Review Article

A notorious vector-borne disease: Dengue fever, its evolution as public health threat

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Abstract

Dengue fever, the most notorious of vector borne diseases is under global resurgence. Incidence has increased 30 fold with global expansion. It is thus imperative to review the origin, history and current epidemiology of dengue, its transmission, factors responsible for resurgence, surveillance and the treatment options available. India being hyperendemic, national level comprehensive studies to estimate the true burden of dengue along with its geographical mapping is the need of the hour. Through integrated and combined efforts from various sectors and policy makers, prevention of dengue must be identified and intensified to control further disease transmission as there is no specific antiviral treatment or vaccine against dengue is available in India.

Keywords: Aedes, dengue epidemiology, surveillance, urbanization

Background

Dengue virus (DENV) is a positive-stranded encapsulated RNA virus of family Flaviviridae having four serotypes referred to as DEN-1, DEN-2, DEN-3, and DEN-4.[1] It is composed of three structural protein genes, which encodes the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein and seven nonstructural (NS) proteins. They are transmitted chiefly by the Aedes Aegypti mosquito and also by Aedes albopictus.[2] Aedes Aegypti also transmits Chikungunya, yellow fever, and Zika infections.[1]

Dengue also referred to as "water poison," "cramp-like seizure," or "break bone fever"[2] is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold along with geographic expansion. Although only nine countries had experienced severe dengue epidemics prior to 1970, the disease is now endemic in more than 120 countries and an estimated 3.9 billion people are at risk of infection with DNVs, with nearly 400 million infections occurring annually.[1,3] This significant public health threat is no longer confined to the tropics — autochthonous dengue transmission has now been recorded in several European countries[4] and in 2014, Japan reported its first outbreak of the disease in 70 years.[5]

With global resurgence, it is imperative to review the origin, history, and current epidemiology of dengue, its transmission, factors associated and the treatment options available for which through search of relevant articles was made in PubMed, Google Scholar, Semantic Scholar, and Ovid. This report gives a comprehensive understanding of the disease and its management, the knowledge of which is a prime importance to practice of primary healthcare. Realizing the importance Government of India has named 16th May 2019 "National Dengue day." The theme was "Fight the bite: Prevent Dengue" which again signifies the importance of prevention and role of primary healthcare providers.[6]

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Epidemiology of Dengue Virus

The epidemiology of dengue significantly changed in south-east Asia during and following World War II.[7] These years of war were responsible for creating conditions (hyperendemicity and high densities of Aedes Aegypti) susceptible for the emergence of DHF in south-east Asia. In the years following World War II, unprecedented urbanization in south-east Asia led to inadequate housing, deterioration of water, sewer, and waste management systems. The Aedes Aegypti and DNVs thrived in this new ecological setting, with increased transmission and frequency of epidemics occurring in the indigenous populations particularly children. Moreover, with economic expansion and continued urbanization along with ever increasing migration of people, those cities and countries that do not have multiple serotypes cocirculating as such have become hyperendemic. The viruses, often all four serotypes, were maintained in a human-Aedes Aegypti-human cycle in most urban centers of south-east Asia.

The epidemiology of dengue in the Indian subcontinent has been very complex and has substantially changed over almost past 6 decades in terms of prevalent strains, affected geographical locations, and severity of disease. The very first report of existence of dengue fever in India was way back in 1946.[8] Notable epidemics are one in the eastern Coast of India (1963-64),[9] Delhi (1967),[9] and Kanpur (1968).[10] The southern part of the country was also involved with wide spread epidemics followed by endemic/hyperendemic prevalence of all the four serotypes of DENV. The epidemiology of DNV and its prevalent serotypes has been ever changing. The epidemic at Kanpur (1968) was due to DV-4 but in the subsequent 1969 epidemic, both DEN-2 and DEN-4 were isolated.[11] It was completely replaced by DEN-2 during 1970 epidemic in the adjoining city of Hardoi.[12] In Delhi, till 2003, the predominant serotype was DEN-2 (genotype IV) but in 2003 for the first time all four DNV subtypes were found to cocirculate thus changing it to a hyperendemic state,[13] followed by complete predominance of DEN serotype 3 in 2005.[14,15] Further, replacement of DEN-2 and 3 with DEN-1 as the predominant serotype in Delhi over a period of 3 years (2007--2009) has been reported.[16] Emergence of a distinct lineage of DEN-1, having similarity with the Comoros/Singapore 1993 and Delhi 1982 strains, but quite different from the Delhi 2005 lineage and microevolution of the precirculating DEN-3 has been reported.[17] Cocirculation of several serotypes of DNVs has resulted in concurrent infection in some patients with multiple serotypes of DEN.[18] Concurrent infection by Chikungunya and DEN-2 was reported from Vellore and Delhi.[19,20]

Transmission cycle

Infection with DNVs is transmitted through the bite of infective female Aedes spp. Mosquitoes.[21] Aedes Aegypti, the principal vector, that prefers to lay its eggs in artificial water-containers commonly found in urban areas of the tropics. After a period of incubation lasting 3 to 14 days (average 4 to 6 days), the person may experience an acute onset of fever accompanied by a variety of nonspecific signs and symptoms. During this acute febrile period, there is a viremia, which may vary in magnitude and duration.[22,23] This phase is responsible for the maintenance of human-Aedes Aegypti-human cycle with an extrinsic incubation period of 8 to 12 days

Viral interhost variation

In humans, infection with DNV results in a spectrum of clinical outcomes, ranging from self-limiting, uncomplicated dengue fever (characterized by a sudden onset of fever and one or more of a number of nonspecific signs and symptoms such as frontal headache, retro-orbital pain, myalgia, arthralgia, nausea and vomiting, weakness, and rash) to the more severe dengue hemorrhagic fever (DHF). The critical stage in DHF is at the time of defervescence when the patient develops a capillary-leak syndrome, with signs of circulatory failure and hemorrhagic manifestations, primarily skin hemorrhages, thrombocytopenia (<100 000/mm^3), and elevated hematocrit being the prominent features. In the most severe cases, these hemorrhagic manifestations lead to potentially fatal hypovolemic shock, a condition known as dengue shock syndrome. Infection with one serotype of DENV confers short-lived immunity against heterologous serotypes and with waning immunity; there is an increased risk of severe disease. This phenomenon, known as enhancement, may be mediated through antibody responses that are directed against the previous instead of the current serotype, leading to increased viral replication.[24]

Factors responsible for global resurgence of dengue

The reasons for the dramatic resurgence of epidemic DF/DHF in the latter part of 21st century are complex and not fully understood, but are most likely associated with demographic and societal changes[25] and significant factors are:

1. Unplanned urbanization: The main factor in dengue resurgence is unplanned urbanization with the overcrowded population, which is characterized by lack of basic infrastructures, substandard housing conditions, deficiencies in water supply, and sewage management.[26] Improper water supply which has resulted from rapid urbanization contributes to the habitat expansion of the vector, Aedes Aegypti as the residents have to reserve water in vessels, which promotes mosquitoes breeding. Evidence from research stated that low-income groups with no air-conditioning and poor street drainage are most likely to be infected.[27] Furthermore, inappropriate disposal of nonbiodegradable materials like plastic containers and old tires are potential breeding sites for mosquitoes due to the ability to serve as water reservoirs. The main effective measure to control vector is source reduction and it is crucial to be able to distinguish and address not only outdoor but also indoor wastes as a study reported that 79% of the total breeding sites was indoor in Singapore.[28]
2. Transportation and migration: Rapid global migration with the aid of modern transport system creates an extensive urban network which increases the potential for vector and virus dissemination to new a territory. Global transmission

and spread of virus leads to genetic expansion of virus which makes it more difficult to control the infection spread. Hence, tourism and immigration are risk factors of dengue transmission.

3. Usage of insecticides: The extensive and indiscriminate use of insecticides worldwide is one of the main challenges in eradication of vector due to global pandemic of insecticide resistance. The ability of larvicides to control vectors also limited as it has low coverage in term of the large pool of breeding sites present in any urban environment. In Asia and America, studies show that after application of the ultralow volume, the population of adult mosquitoes returned to the pretreatment level within 2 weeks and even with multiple applications, the impact resulted was minimal.[28]
4. Public perception: Although community participation in disease control is crucial, but often public perceives that dengue control is solely a responsibility of governmental agencies. Several studies revealed that people from dengue endemic countries understand the disease and its transmission, but the control practices are not equivalent to the knowledge about the disease. There is no sense of urgency within the population even though the incidence of dengue has increased at an alarming rate. Education is important, but solely dependent on the interventions that rely on education strategies shown to have less impact on behavioral and entomologic indices
5. Limited infrastructure and resources: National Vector Borne Disease Control Program (NVBDCP) covers malaria, dengue, Chikungunya, and Japanese encephalitis, and also works for the elimination of Kala-azar and Lymphatic Filariasis. The allocation to the program has seen a 3% decline, from INR 482 crore in 2011-12 to INR 463 crore in 2015-16.[29] Also, the field workers involved are less motivated and poorly supervised as they are under paid and lack communication skills. Most participants involved lose interest in vector control during the low transmission period; thus, resulting in subsequent increase in vector's population. Other factors include limited infrastructure and resources in control and surveillance, limited quality of diagnosis, and clinical care and the need of more advance entomological tools to standardize and classify the vectors.

Surveillance in dengue fever

Surveillance is a prerequisite for monitoring the dengue situation in the area and should be carried out regularly for early detection of an impending outbreak and to initiate timely preventive and control measures. Surveillance should include epidemiological, entomological, and laboratory parameters.[30]

Epidemiological surveillance incudes fever surveillance; diagnosis based on standard case definition; reporting of DF/DHF cases to state health authorities; during an outbreak situation, if 5 to 10% of the samples collected from clinically diagnosed cases are found positive by laboratory, others would be considered epidemiologically linked cases. However, atypical cases (doubtful) samples must be sent for laboratory confirmation.

Vector surveillance[31-33] includes larval surveillance during the premonsoon and monsoon to find out the extent of prevalence of vectors in certain selected high risk localities/areas (from where dengue cases have been reported earlier). House index (percentage of houses positive for larvae of Aedes Aegypti), container index (percentage of water containers positive for Aedes breeding), and Breteau index (number of positive containers for Aedes Aegypti per 100 houses) are usually used. Adult mosquito surveillance will help in finding out the susceptibility status to insecticides. However, a single water container found positive for Aedes breeding warrants for immediate action for source reduction [Table 1].

Laboratory surveillance[34] confirms the clinical diagnosis and provide report to the public health authority. The laboratory should receive selected samples from Sentinel Hospitals from fever of unknown origin for serological surveillance and viral detection for setting up of early warning signals for timely institution of preventive and control measures. The objective of the laboratory surveillance is to detect the introduction of the virus, the new strain or serotype of DNV, and to detect any unusual increase in the spread of dengue transmission.

Treatment and prevention

There is no specific treatment for dengue fever or for severe dengue though medical care by experienced physicians and nurses has shown to decrease mortality rates from more than 20% to less than 1%. Maintenance of the patient's body fluid volume is critical to severe dengue care.[30]

At present, the main method to control or prevent the transmission of DNV is to combat vector mosquitoes through preventing mosquitoes from accessing egg-laying habitats by environmental management and modification; disposing of solid waste properly and removing artificial man-made habitats; covering, emptying, and cleaning of domestic water storage containers on a weekly basis; applying appropriate insecticides to water storage outdoor containers; using of personal household protection such as window screens, long-sleeved clothes, insecticide treated materials, coils and vaporizers; improving community participation and mobilization for sustained vector control; applying insecticides as space spraying during outbreaks as one of the emergency vector-control measures; active monitoring and surveillance of vectors should be carried out to determine effectiveness of control interventions.[30,35]

Table 1: Showing risk of transmission based on Breteau and house index for Aedes Aegypti

Entomological indices	High risk of transmission	Low risk of transmission
Breteau index	>50	<5
House index	>10%	<1%

Resources needed in the detection and management of dengue

Human resources

The most important resource is trained doctors and nurses. Adequate health personnel should be allocated to the first level of care to help in triage and emergency management. If possible, dengue units staffed by experienced personnel could be set up at referral centers to receive referred cases, particularly during dengue outbreaks.[35,36]

Special area

A well-equipped and well-staffed area should be designated for giving immediate and transitory medical care to patients who require intravenous fluid therapy until they can be transferred to a ward or referral health facility.[35,36]

Laboratory resources

The most important laboratory investigation is that of serial hematocrit levels and full blood counts. These investigations should be easily accessible from the health center. Results should be available within 2 hours in severe cases of dengue. If no proper laboratory services are available, the minimum standard is the point-of-care testing of hematocrit by capillary (finger prick) blood sample with the use of a microcentrifuge.[35,36]

Consumables

Intravenous fluids, such as crystalloids, colloids, and intravenous giving sets should be available.

Drugs

There should be adequate stocks of antipyretics and oral rehydration salts. In severe cases, additional drugs are necessary (vitamin K1, Ca gluconate, NaHCO3, glucose, furosemide, KCl solution, vasopressor, and inotropes).

Communication

Facilities should be provided for easy communication, especially between secondary and tertiary levels of care and laboratories, including consultation by telephone.

Blood bank

Blood and blood products will be required by only a small percentage of patients but should be made readily available to those who need them.

Conclusion

Half of the world's population is at risk from dengue and now it has also established its roots in India where it is becoming hyperendemic in our population. National level comprehensive studies to estimate the true burden of dengue in India and its geographical mapping are not sufficient. Through integrated and combined efforts from various sectors and policy makers, prevention of dengue must be intensified to control further disease transmission as there is no specific antiviral treatment or vaccine against dengue is available. The key options for preventing and controlling dengue are: to control larval habitats in and around people's homes, workplaces, unclaimed empty spaces, dump sites, and public areas, such as place of worships/recreational centers, roadsides, playgrounds, and cemeteries; to reduce human–vector contact.[37] Mortality from dengue can be reduced to almost zero by implementing timely, appropriate clinical management, which involves early clinical and laboratory diagnosis, intravenous rehydration, staff training, and hospital reorganization.

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Conflicts of interest

There are no conflicts of interest.

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