UNIT NO. 4

DENGUE EPIDEMIOLOGY, PREVENTION AND CONTROL IN SINGAPORE

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ABSTRACT

Dengue Fever / Dengue Haemorrhagic Fever (DF/DHF) is the commonest vector-borne viral illness globally, with frequent and cyclical epidemics. After a 15-year period of low incidence, dengue has re-emerged in Singapore in the past decade. A combination of factors, namely lowered herd immunity, significant virus transmission outside of the home, and increase in the age of infection all contribute to an increased dengue incidence. Furthermore, adult dengue cases present a unique challenge to Singapore and investment in research on disease pathogenesis and case management will be needed to overcome the disease burden of this emerging trend.

SFP2008; 34(2)Supplement: 21-24

INTRODUCTION

Dengue Fever / Dengue Haemorrhagic Fever (DF/DHF) is the commonest vector-borne disease throughout the world, with an estimated three billion people living at risk of infection every year. The disease is caused by four closely related dengue viruses (serotypes), which are transmitted principally by the *Aedes aegypti* mosquito. Other mosquito species such as *Aedes albopictus* and *Aedes polynesiensis* can also transmit epidemic dengue, but do so less efficiently[1]. Infection confers lifelong immunity to the infecting serotype, but not to the remaining three; hence a person could acquire dengue infection up to four different times. Furthermore, epidemiological studies have indicated that a previous infection increases a person's risk of developing DHF and the severe end of the spectrum, Dengue Shock Syndrome (DSS), in subsequent infections[2]. The main pathology of these conditions is characterised by plasma leakage as a result of alteration in microvascular permeability[3]. If not properly managed, mortality can be as high as 30%[4]. There is as yet no specific treatment for DF or DHF although efforts to develop an anti-dengue drug are in progress. Prevention of this infection is thus imperative. In the absence of an approved vaccine, vector control is the only method for disease prevention.

There have been three instances where dengue was successfully prevented through vector control although all encountered issues with sustainability of results. These are:

1. The Pan American Sanitary Board's highly successful vertically structured paramilitary hemispheric eradication campaign between 1946 and 1970[5].
2. The top-down vector control operation in Cuba, based on intensive insecticidal treatment followed by reducing the available larval habitats (source reduction), in 1981[6].
3. Singapore.

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VECTOR CONTROL IN SINGAPORE

DHF appeared in Singapore in the 1960s and quickly became a major cause of childhood mortality. Public health response to dengue began in 1966, when the Vector Control Unit was set up within the Quarantine and Epidemiology Branch, initially in the Ministry of Health. It was transferred to the Ministry of Environment in 1972 when DHF was made a notifiable disease[7]; DF was made notifiable in 1977. Following a series of entomological surveys in 1966 to 1968[7-11] and a pilot project to control the *Aedes* vectors in an area with high incidence of DHF[12], a vector control system was implemented with the following approach[13]:

- Source reduction or reducing the availability of *Aedes* larval habitats, or larval source reduction.
- Public education. Public involvement is needed for sustainability of source reduction effort.
- Law enforcement.

The implementation of this vector control program was completed in 1973. The premises index since then has been around 2%. With this reduced *Aedes aegypti* population, Singapore experienced a 15-year period of low dengue incidence. However, since the 1990s, the incidence of dengue has surged despite the low premises index (Figure 1).

Why does Singapore still experience endemic dengue with cyclical outbreaks despite our vector control efforts?

LOWERED HERD IMMUNITY

Reduced dengue transmission in the 1970s and 1980s resulted in a concomitant reduction in herd immunity to dengue virus[14]. Hence, cases continue to be reported despite the low *Aedes* mosquito density. This hypothesis is supported by the observations made from a series of serological surveys conducted in 1982-1984, 1990-1991 and 1993, where a declining trend of seroprevalence among children was observed[15].

TRANSMISSION OUTSIDE OF THE HOME

Lowered herd immunity is, however, insufficient to account for the resurgence of dengue in Singapore. After the disappearance of maternal antibodies during late infancy, children would form the group with the lowest herd immunity. However, the incidence of DF/DHF is low in children compared to adults. This could either be due to a large proportion of subclinical infection or a lack of infection; the latter may suggest that transmission outside the domestic environment may be significant.

To investigate this observation, a serological study was carried out on 1,068 children aged 0 to 15 years over an 18-month period in 1996 to 1997[16]. This population would thus have grown up during the period of dengue resurgence in the

1990s. The results showed that pre-school children, aged 10 months to 5 years had a seroprevalence rate of 0.77% while that of formal school aged children from 6 to 10 years and 11 to 15 years were 6.7% and 6.5%, respectively[16]. The formal school aged children were thus nine times more likely to have been infected with dengue compared to preschool children[16]. This statistically significant difference in seropositive rates between these two groups suggests that the risk of acquiring dengue in Singapore is greater when a person spends more time away from the residential environment[16].

The above findings is further supported by the lower premises index in residential places compared to non-residential places in 1997, the same period when our serological study was carried out: construction sites (8.3%), factories (7.8%) and vacant premises (14.6%)[17]. Residential properties in 1997 had very low premises index: landed premises, 2.1% and apartments, 0.6%[17]. In contrast, the premises index in 1966 was highest in residential places: slum houses (27.2%), shop houses (16.4%) and apartments (5.0%)[8]. Collectively, these findings suggest that significant virus transmission occurs in sites away from home.

DENGUE IN ADULTS

As a consequence of the above two factors, adult cases predominate in Singapore. This is reflected in the steady decline in the proportion of cases less than 15 years old while those 25 years and above has conversely increased over the years (Figure 2). This predominance of adult cases has two effects:

- Greater proportion of clinical to subclinical cases.
- Altered clinical outcomes.

Clinical to subclinical ratio

While the majority of dengue infections, particularly the primary infections in young children are mild or silent[18-19], adult infections are more likely to be clinically overt. In a serological survey following a dengue fever outbreak at a construction site in Singapore, 24 out of 27 (88.9%) workers with serological evidence of recent infection sought medical attention for a febrile illness[20]. The significance of this finding can perhaps be appreciated in the fact that these were daily rated workers and for them to seek medical attention suggests that their symptoms were sufficiently debilitating for them to forgo salary for the day. Furthermore, recent studies using mathematical models also indicate that the increase in age of dengue cases has a large impact on the overall incidence of dengue due to an increased likelihood of symptomatic compared to asymptomatic infection[21-22]. These findings indicate that the increase in dengue incidence in Singapore may largely be due to the increase in age of our cases.

Altered clinical outcomes

A second consequence of the increase in the age of the cases may be in the outcome of dengue infection. With increase in the age of the dengue cases, the majority of the dengue cases in Singapore present as DF instead of DHF (Figure 1).

This age-dependant differences in the outcome of dengue infection may be due to the differences in vascular permeability, with the younger age group having a greater propensity for vascular leakage, under normal physiological conditions, compared to adults[23]. This higher baseline of microvascular permeability in children could imply a lesser ability to accommodate extraneous factors, such as dengue infection, that increases vascular permeability[23].

While the risk of DHF in adults is low compared to children, epidemiological observations in Singapore indicate that severe disease and death is not significantly lowered. Accordingly, the current World Health Organization (WHO) scheme for classifying dengue infection appears to underestimate severe dengue in adults[24]. While childhood dengue disease is well-described, adult disease is relatively unexplored and thus, research is urgently needed to enable early diagnosis, optimised case management and reduced disease burden. It is to address these objectives that we launched the early dengue infection and outcome (EDEN) study in early 2005 and will continue to run until 2011[25].

RECENT ADVANCES OF CLINICAL APPLICATION

Dengue illness is often confused with other viral febrile states. While laboratory tests for dengue virus, viral genome or viral antigen can be used to distinguish dengue from other febrile illness, the use of these tests on all who present with acute febrile illness will not be cost-effective. We recently developed a decision algorithm to distinguish dengue from other acute febrile illness within the first three days of illness. Making use of a combination of platelet count, total white cell count, body temperature, absolute lymphocyte and neutrophil counts, in sequential order (Figure 2), we were able to distinguish dengue from non-dengue febrile illness with an accuracy of 84.3%[26]. Furthermore, the use of platelet count, crossover threshold value of real-time RT-PCR (a marker of viraemia levels) and presence of pre-existing anti-dengue IgG antibodies (indicative of secondary infection) appears to be able to predict the development of severe dengue, using a platelet nadir of 50,000/mm^3 or below as indicative of severe disease[26]. While these observations will require further prospective study for validation, our findings indicate that early diagnosis and prognostication is possible following the first consultation the patient seeks, most likely in the primary healthcare setting.

CONCLUSION

In the absence of a safe and effective tetravalent vaccine for dengue viruses, vector control remains the only method to prevent this viral disease. The main lesson learned from Singapore's experience is that for a vector control program to be effective, it must be based on carefully collected and analysed epidemiological and entomological surveillance data, with particular emphasis on the ecological factors that determine where, what and when to attack the vector, which Chan termed "vector epidemiology"[7]. There is also an urgent need, given that over 80% of our cases are young adults, that early diagnosis and optimised case management be developed, based on disease pathogenesis data, to reduce disease burden and the risk of death associated with the infection.

Figure 1. Annual incidence dengue (DF) and dengue hemorrhagic fever (DHF) and the premises indices, in Singapore, 1966-2007. The annual premises index is expressed as a percentage of the premises in which Aedes aegypti and/or Aedes albopictus larvae were found against the total number of premises inspected. Data obtained from Ministry of Health, Singapore.

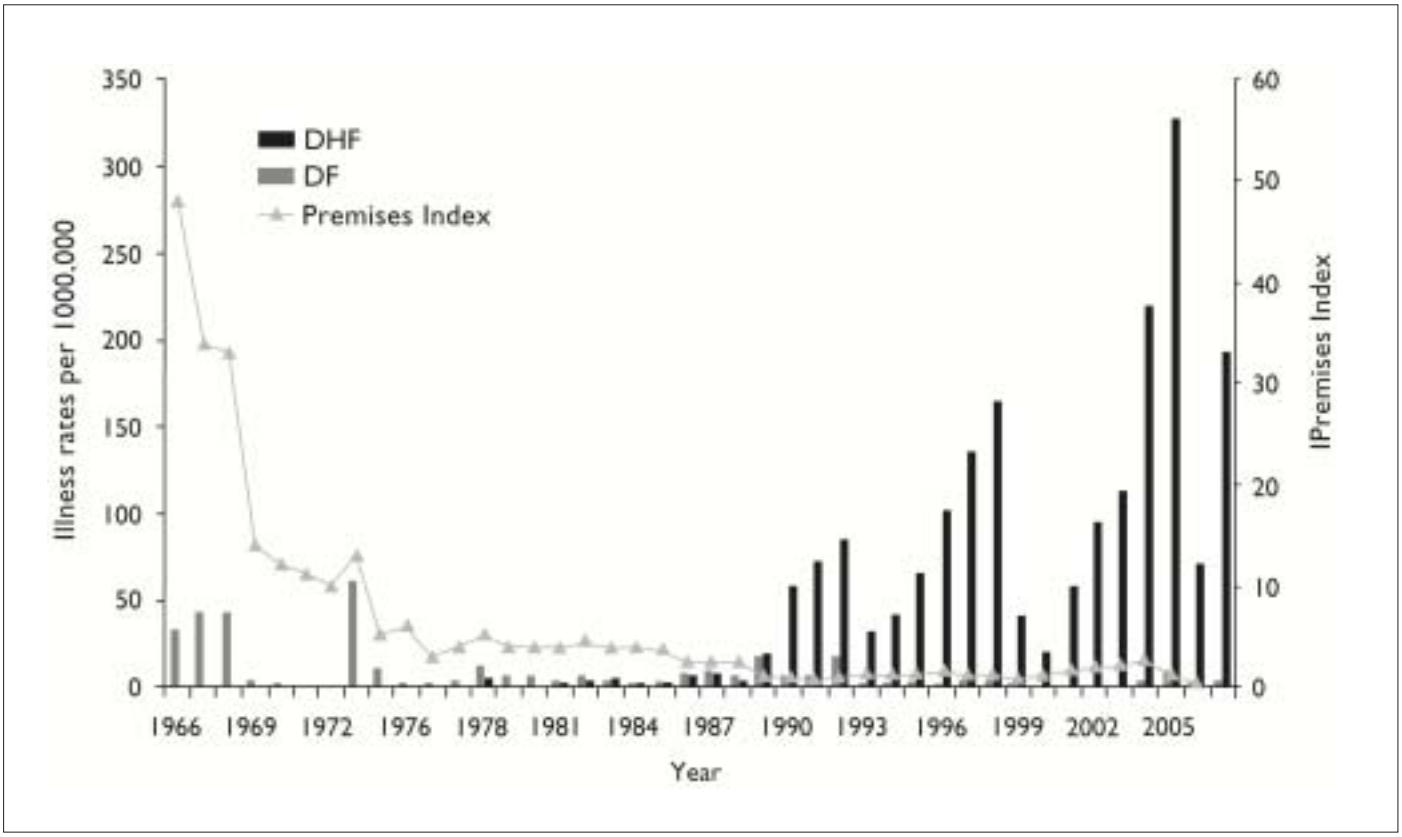
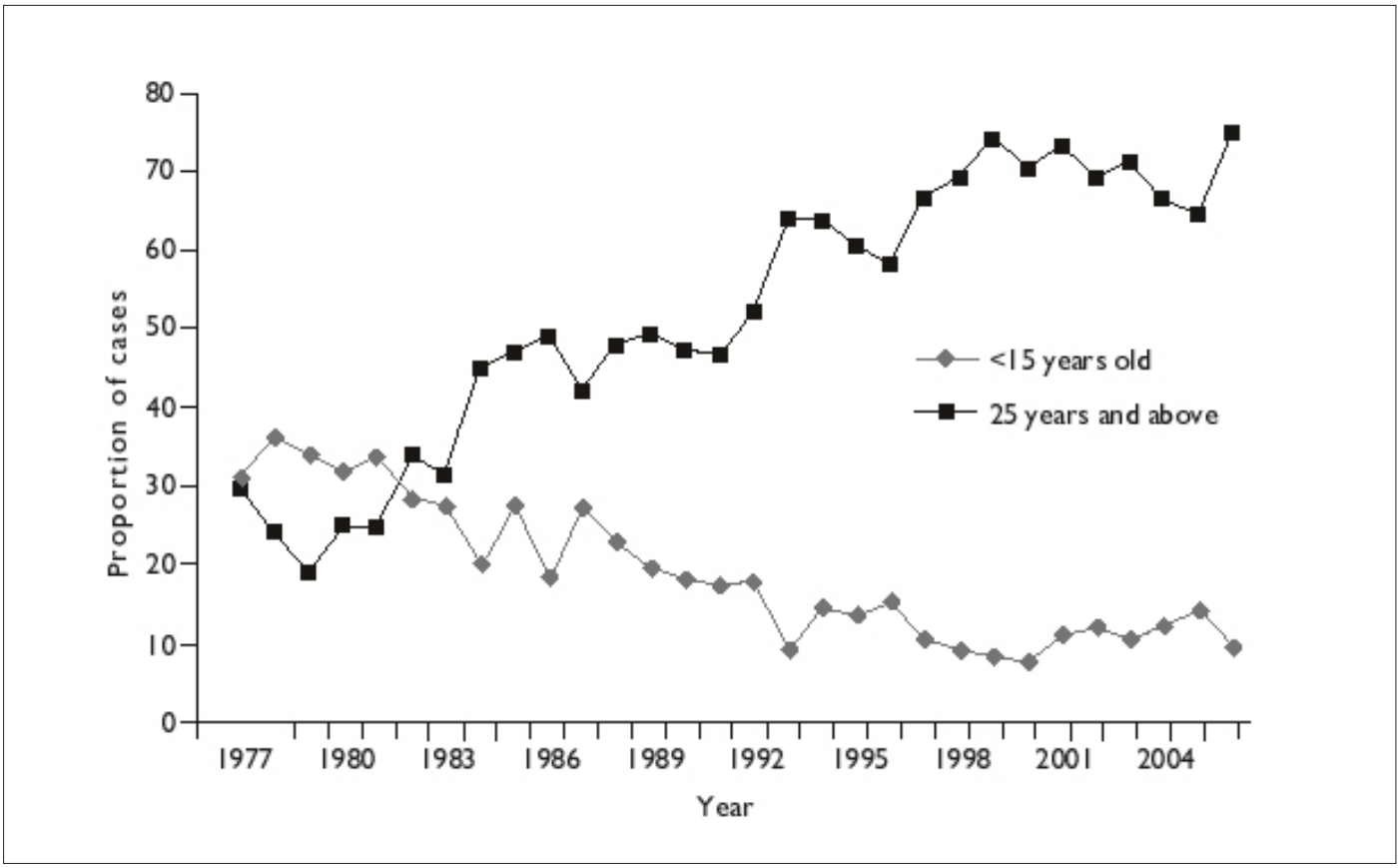


Figure 2. Proportion of annual indigenous cases less than 15 years old or 25 years and older in Singapore, 1977-2006. Data obtained from "Communicable Disease Surveillance in Singapore", an annual publication of the Ministry of the Environment until 2002 and Ministry of Health since 2003.



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LEARNING POINTS

- **Effective dengue prevention programme must be based on carefully collected and analysed epidemiological and entomological surveillance data.**
- **The re-emergence of dengue in Singapore is multi-factorial.**
- **Dengue infection in adults is an increasing trend.**
- **While childhood disease is well-described, dengue in adults is relatively unexplored area.**
- **Research focus needs to be targeted at improving early diagnosis, prognosis and optimised case management for reduced disease burden.**