to 2.48 and $R_{0,2}$ less than one. This means that the trajectory of the solutions in phase space should be that of a stable spiral node. Numerically solving eqns. (2a) to (2e) and plotting I_h versus S_h for the case of $\tau_1 = 90$ days on Figure 1a, we do indeed see a stable spiral node. In Figure 1b, we plot the time development of the infected travelers for this case. In Figure 2, we plot the equilibrium values of the infected travelers as a function of τ_1. As we see, the incidence rates (proportional to I_t) increase (but not linearly) as the tourists stay longer in the endemic region. The risk appears to level off, as the tourists stay longer. This appears reasonable since the risk of infection to the tourists should approach the risk to the host population if they stay long enough

To see whether there is evidence for the risk to infection to increase with the duration of stay, we consider another group of travelers, U.S. soldiers. While not tourists, American military personnel have spent time in various dengue fever endemic regions around the world. They are ideal candidates for this type of determination since their medical care are well documented. They are taken to medical facilities almost as soon as they come down with a febrile illness. Among the 30,000 U.S. troops who participated in Operation Restore Hope in Somalia during 1992-1993, 59 out of 289 febrile cases were confirmed as being due to the dengue virus (Sharp *et al.*, 1996). The average length of time spent in Somalia before they become sick was four weeks. Given the number of troops, this indicates an incidence rate for dengue infection of 195 per 100,000 troops (visitors). In another operation, Operation Uphold Democracy, Haiti, 1994 (CDC, 1994), where 20,000 U.S. soldiers participated, the onset of the febrile illness among the soldiers showed a peak in the fourth week after the soldiers' arrival. 24 out of the 106 cases of febrile illness showed clinical symptoms of dengue fever. This gives an incidence rate of 120 per 100,000 troops (visitors). These incidence rates should be compared to those of the Israeli travelers (600 per 100,000 travelers) who stayed a much longer (three months vs. one month for the U.S. soldiers). Even though we have not given the values of basic reproduction rates for the different endemic regions that the visitors went to so that real comparisons can be made, it does appear that the incidence of dengue fever increases as the travelers (visitors) extend their stays in an epidemic area in keeping with our predictions.

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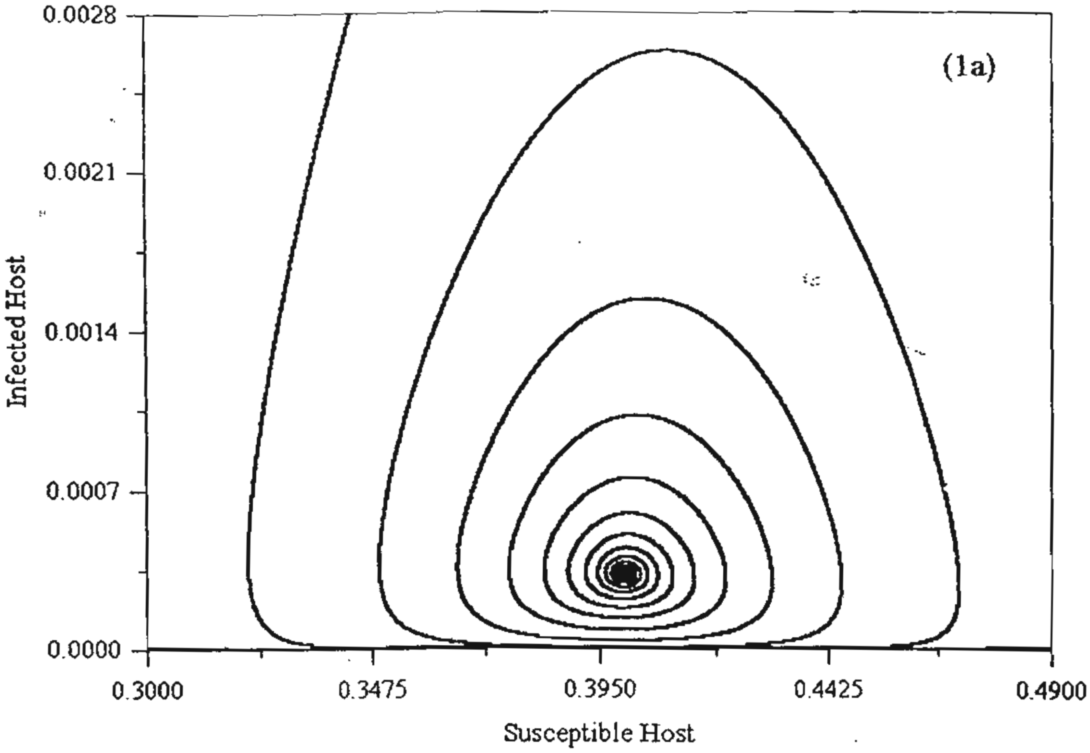
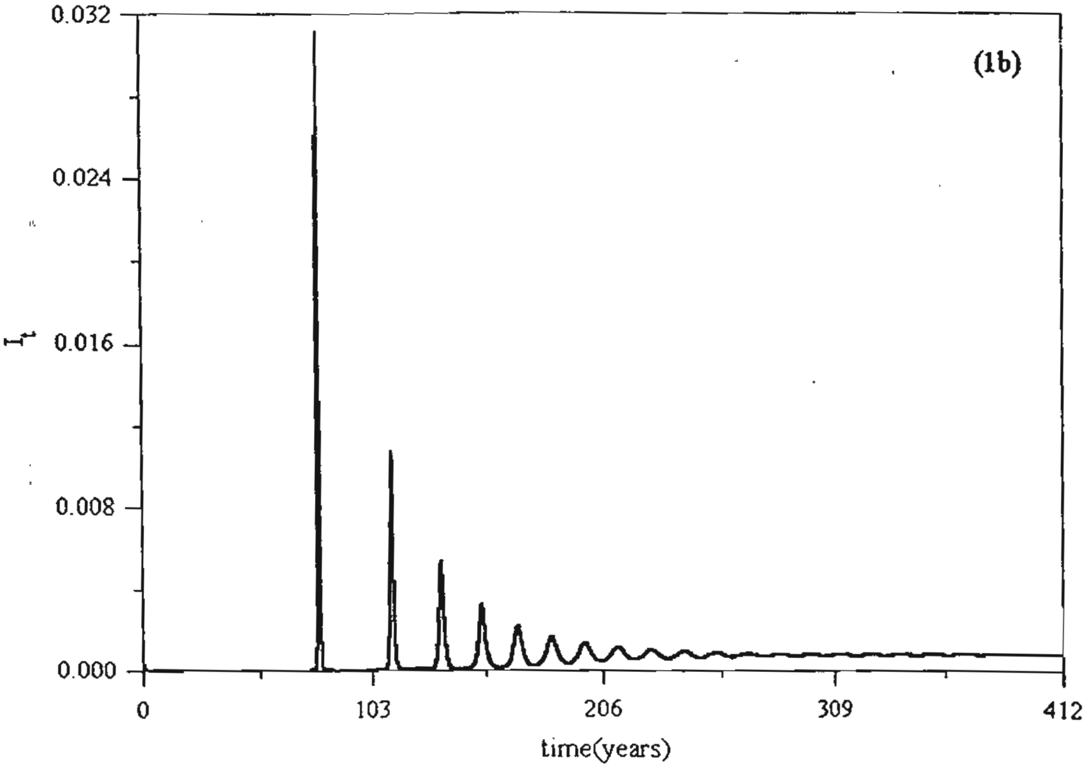
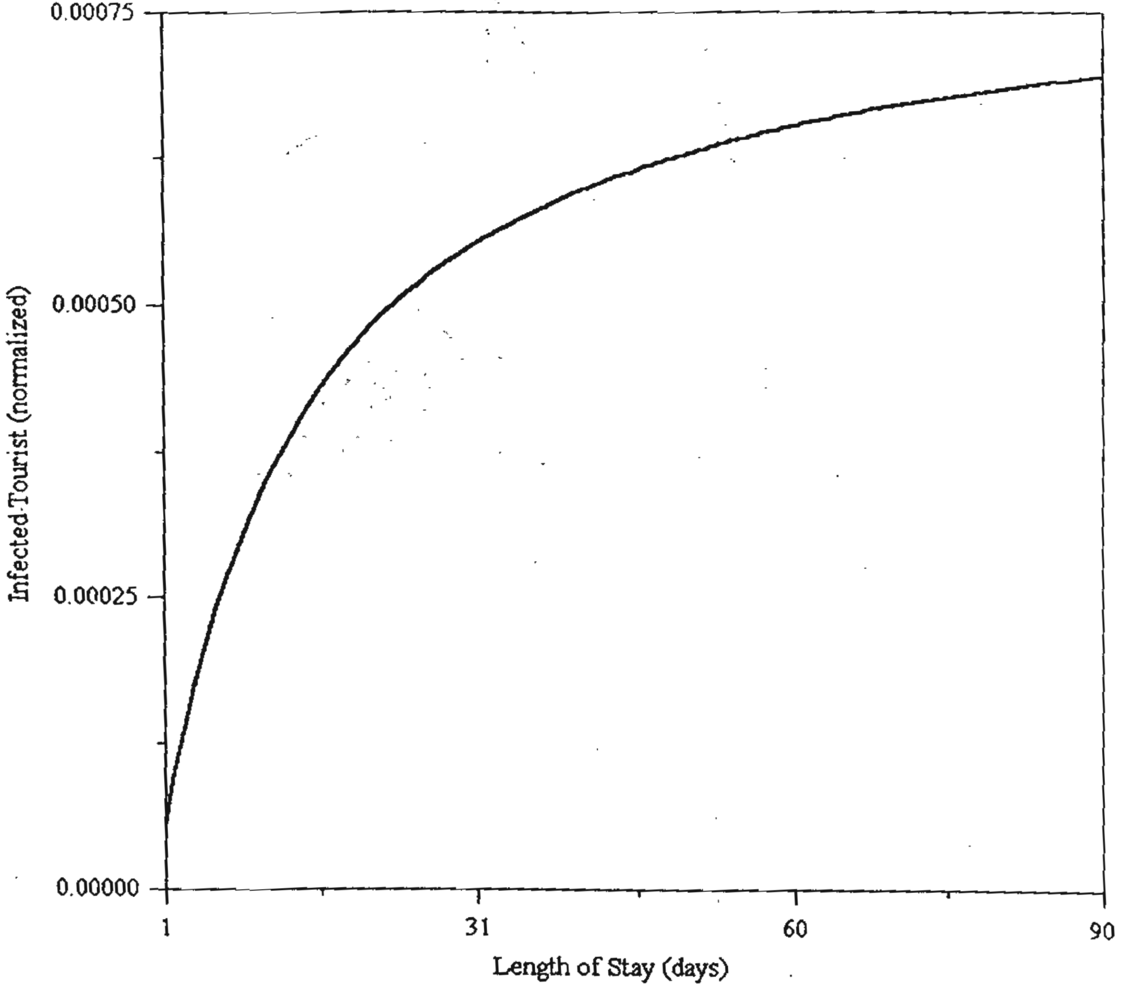
Figure Caption.

Figure 1. **Numerical Solutions of Eqns. (2a) to (2e).** (1a) Phase space trajectory of I_h - S_h for the case of τ_1 = 90 days. (1b) Time development of the infected travelers for this case. Values of other parameters given in the text.

Figure 2. **Equilibrium values of infected travelers population as a function of the time they stay in an endemic area..**


(1a)
0.0028
0.0021
0.0014
0.0007
0.0000
Infected Host
0.3000
0.3475
0.3950
0.4425
0.4900
Susceptible Host


(1b)
0.032
0.024
0.016
0.008
0.000
I_t
0
103
206
309
412
time(years)


0.00075
0.00050
0.00025
0.00000
Infected Tourist (normalized)
1
31
60
90
Length of Stay (days)

Effect of bird-to-bird transmission of the West Nile virus on the dynamics of the transmission of this disease

by

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Abstract. Two recent publications (Komar *et al*, 2003, and Glaser *et al*, 2003) report that direct bird-to-bird transmission of West Nile virus is possible. The effect of a bird-to-bird transmission on the transmission dynamics of this virus is studied through mathematical modeling. The model still treats the bird-to-mosquito-to-bird as the main transmission route. The results of numerical calculations show that there are changes in the dynamics of the transmission of West Nile fever in humans when the non-mosquito transmission route becomes more important.

(Keywords: West Nile virus, disease transmission, mathematical modeling, atypical transmission route)

running title: Bird-to-bird transmission of the WN virus

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Abstract. Two recent publications (Komar *et al*, 2003, and Glaser *et al*, 2003) report that direct bird-to-bird transmission of West Nile virus is possible. The effect of a bird-to-bird transmission on the transmission dynamics of this virus is studied through mathematical modeling. The model still treats the bird-to-mosquito-to-bird as the main transmission route. The results of numerical calculations show that there are changes in the dynamics of the transmission of West Nile fever in humans when the non-mosquito transmission route becomes more important.

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Introduction

The spread of diseases knows no international borders, witness the recent spread of severe acute respiratory syndrome (SARS) (WHO, 2003) and West Nile fever (WNF) (CDC, 2003). The first was spread by the international travel of infected persons from Hong Kong, while the second is believed to be spread by the migration of birds. WNF has been of particular concern to the American public health community because the disease, as was pointed out at the 69th annual meeting of the American Mosquito Control Association (Minnaepolis, and Minn, 2003), is a foretaste of possible newly emerging diseases that can be brought into the USA. Unlike SARS where the spread of the disease to uninfected countries can be controlled by the strict quarantine of the persons exposed to the SARS virus, the WN virus is spread to uninfected areas by the migration of birds (Rappole *et al*, 2000) that can not be controlled.

The spread of WN virus to the Western Hemisphere was preceded by its appearance in Romania in 1996-97. Hubalek and Halouzka, (1999) warned of the possible appearance of WNF epidemics in the temperate countries of Western Europe in the years following the Romanian outbreak. Instead, the migration of birds brought the epidemic to New York City (Bernard *et al*, 2000). From there, it spread to the rest of the Americas (again through the migration of birds' (Rappole *et al*, 2000)). Any regions in the world having the right conditions and are along the flight patterns of the migration of particular birds become candidates for future WNF epidemics. WNF is therefore a potential public health threat to Asia since one of the major bird migration paths in the world is along the West Coast of North America, over the Bering Sea and into North-eastern Asia. The case-fatality rate of this disease has been reported to be as high as 10% in some regions (CDC, 20003; Hubalek and Halouzka, 1999) of the World, which have experienced the epidemic. WNF would therefore be of a great threat to countries that do not have a well-developed public health infrastructure. Also in countries having warmer climates, the transmission of West Nile virus can be year round (CDC, 2003).

A full understanding of the transmission dynamics of the WN virus is still being developed. In 2002, it was reported that human-to-human transmission of the WN virus was possible by 1) blood transfusion, 2) organ transplantation, 3) transplacental transfer, and 4) breast-feeding. Very recently, WN viral infection among turkey farm workers was reported (Glaser *et al*, 2003). Turkeys belong to one of the bird species that do not develop enough viremia to infect the mosquitoes that bite them. The authors suggested that the transmission was accomplished by some less typical routes, e g, exposure of broken skin or mucous to infected turkey feces or exposure to aerosolized infected turkey feces. The last route is believed to be the means by which the 280 people at the Amoy Gardens Apartment Complex in Hong Kong became infected with the SARS (WHO, 2003). Komar *et al*, (2003) have found WN virus in the feces of 71% of the 24 species of (infected) birds they studied and that the American Crow was one of them.

One of the best ways to study the effects of non-typical routes of infections or specific public heath measures is through mathematical modeling. During the early stages of the WNF epidemic in New York City, Thomas and Urena, (2001) introduced a mathematical model to describe the evolution of West Nile-like encephalitis in New York City. Their model was based on several assumptions, which have subsequently turned out to be wrong. This report is concerned with the effects of non-mosquito transmission (through inhalation of aerosolized

In the above, $S_{b(h)}$ is the density of the susceptible bird (human) population and $I_{b(m(h))}$is the density of the infected bird (mosquito(human)) population. We have assumed that the total populations of the three groups are constant and so $S_b + I_b + R_b = 1$, $S_m + I_m = 1$ and $S_h + I_h + R_h = 1$ (where R represents the density of the recovered in each group). The total bird population is denoted by N_b, which we take to be a constant. This occurs if we assume that the no additional deaths are caused disease. This is an approximation given that many dead birds are seen during the epidemic. d_b, μ_b and r_b are the rates at which the birds are introduced in the location, died of natural causes and recover from the virus, respectively. The birth rate, the death rate and the recovery rates of the human population are denoted as λ_h, μ_h and r_h. μ_m is the death rate of the mosquitoes. γ_b, γ_m and γ_h are the rates at which the WN virus is transmitted to a bird by a bite of the mosquito, is transmitted to a mosquito when it bites a bird and is transmitted to a human by a bite of the mosquito. Because the viremia in an infected human is not high enough for the virus to be transmitted to a susceptible mosquito, the transmission rate $r_{h\rightarrow m}$ is zero.

The factor

$$\left[\frac{aI_b}{b+I_b}\right] \qquad (2)$$

is a Holling type II response function. It goes to zero as $I_b \rightarrow 0$ and goes to a non-zero constant as I_b becomes large. Its presence means that the direction transmission of the WN virus only occurs when the density of the birds is large, i e, during the flocking of the birds. In normal situations, the birds are spread out and so the mosquitoes are needed in order to maintain the virus in the bird population. What determines whether the density is small or large is the constant b, whether $I_b < b$ or $> b$.

Results

Numerical Solutions

We have numerically solved eqns (1a) to (1e) for different values of a, a measure of the contribution of the bird-to-bird route to the transmission of the West Nile virus among the birds belonging the *Corvidae* family. B was chosen so that calculated density of birds varied from being a high density and a low density during different periods in the transmission cycle.

Table 1

Other parameters used in the calculations

Rate at which birds are introduced	d_b	1/2,920 days
Death rate of the birds	μ_b	”
Recovery rate of infected birds	r_b	1/3 days
Birth rate of humans	λ_h	1/21,900 days
Death rate of humans	μ_h	”
Recovery rate of infected humans	r_h	1/30 days
Death rates of mosquitoes	μ_m	1/25 days
Transmission probability from an infected mosquito to a bird	γ_b	0.95
Transmission probability from an infected bird to a mosquito	γ_m	0.0792
Transmission probability from an infected mosquito to a human	γ_h	0.275

In Figure 1, we show the trajectory of the human population densities in the I_h-I_b phase space for increasing contributions of the bird-to-bird route to the transmission of the West Nile virus. B is set to 0.001. The value of a is changed from 0 (Fig 1a) to 0.475 (Fig 1b), to 0.95 (Fig 1c) and to 1.9 (Fig 1d). Fig 1a, shows that the trajectory spirals into its equilibrium state. As the contribution of the bird-to-bird route begins to increase, Fig 1b shows that the trajectory is spiraling into a tight limit cycle. As the contribution is further increases, the trajectories exhibit more complicated limit cycles behavior (Fig 1c and 1d).

In Figure 2, we show the trajectories for the case b = 0.0025. The values of a are now; 0.475 (Fig 2a), 0.95 (Fig 2b), 1.9 (Fig 2c) and 2.85 (Fig 2d). Comparing Fig 1b and Fig 2a, we see for the same values of 'a' (measure of the contribution of the bird-to-bid route to the transmission dynamics, an increase in the parameter 'b' delays the transition of the trajectory into a limit cycle. As we mentioned before, 'b' is a parameter that determines at what density the new transmission route makes a difference to the dynamics of the spread of the disease.

Discussion

The present study shows that the presence of bird-to-bird transmission can play an important role in the transmission of West Nile Fever. Bird-to-bird transmission of WN virus has been shown to be possible when the density of birds (including some belonging to the *corvidae* family) is high. We have used a Holling type II response function to represent the existence of two contact rates for this route of infection. Our results indicate that a limit cycle trajectory can be prevented by keeping the density of the birds lower, which can be done by preventing the birds from flocking together before the beginning of the mosquito season.

Acknowledgements

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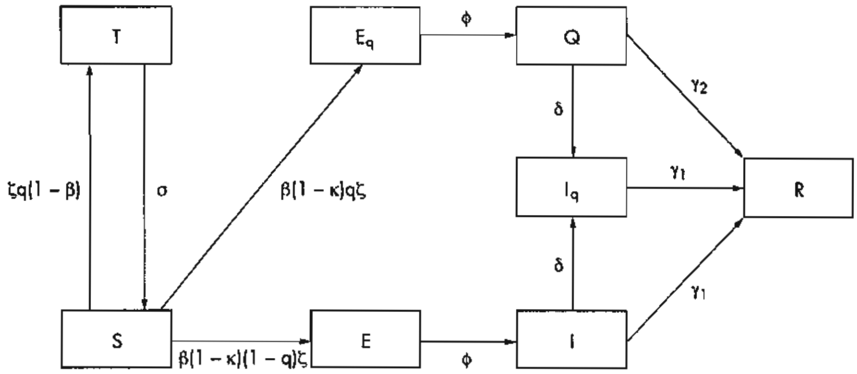

Figure 1 Transmission dynamics of the SARS taking into account the impact of precautionary measures and quarantine system. The subscript *q* denotes whether the new infections are quarantined or not with a proportion *q*. When 100% effective precautionary measures are implemented, a proportion, κ, of the potentially infected contacts is protected. *S* and *I* represent the proportion of the population susceptible and infectious; *E*, the proportion of untraced latent persons; *Eq* the proportion of traced latent contacts; *T*, the proportion of traced uninfected contacts; *Q* the proportion of infectious in quarantine; *Iq* the proportion of infectious isolated; *R* the proportion of recovered and death.

biological and intervention assumptions about the transmission dynamics of SARS (fig 1). An SARS-CoV infection of the susceptible population (S) results first in a non-infectious incubation period, which constitute the latency period (E). A proportion of the exposed persons, who had taken effective precautionary measures, would not be infected.[19] The others become infectious, often being symptomatic with fever followed by rapidly progressive respiratory compromise (these being labelled (I)) and, then slowly recover or die (R).[1] While infectious, they transmit the disease to susceptible persons at a rate dependent on the basic reproductive rate, R_0. Two of the public health interventions for interrupting the transmission are quarantining the people who are known to have been exposed and therefore may be infected but are not yet ill (denoted by the compartments T and E_q, which does each refer to "traced but not infected" and "traced and infected" in fig 1) and moving infectious people into isolation (I_q).[20] We assume each susceptible makes ζ contacts per day with the infectious person. Among the known contacts (in S), some would be infected with the probability of β per contacts (and enter into Eq) and $(1-\beta)$ remains uninfected (and enter into T). These processes can be modelled using an approximately parameterised set of differential equations(1) as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \zeta(q-\beta(q+\kappa-1))SI+\sigma T\\
\frac{dT}{dt} &= (1-\beta)q\zeta SI-\sigma T\\
\frac{dEq}{dt} &= \beta q(1-\kappa)\zeta SI-\phi E_q\\
\frac{dE}{dt} &= \beta(1-q)(1-\kappa)\zeta SI-\phi E\\
\frac{dQ}{dt} &= \phi Eq-(\gamma_2+\delta)Q\\
\frac{dI}{dt} &= \phi E-(\gamma_1+\delta)I\\
\frac{dIq}{dt} &= \delta(I+Q)-\gamma_1 I_q\\
\frac{dR}{dt} &= \gamma_1(I+Iq)+\gamma_2 Q
\end{aligned} \qquad (1)$$

Given that our model is based on the Kermack and McKendrick epidemic model,[21] the situation just before the entrance of infectious persons into the community is given by $(S(t),\ E(t),\ I(t),\ R(t))=(N,\ 0,\ 0,\ 0)$ and its subsequent development by:

$$\frac{dI(t)}{dt}=(\beta(1-q)(1-\kappa)\zeta N-(\gamma_1+\delta))I(t) \qquad (2)$$

where N is the size of the population in which the epidemic occurs. As the condition that SARS becomes possible to invade the community is $\beta(1-q)(1-\kappa)\zeta N-(\zeta+\gamma_1)>0$, the basic reproductive rate, R_0, is given by:

$$R_0=\frac{\beta(1-q)(1-\kappa)\zeta N}{\delta+\gamma_1} \qquad (3)$$

A description of the other principal parameters in the model and of their assigned value is presented below.

Parameter values

Table 1 contains the parameter values for our base case. Assuming that the biological variables for Japan do not differ much from those of Hong Kong because of similar population densities and lifestyles (this clearly being a rough assumption), we use the values given in the epidemic modelling of Hong Kong[14] for those parameters whose values are not available for Japan. The infection rate β ζ is chosen so that $R_0=3$, which is the mean value on the order of 2 to 4 estimated in the previous studies done in similar ways.[14 15 22] We assume that the pattern of contact is linearly related to the population size so that ζ N denotes the daily number of contacts in the population. We varied R_0 while doing sensitivity analyses with regards to q and κ. We assume that an attack of 10 initial cases entered into a population of 287 000 persons, supposedly Shinjuku, Tokyo, as our baseline case but vary the attack size between 0 and 20 cases in our sensitivity analysis. It is somewhat unrealistic to expect that the population at risk would be at the national or prefectural level as it would not be possible to have 100% of this population come into possible direct or indirect contact with the disease within the short time period of concern. We have instead considered the epidemic within a city or ward sized population level, such as Shinjuku. Here, Shinjuku is assumed because of its similar population density to Hong Kong in addition to its population size.

We first estimate the number of newly infected (secondary) cases that results in a failed invasion in certain community for different initial attack size. We defined "failed invasion" as there being no secondary cases within incubation period after contacts with infectious people. We then performed a linear regression analysis to establish the linear correlation using a simple mathematical formula.

Table 1 Parameter values for transmission dynamics of SARS in Japan

Parameters	Description	Baseline values	Reference
β_s	the probability of transmission per contacts	0.0666667 person/day	14
q	the daily rate at which latent individuals are traced	0.75	14, see text
κ	the proportion of exposed person who performed effective precaution	0	See text
ϕ	the average rate at which latent individuals become infectious	0.2/day	27
σ	the rate at which the traced uninfected contacts released into the community	0.2/day	29
ζ	the daily number of contacts per capita	9/person/day	14
δ	the mean daily rate at which infectious cases are isolated	0.0333333/day	14
γ_1	the percapita rate for recovery and death	0.1666667/day	27
$(\gamma_2)^{-1}$	the mean duration for quarantine	10 days	29

Additional assumptions are that no transmission occurs from those people who are quarantined, isolated, dead, and recovered. As for the precautionary measures, we would like to point out that it may be too optimistic to assume that the measures are 100% effective so that there are no spreads of the disease among the people coming in contact with the infected. An analysis on the impact of isolation is not covered in this paper because it has already been well analysed.[14]

In this study, the total number of people in the population is taken to be constant during the epidemic. The background mortality rate is assumed to be negligible over the time periods examined. As the cases of "super-spread" events (SSEs), where a person may generate much more than the average number of secondary cases, has been described as a rare heterogeneous event,[8, 23] we did not take this mode of transmission into consideration as the known values R_0 for SARS were calculated with certain adjustments of the number of secondary infections in this phenomenon and our aim is not to estimate the exact value of the basic reproductive rate but to understand, as a possible scenario in Japan, the role of initial attack size and interventions for the commonest transmission route. We assume that there is homogenous mixing among the infectious and susceptible, so that every infected person will pass the disease to exactly R_0 susceptible persons simultaneously within an infectious period of $(\gamma_1)^{-1}$ days. Simulations were performed with a time step of 0.1 days. The model has been programmed using Turbo Pascal Version 1.5 (Borland International, Scotts Valley, CA, USA) working on Microsoft Windows platform. All data from the program were analysed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA, USA) except regression analysis performed using Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

RESULTS

The results of a simple scenario analysis show the probable dynamics of the SARS epidemics under different conditions (fig 2). The results in the analyses are given for up to 50 days after the onset of epidemic in the figure. It is unrealistic to estimate for longer time periods as one should not expect the health policy and control strategies as well as social reactions to remain static over longer periods. In figure 2A, four possible trajectories are shown for different initial attack sizes—that is, how many infectious persons were first introduced into a specific community having a susceptible population. The number of newly infected cases quickly rises, peaks, and then falls when more than five initial number of infectious ($I(0)N \geqslant 5$) are introduced while dramatic increase is not seen with one initial infectious ($I(0)N < 1$). Even though the control strategy remains the same, a more steep increase and more prolonged epidemic would be caused by bigger initial attack size. Figure 2B shows the model generated maximum number of newly infected as well as cumulative incidence over the time period examined. The maximum number of newly infected denotes the number of newly infected at the peak of the curve in figure 2A. It was found that there exists a linear correlation (coefficient of determination, $r^2 = 0.998$) between the maximum number and the initial attack size. The cumulative incidence, on the other hand, looks like a power two dependence on the initial attack size that is mathematically expected as the cumulative incidence is the area between the curves and x axis in figure 2A. From a regression analysis, the relation between

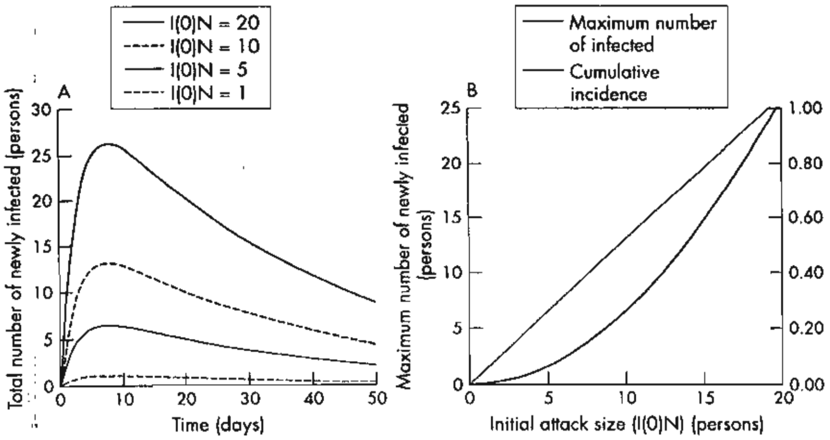

Figure 2 Dynamics of a SARS attack with the basic reproductive rate $R_0 = 3$. Effectiveness of the quarantine denoted by, $q = 0.75$, and of the precautionary measures, $\kappa = 0$. (A) Number of newly infected SARS cases according to initial number of infectious population. (B) Maximum number of newly infected SARS cases and the cumulative incidence as a function of the initial attack size (number of people initially infected).

the proportion of initial attack size ($I(0)$) and the proportion of maximum number of newly infected persons ($(E(t)+Eq(t))_{MAX}$) among total number of population, was found to be (under the assumptions leading to the epidemic)

$$(E(t) + Eq(t))_{MAX} = 1.295 \times 10^{-9} + 1.311I(0) \qquad (4)$$

where 1.295×10^{-9} and 1.311 are the regression coefficient of intercept and slope, respectively. Here, 1.295×10^{-9} can be ignored as it does not lead to a large affect even though it is multiplied by total population N. Performing regression analysis by varying R_0, the correlation was found to be represented by:

$$(E(t) + Eq(t))_{MAX} = \left(\frac{R_0}{2} - 0.167\right)I(0) \qquad (5)$$

when $R_0<1$ because of public health interventions ($r^2 = 0.977$). When we consider the maximum number of newly infected (denoted by m, where $m = N(E(t)+Eq(t))_{MAX}$), we found that it was possible to relate this value with R_0 and $I(0)$ through:

$$I(0)N = \frac{m}{\frac{R_0}{2} - 0.167} \qquad (6)$$

Next, we found the condition that would result in failed invasion (no secondary transmission) for each of the specific communities with population (N), is $m<1$ in equation (6). Based on this, theoretically, at least 0.750 persons infected with SARS must be introduced into the population to produce secondary cases in our baseline simulation.

Figure 3A shows the number of newly infected SARS cases for various values of κ (the proportion of susceptible people who have undertaken the precautionary public health measures) and when no quarantine was carried out. Four possible trajectories are shown. Less effective precautionary measures ($\kappa = 0.30$) lead to an exponential growth of SARS. Even with relatively high proportion of people undertaking precautionary measures ($\kappa = 0.60$), a gradual increase in the number of new SARS cases is seen. When effective precautionary measures are taken by a higher proportion of the susceptible persons, one sees qualitative reductions in the number of cases. This occurs even in the absence of quarantine. The effect of a quarantine system is shown by the linear correlation with R_0 in figure 3B. It is seen that in the absence of any precautionary measures, one needs to quarantine at least 66.7% of the susceptible people who had contacts into compartment Eq and T in order for the epidemic to die down. Other information can be gained from the formula of basic reproductive rate, by noting that by interchangeable variables and q in figures 3A and 3B, we would be looking at the effects of changing the values of q with no precautionary measures being taken. Hence, the condition to break the chain in person to person transmission of SARS can be described as:

$$(1 - q)(1 - \kappa) < \frac{1}{R_0} \qquad (7)$$

Key points

- Initial attack size is one of the determinants of whether SARS can successfully invade or not.
- It is seen that the introduction of only a few cases into certain communities would not lead easily to an epidemic.

This relation is shown in figure 3C. The curve shows the cut off points for R_0 to be 1. Figure 3D shows the changing pattern of R_0 for different combination of quarantine coverage and precautionary measure coverage in a three dimensional illustration. For the baseline simulation where $R_0 = 3$, the left form of equation (7) should be less than 0.33 in order to control SARS effectively.

DISCUSSION

Two important conclusions can be drawn from our analyses on the assessment of the role of initial attack size, and of the impact of interventions on possible SARS epidemic in Japan. Firstly, it is shown that the maximum number of newly infected, or the crude size of epidemic, could be roughly estimated based on initial attack size under certain public health interventions. In other words, it would be possible to predict the fate of an epidemic when SARS infected persons enter each community having approximately the same transmissibility and using the same control strategy. Secondly, the possible trajectories of a SARS epidemic depends on the levels of public health interventions as quarantine and precautionary measures greatly affect the transmissibility. There exist threshold levels of interventions to cause the SARS epidemic to settle down, and improved effective interventions can lead to dramatic decreases in its incidence.

Despite problems with the accuracy and uncertainty with the data released by WHO,[24] a simple dynamical model still gives reasonable simulations of the SARS dynamics. Except for the crucial parameter for the transmissibility, $\beta\ \zeta$, it was determined that the initial attack size is one of the most important factors to determine the course of the epidemic. It should be pointed out the cumulative incidence follows a power two law dependence on the initial attack size while the maximum number has a linear correlation with the size. Thus, a larger epidemic would be experienced if the initial attack size grows. The contribution of initial attack size to a SARS outbreak can be transliterated into equation (6). Although it is obtained within a theoretical framework based on certain assumptions without taking stochastic effect into account, and though the condition such as $I(0)N<1$ might not be practical in the real situation, we showed that the introduction of a few cases into a given community would not necessarily lead to an epidemic using this formula—that is, successful invasion is hard to be achieved with a few initial cases. It might be possible to say that the introduction of only a few infectious persons into Japan was one of the reasons for Japan not experiencing the SARS epidemic so far. Although the fate of epidemic is determined by threshold theorem,[21] that is, $R_0>1$ or not, successful or failed invasion itself can be considered using generalised formula such as ours under the condition when $R_0<1$. The formula could be reasonably applied to other countries.

One must be cautious about its application, however, because the formula is based on mathematical assumptions that might sometimes not be true. As each compartment, denotes the proportion of total population, it could give us the value of real number of persons to be smaller than 1. This may not be practical findings, but theoretically this notion becomes important in analyses such as ours. It should be also noted that it is based on several simple assumptions that may not be the same for all countries. The pattern of contacts between people differs from country to country.[25] Lipsitch *et al*

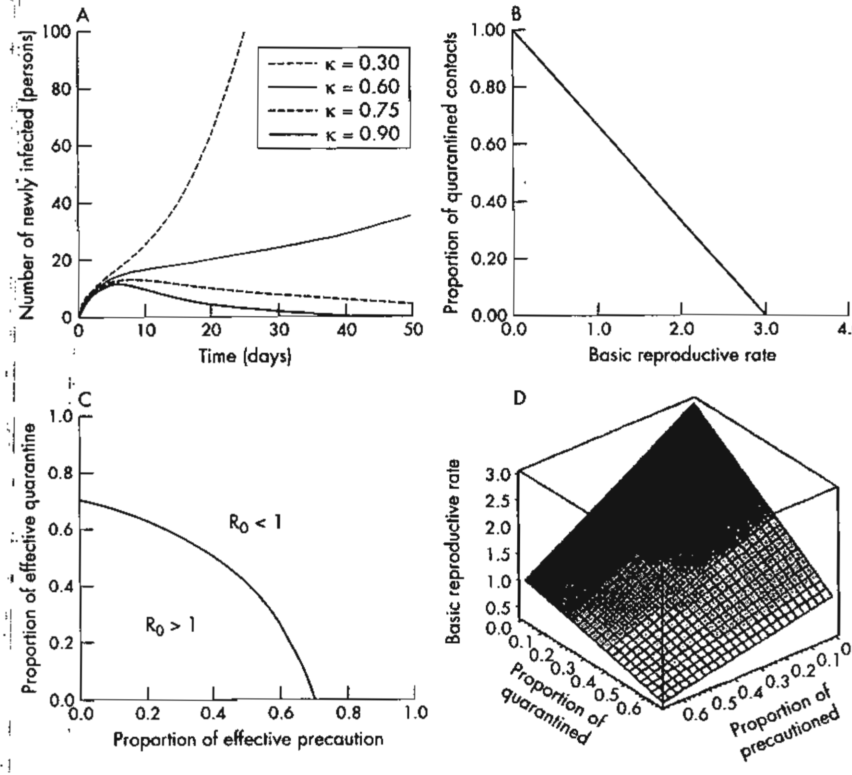

Figure 3 (A) Number of newly infected SARS cases for different proportion of susceptible persons who performed 100% effective precautionary measures for the case of $R_0=3$, and $q=0$. (B) and (C) Sensitivity analysis for model parameters whose values are unknown. Basic reproductive rate, R_0, versus (B) the proportion of quarantined contacts, (C) both the proportion of quarantined contacts and the proportion of exposed persons who took effective precautionary measures. (D) The necessary condition to have the basic reproduction ratio lower than 1 for different values of q and κ.

described an outbreak of SARS through the use of probability theory of non-extinction of a branching process.[14] Such a probability theory should be taken into account when it comes to describe the possibility of a SARS epidemic. It also should be noted that the size of the epidemic does not always depend on the initial attack size. This is clearly evident when we note that 76% of the infections in Singapore[21] were acquired in a healthcare facility. SARS can easily be spread by direct personal contact in the hospital setting.[26] As is well known, air borne transmission is not through the droplet nuclei but is instead through the large droplets, themselves. The wearing of a surgical mask[19] can stop this.

Another example of why the initial attack size may not be the important factor is seen in Hong Kong. There we see that clusters have played an important part in the course of the epidemic in that city.[27] The role of close and casual contacts[28] and the possibility of other routes of transmission such as through touching contaminated objects or other unknown way should be incorporated into the model.

There has been an intensive assessment of the different public health interventions that contributed substantially to the eventual curtailing of the epidemic in Hong Kong.[27] It is well known that an effective strategy requires aggressive public health measures in combination with stringent hospital infection control practices that meet the recommendations of World Health Organisation.[29 30] The SARS pandemic has shown that governments and public health officials need to consider the use of quarantine as a public health tool to prevent the spread of infectious diseases, particularly when other preventive interventions (for example, vaccines and antibiotics) are unavailable.[31] From our study, it is shown that either 100% effective precautionary measures or quarantine would lead to decline in the incidence. Both of them reduce R_0 in a linear way unlike the practice of isolation. The importance in the coverage should be therefore emphasised. Although recent studies with modelling[14 15] provided us with dynamics of SARS including transmissibility as well as the impact of quarantine and isolation, the role of precautionary steps was not taken into consideration. Precautionary measures themselves are quite important especially in hospital settings because a high proportion of the SARS patients were healthcare workers as was pointed out.[23 26]

Policy implications

- There exist threshold levels of interventions at which the SARS epidemic settles down.
- Two of the most effective policy procedures to prevent new infections would be to apply stringent precautionary measures and to impose quicker and more effective quarantine of the exposed populace.

The increased amount of world travel increases the likelihood of this disease spreading faster than past worldwide epidemics. It is therefore critically important to prepare for the possible introduction of SARS into the country by introducing specific public health measures now. Two of the most effective procedures would to introduce stringent precautionary measures and to impose better and quicker quarantine of those exposed. This would reduce the number of people who get a secondary infection from contacts with infectious persons. The important challenge is that some of the most important public health measures have to be taken outside the health sector.[32] These measures include maintenance in a healthy and hygienic environment such as penalties for spitting and closely monitoring the integrity of sewage disposal systems.[32 33] The government distributing free surgical masks and showing how they can be used effectively can overcome the strong fear among the general population about this disease. In addition to infection control measures, it should be noted that case detection, reporting, clear and timely dissemination of information would play important parts in the fight against SARS.[33]

Our study has several limitations, however. Firstly, one of the major problems, which the world must confront, is the absence of knowledge on SARS. In particular, it would be hard to predict the possible trajectories in Japan as the country has no experience with this epidemic. We believe that one approach to overcome the problem of risk management is to model the potential episodes with mathematical modelling. This study was conducted with only a few known parameter values. Although we used a single value of R_0 throughout an epidemic, R_0 is likely to decrease after the onset of an epidemic is detected and announced. The qualitative and quantitative patterns of diminishing R_0, because of behavioural change (that is, if people reduce the frequency of going out), should be incorporated in further studies. We here performed sensitivity analyses of R_0 for parameters whose values are not known. Secondly, we made a simple assumption that either the precautionary measures or the quarantine were perfectly effective (an optimistic assumption) or not. Thirdly, although possible outcomes were determined for a certain population sizes, for example, that of Shinjuku, Tokyo, one should not expect the same outcome for cities of the same size because of regional variances in the age distribution, behaviour, and contact pattern. Intercommunity transportation, migration, should also be taken into account. Further research is therefore necessary. It would be important to incorporate probability theory and contact patterns into the research as the epidemic threshold parameters should be considered based on approximating the infection process, during its initial stages, by a branching process.[34] The mathematical model might be modified so that the effects of changing staffing policy for the healthcare facilities could be simulated. Finally, incorporating quarantine of visitors from overseas might give us more practical simulation.

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Original Article

Modeling for a Smallpox-vaccination Policy against Possible Bioterrorism in Japan: The Impact of Long-lasting Vaccinal Immunity

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BACKGROUND: There has been concern that variola virus might be held clandestinely elsewhere. Through constructing mathematical model based on the detailed epidemiologic data, we focused on simulating the various possible scenarios arising from a bioterrorist attack whereby smallpox virus was introduced into Japan, and sought to develop the most effective way of nationwide vaccination policy based on the theory of residual immunity.

METHOD: The analysis is based on a deterministic mathematical model which predicted the epidemiologic outcome while simultaneously evaluating the effect of any specified control strategy of the smallpox epidemic. To clarify the required amount of vaccines, we performed mathematical analysis for hypothetical population to acquire herd immunity based on long-lasting vaccinal immunity.

RESULTS: It is demonstrated that the crude size of the potential epidemic could be greatly affected by possible level of residual immunity. The results also suggest the possibility to develop optimal distribution of nationwide vaccination according to the immune status. The prevalence at 50th day among population without immunity in our simulation would be approximately 405 times greater than expected population with residual immunity, and required amount of vaccines for equal distribution would be 3.13 times more than optimal distribution.

CONCLUSION: The mathematical model formulated could determine the vaccination priority based on the real status of immunity which required much less amount of vaccinations than would be calculated using an equal distribution program. It is therefore crucial to determine the real immunity status of the population via epidemiologic studies.

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Key words: smallpox; bioterrorism; models, mathematical; vaccination; immunity.

Bioterrorism is the intentional use of micro-organisms, or their products, to cause harm, and may be used to target humans, animals or crops.[1] Variola virus, which causes smallpox, is one of the most dangerous bioterrorism agents to be worried about. If used as a biological weapon, it poses a serious threat to the civilian populations because of its case fatality proportion of 30% or more among the unvaccinated persons and the absence of specific therapy.[2] Furthermore, because the World Health Organization (WHO) announced the total eradication of the smallpox in 1979, routine vaccination gradually ceased worldwide,[3] leaving the younger age individuals today who have never been vaccinated, and are thus extremely susceptible to smallpox infection. There is concern that the virus might be held clandestinely and less securely elsewhere.[4] In the aftermath of the September 11 terrorist attacks in 2001, the United States, after receiving direct threats, began stockpiling 286 million doses of smallpox vaccine, and the Centers for Disease Control and Prevention (CDC) interim response plan calling for targeted vaccination and quarantine.[5] Disaster plans for managing a biological attack must be developed in detail and realistic training provided to ensure effective response to an actual terrorist event.[6]

Japan should not feel that it is exempt from the various terrorist threats. It has been said that if Japan were to become a key ally in a United States-led military campaign against terrorism in Asia,

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