TAK-003 Dengue Vaccine for Seronegative Population in Endemic Areas: A Systematic Review

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BACKGROUND

Dengue
Dengue is a mosquito-borne viral infection that primarily affects people in tropical and subtropical regions. In the first half of 2025, WHO counted there were 4 million incidences and over 3000 mortalities across 97 countries.(1)

Dengue Vaccine
Seronegative dengue cases are more common than seropositive cases in children. Primary infection in seronegative individuals can increase the risk of severe disease in subsequent infections. The WHO recommends TAK-003 for routine immunization in regions with high dengue transmission and significant public health burden.(2,3)

Promising Trial of TAK-003
TAK-003, a tetravalent live-attenuated dengue vaccine, shows promising trial outcomes in endemic countries. However, its efficacy remains uncertain in seronegative populations.(3)

OBJECTIVES

To systematically evaluate efficacy, immunogenicity, and safety of TAK-003 in seronegative population in endemic areas.

METHODS

Design
Systematic Review using PRISMA 2020 guidelines

Database
PubMed, Scopus, Cochrane Library, ScienceDirect

Time frame
2020-2025

Risk of Bias assesment
Cochrane ROB 2

INCLUSION CRITERIA

- Peer-Reviewed Randomized Controlled Trials (RCTs)
- Research was conducted in dengue-endemic areas involving seronegative populations as study subjects.
- Full-text available for data extraction

EXCLUSION CRITERIA

- Vaccines other than TAK-003
- Full text unavailable
- Non-English written article

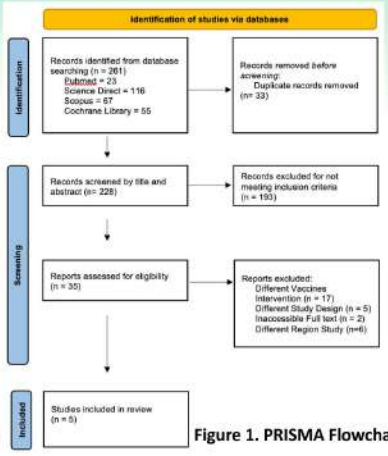

Figure 1. PRISMA Flowchart

RESULTS

Table 1. The Comparation of Efficacy, Immunogenicity, and Safety of TAK-003 in Seropositive and Seronegative Population in Endemic Areas

Author (Year)	Research Region	Timeframe	Population (n)	Age	Doses / Treatment	Time to follow up	Efficacy	Geometric Mean Titer	Overall Outcomes
Sirivichayakul et al (2022) (4)	Puerto Rico, Columbia, Thailand, and Singapore	November 2011 - April 2016	• Part 1 of the study: 148 • Part 2 of the study: 212	1.5 to 45 years old	2 doses administered subcutaneously, 3 months apart with each dose contain 0.5 ml of TAK-003	Month 4 and month 36 (post first dose vaccination)	**N/A**	**Seronegative Baseline:** **Month 4:** Lower than seropositive baseline group but still higher than placebo groups **Month 36:** DENV-1: 49 DENV-2: 102 DENV-3: 28 DENV-4: 8 (similar to the baseline) **Placebo:** DENV-1: 6,2 DENV-2: 6,0 DENV-3: 7,0 DENV-4: 5,3	Immunogenicity varied by age and serotype. Older participants showed higher GMTs against DENV-1 and DENV-2, while younger groups had higher GMTs against DENV-3 and DENV-4. At month 4, baseline seronegative vaccinees showed low DENV-4 GMTs, indicating weaker responses in those without prior exposure. There are no serious adverse events reported.
Biswal et al (2020) (5)	• Southeast Asia (Philippines, Sri Lanka, and Thailand) • Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, and Panama)	7 September 2016 - 18 August 2017	Total: 20 099 Randomly assigned into: • TAK-003 : 13.401 • Placebo: 6.698	Age groups • 4–5 years • 6–11 years • 12–16 years	• 2 doses administered subcutaneously, 3 months apart with each dose contain 0.5 ml of TAK-003. • Placebo : 0.5 ml injection of saline	Up to 18 months post-vaccination	**Against VCD:** • Seropositive baseline: 76,1% (95% CI, 68,5-81,9) • Seronegative baseline: 66,2% (95% CI, 49,1-77,5) • Serotype: ▫ DENV1: 69,8% (95% CI, 54,8-79,9) ▫ DENV2: 95,1% (95% CI, 89,9-97,6) ▫ DENV3: 48,9% (95% CI, 27,2-64,1) ▫ DENV4: 51,0% (95% CI, −69,4-85,8)	**1 month after 2nd dose:** • Seropositive baseline: ◦ DENV-1: 2115, DENV-2: 4897, DENV-3: 176, DENV-4 1129 • Seronegative baseline: ◦ DENV-1: 184, DENV-2: 1730, DENV-3: 228, DENV-4: 114 **15 month after 2nd dose:** • Seropositive baseline: ◦ DENV-1: 1243, DENV-2: 2993, DENV-3: 799, DENV-4: 817 • Seronegative baseline: ◦ DENV-1: 77, DENV-2: 656, DENV-3: 53, DENV-4: 64	TAK-003 was well tolerated and effective against symptomatic dengue in children, regardless of baseline serostatus. Vaccine efficacy varied by serotype, emphasizing the need for continued follow-up to assess long-term protection. However, this study did not include detailed safety or adverse event data.
López-Medina et al (2020) (6)	• Southeast Asia (Philippines, Sri Lanka, and Thailand) • Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, and Panama)	Started in September 2016	Total: 20.099 • TAK-003 recipients: 13.401 • Placebo: 6.698	Age groups • 4–5 years • 6–11 years • 12–16 years	• 2 doses administered subcutaneously, 3 months apart with each dose contain 0.5 ml of TAK-003. • Placebo : 0.5 ml injection of saline	2 years follow up (27 months after initial dose)	**Overall efficacy**: 72,7% (95% CI, 67,1–77,3) • **Baseline:** ▫ Seropositive: 74.8% (95% CI, 68,6–79,8) ▫ Seronegative: 67% (95% CI, 53,6–76,5) • **Serotype-specific efficacy** ▫ DENV-1 (69,0%), DENV-2 (90,8%), and DENV-3 (51,4%), DENV-4: (50,4%; 95%CI, −19,3-79,3)	**GMT trends (months 9, 15, and 27):** • Seronegative baseline: DENV-2 GMTs declined over time, while DENV-1, -3, and -4 remained stable. • Seropositive baseline: Seropositivity rates showed minimal change, from 91.3% at month 9 to 85.9% at month 27.	TAK-003 maintained protective benefit against dengue regardless of baseline serostatus, though efficacy declined slightly in the second year. No vaccine-related serious adverse events were reported.
Rivera et al (2021) (7)	• Southeast Asia (Philippines, Sri Lanka, and Thailand) • Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, and Panama)	September 2016 - March 2017	Total: 20.099 • TAK-003 recipients: 13.401 • Placebo: 6.698	Age groups • 4–5 years • 6–11 years • 12–16 years	• 2 doses administered subcutaneously, 3 months apart with each dose contain 0.5 ml of TAK-003. • Placebo : 0.5 ml injection of saline	3 years follow up	**Against VCD Overall**: 62.0% (95% CI, 56.6 - 66.7) • **Baseline serostatus**: ▫ Seropositive: 65.0% (95% CI, 58.9-70.1) ▪ DENV-1: 56.2% (95% CI, 43.7–66.0) ▪ DENV-2: 83.4% (95% CI, 76.4–88.3) ▪ DENV-3: 52.3% (95% CI, 36.6–64.2) ▪ DENV-4: 60.7% (95% CI, 16.0–81.6) ▫ Seronegative: 54.3% (95% CI, 41.9-64.1) ▪ DENV-1: 43.5% (21.5–59.3) ▪ DENV-2: 91.9% (95% CI, 83.6–96.0) ▪ DENV-3: −23.4% (95% CI, −125.3 to 32.4) ▪ DENV-4: −105.5% (95% CI, −867.5 to 56.4)	• At month 39, tetravalent seropositivity reached 80.5% among baseline seronegative participants and 98.4% among those who were baseline seropositive.	Vaccine efficacy against VCD decreased in year 3, while no significant safety concerns were reported during the study.
Borja-Tabora et al (2024) (8)	• Southeast Asia (Philippines, Sri Lanka, and Thailand) • Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, and Panama)	7 September 2016 - 18 Agustus 2017	Total: 20.099 • TAK-003 recipients: 13.401 • Placebo: 6.698	Age groups • 4–5 years • 6–11 years • 12–16 years	• 2 doses administered subcutaneously, 3 months apart with each dose contain 0.5 ml of TAK-003. • Placebo : 0.5 ml injection of saline	4 years post vaccination (approximately 51- 57 months)	**Against VCD:** **Seronegative baseline:** • 4-5 years old: 54,1% (95% CI, 34,1 - 68,0) • 6-11 years old: 60,5% (95% CI, 46,8-70,7) • 12-16 years old: 63,6% (95% CI, 33,8-79,9) **Seropositive baseline:** • 4-5 years old: 23,2% (95% CI, −20 - 50,8) • 6-11 years old: 64,8% (95% CI, 57,0 - 71,2) • 12-16 years old: 68,6% (95% CI, 57,7-76,7)	• **Seropositive baseline**: GMTs were highest in older children and lowest in 4–5 year-olds; despite some waning, TAK-003 GMTs remained above placebo across all ages. • **Seronegative baseline**: No clear age differences; GMTs declined slightly (especially DENV-2) but stayed above placebo throughout the study.	TAK-003 effectively prevented dengue in children and adolescents (4–16 years) in endemic areas. GMTs remained elevated for ~4 years across all serotypes and age groups. Safety was consistent, with minimal adverse events, and study-related deaths were not observed.

DENV: *Dengue virus*; VCD: *Virologically Confirmed Dengue*; CI: *Confidence Interval*; GMT: *Geometric Mean Titer*

CONCLUSION

- The TAK-003 vaccine is effective in preventing all dengue fever serotypes, although efficacy remains lower in participants with a seronegative baseline status.
- Immunogenicity was observed across all serotypes but was also lower in seronegative participants. While a decline in efficacy and immunogenicity was noted after years 2–3, values remained higher than in the placebo group. No significant adverse events were reported.
- All of the studies mentioned above were continuation studies conducted within a single large clinical trial program. Consequently, despite the large population and broad geographic coverage, there was limited variability in ethnicity and other endemic populations. Furthermore, most participants were children and adolescents, providing insufficient data for adults.
- Further research is needed with a broader age range and wider geographic population. Additional studies focusing on seronegative individuals, particularly for DENV-4, are also required to better assess the vaccine's effectiveness against this serotype.

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