Efficacy of Tetravalent Dengue Vaccine: A Systematic Review and Meta-Analysis

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Abstract

Dengue is one of the neglected tropical diseases caused by flavivirus. Live-attenuated tetravalent vaccine is launched for the age group of 9–45 years. It is given in three doses schedule. Eleven studies were included in meta-analysis by following PRISMA guidelines. Healthy persons in the age group of 2–45 years were included in these studies. Statistical analysis was done by "R" software. Pooled relative risk among vaccinated versus control group was calculated using random-effect model. Pooled dengue vaccine efficacy was calculated from relative risk. Heterogeneity and publication bias were assessed using Baujat and funnel plot, respectively. Adverse effects following immunization were reviewed. Pooled vaccine efficacy is 58% (95% confidence interval 46%-67%). I^2 statistics is 81.4%.

Keywords: Efficacy, meta-analysis, neglected tropical disease, tetravalent dengue vaccine

Introduction

Dengue is vector-borne disease transmitted by Aedes mosquito. There are four serotypes of dengue virus DENV 1, 2, 3, and 4. More than 1 lakh dengue cases are reported in India annually. It is more prevalent in Karnataka, Rajasthan, Maharashtra, Gujarat, and Delhi states/union territory of India.[1] Dengue is one of the neglected tropical diseases (NTD). The target number 3.3 under the sustainable development goal is to end epidemic of NTD by 2030.[2]

Tetravalent dengue vaccine (TDV) is launched under trade name "Dengvaxia."[3] Vaccine has an important role in the specific protection of the disease. This meta-analysis is conducted to find out the pooled efficacy of the vaccine and its safety profile. It may be helpful to develop future vaccination strategies.

Objectives

i. To find out pooled efficacy of TDV irrespective of serotypes
ii. To review the adverse effects following immunization.

Study methodology
Articles search

The primary objective of the meta-analysis is to study efficacy of TDV. Articles were searched systematically from PubMed, Medline, and other electronic databases. Preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines were used for article selection [Figure 1]. Twelve articles were used for a qualitative study.[4-15] Eleven articles included in the quantitative study (meta-analysis).

Inclusion criteria for articles selection

PICOS model was used as a strategy for article searching.

Population

Healthy persons in the age group of 2–45 years were included in these studies.

Intervention

All those studies in which TDV was given in three doses schedule (0 month, 6 months, and 12 months) are included in meta-analysis.

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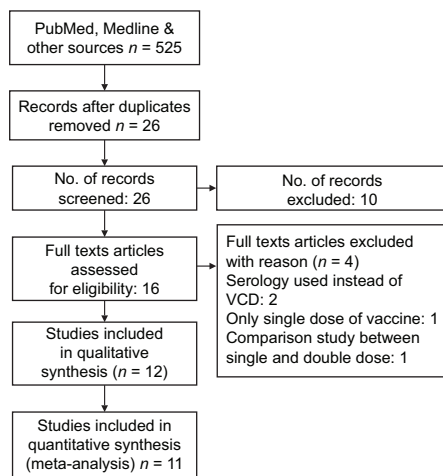
Figure 1: PRISMA diagram

Comparison

Control group in these studies was taken as placebo except three studies. In those three studies, control group was taken as some other vaccine instead of placebo. These vaccines were rabies vaccine, meningococcal polysaccharide vaccine, typhoid Vi polysaccharide vaccine, and pneumococcal vaccine.[4-6]

Outcome

Incidence of dengue cases among vaccinated and control group was confirmed by the presence of virologically confirmed dengue (VCD).

Virological confirmation was done either by nonstructural protein 1 antigen or reverse transcription polymerized chain reaction test. Incidence of VCD cases among vaccinated and placebo group was compared. The pooled relative risk of getting VCD among vaccinated and placebo (nonvaccinated) groups was calculated.

Study design

Only randomized control trials (RCTs) which were conducted in phase two and three are included in meta-analysis:

Timeframe

The follow-up period in these studies was ranged from 12 months to 48 months.

These studies were published between the years 2012 and 2020.

Exclusion criteria

Those studies were excluded in which dengue was confirmed by the tests other than nonstructural protein 1 antigen and reverse transcription polymerized chain reaction. Studies in which outcome was measured by seroprevalence of dengue were excluded from the study.

Data collection and extraction

Eleven articles were found suitable for meta-analysis. Data were entered in excel sheet from each study. Variables included were study name, publication year, number of events in vaccinated and control group, and total sample size in each group.

Statistical analysis

Study was analyzed using "R" software version 3.6.1. Random-effect model was used to estimate pooled effect from studies. From the pooled risk ratio overall vaccine efficacy was calculated. (Vaccine efficacy = 1-Relative risk), I^2 statistics was calculated to measure heterogeneity among studies.

Graphical presentation

A Forest plot was constructed to show graphically pooled estimates. Funnel plot was plotted to determine the presence of publication bias. Baujat plot was drawn to show the heterogeneity among the studies.

RESULTS

Pooled efficacy of TDV from 11 studies is 58% (95% confidence interval [CI] 46%–67%) by random effect model [Figure 2]. I^2 statistics is 81.4% (95% CI 67.7%–89.2%). It shows considerable heterogeneity among the studies. Publication bias is presented graphically by funnel plot. Three studies are out of the area of funnel plot [Figure 3]. Cochran's Q statistics value is 53.63 (df = 10, $P < 0.0001$) and H statistics = 2.32 (95% CI 1.76–3.05). Three studies are showing more heterogeneity as shown in the Baujat plot [Figure 4].

DISCUSSION

Articles were searched systematically from PubMed, Medline, and other databases. PRISMA guidelines were followed for article selection. Eleven studies were found suitable for meta-analysis after considering exclusion and inclusion criteria. These studies were conducted in phase two and three of RCT. These studies were published from 2012 to 2020 [Table 1]. The age group included in the studies was 2–45 years. The vaccinated group was given three doses of the TDV (0, 6, and 12 months). The vaccinated and control groups were followed up for variable period, ranges from 12 months to 48 months. While searching literature, it was found that some trials are still going on. Most of these studies were conducted in Asia and Latin America. There is a need to conduct studies in other regions of the world where dengue is endemic.

Total sample size after pooling is 135,399 (90,805 in vaccinated group and 44,594 in control group) [Figure 2]. A study conducted by Arrendondo Garcia in 2018 has got more weightage (11.9%) with respect to random-effect model of a pooled analysis. Pooled risk ratio from all studies is 0.42 (95% confidence interval [CI] 0.33–0.54). The efficacy of TDV after pooled analysis is 58%. In a study conducted by Hadinegero in 2014, the risk ratio is almost equal to 1 suggests no vaccine efficacy. This study had given more heterogeneous effect compared to other studies. Vaccine efficacy is highest in the studies conducted by Lanata in 2012 and Shibadas in 2019. In the study conducted by Lanata, vaccine efficacy is 83%. Vaccine efficacy found in the study conducted by Shibadas is 80%.[11] These two studies had given more effective results of

Table 1: Summary of the studies included in meta-analysis

Author	Year	Sample size	Age group	Region/Countries	Phase	Follow up period (months)
Sabchareon et al.[4]	2012	3773	4-11	Thailand	2b	25
Lanata et al.[5]	2012	298	2-11	Peru	2	12
Tran et al.[6]	2012	180	2-45	Vietnam	2	18
Capeding et al.[7]	2014	9753	2-14	Asia Pacific	3	25
Villar et al.[8]	2015	17,602	9-16	L. America	3	25
Hadinegoro et al.[9]	2015	10,165	2-14	Asia Pacific	3	25
Hadinegoro et al.[9]	2015	19,898	9-16	L. America	3	25
Arredondo-García et al.[10]	2018	33,904	2-16	Asia Pacific/L. America	3	48
Biswal et al.[11]	2019	19,016	4-16	Asia/L. America	3	12
Biswal et al.[12]	2020	19,016	4-16	Asia/L. America	3	18
Tricou et al.[13]	2020	1794	2-17	Dominion republic, Panama	2	48
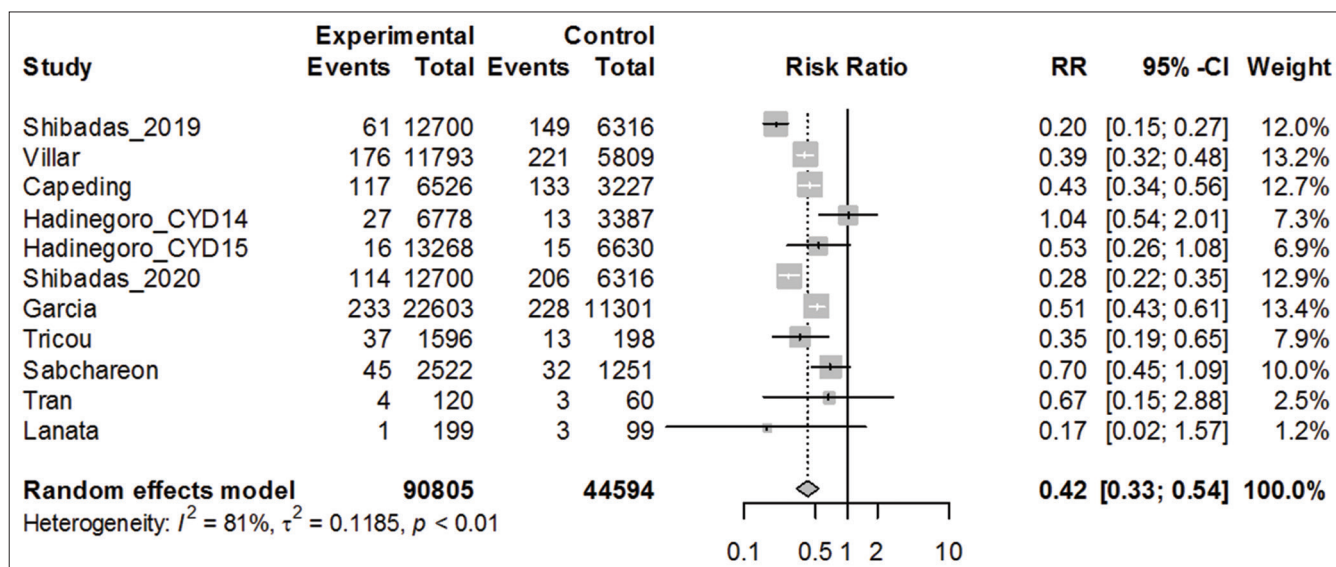
Figure 2: Forest plot showing pooled analysis by random effect model
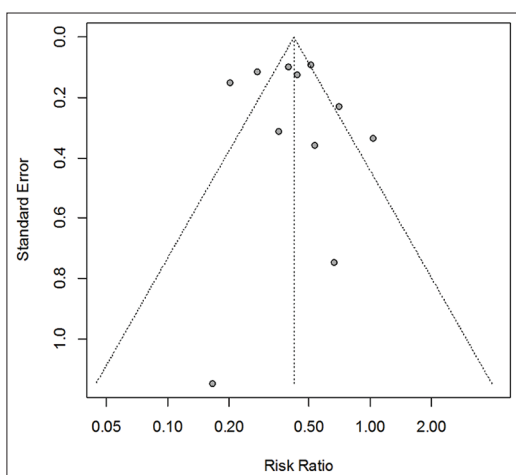

Figure 3: Funnel plot showing publication bias

vaccine efficacy. There may be regional variation in vaccine efficacy according to serotype prevalent in that area.[8]

Findings of the study are presented by various graphs. Pooled estimates of relative risk are shown by forest plot [Figure 2].

Funnel plot is drawn to show the publication bias. Three studies are showing more publication bias [Figure 3]. Baujat plot is drawn by taking Cochran's Q statistics on x-axis and its influence on overall result on y-axis. Studies which are situated on the right side of the graph contribute more to heterogeneity [Figure 4].

Overall serious adverse events (SAEs) reported in the vaccinated group were variable, ranges from 0.5% to maximum 11.8%.[4,7,8,11,12] However, vaccine-related SAEs were none or negligible in vaccinated group.[6,8,14] Deaths reported in most of the studies were nil or negligible (<0.1%). Some studies had monitored systemic as well as local solicited and unsolicited adverse events, which gave variable results.

Most common injection site local reactions were pain, erythema, and swelling. Most of these local reactions resolved within 3 days after giving vaccine.[5] SAEs directly related to vaccine were very less or none. Chances of SAEs reported were same in both vaccinated and placebo groups.[8,11] Most common SAEs were infections and injuries which were not related to vaccination. Fever, headache, and myalgia were reported as
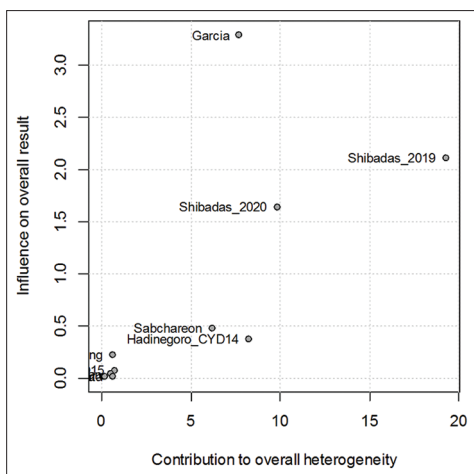
Figure 4: Baujat plot showing heterogeneity among the studies included in meta-analysis

the most common systemic solicited reactions.[6] Safety issues related to vaccine were very less on long-term follow-up after 4 years.[13,14] Further phase IV studies are required to be conducted to better understand safety issues.

One study had assessed the cost-effectiveness of the CYD-TDV vaccine found that it is more cost effective.[15] Some studies also reported less hospitalization rate among the vaccinated group than control group.[9,15] Rate of hospitalization due to VCD was less among persons having age >9 years.[10]

CONCLUSION

From the pooled analysis, it is concluded that TDV has good efficacy and negligible vaccine-associated SAEs. More postmarketing trials are required to be conducted.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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