Letter to the Editor

Effect of increasing age on the trend of dengue and dengue hemorrhagic fever in Singapore

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Guzman et al[1] reported in this journal a retrospective study of the outcome of secondary dengue virus serotype 2 infections in Cuba during 1977 and 1981. It was observed that the morbidity and mortality rates in such secondary dengue infections were different in different age groups, the highest rates being observed in the 3–14-year age group. Within this age group, the death rate was higher in the younger children, and this rate progressively decreased with increasing age. Among adults, dengue hemorrhagic fever/dengue shock syndrome did occur, but at a much lower rate than in children.[1]

In Singapore, the age of the reported dengue cases has increased steadily over the last four decades, since dengue first became a public health concern here in the 1960s. There are several possible reasons for this, among which are lowered immunity[2] and adaptation by the *Aedes* mosquitoes,[3] both as consequences of the vector control program in Singapore. The results of our study are described to determine whether or not the epidemiology of dengue in Singapore, which, unlike Cuba, is hyperendemic for dengue, supports the observations reported by Guzman et al.[1]

Dengue hemorrhagic fever (DHF) and dengue fever (DF) were made notifiable conditions in Singapore in 1977. Clinicians who diagnosed these conditions according to the World Health Organization (WHO) criteria were legally required to notify the Ministry of the Environment. The annual incidences of locally acquired DHF and DF from 1977 to 2000 were extracted from the annual records of the Quarantine and Epidemiology Department for the present analysis.

To study the effects of the age of the cases and the type of reported dengue illness, the cases in this study were grouped into those below 15 years of age and those above 15 years old annually. The age of 15 years was chosen following the observation made by Guzman et al.[1] To remove the annual variation of the incidence of DHF and DF, the ratios of DHF to DF incidence for each of the study years were calculated. The relationship between the proportion of cases below 15 years of age and the DHF/DF ratio was examined using linear regression analysis. Student *t*-test was also used. All statistical analyses were done with Microsoft Excel:mac (Microsoft Corporation, Redmond, WA, USA).

The proportion of cases below 15 years of age decreased linearly from 0.3 in 1977 to 0.07 in 2000. This decrease occurred at a rate of 1.2%/year. Figure 1 shows the relationship between the proportion of cases below 15 years of age and the DHF/DF ratio among the reported cases annually. The DHF/DF ratio increased exponentially with the increase in the proportion of cases less than 15 years of age (R^2=0.81). This relationship is statistically significant according to linear regression analysis after natural logarithmic transformation of the DHF/DF ratio (R=0.90, R^2=0.81, t=9.67, $P < 0.0001$).

The findings of this study support the earlier observations reported by Guzman et al.[1] In the 1970s and early 1980s, when proportionately more of the cases were below 15 years of age compared to the 1990s, dengue infection tended to result in DHF instead of DF, resulting in a high DHF/DF ratio. With increase in the age of the cases in the 1990s, the cases presented as DF instead of DHF, resulting in a low DHF/DF ratio.

Apart from validating earlier assumptions made by those conducting clinical trials on dengue vaccine candidates, the findings also have another implication. Currently, the percentage of cases in Singapore admitted for hospitalized care is high, despite the low incidence of DHF. In 2001, 78% of the 2372 cases reported to us received inpatient treatment, even though, in that same year, only 0.34% of the cases were diagnosed as DHF. The results of this study suggest that a review of our hospitalization criteria may be worthwhile.

Dengue infection among adults may also result in a higher proportion of symptomatic cases versus asymptomatic/subclinical cases compared to similar infections in children, in whom up to 95% of infections had been reported to be mild or subclinical.[4,5] This was suggested by the exponential relationship between DHF/DF ratio and the ages of the cases. Not only is

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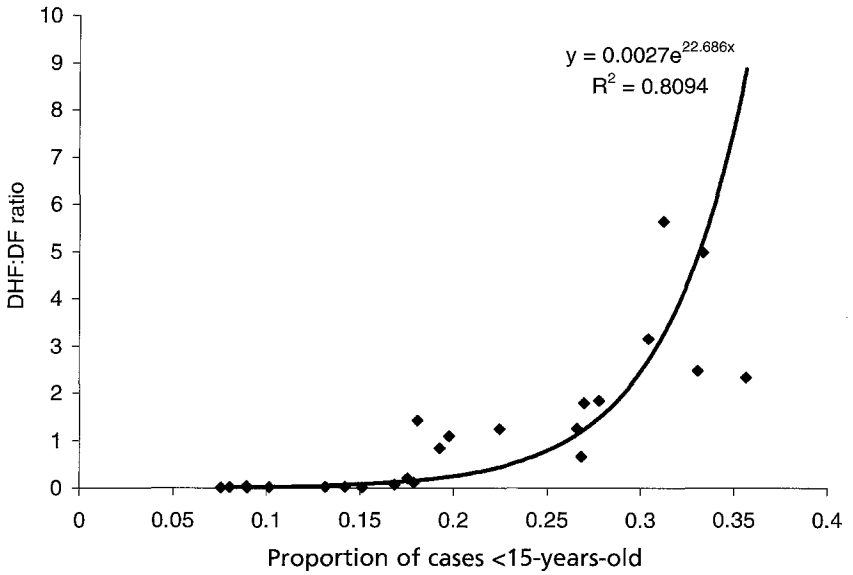

Figure 1. Association between the proportion of dengue cases below 15 years of age with the annual ratio of DHF to DF, 1977 to 2000.

dengue infection in adults less likely to result in DHF, but the patients are more likely to develop symptoms characteristic of DF, with fewer subclinical infections. In a recent serologic survey of Chinese construction workers who were working and living at a site where a DF outbreak occurred, all those who tested positive for anti-dengue IgM antibody sought medical attention for their symptoms (manuscript in preparation). Thus increasing age of the cases may result in an overall increase in the number of dengue cases, although most of these would be DF rather than DHF.

Unlike Guzman et al,[1] we have not separated our cases into primary and secondary infections. Given the information from our past serologic survey,[3] most of the young adults are likely to have a primary dengue infection.

Our data were obtained from the notifications made by clinicians over a period of 24 years. Although misdiagnosis and misclassification of DHF and DF cannot be excluded, the number of such cases is likely to be small, as indicated by a survey done at one of the major hospitals in Singapore.[6]

In conclusion, the likelihood of a dengue infection resulting in DHF decreases when the infection shifts from childhood to young adulthood.

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