THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 4

REVIEW ARTICLE

Integrated Approaches to Dengue Prevention: Vector Control and Vaccine Performance, and Future Directions

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OPEN ACCESS

PUBLISHED
30 April 2026

CITATION
Mudassar, M., Fernandez, E., 2026. Integrated Approaches to Dengue Prevention: Vector Control and Vaccine Performance, and Future Directions. Medical Research Archives, [online] 14(4).

ISSN
2375-1924

ABSTRACT

Dengue fever is a vector-borne disease; it's a global health threat driven by climate change, rapid urbanization, and the expanding distribution of Aedes mosquitoes. With an estimated 100 - 400 million infections annually, dengue can have clinical manifestations ranging from classical, mild manifestations to the potentially lethal severe dengue, which can cause extravasation of fluids, shock and multi-organ impairment, and death. It poses significant challenges for clinical management and public health preparedness because of the need to act on the four viral serotypes causing the infection. Emphasis has been placed on vector control strategies with the use of insecticides, biological methods, and physical elimination of mosquito breeding sites, which have produced mixed results. Environmental, biological, genetic, and chemical vector-control approaches are discussed, including emerging tools such as Wolbachia-infected mosquitoes and sterile insect techniques.

More than three decades of research have led to the development and licensing of two dengue vaccines, Dengvaxia and Qdenga. An analysis of their design, mechanisms, safety profiles, and serostatus-dependent performance highlights the immunological and operational challenges that continue to complicate dengue vaccination. The review outlines the future priorities, such as next-generation vaccine development, improved surveillance systems, and scalable vector-control innovations, underscoring the need for integrated, evidence-based strategies to reduce dengue transmission and the global disease burden.

Keywords: Dengue, severe dengue, mosquito control, vaccine development, licensing.

Introduction

Dengue fever has emerged as one of the most important mosquito-borne viral diseases of the 21st century, affecting populations across tropical, subtropical, and increasingly temperate regions. According to the World Health Organization (WHO), half of the world's population now lives in areas at risk for dengue transmission, with an estimated 100 - 400 million infections each year.[1] The widespread geographic distribution of *Aedes aegypti*, the primary vector, and the expanding range of *Aedes albopictus* have contributed to record numbers of outbreaks in Asia, the Americas, Africa, and even southern Europe.[2] Recent surveillance reports from governments in North America like Canada (2024) highlight the global nature of dengue spread and emphasize the need for strengthened prevention programs.[3]

Dengue virus (DENV), a flavivirus composed of four antigenically distinct serotypes (DENV-1 to DENV-4), presents unique immunological challenges, especially due to the risk of severe disease during secondary infection through **antibody-dependent enhancement (ADE)**. In ADE, sub-neutralizing antibodies from a previous infection facilitate increased viral entry into Fcγ receptor-bearing cells, leading to amplified viral replication and heightened inflammatory responses.[4] This hallmark feature of dengue pathogenesis complicates vaccine development, as an effective vaccine must generate durable, balanced, and tetravalent immunity without predisposing recipients to enhanced disease.

Despite decades of research, no specific antiviral therapy exists for dengue infection. Clinical management remains primarily supportive, relying on careful fluid administration, monitoring warning signs, and early identification of severe dengue presentations.[5] Consequently, vaccine development has been viewed as a critical global health priority.

Dengvaxia (CYD-TDV), the first licensed dengue vaccine, represented a major scientific milestone but ultimately demonstrated critical limitations. While it conferred moderate protection to seropositive individuals, it increased the risk of severe dengue among seronegative recipients due to immunological priming that resembled a silent primary infection.[6] These discoveries led to stringent eligibility restrictions. Qdenga (TAK-003), the second licensed vaccine, offers broader serostatus applicability and improved performance against certain serotypes, particularly DENV-2, although waning immunity and variable serotype-specific efficacy remain important concerns.

Alongside vaccination, innovative biological and genetic vector-control strategies, such as Wolbachia-infected mosquitoes, sterile insect technique (SIT), and gene-drive technologies which offer promising complementary tools for dengue reduction.[7, 8]

Understanding and improving dengue prevention strategies has therefore become a global public health priority. While supportive clinical management has significantly reduced mortality in many regions, preventing transmission remains the most effective strategy for reducing disease burden. Prevention relies on a combination of vector-control interventions, community engagement, and the development of safe and effective vaccines capable of protecting against all four dengue virus serotypes. Evaluating the strengths and limitations of these approaches is essential for guiding future dengue-control policies and public health strategies.

Methodology

This manuscript was developed as a narrative review synthesizing current literature on dengue infection, epidemiology, vector control, and vaccine strategies. Relevant studies were identified through searches of PubMed, the National Institutes of Health database, and Google Scholar using keywords including "dengue," "*Aedes aegypti*," "vector control," "Wolbachia," "dengue vaccines," "Dengvaxia," "Qdenga," and "antibody-dependent enhancement." Literature published between 2010 and 2025 was prioritized, with particular emphasis on recent peer-reviewed articles, clinical trials, systematic reviews, and reports from international public health organizations such as the World Health Organization (WHO), the Pan American Health Organization (PAHO), and the Centers for Disease Control and Prevention (CDC).

Approximately 39 publications were evaluated based on relevance, scientific quality, and contribution to understanding dengue prevention strategies and vaccination knowledge. Recent peer-reviewed articles, systematic reviews, clinical trials, and reports from WHO, PAHO, and CDC were prioritized. No quantitative data were included, and the flow follows the narrative sequence.

Identified literature was grouped into different sub-topics and were discussed in weekly sessions held by both co-authors and edited according to its relevance and recent publication. After 10 sessions of meetings, a first complete draft was developed and discussed by both authors to fulfill the requirements for publication.

Both coauthors discussed the identified contents and participated in the literature analysis, drafting, and revision of the manuscript. The final version was reviewed and approved by both authors.

Finally, this review includes information on dengue infection, epidemiology, infection control, and treatment, with emphasis on antivectorial control, vaccines, and future perspectives.

Global Epidemiology, Virology, And Vector Biology

Dengue has evolved into a rapidly expanding global health threat, driven by a combination of ecological, climatic, and socio-behavioral changes. More than 5.6 billion individuals now reside in regions environmentally suitable for dengue transmission, with Southeast Asia, the Pacific Islands, and the Americas facing the highest burdens.[9] Climate change also plays an important role in the expansion of dengue transmission. Rising temperatures create favorable conditions for mosquito

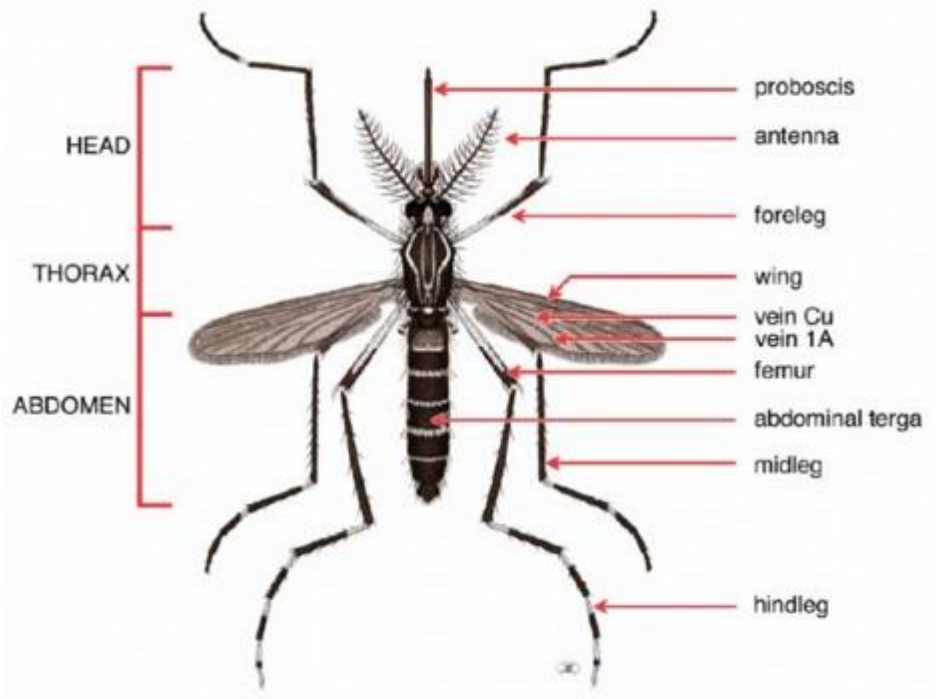
survival and reproduction, while changes in rainfall patterns increase the availability of breeding sites for *Aedes* mosquitoes. These environmental changes contribute to the spread of dengue vectors and increase the risk of dengue transmission in affected regions.[10]

The Infectious Agent: Dengue virus

At the virological level, dengue virus (DENV) is an enveloped RNA virus whose structural organization includes a nucleocapsid enclosed within a lipid membrane containing viral envelope proteins that mediate receptor binding and membrane fusion.[11] Immunity to one dengue serotype provides only short-lived cross-protection against the others, and secondary infections can lead to increased disease severity through antibody-dependent enhancement (ADE).[4] Genetic variation among circulating DENV strains contributes to differences in immune responses and disease outcomes.[12] These features collectively complicate the development of vaccines that must protect across all four serotypes.

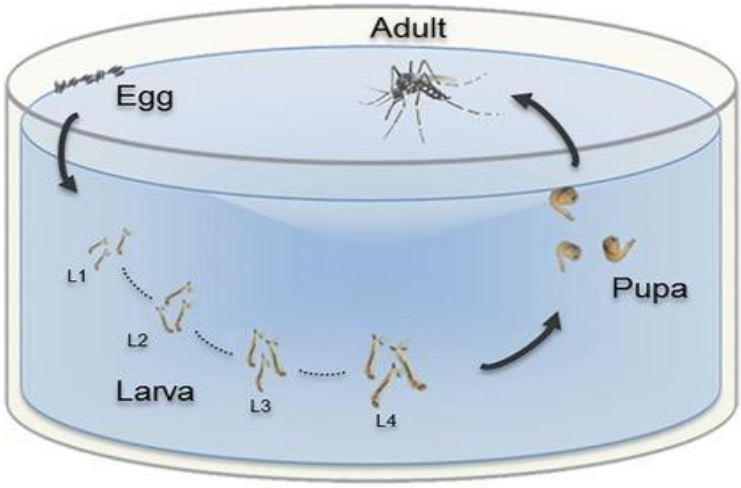
Understanding dengue transmission requires a comprehensive appreciation of *Aedes aegypti* biology. This mosquito species is highly anthropophilic, displaying strong preference for human blood meals and thriving in densely populated urban environments. Morphologically, *Aedes aegypti* is identifiable by its small black body, white leg banding, and characteristic lyre-shaped marking on the thorax. Importantly, only female mosquitoes blood-feed; males rely exclusively on plant nectar. Females possess elongated proboscises specialized for piercing skin and accessing blood vessels, while also displaying heightened host-seeking behavior influenced by carbon dioxide, heat, body odor, and lactic acid emissions as illustrated in figure 1.[13]

Figure 1: Dorsal view of adult female mosquito, Aedes (Stegomyia) aegypti. From https://www.researchgate.net/figure/FIGURE-B-Dorsal-view-of-adult-female-mosquito-Aedes-Stegomyia-aegypti_fig32_228820694



The mosquito's life cycle includes four stages: egg, larva, pupa, and adult. Eggs are remarkably resilient, capable of surviving desiccation for months, which enables the species to persist during dry periods and rapidly expand when water becomes available. *Aedes aegypti* typically breeds in small, stagnant water collections found in artificial containers such as flowerpots, tires, and discarded plastics, conditions that are common in rapidly urbanizing areas lacking water supply, refuse systems and adequate sanitation.[14] These characteristics, combined with the mosquito's daytime biting behavior and tendency for multiple blood meals during a single gonotrophic cycle, significantly enhance its efficiency as a dengue vector.

Figure 2. The Aedes mosquitoes' four life stages: egg, larva, pupa and adult.



The figure is taken from https://www.researchgate.net/figure/The-Aedes-mosquitoes-four-life-stages-egg-larva-pupa-and-adult_fig2_315850678

Vector competence is defined as the ability of a mosquito to acquire, maintain, and transmit a pathogen that is exceptionally high in *Aedes aegypti*. After ingestion of infected blood, dengue virus infects the mosquito midgut, disseminates the hemocoel, and eventually reaches the salivary glands, from which it is transmitted during subsequent bites. This biological permissiveness facilitates a highly efficient transmission cycle. Although *Aedes albopictus* is also capable of transmitting dengue, its lower affinity for humans and broader range of non-human hosts make it a secondary vector in most settings.

The interplay between viral evolution, mosquito biology, and environmental change shapes the complex epidemiology of dengue. These factors also influence vaccine strategy, as regions dominated by certain serotypes or vector species may respond differently to immunization efforts. Therefore, understanding vector ecology is essential when assessing vaccine performance, planning integrated vector control, and predicting future outbreak dynamics.

Pathogenesis and Immune Response in Dengue Infection

Dengue pathogenesis is driven by a complex interplay between viral replication dynamics, innate and adaptive immune responses, and vascular dysfunction. After inoculation through the bite of an infected *Aedes aegypti* mosquito, the dengue virus first infects Langerhans cells, dendritic cells, and tissue-resident macrophages at the skin. These antigen-presenting cells transport the virus to regional lymph nodes, where viral amplification initiates systemic dissemination.[15]

Once viremia is established, the dengue virus targets monocytes, macrophages, and endothelial cells that play central roles in disease progression. Viral replication in these cells triggers release of key inflammatory mediators, including TNF-α, IL-6, IL-8, IL-10, and IFN-γ, contributing to fever, myalgia, and early systemic symptoms.[15,5] However, the most critical immunopathological consequence of dengue infection is increased vascular permeability, which arises not from direct viral cytotoxicity but from immune-mediated endothelial dysfunction.

A major contributor to vascular leakage is the viral non-structural protein 1 (NS1). Secreted in large quantities by infected cells, NS1 directly disrupts endothelial tight junctions, activates complement pathways, and increases production of vasoactive cytokines.[15] These mechanisms collectively weaken endothelial barriers and set the stage for the plasma leakage observed in severe dengue.

Adaptive immunity further shapes the outcome of infection. During a primary infection, the host generates serotype-specific neutralizing antibodies and memory T-cell responses. However, during a secondary infection with a different serotype, pre-existing antibodies may bind but fail to neutralize the virus effectively. This phenomenon is known as antibody-dependent enhancement (ADE) which allows virus-antibody complexes to enter Fcγ receptor-bearing cells more efficiently, resulting in markedly increased viral replication and amplified immune activation.[4,16] ADE contributes to the elevated viral loads and intense cytokine responses associated with severe disease.

Cross-reactive memory T cells also contribute to dengue immunopathogenesis. During a heterologous secondary infection, these memory T cells preferentially recognize previously encountered serotype epitopes, a phenomenon known as *original antigenic sin*. The resulting surge in cytokines promotes endothelial dysfunction, leading to plasma leakage, hemoconcentration, and potentially shock.[17]

Overall, dengue pathogenesis is the result of immune activation that becomes dysregulated rather than protective. The defining features of NS1-mediated endothelial injury, heightened cytokine production, and antibody-dependent enhancement explain why secondary infections carry greater risk and why vaccine strategies must generate balanced tetravalent immunity to avoid enhancing disease. This mechanistic foundation sets the stage for understanding the clinical

manifestations, diagnostic approaches, and treatment strategies described in the following section.

CLINICAL FEATURES, DIAGNOSIS, AND TREATMENT

Dengue infection produces a broad range of clinical presentations that reflect the host's physiological response to viral replication and the degree of vascular involvement. The disease progresses through three phases: **febrile, critical, and recovery**, each of which carries distinct clinical implications.[2] The **febrile phase** begins abruptly with high fever, severe headache, retro-orbital pain, profound myalgia, arthralgia, and generalized flushing. Gastrointestinal symptoms such as nausea and vomiting are common, and some patients develop a transient maculopapular rash. Laboratory findings may include mild thrombocytopenia and leukopenia, features consistent with early marrow suppression.[5] Although the majority of patients remain stable during this phase, careful assessment is essential, as early changes can indicate risk of deterioration.

The **critical phase** typically occurs between days 3 and 7 of illness and marks the period of highest risk. During this phase, increased capillary permeability leads to plasma leakage into the pleural and abdominal cavities, often with rising hematocrit and declining platelet counts. Clinical **warning signs** that predict progression to severe dengue include persistent vomiting, severe abdominal pain, mucosal bleeding, hepatomegaly, lethargy, restlessness, and evidence of fluid accumulation such as pleural effusion or ascites.[18, 2] Patients may rapidly progress to **hypovolemic shock**, characterized by narrow pulse pressure, tachycardia, cold extremities, and prolonged capillary refill. Severe bleeding, although less common, may occur in the context of thrombocytopenia, coagulopathy, and fragile vasculature.

Severe dengue encompasses severe plasma leakage with shock, severe bleeding requiring transfusion, or severe organ involvement. Organ impairment may present as transaminitis, acute kidney injury, myocarditis, or neurological complications. Without timely recognition and fluid resuscitation, severe dengue carries a substantial risk of mortality; however, with appropriate and timely clinical management, case-fatality rates can be reduced to **below 1%**.[5]

DIAGNOSIS OF DENGUE

Diagnosis relies on both clinical suspicion and laboratory confirmation. During the early febrile period, which is typically within the first five days, NS1 antigen testing and RT-PCR provide high diagnostic sensitivity and specificity and are recommended for confirming acute infection. As viremia declines, IgM and IgG serology becomes more informative: IgM is generally detectable after day five of illness, whereas IgG may indicate recent or past infection or reflect secondary dengue.[2,18] Hematocrit trends, platelet counts, and assessment for plasma leakage remain essential for evaluating disease severity and guiding clinical management. [15]

TREATMENT OF DENGUE

Treatment of dengue is entirely supportive, with management tailored to disease severity. Patients without warning signs are classified in WHO as Group A: they may be managed as outpatients with oral hydration, antipyretics such as acetaminophen, and education regarding warning signs that require urgent reassessment.[5,19] Patients with warning signs or comorbidities fall into Group B, requiring closer observation and, when necessary, intravenous fluid therapy with isotonic crystalloids. Fluid administration is guided by hemodynamic status, urine output, and hematocrit trends

Patients with severe dengue are classified as Group C: require immediate intravenous fluid resuscitation and close monitoring, often in an emergency or inpatient setting. Over-resuscitation must be avoided because capillary permeability rapidly normalizes during the recovery phase, and excess fluid may precipitate pulmonary edema or other complications.[5] Blood transfusions may be required for significant bleeding, and organ-specific support may be necessary for hepatic, cardiac, renal, or neurological involvement.

The recovery phase is characterized by gradual clinical improvement, stabilization of vital signs, and normalization of hematocrit as extravasated fluid re-enters the intravascular space. A convalescent rash or pruritus may appear during this period, and monitoring remains important until platelet counts recover and the risk of complications resolves.[5, 19]

Treatment of dengue is primarily supportive, with careful attention to maintaining adequate intravascular volume and preventing complications related to plasma leakage. Isotonic crystalloids such as normal saline or Ringer's lactate are recommended as first-line IV fluids, particularly for patients in Groups B and C, because they effectively replace plasma losses and are safe when titrated appropriately.[20] Initial infusion rates generally begin at 5-7 mL/kg/h, with close reassessment of pulse pressure, urine output, hematocrit, and mental status to avoid both inadequate resuscitation and fluid overload.

In patients presenting with shock, rapid resuscitation with a 10 -20 mL/kg crystalloid bolus over 15-30 minutes is recommended, followed by immediate clinical reassessment.[19] If shock persists after two crystalloid boluses, colloid solutions may be considered for refractory cases because they expand intravascular volume more rapidly; however, they are reserved for select situations due to risks of allergic reactions and coagulation disturbances. As capillary leakage resolves during the recovery phase, excessive IV fluids can lead to pulmonary edema or respiratory distress, making timely reduction or discontinuation of fluids essential.

VECTOR CONTROL STRATEGIES IN DENGUE PREVENTION

Vector control remains the most critical component of traditional dengue prevention, especially in regions where vaccine coverage is limited and transmission is predominantly driven by *Aedes aegypti* mosquitoes.[21] Effective suppression of mosquito populations requires integrated approaches that disrupt the life cycle at multiple points. *Aedes aegypti* thrives in urban settings, feeds preferentially on humans, and breeds in artificial containers such as water storage vessels, discarded plastics, plant pots, and tires.[14] These behavioral and ecological characteristics make eradication difficult and necessitate layered, community-wide interventions.

Environmental Control

Environmental management forms the foundation of dengue vector reduction. Because *Aedes aegypti* lays eggs in domestic water containers and its eggs can survive dry conditions for extended periods, eliminating breeding habitats is essential. Measures include covering water containers, improving waste disposal, and conducting regular community cleanup campaigns. Structural interventions like **Casa Segura**, which uses insecticide-treated window screens and curtains, have been shown to reduce indoor biting, particularly in households where viremic individuals remain indoors during acute illness.[22] These strategies are cost-effective and sustainable when combined with public engagement.

Biological Control

Biological control strategies use natural predators and microbial agents to reduce mosquito populations. For example, copepods have been successfully introduced into household water containers where they prey on early mosquito larval stages, significantly lowering larval densities. [21] Microbial larvicides such as *Bacillus thuringiensis israelensis* (Bti) are also commonly used; Bti produces toxins that damage the mosquito larval gut, leading to rapid death. However, because Bti has a relatively short residual activity, it typically requires reapplication every two to four weeks. [23] Another promising biological approach involves the use of *Wolbachia*, a maternally inherited endosymbiotic bacterium. When *Aedes aegypti* mosquitoes are infected with *Wolbachia*, dengue virus replication is reduced through mechanisms such as competition for cellular resources, stimulation of the mosquito's innate immune responses, and interference with viral transmission. [24] Since *Wolbachia* spreads naturally within mosquito populations through cytoplasmic incompatibility, it represents a potentially sustainable and environmentally safe strategy for long-term dengue vector control.[24, 25]

Genetic and Bio-technological Control

Genetic tools aim to suppress mosquito populations by introducing modified or sterile males into the environment. The Sterile Insect Technique (SIT) uses irradiation to render male mosquitoes infertile, thereby reducing the number of viable offspring. Similarly, RIDL (Release of Insects Carrying a Dominant Lethal Gene) introduces genetic constructs that cause offspring to die before reaching adulthood. While these approaches show substantial promise, they require careful monitoring to avoid unintended ecological consequences and to ensure public acceptance.[25]

Chemical Control

Chemical control remains essential, particularly during major outbreaks when rapid mosquito reduction is needed. Larvicides such as temephos and pyriproxyfen, as well as microbial larvicides like Bti, are commonly used to target immature stages, while adulticides, including pyrethroids and organophosphates, are applied through space spraying and indoor residual spraying. However, widespread insecticide resistance in *Aedes aegypti* and *Aedes albopictus* populations documented across multiple countries in South-East Asia and other endemic regions has reduced the long-term effectiveness of these chemical interventions. Resistance to pyrethroids, organophosphates, along with high frequencies of metabolic and knockdown resistance (kdr) mutation-mediated resistance, underscores the need for rotation of active ingredients and integration with non-chemical strategies.[26]

Integrated Vector Management (IVM)

Integrated Vector Management (IVM) synthesizes environmental, chemical, biological, and genetic tools into a unified strategy. It emphasizes community participation, intersectoral collaboration, and evidence-based deployment of interventions.[27] WHO's COMBI (Communication for Behavioral Impact) initiatives are an example of engagement frameworks that empower communities to eliminate breeding sites and adopt preventive behaviors. Overall, IVM is the most sustainable approach to dengue control, recognizing that no single intervention can effectively suppress *Aedes aegypti* populations across diverse ecological and socioeconomic settings.

CHALLENGES IN DENGUE VACCINE DEVELOPMENT

Developing a safe and effective dengue vaccine poses exceptional challenges that arise from the biological complexity of dengue virus and the host immune response. The presence of four antigenically distinct serotypes, each capable of causing disease, requires vaccines to generate strong and balanced tetravalent immunity. Partial or uneven immunity can predispose individuals to breakthrough infections and potentially more severe outcomes. Incomplete or serotype-skewed immunity may trigger immune responses resembling secondary infections, increasing the risk of severe disease and complicating both vaccine design and evaluation.[25]

A major obstacle is antibody-dependent enhancement (ADE), a central feature of dengue immunopathogenesis. ADE occurs when pre-existing non-neutralizing antibodies facilitate greater viral entry into Fcγ receptor-bearing immune cells, amplifying viral replication and inflammation.[4] This mechanism explains why severe disease is more common during secondary infection and why vaccines must induce durable, high-quality neutralizing antibodies to all four serotypes. The risk became evident during post-licensure evaluation of Dengvaxia, which increased hospitalization and severe dengue in seronegative children because the vaccine mimicked a silent primary infection, thereby priming recipients for ADE upon later natural exposure.[6] These findings led to WHO's recommendation that Dengvaxia

be used only in individuals with confirmed prior dengue infection.

Another barrier is the genetic diversity and rapid evolution of circulating dengue viruses, which can reduce vaccine effectiveness. Substantial genotypic variation exists within each serotype, influencing antigenicity and neutralization patterns and complicating the development of uniformly effective vaccines.[12] This diversity means that immune responses elicited by vaccines tested in one region may not translate uniformly across global settings where different strains predominate. Additionally, the lack of a universally accepted correlate of protection complicates dengue vaccine development. Although neutralizing antibody titers are often used as a proxy for immunity, the absence of a reliable mechanistic marker with a consistent protective threshold limits the ability to predict long-term efficacy.[29]

Operational and ethical considerations further complicate vaccine deployment. Because disease severity is strongly influenced by baseline serostatus, age, and prior exposure, vaccine studies must use carefully stratified cohorts and long-term follow-up to detect late safety signals.[30] Screening for serostatus prior to vaccination is required for Dengvaxia, but the limitations of current serological tests create substantial operational and implementation challenges for vaccination programs, particularly in resource-limited settings.[31] Moreover, evaluating vaccine performance must account for fluctuating transmission patterns, shifts in dominant serotypes, and differences in vector ecology all of which influence real-world effectiveness.[21] Together, these immunological, virological, and programmatic challenges illustrate why dengue vaccine development continues to be one of the most complex undertakings in modern vaccinology.

LICENSED DENGUE VACCINES

Currently, there are two registered vaccines, licensed to be used internationally under certain conditions: Dengvaxia and Qdenga, some others are going under different stages of vaccine trials

DENGVAXIA (CYD-TDV)

Dengvaxia (CYD-TDV), developed by Sanofi Pasteur, was the first dengue vaccine to be licensed and remains a key milestone in dengue control efforts. It is a tetravalent, live-attenuated chimeric vaccine in which the pre-membrane (prM) and envelope (E) genes of each of the four dengue serotypes are inserted into the backbone of the yellow fever 17D vaccine virus. This design allows the vaccine viruses to replicate and express dengue envelope proteins, stimulating neutralizing antibody responses, while relying on the non-structural proteins of yellow fever 17D to provide an attenuated, replication-competent vector.[6] The vaccine is administered as a three-dose series given subcutaneously at 0, 6, and 12 months.

Current recommendations restrict Dengvaxia to a narrow target group because of its complex safety profile. The CDC advises its use only in children and adolescents aged 9-16 years who live in dengue-endemic areas and have laboratory-confirmed evidence of prior dengue infection.[32] This reflects the observation from large phase 2b and phase 3 trials that the vaccine behaves very differently in seropositive versus seronegative individuals. In those with past dengue infection, Dengvaxia boosts pre-existing immunity and reduces the risk of symptomatic and severe disease during subsequent exposures. In contrast, when given to seronegative recipients, the vaccine can mimic a silent primary infection, priming the immune system in a way that increases the risk of severe dengue during a later natural infection.[6]

This paradoxical effect is closely linked to antibody-dependent enhancement (ADE), which is a central feature of dengue immunopathogenesis and a major barrier to safe vaccine design. In seronegative individuals, Dengvaxia appears to generate an immune profile that does not provide durable, balanced tetravalent protection but instead leaves recipients with non-neutralizing or short-lived cross-reactive antibodies. When these individuals subsequently encounter wild-type dengue virus, these antibodies can facilitate viral entry into Fcγ receptor-bearing cells, leading to higher viral loads and an increased likelihood of severe clinical outcomes. Long-term follow-up of trial participants showed that this elevated risk of hospitalization and severe dengue in seronegative vaccines emerged roughly 18-30 months after vaccination, consistent with waning cross-protection and the immunological pattern of a secondary-like infection.[6]

Because of this safety signal, WHO and national regulatory agencies revised their guidance to require evidence of prior infection before vaccination. In practice, this creates substantial operational challenges. Programs must be able to distinguish seropositive from seronegative individuals using serological assays that are both sufficiently specific (to avoid vaccinating truly naive individuals) and sensitive (to avoid excluding those who could benefit). However, currently available tests have imperfect performance and may be difficult to implement reliably at scale, particularly in low-resource settings. These constraints, along with concerns about public trust following early deployment controversies, have contributed to limited uptake of Dengvaxia and, more recently, to the manufacturer's decision to discontinue its production due to lack of global demand.[32]

Overall, Dengvaxia illustrates both the promise and the complexity of dengue vaccination. It can meaningfully reduce disease burden in carefully selected, seropositive populations, but its serostatus dependent performance, requirement for pre-vaccination screening, and association with enhanced disease in seronegative recipients have led to highly cautious, targeted use rather than broad population-level deployment.

QDENGA (TAK-003)

Qdenga (TAK-003), developed by Takeda Pharmaceuticals, is a second-generation live-attenuated tetravalent dengue vaccine that uses a DENV-2 backbone with the prM and E genes of DENV-1, DENV-3, and DENV-4 substituted into the construct.[33] This design

produces reliable replication of all components but results in markedly stronger immunogenicity toward DENV-2.

Phase III trials involving over 20,000 children demonstrated overall efficacy of ~61% against symptomatic dengue and ~84% against hospitalization, with the most robust and sustained protection observed against DENV-2. In seropositive individuals, Qdenga also generated moderate protection to the other serotypes, supported by higher and more durable neutralizing antibody titers.[34]

However, performance in seronegative recipients was more variable. While DENV-2 protection remained high, Qdenga showed minimal or no significant efficacy against DENV-3 and DENV-4 in this group. These serostatus-stratified results, particularly the weaker protection against DENV-3 in younger children, have prompted cautious use of Qdenga in low-transmission or predominantly seronegative populations and underscore the need for continued long-term safety monitoring.[34]

Despite these limitations, modeling suggests Qdenga can reduce hospitalized dengue by 10–22% in high-transmission regions where most children are already seropositive.[34] These settings maximize benefit and minimize risk, supporting WHO's recommendation to administer Qdenga primarily to children aged > 6 years in areas with high seroprevalence.[33] Continued post-licensure monitoring is essential to clarify long-term protection, especially for DENV-3 and DENV-4.

Overall reactogenicity with Qdenga has been similar to other live-attenuated vaccines, with mostly mild injection-site reactions and transient fever reported in trials.[33, 34] To date, no clear overall increase in severe dengue has been demonstrated across all age groups; however, the limited number of seronegative children especially those aged 4 -5 years, and the negative point estimates for DENV-3 mean that a small enhancement risk cannot be excluded, underscoring the need for ongoing post-licensure safety monitoring. [30, 33, 34]

COMPARATIVE ANALYSIS OF DENGVAXIA AND QDENGA

Dengvaxia and Qdenga represent two distinct approaches to dengue vaccination, each shaped by the immunological and epidemiological constraints of dengue virus transmission. Dengvaxia, built on a yellow fever 17D backbone, produces immunity that depends heavily on an individual's prior dengue exposure, offering strong protection to seropositive recipients but posing clinically significant risks to those without previous infection. This serostatus-dependent performance, along with the need for accurate pre-vaccination screening, limits its practical use to highly controlled, well-resourced settings. Qdenga, in contrast, uses a DENV-2 backbone designed to produce balanced tetravalent immunity without requiring serostatus screening. Its strongest and most durable protection lies against DENV-2, while reduced efficacy against DENV-3 and DENV-4, especially in seronegative children, introduces uncertainty about long-term safety and performance.

From a population perspective, both vaccines can reduce severe disease and hospitalizations when deployed under appropriate epidemiological conditions. Dengvaxia is best suited for high-seroprevalence populations with the capacity for reliable laboratory confirmation of prior infection, whereas Qdenga is more advantageous in high-transmission regions where most children are naturally seropositive by early childhood. However, neither vaccine provides uniformly high, durable tetravalent immunity, and both require ongoing post-licensure surveillance to detect rare adverse events, serotype-specific waning, and potential enhancement risks. Collectively, these vaccines demonstrate both the promise of dengue immunization and the persistent challenges posed by viral diversity, transmission dynamics, and immunopathogenesis.

In practice, both vaccines will need to be deployed alongside integrated vector-management strategies, including Wolbachia releases, SIT, and environmental control rather than as stand-alone tools for dengue elimination.

Table 1. Key Differences Between Dengvaxia (CYD-TDV) and Qdenga (TAK-003)

Developer	Sanofi Pasteur	Takeda Pharmaceuticals
Type	Live-attenuated, chimeric (Yellow Fever 17D backbone)	Live-attenuated, tetravalent (DENV-2 backbone)
Doses	3 doses (0, 6, 12 months)	2 doses (0, 3 months)
Licensed	2015	2022–2023 (WHO recommendation 2025)
Target Group	Ages 9–16 with prior dengue infection	Ages ≥ 6 years in moderate–high transmission areas
Safety Concerns	↑ Risk of severe disease in seronegatives	Possible mild enhancement risk in seronegative <6 yrs
WHO Guidance	Use only after confirming past dengue infection	Use in endemic settings without mandatory pre-testing
Program Status	Being phased out by 2025	Rolled out in Brazil (2024) and expanding globally

OTHER DENGUE VACCINE CANDIDATES

In addition to CYD-TDV and TAK-003, several dengue vaccine candidates are advancing through late-stage and early-stage development. Multiple platforms, including live-attenuated vaccines such as Butantan-DV and TV003/TV005, as well as virus-like particle, subunit, DNA/mRNA, adenoviral-vector, and prime boost approaches that aim to improve tetravalent balance,

durability, and safety. These candidates are summarized in Table 2.

Table 2a. Emerging Dengue Vaccine Candidates in Phase II- III trials Adapted from https://www.sciencedirect.com/science/article/pii/S305045622500029X

Vaccine / Platform	Type / Approach	Developer / Country	Clinical Phase (2025)	Key Findings / Highlights
Butantan-DV	Live-attenuated (derived from NIH TV003/TV005)	Brazil (Butantan Institute + NIH)	Phase III	~80% efficacy; balanced neutralizing antibody responses; favorable safety profile
NIH TV003 / TV005	Live-attenuated tetravalent blend	U.S. NIH	Phase II/III	High immunogenicity after a single dose; durable tetravalent neutralization
DENVax	Live-attenuated (DENV-2 PDK-53 backbone)	U.S. / Thailand / Singapore	Phase II → precursor to TAK-003	Strong tetravalent potential; developmental backbone of TAK-003

Abbreviations: ADE = antibody-dependent enhancement; DENV = dengue virus; VLP = virus-like particle; mRNA = messenger RNA; prM = premembrane protein.

Table 2b. Early-Stage and Experimental Dengue Vaccines Platforms (Pre-clinical – Phase I) Adapted from https://www.sciencedirect.com/science/article/pii/S305045622500029X

Vaccine / Platform	Type / Approach	Developer / Country	Clinical Phase (2025)	Key Findings / Highlights
VLP Vaccines	Non-replicating virus-like particles (E protein)	Asia & EU consortia	Preclinical–Phase I	Reduced ADE risk; stable immunogenicity in early models
Recombinant E Subunit Vaccines	Purified E protein + adjuvant	Academic groups	Phase I	Safe; moderate antibody titers; requires strong adjuvants
DNA / mRNA Vaccines	Nucleic acids encoding prM/E	U.S., China, India	Preclinical–Phase I	Rapid manufacturing; scalable; relatively short-lived titers
Adenoviral-Vector Vaccines	Non-replicating adenovirus expressing DENV antigens	Multisite developers	Preclinical	Strong T-cell responses; good candidates for prime–boost
Prime–Boost Strategies	DNA prime + live-attenuated or subunit boost	Multisite research groups	Exploratory	Broad antibody response; enhanced T-cell immunity
Monoclonal Antibodies (mAbs)	Passive immunoprophylaxis (e.g., D23-1G7C2)	Academic / Industry	Early clinical	Useful for outbreak control; rapid protection
Universal Flavivirus Vaccine Concepts	Cross-serotype epitopes	CEPI / WHO Collaborations	Preclinical	Targets conserved envelope epitopes to generate broad protection

Abbreviations: ADE = antibody-dependent enhancement; CEPI = Coalition for Epidemic Preparedness Innovations; DENV = dengue virus; E protein = envelope protein; mRNA = messenger RNA; prM = premembrane protein; VLP = virus-like particle.

FUTURE DIRECTIONS IN DENGUE PREVENTION AND VACCINE STATEGY

Building on the limitations of current vaccines and vector-control approaches outlined above, several key areas require advancement to strengthen global dengue prevention strategies.

Future strategies must integrate improved vaccine technologies, strengthened surveillance, advanced vector-control innovations, and global health policy shifts to effectively reduce dengue burden.

Achieving durable and balanced tetravalent immunity remains one of the most significant barriers for next-generation dengue vaccines. Current platforms frequently generate immune responses that are stronger toward certain serotypes, resulting in incomplete cross-neutralization and potential breakthrough infections. This imbalance resembles the immunological behavior seen in secondary infections and may contribute to heightened disease severity. Both CYD-TDV and TAK-003 show evidence of waning immunity and serotype-specific variability, highlighting why long-lasting, equal immunity to all four serotypes is a central priority going forward.[35]

A central priority for future vaccine development is the creation of serostatus-independent vaccines that are safe and effective for both seropositive and seronegative

individuals. Current vaccines: Dengvaxia and Qdenga are limited by serotype-imbalanced immunity, waning protection, and potential enhancement risks, especially for DENV-3 and DENV-4 in seronegative populations.[34] These challenges highlight the urgent need for next-generation vaccine platforms that elicit durable, balanced, tetravalent neutralizing antibody responses. WHO emphasizes that establishing reliable correlates of protection, particularly standardized neutralizing antibody thresholds, is essential for improving vaccine design and predicting long-term efficacy.[1]

Virus-like particle (VLP) vaccines provide one of the most promising solutions for minimizing ADE risk while strengthening tetravalent immunity. Because VLPs are non-replicating and can be engineered to exclude prM, an epitope strongly associated with non-neutralizing, enhancing antibodies that avoid the immunological patterns that contributed to safety issues in seronegative Dengvaxia recipients.[36] By presenting dengue E proteins in native conformations without ADE-associated components, VLPs generate potent neutralizing responses in non-human primate studies and offer a safer approach for both seropositive and seronegative groups.

Research into booster schedules, alternative dosing intervals, and heterologous prime-boost strategies may also enhance durability and breadth of protection.

Advances in vector control will also remain critical, particularly as climate change expands the geographic distribution of Aedes mosquitoes. Scalable and self-sustaining biocontrol tools such as Wolbachia-infected Aedes aegypti, sterile insect technique (SIT), and genetically engineered mosquitoes offer promising long-term solutions for reducing transmission intensity.[21]

Future dengue prevention efforts must integrate vaccination with strengthened surveillance, genomic monitoring, and data-driven outbreak forecasting. Real-time serotype surveillance is essential because shifts in dominant genotypes can alter vaccine performance and increase the risk of severe outbreaks following prior exposure to different serotypes.[37] Artificial intelligence (AI) assisted prediction models and machine-learning tools can identify high-risk regions before transmission surges, enabling more targeted vaccination and vector-control campaigns.[38]

Large-scale deployments of Wolbachia strains (e.g., wMel) have demonstrated significant reductions in dengue incidence through population replacement effects that inhibit viral replication within the mosquito. Concurrently, SIT field trials have shown substantial suppression of Aedes albopictus densities, and CRISPR-based gene-drive technologies may eventually enable targeted elimination of vector populations, though ethical and ecological concerns require careful regulation and community engagement.

Thermostable dengue vaccine formulations such as spray-dried or lyophilized vaccines represent a critically important advancement for deployment in tropical regions, where limited cold-chain capacity still constrains vaccine delivery.[36]

Enhanced surveillance systems represent another essential future direction. Integration of climate-driven early warning systems, real-time genomic sequencing, and digital outbreak prediction tools will be increasingly important as global warming accelerates dengue transmission dynamics.[9] Strengthening laboratory capacity for NS1 antigen testing, rapid diagnostics, and serological assays will improve case detection and support safe deployment of vaccines that require stratification by serostatus.

Scaling next-generation dengue vaccines will also depend on expanding manufacturing platforms capable of producing vaccines at low cost and high volume. Yeast-based systems enable inexpensive mass production, mammalian cells produce optimally folded and glycosylated antigens, and plant-based platforms offer infrastructure-light production suitable for LMICs.[36]

WHO additionally recommends region-specific seroprevalence mapping to guide vaccine introduction, prioritizing high-transmission areas where Qdenga offers the greatest benefit to risk ratio.

As vaccine technologies continue to evolve, regulatory frameworks must adapt to accelerate safe deployment. Identifying reliable immune correlates such as standardized neutralizing antibody thresholds could streamline evaluation and support earlier approval decisions.[39]

Finally, global dengue control will require coordinated policy frameworks that combine vaccination, community-based vector reduction, sustainable urban planning, and cross-border surveillance. Public health agencies stress that vaccines cannot replace vector control; rather, they must function as part of an integrated strategy combining environmental management, biological control, chemical interventions, and community participation.[1, 21] Continued investment in research, post-licensure monitoring, and health-system strengthening will be essential to reduce dengue morbidity and mortality in an era of rapid ecological and epidemiological change. Collectively, these strategies represent the path toward a more resilient, evidence-driven framework capable of reducing dengue morbidity and mortality globally

Conclusion

Dengue remains a complex and rapidly expanding global health threat, driven by environmental change, vector adaptation, and the unique challenges of DENV immunopathology. Although Dengvaxia and Qdenga represent major progress in vaccine development, both have important limitations related to serostatus, durability, and serotype-specific protection. These constraints highlight that vaccination alone cannot control dengue. Strengthening vector-control programs, improving diagnostics, and investing in next-generation, serostatus-independent vaccines remain essential. A coordinated approach that integrates vaccination with sustainable vector management and improved surveillance offers the most effective path forward to reducing dengue transmission and disease burden worldwide.

COI: The authors have declared no conflicts of interest.

Acknowledgement: The authors would like to thank the Department of Health Science at Brock University for academic support and guidance. The first author also gratefully acknowledges the encouragement and support of her family, whose motivation made this work possible.

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