Dengue Vaccines: Current Status and Future Prospects

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WHAT IS DENGUE?

Dengue is an arboviral (arthropod-borne virus) disease caused by the dengue virus (DENV) and transmitted by Aedes aegypti mosquitoes, which acts as the vector. Dengue is distributed across the globe, usually in tropical and sub-tropical climates, where Aedes mosquitoes breed prolifically. Dengue virus has four serotypes (DENV-1 to DENV-4). The virus, after entering the body, undergoes haematogenous dissemination, resulting in disease manifestation.

Epidemiology and Disease Burden [1]

It is established that dengue causes almost 400 million infections annually worldwide. Over the past half-a-century, dengue prevalence has increased over 30-fold. During this time, it has spread from less than 10 to over 128 countries.

Dengue surveillance data from several endemic countries have shown that approximately 70-90% of individuals can become infected with at least one DENV serotype, by the time they reach adolescence. Although there are many factors that influence the severity of disease, the major risk factor is being infected a second time by a different DENV serotype than the first infection.

The disease burden in India is enormous, as indicated by a 2014 study conducted by the National Institute of Health and Family Welfare (NIHFW), New Delhi. The study revealed that the average number of clinically diagnosed dengue cases in India was almost 6 million annually. Interestingly, this is a staggering 282 times the annual reported cases between 2006 and 2012.

Dengue Types and Symptoms [2]

Dengue fever (DF) is the most common form of the disease and is characterised by severe bone and joint pain, which is why it is also termed as “breakbone fever”. Other common symptoms of DF include myalgia, headache, fever, lymphadenitis, rash, malaise, and generalised fatigue and exhaustion. Of these, the three cardinal symptoms are fever, rash and headache, often termed as the “Dengue Triad”. Dengue haemorrhagic fever (DHF) is much more severe than DF and primarily affects children below 10 years of age. As the name suggests, the condition is characterised by widespread haemorrhage, in addition to fever, rash and headache. The severest form of dengue is dengue shock syndrome (DSS), which is a potentially fatal complication, resulting in circulatory collapse and death, if not treated promptly.

Treatment and Prevention

There is no specific treatment for dengue and antivirals are currently not available. Treatment is hospital-centric and primarily involves supportive care. Interestingly, the global economic burden of dengue towards direct and indirect treatment costs is USD 9 billion annually [1]. Currently, the mainstay of prevention is mosquito vector control.

Why is a Dengue Vaccine Needed?

The burden of dengue in India is huge and the cost of treatment for complications such as DHF and DSS is astronomical, especially in the private sector, where the expenses have to be borne “out-of-pocket”, in the absence of health insurance. The situation is further aggravated by the fact that most government hospitals, especially in rural areas, do not have the infrastructure or trained medical staff to tackle complications arising from dengue infection. Therefore, a dengue vaccine has the potential to bring about a paradigm shift from treatment to prevention. A safe and effective vaccine will dramatically reduce the number of cases, as well as the mortality and morbidity.

Impediments towards Development of an Ideal Dengue Vaccine [3]

Over the past few decades, several dengue vaccine candidates have been undergoing development, but none have proven to be successful, until now. Developing a dengue vaccine is no easy task. This is because there are four dengue virus serotypes (DENV-1 to DENV-4) that circulate, of which one type predominates in a particular dengue season. Attenuation of the virus by chemical treatments so that it does not cause disease, yet is still strong enough to elicit an immune response that confers protection is very tricky. This stems from the fact that all four serotypes require equal levels of attenuation. This impediment has been solved by Sanofi Pasteur, which has developed the first licensed dengue vaccine in the world.

Dengvaxia®: The Sanofi Pasteur Dengue Vaccine [4]

Dengvaxia® (CYD-TDV), which has been developed by Sanofi Pasteur, Lyon, France, is the first licensed vaccine against dengue that is available internationally. This vaccine has been extensively evaluated in over 40,000 people across 15 different countries, including India. Dengvaxia® is recommended by the World Health Organisation (WHO) for use in individuals 9-45 years of age, who reside in dengue endemic areas of the globe. Dengvaxia® is a live-attenuated tetravalent dengue vaccine that contains all four dengue serotypes- DENV-1, DENV-2, DENV-3, and DENV-4.

The vaccine is produced by recombinant DNA technology and has been evaluated in a 3-dose schedule (0/6/12 months) in Phase III clinical trials. It was first licensed in Mexico in December 2015 and first commercially available in 2016 in the Philippines and Indonesia. The vaccine has so far been adopted in 7 other dengue-endemic countries, namely, Paraguay, Peru, El Salvador, Brazil, Guatemala, Singapore, and Costa Rica. In these countries collectively, over 500,000 people have been vaccinated so far, with over 1.5 million doses of the vaccine.

The Indian government is exercising caution about introducing the vaccine, as Sanofi has been seeking exemption from carrying out Phase III clinical trials. The company argues that Dengvaxia® has already been extensively evaluated in clinical trials and so, the exemption would fast-track the introduction of the vaccine in India. In this regard, early introduction of the vaccine in India would help in effectively tackling the disease, where it is a huge public health problem.
**Dengvaxia**: Current Status and Controversies

Currently, Dengvaxia® is licensed in 20 countries. In large-scale clinical trials in Asia and Latin America, spanning over 25 months, the vaccine has been shown to prevent 93% of severe dengue cases and reduce dengue-related hospitalisations by 80%.

Dengvaxia® is currently mired in deep controversy due to the deaths of 10 children in the Philippines, linked to the vaccine [5,6]. Following the Philippines fiasco, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, has recommended that Dengvaxia® should only be administered to individuals who have previously had medically confirmed dengue. SAGE further indicated that it would be unsafe to give the vaccine to individuals who have never been exposed to the dengue virus [7].

Despite concerns about the vaccine, Sanofi Pasteur has been authorised by the European Commission for marketing Dengvaxia® in dengue endemic European countries with effect from 19th December 2018, based on the recommendations of the Committee for Medicinal Products for Human Use (CHIMP) of the European Medicines Agency [8]. Moreover, the United States Food and Drug Administration (USFDA) has also granted priority review of the vaccine for use in the US, where the dengue burden is highest in the Virgin Islands, Puerto Rico, Guam, as well as some other offshore US territories [9].

**Other Dengue Vaccine Candidates [10, 11]**

There are a number of other dengue vaccine candidates that are currently under different stages of development in various countries. A few important ones are briefly highlighted below:

**DENVax**: This vaccine, also known as TAK-003, has been developed by Takeda, Osaka, Japan [12]. This live-attenuated tetravalent dengue vaccine consists of a chimera of all four dengue serotypes (DENV-1 to DENV-4). This dengue vaccine candidate has completed Phase III clinical trials in January 2019. This clinical trial, also known as “Tetravalent Immunization against Dengue Efficacy Study” (TIDES), enrolled 20,100 healthy children and adolescents aged 4-16 years from dengue-endemic countries in Asia and Latin America. The trial evaluated the efficacy, safety, and immunogenicity of two-doses of TAK-003 in dengue exposed as well as unexposed children. The vaccine was found to be efficacious in preventing dengue in children and adolescents in dengue-endemic countries. The vaccine was well tolerated and there were no significant safety issues. TAK-003 is currently not licensed anywhere in the world.

**TV003**: This vaccine, also known as TetraVax-DV, has been developed by the National Institutes of Health’s National Institute of Allergy and Infectious Diseases (NIAID), USA. TV003 is a live-attenuated tetravalent dengue vaccine that contains a mixture of all four dengue serotypes as separate vaccine formulations. The vaccine has previously been shown to confer complete protection against dengue in a human challenge model [13]. As of February 2019, the vaccine is undergoing a Phase II randomised, double-blind, placebo-controlled clinical trial in 56 healthy adult volunteers in Taiwan [14].

TetraVax-DV is simultaneously undergoing Phase III clinical trials in Brazil, which is being conducted by Instituto Butantan, São Paulo, Brazil. The trial has enrolled 16,944 healthy volunteers in the age group 2-59 years. The expected date of completion of the trial is December 2022.

**TDENV-LAV**: This is a tetravalent dengue live-attenuated vaccine (TDENV-LAV) that contains all four dengue serotypes. This vaccine has been jointly developed by the Walter Reed Army Institute of Research (WRAIR), USA and GlaxoSmithKline (GSK). It is currently undergoing two clinical trials, both in Maryland, USA. The Phase I clinical trial has enrolled 40 healthy volunteers in the age group 18-42 years and is expected to end in January 2022. The Phase II/I clinical trial has enrolled 140 healthy volunteers in the age group 20-49 years and is expected to end in June 2019.

**TDENV-PIV**: This is a tetravalent dengue purified inactivated vaccine (TDENV-PIV), which consists of a tetravalent vaccine formulation containing all four dengue serotypes. Like TDENV-LAV, this vaccine has also been developed by GSK and WRAIR, USA. So far, it has completed a Phase I randomised, open-label, single-centre clinical trial in 100 healthy volunteers in the age group 18-39 years. This trial was carried out in Maryland, USA and was completed in September 2018.

**V180**: This is a recombinant protein-subunit dengue vaccine produced in cells of the fruit fly (Drosophila melanogaster). This vaccine, developed by Merck Sharp & Dohme (MSD), has completed Phase I clinical trials in 98 healthy volunteers aged 18-49 years. The trial was completed in December 2014.

**TVDV**: This is a tetravalent “shuffled” pM/E-expressing plasmid DNA vaccine, developed by WRAIR and the US Naval Medical Research Centre (NMRC), USA. This DNA vaccine has completed Phase I clinical trials in 40 healthy volunteers aged 18-50 years in Maryland, USA. The trial was completed in December 2013.

**Indian Efforts to Develop a Dengue Vaccine [11]**

Indian efforts to develop a dengue vaccine are also underway. Two dengue vaccine candidates are currently in the pipeline.

One is a live-attenuated dengue vaccine, TetraVax-DV, which was developed by the National Institutes of Health (NIH), USA. This vaccine has been licensed to Indian vaccine companies Panacea Biotec, Serum Institute of India, and Biological E. These companies have obtained non-exclusive licenses for clinical development and marketing of TetraVax-DV in India. Till date only Panacea Biotec has initiated Phase I/I clinical trials in India. The trial has enrolled 200 healthy volunteers in the age group 2-60 years. The date of completion of this trial is not known.

The other vaccine is being developed indigenously by the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi and Sun Pharma, Mumbai. This is a tetravalent (4-in-1), single-component, non-replicating, protein-subunit dengue vaccine termed “DSV4”. The vaccine is based on the virus-like particle (VLP) platform, derived from Pichia pastoris, which is a methylotrophic yeast. The hepatitis B surface antigen (HBsAg), popularly known as “Australia antigen”, is a component of the VLPs. This vaccine candidate has been extensively evaluated in various animal models, including rodents (mice and rats), as well as rhesus monkeys (Macaca mulatta). The vaccine will next be evaluated in human clinical trials. The researchers indicate that this “Made-in-India” vaccine could be available within the next 4-5 years.

**CONCLUSION**

From the foregoing discussion, it is evident that several promising dengue vaccine candidates are currently in the pipeline, both in the public and private sectors. However, till date the only available WHO-approved dengue vaccine is Dengvaxia®. Despite the current controversies, if this vaccine is integrated into the overall dengue prevention programs in dengue endemic countries, it has the potential of achieving the WHO goals of reducing mortality by 50% and morbidity by 25% by 2020.

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