DENGUE PATIENTS AT PHOTHARAM HOSPITAL: A CLINICAL TRIAL SITE OF DENGUE VACCINE

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Abstract. Between 2005 and 2013, 1,868 dengue patients, 916 male and 952 female, were admitted to Photharam Hospital, Ratchaburi, Thailand. Among these patients, there were 1,209 with dengue fever (DF), 598 with dengue hemorrhagic fever (DHF), and 61 with dengue shock syndrome (DSS) with 1 death. The disease was seen all year round with a higher incidence in the rainy season. A trend of shift in age group towards older children and adults was seen during the study period. These data show that dengue patient admissions to Photharam Hospital are common, causing a heavy burden on the health system. Only one death was seen during the period of study, indicating that early recognition and effective management of dengue patients occurred. The trend towards higher age in dengue patients during the study period is a problem of concern and needs further clarification.

Keywords: dengue, epidemiology, dengue vaccine, clinical trial

INTRODUCTION

Dengue, along with the mosquito vectors that transmit it, is now endemic in over 120 countries throughout the tropical and subtropical regions of the world (Bhatt *et al*, 2013; Thisyakorn, 2014). It is nearly ubiquitous in the Tropics and has continued to emerge or become hyperendemic in new areas as the range of the *Aedes* mosquito vectors continues to expand. Global dengue transmission has increased at least 30-fold in the past 50 years (WHO, 2009a). The burden borne by the health and medical resources of affected countries is enormous, but nowhere is the burden greater than in the Southeast Asia and the Western Pacific regions, where the incidence of dengue is already the highest in the world and continues to increase and to cause epidemics. The estimated annual economic burden for Southeast Asia excluding prevention and vector control was nearly USD1 billion or USD1.65 per capita with two countries, Indonesia and Thailand, accounting for over 60% of this burden (Shepard *et al*, 2013). Currently, over 70% of the global population-at-risk for dengue lives in these regions (WHO, 2012). The global increase in dengue cases and also the potential spread of the disease to non-endemic areas are due to factors such as atmospheric composition, climate change, and human movement. Even with increasing estimates of disease burden, dengue is widely under-reported due to misdiagnosis as well as inconsistencies in diagnostics

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and surveillance systems. Dengue has spread into new geographical areas affecting both children and adults despite being significantly under-reported. Over half of the world's population lives in areas at risk of infection.

There are four antigenically distinct serotypes of dengue virus (DEN 1-4), which can cause a continuum of disease. Dengue fever (DF) causes fever, rash, muscle or joint pain, headache and eye pain, and dengue hemorrhagic fever (DHF) causes abnormal hemostasis and increased vascular permeability with severe cases leading to dengue shock syndrome (DSS) and death. Patients with severe organ involvement such as liver, kidneys, brain, or heart associated with dengue infection have been increasingly reported in DHF and also in dengue patients without evidence of plasma leakage. These manifestations may be associated with co-infections, comorbidities or complications of prolonged shock. Exhaustive investigations should be done in these cases. The clinical spectrum of the infection undermines surveillance activities because the majority of cases are asymptomatic and go undetected.

Complex disease presentation and sudden development of hemorrhagic symptoms in seemingly stable patients can cause fatal outcomes even in well-prepared hospitals. There is currently neither an approved preventive vaccine nor a specific anti-viral treatment against dengue. Main public health preventive interventions consist of mosquito control, which is currently used in endemic countries, and use of vector repellents; both generally have had only limited success. Development of a dengue vaccine is seen as the best hope to fight this disease. In Thailand, a dengue patient was first seen in Bangkok, Thailand in 1958 and then others appeared in other parts of the country (Thisyakorn, 2014). The aim of this study is to describe the epidemiological pattern of dengue patients admitted to Photharam Hospital, Ratchaburi Province, Thailand, a clinical trial site of dengue vaccine.

MATERIALS AND METHODS

Analysis of the data of dengue patients admitted to Photharam Hospital, a provincial hospital in Ratchaburi Province, Thailand from January 2005 to December 2013 was done after the approval of an ethics review committee. Photharam Hospital is among ten clinical trial sites for a dengue vaccine (Capeding *et al*, 2014). The hospital is in Ratchaburi Province, which is approximately 100 kilometer west of Bangkok, and it is among the ten provinces in Thailand with the highest dengue incidences (Capeding *et al*, 2013). Hence, it provides a suitable site for clinical trials of candidate dengue vaccines. A field-site for large scale clinical trials for dengue vaccines has been developed in Ratchaburi from 2005 up to the present time (Sabcharoen *et al*, 2012). The diagnosis of dengue patients adhered to clinical and laboratory criteria for the diagnosis of dengue patients as established by the World Health Organization (WHO, 1997).

RESULTS

Between 2005 and 2013, there were 1,868 dengue patients, 916 male and 952 female, admitted to Photharam Hospital in Ratchaburi, Thailand. According to the

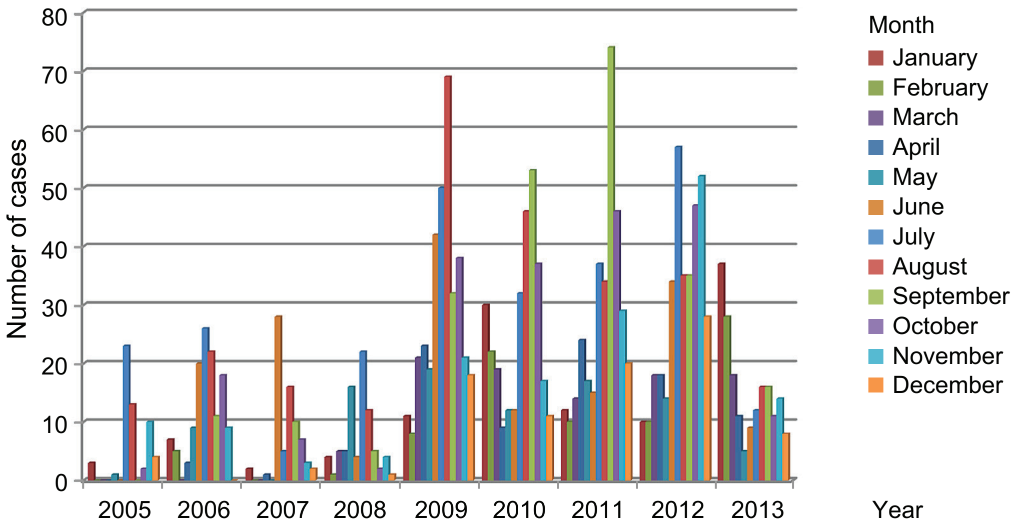

Fig 1–Seasonal distribution of dengue patients in Photharam Hospital, Thailand between 2005 and 2013.

1997 WHO case classification of dengue, there were 1,209 cases of DF, 598 of DHF, and 61 of DSS. The only patient who died in this study was a 17-year-old Down syndrome boy with refractory DSS, hematemesis, and organopathy involving the liver and central nervous system.

The disease was seen all year round and started to increase during the dry hot months of April to June. A higher incidence was observed in the rainy season, and this usually peaked 2-4 weeks after the arrival of the rains, which began anytime between June and September. The rainy season usually finished in October, but could last into November (Fig 1).

Fig 2 shows incidence by age group. Rates were constantly high among children below 15 years old with a trend of increasing mean age with time. Rates in older children and adults increased dramatically throughout the period of study.

Fig 3 shows the severity of dengue disease by age group. It demonstrates that all degrees of dengue severity can be seen in all age group with the trend of higher DSS cases in children in comparison to adults.

DISCUSSION

During the past decades, dengue epidemics are known to have occurred regularly in Ratchaburi, Thailand causing a heavy burden on the healthcare system. Population growth together with a remarkable degree of urbanization has allowed dramatic expansion of the mosquito population through an increase in urban breeding sites (Tanayapong *et al,* 2013). This explains the explosive increase in reported cases. A greater awareness and high reporting behavior could have contributed to some of the increase over time. The reasons for the apparent upsurge in dengue are probably multifactorial. Vector

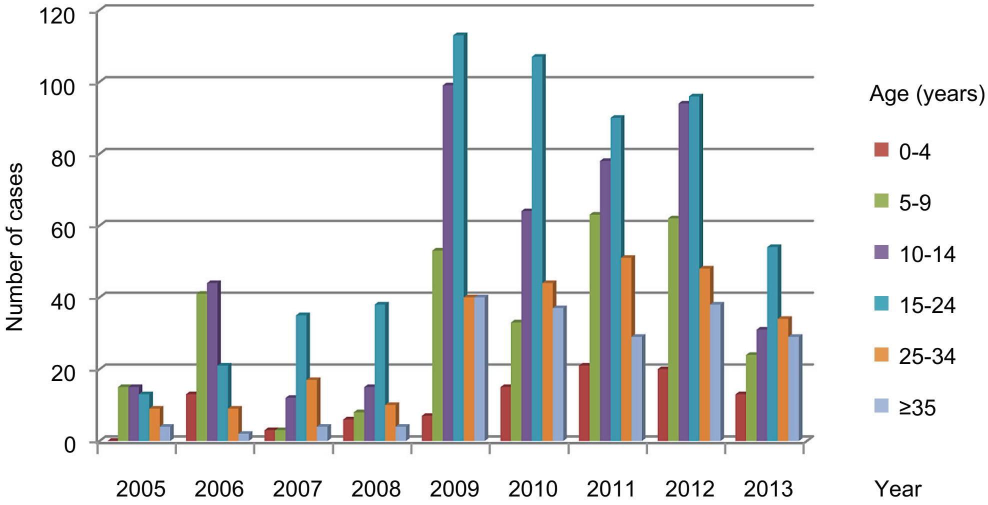

Fig 2–Age distribution of dengue patients in Photharam Hospital, Thailand between 2005 and 2013.

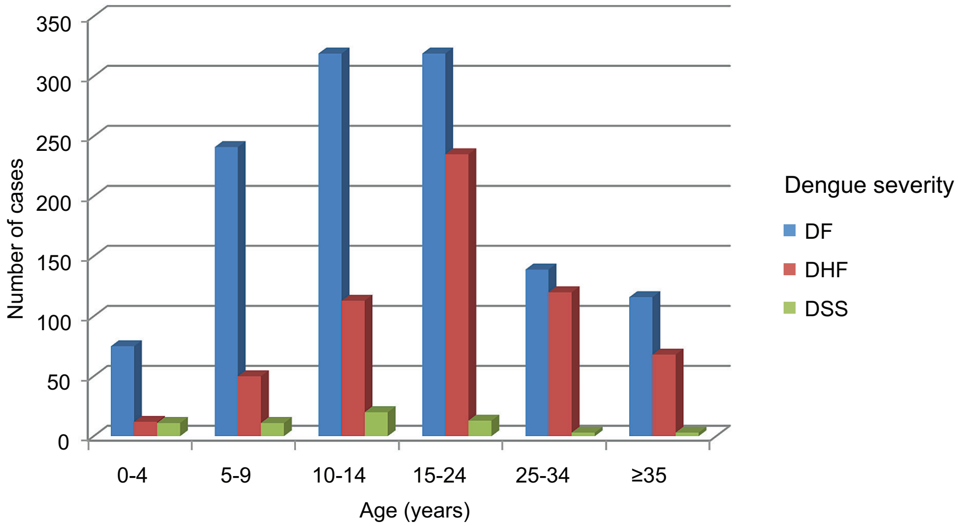

Fig 3–Severity of dengue patients by age group in Photharam Hospital, Thailand between 2005 and 2013.

efficiency of *Aedes aegypti* increases with increasing temperature for dengue virus (Tanayapong *et al,* 2013). This may explain the increasing number of dengue patients during the dry hot season. Global warming may contribute to the wider spread of dengue infection. The availability of more water and higher humidity, including higher biting rates may augment the epidemic during rainy period. Changes in weather patterns with increases in average temperatures and rainfall are classically seen as possible causes (Tanayapong *et al,* 2013). Many factors influence the epidemiologic patterns of dengue besides climate such as movements of mosquitoes, the types of circulating dengue viruses, and environmental factors such as temperature and humidity as well as human behavior and development (Tanayapong *et al*, 2013).

Well-targeted operations such as population-based epidemiological studies with clear operational objectives are urgently needed to progress control and prevention. Dengue remains predominantly a pediatric disease, but the trend towards higher rates in older children and adults during the last decade is incompletely understood (Tanayapong *et al,* 2013). This trend may be due to the lesser frequency of epidemics in the last decades, which may have caused second exposures to dengue virus to be postponed (Tanayapong *et al,* 2013). The only fatal case in this study had severe dengue according to the 2009 WHO dengue case classification with the patient deteriorating to multiple organ failure despite vigorous intensive therapy. The low mortality seen throughout the period of study indicates early recognition and effective management of dengue patients in Photharam Hospital.

Prevention of dengue depends on the control of the mosquito vector by limiting its breeding places and treatment of stored water with larvicide. These measures against dengue are effective only with a high level of government commitment, education, and community participation (Thisyakorn, 2014). Ultimately, the utilization of an effective and long-lasting vaccine is needed. Due to the unique challenges of dengue, including the need to provide protection against the four antigenically-distinct serotypes of the viruses, no vaccine is yet licensed to protect against this disease despite more than six decades of research.

The 1997 WHO dengue case classification, which classifies by clinical manifestations and laboratory findings may not clearly be correlated with disease severity. Therefore, the establishment of a new validated classification system in which cases are categorized by levels of severity has been recommended (WHO, 2009b). Several studies were done to compare the two classification systems regarding applicability in clinical practice and for surveillance. The new classification has shown a high potential for facilitating dengue case management and surveillance, but further evaluation is necessary (Hadinegoro, 2012).

A global strategy aimed at increasing the capacity for surveillance and outbreak response, changing behaviors, and reducing the disease burden using integrated vector management in conjunction with early and accurate diagnosis has been advocated. Antiviral drugs and vaccines that are currently under development could also make an important contribution to dengue control in the future (WHO, 2012).

Understanding the changing epidemiology of dengue will not only feed into operational policy for dengue control but will also inform vaccine application strategies in the future. Epidemiological data of this kind will be valuable for both dengue vaccine efficacy trials and for consideration of age group to be vaccinated, which will lead to universal dengue vaccine implementation in the future.

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