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Challenges in the Development of Dengue Vaccine

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The development of a dengue vaccine presents numerous challenges, largely due to the complexity of the virus and the human immune response. One of the primary hurdles is Antibody-Dependent Enhancement (ADE), where antibodies from a previous dengue infection can facilitate a more severe secondary infection with a different serotype, exacerbating the disease. Cross-reactivity with other flaviviruses, such as Zika, complicates the immune response further. Additionally, the vaccine must elicit a balanced immune response against all four dengue serotypes, which is difficult to achieve. The role of T follicular helper (T_{FH}) cells in enhancing vaccine efficacy has emerged as a critical area of focus. Efficiently targeting and inducing T_{FH} cells through specific adjuvants could enhance neutralizing antibody production and long-lasting immunity, addressing some of the current vaccine limitations. Despite these challenges, ongoing research and trials continue to advance the field towards a more effective dengue vaccine.

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1. INTRODUCTION

Dengue is an increasing public health threat: Dengue poses a growing threat globally with all four virus types (DENV-1 to 4) circulating in endemic areas [1]. Population growth, expanding Aedes mosquito habitats, and travel have fueled rising DENV infections [2]. Globally, over 390 million infections occur annually, with more than 95 million being clinically apparent [3]. Supportive care, administered by experienced practitioners, effectively manages DENV without a specific therapeutic.

DENV infections can vary from asymptomatic to severe, causing mild illnesses or classic dengue fever. Severe cases of dengue can cause plasma leakage, bleeding, shock, and death, especially with multiple DENV infections [4-7]. Dengue is caused by four antigenically different DENV types (DENV-1 to −4). Protection after one infection can be complex for vaccine development due to immune response variations [8]. Various factors interact to either protect against or enhance disease, including viral characteristics, host immunity, genetics, epidemiological context, and their timing [9]. To combat the issue, vaccine developers aim for tetravalent immunity against all DENV types, hindered by incomplete understanding of key immune responses.

Dengue vaccine development landscape: Developing a successful dengue vaccine has been a challenge for 75 years, needed for global prevention and control [10].

Sanofi Pasteur's Dengvaxia® is the only licensed dengue vaccine available in 20 endemic countries, including the EU and US. Implementation is limited to Brazil and the Philippines due to concerns about severe dengue risk in vaccinated individuals [11].

Two other dengue vaccines in phase 3 trials: Takeda's TAK-003 in multi-country trial and Instituto Butantan's Butantan-DV in Brazil. TAK-003 uses DENV-2 backbone with chimeras, while Butantan-DV is an attenuated live virus vaccine with a DENV chimera. Safety and efficacy reports are expected.

2. PATHOGENESIS OF DENGUE

The four dengue virus serotypes (DENV1-4) are closely related and share 65–70% nucleotide sequence identity [12]. A primary infection is the first instance of a certain serotype's infection. Although they can occasionally result in hemorrhagic fever in certain individuals, particularly in newborns delivered to mothers who are immune to DENV, the majority of primary infections are often asymptomatic or present as a moderate fever. Secondary dengue infection is the term for a subsequent infection with a distinct serotype that can cause serious clinical symptoms like dengue shock syndrome (DSS) or dengue hemorrhagic fever (DHF) [13–15].

A person is resistant to contracting the same serotype again after having previously been infected with it. But because the heterologous immunity is transient, infection with a different serotype may subsequently arise. Numerous cohort studies indicate that the heterotypic protective immunity gradually diminishes over the course of the next year or two [16].

Numerous viral and host factors, including the non-structural protein 1 (NS1) viral antigen, DENV genome variation, sub-genomic RNA, memory cross-reactive T cells, anti-DENV NS1 antibodies, and autoimmunity, have been linked to the pathogenesis of dengue. The combined effect of all the aforementioned elements is primarily responsible for the severe dengue symptoms in people.

Complex interplay of viral and host factors in pathogenesis of dengue virus infection:

Dengue virus infection involves viral and host factors leading to immune dysfunction, inflammation, and vascular damage.

- Viral factors: NS1 disruption, antibody enhancement
- Host factors: T-cell dysfunction, complement activation
- Immune response: Inflammatory cytokine release, endothelial dysfunction

1. DENV NS1 disrupts TLR-4, leading to activation of macrophages and PBMCs, as well as complement activation, contributing to the pathogenesis of dengue virus infection.

2. DENV Genome variations, including sfRNA, contribute to an increase in viral

virulence and enhance viral replication, leading to more severe infections.

3. Antibody dependent enhancement through Fcγ receptor mediated amplification in viral replication suppresses the type-1 IFN response and increases IL-10 levels, exacerbating the immune response.

4. Host factors such as anti-NS1 antibodies can lead to autoimmune disorders and endothelial cell autophagy, further complicating the immune response against dengue virus infection.

5. T-cells play a complex role in dengue virus infection, with cross-reactive T-cell activation, T-cell apoptosis, and defective Treg cells contributing to a detrimental immune response and impaired immune suppression.

6. Complement activation, membrane attack complex formation, and inflammatory cytokine release (IFN-γ, IL-2, TNF-α, MCP-1, IL-6, IL-8) lead to endothelial cell dysfunction, plasma leakage, coagulopathy, and thrombocytopenia in dengue virus infection.

7. The interplay between viral factors and host factors in dengue virus infection results in a complex immune response, highlighting the importance of understanding the intricate mechanisms involved in the pathogenesis of the disease [17-19].

3. DENGUE VACCINE TYPES

Various dengue vaccinations have been developed and assessed.

Live-attenuated vaccine: DF protection can be obtained with a live attenuated dengue vaccine. With the attenuated or weakened version of DENV included in these vaccinations, an immune response can be triggered without serious disease [20]. Up to date there are two licensed live-attenuated dengue vaccines are available:

Dengvaxia (CYD-TDV) and Dengvaxia tetravalent (Dengvaxia TV): Approved for use in individuals between the ages of 9 and 45 who reside in dengue-endemic areas and have a history of illness.

Dengvaxia© (CYD-TDV): Dengvaxia, also known as CYD-TDV, is the first approved live tetravalent dengue attenuated vaccine candidate. It employs the yellow fever vaccine strain 17D (YF17D) as a basis by substituting sections from four DENV serotypes for the YF17D premembrane (prM) and envelope (E) regions. It offers protection against every DENV serotype. It produces cross-reactive and serotype-specific T cell responses against DENV structural antigens, which raises the possibility of antibody-dependent enhancement (ADE). The WHO advises against giving this vaccination to anybody who is not seropositive, highlighting the importance of screening or ruling out prior infection in every case before administering the vaccine to mitigate the risk of ADE. Based on efficacy tests done over 30,000 children in ten dengue-endemic Asian and Latin American countries, the vaccine was originally licensed in December 2015. Phase 3 studies have shown the advantages of vaccination at the population level, regardless of age, serostatus, or serotype, although the concern remains about the potential for ADE with tetravalent vaccines [21].

Tetravax (TV003/TV005): Tetravax (TV003/TV005) differs greatly from CYDTDV in terms of features including viral particle structure, immunogenicity, and infectivity. DENV virulence was decreased by nucleotide deletion of 30 untranslated regions and structural gene prM/E chimerization. Comparing CYD to TV003/TV005, CYD showed lesser resistance to DENV type 2, a weaker adaptive immune response, and a greater risk of viremia.

TAK-003: Phase II trials are being conducted on TAK 003, a live attenuated chimeric tetravalent dengue vaccine (also known as DENVax). DENV serotype-dependent protective effect was demonstrated by TAK 003. DENV2 neutralizing antibody levels were greater in TAK 003 but DENV3 and DENV4 protection levels were lower. As a result, its safety profile is not fully known [22].

TDEN F17/F19 vaccine: An alternative to the live-attenuated dengue vaccine is TDEN F17/F19 vaccine.It is a safe, well-tolerated immunogenic DENV vaccine candidate, as shown by the Phase II research. One month following the second dosage, antibody responses to all four forms of DENV were shown in more than half of the babies, toddlers, and kids [23].

Dengue virus DNA vaccine: A vaccine containing nucleic acids has been created and is presently undergoing Phase 1 clinical testing.

D1ME100: The monovalent DNA plasmid vaccine D1ME100 contains the prM and E genes of the DENV 1 virus and is presently undergoing Phase I clinical studies.

Tetravalent dengue DNA vaccine: Equivalent quantities of plasmid DNA inoculum expressing dengue 1, 2, 3, and 4 prM and E genes cloned in VR1012 were combined to develop the tetravalent dengue DNA vaccine [24].

Inactivated vaccine: DENV that has been inactivated or killed is used in inactivated vaccinations. They can trigger an immunological response but cannot itself cause illness. Usually, inactivated vaccinations are administered in multiple doses.

TDEV PIV: As part of a Phase I research trial, Walter Reed Army Research Institute and GlaxoSmithKline developed this quadrivalent DENV purified inactivated vaccine [25].

Subunit vaccine: Subunit vaccines include certain immunogenic DENV proteins or components that might elicit an immune response. Certain proteins, like as non-structural proteins and envelope proteins (E), can be targeted by these vaccines. Subunit vaccinations may call for several doses.

V180 (DEN-80E): DEN 80E, also known as V180, is a highly promising vaccine candidate that has successfully completed Phase I clinical studies. It is a possible quadrivalent vaccine.

Viral-vectored vaccine: They introduce DENV genes and proteins into the body by the use of other safe viruses, such as chimera or adenoviruses. These viral vectors trigger an anti-DENNV immune response.

It is important to remember that country-to-country variations may exist in the dengue vaccine's accessibility and recommended dosage. Guidelines for the administration of dengue vaccinations and their incorporation into dengue preventive and control tactics are provided by the World Health Organization (WHO) [26].

4. PRECLINICAL EVALUATION

Dengvaxia®: Developed initially by the NIH, the University of St. Louis, and Acambis Inc., and later licensed by Sanofi Pasteur, Dengvaxia® utilizes the ChimeriVax™ technology. This approach involves using a yellow fever virus (YFV) vaccine strain where the pre-membrane (prM) and envelope (E) genes of YFV are replaced with corresponding genes from all four dengue virus (DENV) serotypes [27,28]. Preclinical evaluations demonstrated that the tetravalent ChimeriVax™ DENV 1-4 vaccine exhibited reduced neurovirulence in mice and Macaca fascicularis monkeys compared to the parental YFV strain [29]. The vaccine also generated strong neutralizing antibody responses and provided significant protection against wild-type DENV challenges in vaccinated cynomolgus macaques [30].

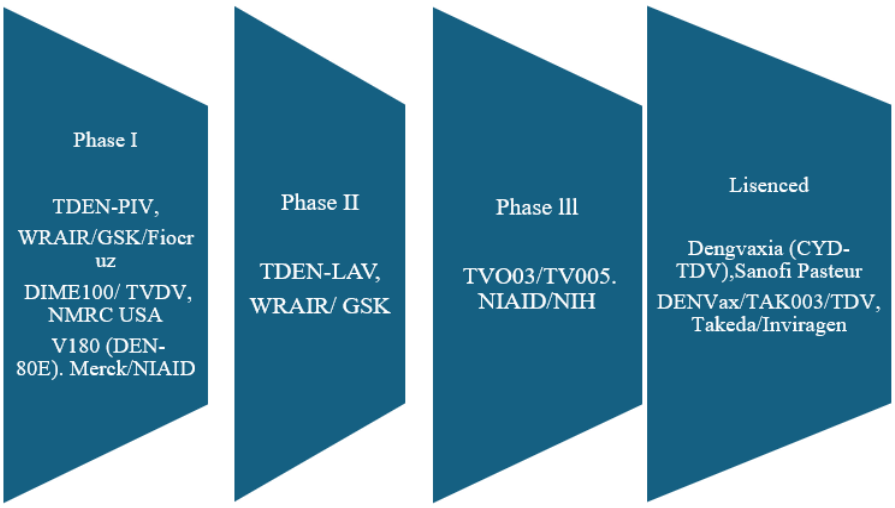

Fig. 1. Current dengue vaccines

TV003/TV005: The TV003/TV005 dengue vaccines, developed by the National Institute of Allergy and Infectious Diseases (NIAID) starting in 1996, use live attenuated DENV strains. The initial attenuation strategy involved deleting 30 nucleotides from the 3' untranslated region (UTR) of DENV-4 [30]. This method was extended to other serotypes to create a tetravalent vaccine. Preclinical studies in rhesus macaques showed that these vaccine candidates induced strong neutralizing antibody responses and provided protection against wild-type DENV challenges [31]. Various attenuated chimeric viruses, combining genetic elements from different serotypes, were evaluated to enhance the vaccine's safety and efficacy, showing promising results in animal models.

TAK-003 (DENVax): TAK-003, developed from the DENV-2 16681 strain isolated in Thailand, involves serial passages in primary dog kidney cells to achieve attenuation [32-34]. This strain was then used to create chimeric viruses for DENV-1, DENV-3, and DENV-4 by replacing their prM and E genes [35]. The resulting tetravalent vaccine formulations exhibited reduced neurovirulence and induced high neutralizing antibody titers in AG129 knockout mice [35]. Preclinical evaluation in cynomolgus macaques showed that TAK-003 was well tolerated and provided robust protection against all four DENV serotypes after two immunizations, supporting its potential as a safe and effective dengue vaccine [36].

5. CLINICAL EVALUATION

Dengvaxia: Phase I and II trials of Dengvaxia® demonstrated its safety and immunogenicity in adults and children, showing mild to moderate side effects and inducing specific T-helper responses without significant severe adverse events [37,38]. Phase III trials in children revealed age-dependent efficacy, higher in those older than 9 years, but a concerning risk of severe dengue in younger, dengue-naïve children [39]. The vaccine showed varied efficacy across DENV serotypes, with DENV-3 and DENV-4 being more effectively targeted than DENV-1 and DENV-2 [40]. Despite high overall efficacy, post-vaccination models predicted substantial hospitalizations, emphasizing the need for ongoing phase IV surveillance.

TV003/TV005: Clinical trials of TV003 and TV005, developed at NIAID, indicated good safety and balanced neutralizing antibody responses in flavivirus-naïve subjects, with TV005 showing improved efficacy against DENV-2 [31]. A single dose of these vaccines induced significant neutralizing antibody responses against all DENV serotypes. The Butantan Institute licensed TV003 as Butantan-DV, and phase II trials in Brazil demonstrated robust and balanced immune responses in both DENV-naïve and exposed adults [41]. A large phase III trial is ongoing to further assess its safety and efficacy across different age groups.

TAK-003 (DENVax): TAK-003, developed by Takeda, showed promising safety and immunogenicity in early trials, with a reformulation improving responses against DENV-4 [42]. Phase II trials in DENV-exposed individuals highlighted robust neutralizing antibody responses, though lower for DENV-4 [43]. A phase III trial in children from dengue-endemic regions revealed high efficacy against DENV-2, with lower but notable efficacy against other serotypes [44]. The vaccine maintained similar efficacy in seronegative and seropositive individuals. Long-term data at three years post-vaccination indicated overall reduced efficacy, stressing the need for extended phase IV trials to assess long-term protection and potential waning immunity [45].

6. CHALLENGES IN DENGUE VACCINE DEVELOPMENT

Antibody Dependent Enhancement (ADE): Dengue fever is a self-limiting febrile disease caused by DENVs in the majority of clinically evident cases. Severe dengue, on the other hand, is only rarely caused by DENV infections. This kind of dengue sickness has the potential to be lethal and is characterized by increased capillary permeability that can cause shock and plasma leakage [46]. Sequential infection with several serotypes of DENVs has been linked to severe dengue. According to several theories, antibodies produced against a particular DENV serotype after an initial infection bind to that serotype but do not neutralize a different DENV serotype that is encountered during a later infection. Actually, through their Fcγ receptors, the cross-reacting or neutralizing antibodies at insufficient levels promote enhanced absorption of the non-neutralized DENV into monocytes and macrophages, which are thought to be the in vivo sites of DENV reproduction. This phenomenon is termed antibody-dependent enhancement [47].

Both pathogenic and protective antibodies are produced by spontaneous DENV infections. The pathogenic antibodies are basically disease-spreading (DENV ADE promoting) antibodies because they allow non-neutralized and immature DENV to enter monocytes and macrophages. Studies have shown that prM and the FL epitope (FLE) induce cross-reactive, disease-spreading antibodies and are highly immunodominant. About 60% of the human antibody response is directed against the prM protein, according to an investigation of memory B cell responses in DENV-infected people. The prM of all four DENV serotypes may be recognized by these highly cross-reactive antibodies. Moreover, anti-prM antibodies strongly stimulate ADE but are ineffective in neutralizing DENV infectivity [48].

The challenges posed by entire DENV-based vaccination approaches force us to redirect our emphasis to the dengue vaccine candidates that have been developed and are primarily able to elicit type-specific immune responses. The ADE phenomenon, which is primarily linked to prM and FLE antibodies, may be avoided if the developed vaccines primarily generated EDIII-directed serotype specific antibodies in the absence of prM and FLE antibodies. By producing type-specific antibodies against each of the four DENV serotypes, the vaccines potentially circumvent the virus's ability to evade the immune system [49].

Three scenarios of dengue virus infection:

A. Without dengue antibodies, the virus causes a mild infection as it interacts with DC-SIGN receptors on macrophages.
B. High affinity dengue antibodies effectively neutralize the virus, preventing infection.
C. Low affinity dengue antibodies lead to increased viremia and antibody-dependent enhancement (ADE), worsening the infection due to ineffective neutralization and enhanced viral entry through FC receptors on macrophages [49].

Cross Reactivity with Other Flaviviruses: The chance of developing severe dengue and dengue with warning signals in the future is increased by prior DENV infection. There is a possibility of cross-reaction between non-neutralizing antibodies produced against the envelope E protein during the initial DENV infection and additional heterologous Flaviviruses or DENV serotypes. Due to antibody-dependent enhancement (ADE), these DENV cross-reactive antibodies may make it easier for myeloid cells to become infected with the virus later on in secondary or tertiary heterologous infections. This might worsen dengue fever in patients. Comparably, peptides shared by DENV serotypes and other Flaviviruses can alter the responses of CD ($CD4^+$ and $CD8^+$) T cells to a heterologous Flavivirus infection. Studies using mice and in vitro challenges have demonstrated that DENV-specific antibodies can amplify ZIKV infection [50].

Targeting T_{FH} Cells To enhance dengue vaccine efficacy: Antigens can be classified into T cell dependent and T cell independent based on their requirement for T cell help in eliciting an immune response. T cell dependent antigens require the assistance of T helper cells to stimulate B cells for antibody production. These antigens typically include proteins that are processed and presented by antigen-presenting cells (APCs) to T helper cells, which then provide the necessary signals for B cell activation and differentiation. In contrast, T cell independent antigens can directly stimulate B cells without T cell help. These antigens are often polysaccharides or repeating epitopes that can cross-link B cell receptors (BCRs) and induce an antibody response.

The "Hapten-Carrier" effect illustrates the mechanism of T cell dependent antigen activation. A hapten is a small molecule that, by itself, is not immunogenic but can become immunogenic when conjugated to a larger carrier protein. The carrier protein is processed and presented by APCs to T helper cells, which then help activate B cells specific to the hapten, leading to a robust immune response.

Specialized $CD4^+$ T cells *called* T follicular helper cells (T_{FH} cells) aid in the establishment of germinal centers (GCs) and have an impact on B-cell responses. T_{FH} cells appear to significantly expand in acute dengue, which associated with clinical disease severity and plasma blast expansion. This increase in frequency also correlated with DENV-specific IgG, Neut50 titres and with NS1-specific antibody titres [51]. Numerous studies have demonstrated a direct link between boosting T_{FH} cells in connection to vaccinations and effectively inducing memory B cells and plasma cells that will generate particular neutralizing antibodies against influenza and Ebola. Future vaccine design will benefit from knowing which possible adjuvants

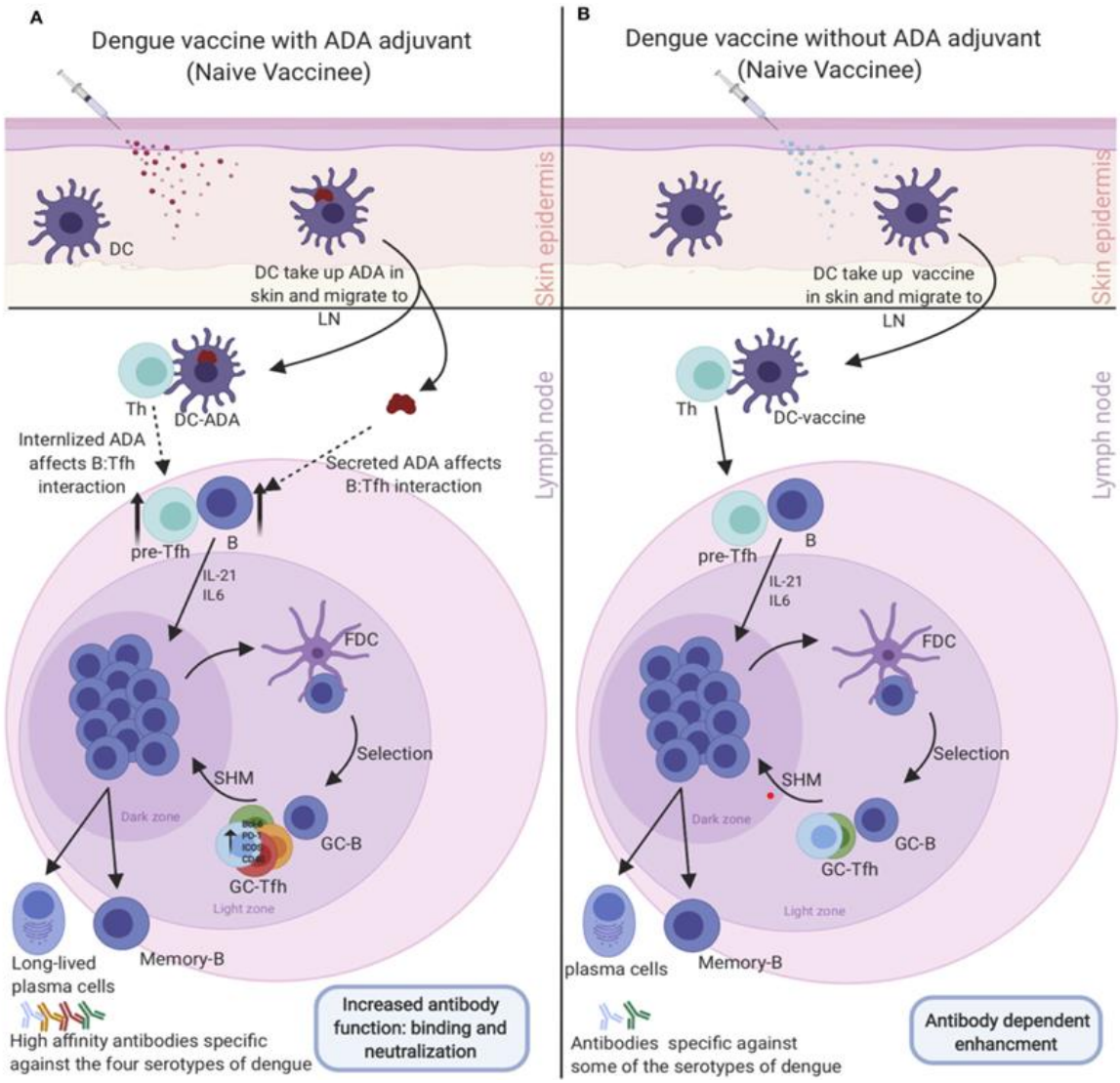

Fig. 2. Enhancement of dengue vaccine by targeting T_{FH} cells to overcome dengue serostatus effect: (A) Administering dengue vaccine to naive dengue individual with T_{FH} Adjuvant (ADA) (B) Administrating dengue vaccine to naive individuals without T_{FH} adjuvant (ADA) [52]

can effectively target and trigger a T_{FH} response. Adjuvants are necessary for most vaccines in order to boost neutralizing antibody titers, create long-lasting immunity, and minimize the number of doses needed. Adjuvants containing water in oil, such as ISA-51, Montanide ISA 720, and incomplete Freund's adjuvant (IFA), have been demonstrated to specifically enhance the T_{FH} response when used in the setting of T_{FH} induction. According to a different study, the MF59 oil-in-water adjuvant directly stimulates GC responses by mediating a strong T_{FH} response. Since TLR agonists can all increase T_{FH} cells, other adjuvants including TLR4, TLR6, TLR7, TLR8, and TLR9 agonists have all shown a great deal of interest in the usage of vaccination adjuvants. To overcome the seronegative group setback in dengue vaccination, the T_{FH} cells must be potently and selectively increased. This can be achieved by utilizing a potent adjuvant like ADA to develop specificity to all four serotypes simultaneously [53].

Need for Screening: A pre-vaccination screening technique, in which only those who test positive for dengue are vaccinated, is the recommended approach for nations contemplating CYD-TDV vaccination as part of their dengue control program, according to the World Health Organization (WHO) [11]. CYD-TDV was authorized by the US Food and Drug

Administration (FDA) in May 2019 for use in seropositive individuals aged 9 to 16 who reside in endemic areas of the country. The use of this vaccination in seropositive persons across a broader age range has also been approved by the European Medicines Agency. Therefore, serostatus screening must be completed before to vaccination in order to use CYD-TDV programmatically. The "test and vaccinate" approach, also known as pre-vaccination screening, can be carried out with IgG-based enzyme-linked immunosorbent assays (ELISAs) or rapid diagnostic tests (RDTs). In order to maximize community level benefit and reduce risk, a screening test should ideally be extremely sensitive and specific, minimizing false positives and negatives and accurately screening for seropositive individuals only. It should also be inexpensive, easy to use, and yield results quickly [54].

Economic Evaluations of Dengue Vaccination: Under certain circumstances, dengue vaccination is seen to be among the most economical measures to stop the spread of dengue disease in many nations. However, since there are currently relatively few research on its economic evaluation and the vaccine's actual use, additional scientific proof of its possible advantages is still needed. A modelling approach was used in economic evaluation studies carried out in multiple countries to forecast the economic impact of vaccination by taking into account multiple possible scenarios. However, before the dengue vaccine is really introduced in each individual nation, modelling studies on the vaccine's cost-effectiveness seem to be essential [55,56].

The dengue vaccine is still not part of many nations' current immunization programs, despite the fact that it has the potential to lessen the burden of dengue disease, particularly in areas with moderate and high endemicity [57]. In order to help policy makers make more precise decisions when allocating resources and budget, a comprehensive economic evaluation study should be conducted. This is because the government or insurance companies require it as a factor in the decision-making process. In certain countries, like those in Southeast Asia, the government may heavily subsidize dengue vaccination, which could have an impact on healthcare policies [58].The study's dengue vaccine CEA results showed that the vaccination is a potentially cost-effective intervention that might be developed and made available in all areas [59].

7. CONCLUSION

In conclusion, dengue remains a significant global health threat, exacerbated by population growth, expanded mosquito habitats, and increased travel. The disease's complexity is evident in the variation of its clinical manifestations and the intricacies involved in vaccine development. Despite the introduction of Sanofi Pasteur's Dengvaxia® and promising advancements with TAK-003 and Butantan-DV, the challenge of achieving effective, broad-based immunity persists. Antibody-dependent enhancement (ADE) and cross-reactivity with other flaviviruses further complicate vaccine efficacy. Targeting T follicular helper (T_{FH}) cells has emerged as a potential strategy to enhance vaccine responses. Continued research and innovation are essential to overcome these obstacles and develop a universally effective dengue vaccine.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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