Review

Dengue Fever Epidemics and The Prospect of Vaccines: A Systematic Review and Meta-Analysis Using Clinical Trials in Children

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Review

Dengue Fever Epidemics and The Prospect of Vaccines: A Systematic Review and Meta-Analysis Using Clinical Trials in Children

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Abstract: About half of the world's population is at risk of dengue infection. Epidemics of dengue fever caused an increased risk of morbidity and mortality in recent years, which led to the exploration of vaccines as a preventive measure. This systematic review and meta-analysis aimed to evaluate the efficacy, immune response, and safety of dengue vaccines in children by analyzing clinical trials. The review followed standard procedures for data extraction using PRISMA guidelines, and searching multiple databases including PubMed, CINAHL, Medline, Health Source, Science Direct, and Academic Search Premiere. Eligible studies involved children (0-17 years). Cochrane Collaboration criteria were used for quality assessment, with thematic data synthesis and meta-analysis. Among 38 selected studies, dengue vaccines showed varying efficacy against all four serotypes. CYD-TDV (Dengvaxia®), and Tekade (TAK-003) vaccines demonstrated strong protection against severe dengue, but their long-term efficacy varied. Vaccines triggered satisfactory immune responses, notably in those previously exposed to dengue. Safety profiles were mostly favorable, noting mild adverse events post-vaccination. Meta-analysis supported vaccine efficacy and immune response, but safety concerns warrant further exploration. In conclusion, dengue vaccines demonstrated promising efficacy and immune response, particularly against severe manifestations.

Keywords: dengue fever; clinical trials; case-cohort studies; children; vaccine; PRISMA; meta-analysis

1. Introduction

Dengue fever, an acute mosquito-borne viral infection caused by the dengue virus (DENV), poses a significant global health threat due to its widespread prevalence and severe impact. Transmitted primarily by infected female Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus [1-3], dengue fever is characterized by fever, severe headache, joint pain, skin rash, and bleeding tendencies [4,5]. Its four serotypes (DENV-1 to DENV-4) lead to a range of clinical manifestations, from mild fever to severe conditions like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [5-9].

Globally, approximately 3.9 billion people across 128 countries are affected annually by dengue fever, primarily in tropical and subtropical regions where favorable climatic conditions sustain mosquito vectors for year-round transmission [4, 5, 10, 11]. Factors such as urbanization, population growth, and increased global travel have contributed to its geographical expansion [12, 13]. Its prevalence is particularly prominent in tropical and subtropical regions, where favorable climatic conditions sustain mosquito vectors, enabling year-round transmission [11]. The global incidence of dengue has nearly doubled in the past 30 years and is projected to rise further, especially in Asia, sub-Saharan Africa, and Latin America. The disease's impact on public health is further intensified by large-scale outbreaks that strain healthcare systems and substantial economic burdens, estimating billions of dollars in medical care and productivity losses [6, 14-17].

Recent outbreaks, such as the surge in Bangladesh in 2023, exemplify the escalating challenge. Between January and August 2023, the Ministry of Health, and Family Welfare (MOHFW) reported

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a significant increase in cases and fatalities, surpassing numbers from previous years [18]. Such outbreaks underscore the urgent need for effective preventive measures, especially vaccines, amidst multifaceted challenges.

Developing a vaccine that provides broad and durable protection against all four dengue serotypes remains a crucial goal [7]. Challenges in disease control include evolving mosquito resistance to insecticides, underreporting of asymptomatic cases, constrained healthcare infrastructure in endemic regions, and the global spread facilitated by international travel and trade and global warming [19-22].

Efforts spanning decades aimed to create a dengue vaccine, starting with whole-virus vaccines showing initial promise against all four serotypes but raising safety concerns [23]. Tetravalent, live attenuated vaccines like CYD-TDV (Dengvaxia®), and Tekade (TAK-003) followed, entering trials but facing challenges with multiple doses and varying efficacy based on prior exposure [24]. Newer methods, like viral vectors and nucleic acid-based vaccines, offer hope by overcoming previous trial hurdles [25,26]. Despite progress, the quest for a safe, comprehensive dengue vaccine continues due to the complexities of dengue immunology. This systematic review and meta-analysis aimed to evaluate the efficacy, immune response, and safety of dengue vaccines in children by reviewing clinical trials.

2. Materials and Methods

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [27] was used as a framework to guide the systematic review. The stages followed to perform the systematic review were based on (a) defining the appropriate keywords, (b) searching databases to find and select articles, (c) critical evaluation of the studies, (d) data selection and analysis, and (e) presentation and interpretation of results.

Eligibility Criteria

This systematic review and meta-analysis concentrated on original, peer-reviewed journal articles that delved into both qualitative and quantitative studies about dengue fever epidemics and the potential for vaccines. The inclusion criteria encompassed studies written in English, specifically journal articles that involved human subjects as the focal population. The primary focus was on original research studies about dengue fever epidemics and vaccine potential. Studies involving children aged 0-17 years were included, and full-text articles were a prerequisite for eligibility. There were no restrictions based on the country in which the study was conducted. On the other hand, exclusion criteria involved non-English articles, literature reviews, systematic reviews, book chapters, and conference papers. Studies that primarily involved animals as the target population were also excluded from consideration.

Search Strategy

During September-October, 2023, a comprehensive search was conducted across six databases, namely PubMed, CINAHL, Medline, Health Source, Science Direct, and Academic Search Premiere. The search aimed to identify relevant articles written in the English language and focused on peer-reviewed journal publications. We applied the following filters: studies on dengue outbreaks, human studies, children subjects (0-17 years), and full-text articles. Manual searches of reference lists were also performed to ensure comprehensive coverage of the literature. The search strategy utilized adapted and inclusive search terms specific to each database to capture a broad range of literature related to the research of interest (Table 1).

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Table 1. Databases searched, the keywords utilized, and the number of articles.

Databases	Search keywords	Number of Articles Found
PubMed (1)	"Dengue fever" OR "Dengue epidemics" OR "Dengue vaccine" OR "Dengue Vaccine prospects"	129
PubMed (2)	"Dengue fever" OR "Dengue epidemics" **AND** "Dengue vaccine" OR "Dengue vaccine development" OR "Dengue vaccine prospects" **AND** "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes"	81
CINAHL	"Dengue fever" OR "Dengue epidemics" **AND** "Dengue vaccine" OR "Dengue vaccine development" OR "Dengue vaccine prospects" **AND** "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes" OR "Clinical trials" OR "Epidemiological studies"	24
Medline	Dengue fever" OR "Dengue epidemics" **AND** "Dengue vaccine" OR "Dengue vaccine development" OR "Dengue vaccine prospects" **AND** "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes" OR "Clinical trials" OR "Epidemiological studies	210
Health Source	"Dengue fever" OR "Dengue epidemics" **AND** "Dengue vaccine" OR "Dengue vaccine development" OR "Dengue vaccine prospects" **AND** "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes"	2
Science Direct	"Dengue fever" OR "Dengue epidemics" **AND** "Dengue vaccine" OR "Dengue vaccine development" **AND** "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes" OR "Clinical trials" OR "Epidemiological studies"	1,381
Academic Search Premiere	"Dengue fever" OR "Dengue epidemics" AND "Dengue vaccine" OR "Dengue vaccine development" OR "Dengue vaccine prospects" AND "Dengue vaccine efficacy" OR "Dengue vaccine safety" OR "Dengue serotypes" OR "Clinical trials" OR "Epidemiological studies"	134

Study Screening Process

The authors conducted independent searches in the respective databases (Table 1) using identical search keywords. The search yielded 1961 articles from the databases, and 28 additional articles were identified by hand-searching. The PRISMA Flowchart shown in **Figure 1** [27], summarized the search process, indicating that a total of 1989 articles were identified. After removing duplicates (n = 540), the remaining 1449 articles underwent a two-phase screening process using Excel. In the first phase, titles and abstracts were screened, and in the second phase, full-text articles were screened. Inclusion criteria were applied during this process. Initially, 61 articles were selected for full-text screening based on consensus among the authors and were independently reviewed. Any discrepancies or conflicts in articles were independently reviewed by the authors and resolved

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through group discussions among the authors. As a result, 23 articles were excluded because the full-text articles were restricted and could not be accessed. A total of 38 articles were included in the systematic review, while 27 of these were further analyzed for the meta-analysis based on the available data focusing on clinical trials.

Quality Assessment

The assessment of bias risk was conducted by the authors individually, employing the Cochrane Collaboration tool to evaluate bias in the clinical trials [28]. The criteria assessed were confounding/performance bias, selection/allocation bias, attrition bias, information (detection) bias, and reporting bias.

Data Extraction

The authors designed a standardized form tailored for data extraction, encompassing fields for study identification details, country of origin, study design, participants' age, main findings, and participant count per intervention (**Table 2**). Thematic analysis, as outlined by Thomas and Harden (2008) [29] was applied to analyze the data gathered from the included studies. The authors independently identified and developed distinct themes. Subsequently, these themes will be cross-referenced, essential themes will be determined by consensus, and a narrative synthesis will be conducted by the authors.

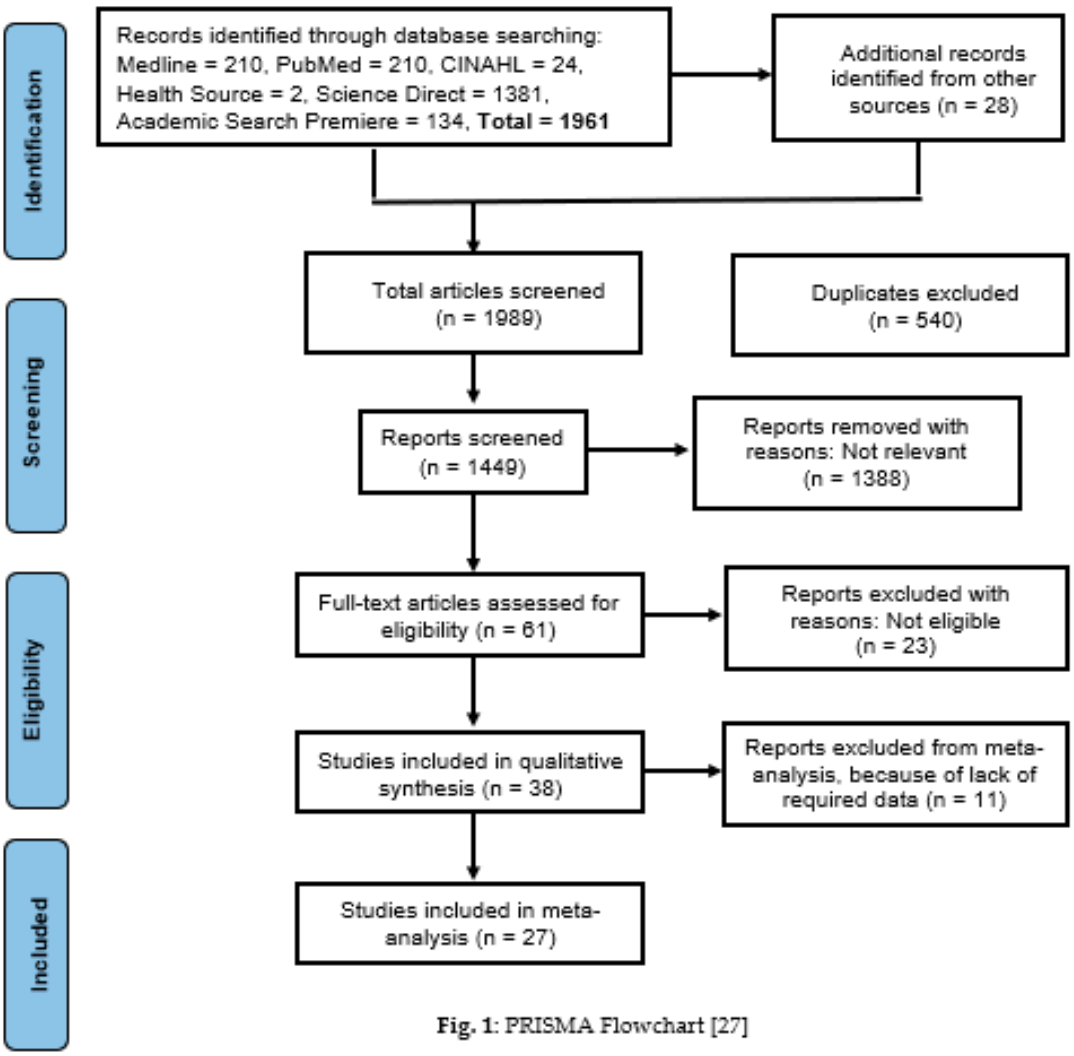

Fig. 1: PRISMA Flowchart [27]

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3. Results

The characteristics of the studies including the author and year of publication, the purpose of the study, participants' age, sample size, study design, countries of the studies, and main findings are summarized in **Table 2**. Out of the 38 studies included most of the studies were conducted in Asian–Pacific countries and Latin American countries where dengue fever is endemic. Also, most studies stratified the ages of the participants to reduce bias. Each of these 38 studies was a clinical trial [30-67], focusing on children aged between 0 and 17 years. The sample sizes across the studies ranged from 56 to as large as 51,253 participants. The studies included 32 randomized controlled trials (RCTs) and 6 prospective case-cohort studies.

Table 2. Characteristics of included studies.

Author & year of publication	Purpose	Study Design	Sample size	Age of participants	Main findings	Country
Forrat et al, 2021 [30]	Assessed hospitalized and severe virologically confirmed dengue (VCD) over the complete 6-year follow-up of 3 CYD-TDV efficacy studies (CYD14, CYD15, and CYD23/CYD57).	RCT	29,229	2-16 years	CYD-TDV demonstrated robust protection against hospitalized and severe VCD over the entire 6-year follow-up in participants who were seropositive and ≥9 years old. Protection was also observed in seropositive 6–8 year-olds.	Asia and Latin America
Thomas et al., 2022 [31]	Evaluated potential associations of host human leukocyte antigen (HLA) alleles with dengue antibody responses, CYD-TDV vaccine efficacy, and virologically confirmed dengue (VCD) cases.	RCT	334	4-11 years	Specific HLA alleles that are significantly associated with dengue NAb titers were identified.	Thailand
España et al., 2019 [32]	Evaluated the vaccine efficacy for susceptibility (VES) as a measure of the protective effects of vaccination against the first symptomatic, virologically confirmed case of dengue.	RCT	51,253	2-16 years	Discovered a distinct bias in VE estimates away from the null due to lower detectability of primary DENV infections among seronegative individuals in the vaccinated group.	Peru
Yang et al., 2018 [33]	Evaluated the dependence of Tetravalent Dengue Vaccine efficacy on baseline immunity status and age groups (children)	RCT	31,125	5 – 11 years	The CYD-TDV vaccine was highly efficacious for all dengue serotypes among children aged >5 years who have acquired baseline immunity from previous exposure.	USA
Plennevaux et al., 2016 [34]	Detected dengue cases by serological testing in a dengue vaccine efficacy trial	RCT	2266	4-11 years	Reliance on serological assessments would lead to a significant number of false positives during routine clinical practice and surveillance following the introduction of the dengue vaccine	Thailand

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Sridhar et al., 2018 [35]	Assessed the risk of hospitalization for VCD in seronegative vaccine recipients who were 9 years of age or older at enrollment (the primary endpoint).	Case–cohort study	3578	2-16 years	CYD-TDV protected against severe VCD and hospitalization for VCD for 5 years in persons who had exposure to dengue before vaccination.	Asia-Pacific region, Latin America, and Thailand
Plennevaux et al., 2018 [36]	Assessed the impact of dengue vaccination on the serological diagnosis of dengue in larger and more diverse epidemiological settings of 2 phase III CYD-TDV efficacy studies.	RCT	31,000	2-16 years	Results showed that baseline dengue serostatus (as defined by the PRNT50) had an impact on the IgM and IgG levels observed in VCD and other febrile episodes among CYD-TDV recipients and controls.	Asia and Latin America
Moodie et al., 2018 [37]	Investigated the association of neutralizing antibody titers with dengue occurrence with the level of vaccine efficacy to prevent dengue	Case-Cohort study	31,144	2-16 years	Neutralizing antibody titers postdose 3 correlates with CYD-TDV vaccine efficacy to prevent dengue. High titers are associated with high VE for all serotypes, baseline serostatus groups, age groups, and both trials.	Asia and Latin America
Olivera-Botello et al., 2016 [38]	Investigated whether vaccination with CYD-TDV protected individuals from asymptomatic infection, using a commonly used surrogate measure, primary, secondary, or other seroconversion	RCT	31,126	2-16 years	Vaccine efficacy was marginally higher in subjects aged 9–16 years (38.6%).	Asia and Latin America (Colombia, Brazil, Mexico, Puerto Rico, and Honduras)
Hadinegoro et al., 2015 [39]	Reported long-term safety phase and integrated analyses of data from the efficacy surveillance phase to provide a global view of the clinical profile of the CYD-TDV dengue vaccine.	RCT	33,266	2-16 years	The risk among children 2 to 16 years of age was lower in the vaccine group than in the control group.	Asia–Pacific countries, and Latin American countries
Villar et al., 2015 [40]	Investigated the efficacy of a Tetravalent Dengue Vaccine in Children in Latin America	RCT	20,869	9-16 years	The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD in five Latin American countries where dengue is endemic.	Colombia, Brazil, Mexico, Puerto Rico, and Honduras
Dayan et al., 2015 [41]	Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) was assessed by age group and baseline dengue serostatus.	Case cohort study	436	3-9 years	CYD-TDV provided long-term efficacy against symptomatic VCD in seropositive participants with evidence of persistent protection up to six years after the first dose.	Asia-Pacific and Latin America
Dayan et al., 2020 [42]	Investigated the effectiveness of a single-	Case-cohort study	31,126	9-14 years	A single dose of CYD-TDV protected children	Philippines

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	dose mass dengue vaccination in Cebu, Philippines				from severe dengue and dengue with warning signs.	
López-Medina et al., 2021 [43]	Investigated the efficacy of a TAK-003 in healthy children 2 years after vaccination	RCT	20,099	4–16 years	TAK-003 demonstrated continued benefit independent of baseline serostatus in reducing dengue with some decline in efficacy during the second year	Latin America (Brazil, Colombia, Dominican Republic, Panama & Nicaragua), Sri Lanka, Thailand, Philippines
Biswal et al., 2020 [44]	Assess the efficacy, safety, and immunogenicity of a live attenuated tetravalent dengue vaccine (TAK-003) in healthy children	RCT	20,099	4-16 years	TAK-003 was well tolerated and efficacious against symptomatic dengue in children regardless of serostatus before immunization.	Asia and Latin America
Rivera et al., 2022 [45]	Investigated a three-year efficacy and safety of Takeda's Dengue Vaccine Candidate	RCT	20,099	4-16 years	TAK-003 was efficacious against symptomatic dengue over 3 years. There were no safety risks.	Latin America (Panama, Nicaragua) and Asia (Philippines, Sri Lanka)
Biswal et al., 2019 [46]	Investigated the efficacy of a Tetravalent Dengue Vaccine in healthy children	RCT	20,071	4-16 years	TAK-003 was efficacious against virologically confirmed dengue fever among healthy children, irrespective of previous dengue exposure.	Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, and Thailand
Saez-Llorens et al., 2023 [47]	Investigated the effect of the Tetravalent Dengue Vaccine TAK-003 on Sequential Episodes of Symptomatic Dengue	RCT	13,380	4-16 years	TAK-003 vaccination resulted in a reduced risk of experiencing sequential episodes of symptomatic dengue in children	Latin America (Columbia) and Asia (Philippines, Sri Lanka, Thailand)
Reynales et al., 2020 [48]	Analyzed the efficacy and safety Trial Data of the Tetravalent Dengue Vaccine in children in Colombia.	Case-cohort study	9740	9–16 years	CYD-TDV protected against severe VCD and hospitalization for VCD among individuals previously exposed to dengue before vaccination.	Colombia
Ylade et al., 2021 [49]	Conducted a case-control study in Cebu province following the dengue mass vaccination.	Case-control study	490	9-14 years	A single dose of CYD-TDV given to nine to fourteen-year-old children through a community-based mass vaccination program conferred protection against dengue with warning signs.	Philippines
Capeding et al., 2014 [50]	Assessed the efficacy of the CYD dengue vaccine against symptomatic,	RCT	10,275	2-14 years	Findings showed that the dengue vaccine is efficacious when given as three injections at	

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Sabchareon et al., 2012 [51]	virologically confirmed dengue in children. Investigated the efficacy and safety of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children	RCT	4002	4–11 years	months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Efficacious but differed by serotype. The dengue vaccine was well tolerated, with no safety signals after 2 years of follow-up after the first dose.	Asia-Pacific countries (Indonesia, Malaysia, Philippines, Thailand, and Vietnam Thailand
Juraska et al., 2018 [52]	Evaluated the efficacy of a tetravalent dengue vaccine in two phase 3 trials	RCT	563	2-16 years	Greater estimated vaccine efficacy of CYD-TDV against serotypes was recorded.	Brazil and Thailand
Sáez-Llorens et al., 2018 [53]	Assessed the immunogenicity and safety of Takeda's tetravalent dengue vaccine (TDV) candidate over 48 months in children living in dengue-endemic countries.	RCT	1800	2-17 years	Takeda vaccine was well tolerated and immunogenic against all four dengue serotypes, irrespective of baseline dengue serostatus.	Dominican Republic, Panama, and the Philippines.
Capeding et al., 2011 [54]	Assessed the safety and immunogenicity of the vaccine among children in a flavivirus-endemic region.	RCT	126	2-17 years	This phase I study of a live attenuated, tetravalent recombinant dengue vaccine in children supports its safety and tolerability in a flavivirus-endemic population.	Philippines
Sirivichayakul et al., 2022 [55]	Reported long-term safety and immunogenicity of Takeda's tetravalent dengue vaccine candidate (TAK-003) in healthy children and adults living in dengue-endemic areas	RCT	212	1-11 years	The trial demonstrated the persistence of neutralizing antibody titers against TAK-003 over 3 years in children living in dengue-endemic countries, with limited contribution from natural infection. TAK-003 was well tolerated.	Puerto Rico, Columbia, Singapore, and Thailand.
Hss et al., 2013 [56]	Evaluated the safety and immunogenicity of Phase III lots of a candidate vaccine (CYD-TDV) in children in Malaysia.	RCT	250	2-11 years	This study demonstrated a satisfactory safety profile and a balanced humoral immune response against all four DENV serotypes for CYD-TDV administered via a three-dose regimen to children in Malaysia.	Malaysia
Vigne et al., 2017 [57]	Investigated an unprecedented integrated summary of the immunogenicity of CYD-TDV to identify the parameters driving the	RCT	5,780	9-17 years	CYD-TDV elicits neutralizing antibody responses against all dengue serotypes, with differences by age and endemicity, which	Asia Pacific (including Australia), Latin America, and USA

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	neutralizing humoral immune response and evolution over time.				persist above baseline levels in endemic countries.	
Tricou et al., 2020 [58]	Assessed the immunogenicity and safety of three different dose schedules of a tetravalent dengue vaccine (TAK-003) over 48 months in children living in dengue-endemic countries	RCT	1800	2-17 years	TAK-003 elicited antibody responses against all four serotypes, which persisted to 48 months postvaccination, regardless of baseline serostatus. No important safety risks were identified.	Dominican Republic, Panama, and the Philippines
Simasathien et al., 2008 [59]	Conducted a pilot, safety, and immunogenicity trial of the vaccine candidate in healthy Thai children to prepare for its eventual evaluation in Thai infants.	RCT	89	6–7 years	The vaccine was well tolerated with no serious adverse events or alert laboratory values.	Thailand
Watanaveeradej et al., 2016 [60]	Evaluated the safety and immunogenicity of two doses of a live-attenuated, tetravalent dengue virus vaccine (F17/Pre formulation) and a booster dose in a dengue-endemic setting in two studies	RCT	56	2-8 years	The results of these two follow-up studies indicate that the live-attenuated DENV candidate vaccine jointly developed by the WRAIR and GSK did not elicit a durable primary humoral immune response.	Thailand
Biswal et al., 2021 [61]	Assessed the immunogenicity and safety of a tetravalent dengue vaccine in dengue-naïve children	RCT	400	12–17 years	TAK-003 was immunogenic against all four serotypes and was well tolerated in dengue-naïve adolescents living in Mexico City. No safety risk either.	Mexico
Villar et al., 2013 [62]	Evaluated the safety and immunogenicity of a candidate recombinant, live-attenuated, tetravalent dengue vaccine (CYD-TDV) on Latin American children	RCT	600	2-16 years	CYD-TDV had a favorable safety profile and elicited antibody responses against all 4 dengue virus serotypes in 9–16-year-olds in Latin America.	Colombia, Honduras, Mexico and Puerto Rico
Dayan et al., 2013[63]	Evaluated the immunogenicity and Safety of a Recombinant Tetravalent Dengue Vaccine in Children.	RCT	150	9-16	CYD-TDV vaccination elicited a neutralizing antibody response against serotypes 1–4 and was well tolerated in children/adolescents in a dengue-endemic region.	Brazil
Arredondo-García et al., 2018 [64]	The study compared the tetravalent dengue vaccine to placebo in 3 clinical trials & examined the risk of hospital admission due to confirmed dengue.	RCT	23,429	2-16 years	The overall Relative Risk in those aged <9 years for Year 1 to Year 4 was 0.786 (95% CI 0.60e1.03), with a higher protective effect in the 6-8 year olds than in the 2-5 year olds.	5-Asian–Pacific countries and 5- Latin American countries and Thailand
Kriengsak et al., 2019 [65]	Investigated the long-term safety of a tetravalent dengue vaccine (CYD-TDV) in children in a phase Π b	RCT	3,997	4-11 years	The risk of hospitalized VCD among children in Thailand vaccinated with CYD-TDV is reduced in those aged	Thailand

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	follow-up study in Thailand				≥9 years over six years of follow-up.	
Sabchareon et al., 2004[66]	Evaluated the safety and immunogenicity of tetravalent live-attenuated dengue vaccines after a three-dose vaccination series in Thai children.	RCT	1587	5-12years	No serious adverse event related to the vaccines occurred. Most children experienced mild to moderate fever, rash, headache, and myalgia occurring within 12 days after Dose 1 and generally lasting 3 days or less.	Thailand
Lanata et al., 2012[67]	Assessed the safety and immunogenicity of a recombinant, live, attenuated, tetravalent dengue vaccine candidate (CYD-TDV).	RCT	300	2-11 years	There were no vaccine-related SAEs, no withdrawals for adverse events after dengue vaccination, and no immediate adverse events.	Peru

3.1. Distribution of 5 Domains Risk of Bias among 32 RCTs

The risk of bias analysis using the Cochrane Collaboration tool [28] revealed that among the 32 randomized controlled trial (RCT) studies, 25 studies [31, 34, 36, 38-40, 43-47, 50-52, 54-57, 59, 62-67] demonstrated a low risk of bias across various domains, including information, confounding, selection, attrition, and reporting biases. Conversely, seven studies [30, 32, 33, 53, 58, 60, 61] displayed "some concerns" of risk of bias due to insufficient detailed information on the randomization process, such as blinding and concealment. The risk of bias domains for each of the study are demonstrated in Figure 2. (Figures 2a and 2b).

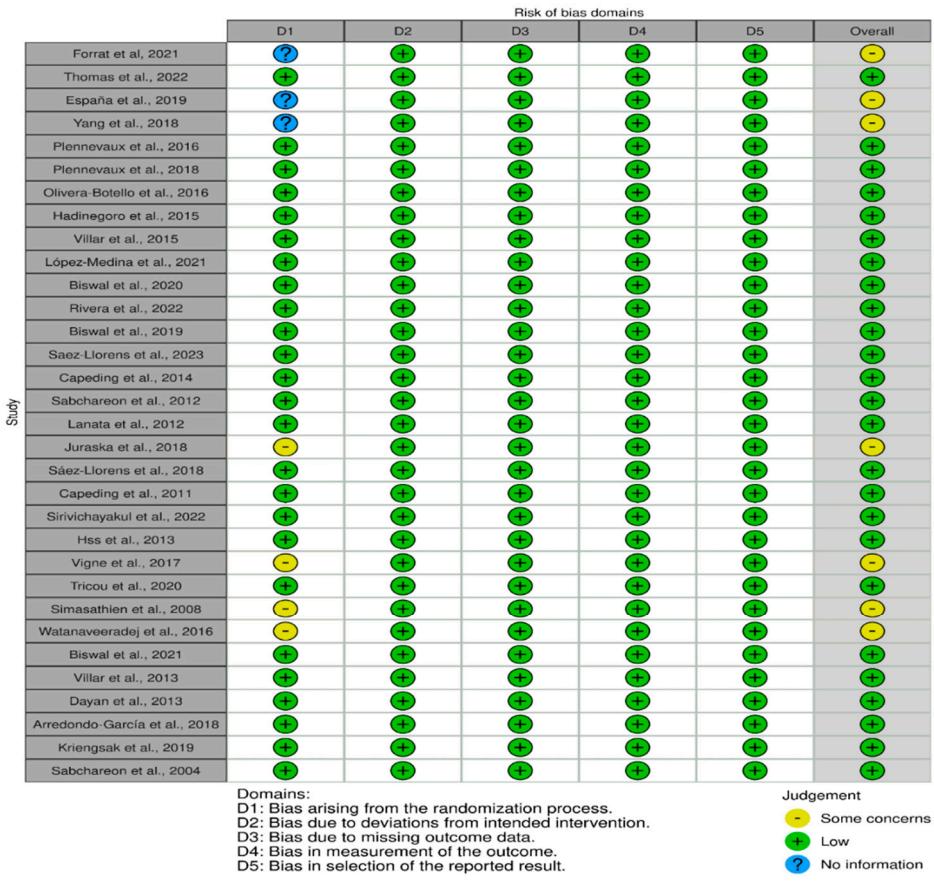

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Figure 2. Risk of bias, presented in 5 domains, and the overall judgement presented as some concerns (yellow), low risk (green), and no information as demonstrated in 32 studies.

3.2. Summary Findings of Risk of Bias of 32 RCTs

The overall assessment of risk of bias was low in more than 75% of the studies (Figure 3). The following one area out of 5 domains raised some concerns in 7 out of 32 RCTs (22%) – the specific area is "bias arising from the randomization process".

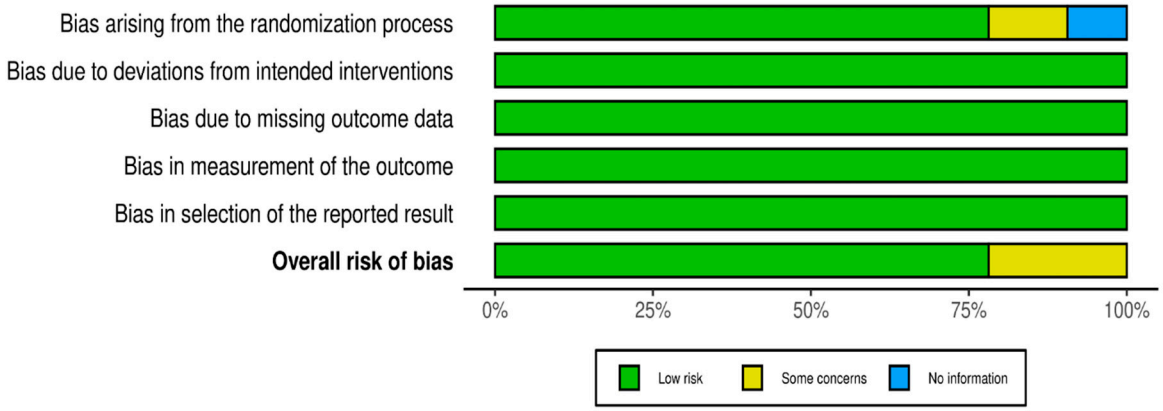

Figure 3. Over distribution of risk of bias in 32 RCTs.

3.3. Evaluating Systematic Review Findings

3.3.1. Efficacy of Dengue Vaccine

Among the 38 studies, 23 demonstrated the effectiveness of dengue vaccines in children involved in clinical trials. The majority of studies consistently demonstrated the efficacy of both CYD-TDV (Dengvaxia®) and Tadeka (TAK-003) vaccines in preventing dengue fever caused by the four serotypes of the dengue virus [30,32,33,35-42,48-51]. However, a few studies reported discrepancies in their outcomes, revealing a lack of efficacy [31,34,52]. The effectiveness of these vaccines varied based on their formulations. While some vaccines displayed differing levels of efficacy against specific serotypes, others showcased broader protection, encompassing multiple serotypes.

3.3.2. Immunogenicity of Dengue Vaccine Candidates

Out of the 38 studies examined, 11 studies confirmed that children administered with the dengue vaccine during clinical trials successfully triggered an immune response, particularly in the production of antibodies against the dengue virus [53-63]. Among these studies, seven focused on evaluating the immunogenicity of CYD_TDV in children, while the remaining four investigated the immunogenicity associated with the Tekade vaccine. Studies [54,56,57,59,60,62,63] illustrated a robust humoral response against all four DENV serotypes when CYD-TDV was administered to children through a three-dose regimen. Conversely, the studies four studies highlighted that the Takeda vaccine exhibited strong immunogenicity against all four dengue serotypes [53,55,58,61].

3.3.3. Safety of Dengue Vaccine

Out of the 38 studies reviewed, 10 studies specifically addressed the safety profile of vaccines administered to children, particularly in regions where dengue is endemic [35,39,50,53,56,58-60,65-67]. These studies reported incidents such as hospitalization due to confirmed dengue cases, occasional deaths, and minor reactions such as rashes and headaches, mainly observed among both vaccinated and control children. These incidents were primarily documented in Asia and Latin America, categorized by the age of study enrollment and the study year.

3.4. Meta-analysis

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To evaluate the efficacy, immunogenicity, and safety of dengue vaccines, a comprehensive meta-analysis was conducted, pooling data from 27 studies. The analysis of these studies is summarized in Figures 4, 5, and 6.

3.4.1. Efficacy of Dengue Vaccine

Of these, 12 studies were utilized to assess the efficacy of dengue vaccines, each study contributing unique perspectives and data elucidating the vaccine's performance and effectiveness, as presented in **Figure 4**. Out of 12 studies, 7 (58%) clearly showed the vaccines are effective; however, a value of I^2 being 95% indicates considerable heterogeneity among the studies, especially because of the types of vaccines used, and the geographic distribution of study subjects. The overall or pooled estimate showed that the vaccines were efficacious.

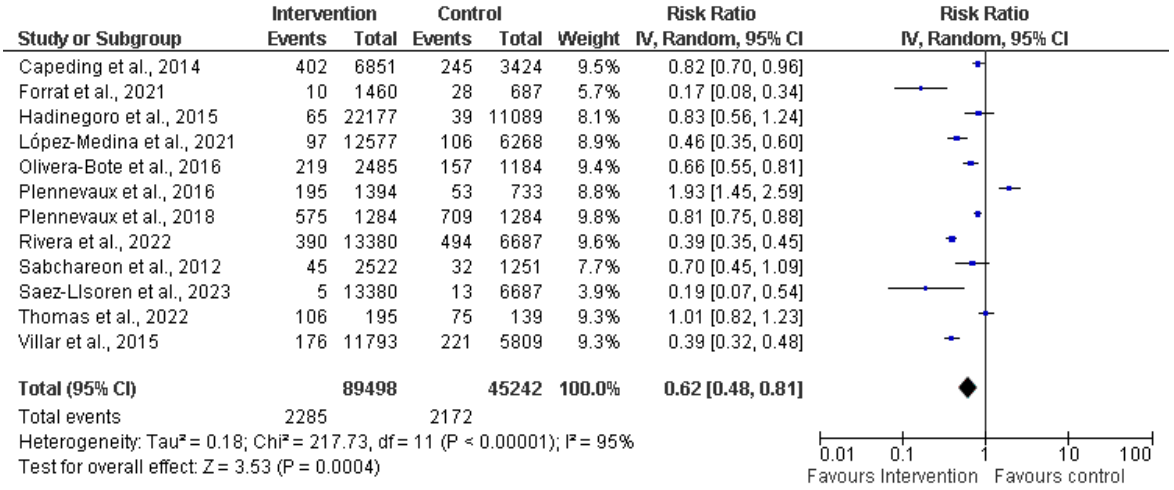

Figure 4. Forest plot showing the efficacy of dengue vaccines.

3.4.2. Immunogenicity of Dengue Vaccine

Simultaneously, nine studies were evaluated for the immunogenicity of these vaccines. In other words, this analysis aimed to find the vaccine's ability to stimulate immune responses in the recipients' bodies. A comprehensive overview of vaccine immunogenicity has been presented in **Figure 5**. Again 5 out of 9 (56%) showed significant favorable responses, while study results were not significant in 4, compared to controls, meaning a mixed effect of the individual studies. The studies that clearly showed significant immunogenicity used the TAK-003 vaccine.

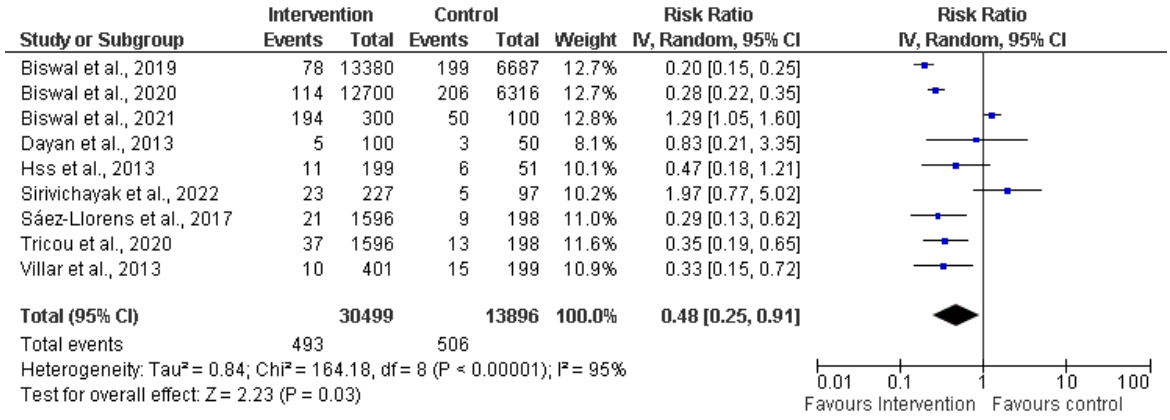

Figure 5. Forest plot showing immunogenicity of dengue vaccines.

3.4.3. Safety of Dengue Vaccine

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Furthermore, this comprehensive meta-analysis assessed six studies specifically focused on the safety profiles of dengue vaccines. These studies evaluated adverse events, potential side effects, and overall safety measures associated with these vaccines. The findings are shown in **Figure 6**, offering a concise yet comprehensive overview of the safety considerations surrounding dengue vaccine administration. The pooled data indicated that the vaccines were safe. However, the sample sizes used in most of these studies (4 out 6) were small, suggesting to evaluate using larger studies.

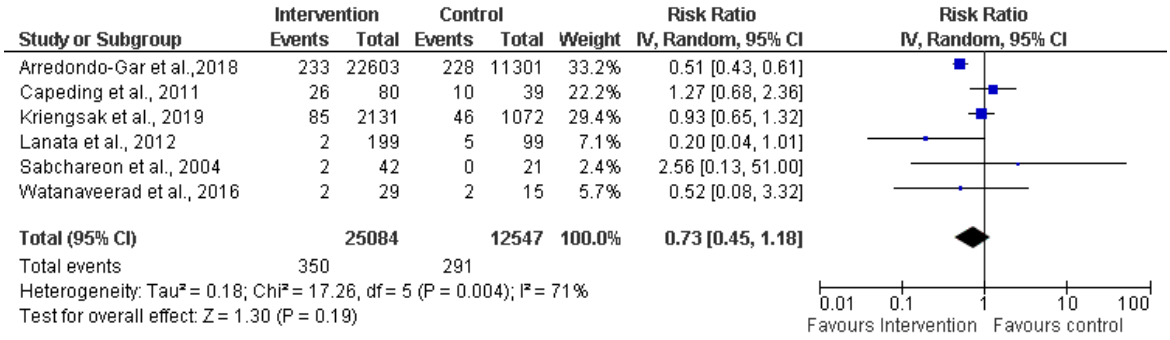

Figure 6. Forest plot showing the safety of dengue vaccines.

4. Discussion

In this systematic review, the authors investigated the potential prospect of various dengue vaccines by examining the efficacy, immunogenicity, and safety of dengue vaccine candidates in children. Based on the findings, children previously exposed to dengue fever (seropositive) before vaccination exhibited superior outcomes in terms of immunogenicity, efficacy, and safety compared to those without prior exposure (seronegative). The clinical studies referenced in this review were registered with ClinicalTrials.gov.

4.1. Efficacy

In terms of efficacy, dengue vaccines showed strong protection against severe virologically confirmed dengue and hospitalization in children, but their effectiveness varied over extended follow-ups in clinical trials. TAK-003 proved effective against symptomatic dengue for three years, with sustained protection against severe cases despite declining overall efficacy. This ongoing study across eight dengue-endemic countries supported TAK-003's usefulness in controlling dengue [45]. CYD-TDV (Dengvaxia®), offered protection to those with prior dengue exposure for up to six years but posed higher risks to individuals without previous exposure during outbreaks [48]. While CYD-TDV (Dengvaxia®) and Tadeka (TAK-003) exhibited high efficacy in clinical trials against the four DENV serotypes, certain studies revealed efficacy biases due to the lower detectability of primary infections among vaccinated seronegative individuals [30, 31, 33-38, 40, 41, 45-50, 52]. Variations and declines in efficacy, regardless of serotype or previous exposure, necessitate ongoing assessments of long-term vaccine performance [32, 39, 42, 43, 44, 51].

4.2. Immunogenicity

Immunogenicity is the ability of a foreign substance, such as an antigen, to provoke an immune response in the body of a human or other animal [68]. Immunogenicity in the context of dengue vaccines pertains to the capacity of a vaccine to elicit an immune response against the dengue virus. Dengue vaccines aim to stimulate the immune system, triggering responses that protect against infection. This may involve the generation of neutralizing antibodies and the activation of T cells, which are essential for combating the virus [69].

According to the studies [53-57, 58, 62, 63], both CYD-TDV and Takeda vaccines were well tolerated and immunogenic against all four dengue serotypes, irrespective of baseline dengue serostatus. Tricou et al [58] who conducted a long-term clinical trial of TAK-003 reported that the

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vaccine elicited antibody responses against all four serotypes, which persisted to 48 months post-vaccination, regardless of baseline serostatus. On the contrary, Watanaveeradej et al [60] reported that the results of two follow-up studies they conducted using the CYD-TDV indicated that the live-attenuated DENV candidate vaccine did not elicit a durable primary humoral immune response. Also, Vigne et al. [57] reported that CYD-TDV elicits neutralizing antibody responses against all dengue serotypes, with differences by age and endemicity, which persist above baseline levels in endemic countries.

4.3. Safety

Safety assessments for CYD-TDV and Takeda revealed generally satisfactory profiles, especially in children with previous dengue exposure [35, 39, 50, 54, 56-58, 65]. CYD-TDV demonstrated effectiveness in shielding these children but had a low risk of vaccinated individuals contracting dengue. Common mild to moderate side effects included fever, rash, headache, and myalgia within 12 days after the first dose, lasting typically for three days or less [66]. While some serious adverse events (SAEs) were observed in the CYD-TDV group, they were mostly unrelated to the vaccine [48]. Long-term surveillance by Hadinegoro et al. [39] noted increased dengue-related hospitalizations among children under 9 years old during the third-year post-vaccination, urging vigilant monitoring. However, for children aged 2 to 16 years, the vaccine group showed lower risks compared to the control group, with reduced hospitalizations for dengue up to 2 years after completing the three-dose schedule among children aged 9 to 16 years.

TAK-003, as documented by Rivera et al. [45], reported deaths during the trials, but none were attributed to the vaccine. Initial phases recorded serious adverse events (SAEs) in recipients, but none directly related to the study vaccine. Similarly, Biswal et al. [61] reported no deaths or adverse effects leading to withdrawal, with limited serious adverse events observed, none of which were linked to the trial vaccination or procedures. Simasathien et al. [59] highlighted the dengue vaccine's overall tolerability, with no serious adverse events or concerning laboratory values, aside from one case of fever and associated vaccine viremia following Dose 2.

4.4. Meta-Analysis Findings

The random-effects model indicated risk ratios (RR) and confidence intervals of 0.62 (0.48-0.81), 0.48 (0.25-0.91), and 0.73 (0.45-1.18) for vaccine efficacy, immunogenicity, and safety respectively. Discrepancies emerged between the outcomes of studies with larger participant numbers and those with smaller cohorts.

4.5. Vaccine Efficacy

Regarding vaccine efficacy, the 95% confidence interval of 10 studies [31,34,36,38,39,40,43,45,50,51] exhibited greater precision, while 2 studies [30,47] displayed wider confidence intervals. This discrepancy suggests that the 10 studies provided more precise estimates concerning vaccine efficacy compared to the other 3 studies. When evaluating individual study effects, only 5 studies crossed the line of null effect indicating no significant effect on vaccine efficacy within the intervention group, favoring instead the control group. Eight (8) studies demonstrated statistical significance, indicating the efficacy of dengue vaccines in the intervention group. However, the overall pooled effect yielded a risk ratio of 0.62 (0.48-0.81), highlighting the greater efficacy of dengue vaccines in the intervention (exposed) group compared to the control group.

4.6. Vaccine Immunogenicity

Based on the findings from the meta-analysis of vaccine immunogenicity, in terms of individual study effects, three studies revealed no significant impact of vaccine immunogenicity within the intervention group, thereby aligning with the null effect [55,56,63]. Conversely, six studies exhibited statistical significance, underscoring the immunogenicity of dengue vaccines within the intervention group [44,46,53,58,61,62]. The overall pooled effect yielded a risk ratio of 0.48 (0.25-0.91), showing

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notably heightened immunogenicity among those receiving dengue vaccines within the intervention group compared to the control group. Despite this, the meta-analysis indicated substantial heterogeneity (I^2) at 95%, indicating the necessity for further studies to comprehensively evaluate the discrepancy.

4.7. Vaccine Safety

The findings from the meta-analysis on vaccine safety revealed varying precision in the 95% confidence intervals across the studies. Three studies displayed greater precision [54,64,65], while three studies showed wider confidence intervals [60,66,67]. This discrepancy indicates that the three studies provided more precise estimates regarding vaccine safety compared to the other three with wider intervals. In terms of individual study effects, among the five studies examined, four demonstrated no statistical significance, crossing the null effect line. This suggests that safety concerns were observed within the intervention group compared to the control group. However, only two studies had statistical significance showing that the dengue vaccine is safe in the intervention group [64,67]. Furthermore, the meta-analysis revealed high heterogeneity (I^2) at 71%, emphasizing the imperative need for further studies to address and clarify these observed discrepancies.

4.8. Study limitations

The study has limitations regarding its focus on English-language articles, potentially excluding valuable non-English research. Additionally, the study concentrated on children aged 0-17 years, which may limit its generalizability to all populations. Most of the studies analyzed were conducted in dengue-endemic regions, which could potentially limit the applicability of the findings to other geographical areas. Variability in study methodologies and durations could affect results consistency, while limited extended follow-up periods may impact long-term efficacy and safety assessments. Furthermore, diverse vaccine formulations and dosages make direct comparisons challenging. There are several ongoing but incomplete studies on some other dengue vaccines (e.g. TAK 005), which could not be evaluated in this meta-analysis because of a lack of sufficient data.

5. Conclusions

This systematic review underscores the promising potential of dengue vaccines in combating the severe impact of dengue fever, particularly in endemic regions. However, the observed variations in efficacy and the influence of prior exposure necessitate further research and long-term follow-ups to ascertain sustained efficacy, safety, and optimal deployment strategies. The meta-analysis underscored the overall efficacy and immunogenicity benefits of dengue vaccines, emphasizing their potential to confer protection against dengue fever. However, safety concerns were evident, albeit without statistically significant differences between the intervention and control groups in the analyzed studies. These findings collectively highlight the positive potential of dengue vaccines for mitigating the disease burden. Yet, it is imperative to address safety concerns, particularly in populations without prior dengue exposure, and optimize vaccine efficacy across diverse epidemiological settings. This study will serve as a valuable resource for guiding future vaccine development, public health policies, and interventions aimed at curbing the global burden of dengue fever.

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