A REALISTIC AGE STRUCTURED TRANSMISSION MODEL FOR DENGUE HEMORRHAGIC FEVER IN THAILAND

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Abstract. The influence of age structure in the susceptible class of the Susceptible-Infected Recovered (SIR) model used to describe the transmission of dengue hemorrhagic fever (DHF) was studied. This was done by first dividing all of the population classes into cohorts and then writing a set of coupled SIR equations for each cohort. The consequences of assuming different behavior of the transmission rates on the age structure in the DHF incidence rates were determined. In order for the predicted incidence rates to be similar to the DHF incidence patterns observed in several provinces in Thailand during the DHF epidemic in 1998, the transmission rates should be age dependent.

INTRODUCTION

Dengue hemorrhagic fever (DHF) is one of the emerging viral disease 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 disease of humans (Monath, 1994). It has been estimated that there are about 20 million cases a year, with approximately 24,000 deaths due to this disease. DHF has been progressively spreading from its primary location in major cities to the smaller cities and towns in the endemic countries. It has established into seasonal and cyclical epidemic patterns with large outbreaks every two to three years, the last outbreak in Thailand being in the year 1998.

The viruses of the genus *Togaviridae* subgenus *Flavirus* cause dengue fever (DF). Four distinct dengue viruses have been identified. The first infection normally produces life-long immunity to the infecting serotype, but only temporary and partial protection against the other three types. Dengue hemorrhagic fever is usually associated with a second infection in a person having pre-existing antibodies at a subneutalizing level (Gubler, 1986). The transmitting vectors are the *Aedes aegypti* Linnaeus, *An. alboptus* Skuse or *An. scultellaris* Walk mosquitos. The presence of some of these mosquitos in the Americas made it possible for dengue fever to become endemic in the New World (Pan American Health Organization, 1994). This occurred when travelers who were infected in Southeast Asia were bitten by one of these mosquitos upon their return. The mosquitos would become infected and under the right conditions, pass the dengue virus to the rest of the human population.

In the World Health Organization (1999) monograph, it is mentioned that in the absence of an effective vaccine against the dengue virus, the control and prevention of DF and DHF should center on the eradication of the transmitting vector. The eradication program would however have to be a continuing one. Using a susceptible-infected-recover (SIR) model to describe the transmission of dengue fever, Esteva and Vargas (1998, 1999) 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 amount of insecticides could reduce the value of R_o to below one. The value of R_o would return to

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the above one value once the application is stopped. In Thailand, a program to develop a tetravalent vaccine against all four strains has been undertaken (Bhamarapravati and Yoksan, 1993). At present, field trials of the vaccine are underway.

It is the purpose of this paper to report on a DHF transmission model, which includes an age structure in the human population. Feng and Velasco-Hernandez (1999) pointed to the need of a model that incorporates age structure into the dengue population dynamics. In the SIR models used by Esteva and Vargas (1998, 1999), no age structure was incorporated into their model. While the lack of an age structure may be appropriate for describing the 1981 DHF epidemic in Cuba (Guzman *et al*, 1990) and the 1997 DHF outbreak in Santiago de Cuba (Guzman *et al*, 2000), it is not appropriate for Thailand. Most DHF cases in Thailand occur in children less than 15 years old. In Fig 1, we show the age distribution of the incidence rates (determined from the Annual Epidemiological Surveillance Report of the Ministry of Public Health, Royal Thai Government) in three provinces during the 1998 DHF epidemic. To account for the age structure observed in the incidence rates in these three provinces, the transmission (infection) rates have to be age dependent.

MATHEMATICAL MODEL

An age structure can be easily incorporated into the SIR (susceptible-infected-recovered) model by placing a subscript 'i' onto the variables S, I and R *ie* S_i, I_i and R_i to denote the fact that the variables are for the humans in the age cohort 'i'. The variables S_i, I_i and R_i are the numbers in each cohort divided by the total human population. The time rate of change of the susceptibles in cohort 'i' ($i \neq 1$ or N (N being the number of cohorts)) is equal to the number of susceptibles entering into the cohort from the previous cohort minus the number becoming infected, the number aging into the next cohort and the number who died. The dynamics are therefore given by

$$dS_i/dt = \alpha S_{i-1} - \beta^H_i S_i I_v - (\alpha+\mu_h)S_i \quad \text{for } i=2,...,N-1 \quad (1)$$

where β^H_i is the transition rate for the virus to be transmitted to the human by the mosquitos; α, the rate at which one cohort ages into the next cohort; μ_h, the death rate of the human population and I_v is the number of infected mosquitos divided by the total num-

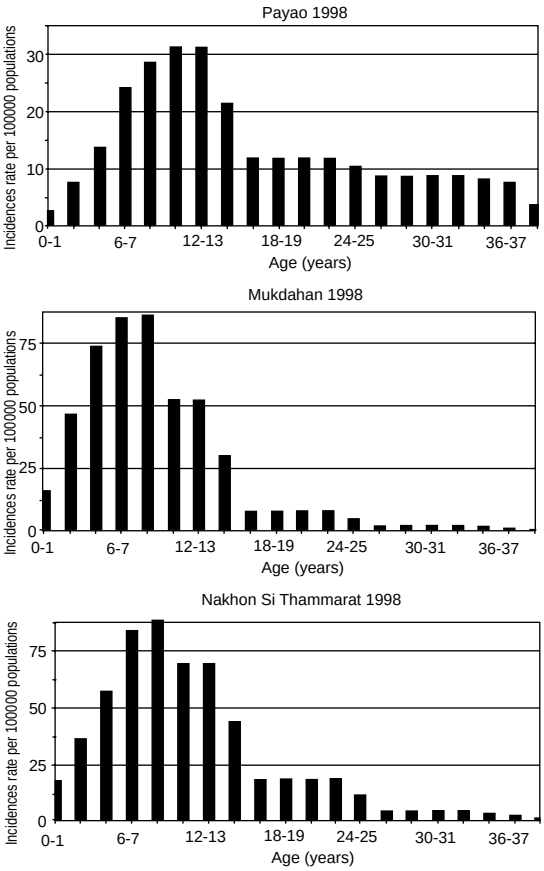

Fig 1–Incidence rates for the different age groups during the 1998 DHF epidemic in Payao, Mukdahan and Nakon Si Thammarat Provinces. The three provinces are located in northern, northeastern and southern parts of Thailand and had the highest incidence rates in their respective regions. The rates were determined by taking the number of DHF cases reported to the Ministry of Public Health, Royal Thai Government and dividing by the population of the province.

ber of mosquitos. The transition rate is given by (Esteva and Vargas, 1998).

$$\beta^H_i = b_i N_v \gamma_{H,i}/(N_T+m) \quad (2)$$

where b_i is the biting rate of the mosquito; N_v, the total number of mosquitos at equilibrium; $\gamma_{H,i}$, the efficacy of the uptake of the virus by the susceptibles in the cohort 'i' from the mosquito; N_T, the total human population and m is the total number of animals which the mosquito might bite. The equations for i = 1 and N are

$$dS_1/dt = \lambda - \beta^H_1 S_1 I_v - (\alpha+\mu_h)S_1 \quad (3)$$

and

$$dS_N/dt = \alpha S_{N-1} - \beta^H_N S_N I_v - \mu_h S_N \quad (4)$$

where λ is the birth rate of the human population (and is equal to μ_h for a constant human population). The dynamics of the infected and recovered cohorts are obtained by similar arguments.

Adding together the N equations for S_i, *ie* equations (1), (3) and (4), we get

$$dS_T/dt = \lambda - <\beta^H> S_T I_v - \mu_h S_T \quad (5)$$

Doing the same with the N (unwritten) equations for the infected cohorts I_i and with the N (unwritten) equations for the recovered cohorts, we get

$$dI_T/dt = <\beta^H> S_T I_v - (r+\mu_h) I_T \quad (6)$$

and

$$dR_T/dt = rI_T - \mu_h I_T \quad (7)$$

where the subscript T now denotes that the variable is for the total population within each class; r, the rate at which an infected person recovers and $<\beta^H>$, the weighted average defined as $<\beta^H> = \sum \beta^H_i S_i/S_T$. Equations (5) to (7) are similar to the ones used by Esteva and Vargas (1998). From these equations we find two equilibrium states; the disease free state, $E_o = (1, 0, 0)$ and the endemic state, $E_1 = (S^o, I^o, I_V)$ where

$$S^o = (\beta + M)/(R_o M + \beta), \quad I^o = (R_o - 1)/(R_o M + \beta) \quad (8a)$$

and

$$I_V = \beta(R_o - 1)/R_o(M + \beta) \quad (8b)$$

with

$$\beta = b\beta_v N_T/\mu_v(N_T + m), \quad M = (r + \mu_h)/\mu_h$$
$$R_o = b^2<\beta^H> \beta_v N_T(A/\mu_v)/(N_T + m)^2 \mu_v(r + \mu_h) \quad (9)$$

and β_v being the efficiency of the transmission of the dengue virus to the mosquito from the human.

Esteva and Vargas (1998) have discussed the local and global stability's of the disease free state and of the endemic state. They showed that if $R_o > 1$,the endemic state would be the fate of the population. However, if R_o could be made to be less than one, the population would enter into the disease free state. The 1997 World Health Organization monograph mentions that through a program of slum clearance and resettlements, Singapore was able to reduce the *Aedes* house infestation from 27.2 % in 1966 to 1.6 % in 1981, thus lowering the value of R_o and reducing the incidence of dengue infection. Looking at the definition of R_o, we see that there are other ways to lower value of R_o such as lowering the weighted average efficacy $<\beta^H>$ or changing the biting rate. The last method (accomplished through the use of insecticide impregnated mosquito nets) has been successfully used to lower the malaria incidence rates in several countries (Richard *et al*, 1993).

DISCUSSION

The differences in the age distribution of the incidence rates in Cuba and in Thailand may be due to the fact that the epidemic in Cuba was in a "virgin" population (one in which there was no prior exposure to the virus). A similar distribution is seen in the measles epidemic in southern Greenland in 1951 (Christensen *et al*, 1953). There, we do not see any age dependence in the incidence rates. Once a disease becomes endemic, an age specific pattern appears in the incidence rates (Anderson and May, 1985). The age structure of the incidence rates at the equilibrium state E_1, can be determined by setting

the time rates of change of all the different cohorts (the RHS of eqns. (1), (3), (4) and the equivalent equations for the infected and recovered cohorts) to zero. Solving for S_i and I_i, we get

$$S_i = \frac{\alpha}{\beta^H{}_i I_v + \alpha + \lambda} S_{i-1} \qquad (10a)$$

with

$$S_1 = \frac{\lambda}{\beta^H{}_1 I_V + \alpha + \lambda} \qquad (10b)$$

and

$$I_i = \frac{\alpha}{\alpha + r + \mu_h} I_{I-1} + \frac{\beta^H{}_1 I_V}{\alpha + r + \mu_h} S_i \qquad (11a)$$

with

$$I_1 = \frac{\beta^H{}_1 I_V}{\alpha + r + \mu_h} S_1 \qquad (11b)$$

We first see what the pattern would be if the transmission rates are the same for all age groups. The curves shown in Fig 2 are for three values of $\beta^H{}_i I_V$ (c in the figure). The numerical values of the other parameters are μ_h^{-1} = 70 yrs, α^{-1} = 2 years and r^{-1} = 14 days. As is seen, the incidence rates for the case of constant transmission rates decrease almost exponentially and are not similar to the patterns seen in Fig 1.

Next, we attempted to fit the incidence rates observed in Fig 1 to equations (10a) to (11b) by varying the values of $\beta^H{}_i$. Doing this, we obtain the values of $\beta^H{}_i$ shown in Fig 3. The values of the other parameters are the same as those used to obtain the curves shown in Fig 2. The shapes of the age dependence of the transmission rates of DHF in the three provinces are similar, *ie* they exhibit an initially sharp increase, followed by a drop back to a lower (constant) value and then a further drop. Similar age specificity in the force of infection was needed to model the age distribution of measles in Baltimore, USA, between 1906 and 1915 (Grenfell and Anderson, 1985).

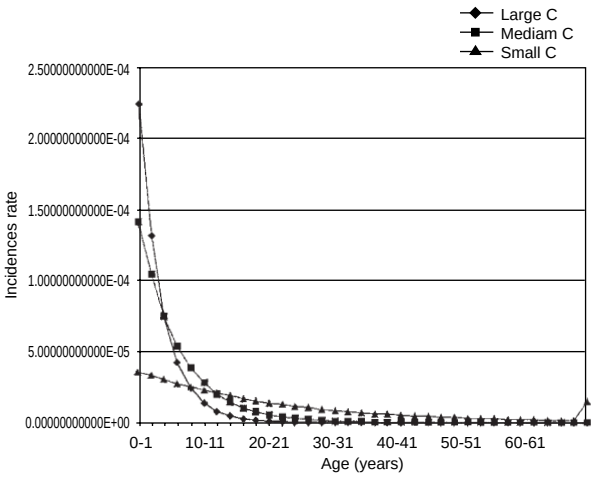

Fig 2–Predicted incidence rates for the case of a constant transmission rate. The curves are the incidence rates predicted by eqns. (10a) to (11b) for three values of $\beta^H{}_i I_v$ (the three values used are c = 0.001, 0.0005 and 0.0001).

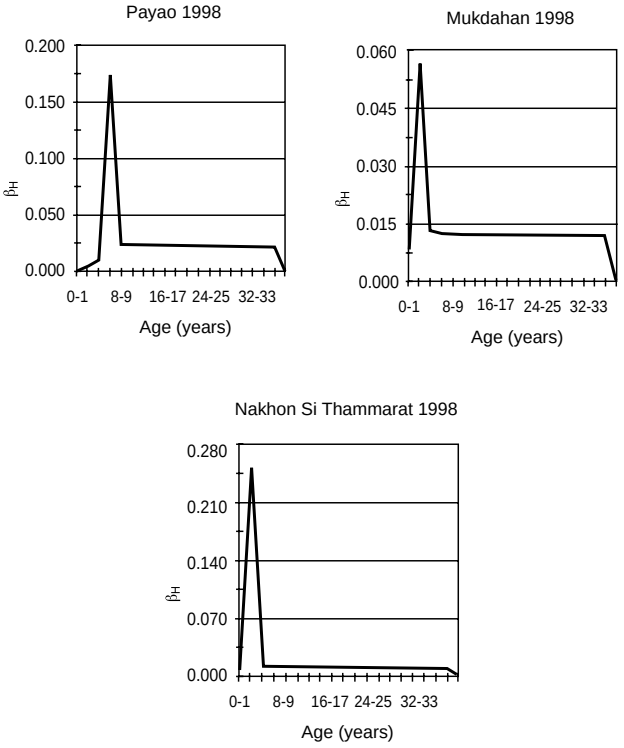

Fig 3–Age specificity of the transmission rates. The values of the transmission rates required for eqns. (10a) to (11b) to fit the incidence rates shown in Fig 1.

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