

## EFFECTIVENESS AND SAFETY OF THE TETRAVALENT TAK-003 DENGUE VACCINE: A SYSTEMATIC REVIEW

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### Abstract

In Argentina, the dengue virus has experienced an increase in recent years. This study aims to conduct a systematic review to evaluate the effectiveness and safety of the TAK-003 tetravalent dengue vaccine in this context.

A systematic review of randomized controlled trials comparing the effectiveness and safety of the vaccine with placebo in the general population was conducted. The search was carried out in Epistemonikos, and two researchers independently assessed the studies. Risk of bias was evaluated using the Cochrane Rob 2 tool. A meta-analysis of the results was performed, and the certainty of evidence was assessed using the GRADE methodology.

We concluded, with high certainty of evidence, that the tetravalent dengue vaccine reduces severe infections (RR 0.17, 95% CI 0.12 to 0.24) and infections by the dengue virus (RR 0.40, 95% CI 0.36 to 0.45) in a population  $\leq 17$  years. The vaccine may not increase the risk of serious adverse events, although it is important to note the low certainty of evidence (RR 1.04, 95% CI: 0.69-1.55).

The use of the tetravalent dengue vaccine decreases the risk of severe and non-severe dengue infections in this population. However, there is low certainty of evidence regarding the vaccine's safety. The decision

to vaccinate should consider the magnitude of benefits relative to the risk of infection.

**Key words:** dengue, tetravalent vaccine, Argentina, GRADE, systematic review

### Resumen

*Efectividad y seguridad de la vacuna tetravalente contra el dengue: una revisión sistemática*

En Argentina, el virus del dengue ha experimentado un aumento en los últimos años. Este estudio se propone realizar una revisión sistemática para evaluar la efectividad y seguridad de la vacuna TAK-003 tetravalente contra el dengue en este contexto.

Se llevó a cabo una revisión sistemática de ensayos clínicos controlados aleatorizados que comparaban la efectividad y seguridad de la vacuna con placebo en la población general. La búsqueda se efectuó en Epistemonikos y dos investigadores evaluaron los estudios de manera independiente. El riesgo de sesgo se evaluó con la herramienta Rob 2 de Cochrane. Se realizó un metaanálisis de los resultados y la certeza en la evidencia se evaluó mediante la metodología GRADE.

Concluimos, con alta certeza de evidencia, que la vacuna tetravalente contra el dengue reduce las infec-

ciones graves (RR 0.17, IC 95% 0.12 a 0.24) e infecciones por el virus del dengue (RR 0.40, IC 95% 0.36 a 0.45) en una población de  $\leq 17$  años. La vacuna podría no incrementar el riesgo de eventos adversos serios, aunque es importante destacar la baja certeza de evidencia (RR 1.04, IC 95%: 0.69-1.55).

La aplicación de la vacuna tetravalente contra el dengue disminuye el riesgo de infecciones graves y no graves por el dengue en esta población. No obstante, existe baja certeza en la evidencia en relación a la seguridad de la vacuna. La decisión de la vacunación debe considerar la magnitud de los beneficios en función del riesgo de infección.

**Palabras clave:** dengue, vacuna tetravalente, Argentina, GRADE, revisión sistemática

## KEY POINTS

### Current knowledge

- Dengue, caused by Flavivirus serotypes transmitted mainly by *Aedes aegypti* and additionally by *Aedes albopictus* mosquitoes, is a significant global public health concern. The virus's four serotypes lead to various manifestations, ranging from mild to fatal cases. Infections with different serotypes increase the risk of severe dengue and mortality, highlighting the need for effective preventive strategies.

### Article contribution to current knowledge

- This systematic review provides insights into the effectiveness and safety of the tetravalent TAK-003 vaccine, particularly in children and adolescents, emphasizing the need for personalized recommendations, ongoing surveillance, thorough research, and evidence-based decisions for dengue prevention and control. This systematic review was utilized by the Hospital Alemán in Argentina to formulate recommendations regarding this vaccine.

Dengue, a febrile syndrome caused by Flavivirus serotypes transmitted through the bite of *Aedes aegypti* or *Aedes albopictus* mosquitoes, imposes a significant burden on global public health. With four distinct serotypes, the dengue

virus has evolved into a persistent threat, affecting millions annually. An estimated 390 million dengue infections occur each year, encompassing a spectrum from mild manifestations to potentially fatal cases. Notably, sequential infections with different serotypes elevate the risk of severe dengue and mortality for affected individuals<sup>1</sup>.

The incidence of dengue has been a perennial cause for concern, with a notable surge in recent years<sup>2</sup>. In Argentina, until July 2023, an alarming 126 431 dengue cases were reported in the country, significantly surpassing the previous four-decade record set in 2016 with 79 455 infected individuals<sup>3</sup>. Among these cases, 0.2% progressed to severe forms, and 0.05% resulted in fatalities<sup>4</sup>. This reality underscores the urgency of effective strategies to prevent and control the spread of the disease.

Against this backdrop, vaccination emerges as a pivotal tool for preventing and mitigating the dengue burden. In this context, the tetravalent dengue vaccine has positioned itself as a promising strategy, addressing multiple serotypes and offering the possibility of reducing the incidence of severe and fatal cases. In April 2023, the National Administration of Drugs, Foods, and Medical Technology (ANMAT) approved the use of the tetravalent dengue vaccine TAK-003 (Qdenga) in Argentina<sup>5</sup>.

Within the internal medicine department of Hospital Alemán of Buenos Aires, a crucial question emerged concerning the effectiveness and safety of this vaccine. To provide a fast and high-quality answer we used novel technological tools that allowed us to perform a systematic review to assess the available body of evidence on health benefits and harms of the dengue vaccine to evaluate the available body of evidence. Subsequently, the evidence-to-decision process was followed, using the GRADE methodology, to formulate a recommendation on this topic. This study aims to describe the process and result of the systematic review.

## Methods

This systematic review was developed following the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) for reporting systematic reviews and meta-analyses<sup>6</sup>.

## 1. Clinical question

What is the safety and effectiveness of the tetravalent dengue vaccine TAK-003 against dengue infection in healthy patients (children and adults) compared to a placebo, regardless of their previous exposure status to the dengue virus?

### PICO question

- Patients (P): Healthy patients (children and adults) regardless of their previous exposure status to the dengue virus

- Intervention (I): Tetravalent attenuated dengue vaccine TAK-003<sup>7</sup>

- Comparator (C): Placebo

- Outcomes (O):

- Mortality: defined as all-cause mortality

- Severe dengue infection according to World Health Organization criteria<sup>8</sup>

- Dengue infection: diagnosis through polymerase chain reaction (PCR) in a patient with fever and compatible symptoms

- Hemorrhagic dengue: patients diagnosed with dengue and thrombocytopenia or shock or signs of bleeding

- Serious adverse events: definition according to primary studies

- Adverse events: definition according to primary studies

It is noteworthy that the immunological status or previous exposure to dengue was not an inclusion criterion in this study.

## 2. Literature search

### 2.1. Electronic search

A search was conducted in the Epistemonikos Database. This database is kept updated through regular searches in multiple sources and has been validated as a comprehensive source of systematic reviews and randomized controlled trials. These sources include the *Cochrane Database of Systematic Reviews* (CDSR), *Database of Abstracts of Reviews of Effectiveness* (DARE), PubMed, LILACS, CINAHL, PsycINFO, EMBASE, EPPI-Centre Evidence Library, Systematic Reviews and Policy Briefs Campbell Library, and The JBI Database of Systematic Reviews and Implementation Reports<sup>9</sup>. All searches covered the period from the database inception dates until 12/18/2023, with no restrictions on publication date, status, or language.

The identification of primary studies was complemented by a specific search in the PubMed database. The search strategy is available in Appendix 1.

### 2.2. Other search sources

To ensure the identification of articles that may not have been detected by the search strategy or are not available in the included databases, we included the following sources of information:

- Randomized clinical trials (RCTs) included in other relevant systematic reviews, identified through a search in the Epistemonikos Database.

- Manual review of references from included studies.

### 3. Study selection

We conducted the study selection process using the *Collaboratron* software, a screening tool developed within the *Sustainable Knowledge* (SK) platform by the Epistemonikos Foundation<sup>10</sup>. Two independent researchers (AB, CS) evaluated the title and abstract of all articles according to the eligibility criteria for population, intervention, comparison, and study design. We obtained the full text of all potentially eligible studies, and two researchers (AB, CS) assessed their eligibility. Any disagreements were resolved through discussion, and if necessary, an additional reviewer (AI) was involved. Exclusion reasons for clinical trials and the selection process were recorded in the PRISMA flow diagram.

### 4. Data extraction

Data extraction was performed by a researcher using standardized forms (AB). Detailed information was collected on demographic characteristics, study methodology, included population, interventions performed, comparison used, and reported results.

### 5. Risk of bias assessment

We assessed the risk of bias in each randomized trial using the *Risk of Bias 2* (Rob 2) tool developed by the Cochrane Collaboration<sup>11</sup>. The five bias domains considered in this tool were: bias derived from the randomization process, bias derived from deviations from the intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of the reported outcome.

### 6. Effect measures

In the analysis of dichotomous outcomes, we expressed the estimation of the therapeutic impact of the intervention through risk measures along with the 95% confidence interval (CI). For continuous outcomes, we used the mean difference and standard deviation along with the 95% CI.

## 7. Heterogeneity assessment

We assessed variations in the treatment effect among different included clinical trials using the  $\chi^2$  test (Q statistic) and the I<sup>2</sup> statistic. Statistically significant heterogeneity was considered when the p-value was <0.1.

## 8. Data synthesis

We conducted a meta-analysis through the SK platform, which integrates multiple statistical approaches, including those recommended by the Cochrane Collaboration<sup>12</sup>. This involved selecting studies exhibiting ample homogeneity in design, population, interventions, comparators, and reported outcome measures. Employing the inverse variance method and a random-effects model, we scrutinized the results of clinically homogeneous studies. In instances lacking sufficient data for meta-analysis, we provided a narrative synthesis.

Notably, for this analysis, the employment of subgroup analysis was foregone, as no potential effect modifiers were identified. Neither age, immunocompromised conditions, nor previous exposures to dengue were deemed effect modifiers. In light of these considerations, we opted not to establish any a priori hypotheses for heterogeneity. This approach ensures a nuanced and unbiased exploration of the data, allowing for a more comprehensive interpretation of the study findings.

## 9. Assessment of evidence certainty

We assessed the certainty of evidence for all outcomes using the GRADE methodology, through the domains of risk of bias, consistency, indirect evidence, imprecision, and publication bias. Certainty was classified as high, moderate, low, or very low. The Summary of Findings (SoF) tables were generated through a technological tool that automatically created them for main comparisons and outcomes<sup>13,14</sup>.

We defined the target of the certainty of the evidence following a minimally contextualized approach<sup>15</sup>. No specific publications reporting specific clinical thresholds for this condition were detected; therefore, the researchers reached a consensus on the following thresholds for minimum clinically important difference for each of the outcomes assessments. The thresholds were established, taking into consideration that this is a primary prevention intervention.

- Mortality: threshold for benefit: 50 per 100 000
- Severe dengue infection: threshold for benefit: 75 per 100 000
- Hemorrhagic fever: threshold for benefit: 100 per 100 000

- Dengue infection: threshold for benefit: 125 per 100 000
- Serious adverse events: threshold for harm: 50 per 100 000
- Adverse events: threshold for harm: 20 per 1000

## Results

### 1. Search results

Through the search strategy, we identified 239 references for screening by title and abstract. Of these, 25 references underwent full-text evaluation, ultimately leading to the inclusion of 5 RCTs reported in 10 references that met the selection criteria<sup>16-25</sup>. Detailed exclusion reasons for clinical trials and the selection process are documented in the PRISMA flow diagram (Fig. 1 and Appendix 2).

### 2. Description of included studies

The included population consisted primarily of children, adolescents, and young adults, and the research was conducted in countries with varying levels of viral circulation, ranging from high to low. The follow-up time varied between 9 and 48 months. Table 1 provides an overview of the characteristics of the studies included for analysis.

### 3. Risk of bias assessment results (Fig. 2)

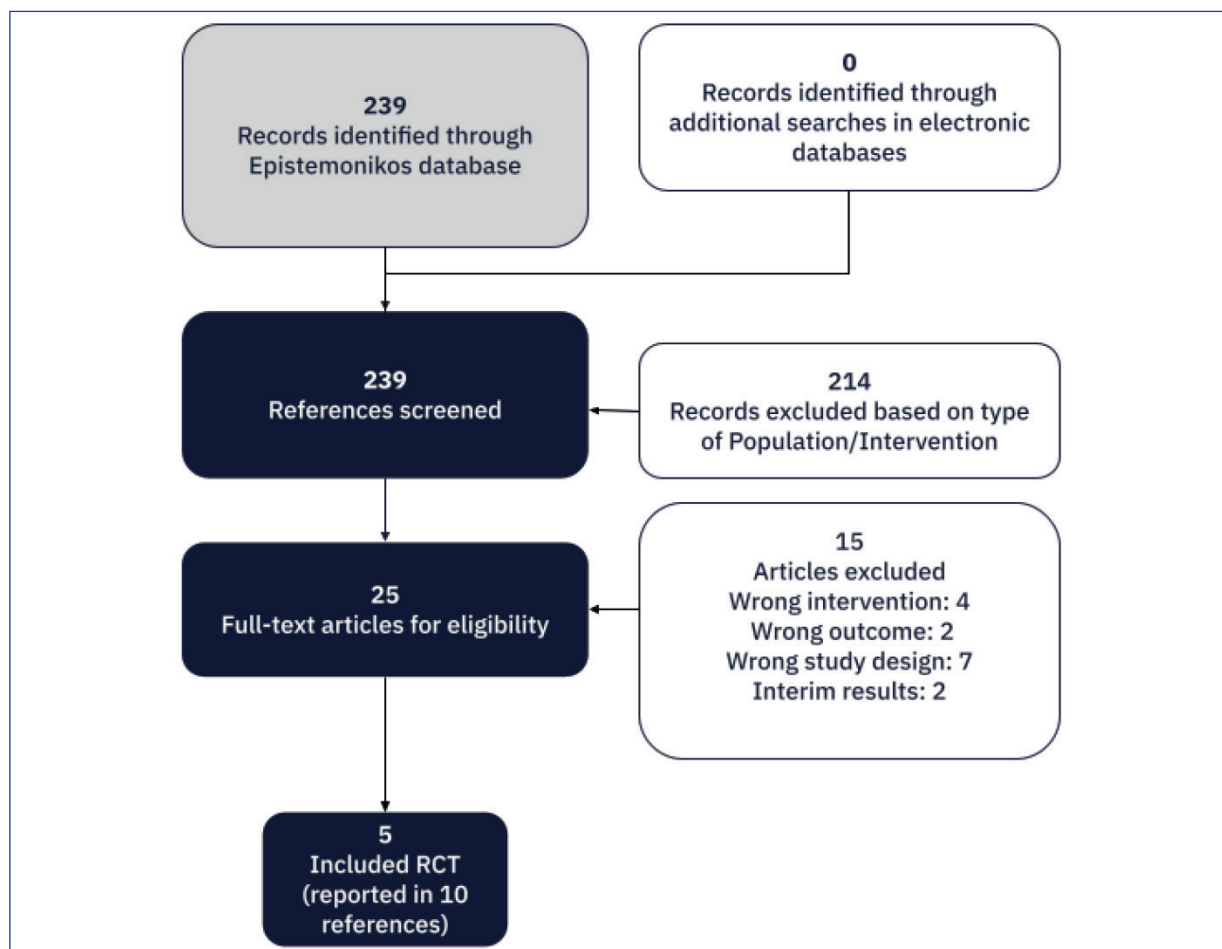
Three clinical trials<sup>17,22,23</sup> were assessed with a low risk of bias, one<sup>25</sup> with some considerations, and another<sup>24</sup> with a high risk of bias across all analyzed outcomes. Comprehensive details of the risk of bias assessment for each domain can be referenced in Appendix 3. Although certain considerations were identified in some domains of Cochrane's Rob 2, the overall interpretation of the risk of bias in the primary studies was low.

### 4. Efficacy and safety of the vaccine (Table 2)

Interactive version: <https://isof.epistemonikos.org/#/finding/65a5653ce3089d04cd692c1d>

#### 4.1. Mortality (Fig. 3)

A clinical trial<sup>21</sup>, involving a total of 20 067 participants aged 4 to 16 years reported on this outcome. The effect of the tetravalent dengue vaccine on mortality is uncertain (RR 1.25, 95% CI 0.22 to 6.44; very low certainty in the evidence). The certainty of the evidence was classified as very low due to extremely serious imprecision. It is worth mentioning the low rate of events in both arms of the study, emphasizing the possibility that this event may be infrequent. However, it is important to note that

**Figure 1** | PRISMA flowchart

RCT: randomized controlled trial

the baseline risk could undergo modifications in an epidemic scenario.

#### 4.2. Severe dengue infection (Fig. 4)

In a clinical trial<sup>21</sup> involving 20 067 participants aged 4 to 16 years, it was reported that the use of the dengue vaccine was associated with high certainty evidence of a reduction in the risk of severe dengue virus infection (RR 0.17, 95% CI: 0.12 - 0.24).

Considering the baseline risk of severe dengue virus infection in Argentina<sup>3,4</sup> (170 per 100 000 patients with dengue fever), the utilization of the tetravalent Dengue vaccine would result in a decrease in severe infections among children and adolescents aged 4 to 16 years, reaching the predetermined threshold (75 per 100 000) with a risk difference of 141 fewer persons per 100 000 (95% CI: 150 to 129 fewer). The certainty of the evidence was rated as high.

Conversely, in a population with a higher risk of severe dengue virus infection, such as Puerto Rico<sup>2</sup> (baseline risk of 4990 per 100 000), the use of the tetravalent Dengue vaccine would lead to a decrease in severe infections among children and adolescents aged 4 to 16 years, according to the determined threshold, with a risk difference of 4142 fewer persons per 100 000 (95% CI: 4391 to 3792 fewer). The certainty of the evidence was rated as high.

It is important to note that global estimates by country were considered, and not by local territory, so the baseline risk of severe infection could vary within different areas of each country.

#### 4.3. Hemorrhagic fever (Fig. 5)

In a clinical trial<sup>21</sup> involving 20 067 participants aged 4 to 16 years, the use of the dengue vaccine was associated with low certainty evidence of a reduction in the risk of developing hemorrhagic fever (RR 0.35, 95% CI: 0.15 - 0.81).

**Table 1** | Characteristics of included studies

Study and Years	Country	Participants % over 17 years	Intervention and comparison	N° Patients Intervention	N° Patients Control	Outcomes	Follow-up
DEN-24 <sup>23</sup> 2014-2014	Dominican Republic, Panama, and Philippines	Healthy children aged 2 to 17 years 0%	TAK-003 or Placebo (0 and 90 days)	1596	198	Serious adverse events, symptomatic dengue infection	48 months
DEN-304 <sup>17</sup> 2018-2019	United States	Healthy adults aged 39 to 54 years 100%	TAK-003 or Placebo (0 and 90 days)	788	131	Adverse events	8.8 months
DEN-315 <sup>24</sup> 2017-2019	Mexico	Healthy children aged 12 to 17 years 0%	TAK-003 or Placebo (0 and 90 days)	300	100	Adverse events	9 months
INV-DEN-203 <sup>16,25</sup> 2011-2016	Puerto Rico, Colombia, Thailand, and Singapore	Healthy children and adults aged 1.5 to 45 years 25.67%	TAK-003 or Placebo (0 and 90 days)	249	111	Symptomatic dengue, adverse events	36 months
TIDES <sup>18-22</sup> 2016-on going	Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, and Thailand	Healthy children aged 4 to 16 years 0%	TAK-003 or Placebo (0 and 90 days)	13380	6687	Dengue infection, hospitalization, severe dengue, hemorrhagic fever	14.8 months

N°: number

In terms of absolute effects, the use of the tetravalent dengue vaccine may result in a reduction in hemorrhagic fever events according to the threshold determined (risk difference of 126 fewer persons per 100 000, 95% CI: 165 to 37 fewer). The certainty of the evidence was classified as low due to very serious imprecision. We decided to downgrade the certainty by two levels, primarily due to imprecision stemming from the low number of events in each group, introducing fragility to the results<sup>26</sup> and, additionally, the confidence interval (CI) being larger than 3, further contributes to reducing the overall certainty of evidence to a low level<sup>27</sup>.

#### 4.4. Dengue infection (Fig. 6)

Three clinical trials<sup>16,19,23</sup> involving a total of 22 221 participants, reported high certainty evidence of a reduction in serious adverse events associated with the use of the dengue vaccine (RR 0.40, 95% CI: 0.36 - 0.45; I<sup>2</sup>=0%). These trials exclusively enrolled healthy children aged 4 to 16 years.

Considering the baseline risk of dengue virus infection in Argentina<sup>3</sup> (256 per 100 000), the utilization of the tetravalent dengue vaccine would result in a decrease in infections among children and adolescents aged 4 to 16 years, reaching the predetermined threshold (125 per 100 000)

**Figure 2** | Risk of bias assessment

Studies	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
DEN-304	+	+	+	-	+	+
TIDES	+	+	+	-	+	+
DEN-24	+	+	+	+	+	+
DEN-315	+	+	+	⊗	+	⊗

Domains:  
D1: Randomization process  
D2: Deviations from the intended interventions  
D3: Missing outcome data  
D4: Measurement of the outcome  
D5: Selection of the reported result

Judgement  
⊗ High risk of bias  
- Some concerns  
+ Low risk of bias

DEN-24 Ref. 23; DEN-304 Ref. 17; DEN-315 Ref. 24; INV-DEN-203 Ref. 16, Ref. 25; TIDES Ref. 18-22

with a risk difference of 154 fewer persons per 100 000 (95% CI: 164 to 141 fewer). The certainty of the evidence was rated as high.

On the other hand, in a population with a higher risk of dengue virus infection, such as Brazil<sup>2</sup> (baseline risk of 1383 per 100 000), the use of the tetravalent Dengue vaccine would lead to a decrease in infections among children and adolescents aged 4 to 16 years according to the determined threshold, with a risk difference of 830 fewer persons per 100 000 (95% CI: 885 to 761 fewer). The certainty of the evidence was rated as high.

Given that the clinical trials included individuals under 17 years of age, these conclusions are particularly pertinent to this demographic.

#### 4.5. Serious adverse events (Fig. 7)

Five clinical trials<sup>16,17,21,23,24</sup> involving a total of 23 540 participants, reported low certainty evidence of an increase in serious adverse events associated with the use of the dengue vaccine (RR 1.04, 95% CI: 0.69 - 1.55; I<sup>2</sup>=25%).

In terms of absolute effects, the use of the tetravalent dengue vaccine may result in a trivial increase in serious adverse events, according to the threshold determined (risk difference of 29 persons more per 100 000, 95% CI: 223 fewer to 396 more). The certainty of the evidence was classified as low due to very serious imprecision.

#### 4.6. Adverse events of any kind (Fig. 8)

Three clinical trials<sup>17,21,24</sup> with a total of 21 348 participants, predominantly children or adolescents, were included. These trials reported low certainty evidence of an increase in adverse events of any type associated with the use of the Dengue vaccine (RR 1.41, 95% CI: 0.79 - 2.52; I<sup>2</sup>=94.6%)

In terms of absolute effects, the use of the tetravalent dengue vaccine could result in a trivial increase in adverse events of any type according to the threshold determined (risk difference of 18 persons more per 1000, 95% CI: 9 fewer to 67 more). The certainty of the evidence was classified as low due to serious imprecision and inconsistency.

#### Discussion

This systematic review provides a comprehensive evaluation of the tetravalent dengue vaccine TAK-003, encompassing both safety and effectiveness. The findings offer robust evidence supporting the vaccine's effectiveness in reducing the incidence of severe dengue infections and dengue virus infections, with a high level of certainty in the population under 17 years. However, the nuanced consideration of baseline infection risks adds complexity to interpre-

**Table 2** | Summary of findings table

Interactive version: <https://isof.epistemonikos.org/#/finding/65a5653ce3089d04cd692c1d>

Outcomes	Key messages	Absolute effect		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Placebo or no vaccination	Dengue virus vaccine	Number of participants and studies	
<b>Mortality</b> Follow-up: median of 14.8 months	The effect of the tetravalent dengue vaccine on mortality is very uncertain.	30 per 100 000	37 per 100 000	<b>RR 1.25</b> (0.24 to 6.44)	⊕○○○ Very low <sup>a</sup>
		Difference: 7 more patients per 100 000 (95% CI: 23 less to 163 more patients)		Based on data from 20 067 individuals in 1 study <sup>21</sup>	
<b>Severe dengue virus infection<sup>e</sup> (low risk)</b> Follow-up: median of 14.8 months	The use of the tetravalent dengue vaccine results in a reduction in severe infection.	170 per 100 000 <sup>c</sup>	29 per 100 000	<b>RR 0.17</b> (0.12 to 0.24)	⊕⊕⊕⊕ High
		Difference: 141 less patients per 100 000 (95% CI: 150 to 129 less patients)		Based on data from 20 067 individuals in 1 study <sup>21</sup>	
<b>Severe dengue virus infection<sup>e</sup> (high risk)</b> Follow-up: median of 14.8 months	The use of the tetravalent dengue vaccine results in a decrease in severe infection.	4990 per 100 000 <sup>c</sup>	848 per 100 000	<b>RR 0.17</b> (0.12 to 0.24)	⊕⊕⊕⊕ High
		Difference: 4142 less patients per 100 000 (95% CI: 4391 to 3792 less patients)		Based on data from 20 067 individuals in 1 study <sup>21</sup>	
<b>Dengue virus infection<sup>f</sup> (high circulation)</b> Follow-up: 14.8-48 months	The use of the tetravalent dengue vaccine results in a decrease in dengue virus infection.	1383 per 100 000 <sup>d</sup>	553 per 100 000	<b>RR 0.40</b> (0.36 to 0.45)	⊕⊕⊕⊕ High
		Difference: 830 less patients per 100 000 (95% CI: 885 to 761 less patients)		Based on data from 22 221 individuals in 3 studies <sup>21,23,25</sup>	
<b>Dengue virus infection<sup>f</sup> (low circulation)</b> Follow-up: 14.8-48 months	The use of the tetravalent dengue vaccine results in a decrease in dengue virus infection.	256 per 100 000 <sup>d</sup>	102 per 100 000	<b>RR 0.40</b> (0.36 to 0.45)	⊕⊕⊕⊕ High
		Difference: 154 less patients per 100 000 (95% CI: 164 to 141 less patients)		Based on data from 22 221 individuals in 3 studies <sup>21,23,25</sup>	
<b>Hemorrhagic fever<sup>9</sup></b> Follow-up: median of 14.8 months	The use of the tetravalent dengue vaccine could result in a reduction of hemorrhagic fever events.	194 per 100 000	68 per 100 000	<b>RR 0.35</b> (0.15 to 0.81)	⊕⊕⊕○ Low <sup>a</sup>
		Difference: 126 less patients per 100 000 (95% CI: 9 less to 67 more patients)		Based on data from 20 067 individuals in 1 study <sup>21</sup>	

(continúa)



(continuation)

Outcomes	Key messages	Absolute effect		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Placebo or no vaccination	Dengue virus vaccine	Number of participants and studies	
<b>Serious adverse events</b> Follow-up: 8.8-48 months	The use of the tetravalent dengue vaccine could result in a slight increase in serious adverse events.	720 per 100 000	749 per 100 000	<b>RR 1.04</b> (0.69 to 1.55)	⊕⊕○○ Low <sup>a</sup>
		Difference: 29 more patients per 100 000 (95% CI: 223 less to 396 more patients)		Based on data from 23 540 individuals in 5 studies <sup>17,22-25</sup>	
<b>Adverse events of any kind</b> Follow-up: 8.8-48 months	The use of the tetravalent dengue vaccine could result in an increase in adverse events of any kind.	44 per 1000	62 per 1000	<b>RR 1.41</b> (0.79 to 2.52)	⊕⊕○○ Low <sup>b</sup>
		Difference: 18 more patients per 1000 (95% CI: 9 less to 67 more patients)		Based on data from 21 348 individuals in 3 studies <sup>21,23,25</sup>	

RR: relative risk; CI: 95% confidence interval; RCT: randomized controlled trial

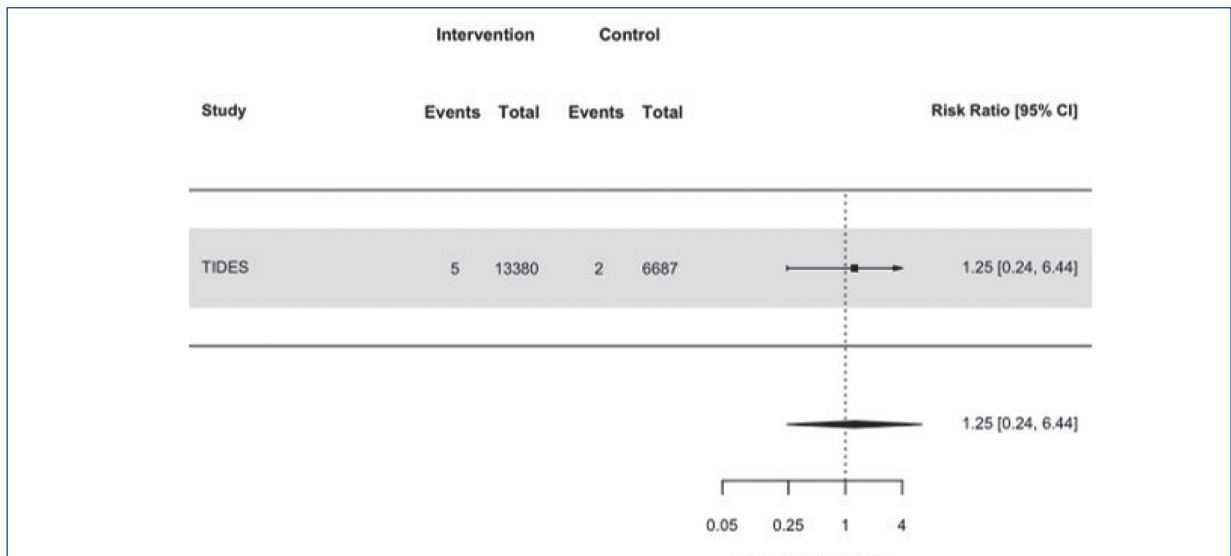
## Explanations

- The certainty of the evidence was classified as very low due to extremely serious imprecision.
- The certainty of the evidence was classified as low due to serious inconsistency and serious imprecision.
- Baseline risks of patients with Dengue taken from: Ministry of Health Argentina. Dengue in Argentina: Epidemiological, clinical, and virological characterization of the current outbreak. Epidemiological Alert. 2023;
- Baseline risks taken from: Pan American Health Organization. Dengue - PAHO/WHO. paho.org.
- Outcome defined according to the World Health Organization: Dengue guidelines for diagnosis, treatment, prevention and control: new edition. World Health Organization (WHO). 2009;
- Outcome defined by symptomatic infection with serological diagnosis by PCR
- Outcome defined as bleeding, thrombocytopenia or shock

## References

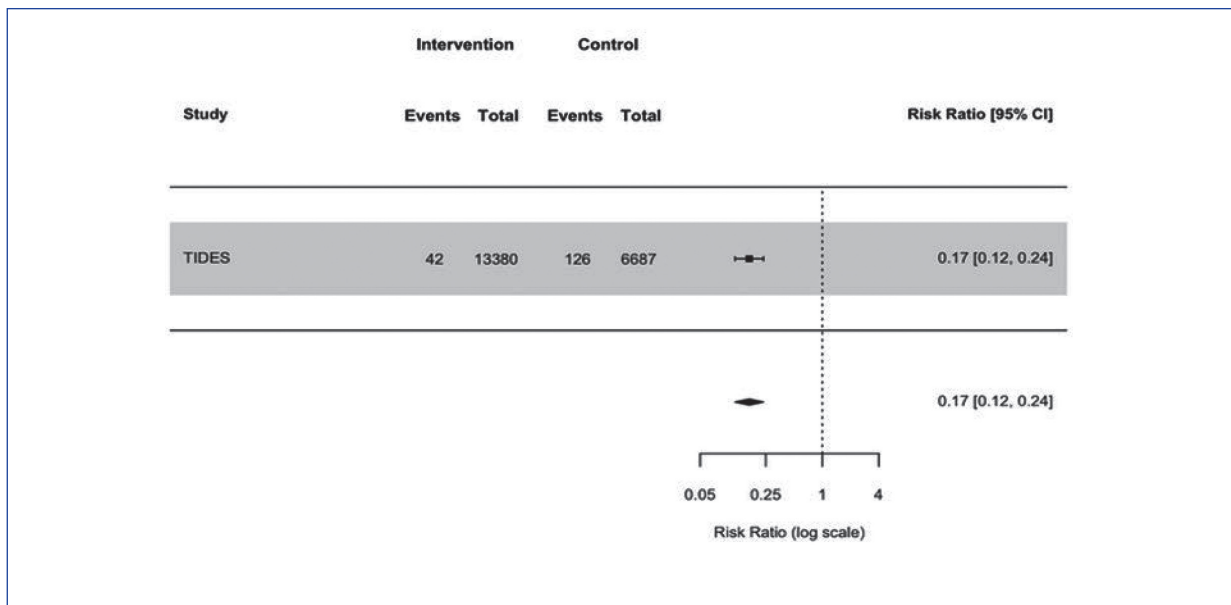
- Tricou V, Winkle PJ, Tharenos LM, et al. Consistency of immunogenicity in three consecutive lots of a tetravalent dengue vaccine candidate (TAK-003): a randomized placebo-controlled trial in US adults. *Vaccine* 2023; 41: 6999-7006.
- Rivera L, Biswal S, Sáez-Llorens X, et al. Three-year efficacy and safety of takeda's dengue vaccine candidate (TAK-003). *Clin Infect Dis* 2022; 75: 107-17.
- Biswal S, Reynales H, Saez-Llorens X, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. *N Engl J Med* 2019; 381: 2009-19.
- Tricou V, Sáez-Llorens X, Yu D, et al. Safety and immunogenicity of a tetravalent dengue vaccine in children aged 2–17 years: a randomised, placebo-controlled, phase 2 trial. *The Lancet* 2020; 395: 1434-43.
- Biswal S, Mendez Galvan JF, Macias Parra M, et al. Immunogenicity and safety of a tetravalent dengue vaccine in dengue-naïve adolescents in Mexico City. *Rev Panam Salud Pública* 2021; 45: e67.
- Sirivichayakul C, Barranco-Santana EA, Esquilin-Rivera I, et al. Safety and immunogenicity of a tetravalent dengue vaccine candidate in healthy children and adults in dengue-endemic regions: a randomized, placebo-controlled phase 2 study. *J Infect Dis* 2016; 213: 1562-72.

**Figure 3** | Meta-analysis for the outcome mortality



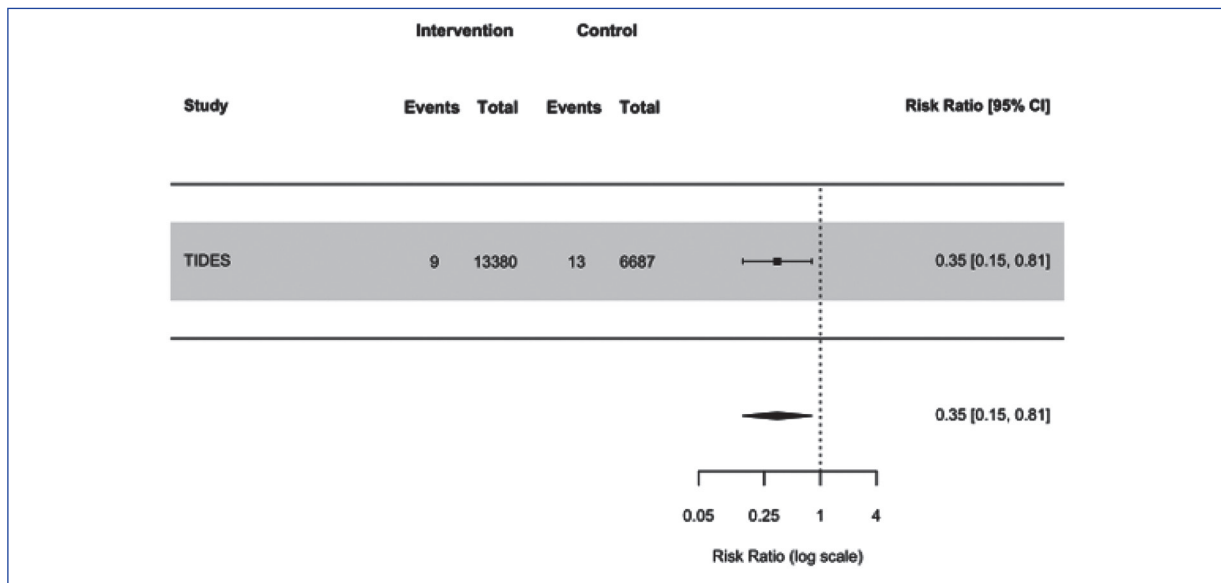
CI: confidence interval

**Figure 4** | Meta-analysis for the outcome of severe dengue virus infection



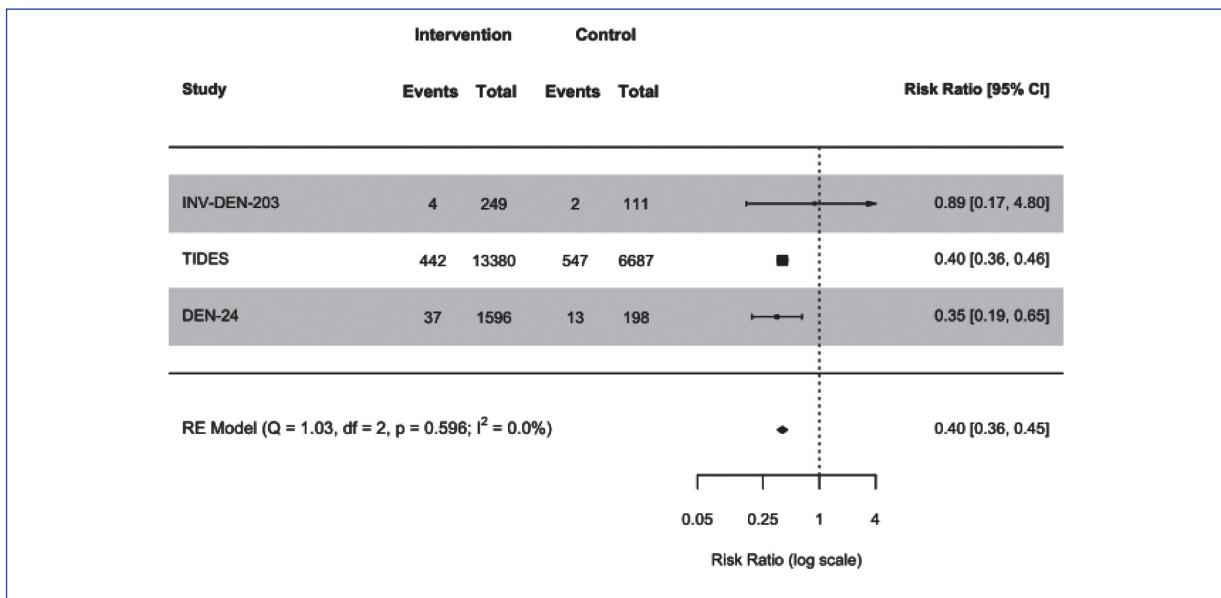
CI: confidence interval

**Figure 5** | Meta-analysis for the outcome of hemorrhagic fever



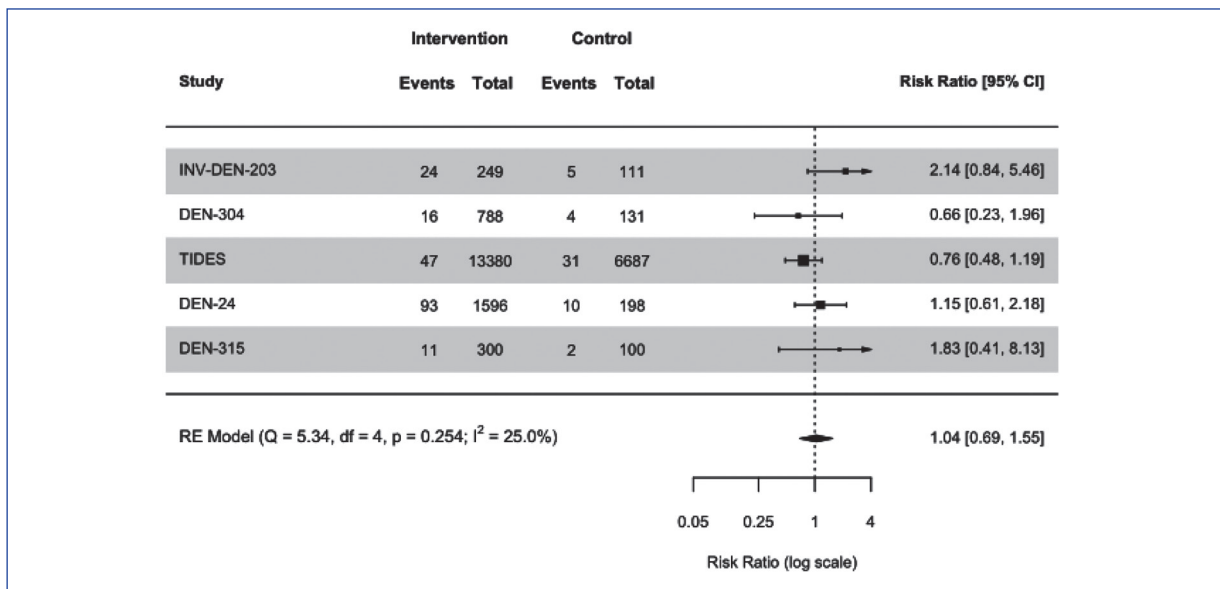
CI: confidence interval

**Figure 6** | Meta-analysis for the outcome of dengue virus infection



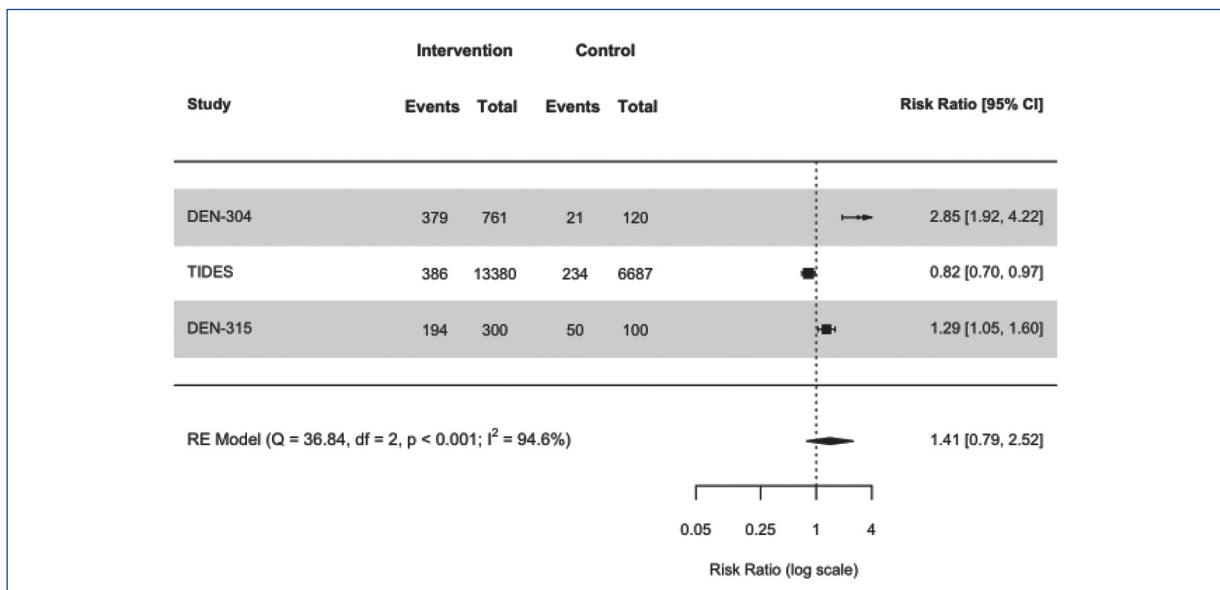
CI: confidence interval; RE: random effects

**Figure 7** | Meta-analysis for the outcome of serious adverse events



CI: confidence interval; RE: random effects

**Figure 8** | Meta-analysis for the outcome of any adverse event



CI: confidence interval; RE: random effects

tation, emphasizing the necessity for tailored recommendations for specific populations. In decision-making, regional differences should be considered, such as variations in prevalence and the risk of severe dengue infection.

While the study confirms the vaccine's effectiveness in preventing severe outcomes, a cautious interpretation of safety profiles is necessary. The observed low certainty underscores the need for ongoing vigilance and post-marketing surveillance to comprehensively assess any potential adverse effects associated with the vaccine. Continuous monitoring, especially in diverse populations and age groups, is essential for understanding its long-term safety. This aligns with the uncertainties identified by the vaccine working group of the Argentinian Ministry of Health<sup>28</sup> regarding vaccination in the most affected regions and variations in risk between different situations. Health policymakers should prioritize surveillance of vaccine-associated adverse events in different populations.

To the best of our knowledge, an important strength is that this study represents the first systematic review of the tetravalent dengue vaccine employing a rigorous methodology such as the GRADE approach. Additionally, this study underscores the importance of considering baseline risk when evaluating the efficacy and safety of different health interventions. It is also important to remark that this review focuses on one tetravalent vaccine, another global vaccine is currently in phase 3 trials<sup>29</sup>.

Several limitations are acknowledged, including a potential lack of diversity in study populations, inadequate duration of follow-up in some

studies, and incomplete coverage of age groups (only one study on vaccine immunogenicity included adults, with a mean age of 41.4 years)<sup>17</sup>. Notably, not all primary studies reported outcomes among the subgroup of individuals with previous dengue infections, a suspected risk factor for severe disease upon reinfection. However, in those that reported it, the effectiveness was similar in both the seropositive and seronegative patients<sup>19-23</sup>. Also, relative effects tend to remain consistent between subgroups<sup>30</sup>, with differences likely related to baseline risk.

In conclusion, this review establishes the TAK-003 tetravalent dengue vaccine as an effective tool for mitigating dengue's impact, particularly in highly endemic regions, with high certainty in evidence for effectiveness. While emphasizing efficacy, it also highlights the need for continued research and surveillance, especially regarding safety across diverse populations and age groups, particularly in older adults since this population was not included in the clinical trials. This study underscores the importance of evidence-based decisions, reinforcing the importance of comprehensive investigations into both effectiveness and safety in dengue prevention and control, which should be validated in different infection risk situations in specific populations.

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**Conflict of interest:** None to declare

## References

1. Pan American health organization / World health organization. Dengue report 2023. In: <https://www.paho.org/es/temas/dengue>; accessed December 2023.
2. Pan American Health Organization / World Health Organization. In: [https://www3.paho.org/data/index.php/es/temas/indicadores-dengue-dengue-nacional.html](https://www3.paho.org/data/index.php/es/temas/indicadores-dengue/dengue-nacional.html) Dengue report; accessed December 2023.
3. Ministerio de Salud de Argentina. Dengue en Argentina: caracterización epidemiológica, clínica y virológica del brote actual. 2023. In: [https://bancos.salud.gob.ar/sites/default/files/2023-04/20230418\\_Alerta\\_dengue.pdf](https://bancos.salud.gob.ar/sites/default/files/2023-04/20230418_Alerta_dengue.pdf); accessed December 2023.

5. Argentina.gob.ar. In: <https://www.argentina.gob.ar/noticias/la-anmat-aprobo-el-uso-de-la-vacunadel-laboratorio-takeda-contrael-dengue>; accessed December 2023.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
7. QDENGGA® vacuna tetravalente contra el dengue (elaborada con virus vivos, atenuados). In: <https://content.takeda.com/?contenttype=PI&product=QDEN&language=ESP&country=ARG&documentnumber=1>; accessed December 2023.
8. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control: new edition.; 2009. In: <http://www.ncbi.nlm.nih.gov/books/NBK143157/>; accessed December 2023.
9. Rada G, Pérez D, Araya-Quintanilla F, et al. Epistemonikos: a comprehensive database of systematic reviews for health decision-making. *BMC Med Res Methodol* 2020; 20: 286.
10. Epistemonikos Foundation. Collaboratron™ [Software]. L.OVE Platf. Published online 2017. In: <https://www.epistemonikos.org/en/documents/647cdbf675135cca583bcfeca7dad0560f80e02>; accessed December 2023.
11. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
12. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. In: <https://training.cochrane.org/handbook/current/chapter-10>; accessed December 2023
13. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* 2013; 66: 158-72.
14. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 2013; 66: 173-83.
15. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. *J Clin Epidemiol* 2021; 137: 163-75.
16. Sirivichayakul C, Barranco-Santana EA, Rivera IE, et al. Long-term safety and immunogenicity of a tetravalent dengue vaccine candidate in children and adults: a randomized, Placebo-Controlled, Phase 2 Study. *J Infect Dis* 2020; 225: 1513-20.
17. Tricou V, Winkle PJ, Tharenos LM, et al. Consistency of immunogenicity in three consecutive lots of a tetravalent dengue vaccine candidate (TAK-003): a randomized placebo-controlled trial in US adults. *Vaccine* 2023; 41: 6999-7006.
18. Biswal S, Borja-Tabora C, Vargas LM, et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2020; 395:1423-33.
19. Sáez-Llorens X, Biswal S, Borja-Tabora C, et al. Effect of the tetravalent dengue vaccine TAK-003 on sequential episodes of symptomatic dengue. *Am J Trop Med Hyg* 2023; 108: 722-6.
20. López-Medina E, Biswal S, Saez-Llorens X, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents 2 years after vaccination. *J Infect Dis* 2020; 225: 1521-32.
21. Rivera L, Biswal S, Sáez-Llorens X, et al. Three-year efficacy and safety of takeda's dengue vaccine candidate (TAK-003). *Clin Infect Dis* 2022; 75: 107-17.
22. Biswal S, Reynales H, Saez-Llorens X, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. *N Engl J Med* 2019; 381: 2009-19.
23. Tricou V, Sáez-Llorens X, Yu D, et al. Safety and immunogenicity of a tetravalent dengue vaccine in children aged 2–17 years: a randomised, placebo-controlled, phase 2 trial. *The Lancet* 2020; 395: 1434-43.
24. Biswal S, Mendez Galvan JF, Macias Parra M, et al. Immunogenicity and safety of a tetravalent dengue vaccine in dengue-naïve adolescents in Mexico City. *Rev Panam Salud Pública* 2021; 45: e67.
25. Sirivichayakul C, Barranco-Santana EA, Esquillin-Rivera I, et al. Safety and immunogenicity of a tetravalent dengue vaccine candidate in healthy children and adults in dengue-endemic regions: a randomized, placebo-controlled phase 2 study. *J Infect Dis* 2016; 213: 1562-72.

26. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. *J Clin Epidemiol* 2011; 64: 1283-93.
27. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach - ScienceDirect. In: <https://www.sciencedirect.com/science/article/pii/S0895435622001871>; accessed February 2024
28. DICEI. Ministerio de Salud Argentina. Vacuna contra dengue. Posición del grupo de trabajo. Reunión CoNaInm 9 11 2023. In: [conain-09-11-23-vacuna-contra-dengue-posicion-grupo-de-trabajo.pdf](#); accessed March 2024.
29. Kallás EG, Cintra MAT, Moreira JA et al. Live, attenuated, tetravalent butantan-dengue vaccine in children and adults. *N Engl J Med* 2024; 390: 397-408.
30. Guyatt G, Zhao Y, Mayer M, et al. GRADE guidance 36: updates to GRADE's approach to addressing inconsistency. *J Clin Epidemiol* 2023; 158: 70-83.

**Appendix 1** | Search strategy

PICO Term	#	Boolean strategy
Intervention	1	dengue*
	2	DENV*
	3	#1 OR #2
	4	vaccin*
	5	immunization*
	6	immunisation*
	7	reactogenic*
	8	#4 OR #5 OR #6 OR #7
	9	#3 AND #8
	10	Dengvaxia*
	11	CYDTDV* OR "CYD-TDV" OR "CYD TDV"
	12	Qdenga*
	13	TAK003* OR "TAK-003" OR "TAK 003"
	14	#10 OR #11 OR #12 OR #13
	15	#8 OR #9
Clinical trials	16	"Randomized trial"[EET]
	17	randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*
	18	#15 AND (#16 OR #17)

EET (Epistemonikos Evidence Taxonomy) is the system used in the Epistemonikos database to index articles. It consists of various descriptors, organized into categories, which are hierarchically related to each other. Some of its categories are specific to the components of questions in PICO format or equivalents.



## Appendix 2 | Exclusion criteria

Reference of excluded studies	Reason for exclusion
1. Jackson LA, Rupp R, Papadimitriou A, et al. A phase 1 study of safety and immunogenicity following intradermal administration of a tetravalent dengue vaccine candidate. <i>Vaccine</i> 2018; 36: 3976-83.	Wrong Design
2. Turner M, Papadimitriou A, Tricou V, et al. Immunogenicity and safety of lyophilized and liquid dengue tetravalent vaccine candidate formulations in healthy adults: a randomized, phase 2 clinical trial. <i>Hum Vaccin Immunother</i> 2020; 16: 2456-64.	Wrong Design
3. Rupp R, Luckasen GJ, Kirstein JL, et al. Safety and immunogenicity of different doses and schedules of a live attenuated tetravalent dengue vaccine (TDV) in healthy adults: a phase 1b randomized study. <i>Vaccine</i> 2015; 33: 6351-9.	Wrong Design
4. Tricou V, Eyre S, Ramjee M, et al. A randomized phase 3 trial of the immunogenicity and safety of coadministration of a live-attenuated tetravalent dengue vaccine (TAK-003) and an inactivated hepatitis a (HAV) virus vaccine in a dengue non-endemic country. <i>Vaccine</i> 2023; 41: 1398-407.	Wrong Intervention
5. Sharma M, Watkins H, Kassa Y, et al. Magnitude and functionality of the NS1-specific antibody response elicited by a live-attenuated tetravalent dengue vaccine candidate. <i>J Infect Dis</i> 2020; 221: 867-77.	Wrong Outcome
6. Michlmayr D, Andrade P, Narvekar P, et al. Characterization of the type-specific and cross-reactive B-cell responses elicited by a live-attenuated tetravalent dengue vaccine. <i>J Infect Dis</i> 2021; 223: 247-57.	Wrong Outcome
7. Patel SS, Rauscher M, Kudela M, Pang H. Clinical safety experience of TAK-003 for dengue fever: a new tetravalent live attenuated vaccine candidate. <i>Clin Infect Dis</i> 2023; 76: e1350-e9.	Wrong Design
8. Tricou V, Low JG, Oh HM, et al. Safety and immunogenicity of a single dose of a tetravalent dengue vaccine with two different serotype-2 potencies in adults in Singapore: a phase 2, double-blind, randomised, controlled trial. <i>Vaccine</i> 2020; 38: 1513-9.	Wrong Design
9. Tricou V, Gottardo R, Egan MA, et al. Characterization of the cell-mediated immune response to Takeda's live-attenuated tetravalent dengue vaccine in adolescents participating in a phase 2 randomized controlled trial conducted in a dengue-endemic setting. <i>Vaccine</i> 2022; 40: 1143-51.	Wrong Design
10. Tricou V, Essink B, Ervin JE, et al. Immunogenicity and safety of concomitant and sequential administration of yellow fever YF-17D vaccine and tetravalent dengue vaccine candidate TAK-003: A phase 3 randomized, controlled study. <i>PLoS Negl Trop Dis</i> 2023; 17: e0011124.	Wrong Intervention
11. Sáez-Llorens X, Tricou V, Yu D, et al. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study. <i>Lancet Infect Dis</i> 2017; 17: 615-25.	Interim results
12. Sabchareon A, Lang J, Chanthavanich P, et al. Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. <i>Pediatr Infect Dis J</i> 2004; 23: 99-109.	Wrong Intervention
13. Halim C, Tricou V, Nordio F, Folschweiller N. Bridging the immunogenicity of a tetravalent dengue vaccine candidate (TAK-003) from children and adolescents to adults. <i>NPJ Vaccines</i> 2023;130: S10.	Wrong Design
14. Sáez-Llorens X, Tricou V, Yu D, et al. Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2-17 years in Asia and Latin America: 18-month interim data from a phase 2, randomised, placebo-controlled study. <i>Lancet Infect Dis</i> 2018; 18: 162-70.	Interim results
15. George SL, Wong MA, Dube TJ, et al. Safety and immunogenicity of a live attenuated tetravalent dengue vaccine candidate in flavivirus-naive adults: a randomized, double-blinded phase 1 clinical trial. <i>J Infect Dis</i> 2015; 212: 1032-41.	Wrong Intervention

**Appendix 3** | Details of Risk of bias assessment

Study identification	
ID Epistemonikos	e6bed0f1e1928e1792d3cd492b3683b7ba1184eb
Study	DEN-24
Author	Tricou V, 2020
Design	Randomized clinical trial
Details of Risk of bias assessment	
Domain	Details of judgment
Risk of bias arising from the randomization process	Low 1.1 Yes 1.2 Yes 1.3 Probably no
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low 2.1 No 2.2 No 2.6 Yes
Missing outcome data	Low 3.1 Probably yes
Risk of bias in measurement of the outcome	Low 4.1 Probably no 4.2 Probably no 4.3 Probably no
Risk of bias in selection of the reported result	Low 5.1 Yes 5.2 No 5.3 No
Overall judgment	Low Risk of bias
Study identification	
ID Epistemonikos	6b522f23c032fa672a62b15dbb4f939c46d8a6bd
Study	DEN-304
Author	Tricou V, 2023
Design	Randomized clinical trial
Details of Risk of bias assessment	
Domain	Details of judgment
Risk of bias arising from the randomization process	Low 1.1 Yes 1.2 Yes 1.3 No
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low 2.1 No 2.2 No 2.6 Probably yes
Missing outcome data	Low 3.1 Probably yes
Risk of bias in measurement of the outcome	Some concerns 4.1 Probably no 4.2 Probably no 4.3 Probably no
Risk of bias in selection of the reported result	Low 5.1 Yes 5.2 No 5.3 No
Overall judgment	Low risk of bias
Study identification	
ID Epistemonikos	fab54ba9094b0789e509015213fb56351188a104
Study	DEN-315
Author	Biswal S, 2021
Design	Randomized clinical trial
Details of Risk of bias assessment	
Domain	Details of judgment
Risk of bias arising from the randomization process	Low 1.1 Yes 1.2 Yes 1.3 Probably no
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low 2.1 No 2.2 No 2.6 Probably yes
Missing outcome data	Low 3.1 Probably yes
Risk of bias in measurement of the outcome	Some concerns 4.1 Probably no 4.2 Probably no

(continúa)

(continuation)

Risk of bias in selection of the reported result	4.3 Probably yes 4.4 Probably yes 4.5 Probably yes Low 5.1 Probably yes 5.2 No 5.3 No
Overall judgment	High risk of bias
<b>Study identification</b>	
ID Epistemonikos	6584891b732ad4a83b704833
Study	INV-DEN-203
Author	Sirivichayakul C, 2022
Design	Randomized clinical trial
<b>Details of Risk of bias assessment</b>	
<b>Domain</b>	<b>Details of judgment</b>
Risk of bias arising from the randomization process	Low 1.1 Yes 1.2 Probably yes 1.3 Probably no
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Some concerns 2.1 No 2.2 No 2.6 No information 2.7 Probably no
Missing outcome data	Some concerns 3.1 No 3.2 Probably no 3.3 Probably no
Risk of bias in measurement of the outcome	Low 4.1 No 4.2 Probably no 4.3 No
Risk of bias in selection of the reported result	Low 5.1 Yes 5.2 No 5.3 No
Overall judgment	Some concerns Study identification
<b>Study identification</b>	
ID Epistemonikos	933ead8561d69383a95eded7ba8583a02b21f385
Study	TIDES
Author	Sáez-Llorens X, 2023
Design	Randomized clinical trial
<b>Details of Risk of bias assessment</b>	
<b>Domain</b>	<b>Details of judgment</b>
Risk of bias arising from the randomization process	Low 1.1 Yes 1.2 Probably yes 1.3 Probably no
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low 2.1 No 2.2 No 2.6 Probably yes
Missing outcome data	Low 3.1 Probably yes Some concerns 4.1 Probably no 4.2 Probably no 4.3 Probably yes 4.4 Probably yes 4.5 Probably no
Risk of bias in measurement of the outcome	Low 5.1 Yes 5.2 No 5.3 No