A COMPARISON OF THE AGE DISTRIBUTIONS IN THE DENGUE HEMORRHAGIC FEVER EPIDEMICS IN SANTIAGO DE CUBA (1997) AND THAILAND (1998)

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Abstract. The age profiles of the infected populations of two dengue hemorrhagic fever (DHF) epidemics, the 1997 epidemic, in Santiago de Cuba and the 1998 epidemic in Thailand, are compared. Using an age-structured model of disease transmission, the dependence of the forces of infection on age was determined for each epidemic. The difference in the behavior of the two epidemics and the role of primary and secondary infection in the development of DHF are discussed.

INTRODUCTION

Dengue hemorrhagic fever (DHF) is an emerging viral disease that is spreading throughout the tropics. Since its first appearance, in the Philippines in 1953, DHF has become the most important arthropod-borne viral disease of humans (WHO, 1997). It has been estimated that there are between 50 and 100 million cases of dengue fever (DF) a year; more than 250,000 annual cases of dengue hemorrhagic fever (DHF) result in some 10,000 infant deaths. Classic 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 (Gubler, 1998). DHF differs from DF: plasma leakage is seen in DHF. Both diseases are caused by one of four serotypes of the dengue virus, (DEN1, DEN2, DEN3, and DEN4) which belongs to the genus *Flavivirus*, family Flaviviridae.

Because two of the mosquito vectors, *Aedes aegypti* and *Aedes albopictus*, exist in the Americas, DF has become endemic in the New World (Pan American Health Organization, 1994). The first severe outbreak of DHF

in the Americas occurred in 1981 in Cuba (Guzman *et al,* 1990) and gave rise to 334,203 DF cases, 10,313 documented DHF cases, and 158 deaths. The serotype responsible for the epidemic was DEN2. An earlier epidemic of mild classic dengue fever, which occurred between 1977 and 1979, was caused by a different strain (DEN1). During this epidemic, the sera of 44.5% of a random sample of 2,000 people contained DEN1 virus antibodies (HI; hemagglutination inhibition). Strict infection control measures adopted after the 1981 epidemic lead to the disappearance of DHF from Cuba for the next sixteen years. A localized outbreak of DHF occurred in Santiago de Cuba in 1997 (Kouri *et al,* 1998; Guzman *et al,* 2000). The culprit was the DEN2 virus.

To get a better understanding of the transmission of this disease, we compared the DHF epidemic that occurred in Santiago de Cuba in 1997 with the one that occurred in Thailand in 1998. We were interested in the age distribution of those infected during the two epidemics. Most literature on DHF mentions that the disease affects mainly those under the age of 16; Guzman *et al* (1997) noted that almost no-one under the age of 17 became sick with DHF (Fig 1a). This is quite different from the age pattern seen in epidemics, which occur in countries in which the disease is fully established. Fig 1b shows the age distribution in

one province of Thailand during the 1998 epidemic (Ministry of Public Health, 1998).

MATERIALS AND METHODS

Before a discussion of the differences between the two distributions can be held, the age distribution of the forces of infection in the 1997 DHF epidemic in Santiago de Cuba must be determined. The force of the DHF infection in Thailand during the 1998 epidemic has already been established. Pongsumpun and Tang (2001) who showed that the percentage of infected people (I) in the i-th age cohort (I_i) is

$$I_i = \frac{\alpha}{\alpha+r+\mu_h} I_{i-1} + \frac{\beta^h i I_v}{\alpha+r+\mu_h} S_i$$

$$\text{for } i = 2,...N\text{-}1 \quad (i)$$

with

$$I_1 = \frac{\beta^h 1 I_v}{\alpha+r+\mu_h} S_1 \quad (ii)$$

$$S_i = \frac{\alpha}{\beta^h i I_v + \alpha + \lambda} S_{i-1} \quad (iii)$$

and

$$S_1 = \frac{\lambda}{\beta^h 1 I_v + \alpha + \lambda} \quad (iv)$$

In the above, β^h_i is the transition rate for the virus to be transmitted to humans by mosquitos (the force of infection); α is the rate at which one cohort age into the next; r is the recovery rate; λ is the birth rate; μ_h is the death rate of the human population; and I_v is the number of infected mosquitos divided by their total number.

RESULTS AND DISCUSSION

The forces of the DHF infections can be determined by fitting the incidence rates given in Fig 1a to equations (i) to (iv) by varying the values of β^h_i: this yields the values of β^h_i that are shown in Fig 2. The behaviors of the forces of infection in the two epidemics look the same, *ie*, an initial increase followed by a drop to a nearly constant force of infection, except that the initial increase is shifted 16 years in the case of the Santiago de Cuba epidemic.

To understand why this happens and why the age distributions shown in Figs 1a and 1b are as they are, two theories of the pathogenesis of dengue hemorrhagic fever must be considered. The first, more commonly accepted theory, is the immune enhancement or secondary-infection hypothesis (Halstead, 1988). According to this hypothesis, the pre-existing heterologous dengue antibody in an infected person recognizes a novel dengue virus and forms an antigen-antibody complex, which then bonds the virus to the membrane of a leukocyte. Because the antibody is heterologous, the virus is not neutralized and remains free to replicate inside the leukocyte. These infected cells then produce and secrete vasoactive mediators in response to the infection; these mediators cause an increase in vascular permeability, leading to hypovolemia and shock.

In the second theory, the dengue virus mutates as it replicates in the human and/or the mosquito. Some of these mutations lead to more virulent viruses: these viruses causing DHF. Because a pre-existing antibody is implicated in the first theory, the infection causing DHF must be a secondary one. In the second theory, no pre-existing antibody is required: primary dengue infection can cause DHF.

If the secondary-infection hypothesis is correct, the paucity of DHF-infected children in the 1997 epidemic in Cuba is under stand able: no-one under the age of 16 would have had pre-existing dengue virus antibodies in his blood because he would have been born after the 1981 epidemic. Of the individuals under the age of 16 years who were tested for dengue antibodies in Santiago de Cuba, only 2% had
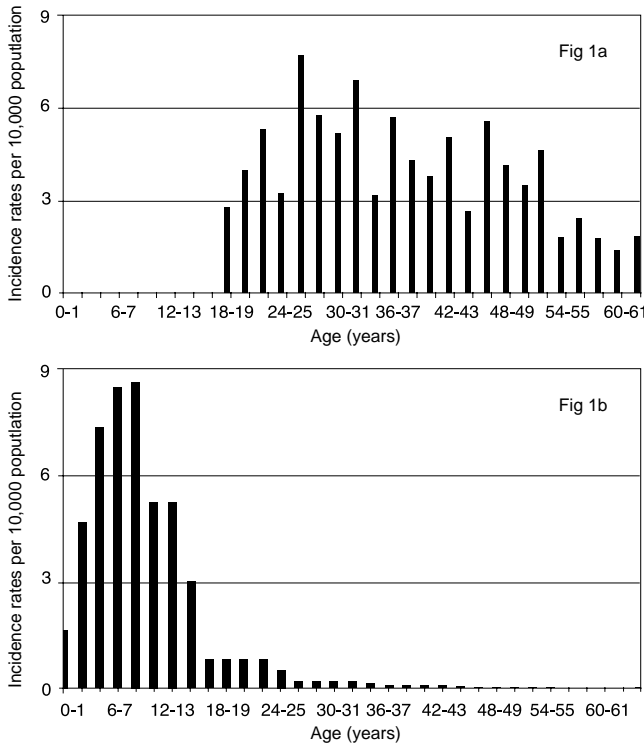
Fig 1–Age distribution of dengue hemorrhagic fever. (1a) Age distribution of the 1997 epidemic in Santiago de Cuba. (Data from Guzman *et al,* 2000). (1b) Age distribution of the 1998 epidemic in Mukdahan Province, Thailand (Data from Ministry of Public Health, 1998).
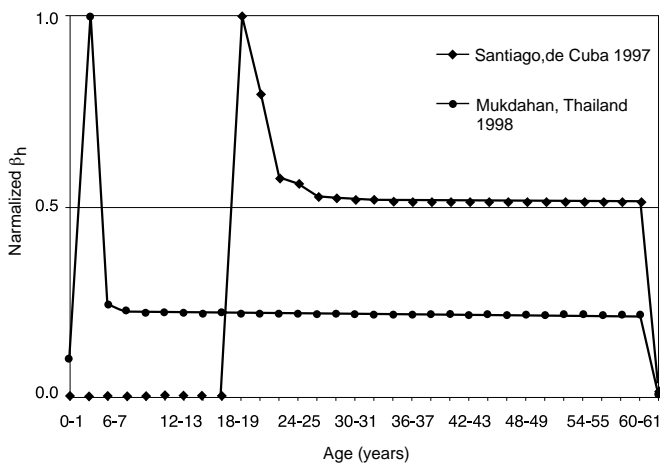

Fig 2–Forces of infection in the two epidemics. Forces of infection in Santiago de Cuba are denoted by (◆); forces of infections in Mukdahan Province, Thailand, are denoted by (●). Values obtained by fitting equations (i) to (iv) to the incidence rates presented in Figs 1a and 1b.

the neutralizing antibodies to DEN2 and none had the antibodies to DEN1 (Guzman *et al,* 2000). Serological tests showed that the dengue infections in 98% of the DHF/DSS cases were secondary. In a study of the 1994 epidemic in Thailand (Vaughn *et al,* 1997) it was found that while 93% (56 of 60) of the children with DHF were experiencing a secondary infection, only 4% were experiencing a primary infection. Vaughn *et al* (1997) also showed that the viremia was correlated with the body temperature of the patient; they were able to isolate the virus in 59 of 60 DHF patients, who were in the early febrile stage.

However, not all the evidence supports the secondary-infection hypothesis. During the 1996-1997 epidemic in Belem, Brazil (Travassos de Rosa *et al,* 2000) none of the 24 individuals, in whom the DEN2 virus was isolated and who were previously infected with the DEN1 virus, developed DHF. Additional evidence was obtained about the 1998 epidemic in Thailand from the serological records of the Department of Pediatrics, Siriraj Hospital (the largest hospital in Thailand). The pediatric ward at Siriraj Hospital admitted 316 children suffering from DHF in 1998. Hemagglutination inhibition assay (HAI) and IgM/IgG capture enzyme-linked immunosorbent assay were conducted for serum samples from all the patients. The dengue virus (49 DEN1, 29 DEN2, 41 DEN3, and 1 DEN4) was isolated in 120 of these patients.

We are interested in this subgroup. Vaughn *et al* (1997) have suggested that the following criteria be used to determine whether an infection is primary or secondary. Primary infection: HAI reciprocal titers ≤ 640; IgM to IgG ratio > 1.8. Secondary infection: HAI reciprocal titers > 1,280; IgM to IgG ratio < 1.8. Applying these criteria to the

serological results, 56 of the 120 DHF patients were experiencing a primary infection by the HAI criterion; 27 were experiencing a primary infection by the IgM/G criterion; and 13 satisfied both criteria. Among this group of 13 children, there were 7 cases in which the primary infection was due to DEN1 virus; 3 cases were due to DEN2 virus, and 3 were due to the DEN3 virus. This would appear to contradict the findings from the 1994 Thai epidemic, in which only 4% of DHF cases were the results of primary infection. We examined the records of Siriraj Hospital for the year 1999. One hundred and thirty-seven children suffering from DHF were admitted to the pediatric ward that year. The dengue virus was isolated in 31 of these patients, none of whom had a primary infection based on both tests. It appears that the DHF epidemics in Thailand during 1994 and 1999 differed from the 1998 epidemic in terms of the primary/secondary cause of infection. The reason for this difference is not clear. It is interesting to note that epidemics in Thailand peak every three years (Hay *et al,* 2001): 1998 was a peak year, while 1994 and 1999 were not. We are now studying this phenomenon to see whether it is of relevance to the problem of primary/secondary infection.

ACKNOWLEDGEMENTS

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