



Vigilance to Limit the Bidirectional Introduction and Co-circulation of Virus Serotypes Aims to Reduce Risk of Severe Dengue Disease in North East India

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Abstract

Dengue is a serious re-emerging arboviral disease that presents a global human health challenge. Infection is caused by one of several recognised serotypes of dengue virus, a member of the mosquito-transmitted Flaviviridae family of human pathogens, which also includes yellow fever, Zika and West Nile viruses. The greatest burden of dengue is borne by countries in the Asia Pacific region, in particular South East Asia and the Indian subcontinent where infection breaks out with increasing frequency and intensity. The World Health Organization South East Asia Region has a population of 1.3 billion people and includes 11 countries, of which Thailand, Myanmar and India have the highest reported incidence of dengue. Infection outcomes vary from the commonly asymptomatic or a self-limiting fever to more severe manifestations such as dengue haemorrhagic fever and dengue shock syndrome. Although primary infection with one serotype elicits lifelong immunity against homologous reinfection, severe dengue is linked to an antibody-related immunopathological response that is triggered by secondary infection with a heterologous serotype. The principal vectors of transmission are the day-biting mosquitoes *Aedes aegypti* and *Ae. albopictus*, the respective preference of which for urban and rural habitats has facilitated the rapid and continued spread of dengue across tropical and sub-tropical climatic zones. The narrow elevated corridor of North East India was considered historically to be non-endemic for dengue and as such separated areas of high endemicity in the Bengal Delta and the other zones of India from those in Thailand and Myanmar. In these regions the predominant serotype is usually distinct, so a breach of this geographical bottleneck would potentially enable the co-circulation of virus serotypes, thus posing an increased risk of severe disease upon secondary infection. This alarming scenario may now be realized following the notification of clinical cases in the states of Arunachal Pradesh, Assam and Manipur in recent years. While incidence is still sporadic in North East India limitation of local outbreaks is required through vigilant adherence to the integrated implementation of clinical management, diagnosis, surveillance and vector control in order to prevent the transcontinental spread of dengue.

Keywords: Dengue; Virus; Mosquito; *Aedes*; Vector; Disease; Serotype; India

Introduction

Dengue is considered as one of the most significant arboviral diseases of humans worldwide, with a distribution predominantly in tropical and subtropical regions that are the habitat of its vector of transmission, female mosquitoes of the genus *Aedes* [1,2]. At present, there is a risk of infection for over 2.5 billion people in about 125 countries worldwide [1]. The most reliable recent estimate of the burden of disease imposed by dengue is that globally each year it causes an estimated 390 million infections, with 96 million symptomatic cases [1]. Among at least 500,000 dengue-related hospitalisations annually [2], an estimated 22,000 are fatal [3]. These statistics indicate that most people remain unaffected by the virus, while a smaller proportion exhibit extreme symptoms, with a low chance of survival without supportive tertiary care. Currently, there is neither a specific anti-dengue therapy nor a commercially available preventive vaccine [4,5].

Dengue Virus, Serotypes and Transmission

The aetiological agent is dengue virus (DENV), an enveloped, single-stranded, positive sense RNA virion of the *Flavivirus* genus, which belongs to the Flaviviridae. This family is closely related to viruses that cause other notable infectious diseases in humans including yellow fever, Zika, West Nile encephalitis, Japanese encephalitis and hepatitis C infection [6]. There are four established serotypes, DENV 1-4, characterized by neutralization assays [6]. The existence of a fifth

serotype was advanced recently [7]. However, definitive demonstration of this serotype awaits the recovery and characterization of an isolate so as to confirm, or conversely to refute, its singularity [8].

While humans are the principal host some DENV serotypes also infect non-human primates such as macaques. Although many potential DENV vectors have been considered, evidence points to *Ae. aegypti*, the yellow fever mosquito, and *Ae. albopictus*, the Asian tiger mosquito, both day-biting, as the major vectors for dengue transmission around the world [9].

Clinical Manifestations and Immunopathology

The possible outcomes of dengue virus infection in humans occur

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in three traditionally recognized clinical forms. These range vastly from asymptomatic cases or those causing mild influenza-like symptoms known as dengue fever (DF), lasting between 2-10 days, through to severe disease, notably dengue haemorrhagic fever (DHF) and the rarer dengue shock syndrome (DSS) [6]. These manifestations lead to metabolically dangerous conditions including increased vascular permeability, hypovolaemia and circulatory failure [10]. DF is due to primary infection with any serotype, is generally mild and self-limiting, and from which recovery is generally completed by lifelong antibody-dependent homotypic immunity [11]. In 2009, the World Health Organization proposed a revised, broader-based clinical classification which is gradually being adopted: dengue; dengue with warning signs; and severe dengue [10].

Secondary infection with a heterotypic serotype generates cross-reactive antibodies, which, when present in the peripheral circulation, increase the potential risk of antibody-dependent enhancement of disease, a form of immunopathology. Hence, recurrent infection is the major risk factor for the serious, often fatal, complications of DHF and DSS. Infants who are immunized passively through receiving maternal antibodies from a dengue pre-immune mother are at high risk of severe dengue infection [12,13]. Different dengue serotypes vary in their capacity to cause severe illness, but there is no expert consensus as to the extent of a causal association [14]. In addition, it cannot be predicted as to which individuals will progress from experiencing only DF to suffering life-threatening DHF or DSS. This places a substantial burden on public health service providers, especially referral hospitals in developing countries where dengue is particularly prevalent.

Recent History of Dengue in Asia

Disruption of ecosystems, increased troop movement, and rapid urbanization after World War II has each promoted the wide dissemination of the dengue vector and virus across Asia [15]. By the end of the war, countries (notably Cambodia, Philippines, Thailand, Vietnam) susceptible to dengue epidemics became hyperendemic for DENV [16]. DENV 1-4 serotypes were first isolated during the 1940s and 1950s in this area although they were probably present earlier [15,17]. DHF emerged in Manila (Philippines) in 1954 [18]; thereafter, it appeared in Thailand in 1958, while Cambodia, Malaysia, Singapore and Vietnam all reported the presence of DHF cases in the 1960s [19]. In India, the first virologically proven epidemic took place in Calcutta and on the Eastern Coast Plains in 1963-1964 [20]. DHF began occurring in various parts of India in 1988 [21]. Pakistan reported cases of DHF in Karachi in 1994 [22].

Current Epidemiology in Asia

In the World Health Organization South East Asia Region now only the Democratic People's Republic of Korea has yet to report any outbreak [23]. Dengue is hyperendemic in South East Asia and in all Indian zones other than North East (i.e. North West, North Central, West Central and Peninsular), where the predominant circulating serotypes vary on a cyclical basis. In Thailand, it was noted that the predominant serotype cycled annually during 2004-10, a phenomenon which was presumed to be due to herd immunity among the human population and to competition between serotypes [24]. The existence of multiple DENV serotypes in the same locality is a major threat to resident communities [10,25]. In the monsoonal countries of Myanmar and Thailand multiple serotypes of dengue virus are in circulation and high rates of hospitalization and death from severe dengue are reported [23,24]. Regions of Myanmar that record the highest number of cases include many in the west of the country, bordering North East India [10].

There are also multiple serotypes in circulation in India and Bangladesh, from where dengue has spread into Nepal and Bhutan in just over a decade [10]. In Bangladesh, DF was documented from the mid-1960s to the mid-1990s, but re-emergence of DHF was reported in 2000 [26]. Epidemics in Bhutan and Nepal were reported only in 2004 [27,28], but these small nations transitioned from non-endemic to hyperendemic status rapidly [29,30]. Bhutan shares borders to the east, south and west with the North East Indian states of Arunachal Pradesh, Assam and Sikkim, respectively (Fig. 1). The primary vector *Ae. aegypti* and secondary vector *Ae. albopictus* were reported to have expanded into the middle mountain ranges of Nepal and were commonly found up to 1,350 m altitude [31].

The Case of North East India

Historically, infections in the Bengal Delta and four of the five geographical zones of India were separated physically from those in Thailand and Myanmar in South East Asia by the land mass of North East India, which is a narrow corridor situated between Bangladesh (to the west), Bhutan (to the north-west), China (Tibet) (to the north) and Myanmar (to the east) [32]. North East India comprises the contiguous so-called 'seven sister states' of Arunachal Pradesh, Assam, Manipur, Mizoram, Meghalaya, Nagaland and Tripura, as well as the Himalayan state of Sikkim (Figure 1), which borders Nepal to its west. This physiographical region was hypoendemic for dengue, despite being surrounded by dengue-endemic countries and so represented a bottleneck to the spread of dengue across the Asian continent [33]. However, of public health concern North East India is now reporting outbreaks of dengue [34-36]. This is occurring in a region in which the incidence of disease was hitherto sufficiently low that the population has limited or no immunity to any DENV serotype. The situation is exacerbated by both an expansion of vector ranges and increased urbanization.

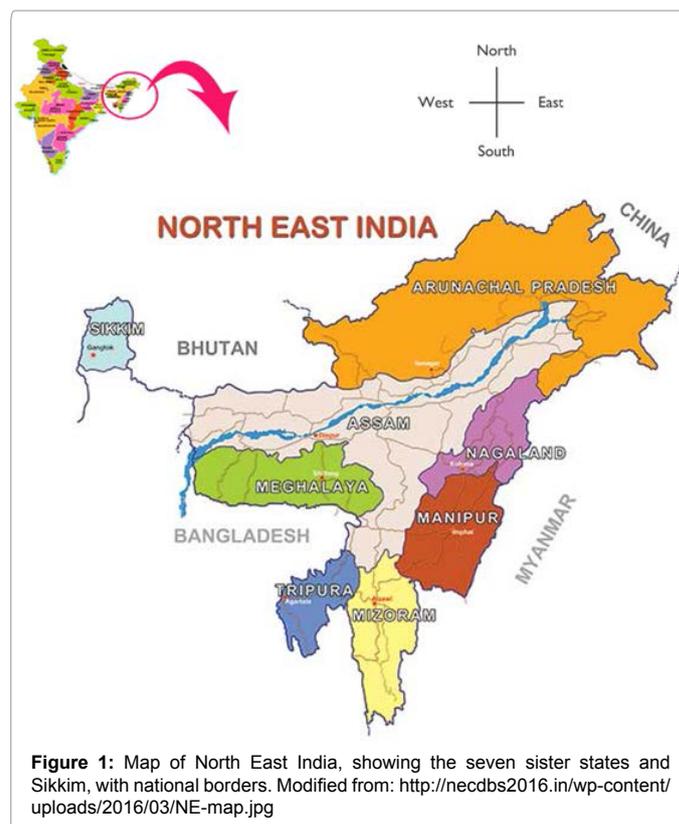


Figure 1: Map of North East India, showing the seven sister states and Sikkim, with national borders. Modified from: <http://necdb2016.in/wp-content/uploads/2016/03/NE-map.jpg>

Vector Distribution

Initially considered to be an urban and peri-urban disease, dengue has extended into rural areas in India [32]. In North East states, *Ae. aegypti* displays a peridomestic habit and is the dominant vector mosquito species in urban areas, whereas *Ae. albopictus* is found more in semi-urban and rural environments [37]. The distribution of *Ae. albopictus* has expanded rapidly [38], and this species is a potential vector in areas where *Ae. aegypti* is not established. In the late 1990s both vectors were identified in waste tyre dumps in townships along the main trunk roads of North East India, up to an altitude of 1,500 m above sea level [39]. Tyre dumps were noted as a preferred habitat of *Ae. aegypti* and a major contributor to its presence, for which community action was advised in order to reduce standing water collection [37]. Both mosquito species were also detected in the hills of Nagaland [40]. Surveillance of vectors for viral infection is considered a critical measure to provide early warning of a possible dengue outbreak [41].

Incidence of Infection

The first major outbreak of dengue in North East India was in Manipur in 2007-08, in a town bordering Myanmar [34]. This incidence was due to a Cambodian strain of dengue and was linked to the increased local presence of *Ae. aegypti* and *Ae. albopictus*. Although Manipur was noted to have a porous border with Myanmar, there was no suggestion that the outbreak originated in Myanmar, so it is probable that it was introduced there by an infectious traveller from Cambodia or elsewhere [34]. Of 275 suspected cases in Manipur, 42 from 2007 and 16 from 2008 were tested using immunoglobulin (Ig)M anti-dengue antibodies (20 and 12, respectively, were also tested by RT-PCR). There were 25/42 and 2/16 positive by IgM, and 17/20 and 10/12 by RT-PCR for DENV-2, respectively [34].

Further outbreaks followed in Assam in 2010, 2012 and 2013 [35], and in Arunachal Pradesh in 2012 [36]. The number of confirmed dengue cases in Assam increased markedly from 237 in 2010 to 1058 in 2012 and then to 4526 in 2013 [35]. The circulating serotype was not confirmed from clinical samples in Assam; however, a study of wild-caught *Ae. aegypti* during the 2013 outbreak identified the presence of serotype DENV-2 [41]. Of 164 suspected cases in Arunachal Pradesh, 107 were confirmed by serology [36]. Of these, 89 were tested by RT-PCR and dengue was detected in 35: 27 instances of single serotype infection of DENV-3; 7 dual infections of DENV-1 and DENV-3; and one case of DENV-2 and DENV-3 mixed infection [36]. A retrospective surveillance study of 430 suspected dengue cases during 2009-2011 found 143 to be dengue positive (92 by IgM-capture ELISA and 51 by RT-PCR); these were collected from Assam (82), Meghalaya (35), Nagaland (15), Manipur (8) and Arunachal Pradesh (3) [42]. All serotypes were identified in the RT-PCR samples and DENV-1 was predominant (45.1%) [42]. Dual infections were also detected: DENV-1 and DENV-2 (3 cases); DENV-1 and DENV-3 (1 case); DENV-1 and DENV-4 (1 case); and DENV-2 and DENV-3 (3 cases) [42].

Current issue and Future Perspective

The region comprising Bhutan, Bangladesh, North East India and Myanmar provides a natural connection between India and South East Asia. Both these latter regions have been hyperendemic for dengue for a long time but the predominant circulating serotypes are usually distinct [33]. While Myanmar is also an established hyperendemic nation, with infections reported to be related to those circulating in Thailand [10], the resident populations of North East India, Bangladesh and Bhutan are at risk of suffering the more severe disease manifestations of dengue

infection. Expansion of the distribution of virus serotypes from both east and west directions will lead to co-circulation of dominant serotypes. In a dengue-naive population this will bring about an increased incidence of mixed infections and the potential for increased virulence.

Conclusions

In North East India there is currently a real possibility of a rise in number of both people infected with dengue and, consequently, of clinical cases that necessitate specialist treatment. In light of this threat to public health, increased vigilance in diagnosis and therapy, as well as with respect to mosquito surveillance and control, is required in order to combat infection at a state level. Virus identification, disease notification and vector management will also have the substantial benefit of reducing an individual's risk of exposure to different virus serotypes that is a major predisposing factor for severe disease manifestations that are consequent to secondary infection. Raising the level of public awareness through community education and engagement in vector control is also central to preventing the urban spread of *Ae. aegypti* and *Ae. albopictus* mosquitoes. Importantly, local implementation of such an integrated program will act to preserve for as long as possible the apparent bottleneck of this most eastern region of India to the otherwise continued spread of dengue across Asia.

Conflict of Interest

The authors declare that they have no competing issues of interest.

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