

Challenges and Opportunities in the Development of Dengue Vaccines: A Comprehensive Review

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Abstract

The dengue virus is the cause of dengue fever, a disease that is prevalent in many regions around the world. Dengue fever is a significant public health concern, particularly in tropical and subtropical areas. The virus has four distinct serotypes and is transmitted to humans through the bites of infected *Aedes* mosquitoes, which can result in potentially fatal infections. There is currently no specific antiviral treatment for this disease; management mainly involves supportive care for those experiencing symptoms. Therefore, prevention is one of the most effective strategies for controlling this infection. The most effective measure for preventing the disease is vaccination. In recent years, substantial efforts have been made to develop a vaccine effective against all four serotypes of the virus. To date, only one vaccine has been approved, while several others are in phase II and III clinical trials to confirm their efficacy. The development of a dengue vaccine faces several challenges, such as the need for effectiveness against all serotypes, issues related to antibody-dependent enhancement, cross-reactive immune responses, and age-related efficacy limitations. This paper examines the key strategies for vaccine development and the latest advancements in creating an effective dengue vaccine.

Keywords: Dengue fever, dengue vaccine, disease management

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INTRODUCTION

The dengue virus (DENV) is part of the Flaviviridae family and is transmitted to humans through the bites of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes.^[1-3] There are four serotypes of this virus, all capable of causing illness in humans through transmission by these mosquito vectors. Infection with DENV can lead to a range of clinical symptoms, from mild fever to severe dengue hemorrhagic fever (DHF).^[4] DHF can further progress to dengue shock syndrome (DSS) and potentially result in death.^[3,5] In the initial stages of infection, the virus primarily targets dendritic cells and macrophages in the body.^[6] Human-to-human transmission of dengue is not possible; the virus is spread only through mosquitoes feeding

on the blood of an infected individual. Effective public health strategies should focus on reducing mosquito populations and protecting individuals from mosquito bites to effectively combat the spread of dengue.^[7] This review examines dengue vaccine development, highlighting its challenges and opportunities.

Dengue fever presents significant public health challenges in tropical and subtropical regions. Each year, over 390 million people are infected with the DENV, with about 96 million experiencing clinical symptoms. Beyond its health implications, dengue also imposes a considerable economic burden. Currently, there is no effective antiviral treatment for dengue, and only one vaccine has been approved.^[8]

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Control measures for dengue face several challenges, primarily due to the lack of specific antiviral treatments.^[8] Efforts to manage DENV transmission mainly focus on controlling the mosquito vectors, such as *Aedes aegypti* and *Aedes albopictus*, as well as reducing human contact with these insects. In some regions, secondary vectors such as *Aedes scutellaris* and *Aedes vittatus* also contribute to the transmission of the DENV. To reduce the disease burden, an integrated vector management strategy has been proposed.^[9]

As effective antiviral treatments for dengue are lacking, supportive management—particularly fluid replacement in severe dengue cases—has become essential in preventing severe disease and mortality. However, the existence of four dengue serotypes (DENV1–DENV4) and the potential for antibody-dependent enhancement (ADE) to worsen disease severity pose significant challenges to vaccine development.^[10] Additionally, developing a vaccine is complicated by cross-reactivity between the DENV and other flaviviruses, which share similar structures and conserved envelope (E) proteins.^[11] As there is still no effective treatment available, vector control measures and vaccine development are considered the main methods for preventing dengue.^[12]

Several vaccines, including the three-dose TDV and tetravalent TAK-003, have shown promising results. TDV demonstrated a favorable safety profile and induced antibody responses against all four serotypes, suggesting potential for further development.^[13] TAK-003, tested in children aged 4–16 years in endemic areas, showed effectiveness in reducing dengue cases regardless of serostatus, and continued efficacy up to 2 years post-vaccination.^[14] TAK-003 also demonstrated 61.2% efficacy in preventing virologically confirmed dengue, 84.1% in preventing hospitalizations, and 70% in preventing DHF at 54 months.^[15] These findings highlight the ongoing potential of vaccines in reducing the global burden of dengue.

RESEARCH METHOD

This review was conducted using reputable databases, including PubMed, covering studies published between 2010 and 2024 to ensure a comprehensive and up-to-date analysis. Keywords utilized for gathering information included DENV, dengue infection, effective vaccines for dengue infection, DENV immune enhancement, and cross-reactive immune response.

Vaccine development strategies

An ideal dengue vaccine should provide lifelong immunity by generating neutralizing antibodies that are effective against all four serotypes of the DENV (DENV1–DENV4).^[16] It is essential to achieve equal protection against all serotypes, as a lack of such protection can lead to a phenomenon known as ADE.^[17] ADE occurs in dengue infections when non-neutralizing antibodies from a previous infection with a different serotype are present.^[18] These non-neutralizing antibodies help the virus enter monocytes and macrophages,

resulting in increased viral replication and more severe symptoms.^[9] ADE is strongly associated with severe forms of the disease, such as DHF and DSS.^[19]

Despite the significant challenges in creating an ideal vaccine, considerable progress has been made over the past decade, with some vaccines entering clinical trials in both endemic and non-endemic areas. The general strategies in dengue vaccine development include;

1. Replicating viral vaccines (live attenuated virus vaccines): These vaccines reduce the virulence of the virus without compromising its survival and are classified into three categories:
 - Cell culture-attenuated vaccines
 - Targeted mutagenesis-attenuated vaccines
 - Chimeric virus vaccines (e.g., DENVaxia, TV003/TV005, DENVax)
2. Non-replicating viral vaccines: Vaccines in this category cannot replicate in the host, providing immunity without the risk of causing infection. The strategies in this category include:
 - Purified inactivated virus (PIV)
 - Recombinant subunit vaccine (e.g., V180, DENV2 NS1, pDENV2 prM/E-CpG)
 - Dengue DNA vaccine (e.g., monovalent DENV1, tetravalent prM/E, pDENV2 EDIII-MBP, D1ME100)
 - Replication-defective virus vectored vaccines (e.g., cAdVax)
 - Virus-like particle (VLP) vaccines.^[20–22]

The most likely targets for a dengue vaccine are the N and NS1 proteins of the DENV. Immunizing animals with these proteins has demonstrated their ability to stimulate the production of specific antibodies that can neutralize the DENV virus.^[22]

To date, the only licensed dengue vaccine that has successfully completed all three phases of clinical trials is DENG VAXIA®. Other vaccines, such as TV-003/TV-005 and TAK-003, are currently undergoing phase III clinical trials, and their results have been promising. The age and serostatus of vaccine recipients significantly influence the immunity and effectiveness of the vaccine. A major concern in evaluating these vaccines relates to the phase III clinical trials in children. So far, only DENG VAXIA and TAK-003 (DENVax) have been tested in children [Table 1].^[23]

DENG VAXIA

DENG VAXIA, also known as CYD-TDV, is the only licensed tetravalent live attenuated vaccine for the DENV. It is derived from the yellow fever 17D virus vaccine, with modifications that replace the pr M and E regions of the yellow fever virus with the corresponding regions from the four DENV serotypes. The overall efficacy of DENG VAXIA ranges from 56.5% to 60.8%, with the highest effectiveness observed against the DENV4 serotype, exceeding 70%.^[24,25]

The immune response to the DENG VAXIA vaccine is significantly influenced by an individual's serological status and

Table 1: Comparison of dengue virus vaccines

Vaccine Candidate	Type	Efficacy (Overall)	Age/Population	Safety Concerns	Current Status
Dengvaxia (CYD-TDV)	Tetravalent live attenuated vaccine	56.5%–60.8%	Ages 9–16 years, dengue-seropositive individuals	Higher risk of severe dengue in seronegative individuals; three-dose schedule required	Approved in dengue-endemic regions
TAK-003 (QDenga)	Weakened DENV2-based tetravalent vaccine	66% (seronegative), ~98% (DENV2)	Approved for all individuals regardless of serological status	Approved in multiple countries with high safety profile; best results for DENV2 serotype	Approved in Indonesia, Brazil, and the EU
Butantan-Dengue Vaccine	Single-dose live attenuated tetravalent vaccine	67.3%–80%	Broad applicability under clinical trial	Satisfactory immunogenicity and acceptable side effects in trials	Phase III trials completed; promising results
TV003/TV005	Live attenuated tetravalent vaccine	Promising (specific data not provided)	Undergoing trials; broader applicability expected	No major safety issues reported in trials	Phase III trials ongoing
Replication-Defective Virus Vected Vaccines (e.g., cAdVax)	Replication-defective virus vectored vaccine	Not detailed in the article	Trials ongoing; applicability unclear	Unclear due to lack of detailed data	Preclinical/early trial stages
Virus-Like Particle (VLP) Vaccines (e.g., V180)	Virus-like particle-based vaccine	Not detailed in the article	Trials ongoing; applicability unclear	Unclear due to lack of detailed data	Preclinical/early trial stages

prior dengue infection. For those who are dengue-seropositive, the vaccine can prevent reinfection for up to 5 years. Additionally, vaccinated individuals aged 9–16 years who are dengue-seropositive experience significantly lower rates of severe disease and hospitalization. Conversely, among dengue-seronegative recipients, vaccination is associated with a notably increased incidence of severe disease and hospitalization. Without prior infection, this vaccine may act like a primary infection, raising the risk of severe dengue in future infections.^[26]

This was highlighted during its use in the Philippines in 2016–2017, where the vaccine was administered to over 830,000 children without prior serological testing. It was later discovered that DENV-seronegative children who received the vaccine were at a higher risk of developing severe disease following breakthrough DENV infection, leading to significant safety concerns. This merging connects the efficacy discussion for seropositive individuals with the safety issues for seronegative individuals while emphasizing the critical need for proper screening before vaccination.^[27]

TAK-003 vaccine

TAK-003, developed by Takeda Vaccines Inc., is derived from a weakened DENV2 strain and offers protection against all four DENV serotypes. Phases I and II of clinical trials for this vaccine have been completed successfully, and phase III trials are currently ongoing in multiple countries. TAK-003 has demonstrated the highest immunogenicity against the DENV2 serotype, achieving an overall vaccine efficacy (VE) of approximately 66% in seronegative individuals and around 98% efficacy specifically against serotype 2.^[28] Recently, TAK-003 (QDenga) has received approval in Indonesia, Brazil, and the European Union for administration to individuals regardless of their serological status.^[29,30]

During the first half of phase 3 of the TAK-003 vaccine trial, there were seven reported deaths (five in the TAK-003 group

and two in the placebo group). Serious adverse events (SAEs) were observed in 2.9% of participants receiving TAK-003 and 3.5% of those receiving the placebo. However, none of these deaths or SAEs were considered to be linked to the vaccine. Throughout the study, no significant safety risks were identified.^[31]

Butantan-Dengue Vaccine (Butantan-DV)

One of the latest vaccines in the fight against dengue is the Butantan-Dengue Vaccine (Butantan-DV). This single-dose, live attenuated tetravalent vaccine targets all four DENV serotypes. It is an advanced version of TAK-003. Phase I and II clinical trials demonstrated satisfactory immunogenicity and demonstrated mild-to-moderate adverse effects, such as fever and injection-site reactions. Phase III trials revealed an overall efficacy ranging from approximately 67.3%^[32] to 80%, indicating that it may play a significant role in controlling symptomatic dengue infections.^[33]

Technical challenges and potential issues

Antibody-dependent enhancement

After a primary infection with the DENV, the immune system generates specific antibodies that create immune memory. These antibodies bind to and neutralize the same serotype of the virus, providing long-term, serotype-specific immunity.^[34] However, during subsequent infections with different serotypes, the previously produced IgG antibodies attach to the new serotype. Instead of neutralizing the virus, these antibodies facilitate its entry into cells, leading to increased viral replication. This phenomenon, known as ADE, can result in vascular leakage and severe dengue disease [Figure 1].^[35-37]

In the context of recurrent infections, the severity of the disease can be worsened by antibodies, which poses significant challenges in developing an effective dengue vaccine. Currently, there is no vaccine that can fully protect against all four DENV serotypes in individuals who have not had

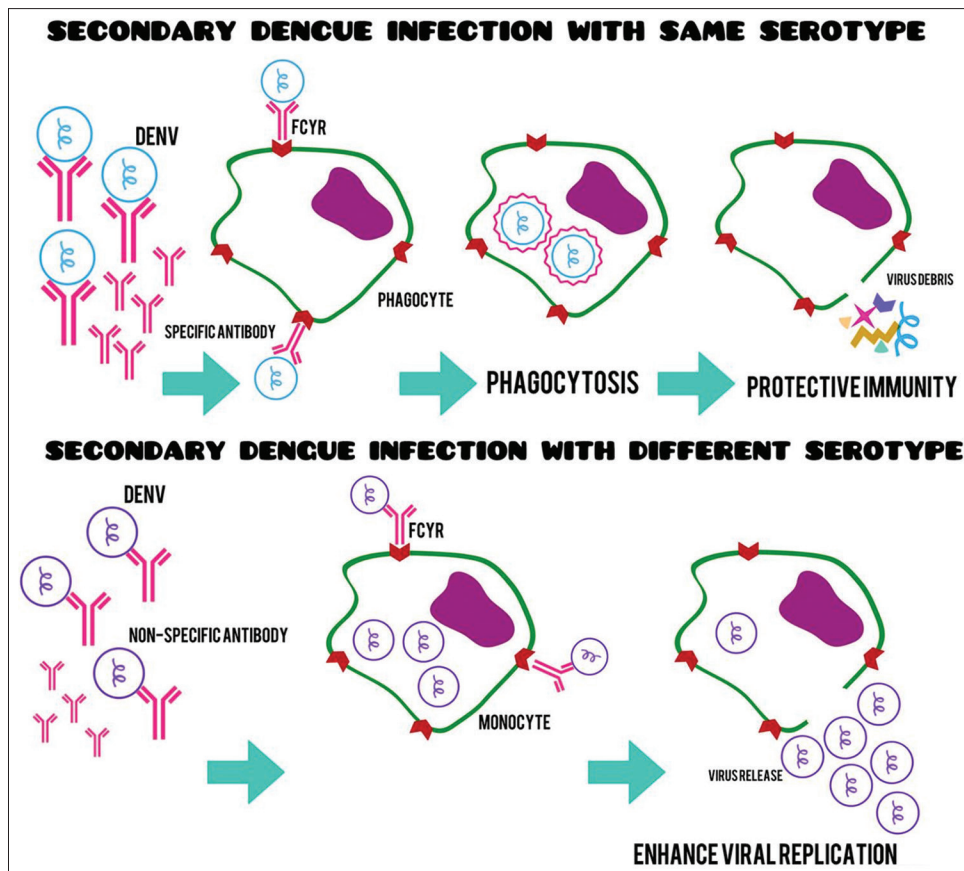


Figure 1: Antibody-dependent enhancement (ADE) in DENV. In secondary infection with a different serotype of the dengue virus, the non-neutralizing antibodies produced during the previous infection are unable to fully neutralize the different serotypes. As a result, some of the viruses enter the cells, where their transcription and replication lead to an exacerbation of the infection

a prior infection.^[38] The most advanced vaccine available is CYD-TDV, a live attenuated tetravalent vaccine that has been approved in several dengue-endemic countries. However, this vaccine may inadvertently increase the risk of severe dengue in those without previous dengue infections. Consequently, the development and distribution of such vaccines raise concerns about exposing individuals lacking prior immunity to the risks of more severe dengue.^[39,40]

Cross-reactivity

After a mosquito bite, the DENV initially infects Langerhans cells in the skin. Once these infected Langerhans cells migrate to the lymph nodes, they can transmit the virus to other phagocytic cells, facilitating the spread of the infection.^[41] Infection by one serotype usually results in strong homotypic immunity, meaning the body becomes immune to that specific serotype. However, heterotypic cross-immunity tends to be weak and short-lived. This is because cross-reactive antibodies can bind to different serotypes but may not effectively neutralize the virus, as these antibodies often lack sufficient binding strength or concentration.^[41-43]

This phenomenon, known as serological cross-reactivity, occurs when antibodies recognize and interact with similar antigenic sites on different pathogens or viral serotypes, leading to diverse outcomes. While it may result in

cross-protection—where antibodies produced against one virus provide some degree of protection against another related virus—it can also cause ADE. In ADE, suboptimal antibodies facilitate viral replication, thereby increasing disease severity.^[44]

Antigenic differences

Primary infection with one DENV serotype typically provides protection against reinfection by that same serotype. While different strains within a serotype often appear antigenically similar, significant antigenic diversity can exist within a single serotype. This intra-serotype antigenic diversity may allow for reinfection by a different strain of the same serotype.^[45]

The exact role of this diversity is not yet fully understood, but some researchers suggest that an increased antigenic distance within the serotype could contribute to epidemic outbreaks. It remains uncertain whether this phenomenon arises from repeated infections of the same serotype or is influenced by the increased impact of ADE.^[45-47] Each DENV serotype consists of multiple genotypes, which may circulate simultaneously within a geographical area or have different distributions across regions. For example, DENV serotype 3 (DENV3) includes four genotypes:

1. Genotype I (in Indonesia, Malaysia, and the South Pacific Islands)

2. Genotype II (in Thailand and Bangladesh)
3. Genotype III (in Sri Lanka and India)
4. Genotype IV (in Latin America and Central America)^[48]

Another challenge in vaccine development for dengue is the structural similarity between the DENV and other members of the Flaviviridae family, including the Zika virus (ZIKV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), and West Nile virus (WNV). The envelope protein (E) is crucial in the immune response and serves as the primary target for neutralizing antibodies; it is structurally similar across Flaviviridae viruses. This protein consists of three distinct structural and functional domains: EDI, EDII, and EDIII.^[49]

Notably, the E protein of the DENV shares over 50% homology with the E protein of the Zika virus, resulting in cross-reactive antibody responses.^[50] Such cross-reactivity can lead to either protection or exacerbate disease during secondary infections with another virus from the same family, depending on the quantity and specificity of the antibodies produced. In 2016, outbreaks of the Zika virus coincided with DENV outbreaks in northern Brazil and Mexico.^[49,51]

Developing a vaccine that provides immunity against all serotypes requires a more complex design to effectively stimulate an adequate immune response for each of the four serotypes.^[52]

An ideal vaccine should simultaneously activate long-term humoral and cellular immunity against all four serotypes of the DENV without causing disease enhancement. During DENV infection, CD8⁺ T cells are generated in response to non-structural antigens (e.g., NS3 and NS5), and through direct cytotoxicity and the production of various cytokines, such as IFN- γ and TNF- α , they reduce disease severity and enhance immunity.^[53] A similar mechanism is observed in response to dengue vaccines, where T-cell activity contributes to improved vaccine immunogenicity. Additionally, the presence of CD8⁺ T cells helps maintain immunity during ADE caused by humoral immunity. Studies recommend that in the development of dengue vaccines, greater attention should be given to the role and function of T cells, alongside antibody-mediated immunity.^[54,55]

CONCLUSION AND FUTURE OF DENGUE VACCINE DEVELOPMENT

Progress in the development of dengue vaccines is highly promising. So far, one vaccine has been approved for use in endemic countries, and two others are currently undergoing phase III clinical trials. However, concentrating primarily on neutralizing antibodies as the key indicator of protection may present a limited view, potentially neglecting the important role of T-cell-mediated immunity in managing dengue infections.

The Dengvaxia® vaccine, developed by Sanofi Pasteur, has undergone extensive clinical trials. However, because it lacks DENV non-structural proteins, its protective efficacy is limited,

especially in children. Vaccination with this product has been linked to an increased risk of hospitalization in this age group. The immunization schedule for DENGvAXIA consists of three doses, and it is not suitable for individuals who have not been previously exposed to flaviviruses. This suggests that relying solely on envelope proteins to achieve complete immunity may be inadequate, and vaccines that only stimulate humoral immune responses may not provide full protection.

This highlights the importance of cellular immunity, particularly T-cell-mediated immunity, in effectively controlling dengue infections. Many key immune targets are found on non-structural proteins that trigger cellular immune responses.^[56-58]

Fortunately, vaccines that incorporate both structural and non-structural proteins are currently undergoing clinical trials. One such vaccine, TAK-003, has shown a protective efficacy of 80.9% in phase III trials.^[59] It is expected that other vaccines with similar or even greater protective capabilities will soon be available for licensing, providing more effective immunization options against dengue.^[60] Future dengue vaccine development should focus on achieving a balance between efficacy and safety, exploring multivalent vaccines with broader immune responses, and leveraging advancements in mRNA and protein-subunit technologies to enhance vaccine design.

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Conflicts of interest

There are no conflicts of interest.

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