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# Dengue: epidemiology, prevention and pressing need for vaccine development

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## ABSTRACT

Dengue fever is a mosquito born viral infection, and the complicated form of dengue is dengue hemorrhagic fever (DHF). In the recent decades incidence and distribution of dengue has increased dramatically. Dengue viruses belong to family flaviviridae with four serotypes and are transmitted mainly by mosquito *Aedes aegypti*. Today almost two-fifth of world's population (2.5 million) is at risk of dengue and no specific antiviral drug or vaccine is available against it. Uncontrolled population growth in Africa and South East Asia has increased number of susceptible hosts in urban and semi urban areas. About 40% of world population resides in the high risk area for dengue transmission. According to latest estimates by WHO, yearly 50 to 100 million infections occur globally, this includes around 500 000 DHF and 22 000 deaths, mostly among children. Only symptomatic treatment in the form of analgesic, antipyretics and body fluid management is provided to the patient. Prevention strategies mainly focus on two approaches, firstly on activities to control vector and secondly on activities to protect human from mosquito bite but there is always concerns regarding their sustainably and effectiveness. Theoretically development of an effective dengue vaccine is feasible and production of an effective and affordable vaccine could be a viable option to save humans from this dreadful disease. Conceptually vaccine production is possible, but it has to be tetravalent, providing immunity against all serotypes. Few candidate vaccines are in advance stage of their development; however international cooperation is needed to make these vaccines available on cheaper rates to the poor and vulnerable countries. Objective of this review is to discuss various aspects related to dengue, its epidemiology, available preventive methods, need for vaccine and challenges in its development.

## 1. Background

Dengue fever (DF) is a mosquito born viral infection typically characterized by symptoms like abrupt onset of high grade fever[(39–40)°C], retro-bulbar pain, muscular pain, joint pain, malaise, nausea, rashes, lymphadenopathy and thrombocytopenia. Complicated form of dengue is dengue hemorrhagic fever (DHF). It may lead to bleeding from nose, gums and nearly fatal internal hemorrhage causing hypovolemic shock known as dengue shock syndrome (DSS)[1,2].

Unlike believed by many, dengue is not a new disease, first written evidence of dengue like disease comes from an old Chinese medical encyclopedia of 992. However, in 18th and 19th century mosquito vector, *Aedes aegypti* and dengue virus started spreading to new geographical location due to increased volume of trade and shipping between different continents[1]. In the recent decades incidence of dengue has increased dramatically. Now almost two-fifth of world's population (2.5 million) is at risk of dengue and there is no specific treatment for dengue[3]. This has raised alarm among the public health professionals, across the globe, to find out the ways to prevent it.

Objective of this review is to discuss various aspects related to dengue, its epidemiology, available preventive methods, need for vaccine and challenges in its development.

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## 2. Epidemiology

Dengue viruses belong to family flaviviridae with four serotypes (dengue-1, dengue-2, dengue-3, and dengue-4) and are transmitted mainly by mosquito *Aedes aegypti*[4]. Principal hosts for dengue virus are human and mosquito, mosquito remains infected though out the life but only human develop illness once they are infected. Infection with one serotype provides lifelong immunity against that serotype, in some instances short life cross immunity is also found for few months[1,5,6].

The virus sustain in the Asia and Africa probably through vertical transmission in mosquitoes and with regular amplification in non human primates. Mosquito *Aedes aegypti* has adopted itself to survive in close vicinity to human settlement. *Aedes aegypti* is found predominantly between 35° N and 35° S throughout the globe. For many reasons it is an efficient vector, it can breed and multiply in close proximity to humans; it feeds on human blood; it is active just after sunrise or just before sunset and it bites several people to have a single blood meal[7].

In the last few decades incidence and distribution of dengue has increased significantly. Uncontrolled population growth in Africa and South East Asia has increased number of susceptible hosts in urban and semi urban areas. Rapid and unmanaged urbanization in tropics has also provided with suitable breeding environment for *Aedes aegypti*. Inadequate management of solid wastes like, disposable containers, used tires and other object which can collect rain or waste water provides suitable place for larvae growth.

In addition to it ever increasing air travel between endemic and non-endemic regions has increased the risk of introducing virus to non endemic areas and subsequently change them to hypo endemic (one serotype) or hyper endemic regions (multiple serotype present)[8]. Dengue typically spreads in tropical region during rainy, humid and warm season. However due to global warming it is expected that infection will further extend both in longitude and altitude. Episodes of dengue can also be expected during low rain fall season due to favorable increase in temperature and available artificial man made breeding sites[9].

Today about 40% of world population resides in the high risk area for dengue transmission. According to latest estimates by WHO, yearly 50 to 100 million infections occur globally, including around 500000 DHF and 22000 deaths, mostly among children. There is sharp increase in number of countries reporting cases, prior to 1970 only 9 countries reported dengue case, since then number has increased many fold and continues to rise[10]. Dengue is predominantly endemic in tropical countries, which includes 100 countries across Asia, Africa, America, Pacific and Caribbean islands[11].

## 3. Current preventive measures against dengue

No specific antiviral drug or vaccine is available against

dengue[12]. Only symptomatic treatment in the form of analgesic, antipyretics and body fluid management is provided to the patient[13]. However Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to associated risk of increased bleeding[14]. In the absence of treatment most of the public health efforts are put together in prevention of this dreadful disease. Prevention strategies mainly focus on two approaches, firstly on activities to control vector and secondly on activities to protect human from mosquito bite.

### 3.1. Activities for vector control

Prime aim of these activities is to control proliferation of vector's population. It can be achieved through environmental, chemical or biological control measures. Environmental management includes periodical cleaning/ draining of objects like flower pots, air conditioners, water coolers, roof top and bowl of domestic animal which can retain water. It also emphasize on efficient and reliable water supply to households, so as need for the water storage can be minimized. However, if storage is unavoidable jars or containers should be covered with lid. Environmental management also focus on 3 R's- "Reduce, Reuse, Recycle" of solid waste management. Some studies, from El Salvador, has shown that solid wastes like discarded plastic containers and unused tires, infested with larva, were risk factor for dengue infection[15].

Chemical control of vector is not new, in beginning of 20th century Cuba and Panama used oil to destroy *Aedes* habitat, followed by DDT use from 1940's onward. After the initial success, resistance to DDT started emerging by 1960's. Subsequently other insecticides like organophosphates (malathion, fenthion, and temephos) were used, with different level of success, to control *Aedes aegypti* vector[3]. Chemicals are not target/organism specific; it not only causes environmental degradation but beside this has many harmful effects on human health.

Biological methods like use of larvicidal fish or biocides to reduce breeding of mosquitoes in household water containers and small natural water bodies have been tried. However, their effectiveness is not well proven and evidences are based on few small field-trials. These organisms are expensive to grow; further their application to water bodies with fluctuating pH and temperature (sunlight) is limited[3]. Reluctance of the residents from using larvicidal, though safe, in potable water also limits their application for long term suppression of *Aedes aegypti* population[15].

### 3.2. Activities to prevent mosquito bites

It primarily include wearing trousers and long sleeves cloths, application of topical mosquito repellent and putting wired mesh on doors and windows to prevent mosquito's entry into house[14]. These measures have their own limitations because of the reliance on individual responsibility and behavior.

### 3.3. Limitations of current preventive activities

Above discussed preventive activities largely depends upon community participation. Behavioral change program not only takes a long time but are also resource intensive. Vector control program in many countries are underfunded and lack human resources. Unfortunately during low transmission season limited resources are channeled to different activities and subsequently vector population rises once again. Sustained dengue vector control program requires coordination among health, municipal, administration and urban planners which seldom is a case in most of the countries. No doubt that these activities can reduce burden of disease but there is always concerns regarding their sustainably.

## 4. Vaccine—prospects and challenges

Thought the dengue virus was discovered more than seventy years back but vaccine against dengue is not available till date. However, at the same time an effective vaccine against yellow fever and Japanese encephalitis caused by viruses of same family, flaviviridae, is available<sup>[16,17]</sup>. This led many scientists to believe that development of vaccine against dengue virus is possible.

### 4.1. Is development of dengue vaccine possible?

Theoretically development of an effective dengue vaccine is feasible. Dengue fever is an acute disease in which replication of the virus is controlled after the initial 3–7 days of viraemia<sup>[18]</sup>. Individuals once infected with one serotype of dengue virus are immune to rechallenge with the same serotype. In small percentage of population, short life, limited cross immunity is also found. Further, experimental studies on mice have show that passive inoculation of virus specific antibodies prevents them from subsequent challenge<sup>[19]</sup>. Therefore, development of vaccine against dengue virus is given high priority by scientific community as well as by WHO.

### 4.2. Problem associated with dengue vaccine development

Gaps in the knowledge about pathogenesis of DHF and absence of perfect animal model for dengue disease are two major limiting factors in successful development of vaccine. In a series of studies it was found that risk of developing DHF was 15–80 times more in persons those who are infected second time than in those who are infected first time<sup>[17]</sup>. There is evidence supporting that pre-existing heterotypic dengue antibody is a risk factor for the development of DHF, therefore, any effective vaccine should be tetravalent and provide immunity against all four serotypes of dengue virus. It has been difficult to produce an effective tetravalent formulation which retains its immunogenicity against all four serotypes and further it require complicated multi dose immunization regime<sup>[18]</sup>.

### 4.3. Dengue vaccines candidates

In the past seventy years many attempts have been made to produce vaccine against dengue virus. Only few could overcome the unusual interplay between human immune response and dengue virus. However, in 2001 WHO took initiative to fasten the progress towards vaccine development by bringing together different phase III trials centers under a single umbrella of Pediatric Dengue Vaccine Initiative (PDVI)<sup>[17]</sup>. Various organizations have used different molecular technology to develop dengue vaccines. Following is a brief account of some of the most important, somewhat successful, vaccine candidates in different phases of clinical trials.

Historically, production of live attenuated viruses by serial passage through nonhuman cell is supposed to be most preferred method to produce viral vaccine. Two vaccines both using attenuated viruses, first by Mahidol University, Thailand and second by Walter Reed Army Institute of Research, USA are in advance stage of development. The Thai tetravalent vaccine, licensed by Aventis Pasture, has show 80%–90% seroconversion in the children, against all four serotypes after two doses. Same seroconversion results were shown in the adult volunteers by, GlaskoSmithKline licensed USA tetravalent vaccine. However concerns have been raised about possible imbalance between immune response generated to different antigens, which may lead to either incomplete protection or enhance severity of disease<sup>[17]</sup>. Further attenuated vaccine virus may also attain virulence through mutation.

Evolution of chimeric dengue vaccine is a very important step to overcome these potential hurdles. This approach uses DNA recombinant technology to produce live attenuated viral vaccine. Chimeric virus is created by replacing structural protein genes of the target virus with corresponding genes of another virus. Robbert *et al* have created a most advanced chimeric yellow fever/dengue virus, ChimericVax–DEN<sup>[20]</sup>. Clinical trials are in progress to establish their potency in production of an effective vaccine. Attempts have also been made by some groups to elicit immune response by delivering nonstructural proteins of dengue virus through recombinant virus vector. This technique was successful to generate protective immunity in the animal models. However, due to lack of complete knowledge about these proteins, concern regarding their safely still remains<sup>[17]</sup>. Recently efforts are also made to utilize recombinant DNA technology such as synthetic consensus (SynCon) human codon optimized DNA vaccine, to manufacture an effective vaccine against all four serotypes of dengue virus<sup>[21, 22]</sup>. Thus conceptually development of an effective dengue vaccine is feasible and few promising candidate vaccines are in pipeline. Still it remains a challenge to scientific community.

### 4.4. Will vaccine be a cost effective solution?

Many concerns have been raised regarding cost effectiveness of the use of vaccine in comparison to medical

treatment of dengue. Shepard *et al* in their 1993 study, using treatment cost \$ 200 and vaccine cost \$ 17.5, found that medical treatment is more cost effective in the countries like, Thailand, where health system is well developed. However, same group concluded that vaccine will be more cost effective in their 2004 study. This difference was explained on the basis of including other indirect costs in later analysis. In 2004 study they included cost of non hospitalized cases, indirect costs, vaccine cost \$0.50 and treatment cost as \$139[23]. Cost effectiveness is context specific, therefore an individual country should carefully consider all important components like incidence of disease, cost of treatment, direct medical cost, indirect cost (loss of daily wages), vaccine cost, immunization cost, cost of treatment of vaccine side effects and other intangible costs, before arriving to any decision regarding cost effectiveness of a vaccine.

## 5. Conclusions

Worldwide, dengue cases are on rise. Tropical countries are particularly under treat, but increase in air travel between endemic and non-endemic areas has put many more countries under its bane. It is expected that this problem will further escalate as a result of global warming and rapid unmanaged urbanization. Preventive measures through vector control largely depend upon community participation. This needs a sustained motivation and periodic resource intensive interventions, which might not be economically sustainable in long run. Moreover, due to poor surveillance system in many countries burden of disease is mostly underestimated. It is expected that magnitude of the problem might be more than what is estimated on the presently available data. Production of an effective and affordable vaccine could be a viable option to save humans from this dreadful disease. Conceptually vaccine production is possible, but it has to be tetravalent, providing immunity against all serotypes. Few candidate vaccines are in advance stage of their development; however, international cooperation is needed to make these vaccines available on cheaper rates to the poor and vulnerable countries.

## Conflict of interest statement

We declare that we have no conflict of interest.

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