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Original research

Impact of prior dengue infection on severity and outcomes: meta-analysis of placebo-controlled trials

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ABSTRACT

Objective. This study evaluated the association between serologically confirmed prior dengue infection and the subsequent risk of virologically confirmed dengue, severe dengue, dengue hospitalization, dengue-related death and all-cause mortality.

Methods. A systematic review and meta-analysis were conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. PubMed, CINAHL, MEDLINE, the Cochrane Library and Web of Science were searched for reports of phase III randomized controlled trials of vaccine efficacy that had data about the placebo group and information about prior infections and were published between January 1994 and March 2024. Random-effects models were used to calculate combined odds ratios (ORs), and heterogeneity was assessed.

Results. Four studies from three phase III trials were included. Participants with prior infection had a lower likelihood of developing virologically confirmed dengue during follow up (OR: 0.85, 95% confidence interval [CI]: 0.75 to 0.98, $P = 0.024$) and the same risk of dengue hospitalization as those without prior infection (OR: 1.18, 95% CI: 0.92 to 1.53, $P = 0.198$). However, they had a higher rate of severe dengue (OR: 2.91, 95% CI: 1.23 to 6.87, $P = 0.015$). No dengue-related deaths occurred during follow up. There were no statistically significant differences in all-cause mortality between individuals with and without prior dengue (OR: 1.74, 95% CI: 0.21 to 14.08, $P = 0.76$).

Conclusions. Prior dengue infection significantly reduced the risk of virologically confirmed dengue and increased the risk of severe dengue, but had no significant effect on dengue hospitalization, dengue-related death or all-cause mortality during follow up. These findings suggest the need to reconsider prior infection as an independent risk factor.

Keywords Dengue; severe dengue; dengue vaccines; meta-analysis.

In the context of the rising incidence and prevalence of dengue (1, 2), several studies have analyzed factors related to severe infections (3). Among these, a second dengue infection has been identified as a significant risk factor for severe dengue in some studies. A review (3) examining 22 studies found that having a second dengue infection was associated with a significantly higher risk of severe dengue (odds ratio [OR]: 2.69, 95% confidence interval [CI]: 2.08 to 3.48). These results are materially similar to another systematic review of observational studies that found an associated risk of 1.75 (95% CI: 1.26 to 2.42) (4). However, a prospective study conducted in Peru (5) investigating the role of second dengue infections in the context of the American genotype of the dengue virus (i.e. DENV-2) concluded that despite the high prevalence of second dengue infections, they were not associated with an increased risk of severe dengue. This suggests that the American DENV-2 genotype might

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not have the characteristics necessary to induce severe forms of the disease. Another study (6) examined how previous infections with different dengue virus serotypes affected the risk and severity of subsequent infections, finding that the presence of pre-existing heterotypic antibodies significantly reduced the risk of severe dengue in subsequent infections (6).

Although narrative reviews (7) emphasize a second infection as a predisposing factor for severe dengue and dengue hospitalization, not all findings are consistent (3–6). The reasons for these discrepancies are numerous, but inherent biases in using cohorts from uncontrolled studies and recall bias in patients with severe dengue may contribute.

The emergence of randomized controlled trials (RCTs) examining the efficacy of various vaccines to prevent virologically confirmed dengue (VCD), severe dengue, dengue hospitalization and dengue-related death provides an opportunity to study this topic by examining better evidence. Unlike retrospective case–control studies, clinical trials have close prospective surveillance and documentation of events, making them less prone to observation bias.

This study investigated the role of second dengue infections in the occurrence of VCD, severe dengue, dengue hospitalization, dengue-related death and all-cause mortality.

METHODS

Search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used for this meta-analysis. This review involved several stages: defining keywords, searching databases for articles, critically evaluating the studies, selecting and analyzing the data, and interpreting the results. The research protocol is registered with PROSPERO (number 542370), the international prospective register of systematic reviews. Searches were conducted of PubMed, CINAHL, MEDLINE, the Cochrane Library and the Web of Science for articles published from January 1994 to March 2024 (information about the search strategy is available from the corresponding author). Additionally, manual searches, including scanning reference lists, were conducted to identify articles that might not have been retrieved by the initial search strategy.

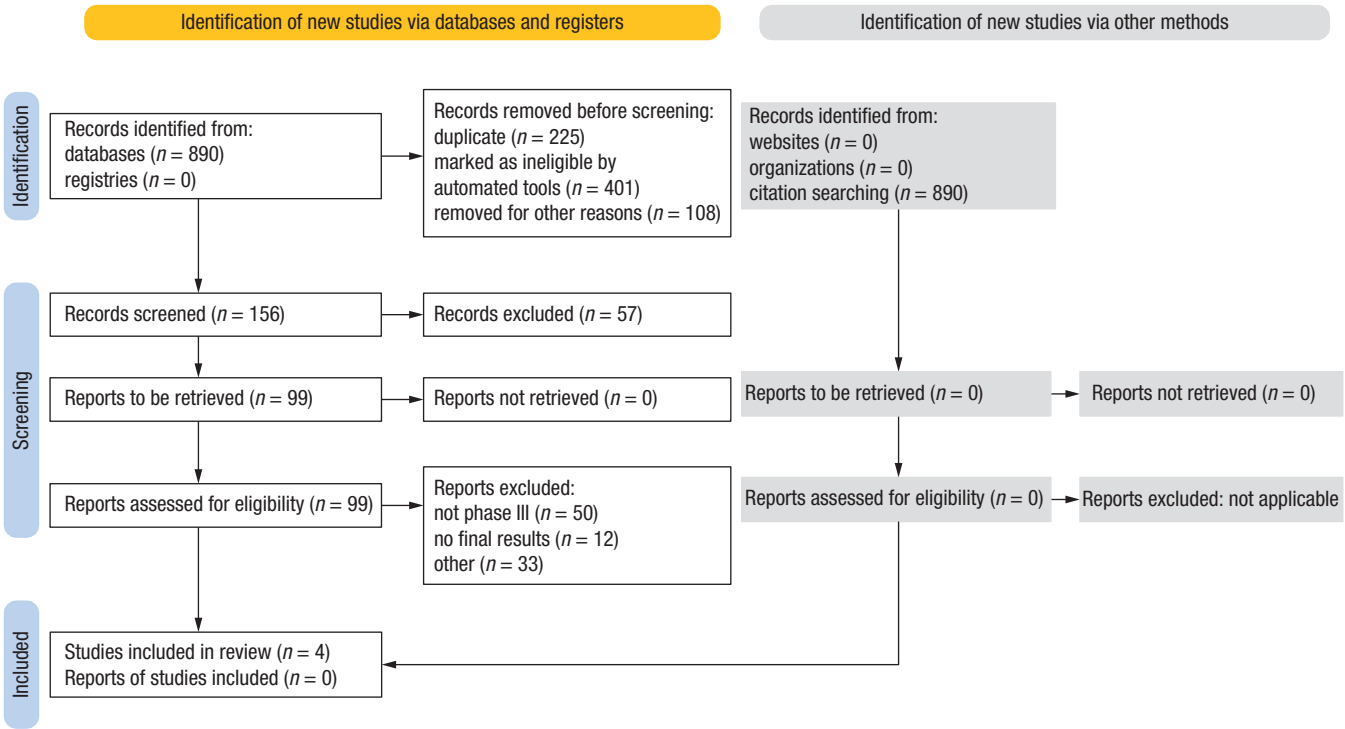
Study selection and eligibility criteria

Two investigators (AM, CB) assessed the title and abstract of all articles to determine the eligibility criteria for the population studied, the intervention, comparisons and study design. The full text of all potentially eligible studies was obtained, and two investigators (AM, FQ) assessed their eligibility for inclusion in the meta-analysis. Any disagreements were resolved through discussion. The reasons for excluding some clinical trials and the selection process were recorded using the PRISMA flow diagram (Figure 1).

Inclusion criteria

Studies were eligible for inclusion if they were peer-reviewed original research articles written in English and examined the immunogenicity, safety or efficacy of various dengue vaccines, and were published within the specified time frame. Only the

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of studies reviewed for the meta-analysis



Source: Figure prepared by the authors based on the results of their study.

final studies about each vaccine were included to eliminate duplication. Only studies that reported the number of participants with documented prior infection in the placebo or control arm were included.

Exclusion criteria

Studies were excluded if they were not written in English and were not a phase III RCT or if they lacked a control or placebo group.

Data extraction

Two authors (SF, CB) extracted data from the included studies and crosschecked the data for accuracy. Using a standardized data extraction sheet, the following information was extracted from the studies: where the study protocol was registered; demographic characteristics of study participants; pre-existing, documented dengue infection; treatment arm; region and country where the study was conducted; the follow-up duration; and outcome data.

Risk of bias

The risk of bias in each randomized trial was assessed using the Risk of Bias 2 tool developed by the Cochrane Collaboration. The five domains of bias considered in this tool are bias arising from the randomization process, due to deviation from the intended interventions, due to missing outcome data, in measuring the outcome and in the selection of the reported results.

Data synthesis

The necessary data were collected from each clinical trial to estimate the risk and 95% confidence interval of dengue infection/100 000 person-years. For each study, we recorded the total numbers of participants, dengue infections, cases severe dengue, hospitalizations for dengue, and all-cause deaths and dengue-related deaths. The number of years of follow up in each study was also recorded.

The risk of each outcome/100 000 person-years was calculated for each study. The risk was computed by dividing the total number of infections by the product of the total number of participants multiplied by the follow-up period, and then multiplying this by 100 000. The probability of each single outcome was computed by dividing the total number of events by the product of the total number of participants multiplied by the follow-up period. The 95% confidence intervals for the risks were determined by first calculating the standard error of a proportion. Then, 1.96 was multiplied by the standard error and this was subtracted from the risk estimate to determine the lower bound; this same amount was then added to the risk estimate to determine the upper bound. The final values were then multiplied by 100 000 to express the risk per 100 000 person-years. After estimating the risk and 95% confidence intervals for each study, the overall weighted risk across all studies was calculated. To obtain the overall risk, the weights for each study were calculated based on the inverse of the variance (i.e. the square of the standard error) of the study's risk estimates. The overall weighted risk was then computed by summing the products of each study's weight and risk, and dividing this by the sum of the weights. The global standard error was derived by taking the square root of the inverse of the sum of the weights.

Separate meta-analyses were conducted for each of the outcomes of interest, identified as VCD, severe dengue, dengue hospitalization, overall mortality and dengue-related death, using the inverse variance–random effects method to calculate the combined odds ratio (OR) for each study. Each meta-analysis is presented as a forest plot, displaying the central estimates along with their 95% confidence intervals. To assess heterogeneity among the studies included in each meta-analysis, the I^2 statistic was used. The I^2 statistic measures the percentage of total variation across studies that is due to heterogeneity rather than chance. Heterogeneity was considered to be substantial when I^2 exceeded 40% and $P < 0.10$ for the χ^2 test. The identification of substantial heterogeneity also influenced the decision to use a random effects model for calculating the odds ratio in each analysis. Additionally, the incidence of each outcome of interest was calculated for each trial individually, as well as collectively for participants with and without prior dengue infection. The incidence is presented on an annualized basis and per 100 000 persons.

Definitions of outcomes used in clinical trials

The studies by Kallás et al. (8) and Tricou et al. (9) used the World Health Organization's (WHO) 2009 criteria, including that for cases requiring hospitalization for VCD. The studies by Capeding et al. (10), Villar et al. (11) and Forrat et al. (12) used WHO's 1997 definitions of dengue hemorrhagic fever, severe dengue and cases requiring hospitalization due to the severity of virologically confirmed infection. An independent study committee also adjudicated cases independently for each trial to reduce bias and ensure that the reported outcomes aligned with the study protocol.

RESULTS

Identification of studies

A total of 39 publications were identified from three RCTs. From these, five studies were selected that contained the most recent data from the three phase III clinical trials and that examined the outcomes of interest (Table 1) (8–12). The PRISMA flowchart for the studies is shown in Figure 1, and the risk of bias assessment is presented in Figure 2.

Incidence in trials

The incidence of VCD during follow up was 1 625 cases (95% CI: 1 536 to 1 715) per 100 000 person-years. The hospitalization rate for dengue was 52 cases (95% CI: 37 to 68) per 100 00 person-years of follow up, the rate for severe dengue was 22 cases (95% CI: 11 to 32), and all-cause mortality was 8 (95% CI: 2 to 14). No dengue-related deaths were recorded in any of the clinical trials during the follow-up periods, which were 6 years in the study by Forrat et al. (12), 4.5 years in the study by Tricou et al. (9) and 2 years for the trial by Kallás et al. (8).

Associations between documented prior dengue and outcomes of interest

Virologically confirmed dengue. Four studies with a total of 19 320 observations and 1 084 reported events were included in the meta-analysis (8–11). Participants with a history of dengue infection had a lower incidence of VCD during the follow-up

TABLE 1. Randomized controlled trials of dengue vaccines meeting inclusion criteria (i.e. they included patients in the placebo arm who had a second dengue infection after a previously documented dengue infection)

Outcome and study	Study information				
	Age group (years)	Years	No. of participants	No. of controls	OR (95% CI)
Virologically confirmed dengue					
Kallás et al. (8)	2–59	2016–2024	3 023	2 690	0.72 (0.49 to 1.08)
Tricou et al. (9)	4–16	2016–2024	4 854	1 832	0.97 (0.80 to 1.18)
Capeding et al. (10)	2–14	2011–2017	444	216	0.91 (0.50 to 1.86)
Villar et al. (11)	9–16	2011–2018	4 821	1 440	0.75 (0.60 to 0.95)
Severe dengue					
Kallás et al. (8)	2–59	2016–2024	3 023	2 390	0.89 (0 to 5702)
Tricou et al. (9)	4–16	2016–2024	4 854	1 832	18.89 (0.04 to 9 881)
Forrat et al. (12)	2–8	2011–2018	135	101	2.28 (0.87 to 6.01)
Forrat et al. (12)	9–16	2011–2018	687	171	7.22 (0.98 to 53.47)
Dengue hospitalization					
Kallás et al. (8)	2–59	2016–2024	3 023	2 390	0.89 (0 to 5 702)
Tricou et al. (9)	4–16	2016–2024	4 854	1 832	0.93 (0.64 to 1.34)
Forrat et al. (12)	2–8	2011–2018	135	101	1.70 (1.01 to 2.89)
Forrat et al. (12)	9–16	2011–2018	687	171	1.33 (0.82 to 2.18)

CI: confidence interval; OR: odds ratio.
Source: Table prepared by the authors based on the results of their study.

period, with an odds ratio of 0.86 (95% CI: 0.75 to 0.98, $P = 0.024$) (Figure 3). Heterogeneity among the studies was low, with an I^2 of 14% and $P = 0.32$ for the heterogeneity test.

Severe dengue. Four studies were included, with a total of 13 493 observations and 57 reported events. The heterogeneity among the studies was very low, with an I^2 of 0% and $P = 0.69$ for the heterogeneity test. The fixed-effects model showed that participants with a history of dengue had a higher risk of severe dengue, with an odds ratio of 2.91 (95% CI: 1.23 to 6.87, $P = 0.0149$) (Figure 4).

Dengue hospitalization. Four studies were included, with a total of 13 493 observations and 381 reported events. Participants with a history of dengue had the same likelihood of hospitalization during the follow-up period as did those who did not have a history of dengue, with an odds ratio of 1.18 (95% CI: 0.92 to 1.53, $P = 0.198$) (Figure 5). The heterogeneity among the studies was moderate, with an I^2 of 20% and $P = 0.29$ for the heterogeneity test.

Dengue-related death. In the four studies with a total of 13 493 observations, no dengue-related deaths were reported. Since no events were recorded in any of the groups, an adjustment was made by introducing a continuity factor of 0.1. This adjustment allowed for the calculation of an estimated odds ratio and its confidence intervals, which were neutral at 0.50 (95% CI: 0.01 to 40.05). Only two studies reported the number of deaths according to seroprevalence in the placebo arm of the trial. This showed that all-cause mortality was similar between participants with and without prior dengue (OR: 1.74, 95% CI: 0.21 to 14.08, $P = 0.76$). The results did not change significantly when two age groups in the trial were analyzed together (i.e. ages 2 to 8 years and 9 to 16 years).

DISCUSSION

This meta-analysis of controlled trials provides valuable information about the severity of events related to a second dengue infection in patients with previously documented dengue. This meta-analysis compared the frequencies of events in individuals randomized to the placebo arm of vaccine efficacy trials based on prior seroprevalence.

Patients who were seropositive had a lower risk of a second dengue infection, had similar hospitalization rates and had the same mortality as seronegative individuals. However, a higher proportion of seropositive individuals was classified as having severe dengue than among those who were seronegative.

The results of this systematic review provide information supporting a critical re-evaluation of the current conceptualization held by the medical community regarding the role of prior dengue infection in worsening subsequent infections.

The clinical trials included in this study (8–12) involve all the dengue vaccines approved to date. International health authorities typically make decisions based on results published in these and similar studies.

The finding of a lower risk of VCD among participants with a previous dengue infection aligns with the well-known fact that prior infection confers homotypic immunity. However, there is evidence that a second infection with a different serotype carries a higher risk of severe dengue due to antibody-dependent enhancement, in which pre-existing antibodies from the initial infection can facilitate the entry of the virus into host cells, increasing viral replication and disease severity (13). In individuals with a previous infection, antibodies generated against the first serotype can facilitate the entry of a different serotype into host cells instead of neutralizing it, increasing viral replication and increasing the severity of the disease.

FIGURE 2. Assessment of risk of bias (a) by domain and (b) by type

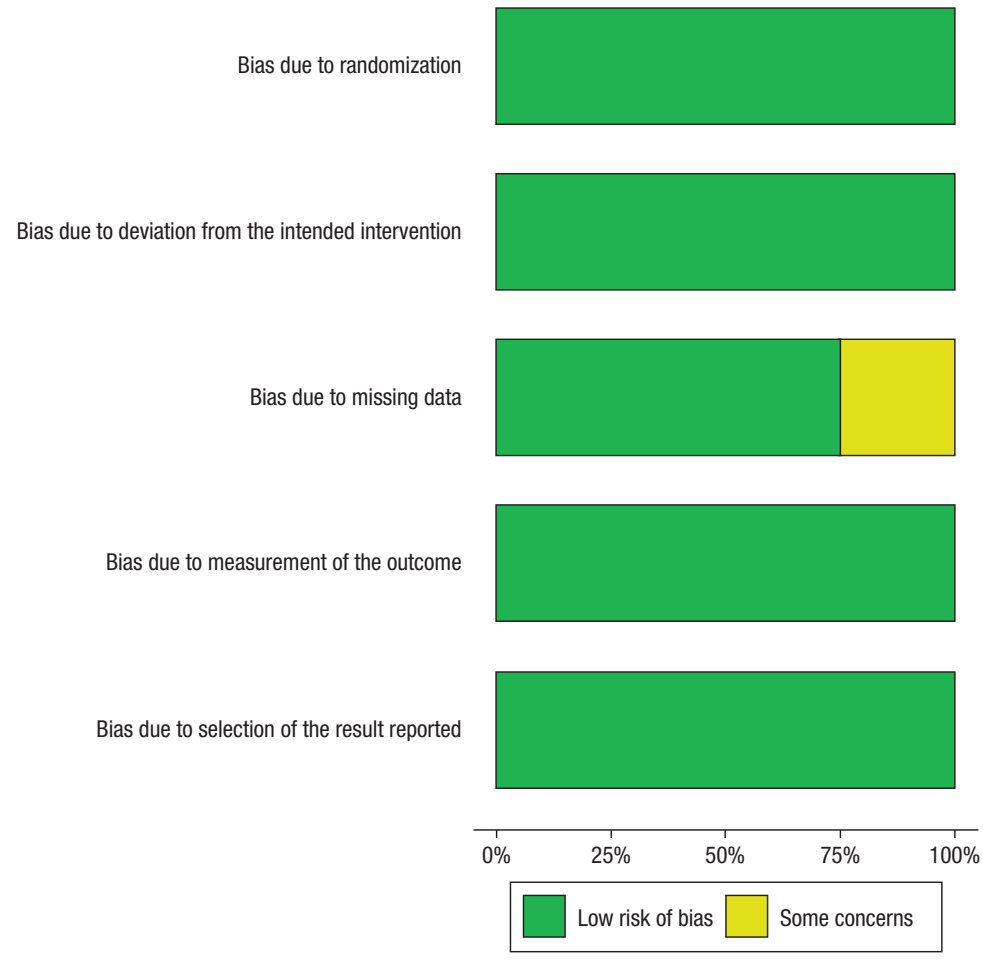
(a)

Study	Domain					Overall
	D1	D2	D3	D4	D5	
Forrat et al. (12)	+	+	–	+	+	+
Kallás et al. (8)	+	+	+	+	+	+
Tricou et al. (9)	+	+	+	+	+	+
Villar et al. (11)	+	+	+	+	+	+

D1: bias due to randomization; D2: bias due to deviation from the intended intervention;
D3: bias due to missing data; D4: bias due to measurement of the outcome; D5: bias due to selection of result reported.

Assessment
+: low risk; – some concerns

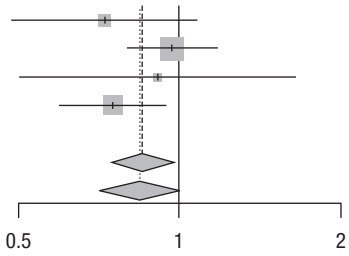
(b)



Source: Figure prepared by the authors based on the results of their study.

FIGURE 3. Association between prior dengue infection and virologically confirmed dengue in the placebo arm of randomized controlled trials, by study

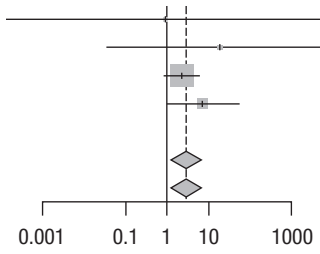
Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds ratio	Odds ratio (95% CI)	Weight (common)	Weight (random)
Kallás et al. (8)	45	3 023	55	2 690		0.72 (0.49, 1.08)	11.7%	16.1%
Tricou et al. (9)	394	4 854	153	1 832		0.97 (0.80, 1.18)	48.5%	41.4%
Capeding et al. (10)	34	444	18	216		0.91 (0.50, 1.66)	5.2%	8.0%
Villar et al. (11)	277	4 821	108	1 440		0.75 (0.60, 0.95)	34.7%	34.5%
Common effect model		**13 142**		**6 178**		**0.86 (0.75, 0.98)**	**100.0%**	**–**
Random effects model						**0.84 (0.71, 1.01)**	**–**	**100.0%**
Heterogeneity: I^2 = 14%, t^2 = 0.0099, P = 0.32								



CI: confidence interval.
Source: Figure prepared by the authors based on the results of their study.

FIGURE 4. Association between prior dengue infection and severe dengue in the placebo arm of randomized controlled trials, by study

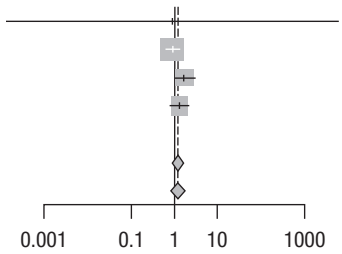
Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds ratio	Odds ratio (95% CI)	Weight (common)	Weight (random)
Kallás et al. (8)	0	3 023	0	2 690		0.89 (0.5702, 54)	1.0%	1.0%
Tricou et al. (9)	5	4 854	0	1 832		18.89 (0.04, 9 881.88)	1.9%	1.9%
Forrat et al. (2–8 years) (12)	17	135	6	101		2.28 (0.87, 6.01)	78.7%	78.7%
Forrat et al. (9–16 years) (12)	28	687	1	171		7.22 (0.98, 53.47)	18.4%	18.4%
Common effect model		**8 699**		**4 794**		**2.91 (1.23, 6.87)**	**100.0%**	**–**
Random effects model						**2.91 (1.23, 6.87)**	**–**	**100.0%**
Heterogeneity: I^2 = 0%, t^2 = 0, P = 0.69								



CI: confidence interval.
Source: Figure prepared by the authors based on the results of their study.

FIGURE 5. Association between prior dengue infection and hospitalization in the placebo arm of randomized controlled trials, by study

Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds ratio	Odds ratio (95% CI)	Weight (common)	Weight (random)
Kallás et al. (8)	0	3 023	0	2 690		0.89 (0.00, 5702.54)	0.1%	0.2%
Tricou et al. (9)	101	4 854	41	1 832		0.93 (0.64, 1.34)	48.9%	40.9%
Forrat et al. (2–8 years) (12)	67	135	37	101		1.70 (1.01, 2.89)	23.7%	28.2%
Forrat et al. (9–16 years) (12)	113	687	22	171		1.33 (0.82, 2.18)	27.3%	30.7%
Common effect model		**8 699**		**4 794**		**1.18 (0.92, 1.53)**	**100.0%**	**–**
Random effects model						**1.23 (0.86, 1.77)**	**–**	**100.0%**
Heterogeneity: I^2 = 20%, t^2 = 0.0480, P = 0.29								



CI: confidence interval.
Source: Figure prepared by the authors based on the results of their study.

Antibody-dependent enhancement has been one of the main hypotheses used to explain the increased severity of second infections, and it has sparked debate over vaccination strategies. While some studies have confirmed the association between antibody-dependent enhancement and increased severity, others have found more variable results, highlighting the need for continued investigation of this mechanism in different epidemiological contexts (14).

The results reported in this meta-analysis also highlight this need, showing that the risk of severe dengue was higher in individuals with a prior dengue infection. However, during follow up in the clinical trials, the most frequently occurring

event after VCD was not severe dengue but hospitalization for dengue. The results reported here show that the risk of hospitalization for dengue was similar between participants with and without previous disease. Similar findings have also been published by other groups (15, 16), and they underscore the need to reconsider the utility of the current clinical classification of severe dengue and to re-evaluate the role of previous infection as a risk factor for severe events.

The results of this meta-analysis suggest that the definition of severe dengue may not adequately capture the true severity of the disease. However, the findings highlight the need to adopt criteria for hospitalization as more robust indicators of dengue severity and to re-examine the interpretation of risk associated with previous infections to improve prevention and management strategies for the disease (15, 16). Some studies suggest that the revised WHO classification for severe dengue is sensitive and specific (13, 16), while others have indicated there are inconsistencies and discrepancies in the definition of severe disease (17–21). Although there is consensus that the new WHO classification is simpler and clearer, some studies have pointed out that there may still be difficulties using it in resource-limited settings (19) because the lack of access to diagnostics and variability in interpreting warning signs may complicate its effective implementation (20, 21).

In the randomized trials, the number of deaths from dengue during follow up was zero. In studies from Brazil, this finding has been attributed to participants having previously been infected with Zika virus (22). While this could be biologically plausible for Brazil, it seems unlikely to explain the absence of deaths in other countries, where Zika transmission has been lower or only occasional. The absence of deaths from dengue in clinical trials contrasts with the substantial number of observational studies distinctly showing its lethality (3, 7). There may be several reasons for these discrepancies. First, observational studies include patients with different levels of access to medical care and they may have higher levels of comorbidity than those recruited into trials. Additionally, patients in randomized studies are closely monitored for symptoms and likely receive earlier medical assistance. This proactive care can prevent the progression to severe forms of the disease and significantly reduce mortality. Second, methodological issues must also be considered. In observational studies, observation bias can lead to an overestimation of the risk of mortality from dengue in patients with previous infection. This bias may arise from several factors, including how participants are selected and monitored, and how data are collected and analyzed. Patients with a history of dengue may be more likely to seek medical care because they are aware of the condition, leading to a higher likelihood of being included in retrospective studies when compared with those without a history of dengue.

Limitations

The limitations of this meta-analysis should be considered. First, although only phase III RCTs were included, the heterogeneity in inclusion criteria and outcome definitions among the studies could have influenced the findings. Second, the limited number of studies and reported events may affect the precision and generalizability of the results. Third, the use of data from the placebo groups of the trials may not fully reflect real-world conditions, as participants in clinical trials often receive more intensive follow up and superior health care compared with the general population. It is likely that in the context of dengue with warning signs, patients participating in a clinical trial may be hospitalized quickly, which could lead to results biased towards lower morbidity and mortality. Fourth, the population of the clinical trials included in this meta-analysis consists of those from phase III trials that tested the efficacy of various vaccines. While the efficacy of the vaccine can be extrapolated to other contexts, it should be noted that this analysis did not assess vaccine efficacy but rather the outcomes of participants in the placebo arm of the trial as an indicator of disease burden without vaccination. Thus, the results obtained are indicative of the disease burden in epidemiological contexts with high viral circulation and do not necessarily represent other contexts. Additionally, the variability in the demographic and geographical characteristics of the populations studied could limit the applicability of the results to other regions and contexts.

Another limitation of this study lies in the evolving nature of the definition of severe dengue, which has varied over time (21, 23, 24), including during the clinical trials analyzed. This lack of a consistent taxonomy to define the cause of hospitalization poses a challenge. While trials provided clear documentation of the event (i.e. hospitalization), they did not always specify the precise criteria that prompted hospitalization. This could lead to overlap between cases of VCD and severe dengue, in which a VCD case might be hospitalized without necessarily being classified as severe dengue. However, events in the trials were not reported in duplicate but under only a single category, which is why outcomes were analyzed separately.

Conclusions

The results of this meta-analysis show that prior dengue infection is associated with a higher risk of severe dengue, but not with a higher risk of hospitalization for dengue and not with increased mortality. Severe dengue in clinical trials represented a smaller proportion of events during follow up, while hospitalization for dengue was more frequent. These findings suggest that the definition of severe dengue should be revisited to better capture the true severity of the disease, emphasizing hospitalization criteria as more reliable indicators. The results underscore the necessity of re-evaluating the role of previous infections to refine prevention and management strategies for dengue.

Authors' contributions. SF, AM and FQ conceived the original idea for the research and planned the analysis. SF and CB collected the data and contributed data analysis and interpreted the results. SF and AM wrote the paper. FQ reviewed the paper. All authors reviewed and approved the final version.

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Impacto de la infección previa de dengue en la gravedad y los resultados: metanálisis de ensayos controlados con placebo

RESUMEN

Objetivo. Este estudio evaluó la asociación entre la infección previa de dengue confirmada serológicamente y el riesgo posterior de dengue confirmado virológicamente, dengue grave, hospitalización por dengue, muerte relacionada con el dengue y mortalidad por cualquier causa.

Métodos. Se llevó a cabo una revisión sistemática y un metanálisis según las directrices PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*). Se realizaron búsquedas en PubMed, CINAHL, MEDLINE, Cochrane Library y Web of Science de presentaciones de ensayos clínicos de fase III aleatorizados y comparativos sobre la eficacia de las vacunas, que incluyeran datos del grupo placebo e información sobre infecciones previas, publicados entre enero de 1994 y marzo del 2024. Se utilizaron modelos de efectos aleatorios para calcular las razones de posibilidades (OR por su sigla en inglés) combinadas y se evaluó la heterogeneidad.

Resultados. Se incluyeron cuatro estudios de tres ensayos de fase III. Los participantes con infección previa tuvieron una menor probabilidad de presentar dengue confirmado virológicamente durante el seguimiento (OR: 0,85; intervalo de confianza [IC] del 95%: 0,75 a 0,98; $p = 0,024$) y el mismo riesgo de hospitalización por dengue que las personas sin infección previa (OR: 1,18; IC del 95%: 0,92 a 1,53; $p = 0,198$). Sin embargo, presentaron una tasa de dengue grave superior (OR: 2,91; IC del 95%: 1,23 a 6,87; $p = 0,015$). No se produjeron muertes relacionadas con el dengue durante el seguimiento. No hubo diferencias estadísticamente significativas en la mortalidad por cualquier causa entre las personas con y sin dengue previo (OR: 1,74; IC del 95%: 0,21 a 14,08; $P = 0,76$).

Conclusiones. La infección previa por dengue redujo significativamente el riesgo de dengue confirmado virológicamente y aumentó el riesgo de dengue grave, pero no tuvo un efecto significativo sobre la hospitalización por dengue, la muerte relacionada con el dengue o la mortalidad por cualquier causa durante el seguimiento. Estos resultados sugieren que es necesario considerar la infección previa un factor de riesgo independiente.

Palabras clave Dengue; dengue grave; vacunas contra el dengue; metaanálisis.

Impacto da infecção prévia por dengue na gravidade e nos desfechos: metanálise de ensaios controlados por placebo

RESUMO

Objetivo. Este estudo avaliou a associação entre uma infecção prévia por dengue confirmada sorologicamente e o risco subsequente de dengue confirmada virologicamente, dengue grave, hospitalização por dengue, morte relacionada a dengue e mortalidade por todas as causas.

Métodos. Foram conduzidas revisão sistemática e metanálise de acordo com as diretrizes PRISMA (sigla em inglês para "principais itens para relatar revisões sistemáticas e metanálises"). Foram feitas buscas nas bases de dados PubMed, CINAHL, MEDLINE, Biblioteca Cochrane e Web of Science por relatos de ensaios clínicos randomizados controlados de fase III sobre a eficácia de vacinas que tivessem dados sobre o grupo placebo e informações sobre infecções prévias e tivessem sido publicados entre janeiro de 1994 e março de 2024. Modelos de efeitos aleatórios foram usados para calcular as razões de chances (RCs) combinadas, e a heterogeneidade foi avaliada.

Resultados. Foram incluídas quatro publicações de três ensaios clínicos de fase III. Os participantes com infecção prévia tiveram menor probabilidade de desenvolver dengue confirmada virologicamente durante o acompanhamento (RC: 0,85, intervalo de confiança [IC] de 95%: 0,75 a 0,98, $P = 0,024$) e o mesmo risco de hospitalização por dengue que participantes sem infecção prévia (RC: 1,18, IC de 95%: 0,92 a 1,53, $P = 0,198$). No entanto, eles tiveram uma taxa mais alta de dengue grave (RC: 2.91, IC de 95%: 1,23 a 6,87, $P = 0,015$). Não houve mortes relacionadas a dengue durante o acompanhamento. Não houve diferenças estatisticamente significantes na mortalidade por todas as causas entre indivíduos com e sem dengue prévia (RC: 1,74, IC de 95%: 0,21 a 14,08, $P = 0,76$).

Conclusões. A infecção prévia por dengue reduziu significativamente o risco de dengue confirmada virologicamente e aumentou o risco de dengue grave, mas não teve efeito significativo na hospitalização por dengue, morte relacionada a dengue ou mortalidade por todas as causas durante o acompanhamento. Os achados sugerem a necessidade de reconsiderar a infecção prévia como fator de risco independente.

Palavras-chave Dengue; dengue grave; vacinas contra dengue; metanálise.