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A COMPREHENSIVE REVIEW OF THE RECENT ADVANCEMENTS IN THE DEVELOPMENT OF A DENGUE VACCINE: IN THE HOUR OF NEED

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Abstract

Dengue fever, caused by the Dengue virus (DENV), remains a critical public health challenge, particularly in tropical and subtropical regions. Despite advancements in vaccine development, achieving an effective and universally safe vaccine remains complex due to the presence of four distinct serotypes (DENV-1 to DENV-4), which contribute to antibody-dependent enhancement (ADE) and inconsistent immune responses. Current vaccines, such as Dengvaxia, TAK-003 (QDENGA®), and TV003/TV005, demonstrate varying efficacy and safety profiles, necessitating further research into balanced immunity, reduced ADE risk, and global accessibility. This review aims to bridge the knowledge gaps present in existing literature by providing a comprehensive analysis of dengue vaccine development, challenges in implementation, and potential future strategies. It seeks to provide a detailed and updated analysis of the advancements in dengue vaccine development, identifying gaps in existing studies and highlighting strategies to overcome current challenges in achieving a safe and effective vaccine. The review includes an examination of the epidemiology and immunology of dengue fever and its impact on global health, an evaluation of the progress and limitations of existing dengue vaccines, including Dengvaxia, TAK-003, and TV003/TV005, an analysis of the challenges in vaccine development such as ADE, serotype-specific immunity, and accessibility in endemic regions, and a discussion of emerging vaccine platforms, including mRNA-based and vector-based approaches. Additionally, it proposes recommendations for future research and policy strategies for improved vaccine deployment and disease management. Through an exhaustive review of existing research, this article aims to contribute valuable insights to the scientific community, fostering further innovation in dengue vaccine development and public health strategies. Key words: Dengue Virus, Dengue Fever, Antibody Dependent Enhancement, Chimeric Yellow Fever-Dengue-Tetravalent Dengue Vaccine, Takeda, Antigen-Antibody, Cluster of Differentiation, Virologically Confirmed Dengue, Dengue Purified Inactivated Vaccine, Tetravalent Dengue DNA Vaccine.

Keywords: Dengue Virus, Dengue Fever, Antibody Dependent Enhancement, Chimeric Yellow Fever-Dengue-Tetravalent Dengue Vaccine, Takeda, Antigen-Antibody.

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INTRODUCTION

Efforts are being undertaken to manufacture an effective vaccine with good efficacy and safety profile for protection against dengue. Dengue virus (DENV) has become a global health threat with about half of the world's population at risk of infection.1 Dengue is one of the most prevalent mosquito-borne diseases in the world, affecting an estimated 390 million people each year, according to models.2 Vaccine productionstrategies are still underway with the intent of clearing clinical trials with sufficient positive results

before initiating distribution on a worldwide scale. The most common clinical manifestations are sudden fever with headache, recurrent eyelid pain, generalized muscle pain and joint pain, blushing, anorexia, and abdominal pain [1]. One modelling estimate places the global burden of dengue at 390 (95% credible interval 284–528) million infections per year, of which 96 (67–136) million manifest with varying levels of disease severity. 3 Case fatality rates (CFR) of approximately 1% have been reported for the World Health Organization (WHO) Southeast Asia region; in India, focal outbreaks away from urban areas have reported CFR of 3%–5%.3 This virus is transmitted through vectors. The dengue virus (DENV) is a type of mosquito-borne flavivirus transmitted from the bite of an infected female belonging to the Aedes genus [4]. Since mosquitoes are present in large numbers around the world, there's a higher chance of people coming across the dengue virus. Four distinct serotypes have been reported (DENV-1 to -4) which differ in the main immunodominant antigen Protein E (Envelope) [5]. Around 2.5 billion peopleworld-wide are at the risk of DENV.It is estimated that 50– 100 million DENV infections occur annually resulting in 2.3 million cases of DF reported to the WHO in 2010 .DENV is an endemic in most tropical and subtropical regions of the world with the highest burden of disease in Asia and America.

An effective vaccine must be one that can target all four serotypes. Although DF is a self-limiting mild disease, some patients will develop the severe form of the disease, characterized by plasma leakage, hemorrhaging, and shock [6]. The percentage of patients who come across these complications is low. The persistent battle against dengue has been characterized by the formidable challenges posed by the virus's complex serotypes and the concerning risks associated with antibody-dependent enhancement (ADE) of infection, a phenomenon observed in some vaccine candidates targeting the envelope glycoprotein [7]. Each of the currently available vaccines for dengue, have their pros and cons. A single dose of Butantan-DV was efficacious in children, adolescents, and adults across an age range of 2 to 59 years in this ongoing phase 3 trial [8]. Our primary efficacy criterion was met, with a vaccine efficacy of approximately 80% for protection against symptomatic, virologically confirmed dengue through 2 years of follow-up [8]. Although, it is necessary to note that Butantan-DV showed some adverse side effects with a small percentage of people. Dengvaxia (CYD-TDV) is another available vaccine, and it is recommended for seronegative individuals. Dengvaxia increases the risk for severe dengue in those who experience their first natural infection after vaccination [9]. Overall, CYD-TDV is highly efficacious in children 9 years or older who have had prior DENV infection due to the high risk of severe disease in seronegative children aged 2–5 years [10]. Hence, this vaccine cannot be considered safe for the seronegative vaccinees. CYD-TDV is currently contraindicated for pregnant or lactating women, immunocompromised persons and travelers with documented dengue illness or seropositivity, given the lack of data at this current time [10]. Thus the need for a vaccine with a good safety profile is mandatory.

EPIDEMIOLOGY OF DENGUE VACCINE

Dengue fever remains a significant global health burden, with over 390 million infections annually, leading to approximately 96 million symptomatic cases and thousands of deaths [1]. The increasing prevalence of dengue, particularly in tropical and subtropical regions, has intensified the need for an effective vaccine. The epidemiology of dengue vaccines focuses on the global demand, distribution, effectiveness, and impact on disease control strategies [2].The first licensed dengue vaccine, Dengvaxia (CYD-TDV), developed by Sanofi Pasteur, was introduced in 2015. However, its administration was restricted to seropositive individuals aged 9–45 years due to the risk of severe dengue in seronegative recipients [3]. The vaccine's selective use has limited its impact on controlling dengue outbreaks, emphasizing the need for vaccines that are effective in both seropositive and seronegative populations [4]. Recently, QDENGA® (TAK-003), a live-attenuated tetravalent dengue vaccine developed by Takeda Pharmaceuticals, was approved for broader use, including both seropositive and seronegative individuals aged 4 and above. Clinical trials demonstrated an efficacy of 80% against symptomatic dengue and 90% against hospitalization, making it a promising option for endemic regions [5]. Another promising candidate, TV003/TV005, developed by the U.S. National Institutes of Health (NIH), is undergoing Phase III clinical trials. It has demonstrated robust immunogenicity against all four dengue serotypes in both seropositive and seronegative individuals [6].The epidemiology of dengue vaccines is shaped by challenges such as variability in serotype distribution, risk of antibody-dependent enhancement (ADE), and vaccine accessibility in resource-limited settings [7]. Future research and policy efforts must focus on expanding vaccination coverage, improving vaccine affordability, and ensuring long-term protection across diverse populations.

IMMUNOLOGY OF DENGUE VIRUS AND VACCINE DEVELOPMENT

The immune response to dengue virus (DENV) is a complex interplay between innate and adaptive immunity, influencing both protection and pathogenesis. The primary immune response is mediated by dendritic cells, macrophages, and monocytes, which detect the virus through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), leading to the activation of interferon (IFN) pathways and inflammatory cytokines [1].

HUMORAL AND CELLULAR IMMUNE RESPONSE

Following infection, B-cells produce neutralizing antibodies, primarily targeting the envelope (E) protein of DENV [2]. However, the presence of four distinct serotypes (DENV-1 to DENV-4) poses a challenge in achieving cross-protective immunity. A primary infection induces long-term immunity against the infecting serotype but only temporary cross-immunity against others, leading to the risk of severe dengue upon secondary heterotypic infection [3]. This phenomenon is largely attributed to antibody-dependent enhancement (ADE), where pre-existing, non-neutralizing antibodies facilitate increased viral entry into Fc receptor-expressing cells, exacerbating the infection [4]. On the cellular level, CD4+ T cells contribute to the immune response by secreting proinflammatory cytokines, while CD8+ cytotoxic T cells play a crucial role in viral clearance[5]. However, excessive immune activation may lead to cytokine storm, vascular leakage, and severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [6].

IMMUNOLOGY OF DENGUE VACCINES

Dengue vaccines aim to induce balanced immunity against all four serotypes while minimizing ADE risks. Dengvaxia (CYD-TDV), the first licensed vaccine, is a chimeric yellow fever-dengue tetravalent vaccine, inducing strong CD4+ and CD8+ T-cell responses but demonstrating higher risk of severe dengue in seronegative individuals, necessitating pre-vaccination screening [7].The QDENGA® (TAK-003) vaccine, based on a DENV-2 backbone, elicits broad serotype coverage with strong T-cell and humoral responses, proving effective in both seropositive and seronegative individuals [8]. Meanwhile, TV003/TV005, a live-attenuated tetravalent vaccine, has demonstrated robust cell-mediated immunity in clinical trials [9]. Future dengue vaccines, including mRNA and vector-based candidates, aim to enhance immunogenicity while reducing ADE risks [10]. The ideal dengue vaccine should generate balanced, durable immunity across all serotypes, minimizing severe disease risk in diverse populations [11].

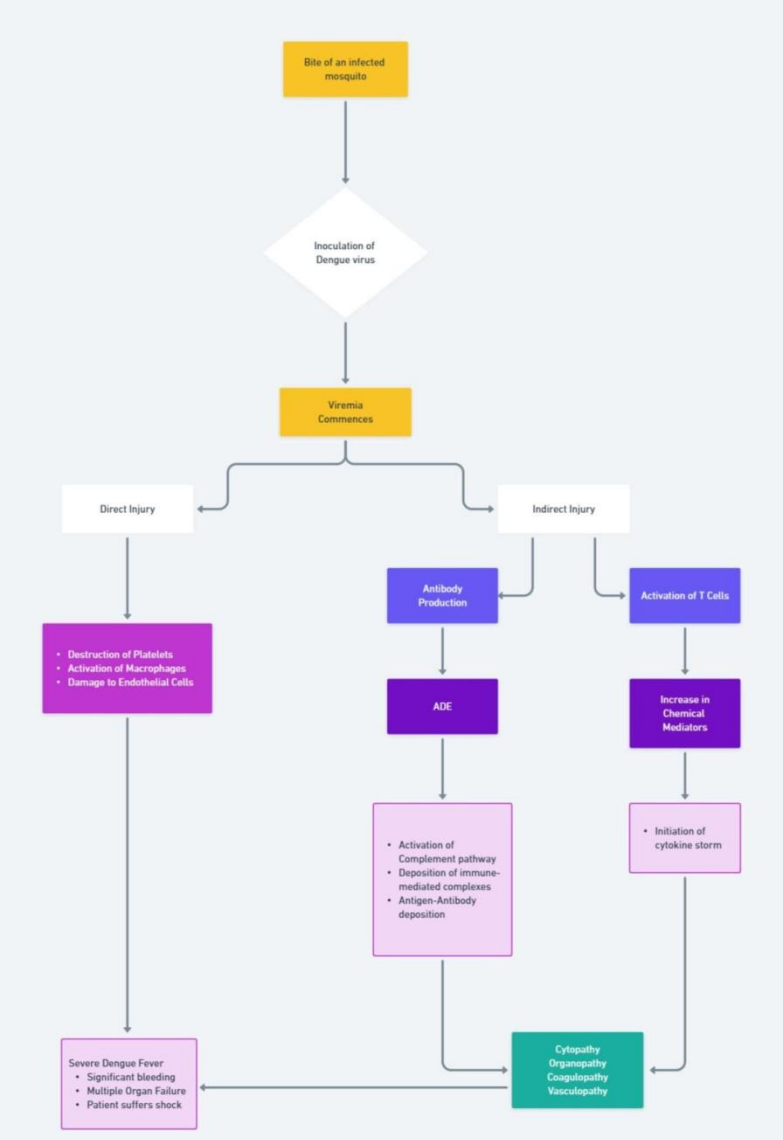

Fig: 01 Immune-Mediated Pathogenesis in Dengue Virus Infection

INOCULATION

Dengue virus, introduced into the body from a mosquito bite can be present in the mosquito's previously taken blood meal. The DENVs are transmitted in tropical and subtropical regions by infected Aedes mosquito species as they take a blood meal from a susceptible host [11]. Upon infection the viral genome is delivered to the cytoplasm and translated into one long polyprotein that is then cleaved by both host and viral specific proteases to yield 10 individual proteins [12]. The proteins include structural and non-structural proteins. The viral polyprotein is cleaved cotranslationally and posttranslationally into at least ten mature proteins: three structural proteins (capsid, prM, and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [13].

HOST IMMUNE RESPONSE

The pathogenesis of DENV infection is attributed to the complex interplay between the virus, host genes, and host immune response, with the host immune response critically involved in the pathogenesis of DENV infection [14]. The onset of viraemia can cause direct or indirect injury mechanism. In the case of direct cell injury, the endothelial cells are damaged, macrophages get activated and the body undergoes destruction of platelets. These can lead to the severe form of the disease. Conversely, if the virus injures the cells indirectly, the T-cells are activated, and the body produces antibodies in order to combat the dengue serotype. As antibodies are produced, the possible complications include ADE. ADE can cause Ab-Ag deposition, complement activation and immune-mediated depositions. Extrinsic ADE occurs when non-neutralizing antibodies forming a virus-antibody complex are recognized and engulfed by other uninfected cells, e.g., monocytes, macrophages, dendritic cells (DCs) and mast cells, via their gamma Fc receptors (FcγR), particularly FcγRI (CD64) and FcγRII (CD32),resulting in an increase in the frequency of DENV-infected cells, and subsequent upsurge in viral production [15]. The activation of T-cells, can lead to increase in chemical mediators, which can initiate cytokine storm. Various proinflammatory, immunoregulatory, and antiviral cytokines are released after the interaction between DENV and host cells [14]. The production of antibodies and T-cell activation causes vasculopathy, coagulopathy, cytopathy and organopathy.

SEVERE DENGUE

Patients who encounter complications may be exposed to severe dengue, which comprises of shock, massive bleeding and multiple organ failure. Dengue is a very serious public health problem that can manifest a wide range of symptoms from asymptomatic to fatal conditions, such as dengue shock syndrome (DSS).[16] As viral genetic factors govern its virulence and the magnitude of viral replication determine disease severity, serotypes with higher replication capacity trigger higher antibody production and may be associated with more severe outcomes [14]. Clinical features of DSS include significant plasma leakage leading to shock, fluid accumulation in the pleural and abdominal regions, increased tendency for bleeding, and organ failure [16].

ANALYSIS OF DENGUE VACCINES

QDENGA®

This vaccine product, also known as TAK-003, is a live-attenuated vaccine that is tetravalent, which was developed by Takeda Pharmaceuticals. It sanctioned a pre-license from WHO on 10 May 2024. TAK-003 contains a DENV-2 backbone whereby the pre-membrane (prM) and envelope (E) structural genes are substituted with the chimeric viruses for DENV1, DENV3, and DENV4 [10]. This vaccine can be effective for people who have been exposed or not have, to the virus. Importantly, the year 3 cumulative data indicated no age effect and showed comparable overall vaccine efficacy against VCD (65% vs 54.3%) and hospitalized VCD (86% vs 77.1%) for seropositive and seronegative individuals [6]. Although, a booster dose may be required to maintain its effectiveness. Immunogenicity studies have shown a decrease in antibody titers to DENV-2 as opposed to DENV-1, DENV-3, and DENV-4 indicating a potential need for booster dosing if data post-3 years reflects the same trends [10]. A study suggested that serious adverse events (SAE) are negligible with TAK-003 vaccine: The overall number of SAEs considered by the investigators to be related to the vaccine or placebo was one among the 15,017 subjects who received two vaccine doses and four among the 7448 controls [17]. Two had hypersensitivity, two received a diagnosis of dengue, and one had dengue hemorrhagic fever[17]Overall, the SAEs were considered as a rare event and a strong relation of the effects to the vaccine was not confirmed [18]. As for all SAEs, no significant association was found between vaccination and product-related SAEs among both adults and children or adolescents [17].

Dengvaxia®

This vaccine obtained its marketing authorizations in the year 2015. Based on a vaccine strain (17D) of yellow fever virus (YFV) in which the pre-membrane (prM) and envelope (E) genes of YFV have been replaced by the homologous genes from each one of the four DENV serotypes derived from DENV isolates obtained in Thailand and Indonesia between 1978 and 1988, this technology enabled the generation of four chimeric YF-DEN viruses that were used in the formulation of a tetravalent DENV vaccine (ChimeriVax™ DENV 1-4) [2]. While the exact mode of action is

unknown, an immune-mediated response occurs as a result of the neutralizing antibody titers that are formed against each viral strain component in the vaccine [4.19]. Regarding vaccine efficacy, children of around 12-14 years have shown higher production of antibodies [20]. Findings illustrated a proportional association between age and the number of children that express higher levels of neutralizing antibodies [2–5 years: 348 of 678 (51%); 6–11 years: 507 of 706 (72%); 12–14 years: 485 of 599 (81%)], implying that older children have the potential to exhibit a stronger defense against viral antigens introduced by the vaccine when compared with children of younger ages [4]. However, it is vital to note that this vaccine has been considered to be safe for seropositive people only, and not for the seronegative population. Dengvaxia has been reported to increase the risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals), due to the phenomenon of antibody-dependent enhancement (ADE) [3,21,22].

TV003/TV005

It is currently undergoing phase-III clinical trials. Live, attenuated tetravalent vaccine developed using recombinant DNA technology by the US NIH's National Institute of Allergy and Infectious Diseases (NIAID) [3,23]. It is tetravalent making it effective for all four DENV serotypes. TV003/ TV005 was developed by introducing 30 nucleotide deletions in the 3' untranslated region and additional mutations in

non-structural proteins to engineer live attenuated dengue virus-rDEN1Δ30, rDEN3Δ30/31 and rDEN4Δ30 [6, 24]. This vaccine has presented good efficacy results among both seropositive and seronegative vaccinees. A double blind, randomized, placebo-controlled phase II trial showed seroconversion for all four dengue serotypes 91-days post single dose of Butantan-DV in both seronegative (76%-92%) and seropositive (77–82%) individuals with rash as the main adverse reaction [6]

OTHER VACCINES

Vaccines such as DPIV, V180 and TVDV which are purified inactivated virus, recombinant proteins of DENV1-4 with many adjuvants and DNA vaccine types respectively are undergoing clinical trials [20,25].

CURRENT DEVELOPMENT OF DENGUE VACCINES

There is an increased requirement for effective vaccine against dengue (DENVserotype 1-4). The first dengue vaccines were introduced in 1929. Primary infection by Dengue virus provides protection against reinfection by that specific type(Homotypic DENV) but not to a

reinfection with a heterotypic DENV.As secondary heterotypic infection from dengue is more severe compared to the homotypic re-infections, result of animmunopathological component in dengue pathogenesis, referred to as immune enhancement of disease**.**Hence, development of vaccine prioritizes an effective and long-term protection against various dengue virus serotypes.Tetravalent vaccine was formulated with the objectiveto induce a primary-type immune responses to all four dengue viruses simultaneouslywhich curtail the risk of disease progression following the initiation of the infection.

Plot in dengue vaccine development includes:

(a)Live attenuated vaccine: Development of live attenuated dengue vaccine began at the University of Hawaii using the conventional method of channeling of virus in a non-human host. This vaccine for further development and trials were transferred to Mahido University in Bangkok.

The attempt was less successful but the initiative lead to a patway that proved progressive for developing a live attenuated tetravalent dengue vaccine. (b)The second tissue-culture-passaged dengue vaccine was developed at the Walter Reed Army Institute of Research (WRAIR) which also showed problems of unbalanced immunogenicity and reactogenicity .

(c)Chimeric virus: The US Centers for Disease Control and Prevention (CDC) developed a tetravalent chimeric dengue vaccine by inserting DENV-1, -3 and -4 prM and E genes into cDNA derived from the successfully attenuated DEN-2 component of the Mahidol University-Sanofi Pasteur live attenuated dengue virus vaccine (DEN-2, 16681 PDK-53).The candidate vaccine has now progressed to phase III efficacy studies.

(d) Inactivated virus:Inactivated vaccines express only the part of the viral genome that encodes structural proteins. Induction of cell-mediated and humoral immune responses has been demonstrated with inactivated flavivirus vaccines.

(e) Subunit vaccines: This have minimal reactogenicity and incomplete post-translational processing of proteins lead to formation of protein, different from the original proteins and antibody responses.

(f)DNA vaccines: DNA vaccines are composed of a plasmid or plasmids containing dengue genes. Certain underlying risks have been proposed for the vaccine such as carcinogenesis and autoimmune diseases.

(g)Vectored vaccines: Several live virus vectors such as adenovirus, alphavirus, and vaccinia virus are designed for direct administration to the host and have been engineered to express DENV E protein for further evaluation as dengue vaccine.

Table 2.Dengue vaccines currently licensed render development [26].

NAME[A]	YEAR[B]	VALENCE[C]	VACCINEFORMULATION	DEVELOPER/MANUFACTURER	EVALUATION	ADJUVANTED
DENGVAXIA	2015	Tetravalent	ChimericvirusesYFV/DEN1–4	SanofiPasteur	Licensed	**NO**
TV003/TV005	2003	Tetravalent	Threegeneticallyattenuatedviruses andonechimericvirus	NIAID[d]andButantan[e]	*Invivo*(phase IIIB)	**NO**
TAK-003	2006	Tetravalent	ChimericvirusesDEN-2PDK-53, DEN-1,–3,or–4	Takeda	*Invivo*(phase II)Tobe licensedinIndonesia in 2023	**NO**
TDEN	2017	Tetravalent	Virusesattenuatedwithpassagesin PDKcells	WRAIR[f]andGlaxosmithKline	*Invivo*(phase I-II)	**NO**
DPIV	2012	Tetravalent	Purifiedinactivatedviruses (DEN1–4),Aluminiumhydroxide AS01, AS03orAS04adjuvants	WRAIR,GllaxosmithKlineand FIOcruz[g]	*Invivo*(phase I)	**YES**
TVDV	2018	Tetravalent	DNAvaccinebasedonprMandE proteincodingsequencesclonedin VR1012plasmidandco-administered withVAXFECTINasan adjuvant	U.S.AMRDC[h],WRAIR,NMRC andVical	*Invivo*(animal and phaseI)	**YES**
V180	2018	Tetravalent	Recombinantproteinsbasedon prM and80%ofEproteinof DEN1–4 combinedwithdifferentadjuvants	Merckand Co.	*Invivo*(phase I)	**YES**
DSV4	2018	Tetravalent	ViruslikeparticlesexpressingEDIII ofDEN 1–4	International Centre for Genetic EngineeringandBiotechnology	*Invivo*(animal)	**NO**
E80-MRNA	2020	Tetravalent	mRNAexpressinghumanIgEandE80 proteinpackagedintoLNP	CASlaboratory ofMolecular VirologyandImmunology, **INSTITUTEPASTEUROFSHANGHAI**	*Invivo*(animal)	**NO**

[a]Current name of the vaccine formulation; [b]Name of the vaccine formulation in its most current stage; [c]Vaccine formulations were evaluated *in vitro*and*invivo*.*Invivo*assaysinvolvedpre-clinicaltestsinanimalmodelsandorphaseI,IIandIIIclinicaltrials;[d]National Institute of Allergy and Infectious Diseases, National Institutes of Health; [e]Butantan Institute,São Paulo,Brazil,[f]Walter Reed Army Institute of Research; [g]Oswaldo Cruz Foundation;[h] U.S.Army Medical Research and Development Command

CHALLENGES IN DEVELOPMENT AND SAFETY

One must take into account the obstacles that can hinder development and successful distribution, when attempts are being made towards the designing and production of the dengue vaccine:

(1) Generation and licensure of a safe and effective tetravalent DENV vaccine(2) The need for targeting four different DENV serotypes, (3) risk of antibody-

dependent enhancement, and having other fatal complications, (4)Vaccine cost and stability (5) safety levels concerning serostatus of the vaccinees, where both seronegative and seropositive individuals should be administered without severe adverse reactions, (6) The geographic distribution of each serotypes can vary, which means that the vaccine should be able to effectively counter the specific serotypes present among the population, in different regions throughout the world, (7) requirement of cold chain and reverse cold chain storage for transport is vital, (8) Vaccine hesitancy and public support are to be considered, where the people of the locality should be supportive for successful advancement and further administration, (9) Long-term surveillance for potential adverse events,(10)Compatibility with current vaccine schedule

RECOMMENDATION

A good dengue vaccine must counter all the challenges encountered and overcome them during production. At present, two dengue vaccines are licenced, Dengvaxia® and QDENGA®. Dengvaxia® is limited to be used for seropositive vaccinees only. Therefore, a screening test is highly recommended before administration. Considering the safety of seronegative individuals, QDENGA® would be suitable, as it has been reported to be safe for vaccinating candidates who had no previous exposure to the virus, andadverse events are of low intensity. All four serotypes can be targeted but a booster dose can be helpful in the event where the antibody titers to DENV 2 decreases. By considering all the pros and cons each vaccine holds, one should select the appropriate vaccine for each individual and hence the community will be protected.

DISCUSSION

The development of a dengue vaccine has been a critical global health priority due to the increasing incidence and severity of the disease, particularly in endemic regions. While significant progress has been made, several challenges remain in ensuring vaccine safety, efficacy, and accessibility across diverse populations [1]. One of the major obstacles in dengue vaccine development is the phenomenon of antibody-dependent enhancement (ADE), where pre-existing antibodies from a previous infection or vaccination can enhance viral entry into host cells, increasing the severity of subsequent infections [2]. Dengvaxia (CYD-TDV), the first licensed vaccine, demonstrated this risk, leading to increased hospitalization rates in seronegative individuals [3]. Consequently, the vaccine is recommended only for individuals with prior dengue exposure, limiting its widespread use [4].The newly licensed QDENGA® (TAK-003), developed by Takeda Pharmaceuticals, has shown promising results in clinical trials, with an overall efficacy of 80% against symptomatic dengue and 90% against hospitalization [5]. Unlike Dengvaxia, QDENGA® has been approved for both seropositive and seronegative individuals, making it a more inclusive option [6]. However, long-term studies are necessary to assess the potential risks of ADE over time and determine the need for booster doses [7].TV003/TV005, a live-attenuated tetravalent vaccine developed by the U.S. National Institutes of Health (NIH), has shown strong immunogenicity in both seropositive and seronegative individuals in Phase III clinical trials [8]. The single-dose regimen and broad serotype coverage make it a promising candidate, especially for endemic regions [9]. Additionally, new vaccine platforms such as mRNA-based and vector-based vaccines are being explored to overcome the challenges faced by live-attenuated and chimeric vaccines [10]. Another key challenge in dengue vaccination is serotype variability. Dengue has four distinct serotypes (DENV-1 to DENV-4), and an effective vaccine must provide balanced immunity across all serotypes [11]. Dengvaxia showed reduced efficacy against DENV-2, while QDENGA® demonstrated lower immune response to DENV-3, highlighting the need for continued optimization of vaccine formulations [12].The geographical and epidemiological factors also play a crucial role in vaccine deployment. The distribution of dengue serotypes varies across regions, requiring tailored vaccination strategies [13]. For instance, QDENGA® has been approved in some countries but awaits broader WHO endorsement for global use [14]. Additionally, the cost of vaccines remains a barrier, particularly in low-income countries where dengue burden is highest [15]. Future research should focus on enhancing long-term immunity, minimizing ADE risks, and ensuring equitable access to vaccines. Strengthening post-marketing surveillance systems to monitor vaccine efficacy and adverse effects will be crucial in refining vaccination policies [16]. Furthermore, integrating vaccination with vector control programs can enhance disease prevention strategies [17]. In conclusion, while significant progress has been made in dengue vaccine development, challenges remain in ensuring global accessibility, long-term safety, and serotype-specific protection. Continued investment in research, surveillance, and public health strategies will be essential in achieving sustainable control of dengue fever and reducing its burden on healthcare systems [18].

CONCLUSION

In conclusion, the development of a dengue vaccine holds great promise for reducing the global burden of dengue fever particularly tropical and subtropical regions. Future research must focus on overcoming key challenges, particularly the development of a vaccine that provides robust, balanced protection against all four dengue serotypes. While challenges remain in terms of vaccine efficacy and safety, cost, accessibility, variability in population immunity, continued research and investment in dengue vaccine development are crucial for achieving sustainable control of this debilitating disease.

The next decade will likely see significant advancements, with ongoing clinical trials of vaccines like TV003/TV005 and continued refinement of existing candidates like QDENGA® and Dengvaxia®. Technological improvements in vaccine design, coupled with enhanced understanding of the virus's complex immunological interactions, may ultimately lead to a breakthrough vaccine that can be safely administered to both seropositive and seronegative populations.

By working together to implement comprehensive prevention and control strategies, we can make significant progress towards eliminating dengue fever as a major public health threat.A multi-faceted approach that integrates vaccination with vector control, surveillance, and public health education will be key to reducing the global impact of dengue fever.Collaborative research and investment in novel technologies, like innovative vaccine platforms such as mRNA-based vaccines ongoing clinical trials, hold promise for upcoming time in current limitations and achieving global public health goals in the fight against dengue.

AUTHORS CONTRIBUTION STATEMENT:

All authors have made a substantial, direct, and intellectual contribution to the work and approved it for publication. Kevin Emmanuel Suresh contributed to the conceptualization and supervision. Dr. Romate John, Dr. John Abraham, Dr. AmbikaAkhoury, Dr. AnietaMerin Jacob, Dr. Clement Prakash played a key role in reviewing and editing the manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

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