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SYSTEMATIC REVIEW AND META-ANALYSIS

Adult Immunogenicity and Descriptive Safety of TAK-003 Dengue Vaccination: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Adult TAK-003 data differ by formulation, baseline dengue status, coadministration, and outcome definition.

Objective: To synthesize adult immunogenicity and safety of the licensed two-dose final formulation of TAK-003.

Methods: We searched PubMed, Scopus, CENTRAL-derived records, registries, regulatory sources, and citations to the final search update. Screening, extraction, appraisal, and analysis used a reproducible computational workflow without independent duplicate verification. Seropositivity and 270-day serious adverse event (SAE) risk were modeled with binomial-normal logit models; comparative reactogenicity used random-effects risk ratios with modified Hartung-Knapp intervals. Certainty was graded by outcome, and a sensitivity analysis added the single-arm DEN307 cohort.

Results: Of 1,090 records, 606 unique records (553 publications and 53 registry records) were screened; 473 publications were excluded and 80 were retrieved. Five trials supplied quantitative outcomes. Among 620 baseline-seronegative adults, pooled seropositivity about 30 days after dose 2 was 98.7% for DENV-1 (95% CI 95.8–99.6), 99.0% for DENV-2 (97.9–99.6), 96.9% for DENV-3 (95.2–98.0), and 98.4% for DENV-4 (97.0–99.1). With DEN307 added, estimates were 98.8%, 99.2%, 97.1%, and 98.5% (752 participants per serotype). Across four cohorts, 29/1,468 participants had an SAE through day 270 (pooled risk 2.0%, 95% CI 1.4–2.8). Pain and headache estimates, each from two studies, were highly imprecise.

Conclusion: Final-formulation TAK-003 gave high short-term seropositivity in selected adult trial populations. The SAE risk was uncontrolled and does not establish comparative safety. Certainty was low or very low, and inference is limited by study size, surrogate outcomes, and uncontrolled safety data.

1. Introduction

Adult dengue vaccination needs evidence that separates immune response from prevention of clinical disease. TAK-003, marketed as Qdenga, is a live attenuated tetravalent dengue vaccine given as two subcutaneous doses, three months apart. Europe authorizes it from four years of age[1]. The World Health Organization (WHO) recommendation for programmatic use is narrower: it centers on children aged 6–16 years in settings with high dengue burden and transmission intensity[2]. Adult-specific evidence is relevant to clinical interpretation. Even so, a regulatory indication and a population vaccination recommendation do not answer the same question[3].

Adult development studies have examined several aspects of TAK-003: early dose and schedule choices[4,5], immunogenicity bridging[6], and how vaccine performed at different points of its shelf-life[7]. Early phase trials and later studies address related but distinct formulations and questions[8]. Linkage matters. An adult immunobridging analysis has to be tied carefully to its source trial, because a later publication may reuse participants already described elsewhere, and counting each publication as a new study would overstate the independent evidence.

Neutralizing antibody responses are informative biological outcomes. Reading them correctly depends on baseline dengue exposure, on the dengue virus (DENV) serotype the assay measures, on the positivity threshold, and on the time elapsed since vaccination. A participant who was already seropositive may remain so without meeting a study's definition of seroconversion. Serotype-specific positivity, tetravalent positivity, geometric mean titers, and within-person fold rises therefore call for distinct estimands. The adult bridging literature gives a reason to examine these responses systematically. It also demands that immunological comparison stay separate from directly observed protection against dengue.[6]

Safety evidence depends on measurement in much the same way. Short-term solicited reactions and cumulative serious adverse events (SAEs) cover different follow-up periods and different levels of clinical severity. A comparative trial can estimate a vaccine-versus-control effect. An uncontrolled cohort cannot; it only describes events among vaccinated participants. Coadministration adds a further difficulty,

because it can alter both the relevant comparator and the attribution of events. Research on adult coadministration with yellow fever vaccine shows why the vaccination context must stay visible in an evidence synthesis.[8]

Earlier meta-analyses have already looked at TAK-003 immunogenicity, safety, or efficacy. This review does not claim to be the first synthesis. Its purpose is to examine adult-specific evidence, linking reports to trials explicitly and separating studies by baseline serostatus, formulation, regimen, and coadministration. Whether that adds value depends on the evidence retrieved and on how comparable it is. A new pooled estimate was not to be produced merely because several reports existed.[9,10]

We aimed to assess systematically the immunogenicity and safety of TAK-003 in adults aged at least 18 years. The primary immunogenicity outcomes were serotype-specific seropositivity about one month after the second dose. The primary safety outcome was the risk of at least one all-cause serious adverse event, counted from the first vaccination to roughly six months after the second dose. Adult-specific clinical dengue outcomes were considered when measured directly and reported separately.

Recent adult and mixed-age studies have widened the evidence on final-formulation immunogenicity, lot consistency, coadministration, cellular responses, controlled human challenge, long-term safety, traveler tolerability, special populations, and implementation. They supply context for the adult-focused estimands used here. The evidence map summarizes them [2,3,11–42].

We designed the review to keep the clinical meaning of each estimand intact. This held even when it reduced the number of studies eligible for a pooled estimate.

Novelty and aim of the study

TAK-003 reports have multiplied quickly, and they use different formulations, baseline dengue classifications, coadministration schedules, outcome definitions and follow-up windows. This creates an evidence gap. We did not treat every adult report as interchangeable. Each report was linked to its parent trial, the licensed final formulation was kept apart from early or coadministered regimens, and immunogenicity, uncontrolled serious-adverse-event frequency and comparative reactogenicity were treated as separate estimands. The review also makes the eligibility boundary visible through a prespecified sensitivity analysis that adds an otherwise eligible final-formulation single-arm cohort. It further presents a certainty summary beside outcome-specific risk-of-bias judgments. The structure is meant to improve interpretability and reproducibility. It also guards against two errors: describing high antibody positivity as adult clinical protection, and reading a single-arm SAE proportion as comparative vaccine safety.

We aimed to synthesize adult evidence on the final two-dose TAK-003 regimen by estimating three quantities: (1) serotype-specific seropositivity about 30 days after dose 2 in baseline-seronegative adults; (2) cumulative all-cause serious-adverse-event risk to about day 270 in compatible vaccinated cohorts; and (3) comparative risks of solicited injection-site pain and headache after dose 1 where placebo data existed. We also aimed to map eligible adult evidence that could not be pooled, to appraise risk of bias and certainty, and to test how including the final-formulation single-arm cohort changes results in an eligibility sensitivity analysis. Finally, we aimed to define the limits of inference on clinical effectiveness and long-term safety.

2. Methods

Protocol and registration

The protocol was registered prospectively in PROSPERO (CRD420261549188). Registration preceded data extraction. The protocol prespecified eligibility, outcomes, time windows, formulation strata, statistical models, and the computational workflow. Independent duplicate verification was not done.

Eligibility

We included adults aged at least 18 years who received TAK-003, Qdenga, or the precursor DENVax. Mixed-age studies needed adult results that could be extracted separately. Randomized trials, nonrandomized comparative studies, and prospective cohorts were eligible. Primary quantitative strata were limited to the final or licensed formulation, given as two doses about three months apart. Early formulations, altered schedules, boosters, and coadministration were analyzed separately. Excluded were reviews, case reports, passive surveillance lacking an analytic denominator, and pediatric data that could not be separated.

Outcomes

Primary immunogenicity outcomes were serotype-specific seropositivity 28–42 days after dose 2 in baseline-seronegative or flavivirus-naive adults. The primary safety outcome was the proportion of participants with at least one all-cause serious adverse event, from first vaccination to about day 270. Secondary comparative outcomes were solicited injection-site pain within seven days, and headache within 14 days, after dose 1.

Search and selection

Searches covered PubMed, Scopus, records derived from the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, European Union Clinical Trials Information System (EU CTIS) records, regulatory documents, and citation sources up to the final search update. Exact searches and raw exports are archived. Of 1,090 source records, 484 duplicates were removed. That left 606 unique records, and the automated workflow screened every one. Records it judged uncertain were kept; none was silently excluded. Two gaps arose. The WHO International

Clinical Trials Registry Platform (ICTRP) returned a gateway error. A native complete CENTRAL export was restricted by authentication. Both remain in the audit trail.

Extraction and risk appraisal

Registry result cells were archived verbatim, with JSON locators and checksums. An integer event count was rebuilt from a percentage and a denominator only when the compatible integer was unique. Every transformation was logged. Vaccine lots in multiarm studies were combined only when participants did not overlap. RoB 2 (Cochrane risk-of-bias tool, version 2) was applied to comparative randomized outcomes. Uncontrolled proportions were appraised with a documented checklist informed by the Joanna Briggs Institute (JBI), aligned with the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data; no software version applies to it. The appraisal covered selection, outcome measurement, completeness, denominator integrity and analytic appropriateness. Single-arm estimates were not turned into causal effects. Judgments were recorded in the structured appraisal dataset and linked to the corresponding study outcome.

Statistical analysis

Proportions were pooled with binomial-normal random-intercept logit generalized linear mixed models, fitted by maximum likelihood with adaptive quadrature (15 points). No arbitrary continuity correction entered the pooled likelihood. Individual studies received exact Clopper-Pearson intervals. Comparative dichotomous outcomes were expressed as risk ratios (RRs) and pooled by restricted maximum likelihood (REML) random effects. A modified Hartung-Knapp variance multiplier was used, constrained to be at least one. Fewer than 10 studies were available, so funnel plots, asymmetry tests, meta-regression, and formal subgroup interaction tests were not performed. Software: R 4.5.3, meta 8.2-1, and metafor 4.8-0.

Search governance and information-source coverage

The search was built to find reports. It did not assume that each publication was an independent study. Identification terms paired TAK-003, TAK003, Qdenga, DENVax, Takeda and Inviragen with dengue and vaccination vocabulary. Adult and outcome filters were not applied at this stage, because mixed-age studies and registry records can hold adult strata that titles and abstracts do not show. The archived search package records the platform, query string, coverage window and export for every source stream. PubMed, Scopus-derived records, CENTRAL-derived records, ClinicalTrials.gov, EU/CTIS records, regulatory material and citation sources were treated as complementary streams. WHO ICTRP was attempted but returned a gateway error. A native complete CENTRAL export was limited by authentication. We report both as coverage limitations. Neither was converted into a negative search. The evidence map thus reflects a completed local disposition of retrieved publication candidates, not a claim that every eligible report in every planned source was captured.

Report-to-study linkage and overlap control

A report, a study, a comparison, an arm and an effect estimate were stored as separate entities. TAK-003 evidence spans primary trial reports, lot-consistency reports, immunobridging analyses, coadministration studies, long-term follow-up, registry result records and real-world cohorts, which made the split necessary. Before a report could join a quantitative pool, we compared trial identifiers, sponsor identifiers, formulation, age eligibility, setting, recruitment period and outcome timing. DEN304, DEN305 and DEN314 counted as distinct randomized trials in the primary immunogenicity synthesis. DEN307 and DEN302 fed the safety evidence only: their adult or baseline-serostatus structure did not match the prespecified primary endpoint, so they could not add immunogenicity trials. Linked publications that added an outcome or context stayed in the evidence map. Their participants were not counted again. The pregnancy report, German survey, CATdenga cohort, TravVacNet network and torque teno virus (TTV) study remained narrative evidence, since their populations, estimands or follow-up windows did not match the principal pools.

Data extraction and management

Extraction drew on literal registry cells, full-text reports and, where available, supplementary material. Each numerical value was stored with its study or report identifier, outcome label, denominator, event definition, timepoint, formulation, baseline-serostatus classification, source locator and actor label. Registry result cells were archived with JSON paths and checksums. The schema kept randomized, tested and analyzed participants apart, together with vaccine and comparator arms, dose, follow-up window and outcome-specific denominators. Values marked not reported (NR) were never converted to zero. A value derived from a rounded percentage was reconstructed only when a unique compatible integer existed for the reported denominator, and the step was recorded as a derivation, not as a directly reported event count. Where a source gave no compatible denominator, the result stayed outside the pool. The point was important for immunogenicity, where the tested denominator was smaller than the enrolled vaccine arm. It was equally important for reactogenicity, where diary completion could differ from the safety population.

Outcome harmonization and estimands

The primary immunogenicity estimand was serotype-specific seropositivity about 30 days after dose 2 in baseline-seronegative or flavivirus-naive adults. Seropositivity followed the study assay threshold. It

was never relabeled as seroconversion, geometric mean titer, fourfold rise or clinical protection. DENV-1 through DENV-4 were four separate outcomes in the same participants. The primary safety estimand was cumulative all-cause SAE risk from first vaccination to about day 270, defined as the proportion of vaccinated adults with at least one event in a defined window. It is not a vaccine-attributable effect. Comparative reactogenicity was analyzed as vaccine-versus-placebo risk ratios for injection-site pain within seven days and headache within fourteen days after dose 1. Coadministration was separated from standalone vaccination. Early formulations, altered schedules and booster observations never entered the licensed two-dose primary strata.

Risk-of-bias, missingness and certainty decisions

Risk appraisal was specific to each outcome. RoB 2 domains were considered for randomized comparative outcomes. Uncontrolled proportions were appraised for selection, ascertainment, completeness and the absence of a counterfactual, and were never treated as causal effects. For seropositivity, the main concerns were selected or per-protocol immunogenicity populations and the indirectness of an antibody surrogate. For comparative reactogenicity, certainty was limited by incomplete demonstration of diary-card denominators and by the two-study sample. For the SAE proportion, event ascertainment was acceptable in the selected cohorts. Sparse events, different endemicity settings and no unvaccinated counterfactual still reduced certainty. The certainty table rates seropositivity and descriptive SAE risk as low and comparative reactogenicity as very low. These judgments inform the certainty ratings. They should be updated if the evidence or the estimand changes.

Certainty of evidence and evidence summary

Certainty was assessed for each pooled estimand with domains informed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach: risk of bias, inconsistency, indirectness, imprecision and publication or reporting bias.[43] Seropositivity is an immunogenicity surrogate and not a clinical outcome, so indirectness was retained even where point estimates were high. The uncontrolled SAE outcome was downgraded for the lack of a counterfactual and for sparse events. Its rating describes the precision and applicability of a cumulative frequency; it says nothing about confidence in a causal vaccine effect. Comparative reactogenicity was downgraded because only two studies contributed, Hartung-Knapp intervals were wide, and diary-card denominators were incompletely documented. The Summary of Findings table lists the resulting judgments with the reasons for downgrading, and they are detailed by outcome in the Results.

Search and reporting completeness

The manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The search description follows PRISMA-S principles.[44,45] Sensitivity checks of the screening tool were applied to the automated workflow.[46] Report-level evidence, study-level linkage and non-randomized descriptive material are reported separately. A full list of publication-level exclusions and their reasons is held in the screening log. Gaps in source coverage are stated openly, not presented as completed negative searches.

Sensitivity and decision thresholds

Sensitivity analyses tested decisions that could change interpretation materially. They were not a search for a favorable result. For seropositivity, the analysis that excluded the DEN305 sequence with later yellow-fever vaccination was retained as a model sensitivity and not promoted to the primary result. Leave-one-out fits were run for each primary serotype and for the day-270 SAE synthesis. For comparative reactogenicity we inspected common-effect estimates. The prespecified random-effects estimates with modified Hartung-Knapp intervals nevertheless stayed primary, because the scientific question concerned variation across settings and only two studies were available. A zero random-effect variance estimate in the SAE synthesis was reported with the sparse-event boundary caveat. Funnel plots, asymmetry tests, meta-regression and formal subgroup interaction tests were omitted; the independent study count was below a defensible threshold. No sensitivity result replaced the primary estimand without an explicit rationale.

3. Results

Search and source disposition

The combined searches produced 1,090 source records. After 484 duplicates were removed, 606 unique records remained: 553 publication records and 53 registry records. Title and abstract screening excluded 473 records and advanced 80 publication records to source assessment. Registries were assessed in a separate stream. Of those 80 publications, the evidence map includes 41 data-bearing or linked reports, and 39 reports were excluded with a recorded reason. No publication candidate remains unresolved. Figure 1 shows this reproducible report-level accounting. Registry records are kept apart because they may reproduce a publication from the same trial. The pooled estimands rely on trial-arm linkage documented in the extraction dataset, and the report-to-study mapping prevents additional independent study counts.

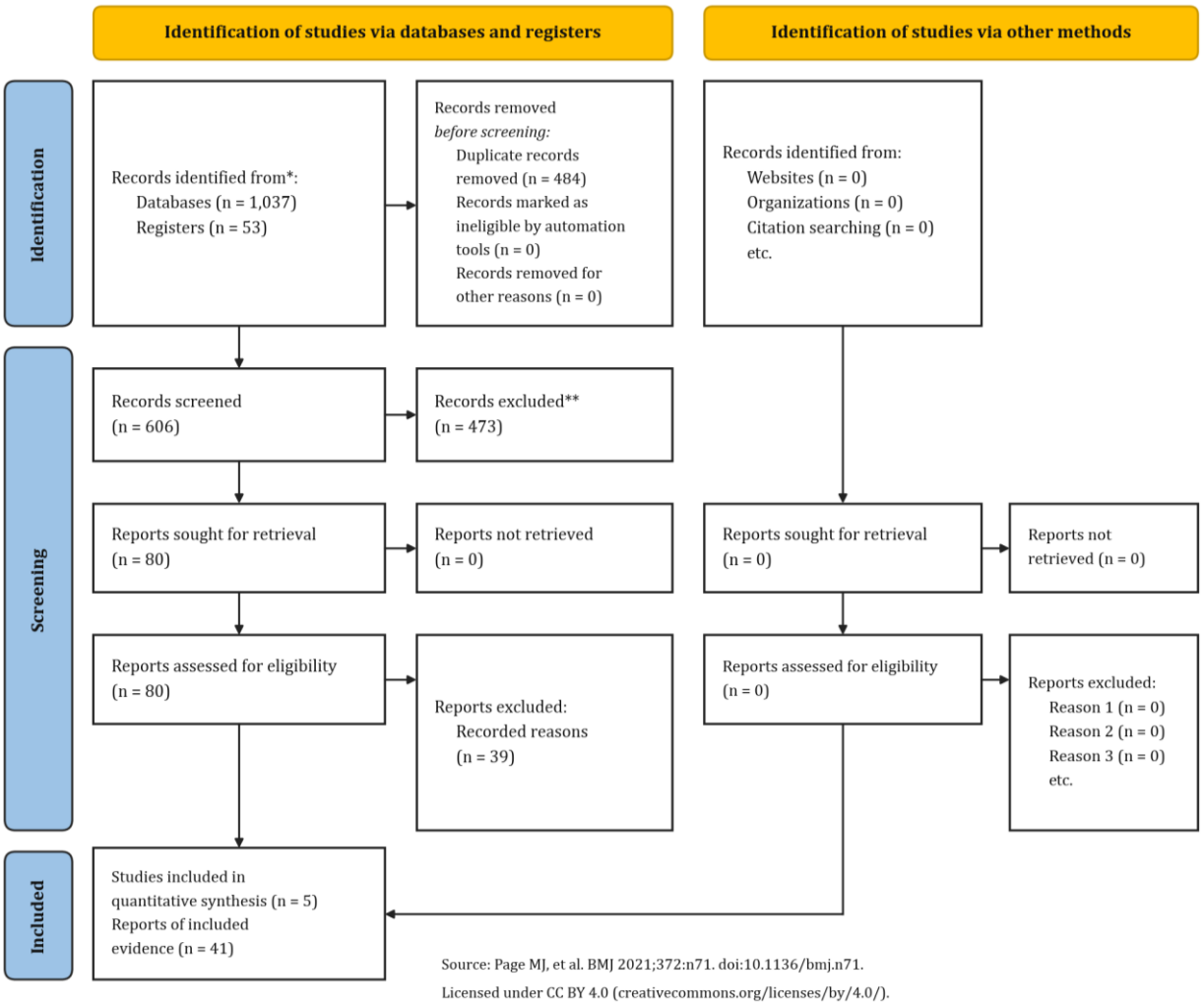


Figure 1. PRISMA 2020 flow diagram for the review. Records and reports are evidence items in the retrieval and selection process. Registry records are shown separately from publication reports to avoid double counting.

Characteristics of the quantitative evidence

Five independent final-formulation trials contributed to at least one quantitative outcome (Table 1): DEN304 (NCT03423173), DEN305 (NCT03342898), DEN314 (NCT03525119), DEN307 (NCT03771963), and DEN302 (NCT06060067). The seropositivity synthesis used selected vaccine arms from three randomized trials in non-endemic settings. The SAE synthesis combined four vaccine cohorts with matching day-270 surveillance. DEN302 was an endemic, mixed-baseline-serostatus adult cohort. DEN305 SAE follow-up ended at day 360, so it was not substituted into the primary day-270 endpoint.

Table 1. Characteristics of trials contributing to at least one quantitative outcome.

Study (registry ID)	Design, setting and regimen	Adult population / analyzed arm	Quantitative contribution	Pooling decision and separation
DEN304 (NCT03423173)	Randomized, placebo-controlled, non-endemic; final two-dose regimen (day 1 and day 90)	Baseline-seronegative immunogenicity subset, n = 367; safety set n = 788; three non-overlapping vaccine lots	Seropositivity: 359–364/367 by serotype at day 120; SAE: 16/788 through day 270; pain 324/761 vs 20/120 and headache 214/761 vs 27/120 after dose 1	Lots combined only within trial. Contributes to all primary pools except the registry-only streams. [Author query: define "registry-only streams"]
DEN305 (NCT03342898)	Randomized coadministration study, non-endemic; standalone TAK-003 sequence before later yellow-fever vaccination	Baseline-seronegative standalone arm, n = 198; day-120 endpoint	Seropositivity: 195–197/198 by serotype at day 120	Only the standalone pre-coadministration sequence entered the primary immunogenicity pool; later coadministration observations were kept separate.
DEN314 (NCT03525119)	Randomized coadministration study, non-endemic; standalone TAK-003 arm on final two-dose schedule	Baseline-seronegative standalone arm, n = 55; safety arm n = 300	Seropositivity: 51–55/55 by serotype at day 120; SAE: 8/300 through day 270	Hepatitis-A coadministration arm excluded from the primary estimands.

Study (registry ID)	Design, setting and regimen	Adult population / analyzed arm	Quantitative contribution	Pooling decision and separation
DEN307 (NCT03771963)	Prospective single-arm trial, non-endemic; final two-dose regimen	Adult vaccine safety set, n = 200; no comparator	SAE: 5/200 through day 270	Used for uncontrolled SAE risk only. Its immunogenicity reports were not substituted into the three-trial baseline-naive primary pool. [Author query: DEN307 seropositivity data (n = 132) are used in the sensitivity analysis but not listed here]
DEN302 (NCT06060067)	Randomized, placebo-controlled adult cohort, endemic setting; final two-dose regimen	Adult vaccine cohort with mixed baseline serostatus; safety n = 180; reactogenicity n = 179 vaccine / 60 placebo	SAE: 0/180 through day 270; pain 27/179 vs 7/60 and headache 14/179 vs 6/60 after dose 1	Kept outside the baseline-naive seropositivity pool; contributes to SAE and comparative reactogenicity.

SAE, serious adverse event.

Linkage and eligibility pattern of included reports

The 41 reports kept in the evidence map are not 41 independent clinical studies. They include primary randomized reports, registry result records, linked immunology analyses, formulation or lot reports, coadministration reports, long-term safety material and observational adult cohorts. The registry stream held 53 records, assessed separately from the 80 retrieved publication candidates. This stops a registry record from being counted as a second report when it reproduces a trial already represented by a publication. It also lets a registry record supply a compatible numeric result when an article gives no complete table, provided the trial identity and arm structure match. The 39 excluded publication reports comprise duplicate or superseded reports, methods or network papers without eligible TAK-003 adult outcome tables, reviews, background sources, passive surveillance without an analytic denominator and reports lacking a compatible adult endpoint. What remains uncertain is study-level reconciliation and human verification. No individual publication candidate is unresolved.

Endpoint-specific denominators and transformations

In each serotype-specific pooled analysis the primary seropositivity denominator was 620 adults. Events numbered 611 for DENV-1, 614 for DENV-2, 601 for DENV-3 and 610 for DENV-4. The denominator is the sum of the three compatible vaccine arms, not the enrolled sample of every parent trial. DEN304 combined disjoint vaccine lots within the trial. DEN305 contributed the standalone sequence given before later yellow-fever vaccination. DEN314 contributed the standalone vaccine arm, not the hepatitis-A coadministration arm. The SAE denominator was 1,468 vaccinated adults across DEN304, DEN314, DEN307 and the adult DEN302 cohort. Events were kept as reported, including zero events in DEN302. Reactogenicity used the outcome-specific denominators of the source registry records: 940 vaccine participants and 180 placebo participants across the two comparisons. All these denominators sit in the versioned CSV inputs. They were not reconstructed from the manuscript prose alone.

Durability, clinical outcomes and evidence kept outside pooling

The registry holds day-270 immunogenicity observations for some trials. Even so, the primary immunogenicity question was fixed at the post-dose-2 window, because the available adult studies gave no common long-term seropositivity estimand across all eligible sources. Durability observations, booster responses, cellular responses, breakthrough infection reports and pregnancy outcomes were kept as linked or narrative evidence unless their definitions and timepoints matched a prespecified pool. No adult clinical efficacy estimate was calculated from antibody positivity. A clinical dengue outcome needs direct ascertainment of symptomatic, virologically confirmed disease or hospitalization in an adult analytic population. The evidence map held no sufficiently comparable adult clinical endpoint for pooling. This limitation is substantive. High neutralizing-antibody positivity can support an immunogenicity conclusion, yet clinical protection and longer-term safety remain uncertain.

Disposition of non-pooled adult evidence

The non-pooled reports were not discarded. Each was given an explicit role in the evidence map. TravVacNet offers a multicenter traveler experience, with age-stratified reactogenicity and frequent coadministration. CATdenga offers prospective Spanish postmarketing follow-up in a mainly adult traveler population with a defined analytic cohort. The German survey provides a large self-reported tolerability denominator across a broad age range, and it also documents reporting bias and co-vaccination. The TTV study offers a mechanistic hypothesis about immune response in an adult cohort vaccinated against dengue (DGV-Vac). Its first-dose design and subgroup correlation, however, do not answer the primary seropositivity question. The pregnancy report adds special-population safety information. In the extraction archive, every report is linked to its source, population,

time window and reason for narrative-only treatment. This avoids a common error: treating every adult report as interchangeable evidence for one estimand.

Consistency checks before interpretation

The analysis pipeline verified that events did not exceed denominators, that denominators were positive, that follow-up windows matched the intended endpoint, and that study identifiers were not duplicated within a pooled outcome. Forest-plot labels were compared with the result CSVs. The manuscript values were checked against the validated outputs for all four serotypes, SAE risk and the two comparative reactogenicity outcomes. The SAE model returned a finite estimate with tau-squared at the boundary. This warning appears in the results narrative and in the result CSV. The analysis outputs came from the prespecified input datasets and scripts. These checks support the reproducibility of the reported estimates. They do not show that every source interpretation is correct, nor that an independent reviewer would reach the same eligibility or RoB decisions.

Immunogenicity

Three independent randomized-trial vaccine arms contributed 620 analyzed adults about 30 days after dose 2. Pooled seropositivity was 98.7% for DENV-1 (95% CI 95.8–99.6; 611/620), 99.0% for DENV-2 (97.9–99.6; 614/620), 96.9% for DENV-3 (95.2–98.0; 601/620), and 98.4% for DENV-4 (97.0–99.1; 610/620). Figure 2 shows the study-level estimates and pooled diamonds. Between-study variance on the logit scale was 0.122 for DENV-1 and zero for the other serotypes. This variance (τ^2) comes from the mixed model, whereas conventional I^2 derives from the Q statistic, so the two can differ. Conventional Q-based I^2 was 0% for DENV-1, DENV-2, and DENV-4, and 54.8% for DENV-3. With only three studies, these figures and their broad uncertainty should not be read as firm evidence of homogeneity or heterogeneity.

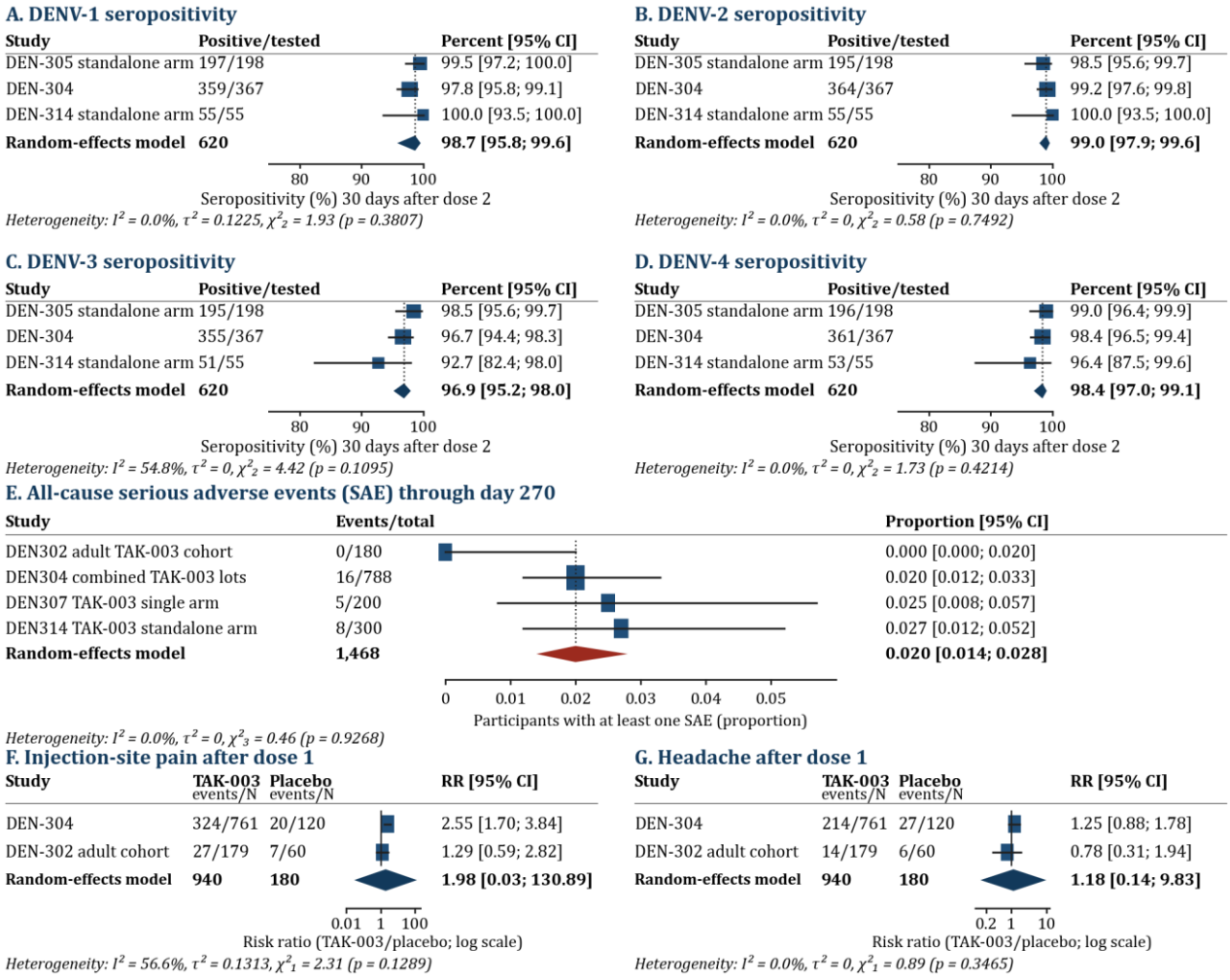


Figure 2. Combined quantitative synthesis. Panels A–D show serotype-specific seropositivity approximately 30 days after dose 2; panels E–G show cumulative serious-adverse-event (SAE) risk, injection-site pain, and headache. Pooled estimates use the prespecified random-effects models. RR, risk ratio; CI, confidence interval.

Safety and reactogenicity

Four final-formulation vaccine cohorts had surveillance through day 270. Among their 1,468 vaccinated adults, 29 had at least one all-cause SAE. The pooled cumulative risk was 1.98% (95% CI 1.38–2.83%). The Wald Q was 0.46 (df=3, p=0.927), tau^2 was zero, and conventional I^2 was 0%. A likelihood-ratio heterogeneity statistic disagreed (p=0.043), which argues against a simple claim of homogeneity when events are sparse. The random-effect variance sat at the boundary, as expected with sparse events, so the figure is best read as a descriptive pooled risk. It has no unvaccinated counterfactual. It cannot show whether TAK-003 raises or lowers SAE risk.

Two randomized comparisons reported compatible dose-1 reactogenicity. For injection-site pain, the random-effects RR was 1.98 (95% CI 0.03–130.89; I^2=56.6%). For headache, the RR was 1.18 (95% CI 0.14–9.83; I^2=0%). Modified Hartung-Knapp intervals with one degree of freedom were extremely wide. Common-effect sensitivity estimates were narrower, but they did not replace the prespecified random-effects inference. These results are exploratory. They do not support a confident comparative conclusion. Figure 2 displays the safety estimates, and the outcome-specific certainty judgments are given under Risk of bias and certainty.

Additional quantitative checks

The seropositivity models used no pooled continuity correction. They relied on exact binomial likelihood contributions for the study arms. For DENV-1 the estimated logit-scale between-study variance was 0.122, and the other primary serotype models estimated tau-squared at zero. DENV-3 had the highest conventional I^2 at 54.8%, with a broad confidence interval because only three independent arms contributed. For the SAE proportion, the pooled likelihood used 29 events among 1,468 participants. It gave a finite estimate of 1.98% with a model-based 95% interval of 1.38–2.83%. The Wald heterogeneity statistic was not significant while the likelihood-ratio statistic disagreed. Both are shown so that the boundary behavior is visible. These diagnostics are descriptive safeguards. They are not evidence that a model with four cohorts can resolve every difference between settings.

Leave-one-out sensitivity

Leave-one-out analyses were run for each primary serotype pool and for the day-270 SAE synthesis. Seropositivity point estimates stayed within 96.2%–99.6% across the serotype-specific exclusions. The DENV-3 interval widened when DEN314 was removed (96.9%; 95% CI 91.0–99.0). SAE risk ranged from 1.62% to 2.25% after dropping one cohort, with wider uncertainty when DEN304 was removed (1.62%; 95% CI 0.56–4.55%). No single cohort reversed the qualitative interpretation. The two- or three-study fits remain unstable, however, and are treated as sensitivity diagnostics, not confirmatory evidence.

Eligibility sensitivity and denominator reconciliation

DEN307 had extractable day-120 seropositivity data (about 30 days after dose 2) for the final formulation. It was a single-arm study, however, and so did not enter the primary randomized-arm estimand. To test this eligibility boundary, a separate sensitivity analysis added DEN307 to the three randomized trials, keeping baseline-seronegative status, the final formulation and the day-120 endpoint. With four studies and 752 analyzed adults per serotype, pooled seropositivity was 98.8% for DENV-1 (95% CI 96.7–99.6), 99.2% for DENV-2 (98.2–99.6), 97.1% for DENV-3 (95.6–98.1) and 98.5% for DENV-4 (97.4–99.2). The direction matched the primary analysis. The added single-arm cohort does not remove the surrogate-outcome or study-design limitations. The primary table and forest plots stay restricted to the prespecified randomized-arm estimand, and the sensitivity output is archived separately. Table 1 details study-level characteristics and analyzed denominators. Event counts reconstructed from rounded percentages were checked against compatible integer bounds. They remain labeled as derived values, not directly reported counts.

Additional adult evidence outside the primary pools

Several retrieved reports add adult safety or mechanistic context, but they were not combined with the prespecified randomized-trial estimands. TravVacNet included 1,176 vaccinated travelers (median age 39 years), with age-stratified dose-specific reactogenicity and 334 coadministrations [24]. Its network design and mixed exposure windows ruled out a compatible pooled comparator. CATdenga followed 1,028 travelers (median age 40 years) after 1,851 doses; 998 completed follow-up, and no serious adverse events were reported in the cohort [25]. The observational design and incomplete adult-only denominators support narrative use only. A German self-report survey with 11,827 completed questionnaires, spanning ages 4–86, reported local reactions in 47.5% and systemic reactions in 41.4% [26]. Age stratification and self-selection make it unsuitable for the primary pool. In an adult DGV-Vac cohort of 84 participants (median age 42 years; 42 dengue-naive and 42 previously exposed), an exploratory inverse association between TTV positivity and DENV-2 response was confined to a TTV-positive subgroup of 33 [27]. It did not provide the primary post-dose-2 seropositivity endpoint. A pregnancy report contributed a special-population safety signal (28 TAK-003 exposure-window pregnancies versus 10 placebo), but it was retained narratively and not pooled with general adult cohorts [28]. These reports broaden the evidence map. They do not change the quantitative estimands.

Risk of bias and certainty

For comparative reactogenicity, the appraisal was low risk overall for DEN302 and raised some concerns for DEN304, because complete diary-card denominators and the effect of missing cards were not fully demonstrated. The three seropositivity estimates raised some concerns because of per-protocol or selected immunogenicity populations, although assays and outcome definitions were objective and prespecified. SAE ascertainment was judged low concern for the selected cohorts. The lack of a counterfactual remained a design limitation. Certainty was rated low for seropositivity and descriptive SAE risk, and very low for comparative reactogenicity. Table 2 summarizes these outcome-specific judgments, and they inform the certainty ratings in Table 3.

Table 2. Outcome-specific risk-of-bias judgments for the three outcome types (seropositivity, comparative reactogenicity and all-cause SAE) across the five trials. RoB 2 was used for randomized comparative reactogenicity; a structured uncontrolled-arm appraisal was used for seropositivity and all-cause SAE proportions.

Study	Outcome	Tool	Domain summary	Overall	Limitation carried into interpretation
DEN304 (NCT03423173)	Seropositivity	JBI-informed uncontrolled-arm appraisal	Low / Low / Some concerns / Low / Low	Some concerns	Selected per-protocol, baseline-seronegative immunogenicity subset; missing or excluded samples may affect the observed proportion.
DEN305 (NCT03342898)	Seropositivity	JBI-informed uncontrolled-arm appraisal	Low / Low / Some concerns / Low / Low	Some concerns	Standalone sequence was measured before later yellow-fever vaccination, but the baseline-naive per-protocol denominator may be affected by exclusions.
DEN314 (NCT03525119)	Seropositivity	JBI-informed uncontrolled-arm appraisal	Low / Low / Some concerns / Low / Low	Some concerns	Reported baseline-naive denominator was smaller than the randomized arm; coadministration arm was excluded.
DEN304 (NCT03423173)	Comparative reactogenicity	RoB 2	Low / Low / Some concerns / Low / Low	Some concerns	Complete diary-card denominators and the effect of missing cards were not fully demonstrated in the registry tables.
DEN302 (NCT06060067)	Comparative reactogenicity	RoB 2	Low / Low / Low / Low / Low	Low	Randomization, masking, prespecified diaries and outcome-specific denominators reconciled to reported totals.
DEN304; DEN314; DEN307; DEN302	All-cause SAE through day 270	JBI-informed uncontrolled-arm appraisal	Low / Low / Low / Low / Low	Low	Event ascertainment and denominators were available, but the pooled risk has no unvaccinated counterfactual and is descriptive.

JBI, Joanna Briggs Institute; RoB 2, Cochrane risk-of-bias tool, version 2; SAE, serious adverse event.

Table 3. Summary of findings and GRADE-informed certainty of evidence. Estimates are outcome-specific and should not be interpreted as comparative vaccine effects unless a comparator is specified.

Outcome	Studies / participants	Effect estimate	Certainty	Main concerns
Serotype-specific seropositivity about 30 days after dose 2	3 randomized trials / 620 baseline-seronegative adults	DENV-1 98.7% (95.8–99.6); DENV-2 99.0% (97.9–99.6); DENV-3 96.9% (95.2–98.0); DENV-4 98.4% (97.0–99.1)	Low	Selected/per-protocol denominator, surrogate outcome, small k and assay/context variation.
All-cause SAE through day 270	4 vaccine cohorts / 1,468 adults	29/1,468; 1.98% (1.38–2.83), descriptive pooled risk	Low	No unvaccinated counterfactual, sparse events, mixed endemicity and limited causal attribution.
Injection-site pain and headache after dose 1	2 randomized comparisons / 940 vaccine and 180 placebo participants	Pain RR 1.98 (0.03–130.89); headache RR 1.18 (0.14–9.83)	Very low	Two-study random-effects models, wide modified Hartung-Knapp intervals and denominator documentation concerns.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio; SAE, serious adverse event. Values in parentheses are 95% confidence intervals.

4. Discussion

The evidence map separates study characteristics, outcome-specific risk of bias and certainty of evidence. The separation matters. A low-risk randomized comparison of short-term reactogenicity does not remove the indirectness of an antibody surrogate, and a low-concern appraisal of SAE ascertainment does not supply a comparator for a pooled single-arm risk. The Summary of Findings table therefore presents certainty by estimand and shows why each was downgraded. Adding DEN307 in the eligibility sensitivity analysis changed the four serotype point estimates by less than one percentage point. That supports the stability of the descriptive immunogenicity signal. It leaves the main study-design limitations in place.

Short-term seropositivity was high for all four dengue serotypes in adults who received the final two-dose TAK-003 formulation. DENV-3 had the lowest pooled estimate and the greatest conventional inconsistency. Even so, its point estimate stayed above 96%. These values describe antibody detectability in selected trial populations. They do not establish a validated adult correlate of clinical protection.

The pooled day-270 SAE risk across four vaccine cohorts was approximately 2%. That gives a useful absolute frequency for the specified surveillance window. It is not a comparative vaccine effect. The

cohorts differed in endemicity and baseline dengue exposure. Serious events were rare. We kept event relatedness deliberately separate from all-cause occurrence.

Two studies are too few for stable random-effects inference, and the comparative reactogenicity analyses show it. Injection-site pain was more frequent in vaccine groups in both studies. The modified Hartung-Knapp interval was nonetheless extremely wide, because between-study variation and a single degree of freedom dominated the estimate. Headache showed no clear comparative difference. Had the narrow common-effect sensitivity interval been presented as the main result, the uncertainty would have been understated.

This synthesis adds an adult-focused analysis in which reports are linked to trials. It keeps final formulation, baseline immune status, coadministration, and surveillance windows apart. Where article reports gave no complete compatible table, registry-level primary results filled the gap. Several publications from one clinical program are therefore not counted as independent studies.

For adult clinical interpretation, the main value of the seropositivity result is its consistency across all four serotypes in the selected baseline-naive trial strata. The estimate is the probability of reaching the assay threshold at a defined time after dose 2. It is not the probability of avoiding dengue. The difference matters: prior exposure, assay threshold, serotype-specific response and time since vaccination can all alter antibody measurements without giving a direct clinical endpoint. We therefore treat the result as immunogenicity evidence that informs adult effectiveness studies but does not replace them.

The absolute SAE estimate is bounded in the same way. A cumulative risk near 2% through day 270 gives a denominator-based frequency for the four cohorts in that window. Whether vaccination caused the events remains unknown. So does the question of whether the risk differs from background adult risk, or whether endemicity and comorbidity explain part of the variation seen. A vaccine-versus-placebo contrast exists for some short-term solicited outcomes, but not for the pooled SAE estimand. Keeping the estimands apart reduces the chance that an uncontrolled safety proportion is read as a causal effect.

The additional adult observational reports give context on real-world tolerability and special populations. Traveler and postmarketing cohorts may capture coadministration, delayed self-reported symptoms and age patterns that tightly controlled trials underrepresent. Their denominators, exposure windows and comparison structures differ from those of the prespecified randomized pools. Their contribution is therefore narrative. The same holds for the pregnancy report and the TTV mechanistic study. They can raise questions for follow-up. They should not be treated as interchangeable evidence for general adult safety or for post-dose-2 seropositivity.

The review also shows what a future update should add. Adult trials and real-world studies should report baseline dengue and flavivirus status, adult-only denominators, dose-specific follow-up, exact assay thresholds, complete diary-card denominators, event relatedness and virologically confirmed clinical dengue outcomes. Registry result tables should keep enrolled, randomized, tested and analyzed populations distinct. Later reviews could then estimate durability and clinical effectiveness without mixing report-level and study-level evidence.

Several limitations are material. All 80 retrieved publication candidates now have a disposition. The separate registry stream is preserved for audit linkage and not counted as additional studies. WHO ICTRP retrieval failed, and the native CENTRAL export was limited by authentication. The principal immunogenicity analysis holds only three trials and selected baseline-naive populations. Sparse-event and two-study analyses give little information on heterogeneity. Finally, neutralizing-antibody positivity is a surrogate outcome. It cannot be converted into adult clinical efficacy.

The findings support high short-term tetravalent seropositivity after the licensed regimen in the adults studied, and they offer a bounded description of day-270 SAE occurrence. Future reports should supply adult clinical endpoints, standardized baseline-serostatus strata, complete analysis denominators, and comparable long-term safety windows. One distinction should stay in view. A reproducible computational synthesis is not evidence that has undergone independent duplicate verification.

5. Conclusion

In selected adult trial populations, final-formulation TAK-003 produced high serotype-specific seropositivity about one month after dose 2, whereas the all-cause SAE risk through day 270, at 2.0%, was uncontrolled and cumulative. Comparative reactogenicity was too imprecise for confident random-effects conclusions. Certainty was low or very low. Outcomes were surrogate and indirect. Interpretation must therefore be cautious.

Declarations

Ethics approval and consent

Not applicable. This review used aggregate published and registry data and recruited no participants. No institutional ethics approval is claimed.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

I.W.B.A.S.: conceptualization, methodology, project administration, supervision, writing – original draft,

writing – review & editing. K.A.P.: methodology, data curation, writing – review & editing. C.A.W.P.: methodology, data curation, writing – review & editing. All authors approved the final manuscript and accept responsibility for the interpretation and publication decision.

Data and code availability

Derived data, analytic scripts, session information, and figures are available from the corresponding author on reasonable request, subject to source licensing and privacy restrictions.

Registration

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Generative AI disclosure

None. No generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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