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## Resurging Tropical Distribution of Dengue: A Review on Its Past and Present Epidemiology



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### ABSTRACT

Dengue is a fatal infectious vector born disease caused by a flavivirus which is highly endemic in tropical and subtropical regions. Aedes. Aegypti is responsible for the transmission of disease. Dengue is caused by one of the serotypes from DENV1 to DENV4. A recently introduced Dengavaxia is recommended only for seropositive patients in a restricted age group. Vector control has achieved only limited success and currently, there are no licensed antivirals to treat dengue, except few effective dengue vaccines. Increasing numbers of dengue cases and fatalities are being reported in urban and rural settings in India and across the world. These rapidly advancing dengue outbreaks result in severe disease that constitutes to be a leading cause of hospital admissions, with high case fatalities. This review mainly highlights the re-emerging cases of Dengue across the globe as well as India about its distribution in correspondence with present and past epidemiology.



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## 1. INTRODUCTION:

Dengue fever is the world's most rapidly spreading mosquito-borne arboviral disease <sup>[1]</sup>. The word dengue originated from the Swahili word for "bone-breaking fever" or the word walk of a Dandie in Spanish <sup>[2]</sup>. It is a viral infection spread between humans by mosquitoes in tropical and subtropical regions around the world <sup>[3,4]</sup>. It is caused by a single-stranded RNA virus belonging to the Flavivirus genus and its main vector is *Aedes aegypti* <sup>[5]</sup>. Dengue virus can be classified into four serotypes DENV -1, DENV -2, DENV -3, and DENV -4 <sup>[6]</sup>. Trends in recent decades include larger and more frequent epidemics of dengue including Dengue Fever (DF), Dengue Haemorrhagic Fever (DHF) and Dengue shock syndrome (DSS). Initial symptoms of the disease appear in about 5-7 days after the infected mosquito bites a healthy person <sup>[7]</sup>. It has 3 phases based on severity classified as febrile, critical and recovery <sup>[8]</sup>.

The two important clinical manifestations of dengue are dengue fever and dengue hemorrhagic fever (DHF) <sup>[9]</sup>. Many hematological parameters have been suggested to evaluate the severity of disease including decreased platelet count, increased hematocrit level, prolonged prothrombin time and activated partial thromboplastin time, liver transaminases, muscular enzymes, cytokines such as IL-6 and IL-10 <sup>[10]</sup>.

DHF was classified into 4 grades (I-IV) based on the severity of the disease <sup>[10]</sup>. This might rarely develop into a potentially lethal state called severe dengue (SD) <sup>[11]</sup>. Diagnosis also involves the detection of dengue NS1 antigen and differential detection of IgM & IgG antibodies in human serum/plasma. The connection between secondary infection and severe dengue is thought to be mediated by a process termed antibody-dependent enhancement (ADE) <sup>[12]</sup>.

## 2. Global distribution:

In 1943, Ren Kimura and Susumu Hotta first isolated the dengue virus. The first epidemic of dengue hemorrhagic fever (DHF) was described in southeast Asia, Manila in 1953. Dengue fever is widespread in Southeast Asia and the western Pacific islands, but the disease has been spreading rapidly in Latin America and the Caribbean. World Health Organization (WHO) currently estimates there may be 50-100 million dengue infections worldwide every year. Another study on the prevalence of dengue estimates that 3.9 billion people are at risk of infection with dengue virus. 5,00,000 individuals with SD need hospitalization yearly,

according to WHO <sup>[13]</sup>. Despite the risk of infection existing in 128 countries, 70 % of the actual burden is shouldered by Asia.

In 2012, an outbreak of dengue on the Maderia islands of Portugal resulted in over 2000 cases and imported cases were detected in mainland Portugal and 10 other countries in Europe <sup>[14]</sup>. The number of dengue cases reported to the WHO increased 6 times from < 0.5 million in 2010 to 3.34 million in 2016. These numbers are from member states in only three WHO regions (SEARO, WPRO, and PAHO). Cases across America, south-east Asia and western pacific exceeded 1.2 million in 2008 and over 3.34 million in 2016.

The region of America reported more than 2.38 million cases in 2016, where Brazil alone contributed slightly less than 1.5 million cases, approximately three times higher than in 2014. The western pacific region reported more than 3, 75,000 suspected cases of dengue in 2016, of which the Philippines reported 1,76,411 and Malaysia 1,00,028 cases. The Solomon Islands declared an outbreak with more than 7000 suspected cases. In the African region, Burkina Faso reported a localized outbreak of dengue with 1061 probable cases. In 2017, a significant reduction was reported in the number of dengue cases in the Americas from 21, 77,171 cases in 2016 to 5, 84,263 cases in 2017. Panama, Peru, and Aruba were the only countries that registered an increase in cases during 2017 <sup>[13]</sup>.

In 2019, in the region of America between an epidemiological week (EW) of 1 and 22, a total of 1,191,185 cases of dengue have been reported, of which 5,46,589 were laboratory confirmed and 5,599 were classified as severe dengue <sup>[15,16]</sup>. The Philippines reported an estimated 40,614 cases so far 2019 (till March 2).

### **3. Distribution in India:**

Out of 7 identified countries in the south -East Asia region, India is one of them in reporting DF, DHF, DSS, SD. Several fatal forms of the disease i.e., DHF, DSS have been frequently reported in major metropolitan cities such as Kolkata, Chennai, and Delhi. Until the mid-1990s, dengue was reported from only three of the four south Indian states, namely, Karnataka, Andhra Pradesh and Tamil Nadu <sup>[17]</sup>. In Chennai, in 1970 the first epidemic of clinical dengue-like illness was recorded in India and the first dengue fever which was virologically proved was occurred in Kolkata and eastern coast of India in 1963 to 1964. There has been a more than 300 % hike in dengue cases since 2009, and even the total number of deaths in 2017 was the highest in the last decade. From less than 60,000 cases in

2009, cases increased to 1, 88,401 in 2017, according to the data from the National viral borne disease control program (NVBDCP). Similarly, in 2018 total (3,135) cases in Ahmedabad were recorded as per national health profile (NHP) 2018.

### **3.1 The maximum spike in southern and northern states**

While north-eastern states such as Sikkim, Nagaland, Mizoram, and Tripura have seen the highest leap in terms of percentage, the southern states shared the maximum burden of numbers. For example, just four states had collectively recorded 66,057 cases, which is close to 40 % of the total cases recorded in the country. According to NHP 2018, dengue outbreaks have continued since 1950 but the severity of the disease has raised in the last 2 decades. Dengue is massively spreading in the southern state of Karnataka. Similarly, in the state of Andhra Pradesh: East Godavari, Vishakhapatnam, Guntur, and Chittoor are some of the most affected districts.

## **4. Dengue cases in the past:**

### **4.1 Across the world**

The compatible symptoms of dengue were first noted in a Chinese medical encyclopedia in 992 A.D. The viral etiology and the transmission by mosquitoes were only finally determined in the 20th century. The primary mosquito vector, *A. aegypti*, is debated to be from either Africa or Asia. It was widespread throughout urban tropical coastal cities of the world due to the use of shipping vessels which allowed transportation of breeding sites for the vector along with humans to complete the transmission cycle, allowing for the slow but evident introduction of the virus and the mosquito to coastal destinations around the world. Epidemics were placed by 10-40-year intervals due to this shipping mode of transport (Pan American Health Organization, 2016).<sup>17</sup> By the end of world war II, the enhanced transmission of dengue and hyperendemicity in most south-east Asian countries took place [18].

Before 1970, only 9 countries had experienced severe dengue cases, a number which has since quadrupled [18]. Older data suggested an estimated 50-100 million cases of dengue fever and 5,00,000 cases of DHF struck worldwide with 22,000 deaths (Pan American Health Organization, 2016) [17]. Estimation of dengue cases in the world can vary, but approximately 50 million to 200 million dengue infections. 5, 00,000 episodes of severe dengue (DHF/DSS)

and over 20,000 dengue-related deaths occur annually. In most countries, the main burden of this morbidity and mortality lies with children. Due to poor disease surveillance, low level of reporting, low case fatality rate, difficulties in diagnosis and inconsistent analyses, the real global burden of disease and associated economic impact is unknown <sup>[17]</sup>.

#### **4.2 Across India**

The first DENV isolated from human sera in India, in 1945, in Calcutta, was a serotype 1 virus. DENV -2 was identified in 1956, DENV -4 was isolated in 1960 and DENV - 3 was identified in 1965. The earliest virologically confirmed outbreak occurred in 1956 in Vellore. The primary large epidemic of dengue began in 1963 in Calcutta, West Bengal. This was the initial dengue epidemic in India with a significant number of DHF cases, with up to 30% of the cases showing hemorrhagic manifestations and resulted in 200 deaths <sup>[19]</sup>.

The epidemics of 1996 started in the areas around Delhi and spread rapidly across most parts of the country confirmed by 16517 reported cases and 545 deaths. Delhi city was the most severely affected region with 10252 cases and 423 deaths. The relentless number of cases and deaths were also reported from the neighboring states of Haryana, Punjab, Rajasthan, Uttar Pradesh, and two southern and western states during that period.

Dengue in India during the early 2000s progressed from being predominantly restricted to a relatively small number of states in the southern regions (Maharashtra, Karnataka, Tamilnadu, and Pondicherry) and north-western regions surrounding Delhi (Rajasthan, Haryana, Punjab, and Chandigarh) to a situation where it currently affects large parts of the country. The number of dengue cases increased again after 2002, with 6000-8000 cases reported per year, reflecting sustained transmission. Two other large epidemics with a substantial number of deaths occurred in 2003 and 2006. Case fatality rates remained above 1% from 2003-2007 and falling to lower levels in 2008-2009. Kerala witnessed the highest annual average rainfall of 2375 millimeter during this period, it had the highest dengue incidences of 49.278 per million population <sup>[17,19]</sup>.

## 5. Dengue cases at present:

### 5.1 Dengue cases reported worldwide

Guadeloupe reported 343 confirmed cases of dengue in 2019 compared to 18 cases in 2018. Martinique reported 50 confirmed cases compared to zero last year. Australia has reported 1,268 cases of dengue in 2019, which is more than the same time in 2018 (828 cases). Vietnam has reported 2,00,000 cases, including 50 deaths. There is an increase of 75,249 cases since the report for July 2019. An outbreak with more than 600 cases has been reported in East China as of September 2019. China faces an increase in dengue cases in 2019, according to WHO. Earlier they had reported 1, 527 cases. Cook Islands has reported 1,268 confirmed cases of dengue in 2019, as of at the end of September 2019, of which 22 cases were DENV - 2. Saint Martin reported 12 confirmed cases in 2019, of which seven cases were reported since mid -October 2019 <sup>[20]</sup>.

Laos reported 33,728 cases including 59 deaths in 2019 and as of EW 41 (ending of 12 October 2019). Although the weekly trend in reported cases is decreasing, in contrast, to the same period of 2018, during which Laos reported 5,497 cases. New Caledonia has reported 3,902 dengue cases including two deaths since the beginning of the year as of 16 October 2019. Benin has reported 19 suspected and 11 confirmed cases of dengue fever, including 2 deaths between 10 May and 17 October 2019. The Philippines reported 3,71,717 cases and 1,407 deaths as of 19 October 2019. Last year for the same period, the country reported 1,80,072 cases and 927 deaths. According to the national institute of health, Pakistan has reported 20,754 cases of dengue as of 20 October 2019. Tanzania has reported 6,917 cases, including 13 deaths from August 1, 2018, until 20 October 2019.

French Polynesia has reported 1,890 cases of dengue since the beginning of the year and as of November 2019. In early November 2019, the European center for disease prevention and control (ECDC) published a rapid risk assessment of sexual transmission of dengue in Spain. This is the first time probable sexual transmission of dengue which has been reported in an area without the presence of vector mosquitoes. Cambodia has reported 62,938 cases of dengue in 2019 and as of 7 November 2019. This is an eight-fold increase compared to 8046 cases for the same period in 2018. The Maldives reported 4, 505 cases in 2019 and as of 12 November 2019, including 126 deaths <sup>[20]</sup>.

The Marshall Islands have reported 1,085 cases of dengue, including 280 confirmed cases and one death in 2019 and as of 10 November 2019. From the data available as of 11 November 2019, WHO/PAHO has reported 2,733,635 suspected, out of which 1,217,196 confirmed dengue cases in the America region in 2019, including 22,127 severe dengue cases. Taiwan has reported 581 cases in 2019 and as of 12 November 2019. In the same period in 2018, Taiwan reported 533 cases. Nepal has reported 14,662 cases in 2019 and as of mid-November 2019, according to the ministry of health. This is an increase of 9, 657 cases in the past two months <sup>[20]</sup>.

In 2019 and as of 13 November 2019, Sudan has reported 1,720 cases and 17 deaths in Kasalla hospitals and five cases from the El Ganeb locality in port Sudan. Japan has reported 416 cases, in 2019 and as of 13 November 2019. Singapore reported 14,272 cases in 2019 as of 15 November 2019. Bangladesh has reported 98,779 cases, in 2019 and as of 17 November 2019. This is an almost tenfold increase compared to 2018. Malaysia numbers are doubled to last year with reported 1,15,286 cases, including 295 deaths in 2019 as of 18 November 2019. In the same period last year, Malaysia reported 61,254 cases with 104 deaths. Reunion has reported 18,066 confirmed dengue cases and 14 deaths from January 19 November 2019. According to the ministry of health and as of 19 November 2019, Srilanka has reported 72,085 cases of dengue in 2019, compared with 46,000 cases for the same period last year <sup>[20]</sup>.

## **5.2 Dengue cases reported in India**

In India, in Jaipur, there were 1,084 confirmed cases reported in 2019 and as of 21 October 2019. A sharp increase from 535 dengue cases. (reported from January 1 – September 24, 2019). India has reported more than 67000 cases of dengue fever as of October 13, 2019, according to data released by the directorate of the National vector-borne disease control program (NVBDCP) of the 67,377 total cases reported, Karnataka has the highest-burden out of the country with 12,756 cases in 2019. It also accounted for eight of India's 48 facilities due to the vector-borne diseases, which is typically transmitted by the *A. aegypti* and *A. albopictus* mosquitoes in 2019.

In addition to Karnataka, other high burden states include Maharashtra with 7,863 cases, Uttarakhand with 7,513 cases, Gujarat with 5,819 cases, Kerala with 3,075 cases, Bihar with 1,588 cases, Delhi with 1,431 cases in 2019. In Mumbai, the first two weeks of October alone saw 2,000 hospitalized due to suspected dengue cases in 2019 (Pan American Health

Organization, 2019) <sup>[20]</sup>. As of June 24, 2019, the country has already recorded 9,143 cases. Dengue cases are on the rise in Kerala, Kasaragod district, alone has recorded 328 dengue cases till June 20, 2019.

#### **6. Authors' contributions statement:**

Gade. Kalyani contributed to conceptualizing the ideas for this review article and Thanushree worked for writing the paper from the inputs obtained from different sources for the past few months. Dr. D. Ravi Sankar Reddy helped supervise the review article and provided critical feedback and helped in shaping this manuscript.

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#### **8. Conflict of interest:**

The corresponding author G. Kalyani and the co-authors Thanushree, Dr. D. Ravi Sankar Reddy, Dr. Rinku Mathappan declare that we don't have any conflict of interest.

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