INFECTION RISK TO TRAVELERS GOING TO DENGUE FEVER ENDEMIC REGIONS

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Abstract. The risk of dengue virus infection to travelers visiting dengue fever endemic regions was studied through the use of mathematical modeling. 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 human, the traveler, 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.

INTRODUCTION

Dengue fever (DF) is an illness that is characterized by a moderately high fever, extreme pain in and stiffness of 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 Flavividae. 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 endemic areas for this disease.

Areas which are potential endemic regions for this disease are those in which the transmitting vectors *Aedes aegypti* and *Ae. albopictus* mosquitos thrive and where the climate is right for the development of the virus. In 1990, almost 30% of the world's 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, so many governmental health organizations (such as Centers for Disease Control and Prevention (CDC, 2003) issue travel warnings. Dengue infection is the second most common infection (after malaria) among travelers who go aboard (Schwartz *et al*, 1996). Because there is no prophylaxis or vaccine against the dengue virus, travelers to dengue-endemic regions are at risk. The only defense is not to be bitten by the mosquitos. Awareness of the risk then becomes the best defense.

Recently there have been reports of increased numbers of travelers to Thailand who are being infected with the dengue virus. A special report issued by the surveillance net TropNetEurop (2002) pointed out that during 2002, 61.4% of the 68 reported cases (among German or Swiss tourists) had become infected while they were visiting Ko Pha-ngan or 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 1998-1999 were infected in Thailand. Similar findings were seen among Israeli tourists during 1994-1995, *ie*, 14/18 confirmed infections originated on the island of Ko Pha-ngan (Schwartz *et al*, 1996). The average duration of the visits in

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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 how 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 the country, we introduce the mathematical model and present the results of dynamical analysis of the system of equations we also present the results of our numerical solutions of the equations and discuss their implications.

MATERIALS AND METHODS

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 the group minus the number leaving the group. For our system, we have two human populations, hosts and travelers, and one mosquito population. Each human population is divided into three classes: susceptible, infected and recovered, *ie*, 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, *ie*,

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

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 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 the 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 hosts, travelers and mosquitos remain constant. It can be easily established that 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 mosquitos and μ_v is the death rate of the mosquitos. 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 mosquitos, 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

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

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

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

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

and

$$\frac{dI_v}{dt} = (\gamma_{v,h} I_h + \gamma_{v,t} I_t)(1 - I_v) - \mu_v I_v \quad (2e)$$

with

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

$$\gamma_{v,t} = b\beta_v m_o \tag{3b}$$

and

$$\gamma_{v,h} = b\beta_v \tag{3c}$$

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 mosquitos 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 $N_T >> B/(\mu_h+(1/\tau_1))$, *ie*, the number of people permanently living in the area is greater than the number of visitors.

RESULTS

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, $E_0 =(1, 0, 1, 0, 0)$ and the endemic equilibrium state, $E_1 = (S_h^*, I_h^*, S_t^*, I_t^*, I_v^*)$ where

$$S_h^* = \frac{1}{1 + \beta_1 I_v^*} \tag{4a}$$

$$I_h^* = \frac{\beta_2 I_v^*}{1 + \beta_1 I_v^*} \tag{4b}$$

$$S_t^* = \frac{1}{1 + \beta_3 I_v^*} \tag{4c}$$

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

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.

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-Hurwitz 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

$$R_{0,1} = \frac{b^2\beta_v\beta_h m}{\mu_v(\mu_h + r)} \text{ and } R_{0,2} = \frac{b^2\beta_v\beta_h m m_0}{\mu_v(\mu_h + r)\,(\mu_h + (1/\tau_1))} \tag{5}$$

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 mosquitos 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 5x5 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 order polynomials is used 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 criterion 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.

Numerical results

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: μ_h = 0.0000391 per day, corresponding to a life expectancy of 70 years; μ_v = 0.071 per day, corresponding to a mean life of 14 days: b = 0.33, one bite providing enough bloodmeal for three days; β_h = 0.5, β_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 1.45 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 τ_1 = 90 days on Fig 1a, we do indeed see a stable spiral node. In Fig 1b, we plot the time development of the infected travelers for this case. In Fig 2, we plot the equilibrium values of the infected travelers as a function of τ_1. As we see, the incidence

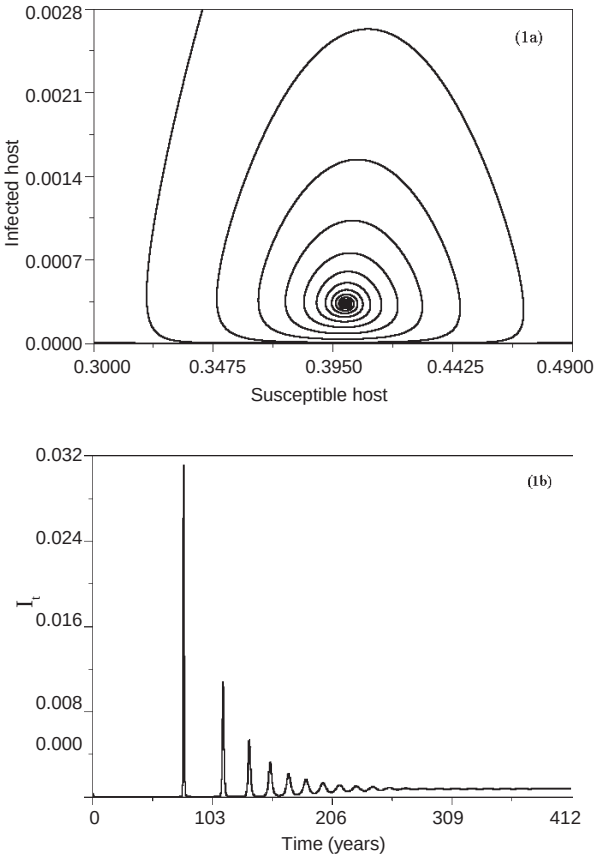

Fig 1–Numerical Solutions of Eqns. (2a) to (2e). (1a) Phase space trajectory of I_h - S_h for the case of τ_1 = 90 days. (1b) Time development of the infected travelers for this case. Values of other parameters given in the text.

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.

DISCUSSION

To see whether there is evidence for the risk to infection to increase with the duration of stay, we consider another group of travelers, US 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 is well documented. They are

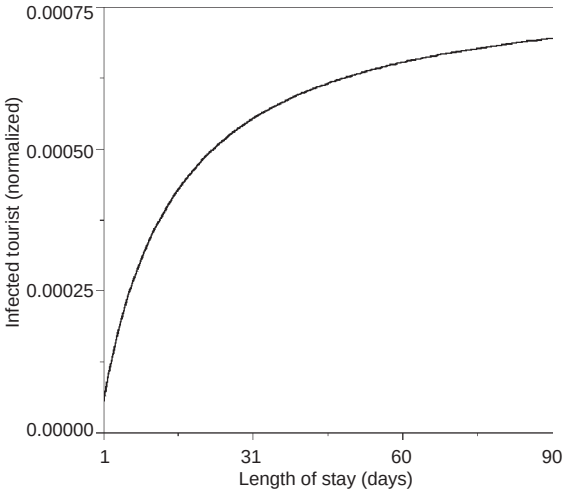

Fig 2–Equilibrium values of the infected traveler population as a function of the time they stay in an endemic area.

taken to medical facilities almost as soon as they come down with a febrile illness. Among the 30,000 US 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 US soldiers participated, the onset of the febrile illness among the soldiers showed a peak in the fourth week after the soldiers' arrival. Twenty-four 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 US 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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