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Progress, Challenges, and Future Prospects of Dengue Vaccine: A Comprehensive Review

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Abstract

Dengue fever, caused by the dengue virus (DENV), is a reemerging global health concern transmitted by Aedes mosquitoes associated with high mortality in the present situation. DENV comprises four distinct serotypes (DENV-1, -2, -3, and -4) with shared genetic elements, but infection with different serotypes enhances the risk of severe dengue. DENV-2 and DENV-3 are prominent in global infections. Accurate diagnosis is crucial for treatment, surveillance, and vaccine research. Immune responses, especially cross-reactive immunity, play a pivotal role in dengue pathogenesis, potentially contributing to severe manifestations. Several dengue vaccines have been developed to combat this viral disease. Due to safety concerns, the first dengue vaccine, Dengvaxia (Sanofi Pasteur's live-attenuated tetravalent vaccine), is only advised for those who have already had dengue. Since 2024, the World Health Organization has prequalified a second vaccine, Qdenga (TAK-003), created by Takeda. It targets all four serotypes, is administered in two doses spaced three months apart, and can be used in high-transmission areas on children aged 6 to 16. However, dengue vaccines face unique challenges. Ensuring that the vaccine provides balanced protection against all serotypes is crucial. This led to changes in vaccine recommendations and emphasized the importance of accurately diagnosing prior dengue exposure. Research and development of dengue vaccines continue to address these complexities and improve their effectiveness and safety. Dengue vaccination remains an important strategy in preventing this mosquito-borne viral disease, especially in regions where dengue is endemic like Bangladesh.

Keywords: DENV; Bangladesh; Qdenga, Dengvaxia®.

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Introduction

Dengue fever is an infectious disease caused by one of four antigenically distinct serotypes of the dengue virus (DENV 1- 4) and is transmitted by the bite of an infected Aedes mosquito, predominantly Aedes aegypti and Aedes albopictus[1]. DENV is a globally alarming pathogen that causes a common self-limiting illness, dengue fever (DF), as well as a less common syndrome manifested by organ failure, capillary leakage, shock, and mortality due to severe dengue, Dengue hemorrhagic fever (DHF)/ Dengue Shock Syndrome (DSS)[2]. Belonging to the members of the Flaviviridae family, DENV has a single positive-stranded RNA genome of about 11 kb. The DENV genomic RNA comprises a single open reading frame (ORF) that encodes 10 proteins, three of which are structural proteins (C, prM, and E), as well as seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5)[3].

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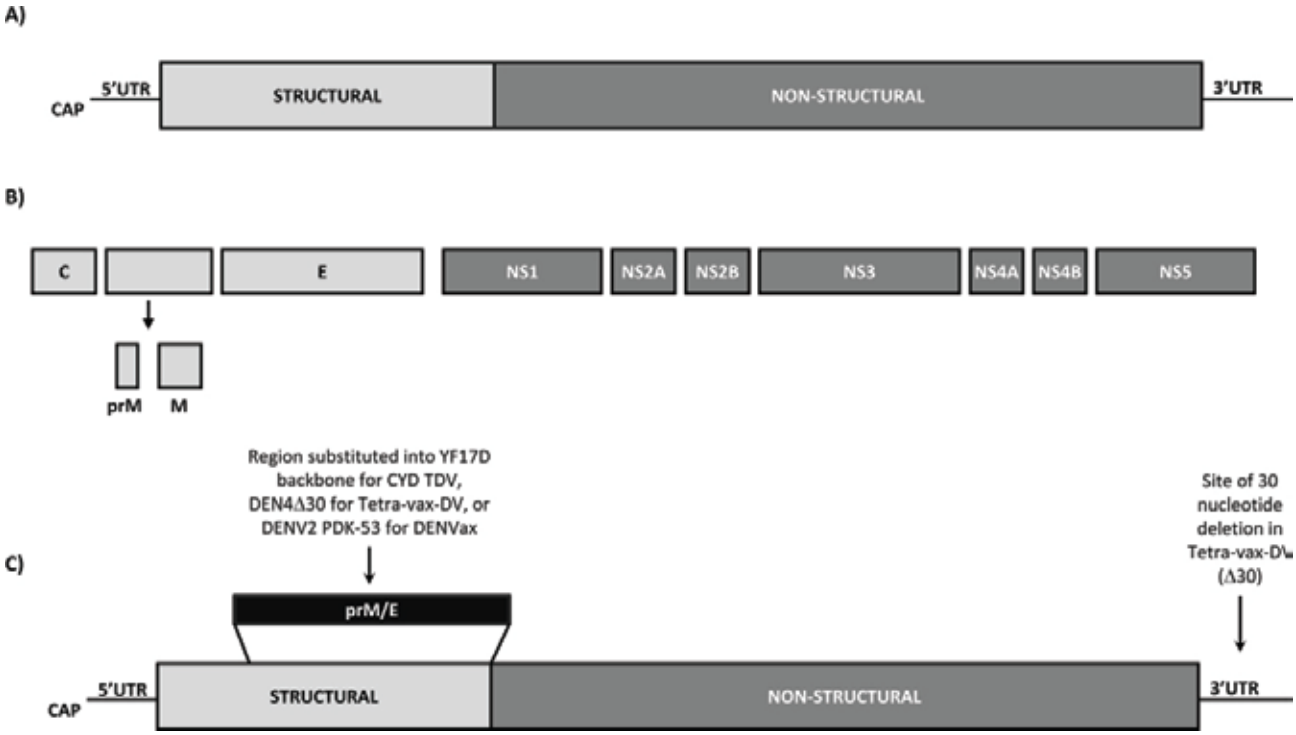

Figure I: Organization of the flavivirus genome[4]; a) RNA genome including 5' and 3' untranslated regions (UTRs) and regions (structural and non-structural proteins); b) Polyproteins are processed by both virus- and host-encoded proteases, resulting in three structural proteins- capsid (C), membrane (M), and envelope (E) and seven non-structural proteins (NS) (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5); c) Schematic representation of DENV genome modifications leading to the production of several live-attenuated virus vaccine candidates

Ren Kimura and Susumu Hotta first isolated the dengue virus in 1943. These two scientists analyzed blood samples from patients in Nagasaki, Japan,1943 during dengue epidemic. A year later, Albert B. Sabin and Walter Schlesinger isolated the dengue virus. In October 2013, DENV-5, the fifth and youngest serotype of the dengue virus, was discovered[5].

Dengue Epidemiology Worldwide and the Prospect in Bangladesh

Dengue is rapidly spreading to different regions, including Europe. As of early 2025, more than three million dengue cases and over 1,400 dengue-related fatalities have been documented across 90 countries and territories within the WHO Regions of the

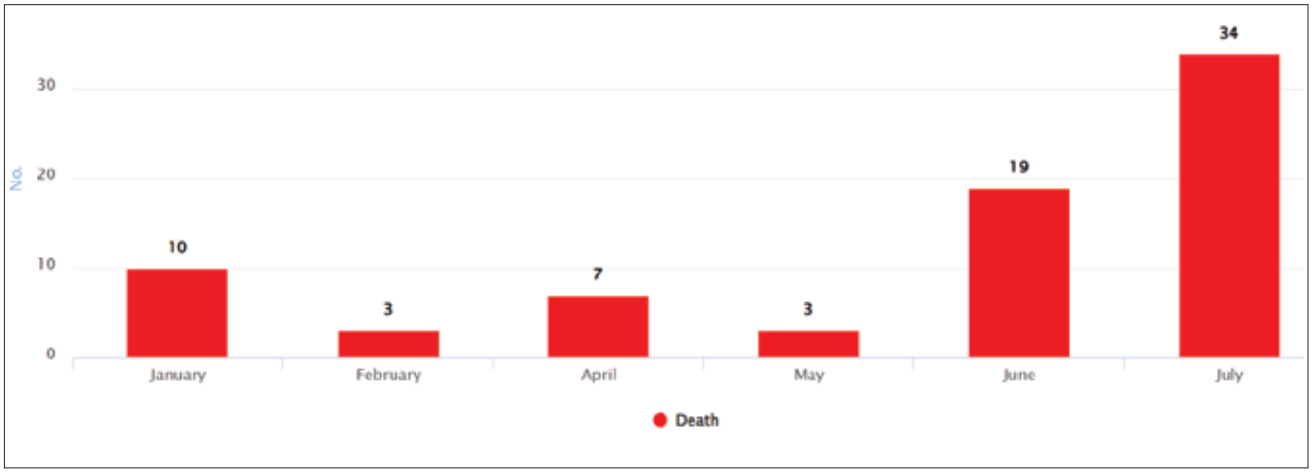

Figure II: Monthly Dengue confirmed deaths by month in 2025[9].

Americas (PAHO), South-East Asia (SEARO), West Pacific (WPRO), Eastern Mediterranean (EMRO), and Africa[6]. In July, Bangladesh experienced a substantial increase in the number of dengue cases, with more than 8,000 cases and 27 fatalities. Dengue cases increased by 8,049 in July, following 5,951 in June. The number of dengue cases has increased to 18,345 thus far this year. Dengue fever is prevalent in Bangladesh during the monsoon season of June to September[7]. In Bangladesh, the current epidemic is atypical in terms of seasonality and early, rapid increase in comparison to previous years[8].

The increased incidence of dengue in Bangladesh is a result of atypical quantities of sporadic rainfall, combined with high temperatures and high humidity, which have led to a rise in mosquito breeding in Bangladesh.

Immunological Perspectives

Dengue Serotypes and Genetic Diversity: Within the dengue (DEN) antigenic complex, DENV is divided into four genetically related but antigenically different serotypes (DENV-1, -2, -3, and -4)[10]. They share 65% of their genome, Infection can occur by any one or more than one serotype. Infection with one serotype affords lifelong homotypic immunity to that precise serotype. It is well established that subsequent infections with different serotypes enhance the risk of developing severe dengue or dengue hemorrhagic symptoms[11]. However, DEN-2 and DEN-3 are considered the major causes of infection in humans worldwide[12]. Accurate and efficient diagnosis of dengue is essential for clinical treatment, surveillance, pathogenesis studies, and vaccine research[13].

Role of host immune response in dengue infection: Serotype cross-reactive protective immunity is initially present after primary infection, but it quickly wears off, leaving the host susceptible to infection with heterologous serotypes[14]. Secondary DENV infection is a substantial risk factor for severe illness. This suggests that cross-protection in certain individuals might persist for an extended period[15]. Children and adults with heterologous secondary infection have an increased risk of severe illness. Infants with decreasing maternal antibodies may be more prone to severe illness during initial infection because of heterologous maternal antibodies mimicking secondary infection[16].

Hypotheses suggest that immune responses to heterologous infection play a direct role in the pathogenesis DHF/DSS. The immune responses to DENV infections are specifically against the structural proteins i.e, E and prM and one non-structural protein NS1. The immune response against NS1 is prone to cross-react among all the DENV serotypes[17]. Multiple non-exclusive mechanisms for increased disease severity due to heterologous immune responses have been hypothesized, including antibody-dependent enhancement (ADE), cell-mediated immunity (CMI), e.g., the generation of cross-reactive T cells, and complement activation. There are no conclusive in vivo data implicating the causal role of these responses in the severe manifestations (plasma leakage) of DENV infection, despite extensive efforts[4]. Cell-mediated immunity's (CMI) proposed mechanism of immune-mediated pathogenesis is that of a "cytokine storm" during which high levels of pro-inflammatory cytokines are released in response to heterologous DENV infection, contributing to vascular hemorrhage and severe dengue disease[18]. The activation of complement may also play a role in the pathogenesis of severe DENV infection. Anaphylatoxins, such as C5b-9, also increase plasma permeability and may therefore play a crucial role in the pathophysiology of severe dengue[4].

Neutralizing antibodies target prM, E, and NS1 proteins during DENV infection. Following primary infection (1°) or vaccination, B cells produce B cell receptors (BCRs) that continuously differentiate into virus-specific antibodies. IgM antibodies are distinguishable and detectable in the blood of 50% of patients within 3–5 days of disease onset and approximately 99% of patients within 10 days. In contrast, IgG antibody levels remain low for approximately one week before rising steadily thereafter. Thus, the levels are detectable for months or even years following the patient's recovery, providing long-term protection against a specific DENV serotype[19]. In addition, when a secondary infection occurs, the level of IgG antibodies targeting the primary infection remains elevated while the IgM level progressively rises. Consequently, an IgG/IgM ratio of 1.10 is frequently used as a clinical indicator to determine if a patient has a secondary infection[20].

Serotype and peak viremia, two viral variables, are also linked to severe illness. Therefore, it is probable that a combination of viral elements and host immune processes is responsible for the plasma leakage linked to severe illness. But it is still not clear how exactly host and viral components interact[21].

Dengue Vaccines: Every year, dengue causes millions of DENV infections, hundreds to thousands of hospital admissions, and tens of thousands of fatalities. There

isn't a single approved anti-DENV treatment or vaccination. The greatest chance to reduce the burden of dengue throughout the world is by the strategic administration of a safe and effective dengue vaccine, in collaboration with initiatives to educate about personal preventative measures and persistent vector control[22]. Disease prevention is more effective than disease treatment. Vaccines have been regarded as the most effective method of disease prevention; consequently, efforts to develop an effective dengue vaccine have been ongoing since the disease's first outbreak. Since the 1920s, five varieties of vaccines have been developed, including live attenuated, inactivated, recombinant subunit, viral vector, and DNA/mRNA vaccines, each with its strengths and weaknesses[23]. Vaccines predominantly stimulate immune responses against the E protein and non-structural protein 1 (NS1) of the DENV[24].

There are several challenges in vaccine development have been reported. First, while DENV antibodies have protective benefits against homotypic or heterotypic DENV infection, DHF and DSS are mostly caused by the ADE impact from a second heterotypic infection. However, incomplete knowledge of the immune response and the etiology of DHF and DSS prohibits the development of a DENV vaccine[25]. As specific immunity with disease protection have not yet been established, a huge number of efficacy trials are required to establish the vaccine across diverse populations and clinical endpoints[26]. Finally, there is no readily available, affordable, sensitive animal model for vaccine development that can replicate the immune responses in host after infection. Since mice are naturally resistant to DENV infection, it has been established to use human cell chimeric mice and immunodeficient mice vulnerable to DENV infection as animal models[27].

There are multiple vaccines for dengue infection in preclinical and phase 3 trials and FDA approved licensed vaccine, TAK-003 (Qdenga, Takeda) and CYD-TDV (Dengvaxia, Sanofi) are the two approved dengue vaccines at this time. Despite being tetravalent live-attenuated vaccines, they vary in terms of effectiveness and safety, as well as the degree of chimerization and the genomic backbone. Another tetravalent live-attenuated dengue vaccine is nearing the end of its clinical testing phase. It was created at the National Institutes of Allergy and Infectious Diseases (NIAID) Laboratory of Infectious Diseases[28]. However, Sanofi-Pasteur will cease the production of its dengue vaccine for children. The vaccine's production is being discontinued by the manufacturer due to a lack of demand in the global market nowadays. Consequently, Dengvaxia is no longer accessible in the United States, except for Puerto Rico, where dengue has become endemic[29].

Importance of Inducing Balanced Immune Responses to All Serotypes for Vaccine Success

The first effective vaccine was accomplished by Albert Sabin in 1945 in New Jersey which was a significant advancement in dengue vaccine development. The dengue vaccine must contain all four serotypes to prevent antibody-dependent enhancement[30]. Usually, infection with one serotype gives prolonged homotypic immunity but enhances the severity of heterotypic infections, which makes the development of vaccines very cumbersome[31].

Live Attenuated Dengue Vaccines

Live attenuated vaccines are living avirulent pathogens containing antigenic substances that provide long-term protective immunity[32]. Recombinant DNA technology has been used to create several live dengue attenuated vaccines, including the DENVax tetra-live attenuated virus dengue vaccine (TAK-003), the chimeric yellow fever 17D virus-tetravalent dengue vaccine (CYD-TDV), and the vaccine containing a recombinant DENV-4 mutant bearing a 30-nucleotide deletion (rDEN430)[33].

Live chimeric dengue vaccines (TAK003 or Denvax/ Qdenga): A tetravalent dengue vaccine candidate (TDV), developed by Takeda Pharmaceutical Company, is a chimeric vaccine[34] and the recombinant RNAs were used to transfect Vero cells to produce a vaccine candidate called DENVax[35]. TAK-003 or Denvax/ Qdenga vaccine was supposed to be licensed in Indonesia in 2023 for the prevention of dengue disease caused by all four DENV serotypes in individuals 6 to 65 years of age[34]. On April 10, 2025, WHO emphasized the recommendations for Q-DENGA in children aged more or equal to 4 years in high-transmission environments. The standard two-dose regimen is administered subcutaneously at a distance of three months. Two doses of vaccination are required for immunity against all dengue serotypes, regardless of seropositive or seronegative status of dengue infection, in several countries including Argentina, Brazil, Colombia, Indonesia, Israel, Malaysia, Switzerland, Thailand, Vietnam, the United Kingdom, and the European Union/European Economic. Following significant controversy

regarding its efficacy over the past two years, it was approved by the WHO[28,36]. In early 2024, TAK-003 was added to the national immunization program in Brazil[36]. TAK-003 vaccine candidate is a DENV-2 (TDV-2)-based (PDK-53) recombinant vaccine. TDV-2 is a molecularly characterized, attenuated DENV-2 strain that was developed by the CDC Division of Vector-Borne Diseases. It is derived from an attenuated laboratory-derived virus, DENV-2 Primary Dog Kidney-53, which was isolated at Mahidol University in Bangkok, Thailand[37]. The vaccine is based on a DENV-2 backbone that has been genetically engineered to express the structural pre-membrane (prM) and envelope (E) proteins of the remaining three dengue virus serotypes (DENV-1, DENV-3, and DENV-4), thereby stimulating immunity against all four serotypes[38]. The vaccine has an 18-month shelf life and has to be kept between 2 and 80 C[28]. A major advantage of Qdenga over its predecessor, Dengvaxia, is that it can be administered regardless of prior dengue exposure, eliminating the need for pre-vaccination serological screening[39]. The Tetravalent Immunization against Dengue Efficacy Study (TIDES) trial, which recruited 20,000 children and adolescents from eight countries in Asia and Latin America, was the primary study that examined vaccine efficacy. There was an 80% efficacy of the vaccine against virologically confirmed dengue fever (VCD) in the first year postvaccination, and it was 95.0% effective in preventing VCD-related hospitalizations. Its efficacy against VCD was highest against DENV-2 at 98.0% and lowest a to gainst DENV-3 at 63.0%. Efficacy against DENV-4 could not be determined at that time due to the limited number of DENV-4 cases. The cumulative vaccine efficacy in preventing VCD decreased to 59.0% at 45 years post-vaccination, and it was 84.0% effective in preventing VCD-related hospitalizations. Compared to dengue-naïve individuals, the vaccine efficacy was detected to be higher in dengue seropositive individuals at 63% than in dengue-naïve individuals at 50.0%[39]. The vaccine has shown particularly high efficacy against DENV-2, though slightly lower protection was observed for DENV-1, DENV-3, and DENV-4. The safety profile of Qdenga has been favorable, with the most commonly reported adverse events being mild and transient, such as injection site reactions, headache, fever, and fatigue[40].

Nevertheless, Qdenga represents a critical step forward in the global fight against dengue and may play a pivotal role in reducing dengue-associated morbidity and mortality in endemic regions.

Live Attenuated Chimeric Yellow Fever–Dengue Vaccines (Dengvaxia): GACVS last reviewed dengue vaccines in June 2015 and in May 2019, Dengvaxia was approved by FDA in the United States as the first licensed vaccine for the prevention of dengue disease caused by all dengue virus serotypes (1, 2, 3 and 4) in people ages 9 through 16 with laboratory-confirmed previous dengue infection and being residents in endemic areas[41]. Several dengue-endemic nations in Asia and Latin America have approved licenses for the use of the clinically produced dengue vaccine CYD-TDV (Dengvaxia®) (Sanofi, Paris, France), which complies with the International Guidelines for New Vaccines[42]. The prM and E genes from virulent DENV strains are recombinant with the backbone of the Yellow fever virus 17D vaccine strain to develop the Dengvaxia vaccine, which is a tetravalent chimeric vaccine with each of the four dengue serotypes[43]. In five dengue-endemic nations in Latin America, the effectiveness of the serotype-specific vaccination were 50.3% for DENV1, 42.3% for DENV2, 74.0% for DENV3, and 77.7% for DENV4. The average vaccination effectiveness in the Asia-Pacific area is 56.5%, so it has the greatest benefit of the avoidance of severe clinical manifestations of dengue and hospitalization[24]. Early phase III trials (CYD14, CYD15) indicated overall efficacy in reducing dengue hospitalizations and severe dengue across the study population[44]. However, post-hoc analyses later revealed that vaccine recipients who were seronegative at baseline had an increased risk of hospitalization and severe dengue upon subsequent natural infection, compared to unvaccinated seronegative controls. This phenomenon might be attributed to antibody-dependent enhancement (ADE), wherein vaccine-induced immunity in seronegatives mimicked a primary infection, predisposing them to more severe disease upon natural exposure to a different serotype[45]. Additionally, a recent long-term follow-up study of 35,000 children aged 2 to 16 years old throughout Latin American and Asia-Pacific nations found an incomprehensible rise in the prevalence of severe dengue hospitalization among children under the age of 9[46]. The reason for the low efficacy of CYD-TDV in seronegative subjects and the increased risk of hospitalization for children under 9 years old is not clear. These results indicate that the efficacy and safety of the Dengvaxia vaccine require further evaluation[47]. The safety and effectiveness of Dengvaxia have not been established in individuals living in dengue

nonendemic areas who travel to dengue endemic areas, are immunocompromised and are over 45 years aged person. Three doses (0.5 mL each) 6 months apart (at months 0, 6, and 12)[48]. The immunity persists for up to 4 years, and the virus serotype, age, and dengue sera status of the individual before vaccination depend on the vaccine's effectiveness[23]. So before the immunization, quick diagnostic tests are required. Given that DENV shares extremely comparable genomes, proteins, and antibodies with other members of the genus Flavivirus, such as Zika virus, yellow fever virus, and tick-borne encephalitis virus, it is difficult to reliably identify these antibodies after vaccination[49].

Live Attenuated rDENΔ30 Vaccines (TV003/ TV005): Several other tetravalent candidate vaccines are in clinical development, including TV003/TV005, which consists of attenuated forms of DENV-1, DENV-3, and DENV-4, with a chimeric DENV-2/DENV-4 backbone that is being developed by the US National Institutes of Health, Butantan Institute and Panacea Biotec[36] . Recently, the phase III trial in Brazil with over 16,000 participants and at least two years of monitoring was announced by the Instituto Butantan, the U.S. NIH, and Merck (MSD). The vaccine (Butantan-DV) was manufactured by the component (the TV003 formulation), which was previously approved by the American NIH. Participants were 2 to 59 years old with both seropositive or negative individuals to dengue, introduced single dose of the vaccine and monitored for any severe dengue symptoms caused by any DENV type. Dengue seropositive had higher effectiveness (89.2%) than seronegative (75.3%), with 79.6% overall efficacy. No immediate or obvious clinical warning symptoms were recorded. The experiment will continue until 2024 and at that time there might be more DENV-3 and -4 cases identified and a better conclusion will be achieved on the vaccine's efficacy against these strains. These statistics are available on the Butantan website but still not published in the peer-reviewed scientific literature[26].

Prospects of the Dengue Vaccine in Bangladesh

Although Qdenga (TAK-003) received WHO prequalification in May 2024 for use in children aged 4-16 years in high-transmission settings, it has not yet been authorised in Bangladesh. The Directorate General of Drug Administration (DGDA) has not received or completed a formal marketing authorisation process for the vaccine, and no local bridging trials have been reported to date. The Ministry of Health and Family Welfare (MoHFW) and the National Immunization Technical Advisory Group (NITAG) are still reviewing the matter, with the government currently prioritising vector control and hospital readiness over mass vaccination[50]. Nevertheless, numerous matters must be resolved before the introduction of the DENV vaccine in Bangladesh, including the vaccine strategy, the cost and coverage of the vaccine, the age group of individuals to be vaccinated, the availability of vaccines, and the ADE-related risk of vaccination in individuals who have not been properly screened due to inadequate diagnostic facilities[51]. DENV infection in children under 15 years in Asia presents a greater risk for severe dengue compared to adults. The use of Qdenga in this population will hopefully reduce both DENV infection rates and the severity of dengue-related outcomes. The Bangladeshi government should consider the introduction of Qdenga as a potential strategy to reduce dengue incidence in countries with a significant disease burden, such as Bangladesh[52]. According to the DGHS, the Bangladeshi government will adopt a watch-and-see approach regarding the approval of Qdenga, depending on the vaccine's efficacy observed in other markets[51]. The Phase II trial of the live attenuated tetravalent dengue vaccine TV005 was conducted in Mirpur, Dhaka, by icddr,b in collaboration with the University of Vermont's Larner College of Medicine and the U.S. National Institute of Allergy and Infectious Diseases (NIAID)[52]. The study, which began in March 2016 and concluded in February 2020, enrolled participants aged 1 to 50 years, including both dengue-naïve and previously exposed individuals[53]. Utilizing a randomized, placebo-controlled, age de-escalating design, the trial administered a single dose of TV005 or placebo, with participants followed for three years to evaluate safety, immunogenicity, and antibody durability[54]. After three years of follow-up, the majority of adults (63 to 86%) maintained their antibody titres to all serotypes. Nevertheless, titres for DENV 1, 3, and 4 decreased by three years in the smallest cohort (1 to 4 year old) as expected for individuals without prior exposure to dengue[54]. Phase III trials have not yet commenced in Bangladesh, despite the promising Phase II results. In contrast, Phase III is advancing in Brazil and India, where organizations such as Panacea Biotech are providing support for development[53]. However, the

efficacy of the TV003 vaccine against hospitalized dengue remained high (83·6% [76·8–88·4]), despite a slight decline in efficacy against virologically confirmed dengue for three years following vaccination (overall vaccine efficacy: 62·0% [56·6–66·7])[55]. A single dose of TV-005, as tested in Bangladesh, not only achieves a higher peak tetravalent seroconversion rate than TV-003, but also maintains strong immunogenicity across all four dengue serotypes through at least three years post-vaccination—a level of durability that exceeds what's observed with TV-003.

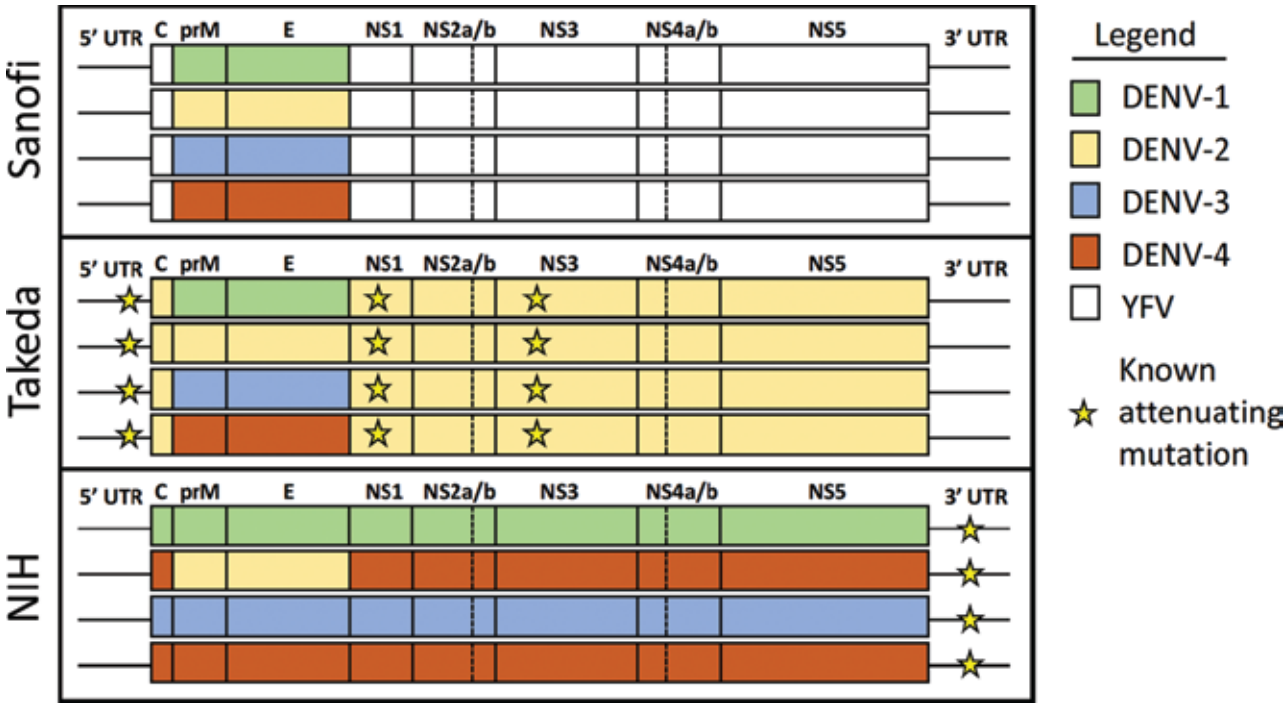

Figure III: DENV genome components of Sanofi, Takeda, and NIH/Bhutan/MSD dengue vaccine candidates with the location of known attenuating mutations[26].

Table 1: Comparative summary of currently available and experimental live attenuated dengue vaccines

Characteristics	Dengvaxia (CYD-TDV)	Dengvaxia (CYD-TDV)	TV003 / TV005
Number of doses	Three, 6 months apart	Three, 6 months apart	Single dose
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Recommended for seronegative individuals	No	No	Yes
Recommended only in seropositive individuals	Yes	Yes	No
Vaccine efficacy in seropositive individuals	High	High	High
Antibody-dependent enhancement	Reported in seronegatives	Reported in seronegatives	None reported
Protection against DENV serotypes	Suboptimal for DENV-1 & DENV-2; better for DENV-3 & DENV-4	Suboptimal for DENV-1 & DENV-2; better for DENV-3 & DENV-4	Broad tetravalent response; good across all four serotypes in trials
Highest efficacy in phase 3	DENV-4	DENV-4	DENV-2 & DENV-4
Prophylactic use	Not recommended	Not recommended	Possible
Vaccination efficacy varies by serotypes	Yes	Yes	Yes
Vaccine backbone	Yellow fever 17D virus	Yellow fever 17D virus	Attenuated monovalent DENV-1, DENV-3, DENV-4 + chimeric DENV-2/DENV-4
Recommended age of vaccinee	16–45 years (only seropositive)	16–45 years (only seropositive)	1–60 years (in trials)
Safety profile	Low in seronegatives	Low in seronegatives	High (trial data)
Approval status	Limited endemic countries are being phased out	Limited endemic countries are being phased out	Phase III trials ongoing (Brazil, India)

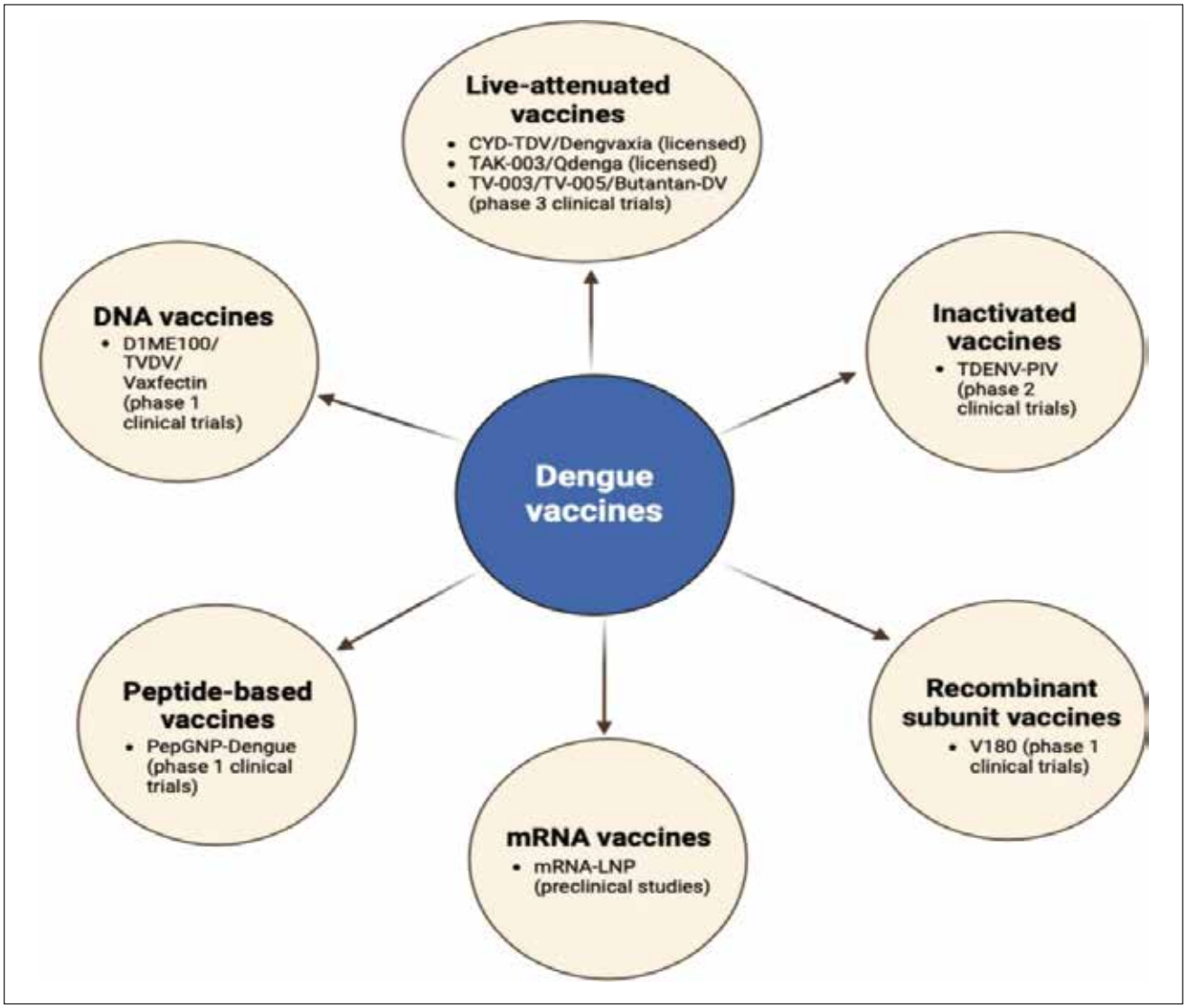

Figure IV: Types of dengue vaccines[56].

Dengue vaccines under preclinical and clinical trials

Additionally, several dengue vaccine candidates are undergoing preclinical or clinical testing, and several methods have been used to generate the vaccine (Figure 4).

Factors Influencing the effectiveness and safety of Dengue vaccines

One of the primary factors to consider is the initial serological status and age of the person receiving the vaccination. The Dengvaxia vaccine has been disputed from the very beginning due to its efficacy being mostly dependent on the recipient's baseline serological state (i.e., previous DENV infection) and age. This poses a significant obstacle to implement widespread immunization efforts. According to a recent retrospective research, individuals between the ages of 2 and 16 who tested negative for dengue virus (DENV) antibodies had a hospitalization rate of 3.1% within five years after receiving the Dengvaxia vaccine. In the placebo group, the incidence of hospitalization was seen to be 1.9%, exhibiting a negative correlation with advancing age[57]. This research demonstrated that Dengvaxia does not provide young individuals who have never been exposed to DENV with effective protection.

Genetic variations in the dengue strain are the second factor that influences vaccination efficacy. The highest effectiveness against DENV4 by Degvaxia and another vaccine, TAK003, exhibits the best efficacy against DENV2 serotypes. The variation in the prM and E

proteins' epitopes in 4 serotypes may influence the neutralization ability of antibodies induced by vaccination or natural infection. However, genetic differences might affect vaccinated individuals less than 9 years old, and thus, the vaccine-induced cellular immune response is not ideal. Lastly, the vaccine-induced immune response also influences the effectiveness of vaccines[31].

In many dengue-endemic areas, co-circulation of different serotypes infects the population, leading to frequent secondary infections and an increased risk of severe disease manifestations such as dengue hemorrhagic fever and dengue shock syndrome. Vaccine developers must pursue the development of tetravalent vaccine formulations containing antigens to each DENV type, but it has been difficult to avoid immunodominance and an imbalance of homotypic immunity to the dominant DENV type and cross-reactive immunity to the others. The vaccine's ability to be administered without prior serological testing simplifies its integration into public health programs, particularly in areas with high dengue transmission. Despite its promise, challenges remain regarding long-term durability of protection, vaccine cost, and accessibility in low-resource settings[58].

Conclusion

Over the last few decades, the number of dengue fever cases has been increasing each year. Future seasonal outbreaks will aggravate if nations overlook the danger and lighten up their attention to preventing and managing dengue. Therefore, there is still an abundance of concern about the establishment of human immunization and vaccination methods for DENV. Stronger cellular immune responses should be developed as well as finding out how to prevent ADE. Next-generation dengue vaccines should be more effective, safer, and easier to administer, regardless of seroprevalence.

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Conflict of Interest
The authors have no conflicts of interest to disclose.

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Authors' contributions
Shamoli Saha was involved in the literature review, revising, and preparing a final manuscript draft. Ritu Saha was involved in the conceptualization of the study and preparing the initial manuscript draft. Hasiba Mahmuda was involved in the literature review, revising, and editing of the manuscript. All authors accepted and approved the final version of the manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Not Applicable

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