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Outlook of dengue in Malaysia: a century later

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Abstract

Dengue continues to be a major health threat to Malaysia a century after its first reported outbreak in 1902. Examination of the available outbreak data suggested that a major DF/DHF outbreak occurred in Malaysia in a cyclical pattern of approximately every 8 years. All four dengue virus serotypes are found co-circulating in Malaysia, but after the first and only major outbreak involving DEN-4 in 1960's, only DEN-1, DEN-2 and DEN-3 were associated with DF/DHF outbreaks. It is argued that perhaps the spread of the later dengue virus serotypes followed the pattern of spread of the mosquito vector *Aedes aegypti*, whereas the former was associated with *Aedes albopictus*, the outdoor and rural area dwelling mosquito. Estimating from the trend and pattern of dengue and the associated dengue virus serotypes, unless there is a major breakthrough in dengue vaccine development, it is likely that dengue outbreaks will continue to occur in Malaysia throughout the 21st century.

Key words: Dengue, Malaysia, epidemiology

INTRODUCTION

Dengue fever (DF) is a mosquito borne disease endemic in Malaysia. It was first described by Skae in 1902 following an outbreak in Penang, almost exactly a century ago in November-December 1901.' Since this first report a few other outbreaks were reported in which almost all had occurred among the urban dwellers of Penang and Kuala Lumpur.[2,3,4,5] Traders and seafarers who brought in *Aedes aegypti* from Africa,[6] however, could have introduced dengue into Malaysia much earlier. The spread of dengue throughout Malaysia is thought to have followed the pattern of spread of *Aedes aegypti* that replaced the local *Aedes albopictus* as the main carrier of dengue viruses.[6,7] By 1960's dengue has become endemic in Malaysia and in November 1962 the first laboratory-confirmed dengue hemorrhagic fever (DHF) case was reported in Penang.[2] This first documentation of the outbreak followed at the heel of similar reports of DHF in the Philippines, Thailand, and Singapore in 1956,1958, and 1960, respectively.[8,9,10]

Dengue virus, the causal agent of DF and DHF is a positive single stranded RNA virus first isolated by Sabin and Schlesinger in 1944.[11] To date only four serotypes of dengue virus are known to cause dengue worldwide. Dengue virus type l (DEN-1) was the first of the four serotypes to be isolated in Malaysia from a small outbreak of DF among teachers and students at the Methodist Girls School in Kuala Lumpur in 1954.[3] Isolation of other serotypes was soon reported and it was apparent that all four serotypes were co-circulating in Malaysia[12] and all four serotypes have also been implicated to cause outbreaks of DF and DHF in Malaysia. In the present report the estimate of DF and DHF cases over the last century and the changing pattern of the predominant dengue virus serotypes were examined.

MATERIALS AND METHODS

Data available from reports of The Arbovirus WHO Reference Laboratories at the Department of Medical Microbiology, Faculty of Medicine, University of Malaya and the Institute of Medical Research, Kuala Lumpur and also those published were analysed.

Statistical analysis was performed using the Data Analysis Tool module of Microsoft Excel 2000 and results were graphically presented using the SigmaPlot 2001 for Windows Version 7.101 software (SPSS Inc.).

RESULTS AND DISCUSSION

The number of DF and DHF cases in Malaysia has increased steadily over the years culminating with the highest number yet of about 28,000 cases in 1998 (Fig. la). In the early 60's to late 70's the number of DF/DHF cases reported stood

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at less than 1,500 cases a year. The average annual incidence rate began to increase in the 80's (−2000) and by 90's a dramatic increase (−9000) in the incidence of DF/DHF was recorded (Fig. 1a). On average the annual incidence rate of DF/DHF in Malaysia ranges from about 400 cases in a 'quiet' year to about 7000 cases in a 'busy' year with the exception of 1998 in which there was an extraordinarily sudden increase in the number of DF and DHF cases recorded. The 'rise and fall' of DF/DHF incidences in Malaysia, however, did not show a definite cyclical pattern as that observed in Thailand in which a cycle of every 3 years has been noted.[13] Significant increase in the number of DF cases was noted in 1974, 1982, 1987, 1991 and 1998. It was observed that there was a longer lull period of 8 and 7 years in DF/DHF incidence between 1974 to 1982 and 1991 to 1998, respectively (Fig. 1a). Whereas, a shorter period with smaller incidence peaks of 5 and 4 years was noted between 1982 to 1987 and 1987 to 1991, respectively. Considering that the peak number of DF/DHF cases in 1987 was lower than that noted in 1982, it became obvious that there was also a lull in the incidence of DF/DHF of approximately 9 years between 1982 to 1991. Hence, the total average lull period of approximately 8 years was noted between the major DF/DHF peaks in Malaysia. This implies that a longer cycle of DF/DHF outbreak is likely in Malaysia. It was noted also that significant rise (> 500 cases/year) in DHF, the more severe form of dengue fever first described in Malaysia in 1962,[2] followed the similar 'rise and fall' of the total DF/DHF incidences with major peaks of approximately every 8 years (Fig. 1a). Examination of cumulative data from each decade revealed a clear exponential increase in the incidence of DF/DHF in Malaysia beginning in the 80's (Fig. 1b). The incidence of DHF followed a similar trend but the ratio of DHF to the total number of cases increased dramatically from about 9.2 and 6.3 per 100 cases in the 60's and 70's, respectively to 21.0 per 100 cases in the 80's. The ratio of DHF to total DF/DHF dropped to 7.4 per 100 cases in the 90's. The substantial increase in DHF ratio in the 80's could reflect the emergence of a more virulent, DHF prone dengue virus in Malaysia. On the other hand, it could also reflect the secondary effects of dengue virus infection subsequent to the initial priming of the population during the earlier (1970's) outbreaks.

Examination of the dengue virus serotypes prevalent in Malaysia since the 60's revealed the presence of all four dengue virus serotypes, with dengue virus type 4 (DEN-4) being the predominant (53.1%) serotype isolated from DF patients in Malaysia during the period between 1967 - 1969 (Fig. 2). Dengue virus type 2 (DEN-2) was the other major serotype during that time and by 1970 it has replaced DEN-4 as the dominant isolate. Since then, DEN-4 accounted to only less than 5% of all dengue virus isolated in Malaysia. The period between 1971 to 1985 revealed the presence of all dengue virus serotypes in Malaysia with none of the serotypes being the dominant serotype. The trend involving domination by one particular serotype during the outbreak year, however, begun in 1986 with dengue virus type 3 (DEN-3) becoming the dominant serotype. DEN-3 was successively replaced by dengue virus type 1 (DEN-1) and DEN-2 in the subsequent years (Fig. 2). By 1992 or six years later, DEN-3 was again by far the most dominant serotype isolated from DF/DHF patients. However, between the period of 1996 to 2000 DEN-3 was no longer commonly isolated and it was replaced by DEN-1 and DEN-2 with DEN-2 being the only major isolate by 1999. Switching of the predominant dengue virus serotypes in the population could have contributed to the cyclical pattern of dengue virus outbreaks in Malaysia. It was noted that the major outbreak of DF/DHF involving predominantly DEN-1 between 1997-1998 was preceded with the presence of high DEN-3 in the population. Similarly, the outbreak in 1990 to 1991 involving mainly DEN-2 was preceded by high occurrence of DEN-1 in the population. Whether the return of DEN-1 as the dominant isolate after almost a decade from the earlier outbreak involving predominantly DEN-1 in 1986-1987 had any relationship with the high DF/DHF incidence yet in Malaysia in 1998 could not be ascertained at this time. Conventional thought, however, would suggest that perhaps the absence of DEN-1 after the relatively small 1986-1987 outbreak actually exposed the Malaysian population to DEN-1 infection leading to the major outbreak with DEN-1 in 1997-1998. Since DEN-2 and DEN-3 were dominant during the intervening period causing high incidences of DF/DHF, it implied that immunity developed against these two serotypes did not accord significant cross protection to render the infection by DEN-1 asymptomatic and neither the immunity against the two serotypes contributed towards increased severity or incidences of DHF in response to infection by DEN-1 as one would expect if

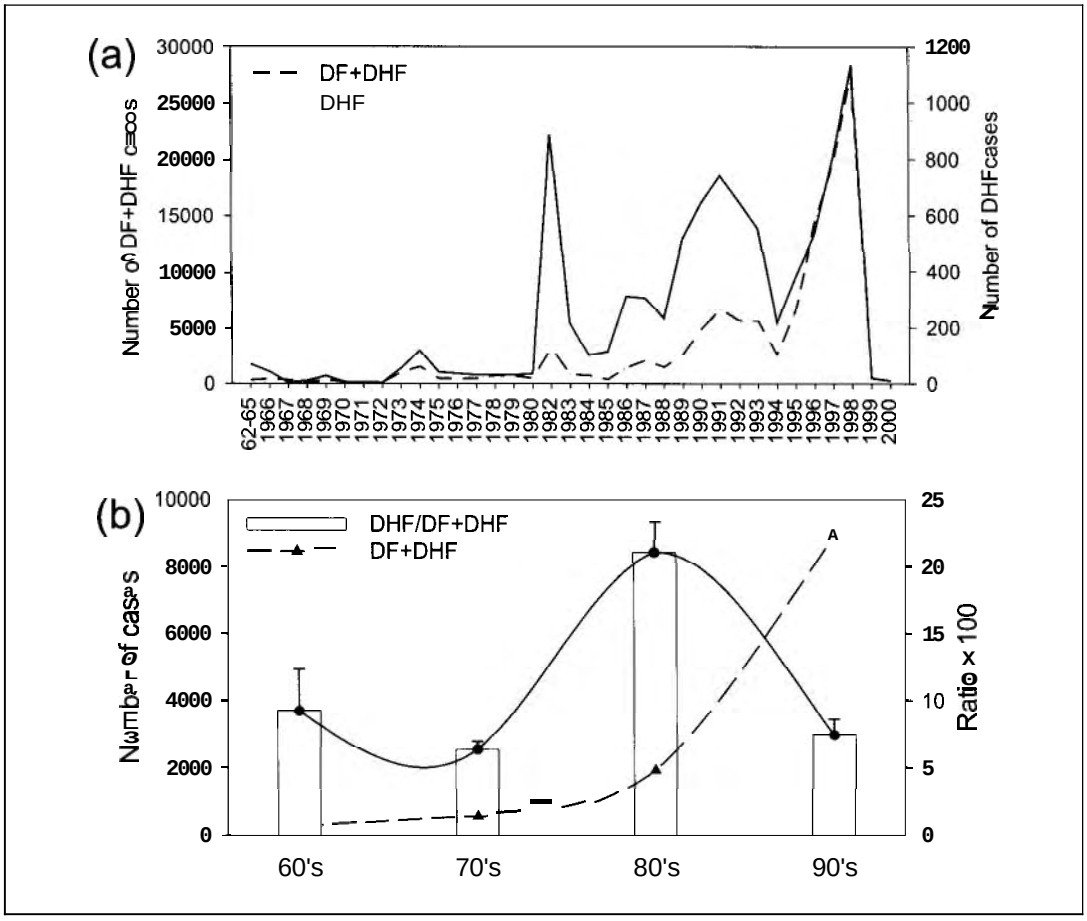

FIG. 1: Incidence of dengue in Malaysia. The total number of reported dengue and dengue hemorrhagic cases in Malaysia (a) were used to determine the ratio of DHF incidences over the decades (b). Statistical significance was determined using ANOVA.

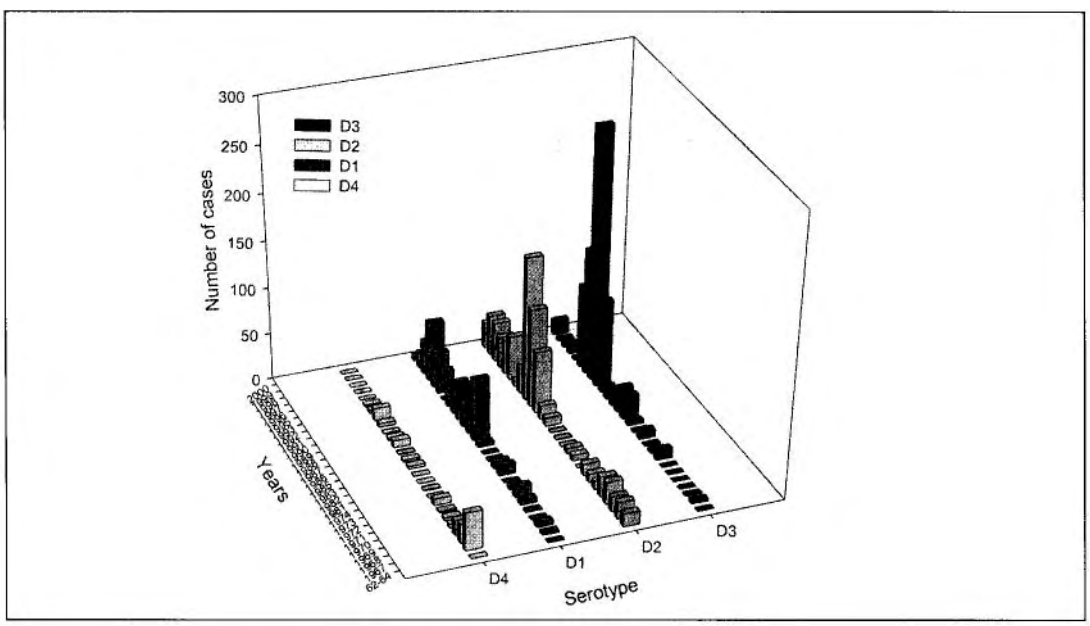

FIG. 2: Distribution of dengue virus serotypes in Malaysia.

antibody enhancement is pivotal in DHF or DSS, since the ratio of DHF to the total number of cases remained unchanged. Nonetheless, it is still possible that ADE enhanced DEN-1 infection but did not significantly affect the severity to result in DHF or DSS but caused sufficient illness to induce the patients to seek medical care resulting in the increased total incidence of DF in 1997-1998. It was noted that the incidence of DF/DHF in the ensuing years (1999 to 2000) was back to pre 1980's levels. This supported the notion that perhaps most of the adult population of Malaysia between the ages of 20 to 45 years has by then acquired natural immunity to the three main dengue virus serotypes with only immunity against DEN-4 still lacking. If this holds true, it is not expected that a large outbreak in magnitude comparable to that, which occurred during the 1991 and 1998 will recur in Malaysia in the next few years to come. It is likely, however, that the incidence would be as it was in the pre 1980's, but if one were to consider the potential contribution of ADE, it is expected that the ratio of DHF/DSS would increase in the immediate future since the population is primed after primary exposure to the different dengue virus serotypes. This is likely since the high DHF/DSS ratio seen in the 80's was also preceded by a period of mixed presence of the different dengue virus serotypes followed by successive change in the dominant serotypes with DEN-3, DEN-1, and DEN-2 appearing in that order.

On the other hand, recent isolation of DEN-4 after an absence of almost five years could also signify a potential re-emergence of this dengue virus serotype among the Malaysian population (unpublished observations). Since only the older (> 50 yrs old) generation of Malaysian is more likely to have had a chance to contract DEN-4 during the 1967 outbreak, the remaining younger adult Malaysian population could be exposed to the virus. The threat of full blown DEN-4 outbreak in the immediate future, however, is unlikely considering the lingering presence of other dengue virus serotypes notably DEN-2 in the population. It is noted that for reasons that are still unknown, DEN-4 is not as easily transmissible as other dengue virus serotypes to cause wide spread infection as evidenced from the rapid disappearance of DEN-4 following a dominant presence in 1967 with concurrent presence of DEN-2; which eventually became prominently present in the Malaysian population. It is speculated that unlike other dengue virus serotypes that are efficiently transmitted by the indoor mosquito, *Aedes aegypti,* DEN-4 is more efficiently transmitted by *Aedes albopictus,* the forest fringe rural area mosquito. Indeed, *Aedes albopictus* was the primary mosquito species vector for the 1966-1968 outbreak[14] in which DEN-4 was the dominant serotype isolated. DEN-4 was eventually replaced with other dengue virus serotypes perhaps as a result of eventual spread of *Aedes aegypti* into most of the developing townships in Malaysia in tandem with the rapid increase in economic activities that begun in 1970's and lasted until the end of the last century. As such, unless there is a major shift in the mosquito species population, which is presently dominated by *Aedes aegypti* in the high-density urban dwelling areas, outbreaks involving DEN-4 are expected to remain sporadic and localized.

While the threat of dengue caused by DEN-4 may not be as ominous, dengue in general will continue to pose a serious health threat to Malaysia for the next few decades to come and may even be just as deadly well into the next century. Judging from the rapid spread of dengue within the region, it won't be surprising that eventually dengue will also become a major health threat globally. As it is now, outbreaks of dengue have become very common in the Americas" and the number of cases had also increased steadily. The disease is fast becoming a menace worldwide with new dengue-afflicted areas appearing on the dengue map every year. This is despite all the modem technologies available and the know how on controlling the potential mosquito vectors, and the much taunted progress in molecular biology and biotechnology which was thought to hold promise for eradication of dengue in the last century. Unless a significant breakthrough in the development of dengue virus vaccine is achieved soon, it is not likely that the spread of dengue will be contained.

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