



Dengue Vaccines: Bridging Innovation and Public Health

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Abstract

Dengue is among the fastest-growing mosquito-borne viral infections worldwide and continues to pose a major public health challenge because no approved antiviral treatment is available. As a result, vaccination has become a cornerstone of dengue prevention. Several vaccine candidates have progressed through clinical development; however, questions remain regarding their efficacy, long-term safety, and ability to provide consistent protection against all four dengue virus serotypes. Over the last five years, findings from phase II and phase III clinical trials, post-licensure safety monitoring, and real-world effectiveness studies have substantially advanced the understanding of vaccine performance and influenced both regulatory recommendations and future vaccine development strategies. Despite these advances, important immunological issues remain unresolved, including the induction of balanced and durable immunity against all serotypes, identification of reliable correlates of protection, and clarification of how age and pre-existing dengue immunity affect vaccine responses. Clinical studies have reported variable outcomes, with several vaccines offering moderate protection against symptomatic dengue while showing differences in efficacy among serotypes and lower effectiveness in individuals without prior dengue exposure. Consequently, vaccination policies have evolved toward more targeted approaches, including pre-vaccination serological testing in selected settings, preferential use among seropositive populations, and integration of immunization programs with vector control and disease surveillance measures. Current research is focused on developing next-generation vaccines that provide stronger tetravalent immune responses, longer-lasting protection, and improved safety for seronegative individuals. In parallel, innovative clinical trial methodologies and detailed immunological analyses are being employed to better define the mechanisms underlying protective immunity. This review summarizes recent clinical evidence, emerging immunological knowledge, and evolving public health policies to provide an updated assessment of dengue vaccines and to identify key research priorities for achieving safe, effective, and equitable dengue prevention through vaccination.

Keywords-Dengue-vaccine, Tetravalent, immunity, Antibody-dependent enhancement, Serostatus-dependent efficacy, Vaccine-effectiveness, Pre-vaccination screening

1. Introduction

Dengue fever is a mosquito-borne viral illness caused by dengue virus (DENV) and predominantly affects populations in tropical and subtropical regions. Infection is frequently asymptomatic or produces a self-limited febrile illness; when symptomatic, clinical onset typically occurs 3–14 days after exposure and commonly includes high fever, severe headache, arthralgia, nausea or vomiting, pruritus, and a characteristic maculopapular rash. Laboratory abnormalities such as leukopenia and thrombocytopenia are common. A small proportion of infections progress to severe dengue—historically referred to as dengue hemorrhagic



fever or dengue shock syndrome—characterized by plasma leakage, haemorrhage, marked thrombocytopenia, and potentially life-threatening hypotension.

DENV comprises four antigenically distinct serotypes (DENV-1 to DENV-4) within the Flavivirus genus, a group of enveloped, positive-sense single-stranded RNA viruses that also includes Zika, West Nile, and yellow fever viruses. The principal vector is the peridomestic mosquito *Aedes aegypti*, which thrives in urban environments and breeds in man-made water containers. (1)

The widespread distribution of *Aedes* mosquitoes has enabled dengue to become one of the most significant mosquito-borne viral diseases globally. It is estimated that nearly 50% of the world's population resides in regions where dengue transmission occurs, with approximately 100–400 million infections reported each year. Laboratory confirmation of dengue depends on the stage of illness. During the early phase of infection, viral detection methods such as reverse transcription-polymerase chain reaction (RT-PCR) are commonly used to identify viral RNA, whereas serological tests are employed later to detect dengue virus-specific antibodies. Preventive strategies primarily emphasize reducing mosquito populations through vector-control programs and limiting human exposure by adopting personal protective measures against mosquito bites.

At present, two dengue vaccines have received regulatory authorization. Dengvaxia, introduced in 2016, is recommended mainly for individuals with evidence of previous dengue virus infection because vaccination of seronegative individuals has been associated with an increased risk of severe disease following subsequent infection. Qdenga, approved in 2022, is indicated for children aged four years and older, adolescents, and adults in accordance with regional regulatory recommendations.

No antiviral medication has yet been approved for the treatment of dengue infection. Clinical management therefore remains supportive and is guided by disease severity, ranging from symptomatic relief in uncomplicated cases to careful fluid replacement, continuous clinical assessment, and hospitalization for patients who develop severe dengue or warning signs. Although decades of research have advanced dengue vaccine development, producing a vaccine that is both broadly effective and consistently safe across different populations remains difficult because of the complex immune responses induced by the virus, particularly the potential for antibody-dependent enhancement. Consequently, dengue continues to represent an increasing public health challenge in many endemic and emerging regions worldwide. (2)

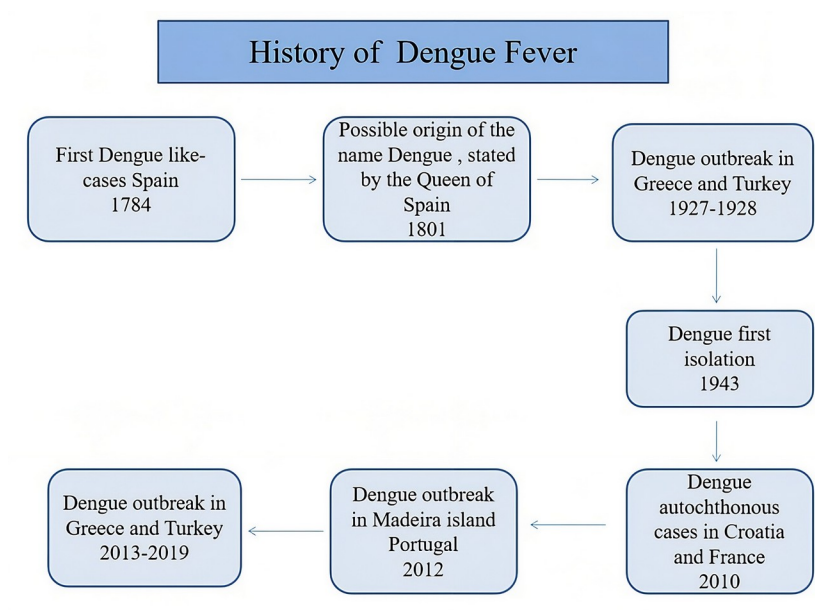


Fig-1: History of dengue fever

Severe dengue

According to the World Health Organization (WHO) International Classification of Diseases, severe dengue is defined by the presence of one or more major clinical manifestations, including extensive plasma leakage, severe bleeding, or impairment of vital organ function. This severe form of the disease can develop suddenly and most commonly emerges during the critical phase, often after the patient's fever has resolved. Extensive plasma extravasation from the capillary bed can precipitate profound hypotension and hypovolemic shock; affected patients may develop pleural effusions or ascites, hypoproteinemia, and hem concentration. Severe dengue constitutes a medical emergency because it can cause multi-organ impairment and death if not promptly recognised and managed. (3)

Clinical differentiation between mild dengue and other common febrile illnesses can be challenging. Early dengue may mimic influenza, measles, chikungunya, or Zika virus infection. Because dengue, chikungunya, and Zika share *Aedes* mosquitoes as vectors and are often co-endemic, concurrent infection with more than one arbovirus is possible.

History

The earliest probable description of dengue appears in a Chinese medical text from the Jin dynasty (266–420), which described a “water poison” associated with flying insects. The principal vector, *Aedes aegypti*, expanded beyond Africa between the 15th and 19th centuries, a spread facilitated by the slave trade and the growth of international commerce. Accounts of dengue-like epidemics date from the 17th century, and outbreaks in Jakarta, Cairo, and Philadelphia in the 18th century were likely dengue. Throughout the 19th and early 20th centuries dengue was probably endemic in many tropical urban centres, although major epidemics were relatively uncommon.

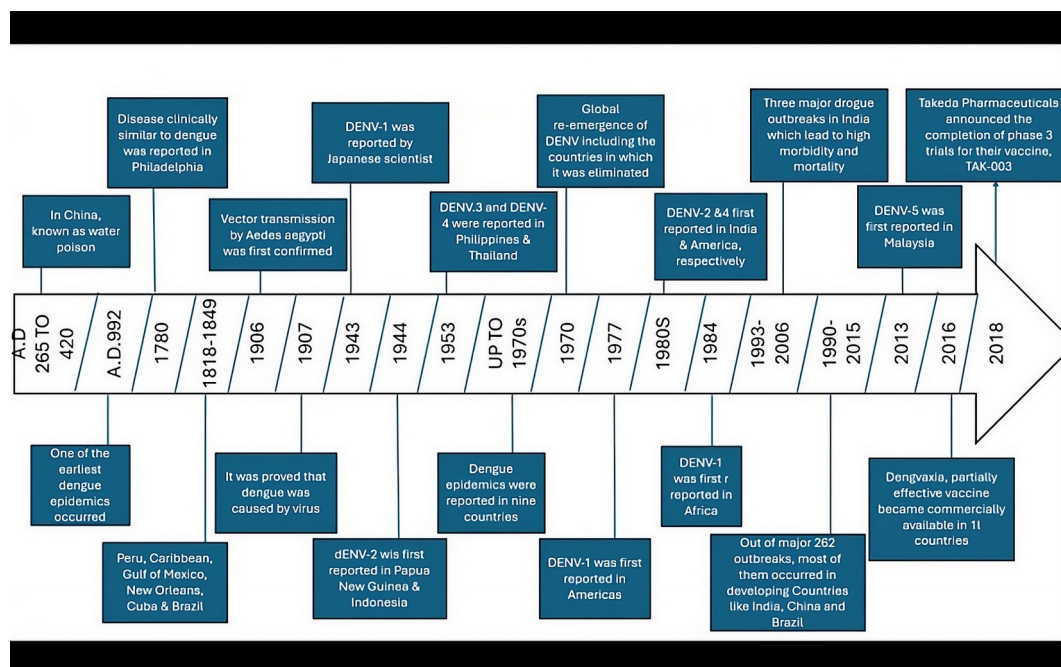


Fig-2: Time line of dengue

The substantial rise in dengue incidence during and after the Second World War has been attributed to wartime disruption and subsequent urbanization in Southeast Asia. Introduction of new serotypes into areas with existing endemic transmission precipitated outbreaks of more severe disease. The hemorrhagic form of

dengue was first documented in the Philippines in 1953 and, by the 1970s, had emerged as an important cause of childhood mortality in Southeast Asia.

In Central and South America, *Aedes* populations had been largely eradicated during the 1950s eradication campaigns; however, these programs were discontinued in the 1970s and by the 1980s dengue re-established transmission across the region, becoming hyperendemic and causing recurrent epidemics. Dengue incidence has continued to rise in the 21st century as *Aedes* vectors expand their geographic range, driven in part by ongoing urbanization and in part by climate warming. (4)

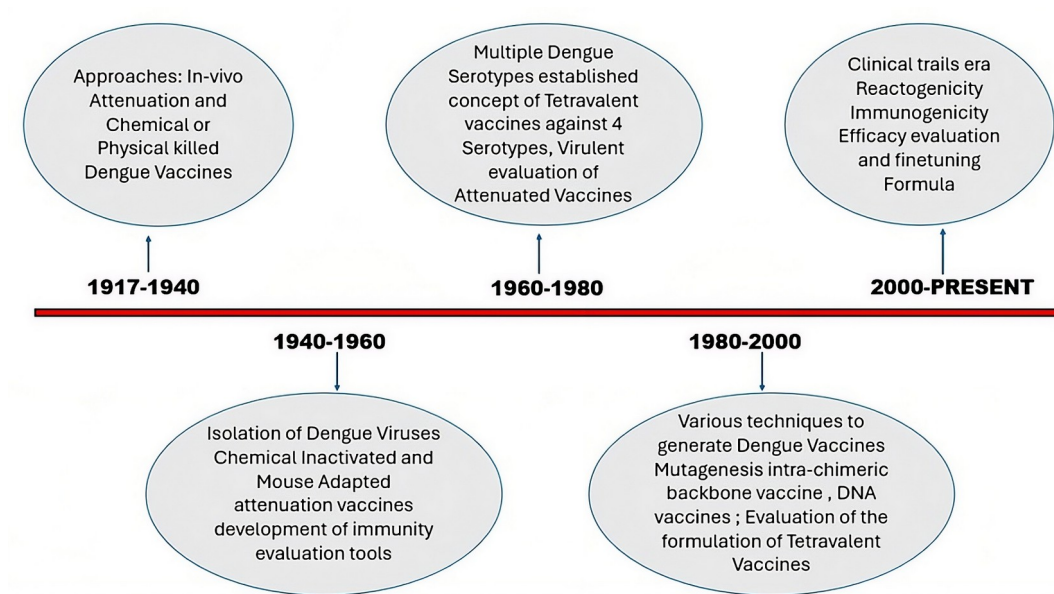


Fig-3: development of dengue vaccine

Symptoms

Most people with dengue have mild or no symptoms and will get better in 1–2 weeks. Rarely, dengue can be severe and lead to death. If symptoms occur, they usually begin 4–10 days after infection and last for 2–7 days.

Symptoms may include:

- high fever (40°C/104°F)
- severe headache
- pain behind the eyes
- muscle and joint pains
- nausea
- vomiting
- swollen glands
- Rash.

Global burden

Dengue incidence has increased markedly over recent decades and is now endemic in more than 100 countries. Reported cases to the World Health Organization rose from 505,430 in 2000 to a record 14.6 million in 2024, although true incidence is substantially higher because many infections are asymptomatic or managed outside formal healthcare systems. The 2024 season produced an unprecedented global surge—

over 14.6 million cases and more than 12,000 deaths reported—with the Region of the Americas accounting for a large proportion (over 13 million cases reported to WHO). (5)

Multiple factors drive expanding dengue transmission: geographic spread of *Aedes aegypti* and *Aedes albopictus* into previously naïve areas; climate change with higher temperatures, altered rainfall patterns, and increased humidity; rapid urbanization and population growth; strained health systems; gaps in surveillance and reporting; and political or humanitarian crises that increase population movement. Model-based estimates suggest approximately 390 million DENV infections annually, of which about 96 million are clinically apparent; other estimates indicate that roughly 5.6 billion people are at risk of dengue and related arboviruses.

Surveillance data for 2025 showed continued high activity, with over 7 million reported cases and nearly 2,000 deaths across nearly 100 countries; major outbreaks occurred in Brazil (≈2.5 million cases, >1,200 deaths) and prompted national alerts in Argentina, Peru, the Philippines, Vietnam, and India. From January to July 2025, WHO received reports of over 4 million cases and more than 3,000 deaths from 97 countries. Dengue is also emerging in new regions—southern Europe, the Eastern Mediterranean, and parts of the southern United States—with sporadic autochthonous transmission reported (e.g., France, Italy, Spain, Mayotte, Réunion). As of early 2026, reported global activity was below the five-year average (approximately 851,000 cases from January–March 2026), though seasonal peaks in the Southern Hemisphere may increase case counts later in the year. (6)

Overall estimates place annual DENV infections between 100 and 400 million, with roughly 100 million symptomatic cases; Asia bears approximately 75% of the disease burden, and about half of the world's population remains at risk.

Vector interactions:

Transmission of dengue viruses (DENVs) depends primarily on the mosquito *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*. The geographic distribution of DENVs closely follows that of these vectors, making mosquito density a key predictor of dengue epidemic risk. Female *Aedes* lay eggs in artificial water-holding containers (for example, tires, cans, and jars), so vector abundance typically peaks during the rainy season, with a corresponding rise in dengue incidence.

Aedes aegypti is highly adapted to urban environments and is an efficient vector owing to its strong preference for human hosts and its intermittent feeding behaviour, which leads to frequent contacts with multiple humans during a single gonotrophic cycle; consequently, a single female may feed on—and potentially infect—several individuals while obtaining a complete blood meal. Because *Aedes* are day-active, personal protection strategies (protective clothing, topical repellents) assume particular importance, whereas bed nets are less effective for daytime transmission. (7)

The ability of mosquitoes to acquire and transmit dengue virus (DENV) varies among vector species. Although *Aedes aegypti* is the principal vector responsible for dengue outbreaks, it generally exhibits lower susceptibility to DENV infection than *Aedes albopictus*. This difference may influence viral evolution by favouring strains capable of producing higher levels of viremia in infected humans, thereby increasing the likelihood of successful mosquito infection. Nevertheless, vector competence is determined by a complex interaction between mosquito genetics and viral genotype, and the molecular basis of these species- and strain-specific differences remains incompletely understood.

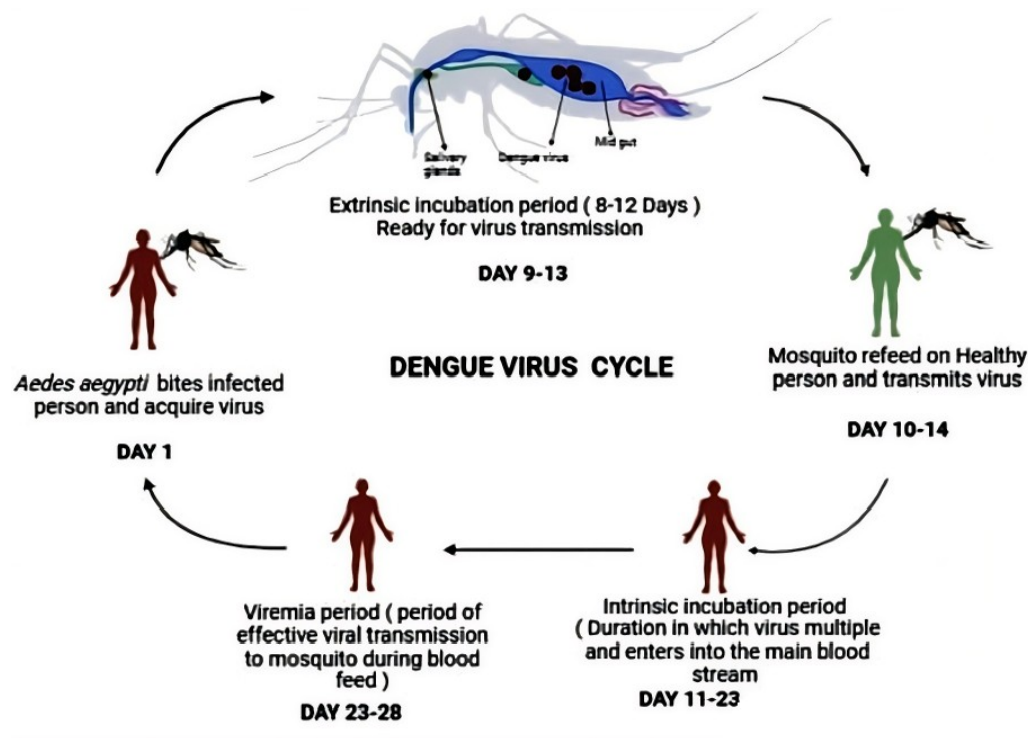


Fig-4: dengue virus cycle

After a mosquito ingests an infectious blood meal, DENV initially infects epithelial cells of the midgut before spreading to other tissues through the hemocoel. Successful transmission requires the virus to overcome the midgut infection and escape barriers, disseminate throughout the mosquito, and ultimately reach the salivary glands, from which it is released into saliva during subsequent blood feeding. Studies in *Ae. Aegypti* have identified multiple chromosomal regions associated with these barriers and with overall vector competence. In laboratory research, mosquito-derived cell lines, particularly those established from *Ae. Albopictus* are extensively used for virus isolation and experimental investigations because they support persistent, non-cytopathic DENV replication and produce high viral yields suitable for virological studies.

Until highly effective vaccines and antiviral therapies become widely available, vector control remains the primary strategy for limiting dengue transmission. Comprehensive control programs combine routine entomological surveillance with insecticide application, elimination of mosquito breeding habitats, improved water storage and environmental sanitation, and community education to reduce human-mosquito contact. Emerging interventions, including the release of genetically modified mosquitoes and mosquitoes carrying biological agents such as *Wolbachia*, are also being explored to suppress vector populations or reduce their capacity to transmit DENV. Rapid urban expansion, particularly in many regions of Southeast Asia and South America, together with inadequate water infrastructure and poor sanitation, has created favourable conditions for *Aedes* breeding, thereby contributing to the continued spread and increasing incidence of dengue. (8)

Immune responses and dengue virus pathogenesis

Dengue virus (DENV) infection is a systemic disease characterized by a wide range of clinical manifestations, extending from mild febrile illness to life-threatening complications. In patients with severe dengue, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), pathological examinations have demonstrated extensive bleeding affecting the skin, subcutaneous tissues, gastrointestinal tract, and cardiac muscle. Additional pathological findings commonly include vascular congestion, dilation of blood vessels,

oedema of arterial walls, and hemorrhagic lesions in multiple organs. These abnormalities are frequently associated with marked plasma leakage, resulting in fluid accumulation within the pleural, pericardial, and peritoneal cavities.

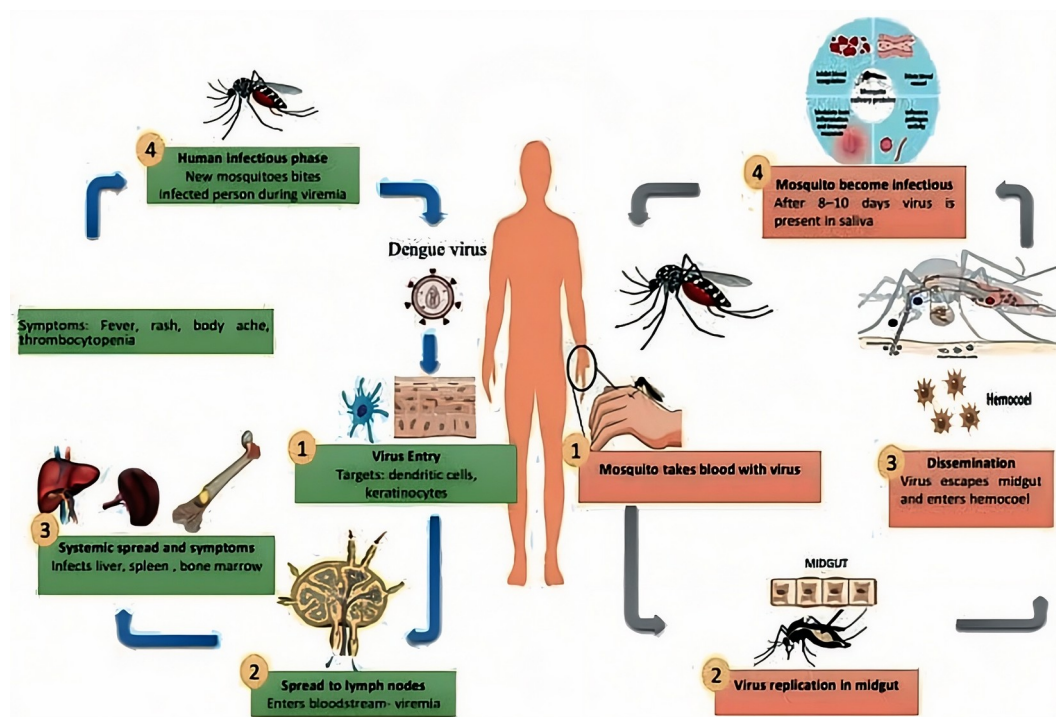


Fig-5: dengue virus pathogenesis

Despite considerable advances in dengue research, the biological processes responsible for vascular permeability and hemorrhagic manifestations remain only partially understood. Increasing evidence indicates that excessive activation of the host immune response plays a central role in disease progression. Elevated levels of pro-inflammatory cytokines, chemokines, and other vasoactive mediators detected before and during the critical phase support the concept that an exaggerated inflammatory response, often described as a cytokine storm, contributes to endothelial dysfunction and increased vascular permeability. The severity of dengue appears to depend on the balance between antiviral immune mechanisms that effectively restrict viral replication and dysregulated immune responses that amplify inflammation and tissue injury. However, a comprehensive understanding of dengue immunopathogenesis remains limited by the absence of validated immunological biomarkers that consistently differentiate protective immunity from pathogenic responses, as well as by the lack of an experimental animal model capable of accurately reproducing the full spectrum of human dengue disease. Consequently, current knowledge of dengue pathogenesis has been derived primarily from clinical investigations, epidemiological studies, and *ex vivo* analyses of immune responses obtained from infected individuals. (9)

Tropism

Identifying the primary cellular sites of dengue virus (DENV) replication has remained a significant challenge in dengue research. Many investigations have relied on immunohistochemical detection of viral structural proteins or *in situ* hybridization to identify positive-sense viral RNA within tissues. However, these methods cannot definitively differentiate productive viral replication from simple uptake of viral particles through endocytosis or phagocytosis. More convincing evidence of active infection is provided by the detection of negative-sense viral RNA intermediates or the expression of dengue virus non-structural (NS) proteins, both of which indicate ongoing intracellular viral replication.

Following transmission through the bite of an infected *Aedes* mosquito, DENV is believed to initiate replication within antigen-presenting cells located in the skin, particularly Langerhans cells and dermal dendritic cells. Once infected, these cells undergo activation and migrate to regional lymph nodes, where they initiate innate immune responses characterized by the production of type I interferons (IFN- α and IFN- β), tumour necrosis factor- α (TNF- α), and other inflammatory mediators that help restrict early viral spread. As infection progresses, viral replication expands within lymphoid tissues, although the precise cellular targets have not been fully established. Current evidence strongly supports cells of the monocyte-macrophage lineage as the principal sites of viral amplification. The release of infectious virions from these tissues into the lymphatic circulation and subsequently into the bloodstream results in viremia, enabling dissemination to peripheral organs, including the spleen, liver, and bone marrow, where tissue macrophages are frequently infected. (10)

The presence of DENV antigens has also been reported in several other cell types, including hepatocytes, endothelial cells, lymphocytes, neurons, and astrocytes. Nevertheless, these observations have been inconsistent across different studies, suggesting that viral dissemination may vary according to disease stage, viral strain, or methodological differences in detection. Although endothelial cells can support DENV replication under laboratory conditions, convincing evidence of productive endothelial infection in human disease remains limited. Current evidence indicates that direct infection of endothelial cells is not essential for the vascular leakage that characterizes severe dengue, implying that immune-mediated mechanisms play a more prominent role in endothelial dysfunction. (11)

The detection of DENV in multiple tissues suggests that host attachment factors capable of facilitating viral entry are broadly expressed. Several candidate receptors and attachment molecules have been proposed, including DC-SIGN, mannose-binding proteins, heparin-sulphate, and chondroitin-sulphate, although their relative contributions may differ among cell types. During the early stages of infection, innate immune defences—including natural IgM antibodies, the complement system, and natural killer (NK) cells—contribute to restricting viral replication and limiting systemic dissemination. As adaptive immunity develops, virus-specific cytotoxic T lymphocytes recognize and eliminate infected cells, promoting viral clearance while also contributing, under certain circumstances, to the immunopathological processes associated with severe dengue disease.

The humoral immune response

Humoral immune responses play a vital role in limiting dengue virus (DENV) infection by preventing viral spread and promoting viral clearance. Infection with one DENV serotype generally generates long-lasting protective immunity against reinfection with the same serotype. In contrast, immunity against the remaining serotypes is temporary and incomplete. During this period, cross-reactive antibodies may provide short-term protection; however, as antibody concentrations decline to sub neutralizing levels, they may facilitate infection rather than prevent it, thereby increasing the likelihood of severe dengue during a subsequent heterologous infection. This phenomenon is largely attributed to antibodies that recognize conserved regions of the viral envelope (E) protein but exhibit limited neutralizing capacity at lower concentrations. (12)

Following natural DENV infection, the antibody response is directed primarily against the precursor membrane (prM) protein, the envelope (E) protein, and the secreted non-structural protein 1 (NS1). Antibodies targeting other viral non-structural proteins, including NS3 and NS5, have also been identified, although these responses are generally less pronounced. Among these targets, the E protein is the principal antigen responsible for eliciting virus-neutralizing antibodies. These antibodies interfere with critical steps in the viral life cycle by preventing attachment to host cells, blocking viral entry, or inhibiting subsequent stages

of replication. Neutralizing epitopes are distributed across all three domains of the E protein; however, their accessibility is influenced by the tightly packed dimeric organization of E proteins on the surface of mature virions. Domain III contains the proposed receptor-binding region and exhibits the greatest sequence diversity among the four DENV serotypes. Consequently, antibodies directed against this domain are typically highly serotype-specific. Nevertheless, mutations within domain III, as well as antigenic variation in other viral proteins such as the capsid protein and NS2B, can reduce antibody recognition and enable viral escape from neutralization.

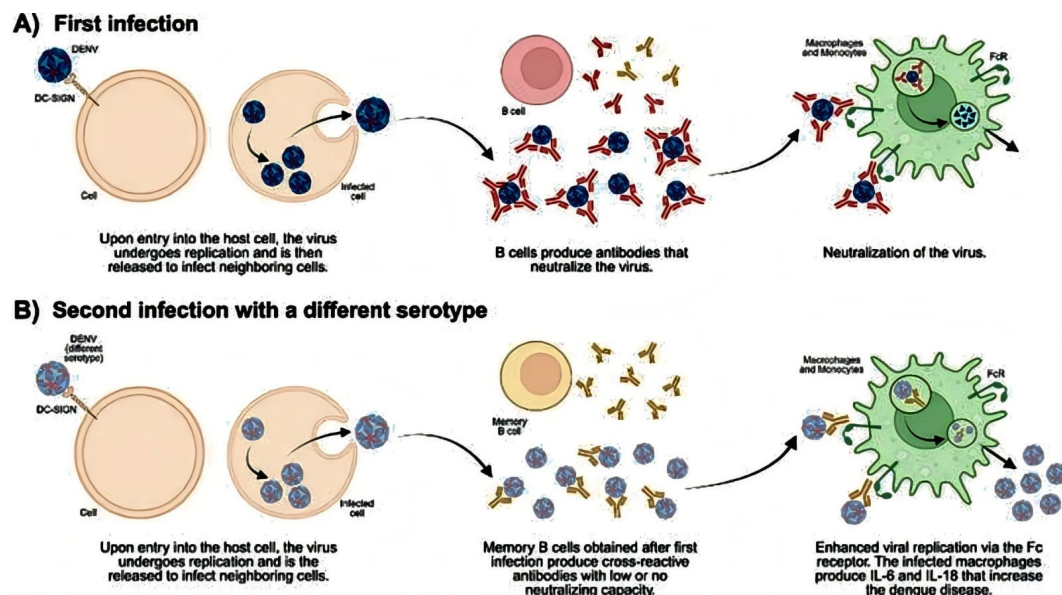


Fig-6: humoral immune response

The complement system also plays an important role in shaping antibody-mediated immunity during dengue infection. Binding of complement components to virus-antibody complexes, particularly those involving anti-prM and anti-E antibodies can enhance viral neutralization and facilitate clearance. However, excessive complement activation has also been implicated in the pathogenesis of severe dengue. Increased complement activity has been observed during the critical phase of illness and correlates with the onset of plasma leakage, suggesting that dysregulated complement responses contribute to endothelial dysfunction, increased vascular permeability, and hemorrhagic complications. In addition, the DENV NS1 protein has been shown to interact with components of the complement cascade, allowing the virus to evade immune elimination while influencing disease severity. For example, NS1 promotes the conversion of complement component C4 into C4b, a process that may reduce complement-mediated neutralization of circulating virions and facilitate viral persistence within the host. (13)

The cellular immune response

Cell-mediated immunity is a critical component of the host response to dengue virus (DENV) infection and contributes to both viral clearance and disease pathogenesis. DENV is capable of infecting CD4⁺ and CD8⁺ T lymphocytes, triggering virus-specific cellular immune responses that may either protect the host or promote immunopathology depending on the nature of the response. Activated T cells exhibit a range of effector functions, including proliferation, cytotoxic activity, and secretion of inflammatory mediators. CD4⁺ T lymphocytes produce several cytokines, such as interferon- γ (IFN- γ), tumour necrosis factor- α (TNF- α), lymphotoxin (TNF- β), interleukin-2 (IL-2), and the chemokine CCL4 (MIP-1 β), all of which have been implicated in the inflammatory processes associated with severe dengue. In comparison, T helper 2 (Th2)-associated cytokines, including interleukin-4 (IL-4), are generally produced at lower levels. Patients with

uncomplicated dengue infection often demonstrate a predominance of CD8+ T-cell responses accompanied by relatively lower circulating concentrations of IFN- γ and TNF- α . Experimental studies in animal models have further shown that adoptive transfer of DENV-specific CD8+ T cells provides partial protection against lethal viral challenge. Although regulatory T cells have also been investigated, their precise contribution to dengue immunity remains uncertain, despite evidence suggesting transient expansion during the acute phase of infection.

Primary DENV infection generates both serotype-specific and cross-reactive memory T-cell populations that persist after recovery. During a subsequent infection with a different serotype, these memory cells are rapidly reactivated. While highly effective memory T cells can suppress viral replication and contribute to protection, cross-reactive populations with limited specificity may instead intensify inflammatory responses. The functional characteristics of these memory cells are influenced by differences in peptide sequences among DENV serotypes, which alter interactions with the T-cell receptor and modify downstream immune activation. Recognition of a fully matched peptide antigen typically induces a polyfunctional response characterized by robust cytokine secretion and efficient destruction of infected cells. In contrast, recognition of partially matched peptide variants may activate cross-reactive memory T cells that produce a narrower range of cytokines and exhibit reduced cytotoxic activity. Consequently, secondary infection with a heterologous serotype may preferentially stimulate memory T and B cells that recognize the new virus with lower affinity, thereby altering the quality of the immune response and potentially contributing to pathological manifestations such as plasma leakage.

This preferential recall of immune memory generated during an earlier dengue infection, rather than the development of an optimal response against the currently infecting serotype, is referred to as original antigenic sin. The phenomenon reflects an imbalance between protective and pathogenic immunity and is influenced by both the sequence of infecting serotypes and the interval between infections. Long-lasting cross-reactive memory T cells may persist for many years and, upon re-exposure to a different serotype, generate immune responses that are less effective at controlling viral replication while promoting excessive inflammation. This concept parallels the mechanisms proposed for antibody-dependent enhancement, in which pre-existing immunity contributes to disease severity rather than protection. Mapping studies have identified numerous CD4+ and CD8+ T-cell epitopes within the viral non-structural protein NS3, a protein that represents approximately one-fifth of the DENV coding genome and serves as one of the principal targets of dengue-specific cellular immune responses. (14)

Cytokines in dengue pathogenesis

The innate immune response constitutes the first line of defence against dengue virus (DENV) infection and is activated immediately after viral entry into host cells. Recognition of the virus is mediated primarily through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) located on cellular or endosomal membranes and cytoplasmic RNA sensors such as retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene-5 (MDA5). Engagement of these receptors initiates intracellular signalling pathways that activate transcription factors, including interferon regulatory factors (IRFs) and nuclear factor- κ B (NF- κ B). These signalling events stimulate the production of type I interferons (IFN- α and IFN- β) together with numerous pro-inflammatory cytokines, promote dendritic cell maturation, and establish an antiviral state that limits viral replication during the early stages of infection. (15)

DENV exhibits a strong tropism for cells of the monocyte-macrophage-dendritic cell lineage. Viral entry primarily occurs through receptor-mediated endocytosis, although antibody-coated virions may also be internalized via Fc γ receptor-mediated pathways during secondary infections. Despite extensive

investigation, the mechanisms responsible for the development of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) have not been fully elucidated. Current evidence indicates that severe disease results predominantly from dysregulated host immune responses rather than direct virus-induced cellular injury. Clinical deterioration frequently develops during the period of defervescence, when circulating viral levels are already declining, suggesting that immune-mediated processes are central to disease progression. Consistent with this hypothesis, patients with severe or secondary dengue infections commonly exhibit markedly increased circulating concentrations of inflammatory mediators, including IL-2, IL-6, IL-8, IL-10, IL-13, IL-18, IFN- γ , TNF- α , and monocyte chemoattractant protein-1 (MCP-1), all of which have been associated with enhanced inflammatory activity.

Although elevated cytokine production is strongly associated with severe dengue, the precise mechanisms by which these mediators disrupt endothelial integrity and induce plasma leakage remain incompletely understood. Recovery from uncomplicated dengue is generally associated with a predominance of T helper 1 (Th1) immune responses, whereas a shift toward T helper 2 (Th2)-associated cytokine production has been linked to more severe clinical outcomes. Interactions between these immune pathways are regulated by cytokines such as IFN- γ and IL-10, which help shape the magnitude and balance of the inflammatory response. Activated macrophages further recruit CD4⁺ T lymphocytes that release additional inflammatory mediators capable of amplifying cytokine production. Molecules previously described as human cytotoxic factors have been reported at elevated levels in severe dengue, while antibodies directed against these factors have been associated with a reduced risk of severe disease in some investigations.

From a pathological perspective, severe dengue is characterized by increased vascular permeability without consistent structural destruction of endothelial cells. Additional abnormalities include leukocyte dysfunction, hem concentration, thrombocytopenia, coagulation disturbances, and impaired fibrinolysis. Reduced platelet counts frequently occur together with plasma leakage and abnormalities in hemostasis, thereby increasing the likelihood of hemorrhagic complications. Pro-inflammatory cytokines, particularly TNF- α , IL-6, and IL-8, have been implicated in disrupting coagulation pathways and promoting endothelial activation. TNF- α enhances vascular permeability by increasing endothelial activation and expression of adhesion molecules, whereas elevated IL-10 levels have been associated with decreased platelet numbers and impaired platelet function, further contributing to bleeding risk. Progressive leakage of plasma into the pleural, pericardial, and peritoneal cavities may ultimately lead to severe intravascular volume depletion and life-threatening hypovolemic shock if not promptly recognized and treated.

Although numerous studies have demonstrated a close temporal relationship between cytokine elevations and the onset of severe clinical manifestations, most available evidence remains observational rather than mechanistic. Consequently, distinguishing inflammatory mediators that directly cause endothelial barrier disruption from those that simply reflect an appropriate antiviral immune response remains a major challenge. Furthermore, many infectious and inflammatory diseases are characterized by substantial cytokine production without producing the profound vascular leakage observed in severe dengue. Future research should therefore focus on identifying the specific molecular pathways and cellular interactions that uniquely connect DENV infection with endothelial dysfunction and increased vascular permeability, thereby providing new opportunities for targeted therapeutic interventions.

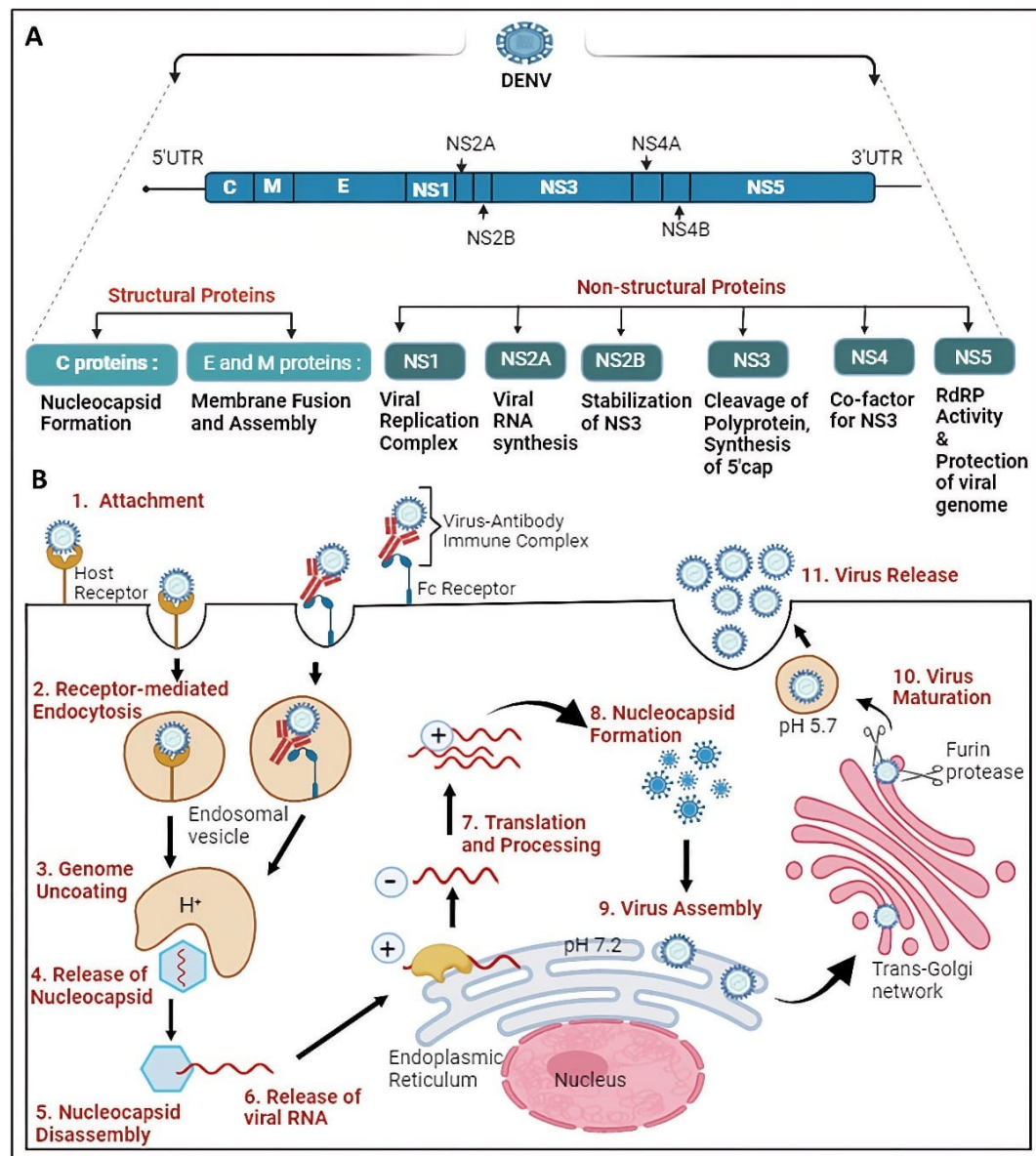


Fig-7: dengue mechanism of action

Development of dengue vaccines

The development of a universally effective dengue vaccine has been particularly challenging because of the complex biology of dengue virus (DENV) and the need to generate equivalent protective immunity against all four antigenically distinct serotypes. Initial vaccine approaches, including whole-inactivated and live-attenuated formulations, demonstrated varying degrees of success but were frequently limited by concerns related to safety, inconsistent immunogenicity, and an inability to induce balanced immune responses across DENV-1, DENV-2, DENV-3, and DENV-4. Natural infection with one serotype generally provides long-term protection against reinfection by the same serotype; however, immunity against the remaining serotypes is incomplete and temporary. As a result, subsequent infection with a different serotype has been associated with an increased likelihood of developing severe clinical manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). (16)

One of the principal mechanisms proposed to explain this increased disease severity is antibody-dependent enhancement (ADE). In this process, pre-existing cross-reactive antibodies that are present at sub

neutralizing concentrations bind to the virus without effectively preventing infection. Instead, these antibody-virus complexes facilitate viral entry into Fcγ receptor-bearing cells, particularly monocytes and macrophages, resulting in enhanced viral replication and a more intense inflammatory response. Because of this immunological challenge, an ideal dengue vaccine must induce strong, durable, and well-balanced neutralizing antibody responses against all four DENV serotypes simultaneously. Achieving comprehensive tetravalent immunity is considered essential to maximize protection while minimizing the potential risk of vaccine-associated immune enhancement.

Live attenuated vaccines

2. Dengvaxia

The CYD-TDV vaccine (chimeric yellow fever 17D-dengue tetravalent, marketed as Dengvaxia) was the first dengue vaccine to receive licensure. Constructed on a YF-17D backbone, CYD-TDV expresses the prM and E structural genes of each of the four dengue virus serotypes. In the recommended schedule for individuals aged 9–45 years, the vaccine is administered subcutaneously in three doses at 0, 6, and 12 months. Pooled phase III efficacy data over 25 months in participants aged 2–16 years reported an overall efficacy of 60.3% against symptomatic, virologically confirmed dengue (95% CI: 55.7–64.5). Efficacy varied by age and serotype: higher protection was observed in older children (9–16 years; 65.6%, 95% CI: 60.7–69.9) compared with younger children (2–8 years; 44.6%, 95% CI: 31.6–55.0). Serotype-specific efficacy estimates were approximately 40% for DENV-1 and DENV-2 and 70–85% for DENV-3 and DENV-4 in the reported analyses.

Combined analyses of clinical trial data showed that the vaccine reduced the risk of hospitalization by 72.7% (95% confidence interval [CI]: 62.3–80.3) and lowered the incidence of severe dengue by 79.1% (95% CI: 60.0–89.0). These pooled efficacy estimates were derived from participants across different age groups while taking baseline dengue serostatus into consideration. (17)

The effectiveness of CYD-TDV is highly dependent on an individual's pre-existing immunity to dengue virus. Clinical studies consistently indicate substantially greater vaccine efficacy among individuals with prior DENV exposure, with protection generally ranging from 70% to 80%. In contrast, efficacy in seronegative recipients has been considerably lower, with reported estimates varying between approximately 14.4% and 52.5%. Long-term follow-up and post-marketing evaluations further revealed that vaccination of individuals without previous dengue infection was associated with an increased likelihood of adverse clinical outcomes. Compared with seronegative individuals who did not receive the vaccine, seronegative vaccine recipients showed higher risks of dengue-related hospitalization (hazard ratio [HR] $\approx$ 1.75) and severe dengue (HR $\approx$ 2.87). Conversely, vaccinated individuals who were seropositive before immunization experienced a marked reduction in these outcomes, with hazard ratios of approximately 0.32 for hospitalization and 0.31 for severe dengue, highlighting the importance of baseline serostatus in determining the benefit-risk profile of CYD-TDV. Age-stratified analyses showed a higher relative risk of hospitalization in younger children: relative risk estimates were increased in the 2–9-year age group compared with older children.

In light of the serostatus-dependent benefit-risk profile, WHO recommendations advise pre-vaccination screening where CYD-TDV is considered for programmatic use and generally support vaccination of individuals with documented prior dengue infection or in settings with high seroprevalence (for example, $\sim$ 80% seropositivity by age 9). These precautions aim to maximize public-health benefit while minimizing the risk of vaccine-associated enhancement in seronegative recipients.

3. QDENG (TAK-003)

Takeda's live-attenuated, tetravalent dengue vaccine (TDV; marketed as QDENG (TAK-003)) is constructed from a DENV-2 backbone (strain 16681 passaged in primary dog kidney cells, PDK-53) with chimeric components representing all four serotypes. The vaccine is administered on a three-dose schedule and has received licensure in Indonesia for persons aged 6–45 years and marketing authorization in the European Union for individuals aged ≥ 4 years irrespective of prior dengue exposure. TAK-003 has also obtained priority review by the U.S. Food and Drug Administration for prevention of dengue caused by all four serotypes.

Regulatory approval was supported by the TIDES program, which enrolled more than 28,000 participants. In the first 11 months after immunization, TAK-003 demonstrated approximately 80.2% efficacy against symptomatic dengue; cumulative efficacy estimates declined to about 62% at 18–36 months in subsequent follow-up analyses. Importantly, protection against severe dengue remained robust in trial data, with point estimates of effectiveness in the range of ~83.6% to 90.4%. Unlike some earlier vaccines, efficacy was similar in individuals irrespective of baseline serostatus. Serotype-specific efficacy varied, with highest protection observed against DENV-2—the serotype from which the vaccine backbone is derived. A booster-dose trial (NCT03999996) is evaluating the immunogenic and protective effects of an additional dose administered at 15 or 24 months after the primary series. (18)

Mechanism of action

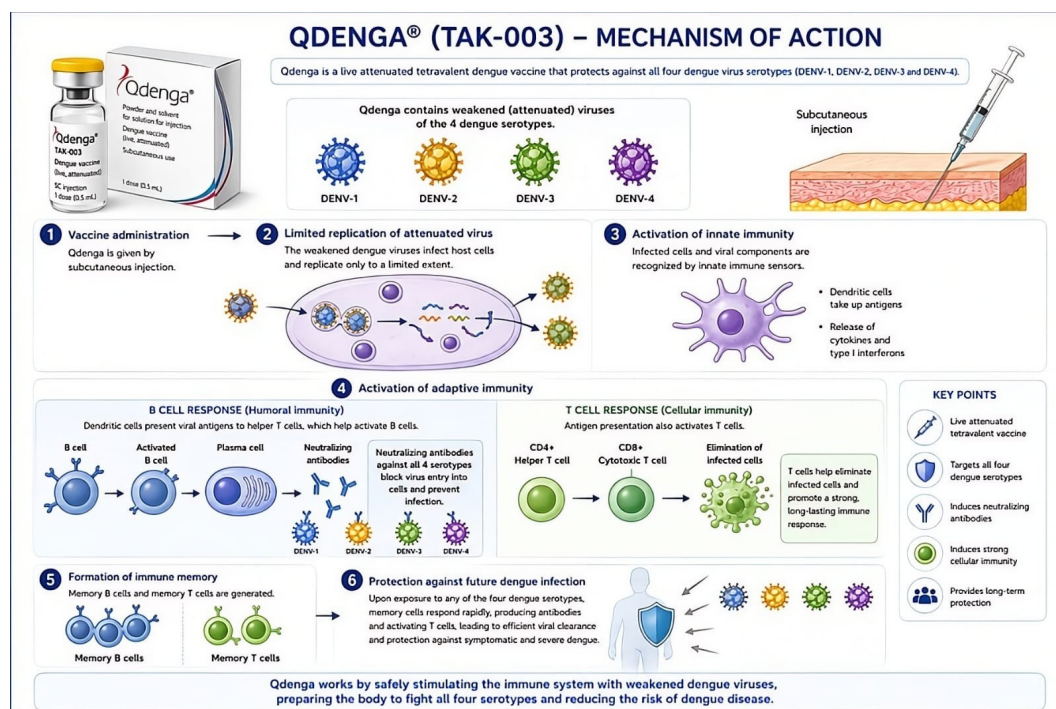


Fig-8: Mechanism of Qdenga

As a live attenuated vaccine, TAK-003 replicates locally after subcutaneous administration, mimicking aspects of natural infection without causing clinical disease. This replication elicits both humoral and cellular immunity. B cell activation generates neutralizing antibodies directed against the surface antigens of DENV-1 through DENV-4. Concurrently, the DENV-2-derived internal backbone promotes potent T-cell responses, which contribute to clearance of infected cells and to the development of durable cellular immunity. Preclinical and early clinical studies indicate that TAK-003 induces balanced antibody responses across serotypes, although quantitative and qualitative differences by serotype are noted and are reflected in

serotype specific efficacy outcomes. The observed combination of neutralizing antibodies and vaccine elicited T-cell responses likely underpins the vaccine's ability to reduce both symptomatic and severe disease. (19)

4. TV003/TV005

TV003 and TV005 are live-attenuated tetravalent dengue vaccine candidates developed by the National Institute of Allergy and Infectious Diseases (NIAID) and are currently undergoing advanced clinical evaluation. The vaccine platform consists of three genetically attenuated wild-type dengue virus strains together with one chimeric virus. Attenuation was primarily achieved through targeted deletions within the 3' untranslated region (3' UTR), supplemented by modifications in selected non-structural proteins. These genetic alterations generated the vaccine strains rDEN1Δ30, rDEN3Δ30/31, and rDEN4Δ30, along with a modified DENV-2 component. The engineered mutations reduce viral replication and virulence while maintaining the capacity to induce protective immune responses.

Early phase I randomized, placebo-controlled studies demonstrated a favourable safety profile. The most commonly reported adverse event was a mild maculopapular rash, which occurred in approximately 50% of vaccinated participants in both the TV003 and TV005 groups. Evaluation of immune responses showed that a single dose of TV003 produced seroconversion rates ranging from 64% to 100% across the four dengue virus serotypes. The attenuated DENV-2 component, rDEN2Δ30, generated durable serotype-specific neutralizing antibodies that remained detectable for at least six months after immunization. In addition, challenge and clinical studies indicated protection against detectable viremia, vaccine-associated rash, and transient neutropenia.

A freeze-dried (lyophilized) formulation of this vaccine has been licensed to the Butantan Institute in Brazil, where it is known as Butantan-DV. The vaccine was evaluated in a multicenter phase III clinical trial conducted at 16 study sites distributed across the five geographical regions of Brazil. Administration of a single dose of the tetravalent vaccine resulted in high protective efficacy over a two-year follow-up period. Vaccine efficacy was estimated at 79.6% (95% confidence interval [CI]: 70.0–86.3) among participants with no serological evidence of previous dengue infection and increased to 89.2% (95% CI: 77.6–95.6) among individuals who were seropositive before vaccination. Serotype-specific analyses showed vaccine efficacy against DENV-1 of 85.6% in seronegative participants compared with 96.8% in seropositive individuals. Protection against DENV-2 reached 57.9% in seronegative recipients and 83.7% in those with prior dengue exposure. Because DENV-3 and DENV-4 were not circulating during the study period, efficacy against these serotypes could not be determined. Overall, the Butantan-DV vaccine demonstrated approximately 80% protection in participants without previous dengue infection and nearly 89% efficacy in those with pre-existing immunity, indicating strong performance in an endemic Brazilian population despite ongoing dengue transmission. (20)

Inactivated virus vaccines

5. TDEV-PIV

Inactivated dengue vaccines employ non-replicating viral particles to stimulate protective immune responses without the possibility of viral replication or infection in the recipient. One such candidate, the tetravalent purified inactivated dengue vaccine (TDENV-PIV, also known as TDEV-PIV), was developed by the Walter Reed Army Institute of Research. This vaccine is adjuvanted with aluminum hydroxide (alum) and contains formalin-inactivated representatives of all four dengue virus serotypes. The viral strains are propagated in

Vero cell cultures before chemical inactivation and include WestPac-74 (DENV-1), S16803 (DENV-2), CH53489 (DENV-3), and TVP360 (DENV-4), thereby providing broad antigenic coverage.

Phase I clinical studies demonstrated that TDENV-PIV was capable of inducing both humoral and cellular immune responses. Assessment of T-cell immunity revealed the generation of interferon- γ (IFN- γ)-producing lymphocytes, although the magnitude of these responses varied considerably among participants. While some individuals exhibited strong cellular responses exceeding 1,000 spot-forming cells per 10 peripheral blood mononuclear cells against multiple dengue serotypes, others showed only limited reactivity. Among the four vaccine components, the DENV-2 antigen consistently generated the highest IFN- γ -mediated T-cell responses across different study groups and evaluation time points. (21)

The immunogenic potential of inactivated dengue vaccines has also been investigated in preclinical studies using *Macaca mulatta* models. In these experiments, animals were initially immunized with either a tetravalent purified protein vaccine (TPIV) or a tetravalent DNA vaccine (TDNA), followed by a booster dose of a tetravalent live-attenuated vaccine (TLAV). Compared with vaccination using a single platform alone, these heterologous prime-boost regimens produced stronger antibody responses against all four dengue virus serotypes. These findings suggest that combining different vaccine technologies may enhance overall immunogenicity and represent a promising strategy for improving the effectiveness of future dengue vaccination programs.

DENV-2 Vaccine S16803

The S16803 dengue virus serotype 2 (DENV-2) vaccine candidates was developed by the Walter Reed Army Institute of Research (WRAIR) as a formalin-inactivated preparation produced in Vero cell cultures and subsequently purified using sucrose density-gradient centrifugation. Preclinical investigations assessed this vaccine in combination with several adjuvant formulations and demonstrated its ability to induce immune responses in multiple animal models, including rhesus macaques. Comparative studies conducted by Punk and co-workers indicated that the live-attenuated DENV-2 vaccine candidate PDK-50 generated more sustained neutralizing antibody responses than either the inactivated S16803 vaccine or the recombinant subunit vaccine candidate R80E. (22)

As with other inactivated viral vaccines, S16803 primarily exposes the immune system to structural viral proteins while providing limited presentation of non-structural antigens. Consequently, repeated immunization and the inclusion of adjuvants are generally required to achieve adequate and durable protective immunity. The restricted stimulation of nonstructural protein-specific immune responses may also limit the development of robust cell-mediated immunity. Despite these limitations, inactivated vaccine platforms possess several important advantages, including a favorable safety profile, excellent stability during storage, and the absence of risks associated with viral replication. Nevertheless, successful implementation requires careful selection of effective adjuvants and optimization of vaccine formulations to achieve an appropriate balance between antibody-mediated and cellular immune responses while minimizing reactogenicity. Addressing these challenges is essential for translating encouraging preclinical immunogenicity into durable and effective protection in human populations. (23)

Subunit vaccines

6. EDIII-P64K

Recent advances in recombinant protein technology have highlighted the envelope protein domain III (EDIII) as a promising antigen for dengue subunit vaccine development. Studies have shown that recombinant EDIII

proteins expressed in *Escherichia coli* are capable of inducing neutralizing antibodies against all four dengue virus (DENV) serotypes in experimental animal models, demonstrating their potential to provide broad protective immunity. One notable candidate, the tetravalent EDIII-P64K vaccine, incorporates EDIII sequences from each DENV serotype fused to the P64K carrier protein derived from *Neisseria meningitidis*. Preclinical investigations in mice and nonhuman primates demonstrated that this construct generated strong serotype-specific antibody responses while maintaining high antigenic specificity. Importantly, immunization with recombinant EDIII-P64K proteins produced relatively low levels of cross-reactive antibodies, a characteristic that may reduce the theoretical risk of antibody-dependent enhancement. (24)

Compared with live-attenuated vaccines, recombinant subunit vaccines offer several safety advantages because they do not contain replication-competent viruses and therefore eliminate the possibility of vaccine-induced infection. Additional recombinant vaccine designs have further strengthened the potential of this platform. For example, a fusion protein incorporating the EDIII regions of DENV-1 and DENV-2 together with those of DENV-3 and DENV-4, joined by a glycine-serine (Gly-Ser) linker and produced in *E. coli*, successfully induced protective immune responses against all four dengue virus serotypes in murine models. These findings support the continued development of EDIII-based recombinant vaccines as promising candidates for achieving safe, tetravalent protection against dengue.

7. V180 (DEN-80E)

V180 (DEN-80E) is a recombinant tetravalent dengue subunit vaccine jointly developed by Merck and Medigen Vaccine Biologics (MVB). The vaccine contains truncated recombinant envelope (E) proteins corresponding to approximately 80% of the E glycoprotein from each of the four dengue virus (DENV) serotypes, including DENV-1 strain 258848, DENV-2 strain PR159 S1, DENV-3 strain CH53489, and DENV-4 strain H241. These recombinant antigens are produced in *Drosophila* Schneider 2 (S2) cells using plasmid-based expression systems and are formulated with either the ISCOMATRIX adjuvant, a saponin-cholesterol-phospholipid complex, or aluminium hydroxide (Alhydrogel) to enhance immunogenicity. As the vaccine does not contain replication-competent virus, it offers a favorable safety profile and avoids the risks associated with live viral vaccines, including vaccine-derived infection and replication-related adverse effects. However, the absence of viral replication may reduce the duration of immune protection, making booster immunizations potentially necessary to sustain long-term immunity. (25)

Clinical assessment of V180 is continuing to determine its efficacy and long-term protective capacity. In clinical studies, the vaccine demonstrated an efficacy of 79.6% against dengue infection, and no cases of severe dengue were reported among vaccinated participants. These findings reinforce the safety advantages of recombinant subunit vaccines over live-attenuated vaccine platforms, as they eliminate the possibility of viral replication and may reduce the theoretical risk of vaccine-associated immune enhancement. Despite these benefits, subunit vaccines present several developmental challenges. Because purified recombinant proteins are generally less immunogenic than live viral vaccines, effective adjuvants are required to generate strong and persistent immune responses. In addition, maintaining the correct three-dimensional structure of recombinant envelope proteins is essential for preserving key neutralizing epitopes, as improper protein folding may diminish antigenicity and compromise vaccine performance. Continued refinement of antigen engineering and adjuvant formulations is therefore essential to maximize the immunogenicity, durability, and protective efficacy of DEN-80E-based dengue vaccines. (26)

Future Protection

After completing the two-dose schedule (given 3 months apart), your immune system keeps "memory" blueprints of these viruses. If a wild mosquito later transmits actual dengue virus into your system, your pre-trained antibodies and T cells can instantly recognize, bind to, and neutralize the virus before it can replicate out of control and cause severe dengue fever. (27)

Unlike older dengue vaccines, Qdenga's unique mechanism allows it to safely mimic a natural, broad immune response regardless of whether you have previously had dengue fever or not.

Vaccines	Nature	Strategy and Target	Strength	Weakness
Dengvaxia (CYD-TDV)	Attenuated	YF-17D backbone with prM and E genes of dengue virus 1–4	Immune response against all four serotypes. (Licensed)	High risk of dengue-related hospitalization of children below 9 years of age. Low vaccine efficacy to DENV-2.
QDenga or TAK-003	Attenuated	DENV2 PDK53 backbone with DENV1/3/4 prM and E gene chimera	A single vaccine dose with high efficacy rates and no serious adverse events reported (Licensed)	Vaccine efficacy data are not available for individuals > 16 years old
TV003/TV005	Attenuated	Full length DENV1,2,3,4 lacking 30 nucleotides in 3' UTR	A single dose of TV-005 produced a tetravalent response in 90% of the vaccinated (phase III trial)	No data available
TDEV-PIV	Inactivated	Tetravalent formalin-inactivated virus (TPIV)	Immune response against all four serotypes (broad protection)	Lower immunogenicity. Adjuvants needed
DENV-2 vaccine <u>S16803</u>	Inactivated	Formalin-inactivated virus (DPIV)	Stable and less pathogenic; Vero cell generated	Need multiple booster injections. Less immunogenicity.
EDIII-P64K	Subunit	Recombinant EDIII derived from <i>E. coli</i>	Immune response against all four serotypes (broad protection)	Not tested in humans
V180 (DEN-80E)	Subunit	DENV recombinant truncated 80 E	Low cross-reactive antibodies. Insect cell	Adjuvants are needed and improper protein folding

			generated (phase III trials)	causes concerns.
TVDV (Vaxfectin)	DNA	Recombinant plasmid vector encoding prM/E proteins of DENV1–4	Potent neutralizing antibodies against all four serotypes (phase 1 trial)	Protein misfolding and exposure to endotoxins in plasmid preparation remain.
DIME100	DNA	Recombinant plasmid vector encoding prM/E	Safe and well tolerated (phase 1 trial)	Lower immunogenicity. No neutralizing antibody response.
DENV EDIII-based (DDV)	DNA	DENV2-EDIII	Safe and well tolerated (phase 1 trial)	Lower immunogenicity. No neutralizing antibody response.
DENVLP	Virus-like particle (VLP)	prM and E protein-coding sequences	Immune responses against all four serotypes.	Impurities like endotoxin or baculovirus. Formulation stability issues
prME-mRNA, E80-mRNA, and NS1-mRNA	mRNA	Consensus sequences of EDIII of DENV1–4 and DENV-2 NS1, and prME, E80, and NS1 of DENV-2	Induce the production of neutralizing antibodies against DENV-2	Relatively new technology and long-term effects are unknown.

Diagnosis

Procedures for diagnosing dengue virus (DENV) infection in pregnant and puerperal women are the same as those applied to the general adult population outside the pregnancy-puerperal period. Diagnostic evaluation typically comprises: clinical assessment (epidemiological context, medical history, and physical examination), generation of a differential diagnosis, assessment of disease severity, and laboratory testing. (28)

As a guiding principle for the management of pregnant women and those up to 14 days postpartum, clinicians working in endemic areas should prioritize DENV as a principal consideration among possible infectious causes when encountering compatible clinical presentations. This recommendation reflects (1) the substantial overlap in early symptoms between DENV and other infections (for example, other arboviruses, SARS-CoV-2, leptospirosis, and measles) and (2) the potential for rapid progression from mild to severe dengue. Prompt recognition of DENV as a leading differential diagnosis facilitates timely and appropriate clinical intervention.

Complications and side effects of dengue vaccine:-

Along with its needed effects, dengue vaccine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Check with your doctor or nurse immediately if any of the following side effects occur while taking dengue vaccine. (29)

Rare side effects

- bleeding in the mouth
- cough
- high fever
- noisy breathing
- persistent vomiting
- redness of the skin
- restlessness
- severe stomach pain or tenderness
- sleepiness or drowsiness
- swollen, painful, or tender lymph glands in the neck, armpit, or groin
- tightness in the chest
- trouble breathing

WHO response

WHO responds to dengue by:

- Assist countries in confirming dengue outbreaks through its global network of collaborating laboratories.
- Provide technical guidance for effective outbreak management.
- Strengthen national surveillance and reporting systems to better capture the true burden of disease.
- Compile official dengue and severe dengue data from more than 100 Member States.
- Deliver regional and country-level training on clinical management, diagnostic methods, and vector control in partnership with collaborating centres.
- Formulate evidence-based policies and support countries in developing dengue prevention and control strategies.
- Promote adoption of the Global Vector Control Response (2017–2030) and the Global Arbovirus Initiative (2022–2025).
- Evaluate and issue recommendations on new tools, including insecticide products and application technologies.
- Publish guidance and handbooks on surveillance, case management, diagnosis, and prevention and control measures for Member States. (30)

8. Conclusion

Dengue remains a major global public health challenge, driven by expanding *Aedes* mosquito populations, rapid urbanization, and increasing international travel. Vaccination has become an indispensable element of comprehensive dengue prevention and control efforts because of its potential to reduce disease transmission, decrease the incidence of severe clinical outcomes, and alleviate pressure on healthcare systems. The ultimate objective of dengue vaccine development is to achieve long-lasting and balanced immunity against all four dengue virus serotypes, thereby maximizing protection while minimizing the risk of antibody-dependent enhancement. Although several vaccine platforms—including live-attenuated, recombinant subunit, inactivated, and vector-based vaccines—have shown encouraging results, differences in efficacy, safety, and durability of protection highlight the need for continued clinical evaluation and long-term post-marketing surveillance. Such evidence is essential for defining appropriate vaccination schedules, identifying populations most likely to benefit, and determining the need for booster immunization.

Successful implementation of dengue vaccination programs requires careful consideration of local epidemiological patterns, population seroprevalence, and the capacity of healthcare systems to support safe and effective vaccine delivery. Vaccination should be incorporated into broader public health strategies rather than viewed as a stand-alone intervention. Sustained vector-control measures, early diagnosis, high-quality clinical care, comprehensive disease surveillance, and active community participation remain fundamental components of dengue prevention. Continued investment in vaccine research is also necessary to improve antigen selection, optimize adjuvant formulations, and develop innovative delivery technologies capable of generating stronger and more durable immune responses. Equally important is transparent communication with healthcare professionals and the public regarding vaccine benefits, potential risks, and the scientific basis of vaccination policies, as this will strengthen confidence and encourage widespread acceptance. Overall, dengue vaccines represent a major advance in disease prevention, but their greatest public health impact will depend on evidence-based implementation, ongoing scientific innovation, and integration with comprehensive dengue control programs.

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(Dr). P K U - Drafting and revise of manuscript

Dr. M R - Final supervision of manuscript

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