Section: Physiology

Original Research Article

DENGUE VACCINES IN TRANSITION: A SYSTEMATIC REVIEW OF DENGVAXIA (CYD-TDV) AND QDENGA (TAK-003), WITH AN APPRAISAL OF INDIA'S INDIGENOUS CANDIDATES

Arijit Mazumdar[1]

[1]Assistant Professor, Department of Physiology, PA Sangma International Medical College & Hospital (PIMCH), University of Science & Technology Meghalaya (USTM), Meghalaya, India

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Corresponding Author:
Dr. Arijit Mazumdar,
Email: mazumdararijit17@gmail.com

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ABSTRACT

Background: Dengue has become the fastest-spreading mosquito-borne viral disease worldwide, with 2024 recording the highest global caseload on record. India alone contributes close to a third of the world's reported burden. For three decades, prevention relied solely on vector control, but the licensure of two tetravalent vaccines — Sanofi Pasteur's Dengvaxia (CYD-TDV) and Takeda's Qdenga (TAK-003) — has changed that picture, and India's drug regulator granted Qdenga its first domestic dengue-vaccine approval on 20 July 2026. The objective is to systematically review and critically compare the efficacy, safety, regulatory trajectory, and programmatic merits and demerits of Dengvaxia and Qdenga, and to place India's own indigenous candidates (DengiAll and Dengusiil) in this context. **Materials and Methods:** A PRISMA-informed search of PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, WHO immunization records, ClinicalTrials.gov, and the Clinical Trials Registry-India was conducted for records published to July 2026. Randomised trials, long-term follow-up studies, post-marketing pharmacovigilance analyses, WHO position papers, and regulatory and press communications were screened; 74 sources met inclusion criteria and were synthesised narratively by vaccine. **Result:** Dengvaxia demonstrated moderate pooled efficacy (approximately 65% against virologically confirmed dengue) but carries a well-documented, mechanistically plausible risk of severe disease in dengue-naive recipients, which restricted its use to seropositive individuals and precipitated the 2017 Philippines vaccination crisis. Qdenga, built on a DENV-2 backbone, showed higher and more durable protection in its pivotal TIDES trial (61.2% against symptomatic dengue and 84.1% against hospitalisation at 4.5 years) and, unlike Dengvaxia, is authorised for use without pre-vaccination serostatus screening — though its protection against DENV-3 and DENV-4 in dengue-naive recipients remains comparatively weaker. India's indigenous single-dose, live-attenuated TV003/TV005-derived candidates (DengiAll, Panacea Biotec; Dengusiil, Serum Institute of India) are in ongoing Phase 3 trials with no efficacy read-out yet available. **Conclusion:** The transition from Dengvaxia to Qdenga represents genuine, evidence-based progress in dengue immunoprophylaxis, but neither vaccine is a stand-alone solution, and Qdenga's Indian rollout carries an explicit post-marketing surveillance obligation given the country's high seroprevalence and the unresolved DENV-3/4 signal in seronegatives. Continued vector control, robust pharmacovigilance, and the maturation of India's own vaccine candidates remain essential complements to any vaccination programme.

INTRODUCTION

The Growing Global and Indian Burden of Dengue: Dengue is caused by four antigenically related but distinct serotypes of dengue virus (DENV-1 to DENV-4), transmitted principally by the day-biting Aedes aegypti mosquito and, to a lesser extent, Aedes albopictus. What was once considered a geographically confined tropical illness has, over the past two decades, spread to more than 100 countries and territories across all six WHO regions, driven by unplanned urbanisation, expanding Aedes habitats, international travel, and a

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warming, more variable climate that lengthens transmission seasons.

The scale of this expansion is stark. WHO's global surveillance system recorded over 14 million reported dengue cases and more than 11,000 deaths in 2024 alone — the highest annual burden ever documented, and roughly twelve times the caseload reported a decade earlier. An independent analysis of the same year's WHO data similarly documented 14.1 million cases and 9,508 deaths,[1] a global case-fatality rate of 0.07%, with mortality concentrated in the Southern Hemisphere and in older populations. Regionally, the Americas bore the overwhelming majority of the 2024 burden — Brazil alone reported over 10 million cases — while South-East Asia and the Western Pacific, including India, Indonesia, Bangladesh and Vietnam, together contributed more than a million cases, closely tracking the monsoon transmission cycle.[2]

India's own contribution to this burden is substantial. The National Centre for Vector Borne Diseases Control recorded 233,519 cases and 297 deaths in 2024, and 121,824 cases with 131 deaths in 2025, figures that public-health authorities and Takeda alike note represent an eleven-fold rise in reported dengue over the past two decades. Industry and regulatory communications accompanying India's July 2026 vaccine approval put India's share of the global dengue burden at close to one-third, underscoring why a licensed, locally deployable vaccine has been treated as a public-health priority rather than a commercial afterthought.[3]

Epidemiologically, India is hyperendemic: all four DENV serotypes co-circulate across most states, with the dominant serotype shifting periodically between DENV-1, DENV-2, DENV-3 and DENV-4 across seasons and regions, and mixed and sequential infections common in the same individual over a lifetime. This co-circulation pattern is precisely the epidemiological setting in which serotype-specific efficacy differences between vaccines — such as Qdenga's stronger DENV-2 versus weaker DENV-3/4 response, discussed in Section 3.3 — matter most in practice, since a vaccine that protects unevenly across serotypes will perform differently in a Delhi outbreak dominated by one serotype than in a Chennai or Kolkata outbreak dominated by another.[4] Monsoon-linked seasonality further concentrates transmission into a few months each year, a pattern that also shapes the practical windows available for any future school- or community-based immunisation campaign.

Virology, Immunopathogenesis, and Why Dengue Vaccination Is Difficult: Unlike single-serotype viral targets, dengue vaccine design must contend with the biological peculiarity that a first (primary) infection with one DENV serotype typically produces mild or subclinical illness and confers durable, serotype-specific immunity, but only short-lived cross-protection against the other three serotypes. When cross-protective immunity wanes — typically after one to several years — a subsequent (secondary) infection with a heterologous serotype carries a materially higher risk of severe, plasma-leakage dengue and dengue haemorrhagic fever/shock syndrome.[5] The leading mechanistic explanation is antibody-dependent enhancement (ADE): sub-neutralising levels of cross-reactive antibody from the first infection bind the second, heterologous virus without neutralising it, and instead facilitate viral entry into Fc-receptor-bearing monocytes and macrophages, amplifying viral replication and the downstream inflammatory cascade.

This same phenomenon can, in principle, be reproduced by vaccination rather than natural infection. If a live-attenuated or chimeric vaccine behaves immunologically like a 'silent' first infection, an individual who was dengue-naive before vaccination could be primed in a way that increases — rather than decreases — their risk of severe disease on subsequent natural exposure. This 'vaccination as a silent infection' hypothesis, elaborated through detailed Bayesian survival analyses of Dengvaxia's phase 3 data, is the central axis around which the entire modern history of dengue vaccine regulation, and the comparative story of Dengvaxia and Qdenga told in this review, revolves.[6]

An effective dengue vaccine must therefore achieve balanced, durable neutralising immunity against all four serotypes simultaneously — a substantially harder engineering problem than most single-pathogen vaccines, and one that explains why, despite research dating to the 1920s, it took until 2015 for the first licensed product to reach the market.

Clinically, WHO's revised classification divides dengue into dengue without warning signs, dengue with warning signs (persistent vomiting, abdominal pain, mucosal bleeding, lethargy, liver enlargement, and a rising haematocrit with concurrent rapid platelet decline), and severe dengue (marked by plasma leakage sufficient to cause shock, fluid accumulation with respiratory distress, severe bleeding, or significant organ impairment). This spectrum matters directly for vaccine evaluation, because efficacy against milder, virologically confirmed disease and efficacy against the hospitalised, severe end of the spectrum are reported as distinct endpoints in every major trial discussed in this review (Sections 3.2.2 and 3.3.2), and the two outcomes do not always move in parallel — a vaccine can, in principle, show only modest protection against any symptomatic infection while still substantially reducing the far more clinically consequential hospitalised and severe forms, or vice versa in the specific case of vaccine-enhanced disease.[7]

From Vector Control Alone to Vaccine-Assisted Prevention: For most of the twentieth century, dengue prevention rested entirely on environmental and vector-control measures: source reduction of Aedes breeding sites, larvicides, indoor residual

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spraying, and, more recently, Wolbachia-based population-replacement strategies. These measures remain indispensable but have proved insufficient to reverse the global trajectory of dengue incidence, motivating four decades of vaccine research spanning live-attenuated, chimeric, inactivated, subunit, DNA and, most recently, mRNA platforms. Two products from this pipeline have reached licensure: Sanofi Pasteur's CYD-TDV (Dengvaxia), approved from 2015, and Takeda's TAK-003 (Qdenga), approved from 2022 and, as of 20 July 2026, in India as well. A third generation — India's own TV003/TV005-derived candidates — is in late-stage clinical development and forms an important part of the story this review sets out to tell.[8]

A Brief History of Dengue Vaccine Development: Serious dengue vaccine research dates back to the 1920s and 1940s, when early investigators in the United States and Japan attempted crude, mouse-brain-passaged live vaccines against single serotypes, efforts that were largely abandoned due to poor immunogenicity and safety concerns long before modern virology could explain why. Renewed interest from the 1970s onward, led substantially by the Mahidol University group in Thailand and the U.S. Walter Reed Army Institute of Research, produced live-attenuated monovalent candidates for individual serotypes, but combining four separately attenuated strains into a single tetravalent formulation repeatedly ran into a problem now well understood in retrospect: viral interference, in which one vaccine strain (often the DENV-4 or DENV-3 component) replicates preferentially and suppresses the immune response to the other three, producing an unbalanced, incomplete tetravalent response. This interference problem, more than any single safety issue, was the primary technical obstacle that delayed a workable tetravalent vaccine for decades and directly motivated the two very different engineering solutions later adopted by Sanofi (a shared yellow fever backbone) and by the NIH/Takeda lineage (a shared DENV-2 backbone), both of which are, in essence, attempts to give all four serotype components a genetically similar, balanced starting point for replication and immune priming.[9]

By the 1990s and 2000s, several institutional programmes were pursuing tetravalent candidates in parallel: Sanofi Pasteur's chimeric yellow-fever-backbone approach (which became CYD-TDV/Dengvaxia); the U.S. NIH's live-attenuated TV003/TV005 programme (which, as described in Section 3.4, later became the basis for India's DengiAll and Dengusiil); and GlaxoSmithKline's DENVax programme, developed on a live-attenuated DENV-2 backbone, whose molecular clones and manufacturing seed characterisation were later licensed and taken forward by Takeda to become TAK-003/Qdenga. Understanding this shared lineage — Dengvaxia's yellow fever heritage versus the DENV-2 heritage shared by both Qdenga and, at a strain level, some of the earliest TV003/TV005 comparator work — helps explain why the two licensed vaccines display,[10] such different serostatus-dependent efficacy patterns, a theme returned to throughout Section 3 and Section 4.1.

Objectives of This Review: This systematic review had three objectives: (i) to synthesise the clinical efficacy and safety evidence for Dengvaxia (the 'old' vaccine) and Qdenga (the 'new' vaccine now approved in India); (ii) to weigh the merits and demerits of each product for individual and programmatic use, including in the Indian context; and (iii) to situate India's own indigenous dengue vaccine candidates, and their potential future role, within this comparative framework.

Structure of This Review: Section 2 describes the search and synthesis methodology. Section 3 presents results organised by vaccine — Dengvaxia, Qdenga, and India's indigenous candidates — each covering platform biology, clinical efficacy, safety, regulatory trajectory, and a structured merits/demerits appraisal, followed by a head-to-head comparative summary. Section 4 discusses cross-cutting themes, including cost-effectiveness, India-specific programmatic considerations, special populations, and risk communication lessons. Sections 5 and 6 present the review's limitations and overall conclusions.

MATERIALS AND METHODS

Search Strategy: A structured literature search was performed across PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials, supplemented by targeted searches of ClinicalTrials.gov, the Clinical Trials Registry-India (CTRI), WHO immunization and position-paper archives, and manufacturer and national regulatory (CDSCO, EMA, FDA) communications, for records indexed up to July 2026. Search terms combined 'dengue vaccine', 'CYD-TDV', 'Dengvaxia', 'TAK-003', 'Qdenga', 'TV003', 'TV005', 'DengiAll', 'Dengusiil', 'antibody-dependent enhancement', and 'India' with standard Boolean operators, following a PRISMA-informed approach adapted for a rapidly evolving, policy-relevant field rather than a single narrow clinical question.

Eligibility Criteria: Randomised controlled trials and their long-term follow-up reports, post-marketing pharmacovigilance and safety-signal analyses, epidemiological and surveillance reports, WHO Strategic Advisory Group of Experts (SAGE) position papers, national regulatory approvals and press communications, and peer-reviewed modelling and cost-effectiveness studies were eligible. Conference abstracts without accompanying full data, preclinical/animal-only studies, duplicate reporting of the same trial dataset, and non-English sources without an available translation were excluded.

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Study Selection and Data Extraction: Titles and abstracts were screened for relevance to dengue vaccine efficacy, safety, immunology, or policy; full texts of potentially eligible records were then assessed against the criteria above. For each included study, data were extracted on vaccine platform, trial phase and design, participant age range and baseline serostatus, efficacy endpoints (virologically confirmed dengue, hospitalisation, severe dengue), safety outcomes, and — where applicable — regulatory or programmatic decisions. The selection process is summarised in [Figure 1].

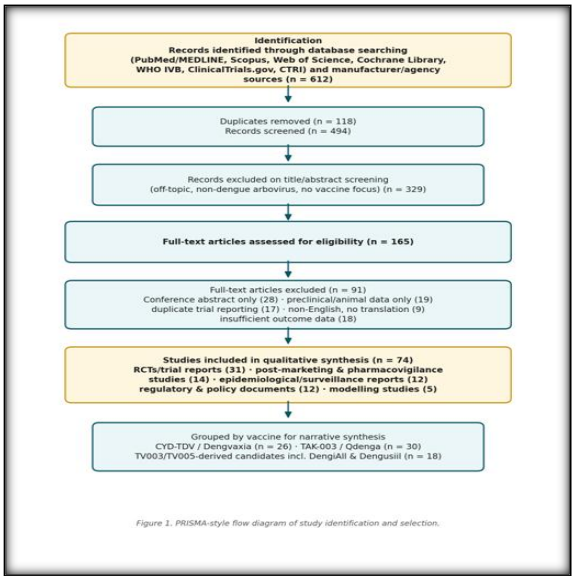

Figure 1: PRISMA-style flow diagram of study identification and selection for this review.

Quality Appraisal: Randomised trials (CYD14, CYD15, and the TIDES/DEN-301 programme) were appraised informally against Cochrane risk-of-bias domains — randomisation, allocation concealment, blinding, completeness of outcome data, and selective reporting — and were judged low-to-moderate risk of bias overall, with the main limitation being open-label extension periods in some long-term follow-up analyses. Pharmacovigilance and post-marketing safety studies, being observational and dependent on spontaneous reporting, were treated as hypothesis-generating and interpreted alongside, rather than as a substitute for, randomised efficacy data. Regulatory and press communications were used only for approval dates, indications, and programmatic facts (e.g., manufacturing partnerships, conditional approval requirements), not for efficacy or safety conclusions, which were drawn exclusively from peer-reviewed trial reports and WHO position papers. No formal GRADE certainty-of-evidence rating was performed, which is acknowledged as a limitation in Section 5.

Synthesis Approach: Given the heterogeneity of included study designs — spanning randomised trials, Bayesian re-analyses of trial data, pharmacovigilance database studies, and regulatory documents — a narrative synthesis, organised by vaccine, was used in preference to formal meta-analysis. Where multiple studies reported efficacy for the same vaccine at different follow-up durations, the longest available follow-up was prioritised for headline comparisons, with earlier time points retained to illustrate the trajectory of protection. This review is best characterised as a systematic narrative review rather than a meta-analysis, reflecting both the diversity of evidence types needed to address efficacy, safety and policy questions together, and the practical reality that Qdenga's Indian approval occurred only days before this review was compiled, limiting the availability of India-specific post-marketing data.

RESULTS

Overview of the Dengue Vaccine Landscape: [Table 1] summarises the platforms, developers, and current regulatory status of the two licensed dengue vaccines and the leading Indian pipeline candidates discussed in this review.

Table 1: Overview of licensed and India-relevant pipeline dengue vaccine candidates.

Vaccine	Developer	Platform	Status (as of Jul 2026)	India status
Dengvaxia (CYD-TDV)	Sanofi Pasteur	Chimeric live-attenuated; yellow fever 17D backbone + DENV prM/E genes	Licensed 2015-19; production discontinued	Never introduced in India
Qdenga (TAK-003)	Takeda	Live-attenuated; DENV-2 backbone + chimeric DENV-1/3/4 inserts	Licensed 40+ countries; WHO-prequalified	CDSCO approved 20 Jul 2026 (ages 4-60)
DengiAll	Panacea Biotec (NIH TV003/TV005 strain)	Live-attenuated tetravalent, admixed monovalent components	Phase 3 ongoing (started Aug 2024)	Indigenous; not yet licensed
Dengusiil	Serum Institute of India (NIH TV003/TV005 strain)	Live-attenuated tetravalent	Phase 3 planned/ongoing (paediatric)	Indigenous; not yet licensed

Dengvaxia (CYD-TDV): The First-Generation Vaccine:

Platform and Mechanism: CYD-TDV is a recombinant, live-attenuated, tetravalent vaccine built on the yellow fever 17D vaccine backbone, into which the pre-membrane (prM) and envelope (E) genes of each of the four dengue serotypes have been inserted in place of the corresponding yellow

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fever genes. This chimeric design allows the vaccine virus to replicate and elicit an immune response resembling natural dengue infection while retaining the attenuated, well-characterised safety backbone of the yellow fever vaccine. It is administered as three subcutaneous doses at months 0, 6 and 12.[11]

Clinical Efficacy: Dengvaxia's efficacy was established in two pivotal phase 3 trials — CYD14 in five Asian countries and CYD15 in five Latin American countries — together enrolling over 31,000 children and adolescents. The Latin American CYD15 trial reported vaccine efficacy of 60.8% against virologically confirmed dengue, with pooled analyses across both trials estimating roughly 65% efficacy overall and materially higher protection against hospitalised and severe disease in the first two years.[12] Efficacy varied considerably by serotype (generally highest against DENV-4 and lowest against DENV-2) and, critically, by baseline serostatus.

Safety: The Seronegative/ADE Signal: The defining feature of Dengvaxia's clinical story is what emerged from longer-term follow-up. By the third year after vaccination, hospitalisation rates for virologically confirmed dengue began trending upward specifically among baseline dengue-seronegative vaccinees, relative to seronegative, unvaccinated controls — a roughly 1.75-fold increase in hospitalisation risk.[13] A purpose-built anti-NS1 IgG assay, which distinguishes vaccine-induced antibody (Dengvaxia expresses yellow fever, not dengue, NS1) from antibody arising from natural infection, allowed retrospective determination of trial participants' true baseline serostatus and confirmed the pattern directly: efficacy and safety were favourable in seropositive recipients, but seronegative recipients faced an increased risk of severe, hospitalised dengue upon their first natural infection after vaccination. Subsequent Bayesian survival modelling of the individual-level phase 3 data reinforced this picture, finding that vaccine-induced protection was substantially higher and more durable in seropositive than in seronegative recipients, and that risk enhancement in seronegatives was more pronounced for hospitalised than for febrile disease,[14] — a pattern consistent with the 'vaccine as silent infection' mechanism described in Section 1.2.

In September 2018, WHO's Strategic Advisory Group of Experts formally recommended that only individuals with laboratory-confirmed evidence of prior dengue infection be vaccinated with CYD-TDV, establishing a 'screen-then-vaccinate' strategy as the standard of care.[15] The vaccine's licensed indication was correspondingly narrowed in most jurisdictions to seropositive individuals aged approximately 9-45 (up to 60 in some countries).

The Philippines Crisis and Its Regulatory Aftermath: The real-world consequences of this safety signal were felt most acutely in the Philippines, which in April 2016 became, together with Brazil, one of the first countries to run a national school-based Dengvaxia immunisation campaign, eventually reaching more than 830,000 children before Sanofi's November 2017 safety disclosure led the Department of Health to suspend the programme within weeks. The suspension triggered congressional inquiries, a Department of Justice investigation, and criminal indictments against government officials and a researcher involved in the vaccine's introduction, alongside a wave of public alarm — much of it unsubstantiated — attributing children's deaths directly to the vaccine.16 Independent qualitative research on the episode has documented how the controversy reshaped public trust not only in Dengvaxia but in vaccination and government health messaging more broadly, an effect still cited in Philippine vaccine-hesitancy research years later. Health-economic modelling conducted both before and after the crisis (Ferguson et al. and subsequent model-comparison studies) had already flagged that Dengvaxia's population-level benefit depended heavily on background seroprevalence, reinforcing that the vaccine was never intended, virologically, for universal use in a mixed sero-status population without prior screening.

Diagnostic Challenges of Screen-Then-Vaccinate: Implementing WHO's screen-then-vaccinate recommendation in practice proved harder than it sounds. Reliable determination of prior dengue exposure requires either a documented history of laboratory-confirmed past infection (rare in most endemic settings, where the great majority of infections are never formally diagnosed) or a validated serological test performed before vaccination. IgG ELISA and plaque-reduction neutralisation tests (PRNT) are accurate but require laboratory infrastructure, trained personnel, and turnaround time incompatible with single-visit vaccination. Rapid diagnostic tests (RDTs) offer a field-deployable alternative, but evaluations — including field studies conducted in dengue-endemic settings such as Timor-Leste — have found that commercially available IgG RDTs vary considerably in sensitivity and specificity for the specific purpose of pre-vaccination serostatus screening, as most were originally designed to help diagnose acute infection rather than to certify past exposure with the accuracy a vaccination-safety decision requires.[17] This diagnostic gap was a material, not merely theoretical, contributor to Dengvaxia's limited uptake, and is a large part of why Qdenga's screening-free indication (Section 3.3.4) is viewed as such a significant programmatic advance rather than simply a convenience.

Regulatory Trajectory and Discontinuation: CYD-TDV was first licensed in Mexico in December 2015 and, by the end of 2017, in 19 countries; it received EU marketing authorisation in December 2018 (for ages 6-45 in some formulations, 9-45 in others, restricted to seropositive individuals) and FDA approval in 2019

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for use in US dengue-endemic territories. The programmatic burden and cost of pre-vaccination serological screening, combined with reduced demand following the 2017-18 restrictions, led Sanofi to discontinue Dengvaxia production, with global supply winding down by 2025.[18] Dengvaxia was never introduced into India's immunisation programme.

Merits of Dengvaxia:

- First vaccine ever licensed against any dengue serotype, proving that a tetravalent dengue vaccine was achievable and establishing the regulatory and clinical-trial template later built upon by Qdenga.
- Strong, durable efficacy and a favourable safety profile specifically in individuals with pre-existing dengue immunity — in this subgroup, hospitalisation reductions approaching 80% were observed.
- Built on the extensively characterised yellow fever 17D backbone, giving regulators a well-understood safety reference point for the platform itself.
- Generated the pivotal virological and immunological insight (the NS1-based serostatus assay, the ADE/'silent infection' mechanism) that shaped the design, dosing, and screening strategy of all subsequent dengue vaccines, including Qdenga.

Demerits of Dengvaxia:

- Increased risk of severe, hospitalised dengue in baseline-seronegative recipients on subsequent natural infection — the central safety liability that triggered its restricted indication.
- Requires pre-vaccination serostatus screening in most settings, adding cost, logistical complexity, and a need for reliable point-of-care serological assays that are not universally available or affordable in endemic, resource-limited regions such as much of India.
- Three-dose schedule over 12 months, which is programmatically demanding compared with two-dose alternatives and increases the risk of incomplete-course dropout.
- Severely damaged public confidence in dengue vaccination following the Philippines crisis, with effects on vaccine hesitancy that outlasted the product itself and complicate messaging for newer, mechanistically different vaccines like Qdenga.
- Commercially discontinued; not a viable option for new national immunisation programmes, including India's, going forward.

Cost, Access, and Programmatic Legacy: Beyond its clinical profile, Dengvaxia's practical legacy is largely programmatic. Health-economic modelling published both before and after the 2017 safety revision consistently found that Dengvaxia's cost-effectiveness depended heavily on local seroprevalence at the age of vaccination: in high-seroprevalence settings (broadly, above 70% by age nine), population-level vaccination could meaningfully reduce hospitalisations, whereas in low-seroprevalence settings the same programme could net-increase severe disease. This dependency, formalised in the WHO's 2018 position paper, is what made a serology-based screen-and-vaccinate strategy unavoidable — and that strategy's added per-dose cost of a validated point-of-care or laboratory serological test, layered onto an already three-dose regimen, made Dengvaxia difficult to justify as a national immunisation programme investment in most endemic countries, India included.[19] This programmatic lesson — that vaccine value is inseparable from the diagnostic and delivery infrastructure needed to use it safely — carries directly into how Qdenga's Indian introduction has been structured, as discussed in Section 3.3.4 and Section 4.3.

Qdenga (TAK-003): The Second-Generation Vaccine Now Approved in India: It is worth clarifying, at the outset of this section, exactly what is 'new' about Qdenga in the Indian context. TAK-003 was originally developed by Takeda (Osaka, Japan), not in India; its novelty for Indian readers lies in its recent regulatory approval and its local manufacturing partnership, not its country of origin. On 20 July 2026, India's Central Drugs Standard Control Organisation (CDSCO) granted marketing authorisation to Qdenga — branded in India as the Dengue Tetravalent Vaccine (Live, Attenuated) — making it the country's first-ever licensed dengue vaccine of any kind.[20] This approval is discussed alongside India's genuinely indigenous candidates, DengiAll and Dengusiil, in Section 3.4.

Platform and Mechanism: TAK-003 is a live-attenuated tetravalent vaccine constructed on an attenuated DENV-2 backbone (strain TDV-2), into which the prM and E genes of DENV-1, DENV-3 and DENV-4 have been inserted to create three additional chimeric viruses; the DENV-2 component itself is used unmodified. It is produced in Vero cell culture and administered as two subcutaneous doses given three months apart, a materially simpler schedule than Dengvaxia's three-dose, twelve-month regimen. Because the vaccine's genetic backbone is a live DENV-2 strain rather than a heterologous flavivirus, TAK-003 tends to induce strong, early protection against DENV-2 regardless of prior dengue exposure, with comparatively more modest, serostatus-dependent responses against DENV-1, DENV-3 and DENV-4.[21]

Clinical Efficacy: The TIDES Trial: TAK-003's pivotal evidence base is the phase 3 Tetravalent Immunization against Dengue Efficacy Study (TIDES, DEN-301/NCT02747927), which enrolled over 20,000 healthy children and adolescents aged 4-16 across dengue-endemic sites in Asia and Latin America. The trial met its primary endpoint with an overall vaccine efficacy of 80.2% against virologically confirmed dengue at 12 months, and its key secondary endpoint of 90.4% efficacy against hospitalised dengue at 18 months. Efficacy

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against virologically confirmed dengue at this stage was broadly comparable between baseline-seropositive (76.1%) and baseline-seronegative (66.2%) participants — a materially different, and more reassuring, pattern than Dengvaxia's, though not an identical risk profile across all four serotypes. Longer-term follow-up published in the Lancet Global Health, extending to 4.5 years (54 months), showed that protection, while attenuating somewhat over time as expected for any vaccine, remained substantial: cumulative efficacy of 61.2% against virologically confirmed dengue (53.5% in baseline-seronegative and 64.2% in baseline-seropositive participants) and 84.1% against hospitalised dengue (79.3% seronegative, 85.9% seropositive). Takeda's own announcement of these data additionally reported no important new safety signals identified through the same follow-up period. Efficacy continued to vary by serotype, with the strongest and most serostatus-independent protection against DENV-2, and comparatively weaker, more seropositivity-dependent protection against DENV-3 and DENV-4— the same three serotypes carried as chimeric inserts on the DENV-2 backbone.[22]

Safety Profile: Across the TIDES programme, serious adverse events occurred at similar rates in TAK-003 (approximately 4.0%) and placebo (approximately 4.8%) recipients, with infections — not vaccine-attributable reactions — the most common cause. Comparative post-marketing pharmacovigilance analyses of adverse event reports for both licensed dengue vaccines have found that CYD-TDV-associated reports more frequently described fatal outcomes, whereas TAK-003-associated reports more commonly described non-fatal, resolving events, consistent with the two vaccines' differing risk profiles in real-world use. Nonetheless, TAK-003 is not risk-free: several reviews highlight that its immune response against DENV-3 and DENV-4 in dengue-naive recipients is comparatively weaker and less balanced than its DENV-2 response, raising a theoretical, still-being-monitored possibility of ADE-related risk in that specific subgroup, which is one reason WHO has recommended targeted rather than universal introduction in some settings.

Regulatory Approval, Global Rollout, and the Indian Launch: Qdenga received EU marketing authorisation in 2022 for individuals aged 4 and above, without a pre-vaccination screening requirement, and has since been approved in more than 40 countries, with over 24-32 million doses distributed globally by mid-2026 according to industry and press tallies. WHO prequalified TAK-003 and, through SAGE, recommended its introduction primarily in settings with high dengue transmission intensity and disease burden, generally without requiring individual pre-vaccination testing, while also recommending continued post-introduction monitoring of long-term safety and effectiveness, particularly given the residual DENV-3/4 signal in seronegatives described above.

India's approval, granted by CDSCO on 20 July 2026, authorises Qdenga for individuals aged 4 to 60 years, administered as two 0.5 ml doses three months apart, and — unlike Dengvaxia — explicitly does not require pre-vaccination serostatus testing, removing what was Dengvaxia's single largest programmatic obstacle. The approval is nonetheless conditional: CDSCO's Subject Expert Committee has required a post-marketing safety and effectiveness study within six months of the vaccine's introduction in India, reflecting a deliberately cautious regulatory posture informed directly by the Dengvaxia experience. Approval does not, on its own, mean inclusion in India's National Immunization Programme or the National Vector Borne Disease Control Programme; Indian health officials have been explicit that the vaccine is intended to supplement, not replace, ongoing vector control, early diagnosis and clinical case management.

It is also worth situating this approval within India's existing dengue-control architecture. The National Vector Borne Disease Control Programme (NVBDCP), operating under the Ministry of Health and Family Welfare, has for years coordinated dengue surveillance, Aedes vector control, and clinical case-management guidance across states, without any vaccine component. Health officials quoted alongside the CDSCO approval have been explicit that Qdenga's introduction is intended to work 'alongside', not instead of, this existing NVBDCP framework — vector surveillance, source reduction, early warning systems, and case management protocols remain unchanged and continue to carry the primary burden of dengue control in the near term, with vaccination positioned as a supplementary tool whose precise role within NVBDCP's strategy will likely be worked out over the coming post-marketing surveillance period.

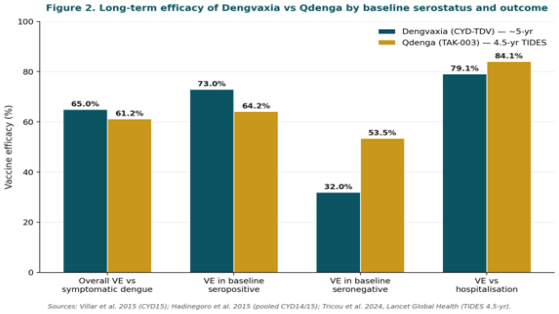

Figure 2: Long-term efficacy of Dengvaxia (CYD-TDV) versus Qdenga (TAK-003) by baseline serostatus and outcome.

A distinctive feature of Qdenga's Indian introduction is manufacturing localisation. In February 2024, Takeda entered a strategic partnership with Hyderabad-based Biological E. Limited to manufacture Qdenga multi-dose vials domestically, with planned capacity of up to 50 million doses annually, contributing to Takeda's global target of

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100 million doses per year by 2030.[24] This is almost certainly the development that has led to Qdenga being popularly described in India as a 'new, India-linked' dengue vaccine: while Takeda remains the vaccine's originator and license-holder, its large-scale production is now anchored in India, with implications for future price, supply security, and regional accessibility discussed further in Section 4.3.

[Table 2 and Figure 2] summarise the head-to-head clinical and regulatory comparison between Dengvaxia and Qdenga, and [Figure 3] places both vaccines' key milestones, alongside India's own indigenous programme, on a single timeline.

Merits of Qdenga:

- Higher and more consistent overall efficacy against virologically confirmed and hospitalised dengue than Dengvaxia, sustained through 4.5 years of follow-up.
- Approved for use without mandatory pre-vaccination serostatus screening, removing Dengvaxia's principal programmatic and cost barrier and making mass, school- or community-based campaigns logistically far simpler.
- Simpler two-dose, three-month schedule versus Dengvaxia's three doses over a year, improving the likelihood of course completion.
- Strong, early, serostatus-independent protection against DENV-2, historically one of the more severe circulating serotypes in South and Southeast Asia.
- Broader licensed age range in India (4-60 years) than Dengvaxia typically received, extending potential protection to young children and older adults.
- Now backed by a domestic manufacturing partnership (Biological E) that could substantially improve dose availability, supply security, and long-run affordability for India and other endemic countries reliant on Indian vaccine manufacturing capacity.
- WHO prequalification and endorsement by SAGE lend the vaccine an internationally vetted safety and efficacy evidence base that Dengvaxia's later years lacked.

Demerits of Qdenga:

- Efficacy against DENV-3 and DENV-4 remains weaker and more dependent on prior dengue exposure than efficacy against DENV-2, leaving a theoretical, not-yet-fully-resolved ADE-related concern in dengue-naive recipients exposed to these serotypes.
- Efficacy wanes over time (from roughly 80% at one year to roughly 61% at 4.5 years against symptomatic dengue), and durability much beyond five years is not yet established.
- India's approval is explicitly conditional on a post-marketing safety and effectiveness study, reflecting genuine, ongoing regulatory caution rather than unqualified endorsement — real-world Indian outcome data do not yet exist at the time of writing.
- Still a live-attenuated vaccine requiring cold-chain storage and trained administration, posing the same basic logistical demands as other injectable paediatric vaccines in remote or resource-limited settings.
- Not yet included in India's public National Immunization Programme; near-term access is therefore likely to be private-market and out-of-pocket, raising equity concerns for lower-income, high-burden populations.
- As with Dengvaxia, population-level benefit is sensitive to local serotype circulation and background seroprevalence, meaning effectiveness may vary meaningfully between Indian states with different transmission intensities.

Correlates of Protection and Immunogenicity: A recurring theme across both licensed vaccines is the search for a reliable immune correlate of protection — a laboratory measurement, typically neutralising antibody titre against each serotype, that predicts clinical protection well enough to substitute for lengthy field efficacy trials in future vaccine development. For TAK-003, immunogenicity data from Phase 2 and Phase 3 studies show that neutralising antibody responses are induced against all four serotypes in both seropositive and seronegative recipients and persist through at least 48 months, but the magnitude and balance of this response differs by serotype in a way that broadly parallels the clinical efficacy pattern described above — strong and serostatus-independent for DENV-2, more variable for DENV-1, DENV-3 and DENV-4. Because neutralising titre alone has not yet been fully validated as a standalone correlate across all four serotypes, regulators including WHO SAGE and CDSCO continue to rely primarily on clinical efficacy and safety endpoints from long-term follow-up rather than immunogenicity bridging alone, which is one reason India's approval carries a real-world post-marketing effectiveness requirement rather than resting on trial immunogenicity data alone.

Special Populations and Practical Considerations: Several population-specific considerations affect how Qdenga is likely to be used in practice. Pregnant and breastfeeding women were excluded from the pivotal TIDES trial, and as a live-attenuated vaccine, Qdenga is generally not recommended during pregnancy pending dedicated safety data, mirroring standard precautions for other live vaccines. Immunocompromised individuals were similarly not systematically studied and require individualised risk-benefit discussion. Travellers from non-endemic countries visiting dengue-endemic regions represent a growing use case increasingly discussed in travel-medicine literature, since — unlike Dengvaxia, which was unsuitable for travellers precisely because most

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would be dengue-naive — Qdenga's screening-free indication makes it a more plausible pre-travel option, albeit with the same caveat about weaker DENV-3/4 protection in this dengue-naive group. Within India, practical rollout considerations include cold-chain maintenance for a live-attenuated product across variable rural infrastructure, the need for trained vaccinators competent in the two-dose, three-month interval schedule, and integration with existing school-health and adolescent immunisation platforms if and when the vaccine is considered for public-programme inclusion.

India's Indigenous Dengue Vaccine Candidates: Dengi All and Dengusiil

Origin and Platform: Distinct from Qdenga, India also has genuinely home-grown dengue vaccine candidates in active clinical development. Both trace their origin to a tetravalent, live-attenuated vaccine strain combination — TV003 and its higher-DENV-2-dose variant TV005 — originally developed by the U.S. National Institutes of Health (NIH), which sub-licensed the technology to several manufacturers worldwide, including three Indian companies. Panacea Biotec has progressed furthest, developing its version under the brand DengiAll and securing a process patent for its formulation work; the Serum Institute of India (SII) is developing a parallel candidate, Dengusiil, and Indian Immunologicals also holds rights to the strain. Controlled human infection model (CHIM) studies of TV005 conducted independently of the Indian programme have shown protective efficacy against experimental DENV-2 and DENV-3 challenge, providing external proof-of-concept support for the underlying platform even before Indian phase 3 data are available.[25]

Clinical Development Status: Panacea Biotec completed Phase 1 and Phase 2 trials of DengiAll in 2018-19 with encouraging immunogenicity and safety results. On 14 August 2024, the Indian Council of Medical Research (ICMR) and Panacea Biotec jointly launched India's first-ever Phase 3 dengue vaccine trial, a multi-centre, double-blind, randomised, placebo-controlled study (CTRI/2024/03/064910) spanning 19 sites across 18 states and union territories and enrolling more than 10,335 healthy adult participants, with two years of planned follow-up; recruitment had passed 7,248 participants by mid-2025. In parallel, the Serum Institute of India has been preparing its own Phase 3 trial of Dengusiil, planned to enrol around 10,000 children aged 2 to under 18, following earlier trials that reported high immunogenicity and no serious safety concerns. Neither DengiAll nor Dengusiil has yet reported phase 3 efficacy data or received regulatory approval anywhere, including India, at the time of this review.

Potential Merits:

- Developed and manufactured domestically, directly supporting India's 'Atmanirbhar Bharat' (self-reliance) objective in vaccine security and reducing long-run dependence on imported or foreign-licensed products.
- Based on the TV003/TV005 platform, for which independent controlled human infection studies have already demonstrated protective efficacy against experimental DENV-2 and DENV-3 challenge, lending biological plausibility ahead of Indian phase 3 results.
- Potential for single-dose administration in some formulations, which — if confirmed in phase 3 — would be programmatically simpler than either Dengvaxia's three-dose or Qdenga's two-dose regimen.
- Large-scale Indian phase 3 trials are specifically designed to generate efficacy and safety data in Indian populations and circulating serotypes, addressing a data gap that neither Dengvaxia nor the initial Qdenga trials fully covered for South Asia.
- Domestic manufacturing capacity (Panacea Biotec, Serum Institute of India, Indian Immunologicals) could ultimately support lower per-dose costs and larger production volumes than an imported vaccine alone.

3.4.4 Current Limitations:

- No phase 3 efficacy data are yet available for either DengiAll or Dengusiil; both remain unlicensed investigational products, and meaningful comparison with Dengvaxia or Qdenga is not yet possible on efficacy grounds.
- Phase 3 follow-up is planned over two years from the August 2024 trial start, meaning licensure — if the trials succeed — realistically remains some years away.
- As with any live-attenuated tetravalent platform, these candidates will need to specifically demonstrate the absence of a Dengvaxia-like enhancement signal in dengue-seronegative recipients before regulators are likely to grant an unrestricted indication.
- Long-term durability of protection, serotype-specific efficacy, and performance across India's genetically diverse circulating DENV strains remain unknown pending trial completion.

3.5 Comparative Summary:

[Table 2] draws together the dosing, indication, efficacy, and regulatory status of Dengvaxia, Qdenga, and India's indigenous candidates side by side, and Figure 3 places the key milestones of all three programmes on a single timeline

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Table 2: Head-to-head comparison of Dengvaxia (CYD-TDV), Qdenga (TAK-003), and India's indigenous TV003/TV005-derived candidates.

Feature	Dengvaxia (CYD-TDV)	Qdenga (TAK-003)	DengiAll / Dengusiil (India)
Schedule	3 doses (0, 6, 12 months)	2 doses, 3 months apart	Under evaluation (potentially single-dose)
Age indication	9-45 yrs (up to 60 in some countries)	4-60 yrs (India)	Adults in Ph.3 (Panacea); children 2-18 planned (SII)
Pre-vaccination screening	Required (seropositive only)	Not required	Not yet determined (pre-licensure)
Efficacy vs symptomatic dengue	~65% pooled (5-yr)	61.2% at 4.5 yrs (TIDES)	No phase 3 efficacy data yet
Efficacy vs hospitalisation	~79% (seropositive-driven)	84.1% at 4.5 yrs	Not yet available
Seronegative safety signal	Increased severe-dengue risk (established)	Weaker DENV-3/4 response in seronegatives (monitored)	Not yet characterised
Regulatory status in India	Not approved / not marketed	Approved 20 Jul 2026 (conditional, post-marketing study required)	Phase 3 trials ongoing; unlicensed
Manufacturing	Sanofi Pasteur (France); discontinued	Takeda + Biological E (India) — up to 50M doses/yr	Panacea Biotec / Serum Institute of India (India)

[Table 3] consolidates the merits and demerits detailed in Sections 3.2.7-3.2.8 and 3.3.5-3.3.6 into a single at-a-glance comparison, which readers may find useful for rapid reference.

Table 3: Merits and demerits of Dengvaxia (CYD-TDV) and Qdenga (TAK-003) at a glance.

	Dengvaxia (CYD-TDV)	Qdenga (TAK-003)
Merits	First proof that a tetravalent dengue vaccine works; strong efficacy in seropositive individuals (~79% vs hospitalisation); generated the key ADE/NS1 science base for later vaccines	Higher, more durable overall efficacy (61.2% at 4.5 yrs); no pre-vaccination screening needed; simpler 2-dose schedule; broad 4-60 yrs Indian indication; local Biological E manufacturing; WHO-prequalified
Demerits	Increased severe-dengue risk in seronegatives; mandatory costly screening; 3-dose/12-month schedule; production discontinued; lasting reputational damage after Philippines crisis	Weaker DENV-3/4 protection in seronegatives; efficacy wanes over time; India approval conditional on post-marketing study; not yet in public immunisation programme; still cold-chain dependent
Bottom line	Proved the concept; no longer a viable choice for new programmes	Best currently available option for India, but requires cautious, transparent rollout and continued surveillance

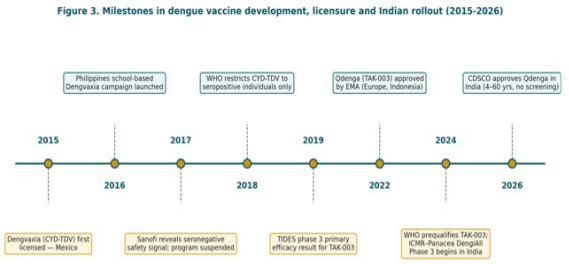

Figure 3: Milestones in dengue vaccine development, licensure, and Indian rollout, 2015-2026.

DISCUSSION

What Actually Changed Between Generations: The clinical distance between Dengvaxia and Qdenga is best understood not as one vaccine simply being 'better' than the other in the abstract, but as a difference in genetic backbone with direct, predictable immunological consequences. Dengvaxia's yellow fever backbone meant the vaccine could not reliably mimic a natural dengue priming infection for all four serotypes at once, leaving seronegative recipients under-protected against three of the four inserted antigens while still carrying some of the immunological risk of a 'first exposure'. Qdenga's live DENV-2 backbone instead uses an actual attenuated dengue virus as its chassis, giving genuinely robust, serostatus-independent protection against DENV-2 specifically, while DENV-1, -3 and -4 protection remains more dependent on the recipient already having some pre-existing dengue immunity — a smaller, more contained version of the same underlying biological challenge, not a complete solution to it. This is why regulators, including CDSCO, have paired Qdenga's more permissive screening-free indication with mandatory post-marketing surveillance rather than an unconditional endorsement.[26]

Programmatic and Cost-Effectiveness Considerations: From a health-systems perspective, the removal of a pre-vaccination screening requirement is arguably Qdenga's single most consequential advance over Dengvaxia, since screening added cost, required reliable point-of-care serological testing, and excluded exactly the dengue-naive children who might otherwise benefit most from protection before their first natural infection. Modelling work on Dengvaxia had already shown that its population-level benefit was highly sensitive to background seroprevalence; similar modelling for Qdenga in moderate-to-high transmission settings suggests vaccination of individuals over roughly age six could reduce dengue-related hospitalisations by an estimated 10-22% over a ten-year horizon — a meaningful but partial reduction that argues for vaccination as one

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layer of a multi-pronged strategy rather than a replacement for vector control.

India-Specific Considerations: India's specific epidemiological and health-systems context shapes how these trade-offs should be read. With hyperendemic co-circulation of multiple DENV serotypes across much of the country, a large proportion of the adult population, and substantial numbers of children, are likely to be dengue-seropositive by the time they would be offered vaccination, a pattern that generally favours both Dengvaxia-type and Qdenga-type vaccines' efficacy profiles. However, the same hyperendemicity also means a non-trivial dengue-naive paediatric population remains exposed to the specific residual DENV-3/4 risk described above, which is precisely why CDSCO's conditional, six-month post-marketing surveillance requirement is a clinically sensible, not merely bureaucratic, safeguard rather than an obstacle to be relaxed.[27]

The Biological E manufacturing partnership is a genuinely distinctive feature of India's Qdenga story relative to most other approving countries: local production at a planned scale of up to 50 million doses annually could, over time, reduce import dependence, improve supply security during outbreak surges, and support regional access across South and Southeast Asia. Whether this translates into public-programme affordability, however, depends on pricing and procurement decisions that had not been finalised at the time of this review; as of the July 2026 approval, Qdenga sits outside India's National Immunization Programme, meaning near-term uptake will be shaped by private-market pricing, out-of-pocket cost, and state-level public health decisions rather than free universal access — an equity consideration that parallels, on a smaller scale, the cost and access debates that shaped Dengvaxia's uneven global rollout a decade earlier.

Risk Communication Lessons from the Dengvaxia Experience: The Philippines crisis offers a directly relevant cautionary template for India's Qdenga introduction, independent of the two vaccines' different risk profiles. Public trust, once damaged by a poorly communicated safety signal, degrades faith in vaccination programmes well beyond the specific product involved, and can take years to rebuild. India's health authorities have so far framed Qdenga's approval carefully — as an addition to, not a replacement for, vector control and clinical care, and subject to structured post-marketing monitoring — which mirrors the transparent, screen-then-vaccinate messaging that WHO ultimately adopted for Dengvaxia, rather than the initially unqualified rollout that preceded the Philippines controversy. Sustaining that careful framing through the mandated six-month surveillance period, and communicating any findings transparently regardless of outcome, will likely matter as much for long-term vaccine confidence in India as the underlying clinical data themselves.[28]

Economic and Health-System Modelling: Cost-effectiveness is ultimately what determines whether a clinically sound vaccine becomes a publicly funded programme. For Dengvaxia, model-comparison studies conducted across multiple independent modelling groups converged on the conclusion that cost-effectiveness — and indeed net population benefit — hinged on baseline seroprevalence at the age of vaccination, with routine vaccination potentially cost-effective, even cost-saving, in high-transmission settings but actively harmful in low-transmission ones, a nuance that was not adequately reflected in some early national rollout decisions. Comparable formal cost-effectiveness modelling for Qdenga in the Indian context is still emerging; mathematical modelling summarised in Section 3.3.4 suggests a 10-22% reduction in hospitalisations over a ten-year horizon in moderate-to-high transmission settings for those vaccinated from around age six, but this has not yet been translated into a formal Indian cost-effectiveness or budget-impact analysis incorporating the Biological E-manufactured dose price, which was not publicly finalised at the time of this review. Given India's size and the heterogeneity of dengue transmission intensity across states, national modelling that accounts for state-level seroprevalence and serotype circulation — rather than a single national average — will likely be necessary before any decision on public-programme inclusion, echoing the state-stratified logic that ultimately shaped global Dengvaxia policy after 2017.

Vaccine Hesitancy, Risk Communication, and the Social Contract: The Dengvaxia experience in the Philippines is frequently cited in vaccine-confidence literature as a case study in how a genuine, mechanistically explicable safety signal can be amplified by poor initial communication, political point-scoring, and media sensationalism into a much broader collapse of trust — one that measurably depressed uptake of unrelated childhood vaccines in the years that followed. The core communication lesson is not that safety signals should be hidden or minimised, but that they should be disclosed early, explained mechanistically in plain language, and paired with a clear, actionable policy response (in Dengvaxia's case, restricting use to seropositive individuals) before speculation fills the vacuum. India's approach to Qdenga so far — a conditional approval explicitly paired with a defined post-marketing surveillance timeline, and public messaging that frames the vaccine as an addition to, not a replacement for, vector control — follows this template reasonably closely. Sustaining it will require Indian health authorities and Takeda/Biological E to commit, in advance, to transparent public reporting of the mandated six-month safety and effectiveness study results, regardless of whether those results are reassuring or concerning, since selective or delayed disclosure is precisely the pattern that eroded confidence in the

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Philippines. Physicians, particularly those in high-throughput outpatient and paediatric settings, are also likely to be the primary point of contact through which patients form their initial impression of the vaccine, making accurate clinician-facing education — covering exactly the serostatus-dependent efficacy nuances detailed in Section 3.3.2-3.3.3 — a practical priority alongside any formal public communication campaign.[29]

Integration with Non-Vaccine Prevention Strategies: None of the evidence reviewed here supports vaccination as a substitute for existing dengue-control measures. Source reduction, larviciding, indoor residual spraying, and emerging biological approaches such as Wolbachia-mediated population replacement continues to address transmission at the vector level, independent of any individual's vaccination or serostatus, and remain the only interventions capable of reducing transmission intensity itself rather than merely individual disease risk.30 Early clinical recognition of warning signs (persistent vomiting, abdominal pain, mucosal bleeding, lethargy, and rising haematocrit with falling platelet count) and appropriate fluid-management protocols remain the primary determinant of survival once symptomatic dengue occurs, vaccinated or not.[31,32] The most defensible reading of the current evidence is that Qdenga, deployed thoughtfully alongside these existing measures and honest about its serotype-specific limitations, can meaningfully reduce — but will not eliminate — India's dengue burden.

Future Directions: Beyond the two licensed vaccines, the broader dengue vaccine pipeline includes inactivated (purified inactivated virus, DPIV), recombinant subunit (V180), DNA (TVDV), and early-stage mRNA candidates, none of which have yet reached late-phase efficacy data. Purified inactivated virus vaccines, in particular, are of interest because — unlike every live-attenuated candidate discussed in this review — they cannot replicate in the recipient and therefore cannot, even in principle, act as a 'silent infection' capable of ADE-related priming, though they typically require adjuvants and multi-dose schedules to achieve comparable immunogenicity, and none has yet been tested at the scale of CYD-TDV or TAK-003. Subunit and nucleic-acid (DNA/mRNA) platforms remain earlier in development but share this theoretical safety advantage, and the rapid mRNA-platform advances driven by the COVID-19 pandemic have renewed research interest in applying similar approaches to tetravalent dengue antigen design.

India's own DengiAll and Dengusiil programmes represent the most immediately consequential near-term addition to this pipeline for the Indian context; their phase 3 read-outs, expected over the next one to two years given trials initiated in mid-2024, will determine whether India ultimately has a genuinely indigenous, potentially single-dose alternative or complement to Qdenga. Continued use of controlled human infection models, as already applied to TV005, may help accelerate down-selection of future candidates without waiting for full-scale field efficacy trials. Whatever the outcome, the consensus across the reviewed literature is that no single vaccine — old or new — is likely to substitute entirely for sustained investment in vector control, diagnostics, clinical case management, and surveillance.

Limitations of This Review: Several limitations should be noted. First, this review synthesises published trial data, regulatory communications, and press reporting rather than accessing primary trial datasets, and therefore inherits any reporting limitations of the underlying sources. Second, India's Qdenga approval occurred only two days before this review was finalised (20 July 2026), so India-specific real-world effectiveness and safety data do not yet exist and could not be included; conclusions about its Indian performance are necessarily provisional pending the mandated post-marketing study. Third, DengiAll and Dengusiil remain investigational, with no efficacy data available at any follow-up point, limiting this review's comparative assessment of these candidates to platform biology, trial design, and developmental status rather than outcomes. Fourth, cross-trial comparisons between Dengvaxia's CYD14/CYD15 programme and Qdenga's TIDES programme, though presented side by side in Table 2 and Figure 2 for clarity, were not derived from a single head-to-head randomised trial; differences in study populations, circulating serotypes, background seroprevalence, and follow-up duration mean the reported efficacy gap should be interpreted as indicative rather than a precise, confounder-free estimate of one vaccine's superiority over the other. Finally, as a narrative rather than quantitative meta-analytic synthesis, this review does not provide pooled effect estimates or a formal GRADE certainty rating, and should be read as a structured qualitative comparison rather than a formal statistical evidence synthesis.

CONCLUSION

Dengue vaccination has moved, within a single decade, from a single, safety-constrained product usable only in a screened, seropositive subset of the population, to a second-generation vaccine authorised for broad, screening-free use and now locally manufactured in India. Dengvaxia's legacy is double-edged: it proved dengue vaccination was scientifically achievable and generated the mechanistic and immunological insight that shaped everything that followed, but its seronegative safety signal and the resulting Philippines crisis left lasting scars on vaccine confidence and ultimately ended its commercial life. Qdenga represents genuine, evidence-based progress — higher and more durable efficacy, a simpler dosing schedule, and no

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mandatory pre-vaccination screening — but it is not a risk-free or complete solution; its comparatively weaker DENV-3/4 protection in dengue-naive individuals, waning efficacy over time, and India's own conditional, surveillance-linked approval all argue for continued caution, transparent post-marketing monitoring, and integration with, rather than replacement of, existing vector-control and clinical-care infrastructure.33,34 India's own indigenous candidates, DengiAll and Dengusiil, remain the programme to watch over the next few years: if their ongoing phase 3 trials succeed, they could offer India a genuinely home-grown, potentially more affordable addition to its dengue-control armamentarium, completing a journey from complete reliance on imported vaccines to a plausible, if not yet realised, position of vaccine self-sufficiency against one of the country's most significant infectious disease threats.[35,36]

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