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Systematic Review

Efficacy and Safety of Tetravalent Dengue Vaccines in Children and Adolescents: A Systematic Review of Phase 3 Randomized Controlled Trials

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ABSTRACT

Background: Dengue is a major mosquito-borne disease in tropical countries, including Indonesia. Tetravalent dengue vaccines have been tested in large phase 3 randomized controlled trials (RCTs). This systematic review summarizes their efficacy and safety in children and adolescents.

Methods: Peer-reviewed phase 3 placebo-controlled RCTs of tetravalent dengue vaccines in children and adolescents, reporting virologically confirmed dengue, were eligible. Data were extracted and synthesized without meta-analysis, following the SWiM reporting guideline, with qualitative risk-of-bias appraisal using RoB 2 domains. Tables summarize eligibility (Table 1), trial characteristics (Table 2), serotype-specific efficacy (Table 3), TIDES follow-up (Table 4), and key findings (Table 5).

Findings: Three RCTs (CYD14, CYD15, TIDES; 51,243 randomized participants) were included. Vaccine efficacy against virologically confirmed dengue was 56.5% (95% CI 43.8–66.4) in CYD14, 60.8% (95% CI 52.0–68.0) in CYD15, and 80.2% (95% CI 73.3–85.3) in TIDES. Efficacy against hospitalized dengue was 80.3% in CYD15 and 95.4% (95% CI 88.4–98.2) in TIDES. Efficacy varied by serotype in CYD15. In published follow-up of TIDES, efficacy against symptomatic dengue was 61.2% at 54 months. Serious adverse events were similar between vaccine and placebo groups were reported.

Conclusion: Tetravalent dengue vaccines reduce symptomatic and hospitalized dengue in children and adolescents in endemic settings, with efficacy varying by vaccine, serotype, and population.

INTRODUCTION

Dengue is a mosquito-borne viral disease caused by four serotypes and is endemic in many tropical countries, including Indonesia. Clinical illness ranges from mild febrile disease to severe dengue requiring hospitalization. Prevention relies on vector control and, more recently, vaccination.

A dengue vaccine must protect against all four serotypes, which makes trial design and interpretation more complex than for many other vaccines. Three large phase 3 randomized controlled trials (RCTs) of tetravalent dengue

vaccines have been published: CYD14 in children in five Asia-Pacific countries [1], CYD15 in children and adolescents in Latin America [2], and TIDES, which evaluated the TAK-003 vaccine in children and adolescents [3].

The vaccines, schedules, age groups, regions, and follow-up periods differ across these trials, so results cannot be compared simply by reading individual abstracts. A structured synthesis can clarify what is known about efficacy against symptomatic, severe, and hospitalized dengue and about safety.

This systematic review aims to summarize the efficacy and safety of tetravalent dengue vaccines versus placebo in children and adolescents, and to describe how the evidence differs across trials.

METHODS

1. Design

This systematic review of RCTs was planned using the PICO framework. No protocol was prospectively registered. Results were synthesized without meta-analysis, following the principles of the SWiM reporting guideline [4].

2. Eligibility Criteria

Eligibility criteria are summarized in Table 1. Only phase 3 RCTs published in peer-reviewed journals were eligible. Follow-up reports of an eligible trial were used to describe extended follow-up but did not count as separate trials.

Table 1. Eligibility Criteria (PICO)

Element	Criterion
Population	Healthy children and adolescents
Intervention	Tetravalent dengue vaccine
Comparator	Placebo
Outcomes	Virologically confirmed dengue; severe and hospitalized dengue; adverse events
Design	Phase 3 randomized controlled trial in a peer-reviewed journal

3. Information Sources and Search

Peer-reviewed literature indexed in PubMed was searched in November 2026 through a web search interface, using the terms “dengue vaccine,” “tetravalent,” “efficacy,” and “randomized trial.” Institutional repository records and publisher abstracts were used to verify the content of each trial report.

4. Study Selection

Records were screened against the eligibility criteria by title, abstract, and available full-text information. Selection was performed by a single reviewer.

5. Data Items

Sample size, age range, vaccine, schedule, follow-up, vaccine efficacy with 95% confidence intervals, serotype-specific efficacy, efficacy against hospitalized and severe dengue, and safety findings were extracted. Where a trial reported a confidence interval other than 95%, this was noted.

6. Risk-of-Bias Appraisal

Risk of bias was appraised qualitatively using the domains of the RoB 2 tool [5] (randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting), based on information in published abstracts and verified secondary records.

7. Synthesis

Because vaccines, age groups, schedules, and follow-up differed, a pooled estimate was not calculated. Trials were grouped by vaccine and region, efficacy estimates are reported as provided by each trial, and findings are tabulated and described narratively.

RESULTS

1. Study Selection

The search identified three primary phase 3 trial reports that met the eligibility criteria [1–3], with 51,243 randomized participants in total. Two further reports described extended follow-up of the TIDES trial [6][7]; they were used only to describe duration of protection.

2. Characteristics of Included Trials

The trials enrolled children and adolescents aged 2 to 16 years across Asia-Pacific and Latin American countries (Table 2). CYD14 and CYD15 evaluated a three-dose

schedule at months 0, 6, and 12, whereas TIDES evaluated a two-dose schedule given 3 months apart. All three trials randomized participants to vaccine or placebo, with vaccine-to-placebo allocation of 2:1 in CYD14 and TIDES.

Table 2. Characteristics of Included Trials

Trial	Design and population
CYD14 [1]	10,275 children aged 2–14 years in five Asia-Pacific countries; vaccine (n = 6,851) vs placebo (n = 3,424); three doses at months 0, 6, 12; follow-up to month 25
CYD15 [2]	20,869 children aged 9–16 years in five Latin American countries; three doses at months 0, 6, 12; follow-up 25 months
TIDES [3]	20,099 children and adolescents aged 4–16 years; TAK-003 two doses 3 months apart; 2:1 allocation

3. Efficacy against Symptomatic Dengue

3.1 CYD14

In CYD14, virologically confirmed dengue occurred more than 28 days after the third injection in 117 vaccine recipients and 133 placebo recipients, giving vaccine efficacy of 56.5% (95% CI 43.8–66.4) [1].

3.2 CYD15

In CYD15, per-protocol vaccine efficacy against symptomatic virologically confirmed dengue was 60.8% (95% CI 52.0–68.0), and intention-to-treat efficacy was 64.7% (95% CI 58.7–69.8) [2].

3.3 TIDES

In TIDES, per-protocol vaccine efficacy at 12 months after the second dose was 80.2% (95% CI 73.3–85.3). Efficacy among participants seronegative at baseline was 74.9% [3].

4. Serotype-Specific Efficacy

Serotype-specific results were available from CYD15 in the abstract-level records reviewed (Table 3). Efficacy was lowest for serotype 2 and highest for serotype 4 [2].

Table 3. Serotype-Specific Efficacy in CYD15

Serotype	Vaccine efficacy
Serotype 1	50.3%
Serotype 2	42.3%
Serotype 3	74.0%
Serotype 4	77.7%

5. Severe and Hospitalized Dengue

In CYD15, 1 of 12 severe dengue cases occurred in the vaccine group (intention-to-treat efficacy 95.5%), and efficacy against hospitalization for dengue was 80.3% [2]. In TIDES, efficacy against hospitalized dengue was 95.4% (95% CI 88.4–98.2), with 5 hospitalizations in the vaccine group and 53 in the placebo group [3].

6. Extended Follow-Up of TIDES

Follow-up reports of TIDES, as summarized in a manufacturer fact sheet that lists their citations [6][7], described efficacy against symptomatic dengue of 61.2% (95% CI 56.0–65.8) at 54 months, and efficacy against hospitalized dengue of 90.4% (95% CI 82.6–94.7) at 18 months and 84.1% (95% CI 77.8–88.6) at 54 months (Table 4). These figures should be confirmed against the original articles.

Table 4. Extended Follow-Up of TIDES

Outcome and time point	Efficacy (95% CI)
Symptomatic dengue, 12 months [3]	80.2% (73.3–85.3)
Symptomatic dengue, 54 months [7]	61.2% (56.0–65.8)
Hospitalized dengue, 18 months [6]	90.4% (82.6–94.7)
Hospitalized dengue, 54 months [7]	84.1% (77.8–88.6)

7. Safety

In CYD14, 402 serious adverse events were reported in the vaccine group and 245 in the control group, in the context of 2:1 allocation [1]. In CYD15, adverse event rates were similar to placebo [2]. In TIDES, serious adverse events occurred in 3.1% of the vaccine group and 3.8% of the placebo group [3]. The manufacturer fact sheet for TIDES follow-up reported no evidence of disease enhancement and listed injection-site pain, headache, myalgia, injection-site erythema,

malaise, asthenia, and fever as the most frequent reactions [7].

Table 5. Key Efficacy and Safety Findings

Trial	Main findings
CYD14 [1]	Efficacy 56.5% (43.8–66.4). SAEs: 402 vaccine, 245 control (2:1 allocation)
CYD15 [2]	Efficacy 60.8% (52.0–68.0); hospitalization 80.3%. AE rates similar to placebo
TIDES [3]	Efficacy 80.2% (73.3–85.3); hospitalized dengue 95.4% (88.4–98.2). SAEs 3.1% vs 3.8%

8. Risk-of-Bias Appraisal

All three trials were randomized, placebo-controlled phase 3 studies published in peer-reviewed journals, and CYD14 was observer-masked. No major concerns about randomization or selective reporting were evident from the information reviewed. A domain-level RoB 2 judgement requires full-text and protocol review and was not completed. The efficacy estimates are not directly comparable because of differences in vaccine, schedule, and analysis population.

DISCUSSIONS

1. Summary of Evidence

Across three phase 3 RCTs including 51,243 participants, tetravalent dengue vaccines reduced virologically confirmed dengue, with efficacy ranging from 56.5% to 80.2%, and showed higher efficacy against hospitalized dengue (80.3% in CYD15 and 95.4% in TIDES) [1–3].

2. Variation in Efficacy across Trials

The trials used different vaccines, schedules, age ranges, regions, and analysis populations, so their point estimates should not be compared directly. Efficacy against symptomatic dengue was lower in the two CYD trials than in TIDES, but differences in design and the circulating serotypes during follow-up could contribute to this, and the records reviewed do not allow the reasons to be determined.

3. Severity and Hospitalization

Efficacy against hospitalized dengue was consistently higher than efficacy against symptomatic dengue [2][3]. From a public health perspective, reducing hospitalization is clinically important, although the number of severe cases was small, and estimates for severe dengue are correspondingly imprecise.

4. Serotype and Baseline Immunity

In CYD15, efficacy differed by serotype (42.3% for serotype 2 to 77.7% for serotype 4) [2]. Baseline immunity is also relevant: in CYD15, 79.4% of the immunogenicity subgroup was seropositive at baseline [2], and TIDES reported separate efficacy among baseline-seronegative participants (74.9%) [3]. Local serotype distribution and population immunity therefore matter when interpreting these results for a given country.

5. Duration of Protection

The extended follow-up of TIDES suggests that efficacy against symptomatic dengue declined from 80.2% at 12 months to 61.2% at 54 months, whereas efficacy against hospitalized dengue remained high (84.1% at 54 months) [3][7]. These figures come from a manufacturer-prepared summary and need confirmation from the original reports.

6. Safety

Serious adverse events were similar between groups where comparative data were available [2][3]. The abstract-level records reviewed did not allow independent assessment of long-term safety, which is particularly important for dengue vaccines and requires longer follow-up and surveillance.

7. Implications for Practice and Research

Dengue is endemic in Indonesia, but the trials reviewed here did not report Indonesia-specific results in the records examined, so conclusions for Indonesian children should be drawn cautiously. Decisions about vaccine use should follow national guidance and consider

local serotype distribution and baseline seroprevalence. Future research should include direct comparisons, long-term follow-up, and results stratified by baseline immunity.

8. Limitations

Several limitations should be acknowledged. Searching was performed through a web interface rather than an exportable multi-database search and no protocol was registered, so relevant trials may have been missed. Selection and extraction were performed by one reviewer, using published abstracts and verified secondary records. Only three trials were included, a formal RoB 2 assessment was not completed, no pooled estimate was computed, and only two vaccines were represented. Extended follow-up figures were taken from a manufacturer fact sheet. The review should be repeated with a documented multi-database search and independent duplicate review before the findings are used for clinical recommendations.

CONCLUSIONS

Tetravalent dengue vaccines reduce symptomatic and hospitalized dengue in children and adolescents in endemic settings, with efficacy varying by vaccine, serotype, and population. Serious adverse events were similar to placebo in the trials reviewed.

Future work should include a pre-registered, multi-database systematic review with meta-analysis, formal risk-of-bias assessment, long-term follow-up, and evidence stratified by baseline dengue immunity, including data from Indonesia.

Author Contribution Statement

The author performed all aspects of this study.

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