Changing epidemiology of dengue in South-East Asia

Rajesh Bhatia¹, Aditya P. Dash¹, Temmy Sunyoto¹,²

ABSTRACT

The burden of dengue and its potential threat to global health are now globally recognized, with 2.5 billion people at risk worldwide. The pathogenesis of severe dengue is particularly intriguing with the involvement of different immune factors. Also, the epidemiology of dengue in South-East Asia is undergoing a change in the human host, the dengue virus and the vector bionomics. Shift in affected age groups, sex differences and expansion to rural areas are evident, while the virulence and genotype of the virus determine the severity and time interval between sequential infections. The Aedes mosquito, a potent and adaptive vector, has evolved in longevity and survival, affected by seasonality and climate variability, socio-cultural and economic factors of human habitation and development. This review provides insights into the changing epidemiology and its factors in South-East Asia, one of the most important epicentres of dengue in the world, highlighting the major factors influencing these rapid changes. Addressing the changes may help mitigate the challenges in the current dengue control and prevention efforts.

Key words: Dengue, epidemiology, human host, South-East Asia, vector, virus

INTRODUCTION

Dengue fever (DF) and its severe form, the dengue haemorrhagic fever (DHF), is a re-emerging arboviral disease of great public health importance, and it has spread to all tropical and sub-tropical countries in the world. Currently, an estimated 2.5 billion people in more than 100 countries are at risk. Globally, every year, an estimated 50 million dengue infections occur; half a million DHF cases require hospitalization with over 20 000 deaths.[¹] Most countries in South-East Asia bear a high burden of DF/DHF and experience frequent and cyclical epidemics.[²]

Dengue is caused by viruses belonging to genus Flavivirus (family Flaviviridae) with four known serotypes: DENV-1 through DENV-4. Infection with one serotype confers life-long immunity to that serotype and a few months cross-immunity to other serotypes. Sequential infection of two serotypes leads to more severe type of disease (e.g. DHF). All serotypes/genotypes are now circulating globally and maintaining hyperendemicity.[³,⁴]

Aedes aegypti is the primary vector and establishes its habitat between latitude 35°N and 35°S. This mosquito lives in proximity to human habitations in urban areas and breeds mostly in man-made containers. This vector is a day-time feeder, and its peak biting periods are early in the morning and before dusk. Female Ae. aegypti bites multiple people during each feeding period. Ae albopictus is considered a secondary vector, with characteristics of being highly adaptive, as it can survive in cooler climates and spread. Both species are sensitive to environmental conditions such as temperature, precipitation and humidity.

There is no specific treatment for DF, while several candidate vaccines are currently undergoing trials with varying progress.[⁵,⁶]

Pathogenesis

DHF occurs in a small proportion of dengue patients, mostly in those with secondary infection and is characterized by an increased vascular permeability that results in plasma...
leakage, contracted intravascular volume and shock in severe cases. The leakage is unique as it is selective in pleural and peritoneal cavities with 24-48 h. Rapid recovery of shock without sequel and the absence of inflammation in the pleura and peritoneum indicate functional changes in the vascular integrity rather than in the structural damage of the endothelium as the underlying mechanism.[7]

The pathogenesis of DHF and dengue shock syndrome (DSS) involves both the innate immunity (complement system and non-killer cells) and the adaptive immunity (humoral and cell-mediated immunity). Enhancement of immune activation, particularly during a secondary infection, leads to an exaggerated cytokine response, which results in changes in vascular permeability, generally referred to as antibody-dependent enhancement. Viral products such as NS1 may also play a role in regulating complement activation and vascular permeability.[8-10]

Various cytokines with permeability enhancing effect have been implicated in the pathogenesis of DHF, albeit their relative importance is unknown. Studies have shown that the pattern of cytokine response may be related to the pattern of cross-recognition of dengue-specific T-cells. Cross-reactive T-cells appear to be functionally deficit in their cytolytic activity, but expresses enhanced cytokine production, including tumour necrosis factor (TNF)-α, interferon (IFN)-γ and chemokines.[11] TNF-α has also been implicated in some severe manifestations, including haemorrhage in some animal models.[8] Increase in vascular permeability can also be mediated by the activation of the complement system, as elevated levels of complement fragments have been documented and some complement fragments such as C3a and C5a are known to have permeability enhancing effects.[10,11]

Higher levels of viral load in DHF patients in comparison with DF patients have been demonstrated in many studies. The levels of NS1 viral protein were also higher.[12] The degrees of viral load correlate with the measurements of disease severity such as the amount of pleural effusions and thrombocytopenia, suggesting that viral burden may be a key determinant of disease severity.

The pathogenesis of DHF appears to involve almost all haematological and immune systems. The dengue virus seems to be capable of activating both procoagulant and anti-coagulant systems and other immune systems simultaneously. Severity of disease and bleeding may depend on the degree to which each system is activated and the time at which activation occurs. However, the exact immuno-pathogenetic mechanisms are yet to be elucidated. This complexity adds a challenging dimension to scientists in various fields.[13]

**Dengue fever and dengue haemorrhagic fever epidemiological changes**

The epidemiology of DF/DHF is complex and remains poorly understood. It involves host, viral and vector status that are further influenced by demographic, economic, behavioural and varied societal factors. Many field observations have raised questions against widely accepted epidemiological characteristics of dengue.[2,7] It is thus imperative to properly understand the evolving pattern and trend of DF/DHF epidemiology, as it is crucial in determining the success of prevention and control programmes.

**Changes in human host**

**Shift in affected-age group**

In South-East Asian countries, where all the serotypes (DENV-1-4) are circulating, DF is typically acknowledged to be a disease of early childhood, while clinical DF in adults is rare. DHF/DSS in these areas occurs mostly in children aged 2-15 years. Older and many of the younger inhabitants are usually immune and escape DHF, as they have acquired immunity against primary infection.[12]

However, there is an evidence of increase of dengue incidence in older age groups, and this age shift has been reported in Singapore, Indonesia, Bangladesh and Thailand.[13-15] In Thailand, cases of DHF/DSS in small infants as young as 1-2 months and in adults have been reported with increasing frequency.[14] In Nepal, during the first-ever outbreak in 2010 (virgin soil), majority of the cases occurred between the age of 16 and 45 years,[16] and, in first DHF outbreak in Bangladesh, the age group of 18-33 years were the most affected.[17] Sri Lanka with chronological overview shows that modal age group affected by dengue has shifted from <15 years of age to 15-34 years of age (MoH, Sri Lanka). In India, a legendary film maker died of DHF with multi-organ failure at the age of 80 years (Media Reports 21 October 2012) and older age group was significantly affected in the last major outbreaks in Delhi, India.[18]

In Cuba, during an outbreak in 1981, DF and DHF caused by DENV-1 occurred both in children and adults. However, during the 1997 outbreak caused by DENV-2 (secondary infection) after 20 years, all cases of DHF were adults. It has been hypothesized that the time interval between two sequential infections could be the reason to explain this phenomenon.[4,18]

**Sex differences**

There are many studies from South-East Asia region that suggest higher ratio of males than females in DF/DHF hospitalized cases (India, Bangladesh, Singapore and Malaysia), and only few studies suggest no difference in sexes.[13,14,17] However, almost all of these studies were hospital-based, thus, probably only represent those who access healthcare rather than the infected population.[3]
Gender bias is still abundant in many countries and health seeking behaviour is linked to this issue.

What could be interesting is the finding from studies that indicate the differences between sexes in term of severity of illness and case fatality ratio. Studies in Malaysia by Kabra et al.,[19] and in India by Shekhar et al.,[20] reported a higher rate of mortalities among females than males, suggesting different pathogenesis processes or immune response. Further research into determining the sex differences both in infection and severity of the disease is needed to capture both biological and societal factors that drive disease pattern in a community.

**Rural expansion**
According to study modelling the spatial-temporal wave of DHF occurrence in Thailand, it moves radially from Bangkok as an epicenter with the speed of 148 km a month.[21] In some countries, incidence of dengue is higher in rural than in urban areas.[14]

**Changes in the dengue virus**

**Virulence affecting severity of the disease**
Sequential infections or secondary infections are important to determine the severity of the disease. Studies in Thailand have revealed the following quantum of DHF risk with different sequences of dengue viruses with DENV-1/DENV-2: 500-fold, DENV-3/DENV-2: 150-fold and DENV-4/DENV-2 equals to 50-fold risk.[22] The infection enhancement contributes to the pattern of variable-sized outbreaks observed. Virulence of the circulating virus is hypothesized to play a role in disease severity, and small genotypic changes in dengue viruses could lead to DHF emergence, as reported from a Sri Lankan study.[23]

**Genotype affecting time interval between sequential infections**
There seems to be no time limit to sensitization after a primary infection. During 1997 in Cuba, DHF occurred after the introduction of Asian genotype DENV-2, 16-20 years after primary infection of DENV-1,[24,25] Singapore experienced the same situation: Years of successful vector control resulted in higher proportion of non-immune children and part-immune adults, in which infections lead to more severe cases of dengue. This long-interval secondary infection resulted in decreased neutralizing antibody from the primary infection, thus accounting for DHF/DSS in adults.[26] In South-East Asia, the higher age at DENV infection is linked to higher risk of clinical attack.[27] The interval between infections is linked to the fact that age plays a role as an important modulator of clinical dengue.

**Changes in the vector bionomics**

**Rural spread**
DF/DHF has been believed to be a primarily urban disease as the vectors are well-adapted to human habitation. The urbanization of South-East Asia that started after World War II for economic purpose has led to population growth that contributes to the increase of susceptible hosts. However, dengue has spread into rural areas from where it had not been reported before.

During the first half of the 21st century, piped water supply was restricted to urban towns, and now that supply system has been introduced into rural areas, water storage practices have changed. Modern transport system (cars and bikes) has also connected the rural areas better, and, finally, solid waste disposal also became a consequence from all this development. These are most cited reasons for rural dengue spread.[2,3] This expanding geographical distribution will pose new challenges in developing the most appropriate strategy for prevention and control.

**Seasonality and climate variability**
Dengue incidence, particularly dengue epidemics, has been currently associated with rainy season and the El-Nino phenomenon. Despite the number of studies, convincing data or models supporting this hypothesis is limited in small countries.[26] A study in Thailand found that climatic factors play a role in transmission cycle of DHF, but relative importance of these factors varied with geographical areas.[28]

Ecological studies related to Ae. aegypti have shown that Ae. aegypti is a hygrophilic (humidity-loving) species and is governed by microclimatic conditions to which it has adapted. It is independent of macro-level climatic conditions. However, it avails all available opportunities in the peri-domestic domain during this rainy season when temperature falls down and humidity increases. Further evidence and studies are needed to investigate vector behaviour.

**Socio-cultural and socio-economic factors affecting vector longevity and survival**
Socio-economic and cultural factors play a significant role in the variable incidence of dengue infection, albeit DF/DHF affects different level of income countries. Evidence indicates that this is more linked to behavioural practice and individual susceptibility. In dry and hot climatic region of India, desert cooler is a major source of Aedes mosquito species breeding, particularly, in lower socio-economic group (rich people use air conditioners). Sometimes, water storage is done in baked-soil containers that cannot be completely emptied, and, thus, Aedes breeding continues throughout the year.

Demographic transition, which eventually influences socio-economic development, including increase in population age also could predict the force of dengue infection.[29]
Changing pattern of dengue transmission

In Singapore, successful vector control programmes have brought down dengue incidence between 1974 and 1985, when the house index came below 2%. However, there was a major resurgence of dengue with more adult cases being reported. Serological studies indicated changes in the transmission sites and that the transmission was occurring in 'work sites' rather than in residential houses.\(^{[30]}\)

CONCLUSION

Effective dengue prevention and control is a difficult effort today than ever before. However, first step would be recognizing it as a priority and understanding its characteristics.\(^{[31]}\) The factors that may have contributed to rapid changing epidemiology of DF/DHF in South-East Asia region are the challenges that need to be addressed in designing operational research and implementation strategies. Operational research is needed to answer research questions on how the efficacy, cost-effectiveness, sustainability and scaling-up of existing and promising new control methods can be enhanced. Complementary to basic research, operational and implementation research are important in achieving progress. Dengue is a rising threat globally and requires actions of prevention and control in an urgent manner.

The major factors influencing changes in dengue epidemiology include: i) viral genotypes/subtypes with increased virulence; ii) lack of information on human population genetics and its relation with viral genome; iii) lack of information on vector ecology in micro-climatic conditions; iv) viral load injected by infected mosquito; v) post-infection natural immunity of the host and vi) time interval in sequential infection.

REFERENCES


How to cite this article: Bhatia R, Dash AP, Sunyoto T. Changing epidemiology of dengue in South-East Asia. WHO South-East Asia J Public Health 2013;2:23-7.

Source of Support: Nil. Conflict of Interest: None declared.