

Review Article



Dengue Vaccine: Challenges and Limitations

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Abstract

Dengue is a common mosquito-transmitted viral infectious disease. Due to global warming and other climate changes, the dengue virus vector *Aedes aegypti* mosquito is breeding rapidly and spreading the dengue worldwide. As a result, every year, millions of people are infected by the dengue virus and tolls thousands of lives across the world. World Health Organization (WHO) has given a terrible message that dengue can become as an epidemic. Therefore, the invention of an effective dengue vaccine is a way to build the body's immunity to fight against the disease. Efforts to develop a vaccine against dengue have been ongoing for decades. Currently, Dengvaxia is approved for use by individuals to prevent dengue with some limitations. Another vaccine, Qdenga is also shown to be effective against verities of dengue virus serotypes but this vaccine is not approved by the USA Food and Drug Administration (FDA) yet. Neither Dengvaxia nor Qdenga has approved in Bangladesh and other low and middle-economic countries due to its conservative approach, controversy and lack of WHO guidelines on dengue vaccine.

Key words: Bangladesh, Dengue vaccine, Denvaxia, Qdenga vaccine.

Date of received: 15.05.2023

Date of acceptance: 25.09.2023

DOI: <https://doi.org/10.3329/kyamcj.v14i03.70616>

KYAMC Journal. 2023; 14(03): 172-174.

Introduction

Dengue is a mosquito-borne infection caused by dengue viruses (DENVs), which are mostly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitos. DENVs are members of flavivirus group from the family flaviviridae. Dengue viruses have four serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. Generally, all four serotypes of DENVs are present in most countries where dengue is endemic. These four serotypes have few similar sharing structural antigens, but still serologically and geneticaly they are distinct.¹

Every year, dengue viruses infect millions of people across the globe. It tolls thousands of lives. The carrier of the dengue virus, *Aedes aegypti* mosquito, is breeding rapidly due to global warming and other climate changes. As a result, dengue is spreading all over the world. According to WHO's observation, a total of 5.2 million people were infected with dengue in 129 countries in 2022.² In the same year, a total of 62,382 dengue cases have been recorded in Bangladesh including 21,932 cases in the month of October alone, which is the highest number of recorded cases for this month since 2000. Dhaka division witnessed 70% of patients and 61% of mortalities; however, the Chattogram Division reported 14% of patients and 23.64% of deaths in 2022. Only Dhaka city recorded 63% (n = 41321) of

the total cases and was one of the most affected regions in 2022.³ During the year of 2022, among the Asian countries the highest rates of reported dengue were in: Vietnam 145,536 cases, the Philippines 52,597, and Indonesia reported 68,903 cases; the only country outside Asia with higher dengue incidence was Brazil. As on 27 July 2023, European Centre for Disease Prevention and Control has reported over three million cases and over 1500 dengue-related deaths globally.⁴

Bangladesh has been going through its worst dengue outbreak this (2023) year. Between the 1st January to the 7th August 2023, Ministry of Health & Family Welfare (MOHFW) reported a total of 69,483 dengue cases including 327 fatalities, which is the highest compared to the similar period in the last five years.⁵ As on 16 July 2023, the total number recorded of 20,878 patients who were admitted to the hospital and a total of 106 patients died due to dengue infection. However, all dengue patients and fatalities are not reported and recorded like many others developing and least developed countries due to scarcity of awareness and health cases amenities to all people.

During the first half of 2023 about 4 million people are already infected with dengue in Latin America. In Argentina, Bolivia, Peru, Paraguay, dengue has taken a terrible form. Dengue can

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become as terrible as Corona - such is the fear of WHO. Disease Control Department says - *Aedes aegypti* is changing its common characteristics. The timing of the bite is also changing. It was known that the mosquito used to lay eggs in clean water and now capable to hatch in dirty water too. Regarding the biting time is also changed to 24 hours of the day round including night. Though several preventing measures are recommended to control dengue or *Aedes* mosquito, research on dengue vaccine is going on for last few decades. Dengue vaccine production is one of the most important demand to prevent & control the disease.

Importance to develop a good dengue vaccine

A vaccine is a way to build body's immunity to a disease before one gets sick. This keeps people away from getting and spreading the disease. Two important reasons to get vaccinated are to protect ourselves and to protect those around us. Global warming, climate changes and rapid urbanization become an important cause of increased breeding of *Aedes* mosquito. These factors are difficult to control. For this reason, invention of an effective vaccine is an urgent demanding issue of this time.

Why is it difficult to develop a vaccine for dengue?

Vaccine against dengue is remarkably difficult to develop. One important reason is that the DENV has four varieties of serotypes.

Development of dengue vaccines has the following barriers have to overcome:

1. The expected vaccines should simultaneously protect against all four serotypes of dengue virus. That means that dengue fever behaves like four different viruses. Development of a dengue vaccine is extremely challenging due to the fact that the virus has four antigenically different serotypes (DENV1-4).
2. Development of "immune enhancement" leading to more serious disease following the waning of vaccine-induced immunity.
3. Unavailability of a proper animal disease model for vaccine experiment, design and testing.

During the challenge to develop a dengue vaccine, the appearing of non-neutralizing antibody responses to enhance dengue virus infection and disease showed a significant drawback. A dengue vaccine must induce antibody responses to all four serotypes simultaneously, and must provide long-lasting immunity to avoid the risk of antibody-dependent enhancement (ADE).

What is the current status of the dengue vaccine?

Currently, only one live attenuated chimeric dengue vaccine, the Dengvaxia® (CYD-TDV), dengue vaccine, has completed its third phase of trial and has been licensed. DENVax and TetraVax-DV-TV003 (TV003) are in the third phase, while others are still in the first trial phase. Dengvaxia® (CYD-TDV), developed by the Sanofi Pasteur is a live recombinant tetravalent dengue vaccine, given as a 3-dose series on a 0/6/12-month schedule.

TAK-003 dengue vaccine, another name Qdenga introduced by the Takeda Pharmaceuticals Japan. Recently Takeda has

withdrawn the biologics license application (BLA) submitted to the US Food and Drug Administration (FDA) for TAK-003, a tetravalent dengue vaccine candidate. FDA sought additional data of travelers and those living in dengue-endemic areas of the U.S., such as Puerto Rico," that were not captured by the phase 3 TIDES trial used for the application. However, currently, TAK-003 is approved for use in Europe, the U.K., Brazil, Argentina, Indonesia and Thailand.

What is the limitation of Dengvaxia?

Dengvaxia is not approved for use in individuals who are not previously infected by any dengue virus serotype or for whom this information is unknown. Age of the recipients must be 9 years through 16 years because most of the clinical trials testing were done in children age 16 years and younger. It is presumed those age groups are at risk for dengue where dengue occurs frequently.

Why has the development of a dengue vaccine taken so long?

Antibody Dependent Enhancement (ADE), unlike other highly effective vaccines developed against other flaviviruses, the development of a dengue vaccine is highly challenging due to that fact that the virus has four antigenically different serotypes (DENV1-4) causing cross-reactions.

How effective is the dengue vaccine?

Overall, Dengvaxia protects children from dengue illness, hospitalizations, and severe dengue 8 out of 10 times (80%) in children who had dengue before vaccination. The vaccine protects against all four dengue virus types: dengue 1, 2, 3, and 4. While the vaccine is highly effective, there is a low risk that some vaccinated people can still get infected with dengue.

Brand names of dengue vaccine

DENGVAXIA® (Dengue Tetravalent Vaccine, Live) is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Another vaccine named Qdenga vaccine is shown to be effective against varieties of dengue virus serotypes 1, 2, 3, and 4 – manufactured by Takeda Pharmaceuticals, Japan.

Who Should Get a Dengue Vaccine?

In 1997, the French multinational pharmaceutical and healthcare company Sanofi began its work on a dengue vaccine and won Mexican approval for Dengvaxia in 2015. The vaccine was soon introduced in 19 countries. But a later study, which was confirmed by Sanofi's, found that in rare cases, Dengvaxia can backfire. In people who never had dengue are vaccinated and later become infected, the vaccine may provoke a much more severe form of the illness with hemorrhagic manifestations.

Center for Disease Control (CDC) recommends dengue vaccine (Dengvaxia) for children the age in between 9 years to 16 years but only when they have been previously infected with dengue and living in areas where dengue is common. The previous infection should be confirmed by laboratory testing. This

vaccine is different from other vaccines in that it is only recommended for people who have already been infected with dengue virus. The reason is that children without previous dengue infection are at increased risk for severe dengue disease and hospitalization if they get dengue after they are vaccinated with Dengvaxia. Therefore, healthcare providers should check for evidence of a laboratory-confirmed previous dengue infection before starting the vaccination.

Children of 9 through 16 years old

- i. The dengue vaccine is approved for use in children of particular age group (9 years through 16 years) who have a previous history of laboratory-confirmed dengue infection.
- ii. Only children with laboratory-confirmed evidence of previous dengue infection should be vaccinated.
- iii. Children must also be living in areas where dengue occurs frequently or continuously, which include American Samoa, Puerto Rico, and the U.S. Virgin Islands, and the freely associated states of the Federated States of Micronesia, the Republic of Marshall Islands, and the Republic of Palau.

Takeda's research to Qdenga began in 2013 when it bought Inviragen Inc., a company in Colorado that had been working on the vaccine. Proving its efficacy and safety was complicated because dengue can be caused by four distinctive strains, and protection must be built against all of them. In some cases, patients who are reinfected with a different strain can suffer more severe symptoms, because the neutralizing antibodies generated from the first infection may bind themselves to the virus and increase its ability to enter cells. Although it is not clear, some researchers say a similar pattern may occur in vaccinated people — possibly the root cause of Dengvaxia's difficulties.

Takeda's two-shot immunization is based on what is called the serotype 2 variant, with components of the three other strains attached. In a trial involving 1,800 young people in the Dominican Republic, Panama and the Philippines, the vaccine induced an immune response against all four strains that lasted at least four years after the injections.

Why dengue vaccine is not given frequently?

An analysis by WHO, Sanofi, and several other researchers observed that individuals who were never infected — seronegative people — were more likely to develop a severe reaction to a first-time infection if they received the Dengvaxia vaccine.

Who should not get a dengue vaccine?

According to CDC & FDA, the vaccine should not be administered to

I. Children under 9 years old

a. Children under 9 years of age are less likely to have had a prior dengue infection. But recently in Bangladesh younger children are getting more and more infections. For this reason, if children under the age of 9 years, they are not eligible for dengue vaccination because of less favorable efficacy and safety.

II. People over 16 years of age

a. The dengue vaccine is not licensed for people over 16. There is not enough data to show how well the vaccine works in that population.

III. Children who have not had a prior dengue infection.

IV. Children who have had a severe (life-threatening) allergic reaction to a previous dose of the vaccine.

V. Immunocompromised children.

VI. Children who have a severe (life-threatening) allergy to any ingredient in this vaccine.

VII. Travelers and non-residents of areas where dengue is common. The FDA did not approved dengue vaccine for use in travelers.

Is dengue vaccine approved in Bangladesh?

Dengue vaccine is not approved only in Bangladesh but many other low and middle economic countries due to the conservative approach towards the dengue vaccine and controversy on dengue vaccine. Dengvaxia vaccine developed by Sanofi said that the vaccine could give previously uninfected people at higher risk of severe dengue complications if they were infected later by dengue virus. Moreover, there are no WHO guidelines on the vaccine.

Conclusion

Further research should be carried on to find an effective dengue vaccine regardless the age barrier. Although Dengvaxia give some protections against the illness, still there are some limitations of using Dengvaxia. Qdenga vaccine is indicated for the prevention of dengue disease in individuals from 4 years of age. Finally due to its controversy, dengue vaccine is not approved in Bangladesh.

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