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Review Article

The Quest for an Effective Dengue Vaccine: Hope or Hype

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Abstract

Several trials are ongoing to develop a safe and effective vaccine to prevent dengue virus (DENV) infections, especially avoiding the risk of antibody-dependent enhancement. Only three of them (Dengvaxia/CYT-TDV, Takeda TAK-003, and NIH TV-003/TV-005) have shown promising results. The issue of 'hyperendemicity' and 'quasi-species the major challenge behind developing a successful vaccine. The overall efficacy of first successful vaccine 'Dengvaxia' showed 30.2%–60.8% efficacy with limited protection against DEN 1 and DEN 2. In Bangladesh, since 2019, outbreaks have mostly been caused by DEN 2 and DEN 3, and the trend is predicted to continue for the coming years. TAK-003 gives almost no protection against DEN 3, which is the most notorious serotype encircling Bangladesh. The overall efficacy of this vaccine is 62%, with limited protection against DEN 4. NIH TV-003/TV-005 currently shows more promise with an overall efficacy of 80%. However, we have to wait until June 2024 for the final results. All of these vaccines are safe and effective for travelers. However, for mass vaccination, a country should make a decision based on their prevalent serotypes and the potential serotypes that might cause the next epidemic. To gather these data, a robust serotype- and genotype-based surveillance system and warning system should be in place.

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Introduction

Dengue is one of the most prevalent vector-borne viral infections caused by dengue virus (DENV), a single-stranded RNA virus of the Flaviviridae family with four genetically distinct serotypes (DENV1, DENV2, DENV3, and DENV4)[1,2]. DENV is transmitted primarily by Aedes aegypti and

A. albopictus of the genus Aedes[3]. Dengue fever (DF) is a significant public health problem worldwide, and it is more common in tropical and subtropical areas[4]. More than 100 countries are endemic to dengue, especially in America, South Asia, Africa, and the Mediterranean, affecting an estimated 400–500 millions of cases each year[5]. Developing countries are more vulnerable to the virus's proliferation because of their unfavorable environmental circumstances, such as climate change, deforestation due to unplanned urbanization, overpopulation, and the emergence of insecticide-resistant mosquitoes[3]. Despite being considered a neglected tropical illness, dengue causes millions of infections annually and thousands of fatalities. In the last two decades, there has been an eightfold increase in the number of reported cases to the World Health Organization (WHO), including in the Asia-Pacific region, which is home to more than half of the world's population and more than 70% of dengue cases[6]. Outbreaks are increasing in number, magnitude, and intensity in the large populations of Bangladesh, India, and Pakistan.

Bangladesh is an endemic country for DF. Since the first documented dengue (DENV 3) outbreak in 1964, Bangladesh has experienced sporadic incidents until the first significant outbreak occurred in 2000, with over 5,500 confirmed cases[4]. Thereafter, dengue outbreaks have become

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significant annual events, resulting in thousands of hospitalizations, including pediatric cases. Bangladesh has experienced the largest and most catastrophic dengue outbreak this year[7,8]. As of November 12, 2023, a total of 2,91,832 confirmed dengue cases were reported, exceeding the previous highest record of approximately 101,300 for the entire year 2019[9]. The country recorded 1476 related deaths with an overall case fatality rate (CFR) of 0.5% until November 12, 2023[9]. The increased dengue prevalence is occurring during the backdrop of unusually high temperatures, high humidity, episodic rains, rapid urbanization, and ongoing massive infrastructure development throughout the country, all of which have led to a rise in mosquito populations across Bangladesh[10].

Dengue is an acute febrile illness with a wide spectrum of clinical features ranging from mild illness to severe disease, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The highest risk factor for developing severe dengue is antibody-dependent enhancement (ADE), which occurs following a secondary DENV infection, such as exposure to a heterotypic serotype[3,11]. In short, after exposure to the first DENV serotype, cross-reactive antibodies are produced. These antibodies then bind with the second DENV serotype to form infectious immune complexes, which in turn accelerate the inflammatory process and release more cytokines, causing severe disease[3]. Therefore, to prevent ADE, DENV vaccinations must provide protection against infection from all four serotypes. This review discusses the prospects and limitations of a future vaccine for endemic areas.

Several DENV vaccines have been developed and are undergoing different phases of clinical trials or preclinical research. These vaccines are based on numerous platforms, including live attenuated viruses, inactivated viruses, chimeric live attenuated viruses, DNA, and

Table 1. *Different vaccination strategies against DENV and their mechanism of action*

Sl no	Vaccine Strategy	Mechanism of action and vaccine development	Vaccine candidates under this group	References
1	Envelope protein-based vaccine	The structural viral antigens that target envelope proteins of DENV prevent viral-host interaction and the ensuing activation process, which is crucial for the control of the viral genome.	• E85-VRP and prM-E-VRP • Modified vaccinia Ankara virus-E proteins • Venezuelan equine encephalitis virus replica particles infused M and E proteins	(15,33,39–42)
2	Live attenuated vaccine candidates	• Attenuated vaccination protocols using nonstructural proteins of DENV to induce enhanced immunogenicity, such as envelope E and NS1 proteins of DENV, induce complement-mediated antibody responses in the host immune system. • Reverse genetics is used to modify recombinant DENVs by deletion or antigenic chimerization, producing attenuated vaccines against all four DENV serotypes.	• Tetravale nt dengue vaccine, CYD - TDV (Dengvaxia®) • Takeda's tetravalent • TAK-003 (Denvax) • TV003/TV005 (NIH) • DENV2 NS1 • DENV2-E and NS1 fused to a staphylococcal A protein. • Tetra-live attenuated virus (TLAV). • DENV-2 NS1 recombinant proteins – + adjuvant (alum) and Freund's adjuvant (FA). • Tetra DIIIC. • DENV2 16681 mutant strains. • DENVax-based vaccines.	(34–39,41,43–46)
3	DNA vaccine candidates	The plasmid DNA, which by encoding several viral proteins, such as DENV-NS1, can trigger an immune response. In addition, immune cells like IL-12 can be added to the plasmid to get a greater immune response.	• DENV-2 plasmid, pEII*EIII/NS1 • DENV2 NS1 fused to a t-PA signal (NS1-tPA). • DENV1 E80 • D1ME100 • DENV2 prM/E - CpG motif • DENV2 prM/E DNA • Tetravalent DNA • Vaccine (TVDV) (Vaxfectin®)	(34,36,38,39,42,44)

(table continued)

Table 1. *(cont'd)*

Sl no	Vaccine Strategy	Mechanism of action and vaccine development	Vaccine candidates under this group	References
4	Vector vaccine candidates	Virus vector candidates undergo similar viral responses in a host cell, such as glycosylation, and sedimentation. The viral species with low pathogenicity and good deliverability, such as vaccinia virus, adenovirus, and alphavirus, are mostly used.	• DENV4 NS1 and NS2A recombinant vaccinia virus. • Baculovirus-expressed NS1 candidate. • Baculovirus - DENV-4 NS1 • Modified vaccinia Ankara (MVA) virus - E proteins • CAdVax-Den1–2 • CAdVax-Den3–4 • Venezuelan equine encephalitis virus replicon particles (VRP)- infused M and E proteins	(21,36–39,46)
5	Inactivated vaccine candidates Several	A number of protein entities, including C, M, E, and NS1, are employed to develop antigenic components for inactivated vaccine candidates. To reduce their infectiousness in individuals, pathogens and antigenic materials are treated with a variety of chemicals and radiation.	• DENV2 vaccine (S16803) • S16803 vaccine-associated drug adjuvants • Recombinant vaccine S16803- (R80E) and LAV (DENV2 PDK-50) • Tetravalent purified formalin-inactivated virus (TPIV) or tetravalent DNA vaccine (TDNA) – coupled with tetravalent live attenuated vaccines (TLAV) • Dengue purified inactivated vaccine (DPIV)-AS03$_B$ adjuvant • Tetravalent purified formalin-inactivated virus (TPIV).	(20,47–49)
6	Recombinant vaccine candidates	Includes the combination of lipoproteins and E proteins, which cause the host's immune system to respond to the corresponding antigenic representation.	• Tetravalent lipidated rEDIII formulation. • DENV1-rEDIII linked with DENV2-rEDIII • DENV3-rEDIII linking with DENV4-rEDIII • Tetravalent subunit vaccine V180	(20,37–39,41)
7	mRNA vaccine encoded vaccines	Lipid nanoparticles (LNPs) encapsulated with modified mRNA and DENV1-NS are the basis for certain vaccination designs. Proper design of mRNA-LNP vaccine candidates could generate immune responses specific to a serotype.	• DENVI-NS vaccine [• prM/E mRNA-LNP vaccine	(50,51)

recombinant proteins (Table 1). Among them, only a few vaccines successfully completed the phase III trial. Dengvaxia (CTD-TDV), Takeda Denvax (TAK-003), and NIH TV-005/ TV-003. This review will address the effectiveness of these vaccines in different phase of trials, including their mechanism of action, safety, and risks, particularly emphasizing the possibility of vaccine-induced DHS/DSS.

Dengvaxia (CYD-TDV)

It is a recombinant, live-attenuated tetravalent DENV vaccine candidate that takes advantage of the ChimeriVax™ technology. The WHO and the United States Federal Drug Authority (USFDA) have approved Dengvaxia to be implemented in US territories against all serotypes of the dengue virus, subsequently licensed by Sanofi Pasteur (CYD-TDV)[3,5]. It was first developed in the early 2000s by the National Institutes of Health (NIH), the University of St.

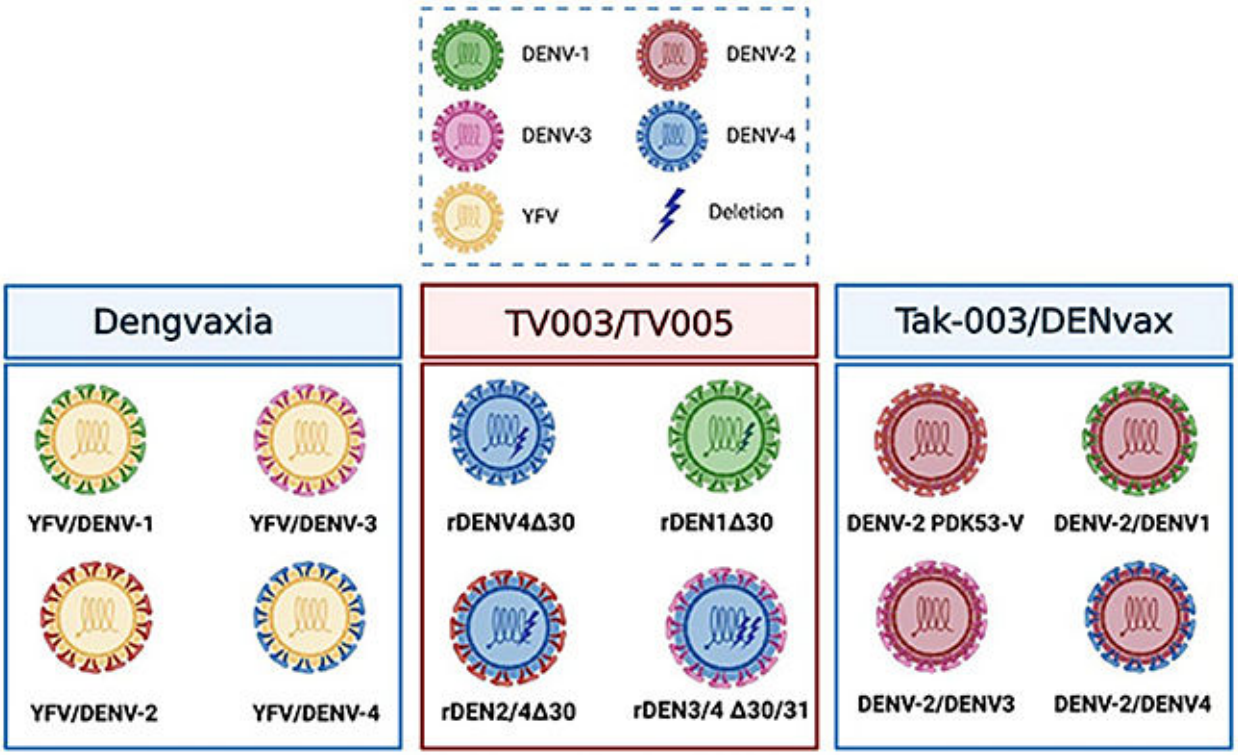

Figure 1: *Molecular design of the three most promising Dengue vaccines*[3]

Louis, and Acambis Inc. It was later licensed by Sanofi Pasteur. This vaccine uses ChimeriVaxTM technology.

Structure of the vaccine:

Based on a vaccine strain (17D) of yellow fever virus (YFV), the pre-membrane (prM) and envelope (E) genes of YFV have been replaced by homologous genes from each of the four DENV serotypes derived from DENV isolates obtained in Thailand and Indonesia between 1978 and 1988. This technology allowed the formation of four chimeric YF-DEN viruses (Figure 1), which were used in the formulation of a tetravalent DENV vaccine (ChimeriVaxTM DENV1-4)[3,5].

Findings of Pre-clinical trials:

Preclinical testing of the safety and efficacy of this vaccine showed a good safety profile, which revealed a lower neurovirulence profile in mice compared with the parental YFV vaccine strain (YF-VAX)[12]. The same result was obtained when a neurovirulence test was performed on *Macaca fascicularis*[13]. In addition, after one injection of the vaccine, at either a high or low dosage, in Cynomolgus macaques, it produced seroconversion and robust neutralizing antibody responses against all four DENV serotypes and limited viremias compared with the parental DENV strains. It is interesting to note that 92% of the immunized monkeys were protected against a challenge with wild-type DENV 1-4[14].

Findings of the clinical trials:

Early phase I and phase II clinical trials were conducted in the USA, the Philippines, Australia, Mexico, Vietnam, Singapore, and India to assess the safety, immunogenicity, and reactogenicity of the tetravalent DENV vaccine Dengvaxia in healthy adults aged 18–45 years. Some of these studies also included pediatric populations between the ages of 2 and 18[15].

The primary safety evaluation of this vaccine in adults revealed that it was safe and well tolerated in a three-dose regimen at 0, 4, and 12 months. It caused mild to moderate transient local and systemic adverse events, including headaches, injection site pain, malaise, and low-grade fever, but no severe adverse events (SAEs) related to the vaccine were reported[16].

Two Phase 3 clinical trials in Asia and Latin America have assessed CYD-TDV in over 35,000 school-aged children between the ages of 2 and 16 years. The trials used a three-dose series on 0, 6, and 12-month schedule[17]. Vaccine efficacy (VE) in the seronegative group was 38.1%, majority

Observed in the context of DENV4. However, in the seropositive group, overall, VE was 78.2%, with VE highest against DENV3 and DENV4 (89.9% and 75.4%, respectively) compared with DENV1 and DENV2 (70.2% and 67.9%, respectively), with a trend of higher efficacy among older age groups, particularly those aged 9 years[17]. The risk of hospitalization for dengue was highest (7.45%) among the seronegative group, particularly in children aged 2–5 years[17].

Indication and contraindication of Dengvaxia (CYD-TDV):

Individuals aged 9–45 years with previously laboratory-confirmed dengue and residing in endemic areas, for the prevention of dengue disease caused by all serotypes[18,19]. Screening tests, including conventional serological testing and rapid diagnostic tests (RDTs), are recommended tools for the pre-vaccination screening strategy, subject to appropriate sensitivities and specificities depending on transmission settings. CYD-TDV is currently contraindicated for pregnant or lactating women, immunocompromised persons, and travelers with documented dengue illness or seropositivity[18].

Takeda Denvax (TAK-003)

Denvax is a live attenuated dengue vaccine developed by the Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention (CDC). After obtaining a license from Takeda (Japan), it was called TAK-003. TAK-003 preserves immunity for up to 48 months against all four serotypes without exacerbating the disease. Overall, TAK-003 is approximately 80% effective against DENV infection[15,20,21].

Structure of the vaccine:

Researchers from Mahidol University in Bangkok, Thailand, initiated the development of Denvax in the late 1980s by isolating a DENV-2 strain (DENV-2 16681) from the serum of a patient with DHF[3]. Then, attenuation of the DENV-2 16681 strain was performed by 53 serial passages in primary dog kidney cells (PDK cells), leading to the development of the DENV-2 PDK-53-V strain, which has attenuation-related mutations in the 5′UTR and NS1 gene. It also possesses an additional non-synonymous mutation in the NS3 gene[22,23]. Tetravalent Denvax/TAK-003 vaccine developed on the backbone of DENV-2 (Figure 1). In which the pre-membrane (prM) and envelope (E) structural genes of the chimeric viruses DENV1, DENV3, and DENV4 were replaced from the DENV-2 PDK53-V strain[14].

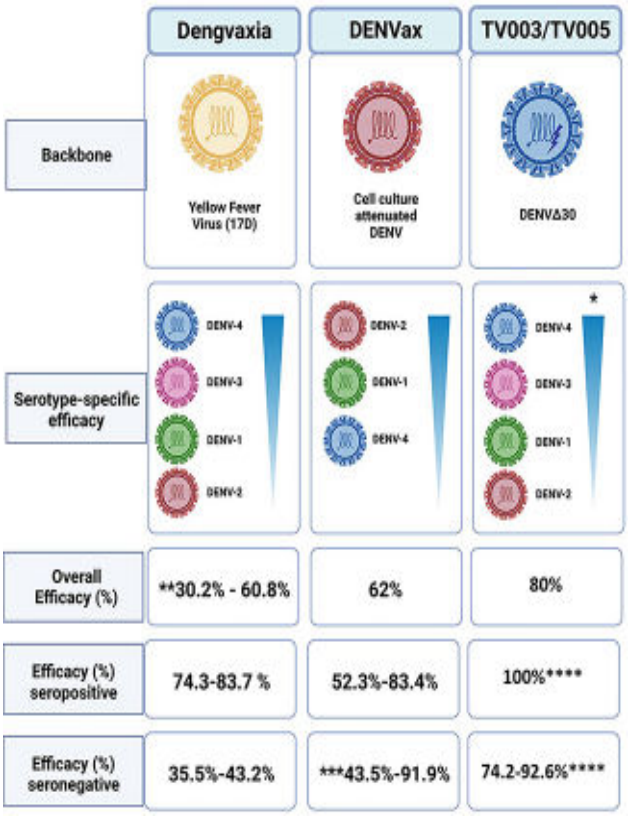

Figure 2: Comparative illustration of the three most successful Dengue vaccine[3].

*The seroconversion rates for TV003/TV005 observed in phase II clinical trials are illustrated. **The lower value of the efficacy range depicted corresponds to the efficacy observed during the phase IIb trial conducted in Thailand. ***DENVax was only efficacious against DENV-1 and DENV-2 in seronegative individuals. ****TV003/TV005 is currently undergoing phase III clinical trials.[3].

Findings of the Pre-clinical trials:

A promising vaccination safety profile was observed in preclinical testing of the tetravalent Denvax/Tak003 vaccine in cynomolgus macaques (*Macaca fascicularis*). After two high-dose vaccinations, it produced protection against all four DENV serotypes and was well tolerated when administered subcutaneously[58].

Findings of the clinical trials:

A phase I clinical trial was conducted by Takeda in Rionegro, Antioquia, Colombia, for the initial clinical evaluation of TAK-003. This double-blind, randomized, and dose-escalating trial was designed to assess the immunogenicity

and safety of a two-dose scheme of TAK-003 administered intramuscularly (IM) or intradermally (ID) to adults (18-45 years) who were seronegative (26). The vaccination caused brief local reactogenicity and modest systemic side effects, but overall, it was safe and well tolerated by the trial participants. Neutralizing antibodies against all four DENV serotypes were produced because of vaccination, whereas participant antibody titers against DENV-3 and DENV-4 were lower[27].

Tetravalent Immunization against Dengue Efficacy Study: The TIDES trial was conducted to evaluate the efficacy and safety of Takeda's Dengue Vaccine (TDV/TAK-003) in Asia and Latin America[24]. A total of 20,099 participants (healthy children aged from 4 to 16 years) were studied in a phase 3 double-blind, randomized, placebo-controlled trial in 26 sites, including Brazil, Columbia, the Dominican Republic, Nicaragua, Panama, the Philippines, Sri Lanka, and Thailand, to evaluate the safety and efficacy of TAK-003[24].

VE against virologically confirmed dengue caused by any type of serotype was 80.2% (figure 2). It was most effective against DENV2 (among seronegative individuals 96.5% compared to 100% of seropositive individuals) and DENV1 (79.8% among seronegative individuals compared to 67.2% among seropositive individuals)[3,5,24]. It was less effective against DENV3 (62.6%) and inconclusive against DENV4. Overall efficacy was similar across different age groups, regardless of baseline serostatus (72.8–83.3%)[21,24]. There were transient local reactions and mild systemic side effects following vaccination among the participants. However, overall, the vaccine was safe and well-tolerated[3]. Currently, the second part of the Phase 3 TIDES clinical trial (NCT02747927) is ongoing and is estimated to be completed in March 2024. Takeda Dengue Vaccine (TDV/TAK-003) is expected to be launched in 2024 if the results of the second part of the trial are favorable.

Indication and contraindication of TAK-003:

At present, TAK-003 is only approved (approved by individual countries) for use in endemic areas between the ages of 6 and 16 years. It is administered subcutaneously(SC) (0.5 ml) in two doses within 90 days apart[28]. TAK-003 is not recommended for pregnant women, and women of childbearing potential should avoid pregnancy for at least 1 month following vaccination. TAK-003 is contraindicated in immunocompromised persons[28].

NIH TV-005 and TV-003

The National Institutes of Health (NIH) of the United States has developed two live-attenuated single-dose vaccination candidates, TV003 and TV005. A single dose of either TV003 or TV005 resulted in near-sterilizing immunity to a second dose of vaccination administered 6–12 months later and promoted seroconversion to four DENV serotypes in 74%–92% (TV003) and 90% (TV005) of flavivirus seronegative individuals[29].

Structure of the vaccine:

The National Institute of Allergy and Infectious Diseases (NIAID) Laboratory of Infectious Diseases (LID) started developing live-attenuated DENV vaccines known as TV003/TV005 in 1996. The development of TV003 and TV005 was based on deletions in the 32 untranslated region and structural gene chimerization. TV003 and TV005 use attenuated DENV-1, DENV-3, and DENV-4 strains with 30 nucleotide deletions on the DENV-4 backbone (Figure 1). The prM and E proteins of the DENV-4 backbone are then replaced with DENV-2 prM and E proteins with a higher dose of the DENV-2 component in TV005[29,30].

Findings of the Pre-clinical trials:

In non-human primates, preclinical testing of this vaccine demonstrated acceptable safety, undetectable viremia, and robust neutralizing antibody responses. All of which were adequate to protect the immunized monkeys when challenged with wild-type DENV-3[31].

Findings of the clinical trials:

The safety and immunogenicity of TV003 and TV005 have been assessed in two randomized placebo-controlled trials in seronegative individuals[3,5]. The trials revealed that both TV003 and TV005 were well tolerated and showed a good safety profile. A mild rash was the most common (76%) adverse event in both studies[30]. A single dose of the TV003 vaccine results (figure 2) in the development of a neutralizing antibody against the four DENV serotypes, with seroconversion rates of 64% (DENV-2) and 100% (DENV-4). The specific response to DENV-2 was improved with the TV005 vaccine (84% after a single dose)[30].

At present, some phase 2 and phase 3 trials are ongoing in different countries, including Bangladesh, with excellent safety profiles, immunogenicity against all strains, and high tolerability in the 50-to 70-year-old populations[4,5]. A single-dose TV005 vaccine was successfully tested in Bangladesh. TV005 was well tolerated and immunogenic for all four serotypes in young children and adults, including individuals with no previous dengue exposure[4]. This study represents the first evaluation of the single-dose tetravalent dengue

vaccine TV005 in South Asia (Bangladesh) in all age groups and in both dengue-experienced and dengue-naive individuals. The promising results of phase II and the preliminary findings of phase III trials could bring this vaccine into the pipeline for US FDA approval.

Indications and contraindications of TV003/TV005

The trial included 24 months to 59 years (child and adult) for vaccination. It is a single-dose subcutaneous vaccine. TV003/TV005 is not recommended for pregnant and lactating women or those who are immunocompromised.

The theory of 'quasispecies' and 'hyperendemicity':

Although the substantial initiative for developing an effective vaccine against dengue started in the early 1960s, we are yet to get an effective one to be used for mass vaccination. Two major challenges are 'quasi-species' and 'hyperendemicity' of the dengue virus[32].

In virology, the word "quasi-species" is frequently used to characterize the genetic variety found within a single serotype of viral populations. There may be several viral strains or variations with different genetic makeup within each serotype[33,34]. These variations result from errors made during viral genome replication. Genetic variations in quasi-species can affect the severity of dengue because some variants may be more virulent or have a greater ability for immune evasion. Moreover, the existence of different variations within the quasi-species may present difficulties in developing vaccines [33–35]. The quasi-species in dengue virus populations play an important role in disease outcome, transmission dynamics, and vaccine development. Immunization against one strain or serotype in particular might not offer sufficient protection against other variations within the quasi-species[36].

The term "hyperendemicity" describes the presence of multiple dengue stereotypes in a specific area at the same time[32]. Hyperendemicity of dengue greatly hampers vaccine development. First, because there are multiple serotypes of DENV, an effective vaccine must elicit a robust and balanced immune response to all serotypes[15,20,37]. Second, the risk of ADE is also increased in the presence of multiple serotypes. ADE can result in more severe dengue infections, such as DSS or DHF. To overcome this problem, vaccine candidates must have a potent neutralizing immune response to every serotype to avoid ADE[38].

Hope or hype

The most important issue for the design and development of a successful dengue vaccine was the need for tetravalent, equally effective immunization for all four DENV serotypes.

Dengvaxia is the US FDA- and WHO-approved vaccine; however, it raised serious safety concerns when data showed an increased risk of hospitalization in seronegative individuals when they were exposed to a natural infection[19]. The overall efficacy of this vaccine is only 30.2%–60.8%, with considerable protection against DEN 4 and DEN 3 (figure 2). However, it provides minimal protection against DEN 1 and DEN 2. In Bangladesh, since 2019, outbreak is mostly caused by DEN 2 and DEN3. This serotype trend is predicted to continue in the coming years.

On the other hand, Takeda TAK-003 recently received limited approval from the WHO[24]. The vaccine has the greatest VE against DENV 2 with no safety risks to seronegative individuals. However, TAK-003 provides almost no protection against DEN 3 (24), which is the most notorious serotype encircling Bangladesh. The overall efficacy of this vaccine is 62% (figure 2), with limited protection against DEN 4[21].

Probably the two most promising vaccine candidates are TV003 and TV005. The overall efficacy is 80% and can reach 100% (figure 2) if the individual is previously exposed to dengue[4]. Even in naïve population, a single dose can provide 92.6% efficacy[5]. Serotype wise, it showed less efficacy against DEN 2; however, we must wait for more data before making a conclusion. The trial in Brazil will end in June 2024, and the world is looking forward to the findings[32].

Conclusion

Despite many challenges, the quest for an effective dengue vaccine is continuing and probably the world is very close. There are many formulations in the pipeline that will expedite attempts to effectively reduce transmission and meet the WHO's global strategy for dengue prevention and control. These vaccines have been found to be safe and effective for travelers. However, for mass vaccination, a country should make a decision based on their prevalent serotypes and the potential serotypes that might cause the next epidemic. To gather these data, a robust serotype- and genotype-based surveillance and warning system is crucial.

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