



Review on current status of dengue and its prevention in India

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ABSTRACT

Dengue is an acute viral infection with potential deadly complications transmitted by both *Aedes aegypti* and *Aedes albopictus* female mosquitoes and is said to be a severe and increasing public health problem with 2.5 billion individuals at risk. WHO currently estimates that with around 24,000 fatalities, 50 million cases of dengue disease may occur globally once a year. In India, too, the condition is getting worse as morbidity and mortality rise. Several policies have been adopted to decrease dengue burden through applied research, field-based training, and capacity building among appropriate regional and national public health stakeholders.

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INTRODUCTION

Dengue is an intense viral disease with potential deadly complexities transmitted by the *Aedes aegypti* bite and also by female mosquitoes from *Aedes albopictus*. It consists of an antigenic sub-collection of infection; DENV1-4 serotype, among the genus *Flavivirus*, Family *Flaviviridae*.

It is asserted that dengue infection is a severe, overall medical problem with a measurable 2.5 billion individuals at risk. They may trigger a good clinical disease from delicately symptomatic dengue fever

(DF) to many hazardous clinical circumstances such as dengue shock syndrome (DSS) and dengue haemorrhagic fever (DHF) (Gubler, 2004). It is a self-constraining disease found throughout the globe in tropical and subtropical locations, predominantly in urban and semi-urban areas. In the 1950s, the dengue pestilence in the Philippines and Thailand originally acknowledged haemorrhagic fever (DHF) that could be a deadly problem. Dengue's global omnipresence has tremendous regard in the continuing decades. Currently, the ailment is prevalent in more than 100 countries in South-East Asia, Western Pacific, East Mediterranean, Africa, the America within which South-East Asia and Western Pacific are truly affected. Before 1970, DHF plague had been experienced by 9 countries, an assortment that had gathered more than fourfold by 1995. The WHO is currently assessing that 50 million instances of dengue infection could occur globally once a year with approximately 24,000 passings.

MODE OF TRANSMISSION

When the mosquitoes take blood from them, an infected person transmits the DENV. Inside the

mosquito, the mid gut epithelium is a DENV replication area. In this way, it extends through the hemolymph to replicate in various bodies such as the fat body and trachea and lastly infect the salivary organ at about 10–14 days after the dinner of the blood. Once the mosquito receives a blood supper, DENV is inoculated into a human host, thus spreading the disease. The mosquito vectors, basically *Aedes aegypti*, become infected through the normal 5-day viraemia moment once they feed on individuals. Once an adventitious period, the virus moves from the intestinal tract of the mosquito to the salivary glands, a process that lasts about ten days and is fastest at elevated ambient temperatures. Mosquito bites once the adventitious period ends in an infection that may be promoted by salivary proteins from mosquitoes. The space of transmission of this disease continues to expand due to a few direct and indirect components linked to the populated region, increased transport and warming (Racloz *et al.*, 2012).

Dengue infection: A pathophysiologic approach

Infection with dengue may be a general and dynamic disease. It includes clinical indications ranging from non-serious to serious; it is said to have a broad variety of clinical indications. The ailment begins instantly after the incubation moment and is pushed through the three phases— febrile, critical, and recovery.

Management is comparatively easy, inexpensive and highly feasible in sparing life for a disease that is advanced in its signs as soon as proper and timely interventions are instituted (Martinez-Torres *et al.*, 2008). The key is early recognition and knowledge of clinical problems throughout the various phases of the condition, resulting in a rational approach to case management and a reasonable clinical outcome.

Febrile phase

Patients develop suddenly high-grade fever. This intense febrile phase usually lasts 2-7 days and is usually accompanied by facial flushing, skin erythema, widespread body ache, myalgia, arthralgia and headache. There may be some patients with a sore throat, pharynx infection, and conjunctival infection. It is normal to have anorexia, nausea and regurgitation. It is difficult to differentiate dengue from non-dengue febrile diseases in the early febrile stage. A positive tourniquet test will reveal the probability of dengue. Similarly, petechiae and mucosal layer bleeding (e.g. nose and gums) are also noted as some of the benign hemorrhagic manifestations. In particular, in women of childbearing age and gastrointestinal bleeding, immense bleeding of the

vagina could occur throughout this stage anyway is not normal. After several days of fever, there will be hepatic enlargement and tenderness. The most notable shot of dengue that alarms the doctor is the gradual decrease in the number of white blood corpuscles.

Critical phase

Around the defervescence season, when the temperature drops to 37.5–38 °C or less and remains below this aspect, usually on illness days 3–7, an increase in capillary permeability could occur in conjunction with growing concentrations of hematocrits. This indicates the critical stage start. Clinically essential spillage of plasma usually continues 24–48 hours. Progressive leukopenia followed by a rapid decrease in the number of platelets in the blood usually comes before the spillage of plasma. Additionally, pleural effusion and ascites can be clinically distinguished by the plasma spillage rate and the quantity of fluid therapy. Chest X-ray and abdominal ultrasound will be helpful diagnostic instruments along these lines. The increment concentration above the normal hematocrit usually reflects the plasma spillage's seriousness. Once a critical plasma volume is lost through spillage, shock occurs. It's usually passed before by signs of notice. Additionally, once a shock happens, the body temperature is subnormal. The resulting organ hypoperfusion winds up with delayed shock in progressive organ weakness, metabolic acidosis, and intravascular coagulation disseminated. This gradually winds up in severe hemorrhage resulting in the decrease of the hematocrit in severe shock. Unlike leukopenia usually found throughout this era of dengue, in patients with severe bleeding, the entire white blood corpuscle count could improve. In addition, a severe weakening of the organ, such as severe hepatitis, encephalitis or myocarditis, or possibly severe bleeding, can cause plasma spillage or shock without apparent shock.

Recovery phase

If the patient endures the critical phase of 24–48 hours, slow reabsorption of extravascular compartment fluid occurs within 48–72 hours of the accompanying phase. Improves general prosperity, decreases in appetite subsides gastrointestinal side effects, settles hemodynamic status, and outcomes in diuresis. Some might experience pruritus; throughout this phase, bradycardia and electrocardiographic changes are normal. In perspective of the dilutional effect of reabsorbed liquid, the hematocrit balances out or is equally smaller. White blood cell count usually starts to increase shortly after defervescence. However, blood platelet count recovery is

frequently later than white blood cell count recovery. Whenever excessive intravenous fluids are administered, respiratory distress from enormous pleural effusion and ascites can occur. Excessive fluid therapy is associated with pulmonary edema or congestive heart deception throughout the critical and recovery stages (Lalla *et al.*, 2014).

Dengue genotypes and vectors in india

Dengue is one of the Flaviviridae family's most critical human pathogens, which also includes yellow fever infections, Japanese encephalitis, and West Nile encephalitis. For a considerable length of time, four serotypes (DENV-1 to 4) are far-framed. A mooted fifth serotype has been accounted for as recently as possible (Mustafa *et al.*, 2015), but its recognition remains to be endorsed. DENV is a single-stranded positive RNA virus with a diameter of about 50 nm. Basically, a capsid (C) and an external shell of glycoprotein and an inner lipid bilayer enclose its genome. Envelope (E) and film (prM / M) glycoproteins are incorporated in surface projections within the lipid layer. The genome is approximately 11 kb in size and encodes three structural genes (C, prM and E) and seven non-structural (NS) genes (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). NS-coded proteins suppose viral replication and assembly employment (Henchal and Putnak, 1990). Because of the nature of human transmission and the severity of clinical infection, DENV serotypes are instructed to have a small, medium or high epidemiological impact (Åström *et al.*, 2012). A claimed discovery of another serotype, DENV-5, is giving the dengue management an extra challenge. Each serotype has unique features and, depending on its communication with the host response, may offer extreme signs in a specific population. DV-1 was isolated at Vellore in 1956. All the isolates of Indian DV-1 have a position with the genotype of American African (AMAF). The Indian DV-1 segregates divided into four lines, India I, II, III and the African lineage in addition. Of these, India III is the most seasoned and wiped out heritage; Afro-India is a temporary lineage, whereas India I is imported from Singapore, and India II is the present lineage, evolving in situ (Patil *et al.*, 2011). The Cosmopolitan genotype eventually replaced the American genotype of DV-2, which dominated India throughout the pre-1971 era. Post-1971 Indian isolates placed within the Cosmopolitan genotype a distinct subclade. DV-2 strains have been isolated for 50 years (1956-2011) in India. In 2003, the re-development of a DV type-3 pandemic strain in Delhi and its persistence in subsequent years indicated a vibrant trend in DV dissemination in this portion of India (Kukreti *et al.*, 2008). There are also occasional reports of DV-

4 flow, but this is not the common form in India (Dar *et al.*, 2003).

Epidemiology and outbreak

Since 1963, when the first epidemic was recorded in Calcutta, Dengue has been present in India and gradually distributed throughout India in 1967, and all four virus serotypes were recorded by South India. In 1996, 10,252 instances and 423 fatalities were recorded as the first significant DF/DHF epidemic induced by DENV-2 serotype in Delhi after three decades. Almost all of the four serotypes were noted, and by 1996-2003 the frequency of outbreaks in the population also increased. In 2003, with 12,754 cases and 215 fatalities, another major outbreak spread to Northern and Central India [Delhi and Gwalior]. DENV-3 was recorded as the main serotype. Andhra Pradesh, Delhi, Goa, Haryana, Gujarat, Karnataka, Kerala, Maharashtra, Rajasthan, Uttar Pradesh, Pondicherry, Punjab, Tamil Nadu, West Bengal, and Chandigarh were accounted for a flare-up of DF/DHF in the year 2005-2008. There were 28,292 cases and 110 fatalities recorded in 2010 (Gupta and Ballani, 2014). India experienced a widespread epidemic of dengue fever in 2012. Tamil Nadu recorded 12,826 cases with 66 fatalities, followed by West Bengal, which reported 6,456 cases, the largest number of cases in the nation. The amount of dengue cases also risen in Maharashtra, Kerala, Karnataka, Odisha, Delhi, Gujarat, Puducherry, Haryana and Punjab (Bandyopadhyay *et al.*, 2013).

The latest research conducted at Oxford University estimated that India has the biggest amount of cases of dengue owing to a rise in human population size (15% of the world population). The age group reported the largest number of cases 11-30 years and males obviously outnumbered women. During the monsoon and post-monsoon seasons, most cases were recorded. According to the reports, all four dengue virus serotypes are co-circulating in India (Gupta *et al.*, 2012). Any negative climate circumstances affect the vector to select a more favourable settlement environment. An increase in global temperatures over the past four decades may correlate with enhanced danger of outbreaks of dengue. Changes in climate, high global average temperature and humidity boost dengue's epidemic potential (Wilder-Smith *et al.*, 2013). Urban and suburban growth can provide abundant ready-made breeding sites as well. Increased travel and trade is an impact of globalization, which are significant considerations for enhanced dengue transfer. Travel and tourism are important problems in the context of dengue transmission, as it is believed that

the movement of dengue-infected people is a major driver of worldwide disease development (Nepal *et al.*, 2014).

Generally low economic status, high population density and ideal condition for mosquito maintenance in developing nations promote DENV transmission. Many dengue outbreaks in nearby/neighboring nations have been affected by dengue epidemics (Guo *et al.*, 2017). Usually, urban regions are at high danger, with high population density, bad hygiene and a big amount of desert coolers, flower vases, building sites, overhead tanks, discarded buckets, tyres, utensils, etc. promoting mosquito breeding. Dengue fever / DHF can also happen in rural regions where the environment is friendly to mosquito breeding such as storage water for cattle feeding and drinking, cement cisterns, coconut shells, underground cemented water sumps, discarded tins, tyres, bottles etc. that are not periodically emptied and altered.

Current situation of Dengue in India

Epidemiological studies conducted in India in 2017 showed more incidence of dengue in Kerala followed by Tamil Nadu owing to climatic circumstances, as shown in Figure 1. Tamil Nadu has a higher death rate, followed by Kerala and Uttar Pradesh (Nvbdc, 2017). There was also a concomitant infection with various dengue serotypes (Bharaj *et al.*, 2008). In this manner, it is evident that there is now a definite increase in the recurrence and amount of flare-ups in India alongside the co-dissemination of each of the four serotypes, which implies dengue hyperendemicity in India.

Treatment of Dengue virus infection

There are currently no convincing antiviral agents available for treating dengue infection. Managing the infection with dengue virus is fundamentally stable and symptomatic. The therapy of choice is intravenous rehydration; this intervention will reduce the morbidity rate to less than 1% of severe cases. Dengue's vibrant nature requires close surveillance and repeated clinical and laboratory evaluations. There is a rapid response to platelet and fresh frozen plasma and cryoprecipitate transfusion (Chaudhary *et al.*, 2006). Furthermore, since the hepatitis C virus (HCV) is an individual of the *Flaviviridae*, underlying antiviral enhancement in disease management due to HCV may also be potent against dengue infections (Mishra *et al.*, 2017). In modern medicine, the cytostatic and inhibitory effects of ribavirin, glycyrrhizin and 6-azauridine on dengue infection are reported. Another promising medication currently under consideration is 'NITD008'

an adenosine analogue. Water and electrolyte status should be kept away from under and over fluid administration throughout therapy many Ayurvedic herbs, such as Amaltas, Datura, Hara dhanian, Hermal and Kanghi, seem viable in the therapy of dengue fever (Lalla *et al.*, 2014).

Future Endeavors

The proposal that public health issues regarding dengue should turn out to be increasingly extreme is substantially verified (Wilder-Smith *et al.*, 2013; Messina *et al.*, 2015). Vaccination and vector control therapy are the key to fighting dengue despite the lack of convincing ways at present. There are still clinical trials of vaccines; so far, there are no effective antiviral drugs. An extended focus should be coordinated in this manner towards avoiding ailment and controlling mosquitoes. No matter how many awareness programs are dispatched, different problems continue to be dealt with efficiently. Fast urbanization, lack of vital sanitation, and exaggerated intra-and inter-migration operations have exacerbated the problem in many places. In this particular scenario, it is also worth considering potential factors that drive dengue movement, comparable to modifications in the development of viruses (viral genotype exchange), diversity of the atmosphere, industrialization, urbanization and thus the trade cycle, and the potential for spread from urban to rural areas (Gyawali *et al.*, 2016).

Prevention

Vector control

Compelling vector control methods are an important component of reducing dengue-related mortality and morbidity with helpful restricted approaches and, moreover, the current lack of a vaccine (Gupta and Ballani, 2014). In view of the reality that the conveyance of stray cases during the time focuses on the enduring transmission of dengue infection, care is therefore needed for effective vector control interventions. As dengue diseases are discovered in the post-monsoon season throughout pandemic and non-epidemic years, preventive measures should be in complete swing at the very start of the monsoon (Bandyopadhyay *et al.*, 2013). The papaya leaf juice was thought to catch the platelet pulverization that caused several fatalities. Researchers in Ayurveda have found that enzymes within the papaya leaf will battle a large group of viral infections (Lalla *et al.*, 2014).

Individual protection guidelines

For the Indian environment, some dengue instructions do not seem to be entirely practical. India's warm climate and traditional clothing do not add

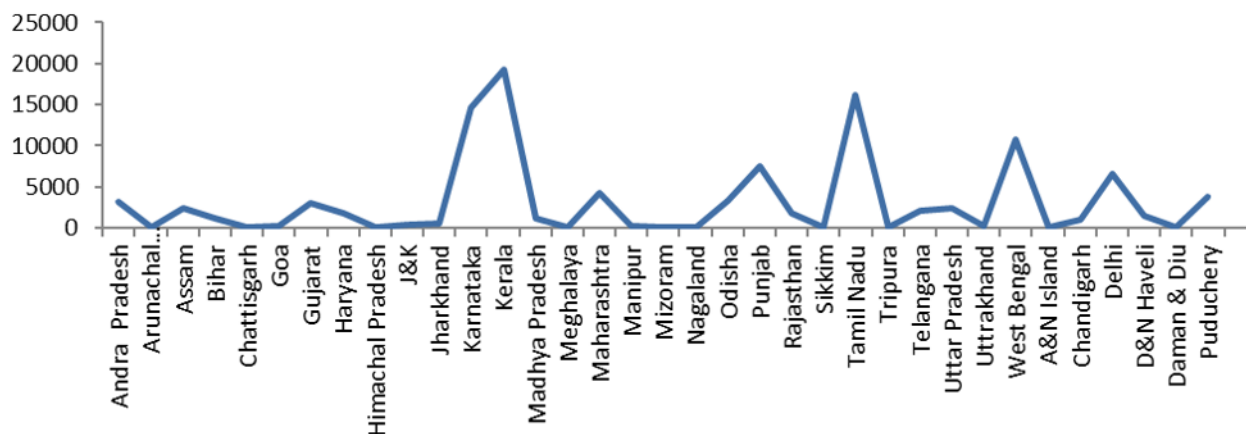


Figure 1: Dengue cases and deaths in 2017

to individual defensive measures such as wearing long-sleeved clothing; however, this measure is set out in most government rules. The use of insect repellents is equally important for individuals with middle and high incomes; however, the poor are unlikely to notice such an affordable product. In rural and urban regions, the use of mosquito coils, electrical fans and mats were observed; these measures were used daily by only 40 percent of rural employees. Approximately half of the urban members thought that private protective measures were dangerous for their well-being, and rural members spent considerably less money on such measures than in urban areas. Protective creams and sprays for procurement were not widely used or available. Cheap, efficient, enjoyable to use, widely available and accepted should be a strong insect repellent for the Indian environment.

Vector surveillance

Vector surveillance was performed with completely distinctive ports all through flare-up in separate areas. The container index was 22 percent throughout Calcutta City's first episode of dengue. Thus, the container index for *Ae. aegypti* in Visakhapatnam was high in the most over-affected area III. The absence of water and elevated stockpiling practices in Jalore City extended the *Ae. aegypti* population and episode of dengue throughout April-May 1985 (Sharma et al., 2014).

Initiatives

- 1) Improve disease observation: Expand vibrant blood supply and vector monitoring to improve the perception of dengue transmission dynamics and spot epidemics. The dynamic observation could be coordinated into current primary care centers with further subsidization.
- 2) Enforce vector control: Increasing punishment

for people and organizations does not discover a way to reduce the multiplication of vectors. This will provide incentives to involve individuals and the community. Moving policy actions from top-down to the community—based ways of preventing dengue transmission can expand ability.

3) Establish dengue as a research center: Priority for the Indian Council of Medical Research and increment subsidizing openings and recognition for advances in dengue research. Much remains obscure about the research of transmission of disease, patterns of transmission, and pathogenesis of the development of ailment. Research in incidence and seriousness is anticipated to get prepared and plan for future trends.

4) Prioritize: Collection of solid waste and water management to reduce the inexhaustible local reproductive vector. Without enhanced frameworks for waste management and sanitation, vector-borne diseases are going to be severe, if not hard to manage.

5) Create incentives for community education and vector monitoring: The NVBDCP now has a broad cluster of phenomenal IEC to mobilize and educate the community on *Aedes*-borne disease and vector control. KAP surveys have shown that much of the public stays credulous about vector control and transmission of disease. Incentives to encourage extended IEC can make it easier for individuals to activate against *Aedes* in particular.

Future options for Dengue control

Integrated vector management

WHO maintains integrated vector management (IVM) as an extra approach to combat *Aedes* dengue transmission (Messina et al., 2014). IVM is described as 'a rational decision-making technique for the best use of vector control resources'. The rea-

son behind IVM is an integrated collaborative initiation among various contributing sectors for support, social mobilization and legislation.

Biological control

Another vector control instrument for suppressing and substituting the *Ae.aegypti* population is currently under inquiry. This is the 'release of insects carrying a dominant lethal' (RIDL) structure for male mosquito mass-rearing with the presentation of a deadly inherited transition (Franz *et al.*, 2014). Another advancement for biological control of the vector is to present strains of a normally happening intracellular endosymbiotic bacterium alluded to as *Wolbachia* into *Ae. aegypti*.

Vaccines

Despite actual problems, improvement in dengue immunization has been a field of vibrant studies for a long time. In any event, recombinant approaches to DNA have made significant progress and product assortment in a few clinical stages (Ishikawa *et al.*, 2014). The ideal dengue vaccine should be free from essential reactogenicity, provide long-lasting disease protection with any of the four DENV serotypes, and be inexpensive. The applicant has progressed to stage III efficacy trials straight at the most outstanding point of clinical development, a live-attenuated tetravalent vaccine based on the chimeric yellow fever-dengue virus (Thisyakorn and Thisyakorn, 2014). A broad variety of applicants for vaccines such as live-attenuated, subunit, deoxyribonucleic acid (DNA) and refined inactivated vaccines are at previous clinical development stages. Extra innovative methodologies are being evaluated in preclinical inquiries, for instance, vector viruses and viruses such as particle-based immunizations. The vibrant period of two crucial IIb / III effectiveness research for ChimeriVax, a DENV 1-4 vaccine conducted in Asia and Latin America, has been completed by Sanofi biologist.

DENVax

In 2011, Inviragen completed DENVax's Phase I clinical study, which was conducted as a team with PECET (Program for the Study and the board of Tropical Diseases) in Colombia, South America. As of now, in an additional stage 1b clinical study in the U.S., DENVax is being examined, and a few clinical trials in the U.S. (Puerto Rico), Colombia, Singapore, and Thailand are being phased out.

Public knowledge, attitude and practice

The present knowledge dimension of the population as a whole, their attitude and conduct all assume significant roles in choosing the after-effect of programs that are maintained to restrict dengue.

Failure to prioritize the installation of residential door and window screens, imprudent disposal of local waste, absent-minded maintenance of internal household containers (e.g. disposed tyres, broken plates and mugs, flower pots) in which water can be collected and along these lines give mosquito rearing locations, all contribute to vector multiplication and dispersal (Gyawali *et al.*, 2016).

New Challenges

As the operations of development viz. Highways and rainwater harvesting projects occur massively within the country, with the potential for mosquito vectors extending in the lack of a Health Impact Assessment (HIA). As of late, there has been an episode of dengue in Kolkata owing to heavy breeding in fringe areas of *Aedes aegypti* owing to elevated approach growth. In addition, rainwater harvesting operations are cordial mosquito vectors in certain metropolitan towns such as Chennai and Delhi and add significant potential for future Vector-Borne Diseases flare-ups (Sharma *et al.*, 2014).

CONCLUSION

Dengue in India has set up its underlying foundations. Methods such as vector control, vaccine development and antiviral drug regimens are the future options to fight with this disease. Currently, vector control is the only efficient method that can be used to control the disease due to lack of immunizations and specific treatments.

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