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Tinjauan Pustaka

Efektivitas Vaksin Dengue TAK-003 dalam Mencegah Infeksi Dengue pada Anak: Sebuah Tinjauan Sistematis

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Abstrak

Pendahuluan: Demam dengue masih menjadi masalah kesehatan global yang penting, terutama di kalangan anak-anak. Mengembangkan vaksinasi yang efektif dan aman terhadap keempat serotipe virus dengue masih menjadi tantangan. TAK-003 adalah kandidat vaksinasi tetravalen berbasis virus DENV-2 hidup yang dilemahkan dengan efikasi tinggi dan profil keamanan yang baik.
Metode: Tinjauan sistematis ini dilakukan menggunakan pedoman PRISMA 2020 dan penelusuran literatur di basis data PubMed, Scopus, dan Wiley hingga 15 Oktober 2025. Uji klinis dan studi observasional yang mengevaluasi efikasi dan keamanan TAK-003 pada anak-anak termasuk dalam kriteria inklusi. Risiko bias dinilai menggunakan ROB 2.0 dan Skala Newcastle-Ottawa.
Pembahasan: Dari 132 artikel yang dievaluasi, empat studi unik (2 RCT, 1 studi single arm, dan 1 uji case-kontrol) memenuhi kriteria inklusi. Sebuah uji klinis fase III (NCT02747927) yang melibatkan 20.099 anak berusia 4 hingga 16 tahun menemukan efektivitas vaksinasi secara keseluruhan sebesar 73,3% terhadap demam berdarah simptomatik, dengan perlindungan terkuat terhadap DENV-2 (95,1%) dan DENV-1 (69,8%). Hasil tindak lanjut hingga 4,5 tahun setelah vaksinasi menunjukkan efikasi jangka panjang yang berkelanjutan, termasuk perlindungan pada orang yang seronegatif terhadap DENV-1 dan DENV-2.
Simpulan: TAK-003 terbukti aman, imunogenik, dan efektif dalam mencegah demam berdarah simptomatik dan berat pada anak-anak dan remaja yang tinggal di negara-negara endemis maupun non-endemis. Vaksin ini memiliki potensi luar biasa sebagai strategi pencegahan demam berdarah global, sementara perlindungan terhadap DENV-3 dan DENV-4 masih perlu ditingkatkan.

Kata Kunci: anak-anak, efikasi, keamanan, TAK-003**,** vaksin dengue

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Effectiveness of the TAK-003 Dengue Vaccine in Preventing Dengue Infection in Children: A Systematic Review

Abstract

***Introduction**: Dengue fever remains an important global health issue, particularly among children. Developing an effective and safe vaccination against all four dengue virus serotypes is still a challenge. TAK-003 is a tetravalent vaccine candidate based on a live attenuated DENV-2 virus with great efficacy and a favorable safety profile.*

***Method**: This systematic review was conducted using the PRISMA 2020 guidelines and a literature search of the PubMed, Scopus, and Wiley databases until October 15, 2025. Clinical trials and observational studies evaluating TAK-003's efficacy and safety in children were among the inclusion criteria. The risk of bias was assessed using ROB 2.0 and the Newcastle-Ottawa Scale.*

***Discussion**: Out of 132 publications evaluated, four unique studies (2 RCTs, 1 single-arm study, and 1 case-control trial) fulfilled the inclusion criteria. A phase III clinical trial (NCT02747927) of 20,099 children aged 4 to 16 years found an overall vaccination effectiveness of 73.3% against symptomatic dengue, with the strongest protection against DENV-2 (95.1%) and DENV-1 (69.8%). Follow-up results for up to 4.5 years after vaccination showed continuous long-term efficacy, including protection in people seronegative for DENV-1 and DENV-2.*

***Conclusion**: TAK-003 has been found to be safe, immunogenic, and effective in avoiding symptomatic and severe dengue in children and adolescents living in both endemic and non-endemic countries. This vaccine has tremendous potential as a global dengue preventive strategy, while protection against DENV-3 and DENV-4 need further improvement.*

***Keywords:** children, dengue vaccine, efficacy, safety, TAK-003*

1. INTRODUCTION

Dengue fever remains a global public health threat, especially among children and adolescents. It has been the most prevalent infectious disease in the past 13 years.[1] The world experienced the highest increase in dengue cases in 2023, occurring in more than 80 countries.[2] The United Nations International Children's Emergency Fund (UNICEF) reports that one in five children suffers from dengue fever, and one in six deaths occurs in Bangladesh.[3] Children are at higher risk of developing severe dengue fever, which can progress

to Dengue Shock Syndrome (DSS) and may result in death.[4]

Dengue vaccine discovery and research has been an extensive and complex endeavor, with a variety of approaches. One notable achievement in recent years was the launch of the first licensed dengue vaccine, Dengvaxia. This vaccine has been approved in several dengue-endemic countries and has demonstrated high efficacy in preventing dengue transmission. However, its use is limited due to the risk to children who have not previously been infected with dengue.[5] Although initial infection provides protective immunity for a period of time against the infecting serotype, secondary infection with a different serotype increases the risk of more severe disease.[5] This presents a challenge in dengue vaccine development. Ideally, a vaccine should protect against all four serotypes. Not all vaccine candidates achieve the same level of protection against all four serotypes.[6]

A vaccine that protects against all dengue serotypes while limiting potential side effects is required. TAK-003 is a new tetravalent dengue vaccine candidate because it is based on a live, attenuated DENV-2 virus, which serves as the genetic underpinning for all four viruses in the vaccine.[7] To the authors' knowledge, no studies have comprehensively reviewed the effectiveness and safety of the TAK-003 vaccine, particularly in pediatric and adolescent populations. Therefore, this systematic review aims to comprehensively assess clinical trials of the TAK-003 vaccine in preventing dengue fever in children.

2. METHOD

Information Sources and Search Strategy

This systematic review was prepared based on the PRISMA 2020 guidelines.[8] The study was registered in the International Prospective Register of Systematic Reviews (CRD420251171632). We searched PubMed, Scopus, and Wiley databases until October 15, 2025, using the following search terms: "Dengue OR Dengue Fever", "TAK-003 OR Tetravalent Dengue Vaccine", and "Child OR Pediatric OR Adolescent". We limited the literature search to English-language studies.

Eligibility Criteria

The review question and eligibility criteria were defined according to the PICO framework: Population (pediatric individuals aged ≤18 years), Intervention (TAK-003 dengue vaccine), Comparison (placebo or no vaccination), and Outcomes (efficacy, immunogenicity, and safety,

including virologically confirmed dengue and adverse events).

Inclusion And Exclusion Criteria

Following a literature search, studies were screened based on the following inclusion criteria: (1) studies assessing the effectiveness of the TAK-003 vaccine in pediatric populations (defined as individuals aged ≤18 years), (2) observational study design (cohort, case-control, or cross-sectional), (3) ongoing clinical trials, and (4) assessment of vaccine effectiveness and side effects. Exclusion criteria were then determined, including (1) inaccessible full-text articles and (2) inappropriate study designs.

When multiple published articles reported data from the same clinical trial, they were treated as a single study, and the most complete or most recent report was used as the primary data source. Previous or additional publications were reviewed for additional details on methods, subgroup analyses, or long-term outcomes. The literature search procedure is detailed in figure 1.

Data Extraction and Quality Assessment

Duplicate articles were removed before initial screening using Rayyan software. Title and abstract screening was then performed based on inclusion and exclusion criteria. Disagreements between reviewers were then further discussed until consensus was reached. We then extracted data from the articles obtained after screening. Data extraction included author, year of publication (including primary and supplementary publications), study design, location, study objectives, and outcomes.

Articles were also quality assessed using the Cochrane Risk of Bias Tool for Randomized Trials (ROB 2.0) for randomized controlled trials and the Newcastle–Ottawa Scale (NOS) for observational studies. Quality assessment was independently performed by two reviewers (M.L. and R.H.N.I). Discrepancies were resolved by discussion and unresolved disagreements were adjudicated by a third reviewer (S.W.E.N.).

3. RESULTS AND DISCUSSION

Search Results and Study Selection

The literature search yielded 132 articles, with 45 articles from PubMed, 63 articles from Scopus, and 24 articles from Wiley. After removing duplicates, title and abstract screening identified 13 full-text articles for eligibility, with 12 meeting the inclusion criteria. Several published articles reported outcomes from the same clinical trial (DEN-301, ClinicalTrials.gov ID

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NCT02747927); therefore, these publications were treated as a single study in the synthesis. Ultimately, 4 unique studies consisting of 2 RCTs, 1 single-arm trial, and 1 case-control study were included in the systematic review (Figure 1).

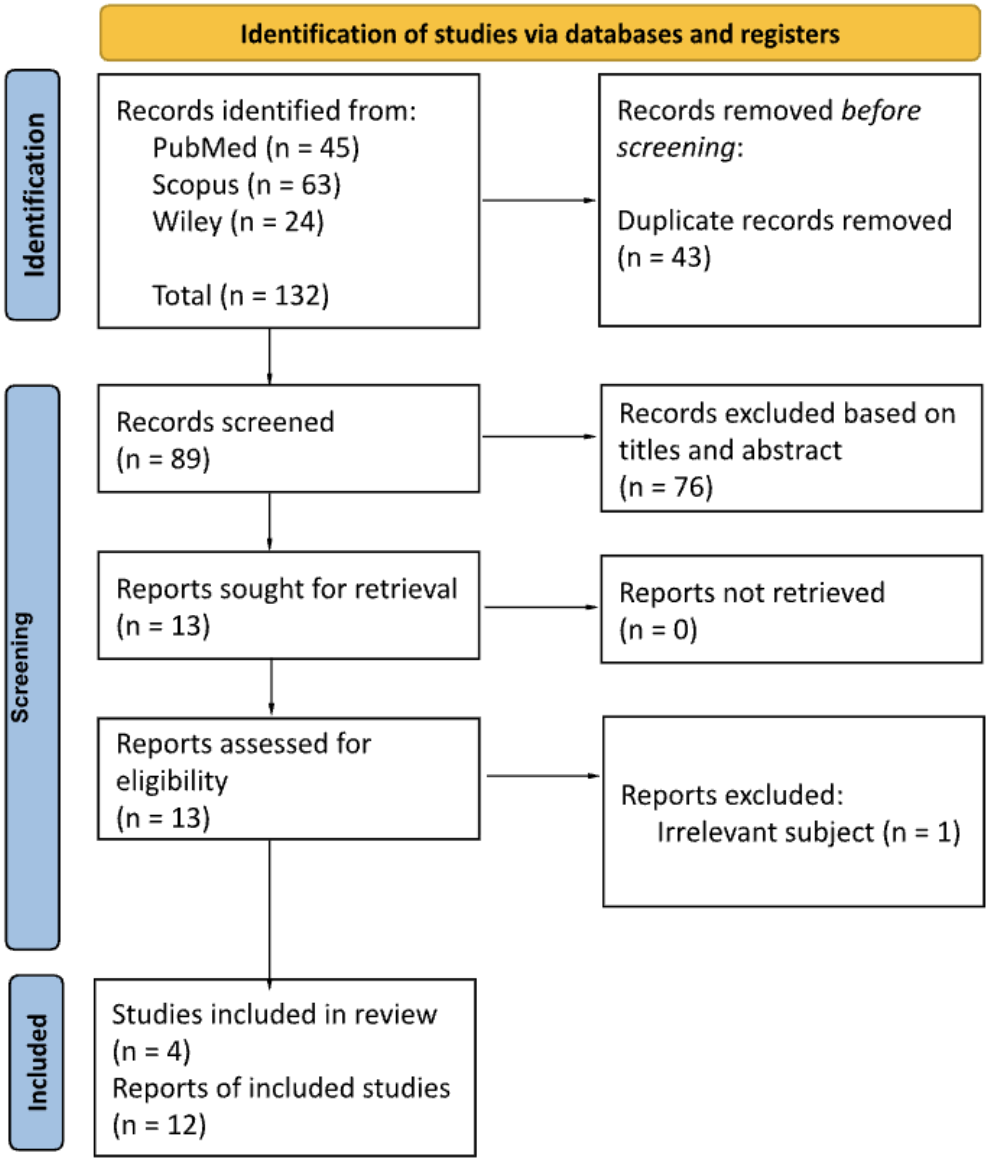

Figure 1. Diagram Flow of Searching Strategies

Study Characteristics

Study characteristics are presented in Table 1. Biswal et al. conducted a phase III randomized, double-blind, placebo-controlled trial across 26 sites in eight dengue-endemic countries, enrolling ~29,000 children and adolescents aged 4–16 years randomized (2:1) to

receive two doses of TAK-003 or placebo at a 3-month interval. The study evaluated efficacy, safety, and immunogenicity against virologically confirmed dengue using serotype-specific RT-PCR. A total of 19,021 participants (94.8%) completed both doses and were included in the per-protocol analysis. The cohort was geographically balanced between Asia-Pacific (46.5%) and Latin America (53.5%), with a mean age of 9.6 years; 27.7% were seronegative at baseline.

A phase III randomized, double-blind, placebo-controlled trial in Mexico City evaluated TAK-003 in 400 healthy adolescents aged 12–17 years randomized (3:1) to receive two doses of vaccine or placebo at a 3-month interval. The vaccine (0.5 mL, subcutaneous) contained live attenuated TDV-1 to TDV-4, while placebo was saline. Completion rates were high in both vaccine (98.7%) and placebo (95.0%) groups. The primary endpoint was immunogenicity assessed by microneutralization assay (MNT50) against four dengue serotypes at months 4 and 9, with safety (post-immunization adverse events) as a secondary outcome.

Ranzani et al. (2025)[9] conducted an observational study using a test-negative, case-control design. The study aimed to assess the efficacy of the TAK-003 dengue vaccination for adolescents aged 10-14 years during the 2024 outbreak in São Paulo, Brazil. The analysis contained 92,621 test findings (NS1 antigen or RT-PCR) from 91,852 individuals, with 43,873 dengue-positive cases and 48,748 negative controls. The average age of participants was 12 years, with 56% being male and around 2% having chronic comorbidities. The majority of the sample comes from the metropolitan area of São Paulo.

Sanja et al. conducted an open-label phase II trial in Panama and the Philippines to evaluate long-term T-cell responses and safety of TAK-003 in healthy children and adolescents in dengue-endemic settings. A total of 200 participants (aged 4–16 years in Panama and 4–8 years in the Philippines) were enrolled, with 56% seropositive at baseline. All participants received two subcutaneous doses (0.5 mL) on days 1 and 90 and were followed for up to three years post-vaccination.

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Tabel 1. Study Characteristics

Author (Year)		Study Design	Location	Subject Purpose		Outcomes
Study ID	**additional sources**					
Trial ID: DEN-301 (NCT02747927)	Biswal et al., 2019 [7]	**RCT**	**Latin America - Asia Pacific**	Assessing vaccine efficacy in 26 dengue-endemic areas: Brazil (4), Colombia (4), the Dominican Republic (2), Nicaragua (1), Panama (4), the Philippines (4), Sri Lanka (4), and Thailand (3). 20.099 children with age 4 – 16 years (13.401 in TAK-003 & 6698 in placebo).	Phase 1	TAK-003 was efficacious against symptomatic dengue in countries in which the disease is endemic.
	Tricou et al., 2020 [10]				Phase 2	TAK-003 induced an antibody response against all four dengue virus serotypes, which persisted for up to 48 months after vaccination. No risk of serious adverse events was observed, and there was a trend toward a reduced long-term risk of symptomatic dengue disease in vaccinated individuals.
	Biswal et al., 2020 [11]				Phase 3	TAK-003 demonstrated good tolerability and effectiveness in preventing symptomatic dengue fever in children. However, vaccine efficacy varied across serotypes, requiring further follow-up to assess long-term performance.
	Biswal et al., 2021 [12]		**Mexico**	Assessing vaccine efficacy in non-endemic dengue areas	Phase 3 in non-endemic area	TAK-003 was immunogenic against all four serotypes and was well tolerated in dengue-naïve adolescents living in Mexico City.

		(Mexico). 400 children with age 12 – 17 years (300 in TAK-003 & 100 placebo).		
Saez-Llorenz et. al (2023) [13]	**Latin America - Asia Pasific**	20.067 participants (13.380 in the TAK-003 group and 6.687 in the placebo group).	Sequential Episodes of Symptomatic Dengue	TAK-003 vaccination resulted in a reduced risk of experiencing sequential episodes of symptomatic dengue in children and adolescents age 4 to 16years in dengue-endemic areas.
Tricou et al., 2024 [14]			Long term Efficacy	TAK-003 showed sustained long-term efficacy in preventing symptomatic dengue caused by all four DENV serotypes.
Sirivichayakul et al., 2024 [15]			previous vaccination JE & YF	TAK-003 was well-tolerated in children with previous JE or YF vaccination.
Borja-Tabora et al., 2025 [16]			Immunogenicity analysis by age group	Analysis shows that TAK-003 is effective in preventing dengue fever across various age groups of children and adolescents aged 4–16 years living in dengue-endemic areas.

	El Hindi et al. (2025) [17]	**RCT**	**Latin America - Asia Pasific**	3765 participants (2518 in TAK-003 Group and 1247 in Placebo Group)	Efficacy Against Asymptomatic Dengue Infection	TAK-003 had a modest impact on asymptomatic dengue infections in the first months postvaccination, mainly in participants with baseline seropositivity.
Fernando et.al. (2024)[18]		**RCT**	**Sri Lanka**	2.100 participants (703 in placebo group and 1.397 in TAK-003 group)	TAK-003 has the potential of meaningful utility in dengue outbreaks in endemic areas.	
Sanja et. al. (2024)[19]		**RCT**	**Panama & Philippines**	200 participants (100 in Panama and 200 in the Philippines)	TAK-003-elicited CD4 and CD8T cells were multifunctional and persisted up to 3 years post-vaccination.	
Ranzani et al. (2025)[9]		**Case Control**	**Brazil**	children age 10-14 years 92.621 participants (43.873 Case and 48.748 Control)	TAK-003 demonstrated effectiveness in preventing symptomatic dengue and dengue-related hospitalizations among adolescents during a large outbreak predominantly caused by dengue virus serotypes 1 and 2.	

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Risk Of Bias And Certainty Of Evidence

The risk of bias assessment is summarized in Figure 2. Based on the Cochrane Risk of Bias (RoB 2.0) tool, all included randomized controlled trials were judged to have a low risk of bias across all domains, including bias arising from the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of outcomes (D4), and selection of reported results (D5). Consequently, the overall risk of bias for all studies was rated as low. No concerns were identified in any individual domain, indicating a consistently high methodological quality across the included trials.

Similarly, observational studies assessed using the Newcastle–Ottawa Scale demonstrated high methodological quality, with most studies achieving high scores across selection, comparability, and outcome domains. Overall, all studies had a low risk of bias.

Figure 2. Risk of Bias Assessment Graph

Table 2. Risk of Bias Case Control Study Included

Study	Selection				Comparability	Outcome		Risk of Bias
	1	2	3	4	5	6	7	
Ranzani (2025)	*	-	*	*	**	*	*	Low risk

1) Is the case definition adequate?,
2) Representativeness of the cases,
3) Selection of controls,
4) Definition of controls,
5) Comparability of cases and controls on the basis of the design or analysis controlled for confounders,
6) Assessment of exposure,
7) Same method of ascertainment for cases and controls
8) Non-response rate.

Vaccine Efficacy in Phases I and II

The TAK-003 vaccine study in pediatric populations was initiated by the DEN-301 clinical trial, registered number NCT02747927, which has been running since 2016. The study, which recruited 20,099 participants, was conducted in children aged 4–16 years in dengue-endemic areas across 26 regions in Latin America and the Asia-Pacific.[7] A 2019 phase 1 report described an overall vaccine efficacy of 80% against virologically confirmed dengue in the first phase of the clinical trial. Recruitment of participants in multiple regions across eight countries enabled the detection of dengue cases caused by all four dengue virus serotypes during part 1 of the trial.[7]

Meanwhile, a 2020 phase 2 report by Tricou et al. stated that TAK-003 was proven safe and capable of eliciting antibodies against all four dengue serotypes that persisted for up to 48 months, as well as reducing the risk of symptomatic dengue in the long term.[10] These phase 2 findings provide baseline data on long-term safety and support vaccine evaluation in ongoing phase 3 efficacy trials.[10]

Phase III Findings in Endemic and Non-Endemic Areas

Biswal et al. (2020) conducted a phase III study on 20,009 healthy children aged 4-16 years in eight endemic countries in Asia and Latin America and found considerable efficacy against symptomatic dengue infection.[11] In an 18-month post-vaccination analysis, overall efficacy against virologically confirmed dengue

reached 73.3% (95% confidence interval 66.5%-78.8%), with efficacy staying high in both seropositive (76.1%) and seronegative (66.2%) children prior to immunization. The maximum efficacy was achieved against DENV-2 (95.1%) and DENV-1 (69.8%) serotypes, but protection against DENV-3 (48.9%) and DENV-4 (51.0%) was less consistent.[12] These findings suggest that TAK-003 can provide significant protection against numerous dengue serotypes, even in groups of children who have never been exposed to the virus before.

TAK-003 demonstrated high efficacy in reducing severe dengue and dengue-related hospitalizations, with 90.4% efficacy against hospitalization (95% CI 31.9%–97.1%). Rates of serious adverse events were comparable between vaccine and placebo groups (4.0% vs 4.8%), with no vaccine-related events reported. These findings support a favorable safety and efficacy profile in pediatric populations, irrespective of baseline serostatus. Consistently, a phase III trial in Sri Lanka reported 94.7% efficacy against virologically confirmed dengue at 12 months post-second dose, with a 95.7% reduction in dengue-related hospitalizations among children aged 4–16 years.

The epidemiological context of this study is enriched by the massive outbreak of dengue infection dominated by the DENV-2 serotype, recording 186,000 cases in Sri Lanka in 2017.[18] An outbreak simulation model incorporating demographic, vector, and spatial factors, focused on Colombo District demonstrated that rapid vaccination deployment (within 30 days of outbreak declaration) with 65% coverage could reduce virologically confirmed dengue cases by 69.1% and hospitalizations by up to 72.7%. These findings highlight the potential of vaccination to mitigate outbreak severity and reduce healthcare system burden.

Based on the results of a phase III study conducted in Mexico City, an area considered non-endemic for dengue, the TAK-003 vaccine demonstrated strong immunogenicity and a favorable safety profile in healthy adolescents aged 12-17 years, most of whom were dengue-naive (seronegative).[12] After two doses of the vaccine, spaced three months apart, neutralizing antibody responses against all four dengue virus serotypes increased significantly, with high seropositivity rates against DENV-1 and DENV-2, and lower responses against DENV-3 and DENV-4. These results indicate that TAK-003 is capable of

inducing protective antibody production even in a dengue-naive population.

Furthermore, these immunogenicity results in Mexico City are consistent with data from phase 3 trials in endemic areas of Latin America, although antibody levels in non-endemic participants were slightly lower, possibly due to the lack of natural exposure to dengue virus. No serious safety concerns were identified, and adverse events were mostly mild to moderate, such as injection site pain or transient headache.[12] Therefore, this study demonstrates that TAK-003 is safe and immunogenic in adolescents in a non-endemic area, strengthening the vaccine's potential as a global candidate for dengue prevention in both endemic and non-endemic areas.

Long-Term Efficacy

A 2024 report on the long-term efficacy of TAk-003, 4.5 years after Phase III, found that TAK-003 has exhibited long-term efficacy and safety against all four DENV serotypes in previously infected persons, a i'm well as against DENV-1 and DENV-2 serotypes in dengue-naive individuals.[14] Serious adverse effects occurred in 5% of TAK-003 patients, but were not linked to the immunization research. Another subgroup analysis by Sirivichayakul et al., (2024) evaluated the effect of TAK-003 on children who had previously received Japanese Encephalitis (JE) or Yellow Fever (YF) vaccines.[15] The results showed that prior JE or YF vaccination did not have a clinically significant impact on the effectiveness of TAK-003. Overall, the TAK-003 vaccine was shown to be safe, well-tolerated, and effective across a range of epidemiological settings.[15]

The role of TAK–003 in dengue outbreaks

Another study reported the role of TAK-003 vaccination in dengue outbreaks in several regions. LakKumar et al., (2024) through their RCT study showed that TAK-003 has the potential to provide significant benefits in controlling dengue outbreaks in endemic areas of Sri Lanka.[18] Meanwhile, a case-control study in Brazil in 2025 by Ranzani et al. which included 92,621 subjects, with 43,873 cases and 48,748 controls showed that TAK-003 was proven effective in preventing dengue fever in adolescents during an outbreak dominated by dengue virus serotypes 1 and 2.[9] These results emphasize the importance of real-world data as a basis for formulating dengue vaccination strategies, especially in areas with high transmission rates and in emergency response situations.

Vaccine Efficacy in Preventing Asymptomatic Dengue

A clinical study by El Hindi et. al, (2025) aimed to estimate the efficacy of the TAK-003 vaccine as protection against asymptomatic dengue infection based on the increase in Neutralizing Antibody (NAb) detected through immunoassay as a marker of infection.[17] This phase 3 study analyzed 3,765 children and adolescents aged 4–16 years who had completed a two-dose regimen of vaccine or placebo with a randomized and blinded method. Efficacy assessment was carried out at three post-vaccination periods (months 4–9, 9–15, and 15–27), with the definition of asymptomatic infection determined through three algorithm criteria: (1) a minimum fourfold increase in NAb; (2) a fourfold increase accompanied by a minimum NAb titer of 40; and (3) a fourfold increase with a titer of at least four times the Lower Limit of Quantification (LLOQ). In the baseline period (months 4–9), estimated vaccine efficacy (VE) varied significantly depending on the algorithm, namely 51.1% (95% CI, 30.4%–65.6%), 36.1% (95% CI, 6.7%–56.3%), and 27.3% (95% CI, –8.2% to 51.2%) for algorithms 1, 2, and 3, respectively.[17]

DISCUSSION

To the best of our knowledge, this systematic review is the first available study on the development of the TAK-003 virus that is given to children and adolescents. The results of the study show that TAK-003 provides effective protection against dengue fever, with efficacy of 70-80% against DENV-1 and DENV-2. This concept is consistent across many ecosystems in Asia and Latin America, and it allows for the continuation of protection for up to 4.5 years after vaccination without the presence of serious vaccine-related effects.[13,18,20] The higher efficacy of TAK-003 against DENV-1 and DENV-2 serotypes compared to DENV-3 and DENV-4 is likely related to the vaccine's formulation using a live, attenuated DENV-2 virus backbone. However, protection against DENV-3 and DENV-4 remains moderate and shows potential for enhancement through booster doses. Similar results were reported in studies in Sri Lanka and Mexico, confirming that the vaccine remains immunogenic in seronegative populations, an advantage over CYD-TDV (Dengvaxia), which is limited to individuals with prior dengue infection.[21]

Immunogenicity and mechanism of protection

Recent immunological analyses highlight that TAK-003 elicits a durable and multitypic immune response encompassing both

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humoral and cellular immunity.[20,21] A study by Sanja et.al (2024) and data from npj Vaccines (Tricou et al., 2024) demonstrated that TAK-003 induces robust $CD8^+$ and $CD4^+$ T-cell responses targeting DENV-2 non structural proteins (NS1, NS3, NS5), with cross reactive responses to other serotypes persisting for at least three years post-vaccination, regardless of baseline serostatus.[10,21] These multifunctional T cells, capable of secreting IFN-γ and TNF-α, are associated with protection against severe dengue.[22] In contrast to CYD-TDV (Dengvaxia), which relies on a yellow fever virus backbone and provides limited protection to seronegative individuals, TAK-003's DENV-2 based design stimulates both neutralizing antibody and cellular responses across serotypes, reducing the risk of antibody dependent enhancement (ADE).[23]

Long-term effectiveness and safety profile

Long-term surveillance revealed that neutralizing antibodies against all four serotypes remained for 48-57 months following vaccination.[24] Furthermore, there was no significant difference in the rate of major adverse events between the vaccine and placebo groups. Adverse effects were mainly mild to moderate, such as injection site soreness, mild fever, or a temporary headache. These data support TAK-003's excellent safety profile in endemic and non-endemic populations. Compared to Dengvaxia (CYD-TDV), TAK-003 has broader immunological and epidemiological benefits, including protection in dengue-naive patients while lowering the likelihood of antibody-dependent enhancement (ADE), a major concern with previous-generation vaccines. Furthermore, TAK-003 showed consistent efficacy across age groups in children and adolescents without increasing the risk of significant adverse events.[25] Several follow-up trials found that TAK-003 provided protection against silent dengue infection, while its efficacy was lower than in symptomatic infections. Individuals with baseline dengue immunity (seropositive) exhibited a stronger protective effect. Furthermore, TAK-003 immunization decreased the incidence of recurrent infection (sequential symptomatic episodes), implying that the resultant immune response is not just short-term protective but also reduces the likelihood of further, often more severe, infections.[26]

Implications for outbreak control

Clinical trials in Sri Lanka and observational studies in Brazil show that TAK-003 can be effective as a public health intervention during dengue

outbreaks.[9,18] Rapid vaccine delivery with high coverage (≥65%) reduces dengue incidence by up to 70% and hospitalizations by up to 73%, according to epidemiological model simulations. This highlights the vaccine's potential as an epidemic prevention strategy, especially in places with high vector density and weak health services.[9,18]

Efficacy Against Asymptomatic and Sequential Infections

Although TAK-003 shows strong protection against symptomatic disease, its efficacy against asymptomatic dengue infection remains moderate. El Hindi et al. (2025) found variable protection (27-51%) depending on the serological algorithm used, with higher efficacy observed among seropositive individuals. Nonetheless, TAK-003 reduces the likelihood of sequential symptomatic infections important for preventing severe dengue manifestations associated with secondary infections.[17,19]

Comparative Perspective and Policy Implications

Compared to CYD-TDV, TAK-003 demonstrates broader efficacy, particularly in seronegative children, addressing one of the major limitations of earlier dengue vaccines. Its use in both endemic and non-endemic regions, including populations without prior dengue exposure, represents a significant advance in global dengue prevention.[13] The integration of TAK-003 into national immunization programs, particularly in high-transmission and outbreak-prone areas, could substantially reduce dengue-related morbidity and healthcare costs. Modeling evidence supports the cost-effectiveness of rapid, large-scale vaccination rollouts to flatten epidemic curves and prevent healthcare system overload during outbreaks.

Limitations

There are some limitations to this review. First, the majority of the data is from the same clinical trial (DEN-301) with many follow-up publications, so potential data overlap cannot be totally avoided. Second, geographic variance, baseline serological status, and regional transmission intensity differences may all have an impact on efficacy estimates. Third, in certain studies, the follow-up period was insufficient to determine the requirement for booster dosages and effectiveness against DENV-3 and DENV-4. Furthermore, there is little real-world evidence assessing vaccination performance outside of controlled clinical studies.

4. CONCLUSION

Overall, the findings of this study suggest that TAK-003 is a successful and safe dengue

vaccine that has the potential to be an important method for dengue prevention in children. The vaccine was highly effective against DENV-1 and DENV-2, providing considerable protection against symptomatic and severe illness, and exhibiting prolonged antibody persistence. More research is needed to determine the vaccine's real-world effectiveness, the effect of booster doses, and the long-term effects on DENV-3 and DENV-4 serotypes, so that TAK-003 can be fully integrated into worldwide immunization programs.

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